



Contemporary menopausal hormone therapy and thrombotic disease: nationwide nested case-control study

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ABSTRACT

OBJECTIVES

To investigate associations between current use of menopausal hormone therapy and development of venous thromboembolism, ischaemic stroke, and myocardial infarction.

DESIGN

Nationwide nested case-control study.

SETTING

National Danish health registries.

PARTICIPANTS

9807 women with venous thromboembolism, 18 460 women with ischaemic stroke, and 11 974 women with myocardial infarction were identified in a cohort of women of 50-69 years living in Denmark between 2003 and 2021 without a medical history of venous thrombosis, arterial thrombosis, cancer, liver disease, thrombophilia, oophorectomy, infertility treatment, endometriosis, or polyendocrine metabolic ovarian syndrome (PMOS, previously known as polycystic ovary syndrome). Cases were matched by birth year to a total of 49 035, 92 300, and 59 870 women without thrombotic disease, respectively.

MAIN OUTCOME MEASURES

Receiving a first time diagnosis of venous thromboembolism, ischaemic stroke, or myocardial infarction.

RESULTS

Among women who had not used menopausal hormone therapy, incidence rates of venous thromboembolism, ischaemic stroke, and myocardial infarction per 10 000 person years were 15.8, 20.3, and 13.0, respectively. Compared with no current use, current use of oral oestrogen therapy (alone or combined with progestin) was associated with increased rates of venous thromboembolism (hazard ratio 1.6, 95% confidence interval (CI) 1.5 to 1.8), ischaemic stroke (1.3, 1.2 to 1.4), and myocardial infarction (1.2, 1.1 to 1.3). The absolute risk increase per year was 0.09% (95% CI 0.08 to 0.13%) for venous thromboembolism, 0.06% (0.04 to 0.08%) for ischaemic stroke, and 0.03% (0.01 to 0.04%) for myocardial infarction, corresponding to numbers needed to harm for one year of use of 1055 (95% CI 791 to 1266), 1642 (1232 to 2463), and 3846 (2564 to 7692), respectively.

Use of oral forms of oestradiol was consistently associated with increased venous thromboembolic risk compared with no current use. Oral oestradiol doses >1 mg/day used for more than one year was associated with increased risks of ischaemic stroke and myocardial infarction, with risks increasing with treatment duration (stroke hazard ratio 1.8, 95% CI 1.4 to 2.2 and myocardial infarction hazard ratio 1.8, 1.4 to 2.4 for >5 years of use compared with no current use).

Transdermal therapy was not associated with increased thrombotic rates compared with no current use, with the exception of increased risk of myocardial infarction with transdermal combined cyclic therapy (hazard ratio 2.1, 95% CI 1.1 to 4.1).

CONCLUSIONS

Compared with no current use of any hormone therapy, oral menopausal hormone therapy was associated with increased venous thromboembolic risk regardless of dosage and treatment duration, while prolonged use of high dose oral oestradiol (>1 mg/day) showed elevated risks of ischaemic stroke and myocardial infarction. No increased thrombotic risks were observed with transdermal therapy.

Introduction

Cardiovascular disease is the leading cause of death among women worldwide,¹ with risk increasing after menopause as endogenous oestrogen levels decline.² Mechanistic studies have demonstrated that endogenous oestrogen improves cardiovascular health by promoting angiogenesis and vasodilation, reducing fibrosis, enhancing mitochondrial function, and lowering oxidative stress.³ While the cardioprotective effects of endogenous oestrogen are well acknowledged,

WHAT IS ALREADY KNOWN ON THIS TOPIC

Oral menopausal oestrogen therapy has been associated with increased risk of venous thromboembolism and stroke, but evidence for an increased risk of myocardial infarction remains inconsistent

Evidence suggests that no increased thrombosis risk exists with use of transdermal menopausal hormone therapy

Studies comparing the risk of thrombosis across contemporary methods of use, regimens, active ingredients, dosages, treatment durations, and ages at treatment initiation remain limited

WHAT THIS STUDY ADDS

In this nationwide study, current use of oral menopausal hormone therapy was associated with an increased risk of venous thromboembolism across treatment characteristics, whereas increased risks of ischaemic stroke and myocardial infarction were observed only with oral high dose therapy used for more than one year

The numbers needed to harm for one year of oral therapy were 1055 (95% confidence interval (CI) 791 to 1266) for venous thromboembolism, 1642 (1232 to 2463) for ischaemic stroke, and 3846 (2564 to 7692) for myocardial infarction. Transdermal therapy was not associated with elevated thrombotic risk regardless of dosage and duration of use, supporting the importance of method of use in minimising risk of thrombosis

the cardiovascular impact of menopausal hormone therapy with exogenous oestrogen remains a subject of ongoing debate.

Systemic exogenous oestrogen is the key component of menopausal hormone therapy, prescribed to alleviate disabling vasomotor symptoms, including hot flushes and night sweats. In women who have not undergone hysterectomy, a progestogen is added to prevent endometrial proliferation induced by oestrogen. In contrast with oestrogen, substantially less is known about the independent cardiovascular and thrombotic effects of exogenous progestogens, despite their mandatory use in a large proportion of menopausal hormone therapy regimens.

Early epidemiological studies suggested that menopausal hormone therapy confers reduced cardiovascular risk.^{4 5} However, a subsequent randomised controlled trial reported an increased risk of venous thromboembolism, ischaemic stroke, and myocardial infarction.^{6 7} These conflicting findings have been attributed to methodological discrepancies involving variation in time since menopause onset and length of follow-up; reanalysing observational studies controlling for these discrepancies have yielded risk estimates more consistent with those from randomised trials.⁸

Despite these insights, critical knowledge gaps remain regarding the cardiovascular effects of contemporary menopausal hormone therapy, with limited evidence on the impact of regimen, active ingredients, dosages, durations, and different ages of initiation. Considering the increasing life expectancy and the rising number of postmenopausal women, updated evidence is needed to guide safe and evidence based clinical decision making. In this nationwide study, we aimed to assess the association between contemporary systemic menopausal hormone therapy use and the rates of venous thromboembolism, ischaemic stroke, and myocardial infarction according to method of use, regimen, active ingredients, dosage, duration, and age at treatment initiation.

Methods

Study cohort

We conducted a nationwide nested case-control study using Danish national registries. All cases of first time thrombosis and age matched controls were identified from a nationwide cohort of all Danish women aged 50-69 years between 2003 and 2021 with no medical history of arterial or venous thrombosis, cancer (except non-melanoma skin cancer), liver disease, thrombophilia, oophorectomy, infertility treatment, endometriosis, or polyendocrine metabolic ovarian syndrome (PMOS, previously known as polycystic ovary syndrome) (supplementary appendix). We based the lower age limit on the average age of menopause onset in Denmark (51 years) to primarily capture postmenopausal women. The upper age limit excluded women aged 70 years or older, among whom menopausal hormone therapy is less commonly used. Together, we chose these criteria to approximate the

target population (women likely to start menopausal hormone therapy) and to improve comparability in hormonal status across the study population. The participants were followed from 1 January 2003 or from their 50th birthday—whichever occurred last—until 30 June 2021, their 70th birthday, emigration, death, a thrombotic event, or the occurrence of an exclusion criterion, whichever occurred first. To ensure eligibility data and complete assessment of menopausal therapy use, women who immigrated to Denmark after 1994 were excluded, because assessment of use was available from 1995 with the establishment of the national prescription registry. The study period began in 2003, coinciding with revised Danish clinical guidelines on menopausal hormone therapy. These guidelines recommended a more restrictive and individualised approach, including use at the lowest effective dose and for the shortest possible duration, following safety concerns raised by the Women's Health Initiative trial in 2002.⁶ Furthermore, earlier Danish registry based research has suggested differences in the safety profile of hormone therapy before and after the Women's Health Initiative trial, indicating potential changes in the population who used menopausal hormone therapy.⁹ This research motivated us to examine associations in a contemporary context.

We identified the study population through three national registries: the Danish Civil Registration System,¹⁰ which contains birth year, sex, death, and migration data for all Danish residents since 1968, the Danish National Patient Registry,¹¹ which contains all diagnoses received in hospital since 1977 and all diagnoses received emergency department and outpatient clinic since 1995, and the Danish National Prescription Registry,¹² which contains all prescription redemptions since 1995.

A unique identification number given to all Danish residents was used to reliably link information from the registries.

Cases and controls for thrombosis

We investigated three thrombotic outcomes, all identified as first time thrombosis events diagnosed in hospital through the Danish National Patient Registry and the Danish Registry of Causes of Death.¹³ The three outcomes were (a) venous thromboembolism (deep vein thromboses ICD-10 (international classification of diseases, 10th revision) codes I80.1-I80.3) and pulmonary embolism (ICD-10 code I26), diagnosed in a hospital department, outpatient clinic, or in the emergency department, excluding diagnoses recorded exclusively in the emergency department and not subsequently confirmed by a medical department, (b) ischaemic stroke (ICD-10 codes I63 and I64), and (c) myocardial infarction (ICD-10 code I21). These outcome definitions have been previously validated and have high positive predictive values (venous thromboembolism 88%, ischaemic stroke 97%, myocardial infarction 97%).^{14 15} We matched each case on the date the thrombosis diagnosis was received (index date) to five controls without an earlier

diagnosis of thrombosis using incidence density matching by birth year. The risk sets were pooled by outcome to create three different matched populations.

To enhance the validity of venous thromboembolism case identification, we conducted a sensitivity analysis restricted to cases with additional confirmation. Specifically, we included only participants who had had relevant imaging or received an anticoagulant prescription redemption after receiving a thrombosis diagnosis. This combined approach was necessary because imaging codes were inconsistently available early in the study period, and some patients received anticoagulant treatment free of charge from the hospitals without a corresponding prescription record.¹⁶

Menopausal hormone therapy

The treatment of interest was current use of systemic menopausal hormone therapy, defined as use within 90 days up to and including the index date, consistent with definitions used in previous studies.¹⁷ Women were classified as users if they had redeemed a prescription, since all systemic formulations require a prescription in Denmark. We obtained individual level, daily updated information on type, amount, and timing of purchased menopausal hormone therapy from the National Prescription Registry (Anatomical Therapeutic Chemical codes G03C (oestrogens), G03D (progestogens), G03F (combined products), and G02BA03 (levonorgestrel releasing intrauterine device)) from 1 January 1995 to the index date. A list of available products during the study period can be found in the supplementary appendix.

For fixed dose products (combined oestrogen and progestin oral/patch formulations, oestrogen only patches, and the hormonal intrauterine device), the drug unit size was considered the daily dose, and duration of use was calculated according to the amount of defined daily dose purchased. For single drug formulations allowing for individualised dosing (oral, gel, or spray oestrogen and oral progestins), doses and duration were estimated using the programme *medicinMacro* (tagteam/heaven R package), which calculates the most probable daily dose and duration according to the prescription pattern of the five most recent prescriptions.¹⁸ Besides prescription data, the *medicinMacro* incorporates recommended default, minimum, and maximum doses from the respective summaries of product characteristics.

Confounding factors

A directed acyclic graph was used to guide confounder selection based on assumed causal relationships (supplementary appendix). We retrieved information on potential confounding factors at the index date for all cases and controls and included yearly income, education, cohabitation status, and a medical history of hypertension, atrial fibrillation, cardiomyopathy, heart failure, valvulopathy, diabetes, thyroid disease, kidney disease, chronic obstructive pulmonary disease, migraine, hysterectomy, use of statins, use of bisphosphonates, and concomitant

use of anticoagulants, aspirin, antidepressants, or antipsychotic drugs (supplementary appendix).

Information on body mass index and smoking status was not available in the Danish registries.

Statistical analysis

We used conditional logistic regression to estimate adjusted hazard ratios and corresponding 95% confidence intervals (CIs) for incident venous thromboembolism, ischaemic stroke, and myocardial infarction, according to current use of systemic menopausal hormone therapy and method of oestrogen use (oral or transdermal). Additional analyses examined the influence of regimen (oestrogen only, combined oestrogen-progestin with continuous use of progestin, combined treatment with cyclic use of progestin), active ingredients (oestradiol only, oestradiol and norethisterone, oestradiol and medroxyprogesterone, oestradiol and levonorgestrel), and daily dose of oestradiol (oral low dose ≤ 1 mg v high dose >1 mg, transdermal low dose ≤ 50 μ g v high dose >50 μ g).¹⁷

The sampling assumptions for the risk set design were met by selecting controls using incidence density sampling from individuals who remained at risk of thrombosis at the time of the corresponding case event. Using this approach, individuals could be selected as controls more than once and could subsequently become cases. Estimates from the conditional logistic regression are therefore equivalent to those from a Cox proportional hazards model and are reported as hazard ratios.¹⁹ We assessed the proportional hazards assumption by including interaction terms between exposure and follow-up period in the models, with follow-up categorised as <2 years, 2-5 years, and >5 years. These interaction terms were used to assess whether hazard ratios varied across follow-up periods, using likelihood ratio tests comparing adjusted models with and without the interaction terms.

In all analyses, the reference group was women with no current use of any systemic or local oestrogen, progestogen, or testosterone including hormonal contraceptives and perimenopausal progestogen therapy (supplementary appendix). We categorised current use of these products as separate use categories in the statistical models and therefore controlled for them by design. Similarly, women having used multiple menopausal hormone therapy types within the 90 days were categorised separately in the statistical model as mixed users. All statistical models were adjusted for all the previously mentioned confounders.

To properly investigate the impact of treatment duration (<1 year, 1-5 years, >5 years of uninterrupted use including gaps of up to 90 days) and age at treatment initiation (<50 years, 50-54 years, 55-59 years >59 years) on thrombosis risk among current users, we analysed a subcohort of new users. From the original study cohort, we excluded women who began treatment before 1 January 1996, to ensure at least one year without drug use (the prescription registry started in 1995) and thereby correct identification of

Table 1 | Characteristics of the study populations. Data are number (%) unless otherwise specified

Characteristics	Venous thromboembolism		Ischaemic stroke		Myocardial infarction	
	Cases (n=9807)	Controls (n=49 035)	Cases (n=18 460)	Controls (n=92 300)	Cases (n=11 974)	Controls (n=59 870)
Age						
Median (IQR) age (years)	62 (56-66)	62 (56-66)	62 (57-66)	62 (57-66)	62 (57-66)	62 (57-66)
Income*						
Low	2173 (22.2)	12 538 (25.6)	4420 (23.9)	23 270 (25.2)	2964 (24.8)	14 997 (25.0)
Medium	5502 (56.1)	23 918 (48.8)	10 200 (55.3)	45 180 (48.9)	6570 (54.9)	29 352 (49.0)
High	2132 (21.7)	12 579 (25.7)	3840 (20.8)	23 850 (25.8)	2440 (20.4)	15 521 (25.9)
Education						
Basic	4134 (42.2)	20 081 (41.0)	8199 (44.4)	38 187 (41.4)	5589 (46.7)	24 954 (41.7)
Upper secondary	3684 (37.6)	17 189 (35.1)	6794 (36.8)	32 373 (35.1)	4310 (36.0)	20 603 (34.4)
Bachelors degree	1718 (17.5)	9926 (20.2)	3000 (16.3)	18 446 (20.0)	1843 (15.4)	12 055 (20.1)
Masters degree or doctorate	271 (2.8)	1839 (3.8)	467 (2.5)	3294 (3.6)	232 (1.9)	2258 (3.8)
Cohabitation						
Living alone	2811 (28.7)	14 120 (28.8)	5591 (30.3)	27 138 (29.4)	3218 (26.9)	17 537 (29.3)
Comorbidities†						
Hypertension	590 (6.0)	2251 (4.6)	1565 (8.5)	4385 (4.8)	1011 (8.4)	2740 (4.6)
Atrial fibrillation	318 (3.2)	725 (1.5)	818 (4.4)	1438 (1.6)	477 (4.0)	939 (1.6)
Cardiomyopathy	54 (0.5)	106 (0.2)	106 (0.6)	184 (0.2)	124 (1.0)	100 (0.2)
Heart failure	258 (2.6)	267 (0.5)	376 (2.0)	556 (0.6)	447 (3.7)	294 (0.5)
Valvulopathy	131 (1.3)	368 (0.7)	353 (1.9)	685 (0.7)	301 (2.5)	453 (0.8)
Diabetes	797 (8.1)	2396 (4.9)	1963 (10.6)	4491 (4.9)	1510 (12.6)	2809 (4.7)
Thyroid disease	1410 (14.4)	5415 (11.0)	2505 (13.6)	10 132 (11.0)	1651 (13.8)	6564 (11.0)
Kidney disease	193 (2.0)	163 (0.3)	302 (1.6)	349 (0.4)	243 (2.0)	204 (0.3)
COPD	817 (8.3)	1118 (2.3)	1059 (5.7)	2143 (2.3)	992 (8.3)	1363 (2.3)
Migraine	1639 (16.7)	6434 (13.1)	3086 (16.7)	12 157 (13.2)	1986 (16.4)	7909 (13.2)
Hysterectomy	958 (9.8)	3885 (7.9)	1761 (9.5)	7285 (7.9)	1174 (9.8)	4760 (8.0)
Statin use	2165 (22.1)	8576 (17.5)	5293 (28.7)	16 348 (17.7)	3811 (31.8)	10 343 (17.3)
Bisphosphonate use	695 (7.1)	2209 (4.5)	1217 (6.6)	4184 (4.5)	743 (6.2)	2637 (4.4)
Concomitant medication use‡						
Anticoagulants	341 (3.5)	375 (0.8)	400 (2.2)	763 (0.8)	244 (2.0)	488 (0.8)
Aspirin	905 (9.2)	2549 (5.2)	2480 (13.4)	4765 (5.2)	1650 (13.8)	3101 (5.2)
Antidepressants	1681 (17.1)	4406 (9.0)	3230 (17.5)	8123 (8.8)	1774 (14.8)	5305 (8.9)
Antipsychotic drugs	647 (6.6)	1114 (2.3)	1073 (5.8)	2108 (2.3)	513 (4.3)	1368 (2.3)

IQR=interquartile range; COPD=chronic obstructive pulmonary disease.

Median (IQR) follow-up period for the study population was 6 years (3-10 years), and reflects the interval between entry into the cohort and the index date. The population characteristics were defined at the case index date.

*Low, medium, and high income was defined according to the income distribution of each matched population with low as below first quartile, medium as between first and third quartile, and high as above third quartile, respectively.

†Comorbidities were defined as diagnoses received before to the index date.

‡Concomitant medication was defined as prescription redemption within 180 days before the index date.

treatment initiation. Following the same approach as previously, three matched case-control populations of women aged 50-69 years between 1 January 2003 and 30 June 2021 were created within this new user cohort. Similarly, we created a subcohort of new users initiating treatment after 31 December 2002 to fully capture potential changes in prescribing patterns and user characteristics following the publication of the Women's Health Initiative trial findings in 2002.

Sensitivity analyses were conducted to assess the robustness of the findings, including restriction to current use defined as use within 60 days before the index date (instead of 90 days), earlier use of systemic menopausal hormone therapy (five years to 90 days before the index date), restriction to women aged 50-59 years, restriction to a healthy subgroup without earlier diagnoses of hypertension, diabetes, chronic kidney disease, atrial fibrillation, heart failure, thyroid disease, or chronic obstructive pulmonary disease, and restriction of the study period to 1997-2002 to account for changes in prescribing patterns after the Women's Health Initiative trial.

We calculated number needed to harm for one year of menopausal hormone therapy. The numbers were calculated from the age specific adjusted hazard ratios and the incidence rate of a first time diagnosis of venous thromboembolism, ischaemic stroke, or myocardial infarction in the unexposed Danish population.

All data management and analyses were carried out using R statistical software (R Core Team, 2024).

Patient and public involvement

Patients or the public were not involved in any part of this study, including design, analysis, or manuscript preparation. Given the registry based study design and limited resources available, such involvement was not feasible. Findings will be disseminated to the public and healthcare professionals through press releases, conference presentations, and social media.

Results

Among 1 060 082 eligible women followed for a median of 9 years (interquartile range (IQR)) 5-14 years), we identified 9807 incident cases of venous

Table 2 | Treatment use characteristics of the study populations. Data are number (%) unless otherwise specified

Characteristics	Venous thromboembolism		Ischaemic stroke		Myocardial infarction	
	Cases (n=9807)	Controls (n=49 035)	Cases (n=18 460)	Controls (n=92 300)	Cases (n=11 974)	Controls (n=59 870)
User status						
Current use*	714 (7.3)	2304 (4.7)	1147 (6.2)	4338 (4.7)	689 (5.8)	2846 (4.8)
No current use of any hormonal therapy	8099 (82.6)	42 191 (86.0)	15 791 (85.5)	79 418 (86.0)	10 299 (86.0)	51 440 (85.9)
Use of other hormonal therapies						
Hormonal contraception†	224 (2.3)	282 (0.6)	143 (0.8)	431 (0.5)	88 (0.7)	303 (0.5)
Progestogen only	19 (0.2)	92 (0.2)	22 (0.1)	132 (0.1)	11 (0.1)	78 (0.1)
Testosterone‡	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vaginal oestrogen only	751 (7.6)	4166 (8.5)	1357 (7.4)	7981 (8.7)	887 (7.4)	5203 (8.7)
Users of menopausal hormone therapy						
Method of use:						
Oral	661 (92.6)	1997 (86.7)	1040 (90.7)	3770 (86.9)	625 (90.7)	2487 (87.4)
Transdermal	53 (7.4)	307 (13.3)	107 (9.3)	568 (13.1)	64 (9.3)	359 (12.6)
Regimen						
Oestrogen only	191 (26.8)	633 (27.5)	351 (30.6)	1178 (27.2)	196 (28.4)	758 (26.6)
Combined, continuous	362 (50.7)	1205 (52.3)	570 (49.7)	2298 (53.0)	350 (50.8)	1531 (53.8)
Combined, cyclic	147 (20.6)	418 (18.1)	209 (18.2)	778 (17.9)	125 (18.1)	503 (17.7)
Combined, unknown	14 (2.0)	48 (2.1)	17 (1.5)	84 (1.9)	18 (2.6)	54 (1.9)
Active ingredients:						
E2	181 (25.4)	603 (26.2)	339 (29.6)	1123 (25.9)	191 (27.7)	720 (25.3)
E2 + NETA	411 (57.6)	1323 (57.4)	661 (57.6)	2514 (58.0)	398 (57.8)	1682 (59.1)
E2 + MPA	54 (7.6)	183 (7.9)	83 (7.2)	312 (7.2)	56 (8.1)	214 (7.5)
E2 + LNG	19 (2.7)	94 (4.1)	25 (2.2)	176 (4.1)	22 (3.2)	92 (3.2)
Mixed/other	49 (6.9)	101 (4.4)	39 (3.4)	213 (4.9)	22 (3.2)	138 (4.8)
Daily dose of oestradiol§:						
Low dose	257 (36.5)	1014 (44.6)	366 (32.2)	1856 (43.4)	228 (33.3)	1232 (43.9)
High dose	448 (63.5)	1259 (55.4)	769 (67.8)	2425 (56.6)	456 (66.7)	1573 (56.1)
Age at treatment initiation (years)¶:						
<50	124 (31.7)	378 (30.6)	233 (40.7)	716 (30.6)	136 (39.9)	460 (30.0)
50-54	197 (50.4)	617 (50.0)	274 (47.9)	1190 (50.9)	160 (46.9)	786 (51.2)
55-59	57 (14.6)	204 (16.5)	54 (9.4)	345 (14.7)	32 (9.4)	243 (15.8)
>59	13 (3.3)	36 (2.9)	11 (1.9)	88 (3.8)	13 (3.8)	45 (2.9)
Treatment duration (years)¶:						
<1	135 (34.5)	373 (30.2)	132 (23.1)	646 (27.6)	80 (23.5)	482 (31.4)
1-5	145 (37.1)	504 (40.8)	218 (38.1)	958 (41.0)	130 (38.1)	589 (38.4)
>5	111 (28.4)	358 (29.0)	222 (38.8)	735 (31.4)	131 (38.4)	463 (30.2)

E2=oestradiol; NETA=norethisterone; MPA=medroxyprogesterone; LNG=levonorgestrel.

The characteristics of hormonal therapy use were defined at the case index date.

*Current use was defined as use of systemic menopausal hormone therapy within 90 days before the index date.

†Hormonal contraception comprised contraceptives classified under Anatomical Therapeutic Chemical code G03A.

‡No women were current users of testosterone

§Low daily dose was defined as ≤1 mg oral or ≤50 µg transdermal oestradiol, high daily dose was defined as >1 mg oral or >50 µg transdermal oestradiol.

¶Age at treatment initiation and duration of use are reported only for women who did not redeem a prescription of menopausal hormone therapy within the first year of available use history to ensure accurate information on treatment initiation.

thromboembolism, 18 460 incident cases of ischaemic stroke, and 11 974 incident cases of myocardial infarction and matched these with 49 035, 92 300, and 59 870 women without thrombotic disease, respectively. The supplementary appendix shows the flow diagram of the creation of the study population.

Table 1 provides the characteristics of the three case-control populations at the index date. The median ages at case index were 62 years (IQR 56-66 years), 62 (57-66), and 62 (57-66) for the case-control populations of venous thromboembolism, ischaemic stroke, and myocardial infarction, respectively. The prevalence of comorbidities was higher among cases than controls.

Table 2 provides information on menopausal hormone therapy use at the index date. The proportion of current users of systemic menopausal hormone therapy was higher among cases than controls for venous thromboembolism, ischaemic stroke, and myocardial infarction (7.3%, 6.2%, and 5.8% v 4.7%,

4.7%, and 4.8%, respectively). Across current users of systemic therapy in the three matched populations (n=12 038), menopausal hormone therapy was predominantly oral (88% of all users), combined oestrogen-progestin therapy (73% of all users) with continuous progestin use (72% of combined therapy). Oestradiol was the most common oestrogen used (>96% of all users). Fewer than three current users received conjugated equine oestrogen, which was only available until 2004. Ethinyl oestradiol was not used during the study period, while oestradiol accounted for about 1% of current users. Norethisterone was the most common progestin used (80% of combined therapy).

Users of oral oestrogen and oral or intrauterine levonorgestrel most commonly took levonorgestrel in the form of intrauterine devices (90% of combined oestrogen and levonorgestrel users in the venous thromboembolism population and 62% of all combined oestrogen and levonorgestrel users). Oral

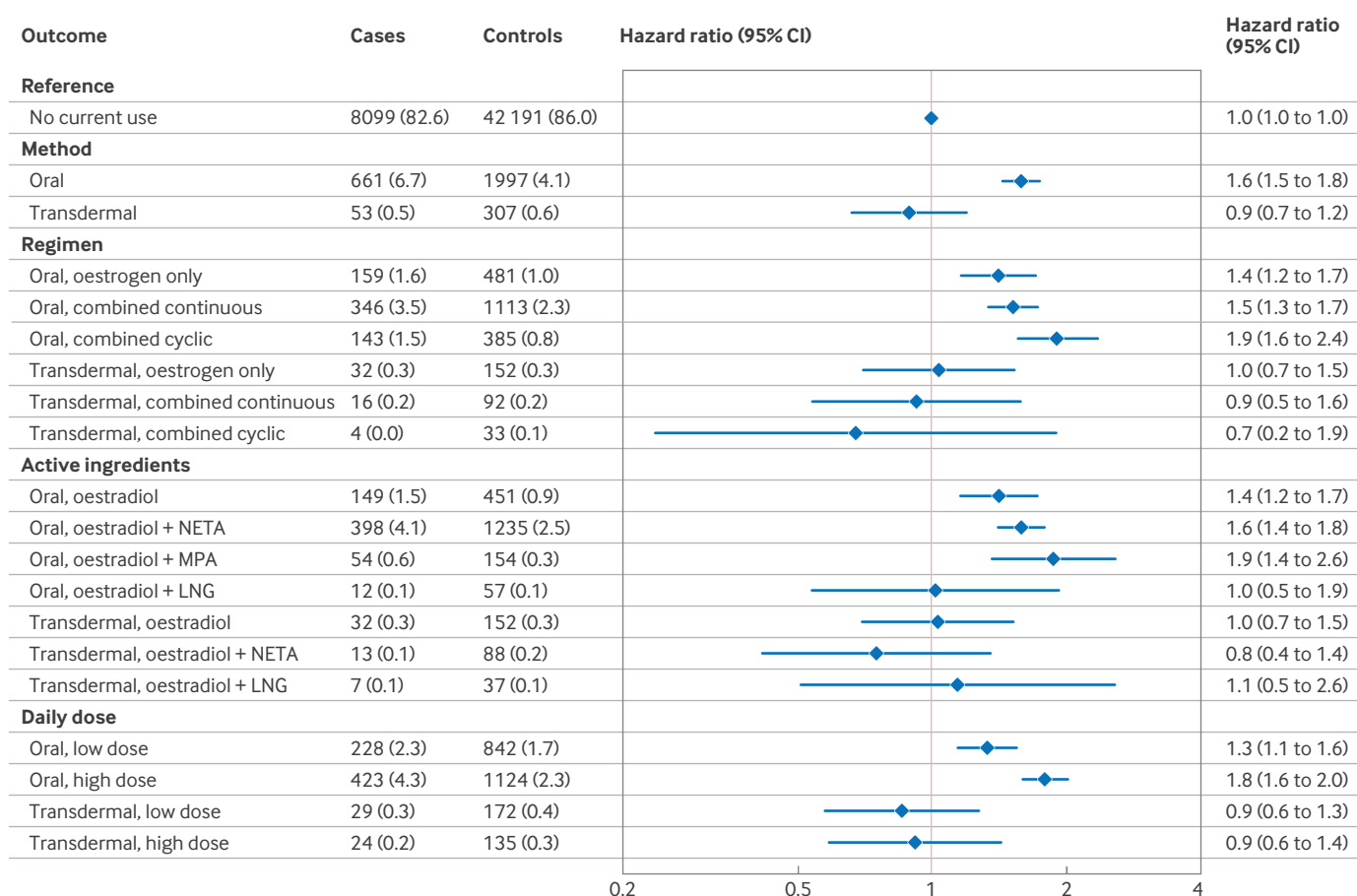


Figure 1 | Adjusted hazard ratio for venous thromboembolism with current use of systemic menopausal hormone therapy compared with no current use of any hormone therapy according to treatment characteristics. Data are number (%). Regression models were adjusted for yearly income, education, cohabitation, hypertension, atrial fibrillation, cardiomyopathy, heart failure, valvulopathy, diabetes, thyroid disease, kidney disease, chronic obstructive pulmonary disease, migraine, hysterectomy, use of statins, bisphosphonates, anticoagulants, aspirin, antidepressants, and antipsychotics. The reference group was women without current use of systemic or local oestrogen, progestogen, or testosterone. Current use of these products was categorised as separate use categories in the statistical models and was therefore controlled for by design. Current use was defined as use of systemic menopausal hormone therapy within 90 days before the index date. Low and high oral dosage was defined as ≤ 1 mg and > 1 mg oestradiol daily. Low and high transdermal dosage was defined as ≤ 50 μ g and > 50 μ g oestradiol daily. The sample size in the figure is smaller than reported in the text, as women with current use of hormonal contraception, progestogen only therapy, testosterone, or vaginal oestrogen are not shown in the figure (see table 2 for the corresponding numbers). Data from women with use of mixed/unknown combined regimens or mixed/other active ingredients are also not shown. CI=confidence interval; E2=oestradiol; NETA=norethisterone acetate; MPA=medroxyprogesterone acetate; LNG=levonorgestrel

oestradiol users most frequently received high dose therapy (60% of oral users used > 1 mg daily), whereas transdermal oestradiol users more often received low dose therapy (56% of transdermal users used ≤ 50 μ g daily). Treatment was usually initiated before 55 years of age (82% of new users), and the majority were treated for fewer than five years (68% of new users). The incidence rates of venous thromboembolism, ischaemic stroke, and myocardial infarction per 10 000 person years among unexposed women followed for a median of 9 years (IQR 4–14 years) were 15.8, 20.3, and 13.0, respectively.

Venous thromboembolism

Compared with no current use, current use of oral menopausal hormone therapy was associated with an

increased rate of venous thromboembolism (hazard ratio 1.6, 95% CI 1.5 to 1.8, fig 1), corresponding to an absolute risk increase per year of 0.09% (0.08 to 0.13%), which calculates to a number needed to harm for one year of 1055 (95% CI 791 to 1266, fig 5). The increased hazard ratio persisted across age strata (1.7, 95% CI 1.5 to 2.0 for 50–59 years, 1.5, 1.3 to 1.7 for 60–69 years). Figure 5 shows the excess number of venous thromboembolism events per 10 000 women per year and the number needed to harm, according to age strata.

Oral high dose oestradiol use (> 1 mg daily) was associated with a higher venous thromboembolic rate compared with oral low dose (≤ 1 mg daily) oestradiol use (high v low oral dose hazard ratio 1.3, 95% CI 1.1 to 1.6). Compared with no current hormone therapy

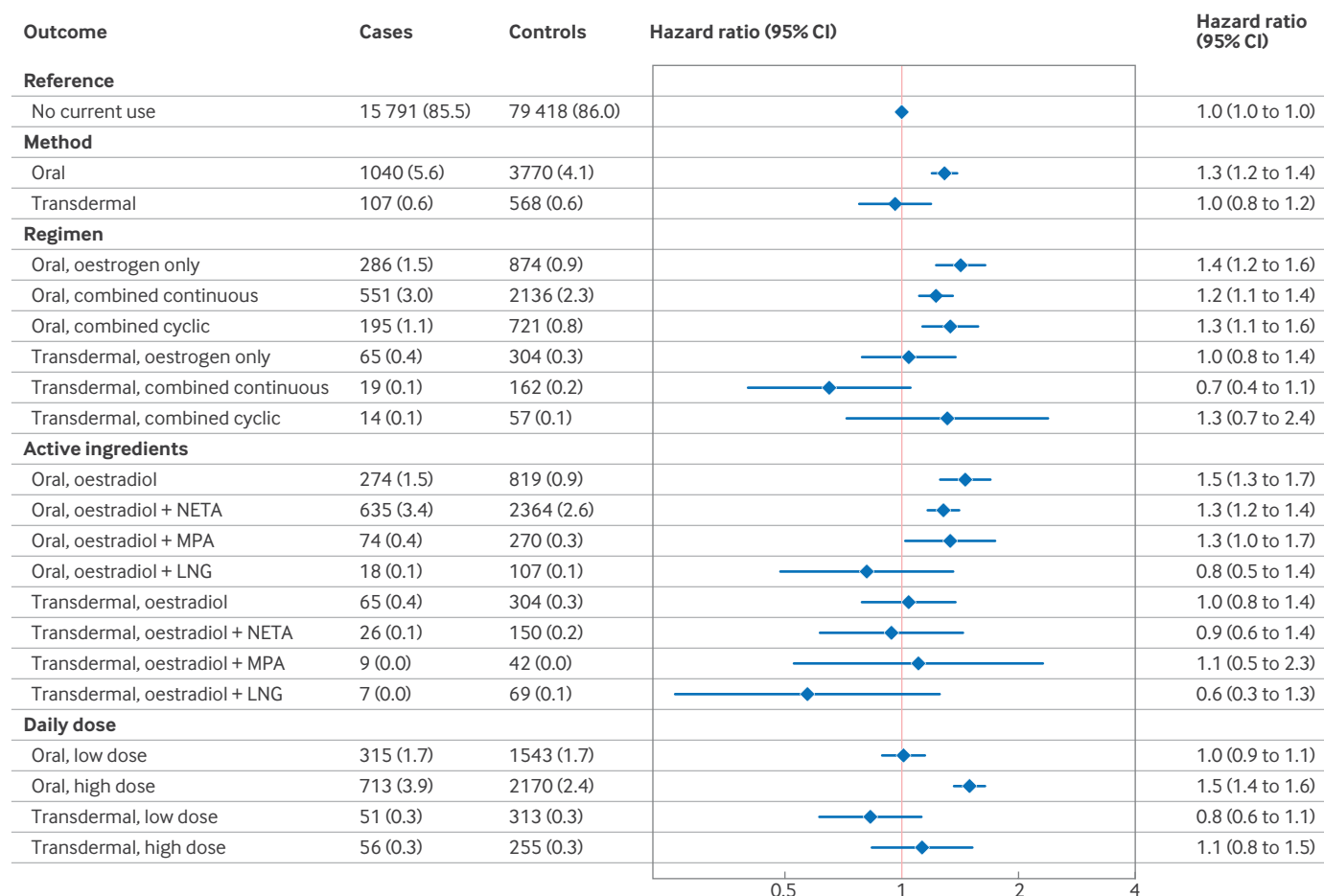


Figure 2 | Adjusted hazard ratio for ischaemic stroke with current use of systemic menopausal hormone therapy compared with no current use of any hormone therapy according to treatment characteristics. Data are number (%). Regression models were adjusted for yearly income, education, cohabitation, hypertension, atrial fibrillation, cardiomyopathy, heart failure, valvulopathy, diabetes, thyroid disease, kidney disease, chronic obstructive pulmonary disease, migraine, hysterectomy, use of statins, bisphosphonates, anticoagulants, aspirin, antidepressants, and antipsychotics. The reference group was women without current use of systemic or local oestrogen, progestogen, or testosterone. Current use of these products was categorised as separate use categories in the statistical models and was therefore controlled for by design. Current use was defined as use of systemic menopausal hormone therapy within 90 days before the index date. Low and high oral dosage was defined as ≤ 1 mg and >1 mg oestradiol daily. Low and high transdermal dosage was defined as ≤ 50 μ g and >50 μ g oestradiol daily. The sample size in the figure is smaller than reported in the text, as women with current use of hormonal contraception, progestogen only therapy, testosterone, or vaginal oestrogen are not shown in the figure (see table 2 for the corresponding numbers). Data from women with use of mixed/unknown combined regimens or mixed/other active ingredients are also not shown. CI=confidence interval; E2=oestradiol; NETA=norethisterone acetate; MPA=medroxyprogesterone acetate; LNG=levonorgestrel

use, venous thromboembolism rates were increased for all oral regimens (oestrogen only; combined continuous; combined cyclic) and across progestins, except for oral oestradiol with levonorgestrel, which was not associated with an increased rate, although CIs were wide (hazard ratio 1.0, 95% CI 0.5 to 1.9, fig 1). Transdermal therapy was not associated with increased venous thromboembolic rate compared with no current use of any hormone therapy (hazard ratio 0.9, 95% CI 0.7 to 1.2) regardless of regimen, progestin type, and daily oestradiol dose (fig 1). Our findings persisted when exclusively including confirmed venous thromboembolic diagnoses (supplementary appendix).

Ischaemic stroke

The rate of ischaemic stroke was higher with current use of oral menopausal hormone therapy compared with no current use (hazard ratio 1.3, 95% CI 1.2 to 1.4, fig 2), corresponding to an absolute risk increase per year of 0.06% (95% CI 0.04 to 0.08%), which calculates to a number needed to harm for one year of 1642 (95% CI 1232 to 2463, fig 5). The increased hazard ratio persisted across age strata (1.3, 95% CI 1.2 to 1.5 for 50-59 years, 1.3, 1.2 to 1.4 for 60-69 years). Figure 5 shows the excess number of ischaemic stroke events per 10 000 women per year and the number needed to harm, according to age strata.

Only oral high dose oestradiol use (>1 mg daily) was associated with a higher ischaemic stroke rate

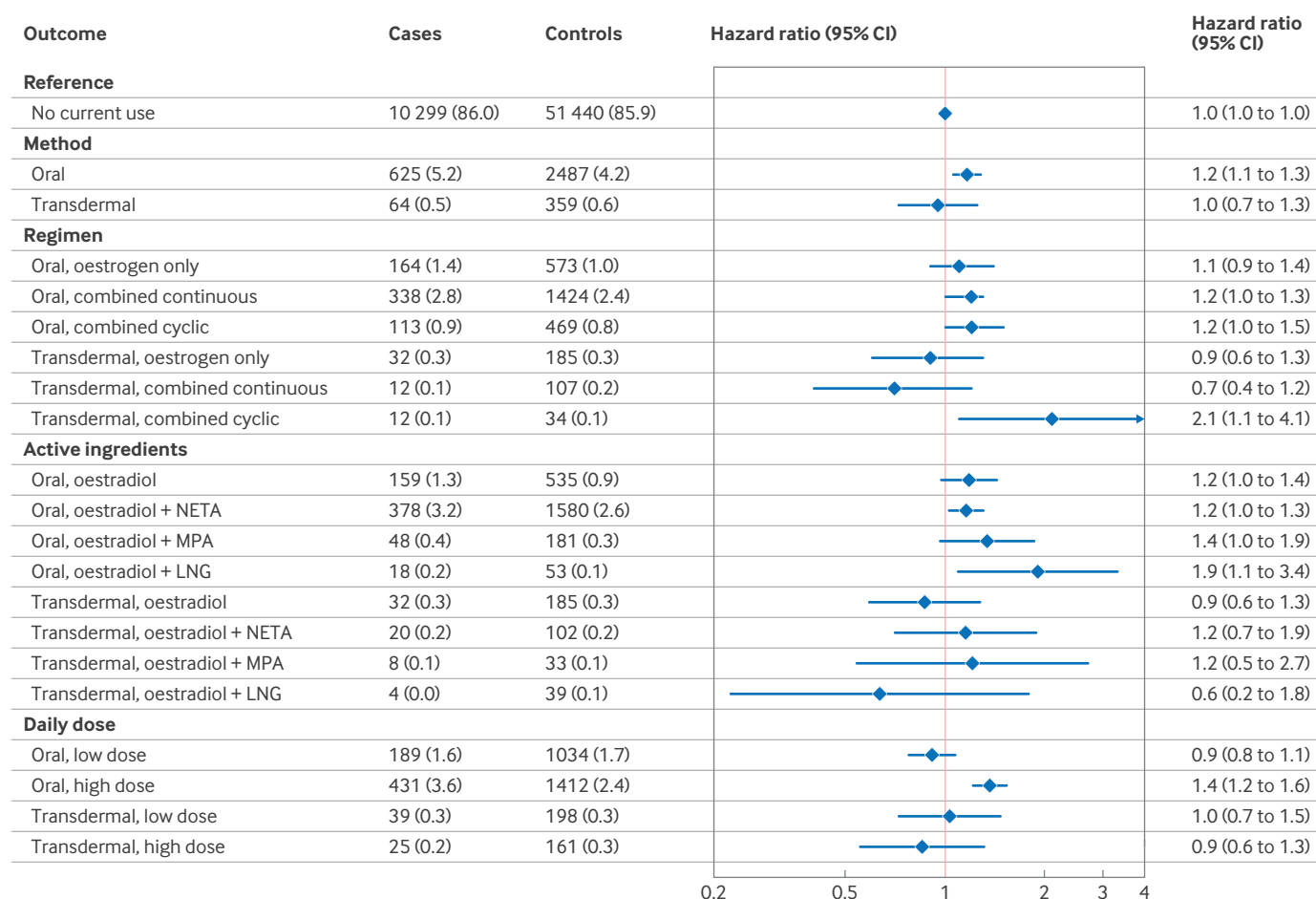


Figure 3 | Adjusted hazard ratio for myocardial infarction with current use of systemic menopausal hormone therapy compared with no current use of any hormone therapy according to treatment characteristics. Data are number (%). Regression models were adjusted for yearly income, education, cohabitation, hypertension, atrial fibrillation, cardiomyopathy, heart failure, valvulopathy, diabetes, thyroid disease, kidney disease, chronic obstructive pulmonary disease, migraine, hysterectomy, use of statins, bisphosphonates, anticoagulants, aspirin, antidepressants, and antipsychotics. The reference group was women without current use of systemic or local oestrogen, progestogen, or testosterone. Current use of these products was categorised as separate use categories in the statistical models and was therefore controlled for by design. Current use was defined as use of systemic menopausal hormone therapy within 90 days before the index date. Low and high oral dosage was defined as ≤ 1 mg and >1 mg oestradiol daily. Low and high transdermal dosage was defined as ≤ 50 μ g and >50 μ g oestradiol daily. The sample size in the figure is smaller than reported in the text, as women with current use of hormonal contraception, progestogen only therapy, testosterone, or vaginal oestrogen are not shown in the figure (see table 2 for the corresponding numbers). Data from women with use of mixed/unknown combined regimens or mixed/other active ingredients are also not shown. CI=confidence interval; E2=oestradiol; NETA=norethisterone acetate; MPA=medroxyprogesterone acetate; LNG=levonorgestrel

(hazard ratio 1.5, 95% CI 1.4 to 1.6) compared with no current use, whereas oral low dose oestradiol use was not (hazard ratio 1.0, 95% CI 0.9 to 1.1, fig 2). In a direct comparison between the two groups, we observed a significant increase in risk with oral high dose therapy compared with oral low dose therapy (hazard ratio 1.5, 95% CI 1.3 to 1.7, $P<0.001$).

Compared with no current use of any hormone therapy, ischaemic stroke rates were increased for all oral regimens (oestrogen only, combined continuous, combined cyclic) and across progestins, except for oral oestradiol with levonorgestrel, which was not associated with an increased rate, although CIs were wide (hazard ratio 0.8, 95% CI 0.5 to 1.4, fig 2). Transdermal hormone therapy use was not associated

with ischaemic stroke rate compared with no current use of any hormone therapy (hazard ratio 1.0, 95% CI 0.8 to 1.2) regardless of regimen, progestin type, and daily oestradiol dose (fig 2).

Myocardial infarction

Compared with no current use of any hormone therapy, current use of oral menopausal hormone therapy was associated with an increased rate of myocardial infarction (hazard ratio 1.2, 95% CI 1.1 to 1.3, fig 3), corresponding to an absolute risk increase per year of 0.03% (95% CI 0.01 to 0.04%), which calculates to a number needed to harm for one year of 3846 (95% CI 2564 to 7692, fig 5). The increased hazard ratio persisted across age strata (1.2, 95% CI 1.0 to 1.4, for

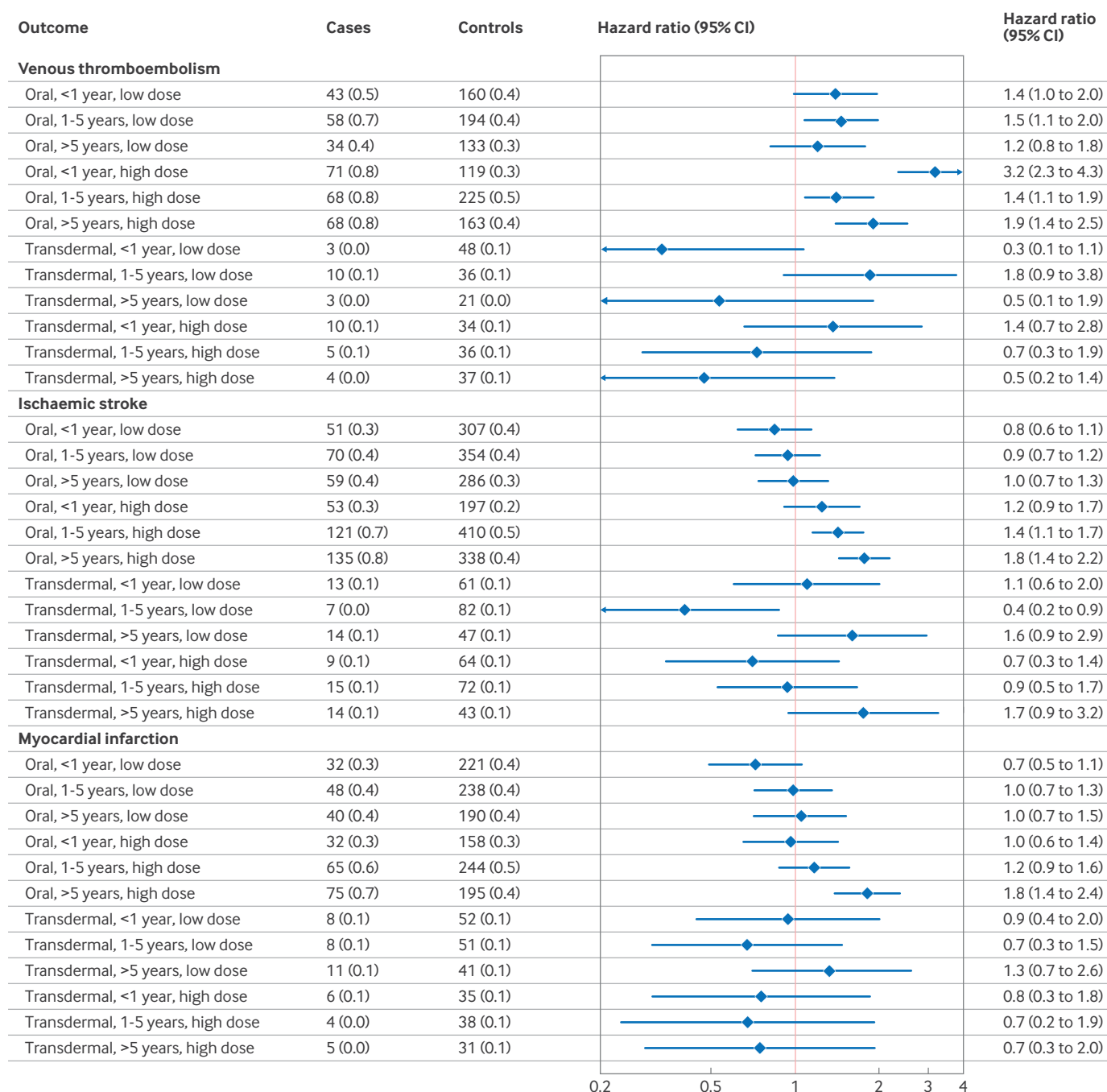


Figure 4 | Adjusted hazard ratio for venous thromboembolism, ischaemic stroke, and acute myocardial infarction with current use of systemic menopausal hormone therapy compared with no current use of any hormone therapy according to treatment duration and daily oestradiol dose. Data are number (%). Regression models were adjusted for yearly income, education, cohabitation, hypertension, atrial fibrillation, cardiomyopathy, heart failure, valvulopathy, diabetes, thyroid disease, kidney disease, chronic obstructive pulmonary disease, migraine, hysterectomy, use of statins, bisphosphonates, anticoagulants, aspirin, antidepressants, and antipsychotics. The reference group was women without current use of systemic or local oestrogen, progestogen, or testosterone. Current use of these products was categorised as separate use categories in the statistical models and was therefore controlled for by design. Current use was defined as use of systemic menopausal hormone therapy within 90 days before the index date. Low and high oral dosage was defined as ≤ 1 mg and >1 mg oestradiol daily. Low and high transdermal dosage was defined as ≤ 50 μ g and >50 μ g oestradiol daily. Users of other oestrogens than oestradiol were excluded from this analysis. New users were defined as women who initiated treatment after 1 January 1996, to ensure at least one year of drug use history and correct identification of treatment initiation. Data from women with use of mixed/unknown combined regimens or mixed/other active ingredients are not shown. CI=confidence interval; E2=oestradiol; NETA=norethisterone acetate; MPA=medroxyprogesterone acetate; LNG=levonorgestrel

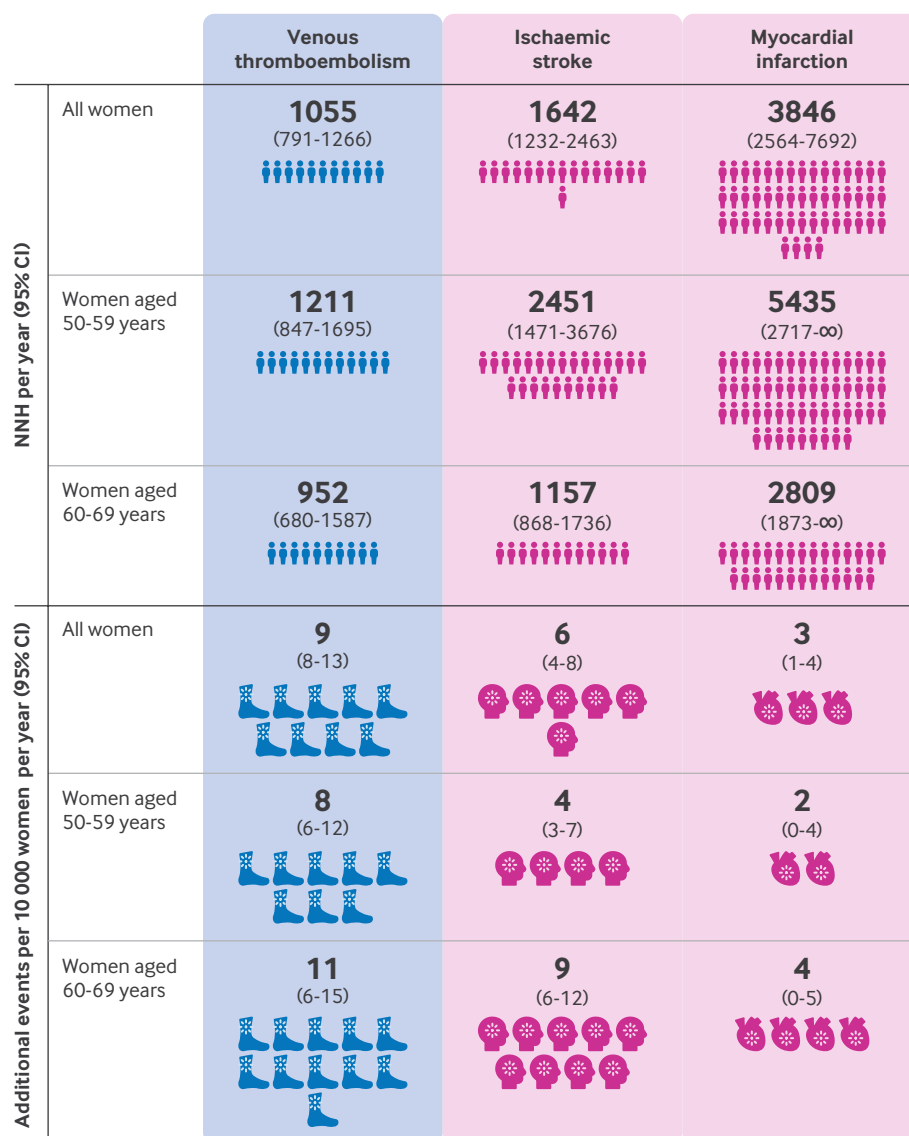


Figure 5 | Absolute risk differences and numbers needed to harm for one year with current use of oral menopausal hormone therapy compared to no current use of any hormone therapy for venous thromboembolism, ischaemic stroke, and myocardial infarction. Absolute risks were derived from age specific incidence rates of first time venous thromboembolism, ischaemic stroke, and myocardial infarction among unexposed Danish women (2003-21), combined with age-specific hazard ratios and 95% confidence intervals for oral menopausal hormone therapy from conditional regression models. The models were adjusted for yearly income, education, cohabitation, hypertension, atrial fibrillation, cardiomyopathy, heart failure, valvulopathy, diabetes, thyroid disease, kidney disease, chronic obstructive pulmonary disease, migraine, hysterectomy, use of statins, bisphosphonates, anticoagulants, aspirin, antidepressants, and antipsychotics. The reference group was women without current use of systemic or local oestrogen, progestogen, or testosterone. Each female symbol represents about 100 women. NNH=number needed to harm; CI=confidence interval

participants aged 50-59 years, 1.2, 1.0 to 1.3 for 60-69 years).

Only oral high dose oestradiol use (>1 mg daily) was associated with increased myocardial infarction rate (hazard ratio 1.4, 95% CI 1.2 to 1.6) compared with no current use, while oral low dose treatment was not (hazard ratio 0.9, 95% CI 0.8 to 1.1, fig 3). In a direct comparison between the two groups, we found a significant increase in risk with oral high dose treatment compared with oral low dose therapy (hazard ratio 1.5, 95% CI 1.2 to 1.8, $P<0.001$).

Increased hazard ratios for oral therapy were observed across regimens and progestin types; however, subgroup stratification resulted in small strata, and most comparisons were not statistically significant (fig 3).

Transdermal therapy was not associated with myocardial infarction risk compared with no current use (hazard ratio 1.0, 95% CI 0.7 to 1.3, fig 3) across progestin types and oestradiol dose. However, when stratified according to regimen, we found an increased myocardial infarction rate among current users of

combined transdermal cyclic therapy compared to no current use, although the estimate is based on sparse data (fig 3).

The results were consistent with the proportional hazards assumption, as we observed no evidence that the associations varied across follow-up periods (<2 years, 2-5 years, and >5 years) for venous thromboembolism, ischaemic stroke, or myocardial infarction (likelihood ratio test for interaction $P=0.39$, $P=0.37$, and $P=0.23$, respectively).

Treatment duration and age at treatment initiation

In the subcohort applying a new user design to allow identification of treatment duration and age at initiation of hormone therapy, risk estimates for venous thromboembolism were highest during the first year of oral high dose therapy (>1 mg oestradiol daily), when compared with no current use (hazard ratio 3.2, 95% CI 2.3 to 4.3, fig 4). We observed no association between transdermal therapy and venous thromboembolism risk across doses and durations.

Compared with no current use of any hormone therapy, risk estimates for ischaemic stroke and myocardial infarction among new users were only increased with current use of oral high dose therapy (>1 mg oestradiol daily) for more than one and five years, respectively, and highest when used for more than five years (hazard ratio for ischaemic stroke for >5 years 1.8, 95% CI 1.4 to 2.2, myocardial infarction 1.8, 95% CI 1.4 to 2.4, fig 4). Among current users of oral high dose therapy (>1 mg oestradiol daily), treatment duration >5 years (compared with <1 year as the reference) was associated with increased risk of myocardial infarction (hazard ratio 1.9, 95% CI 1.2 to 3.0) and ischaemic stroke (1.4, 1.0 to 2.1), but a reduced risk of venous thromboembolism (0.6, 0.4 to 0.9). Oral low dose and any transdermal therapy was not associated with increased ischaemic stroke or myocardial infarction risk regardless of treatment duration.

When restricting to participants who initiated hormone therapy after 2002—to account for potential changes in prescription patterns following the safety concerns raised by the Women's Health Initiative trial in 2002—risk estimates of thrombosis according to treatment duration and oestradiol dose remained materially unchanged (supplementary appendix).

The elevated venous thromboembolism risk with oral therapy compared with no current use of any hormone therapy persisted and was similar across all ages of treatment initiation (supplementary appendix). Compared with no current use of any hormone therapy, current use of oral therapy was associated with the greatest risk estimates for ischaemic stroke and myocardial infarction when treatment began before 50 years of age (hazard ratio for ischaemic stroke 1.5, 95% CI 1.3 to 1.8, myocardial infarction 1.5, 1.2 to 1.8). These findings remained unchanged after further stratification by daily oestradiol dose and treatment duration.

Estimates for women initiating hormone therapy after 59 years of age were based on small numbers and should be interpreted with caution owing to imprecision.

Additional sensitivity analyses

Compared with no current use, past use of oral or transdermal menopausal hormone therapy between five years and 90 days before the index date was not associated with increased risk of venous thromboembolism (hazard ratio for oral therapy 0.9, 95% CI 0.8 to 1.0, $P=0.01$), ischaemic stroke (oral therapy 1.0, 0.9 to 1.1, $P=0.89$), or myocardial infarction (oral therapy 1.0, 0.9 to 1.1, $P=0.88$) (supplementary appendix).

Findings regarding method of use, regimen, active ingredients, dose, duration, and age at initiation of current use did not materially change when restricting the analyses to women aged 50-59 years (supplementary appendix). Results were similar when restricting current use to use within 60 days before the index date, when restricting to a population of healthy women only, and when analysing the study period 1997-2002 before the Women's Health Initiative publication (supplementary appendix).

Discussion

Principal findings

In this Danish nationwide study, current use of oral menopausal hormone therapy containing oestradiol was associated with an increased risk of venous thromboembolism across regimens, daily doses, durations, and treatment initiation ages. Ischaemic stroke and myocardial infarction risk was only increased with oral high dose therapy for more than one year. Transdermal therapy was not associated with venous thromboembolism, ischaemic stroke, or myocardial infarction. Because use of conjugated equine oestrogens was negligible in our cohorts, these findings specifically apply to oestradiol formulations.

Strengths and limitations

This nationwide study on menopausal hormone therapy and thrombosis investigates the effect of multiple characteristics including method of use, regimen, active ingredients, dosage, treatment duration, and participant age at initiation. Key strengths included the large, population based design, detailed menopausal hormone therapy prescription data reflecting real world use, validated outcome definitions, nearly two decades of follow-up, and statistical adjustment for multiple important confounders.

Given the observational nature of the study, residual and unmeasured confounding may, however, remain. Information on body mass index and smoking status were unavailable, which may have caused an underestimation of the associations between menopausal hormone therapy use and thrombosis risk, since clinicians may be more reluctant to prescribe menopausal hormone therapy to women with increased cardiovascular risk factors. However, we

believe that this potential bias is small; we considered socioeconomic and educational status in the study, which is highly correlated with body mass index and smoking status in Denmark.²⁰

Although residual confounding by lifestyle factors cannot be fully excluded, several aspects of our findings contradict this as the main explanation. After the Women's Health Initiative, prescribing menopausal hormone therapy has become more restrictive and individualised. If selection bias were driving the results, the effect would most plausibly reflect healthier women being more likely to use hormone therapy overall, whereas transdermal therapy is often preferentially prescribed to women with higher baseline cardiovascular risk profiles. Despite this, we observed an increased risk among users of oral hormone therapy and no increased risk with transdermal therapy. Moreover, unmeasured confounding by factors such as body mass index and smoking is unlikely to fully explain the findings, as these are generally stable characteristics that would be expected to influence both current and past users; however, we observed no increased risk among past users. To further consider potential temporal changes in prescribing and selection, we conducted analyses restricted to the period before the publication of the Women's Health Initiative trial and subsequently observed similar results. Finally, our findings of increased thrombotic risk with current oral therapy are consistent with randomised controlled trial evidence, wherein confounding by lifestyle factors is minimised, supporting a pharmacological explanation rather than one purely based on selection.

A limitation of this study is the lack of information on age at onset of menopause. Although the new user study design ensured accurate identification of menopausal hormone therapy initiation and duration, we could not account for differences in menopausal timing or underlying endogenous hormonal exposure between users and non-users. This information gap is particularly relevant for the higher observed risk among women starting menopausal hormone therapy before the age of 50 and those with long term, high dose use, which may partly reflect confounding by indication and differences in baseline risk related to menopausal history.

Finally, external generalisability of our findings may be limited: the study was conducted in a predominantly ethnically homogeneous Danish population. Differences in genetic background, baseline risk of thrombosis, and clinicians' prescribing patterns may influence the observed associations. In addition, our analyses focused on specific formulations of oestradiol and synthetic progestins, reflecting the regimens most commonly used in Denmark during the study period, and therefore did not capture the effects of other treatments, including bioidentical progesterone, use of which is increasing in Denmark. Notably, oestradiol is generally considered to have a more favourable risk profile compared with conjugated equine oestrogens and ethinyl oestradiol.²¹ Nonetheless, the underlying

biological mechanisms linking exogenous sex hormones to thrombotic risk are unlikely to differ substantially across populations, and the nationwide design with complete follow-up supports high internal validity.

Comparison with other studies

The increased venous thromboembolism risk with current oral, but not transdermal, therapy is consistent with randomised trial evidence. A National Institute for Health and Care Excellence (NICE) synthesis of seven randomised trials ($n=34\,379$) reported a risk ratio of 1.8 (95% CI 1.5 to 2.1) for oral menopausal hormone therapy compared with placebo, comparable to our estimate of 1.6 (1.5 to 1.8).²² However, these comparisons should be interpreted with caution, as most randomised trials were based on conjugated equine oestrogens rather than oestradiol formulations. The similarity in effect estimates may reflect that a substantial proportion of women in our study used high dose oral oestradiol, which may also explain why our estimate is somewhat higher than in other observational studies with lower use of high dose therapy.¹⁷ Our study focused on contemporary oestradiol and extends the evidence by demonstrating a dose-response relationship, with higher risk at increasing daily doses. In line with trial findings, the relative risk was highest during the first year of high dose treatment and did not vary substantially by age at initiation.

Oral menopausal hormone therapy has been associated with an increased risk of stroke in early and later analyses of the Women's Health Initiative trial,^{6 23-27} consistent with our findings. Other trials have reported no association,²⁸⁻³³ however, high dose oestrogen therapy was not evaluated. Most trials evaluated conjugated equine oestrogens as the oestrogen component,^{6 30-33} and did not compare routes, active ingredients, or dosages. Observational studies similarly reported an association with oral therapy,³⁴⁻³⁸ but not transdermal,³⁶⁻³⁸ aligning with our results. In contrast with these studies, a recent emulated trial found no association between menopausal hormone therapy and stroke regardless of route and regimen,³⁹ but did not differ between dosages or treatment duration. Importantly, we observed that oral low dose therapy was not associated with stroke, regardless of duration of use.

For myocardial infarctions, the Women's Health Initiative trial initially reported an increased risk with menopausal hormone therapy,⁶ but retrospective analysis attenuated the association,⁴⁰ aligning with other randomised trials.^{31 41-43} However, follow-up was often less than five years in length,^{31 42 43} and the oestrogen component was conjugated equine oestrogen in most trials.^{31 40 42 43} One observational study reported an association with oral menopausal hormone therapy and myocardial infarctions,⁴⁴ whereas others did not.^{45 46} No study assessed the influence of active ingredients, dosage, treatment duration, and age at initiation. Thus, no studies are

directly comparable to our finding of an increased risk of myocardial infarction with oral high dose therapy for more than five years of therapy use.

Exogenous oestrogen is known to cause hypercoagulability by increasing multiple coagulation factors involved in the development of venous thromboembolism.⁴⁷ The effects on the arterial system are less well understood, although post trial analyses have indicated that oral combined oestrogen-progestin therapy may promote atherogenesis,⁴⁸ which could potentially explain the increased arterial thrombotic risk observed with oral high dose and long term treatment observed in this study. Transdermal use bypasses the hepatic first pass metabolism which is thought to increase the hepatic synthesis of prothrombotic factors,⁴⁹ providing a plausible explanation for the different risk profiles between oral and transdermal formulations.

The findings from this study, together with earlier evidence, indicate that the thrombotic risk associated with contemporary systemic menopausal hormone therapy is influenced by the method of use, the daily oestrogen dose, and treatment duration. These insights may inform clinical practice, guiding clinicians and patients in making evidence based decisions to minimise thrombotic risk of hormone therapy. Future research should further explore the long term cardiovascular risks associated with different treatment regimens and the influence of individual cardiovascular risk profiles including age at menopause onset.

Conclusion

Current use of any oral menopausal hormone therapy was associated with an increased venous thromboembolism risk, whereas ischaemic stroke and myocardial infarction risk was only increased with oral high dose therapy used for more than one year. Transdermal therapy was not associated with increased thrombotic rates regardless of regimen, active ingredients, dosage, and duration of use.

Contributors: This study was initiated by AM and CTP and designed by JB and AM with contributions from CTP. Data management was carried out by JB, HW, and AM. Data analyses were conducted by JB, AM, and NP. Interpretation of results and writing of the manuscript were led by JB, AM, and EL. The final version was approved by all authors, and all agreed to submit for publication. JB, HW, NP, AM, and CTP had full access to all the data in the study, and JB and AM take responsibility for the integrity of the data and the accuracy of the data analysis. JB is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Ethical approval: Danish legislation specifies that studies conducted solely for statistical and scientific purposes of significant societal

importance are exempt from obtaining ethical approval and patient informed consent if the processing of data is necessary for the conduct of the studies. This study was approved by the Danish Health Data Board (approval ID FSEID-00005931) and the Danish Data Protection Agency (approval ID P-2019-280).

Data sharing: The raw data used for this study are available only with approval from the Danish Health Data Board and the Danish Data Protection Agency. Because individual, personal data were accessible, data sharing is restricted by the General Data Protection Regulation of European Union law. JB, NP, HW, CTP, and AM had access to the data used to create the study population.

Transparency: The lead author (AM) 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: Individual study participants will not be contacted, because this is a national register based study. Findings will be disseminated to the public and healthcare professionals through press releases, conference presentations, and social media.

Provenance and peer review: Not commissioned; externally peer reviewed.

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- <https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death>. 2024.
- El Khoudary SR, Aggarwal B, Beckie TM, et al. Menopause Transition and Cardiovascular Disease Risk: Implications for Timing of Early Prevention: A Scientific Statement From the American Heart Association. *Circulation* 2020;142:e506-32. doi:10.1161/CIR.0000000000000912
- Iorga A, Cunningham CM, Moazeni S, et al. The protective role of estrogen and estrogen receptors in cardiovascular disease and the controversial use of estrogen therapy. *Biol Sex Differ* 2017;8:33. doi:10.1186/s13293-017-0152-8
- Grodstein F, Stampfer MJ, Manson JE, et al. Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. *N Engl J Med* 1996;335:453-61. doi:10.1056/NEJM199608153350701
- Grodstein F, Manson JE, Colditz GA, et al. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. *Ann Intern Med* 2000;133:933-41. doi:10.7326/0003-4819-133-12-200012190-00008
- Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the women's health initiative randomized controlled trial. *J Am Med Assoc* 2002; 288: 321-33. doi:10.1001/jama.288.3.321
- Manson JE, Hsia J, Johnson KC, et al. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med* 2003;349:523-34. doi:10.1056/NEJMoa030808
- Hernán MA, Alonso A, Logan R, et al. Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease. *Epidemiology* 2008;19:766-79. doi:10.1097/EDE.0b013e31818175e61
- Løkkegaard LE, Thinggaard M, Nygaard M, et al. Systemic hormone therapy and dementia: A nested case-control and co-twin control study. *Maturitas* 2022;165:113-9. doi:10.1016/j.maturitas.2022.04.007
- Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011;39:22-5. doi:10.1177/1403494810387965
- Schmidt M, Schmidt SAJ, Sandegaard JL, et al. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;7:449-90. doi:10.2147/CLEP.S91125
- Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health* 2011;39:38-41. doi:10.1177/1403494810394717
- Helweg-Larsen K. The Danish Register of Causes of Death. *Scand J Public Health* 2011;39:26-9. doi:10.1177/1403494811399958
- Sundbøll J, Adelborg K, Munch T, et al. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ Open* 2016;6:e012832. doi:10.1136/bmjopen-2016-012832

- 15 Krarup LH, Boysen G, Janjua H, et al. Validity of stroke diagnoses in a National Register of Patients. *Neuroepidemiology* 2007;28:150-4. doi:10.1159/000102143
- 16 Lidegaard Ø, Nielsen LH, Skovlund CW, et al. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9. *BMJ* 2011;343:d6423. doi:10.1136/bmj.d6423
- 17 Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of venous thromboembolism: Nested case-control studies using the QResearch and CPRD databases. *BMJ (Online)* 2019; 364: k4810. doi:10.1136/bmj.k4810
- 18 Meaidi M, Støvring H, Rostgaard K, et al. Pharmacoepidemiological methods for computing the duration of pharmacological prescriptions using secondary data sources. *Eur J Clin Pharmacol* 2021;77:1805-14. doi:10.1007/s00228-021-03188-9
- 19 Ryung S K. Lesser Known Facts about Nested Case-Control Designs. *J Transl Med Epidemiol* 2013; 1: 1007.
- 20 Osler M, Holstein B, Avlund K, et al. Socioeconomic position and smoking behaviour in Danish adults. *Scand J Public Health* 2001;29:32-9.
- 21 Weller SC, Davis JW, Porterfield L, et al. Hormone exposure and venous thromboembolism in commercially insured women aged 50 to 64 years. *Res Pract Thromb Haemost* 2023;7:100135. doi:10.1016/j.rpth.2023.100135
- 22 <https://www.nice.org.uk/guidance/ng23>. 2015. (Appendix J.7.1)
- 23 Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007;297:1465-77. doi:10.1001/jama.297.13.1465
- 24 Anderson GL, Limacher M. Effects of Conjugated Equine Estrogen in Postmenopausal Women with Hysterectomy: The Women's Health Initiative Randomized Controlled Trial. *J Am Med Assoc* 2004; 291: 1701-12. doi:10.1001/jama.291.14.1701
- 25 Hendrix SL, Wassertheil-Smoller S, Johnson KC, et al. Effects of conjugated equine estrogen on stroke in the Women's Health Initiative. *Circulation* 2006;113:2425-34. doi:10.1161/CIRCULATIONAHA.105.594077
- 26 Prentice RL, Aragaki AK, Chlebowski RT, et al. Dual-Outcome Intention-to-Treat Analyses in the Women's Health Initiative Randomized Controlled Hormone Therapy Trials. *Am J Epidemiol* 2020;189:972-81. doi:10.1093/aje/kwaa033
- 27 Wassertheil-Smoller S, Hendrix SL, Limacher M, et al. Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. *JAMA* 2003;289:2673-84. doi:10.1001/jama.289.20.2673
- 28 Cherry N, McNamee R, Heagerty A, et al. Long-term safety of unopposed estrogen used by women surviving myocardial infarction: 14-year follow-up of the ESPRIT randomised controlled trial. *BJOG* 2014;121:700-5. doi:10.1111/1471-0528.12598
- 29 Viscoli CM, Brass LM, Kernan WN, et al. A clinical trial of estrogen-replacement therapy after ischemic stroke. *N Engl J Med* 2001;345:1243-9. doi:10.1056/NEJMoa010534
- 30 Simon JA, Hsia J, Cauley JA, et al. Postmenopausal hormone therapy and risk of stroke: The Heart and Estrogen/progestin Replacement Study (HERS). *Circulation* 2001;103:638-42. doi:10.1161/01.cir.103.5.638
- 31 Veerus P, Hovi SL, Fischer K, et al. Results from the Estonian postmenopausal hormone therapy trial [ISRCTN35338757]. *Maturitas* 2006;55:162-73. doi:10.1016/j.maturitas.2006.01.012
- 32 Grady D, Herrington D, Bittner V, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and estrogen/progestin replacement study follow-up (HERS II). *J Am Med Assoc* 2002; 288: 49-57. doi:10.1001/jama.288.1.49
- 33 LaCroix AZ, Chlebowski RT, Manson JE, et al. Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: a randomized controlled trial. *JAMA* 2011;305:1305-14. doi:10.1001/jama.2011.382
- 34 Arana A, Varas C, González-Pérez A, et al. Hormone therapy and cerebrovascular events: a population-based nested case-control study. *Menopause* 2006;13:730-6. doi:10.1097/O1.gme.0000233494.28335.71
- 35 Grodstein F, Manson JE, Stampfer MJ, et al. Postmenopausal hormone therapy and stroke: role of time since menopause and age at initiation of hormone therapy. *Arch Intern Med* 2008;168:861-6. doi:10.1001/archinte.168.8.861
- 36 Løkkegaard E, Nielsen LH, Keiding N. Risk of Stroke With Various Types of Menopausal Hormone Therapies: A National Cohort Study. *Stroke* 2017;48:2266-9. doi:10.1161/STROKEAHA.117.017132
- 37 Renoux C, Dell'Aniello S, Garbe E, et al. Transdermal and oral hormone replacement therapy and the risk of stroke: A nested case-control study. *BMJ (Online)* 2010; 341: c2519. doi:10.1136/bmj.c2519
- 38 Canonico M, Carcaillon L, Plu-Bureau G, et al. Postmenopausal Hormone Therapy and Risk of Stroke: Impact of the Route of Estrogen Administration and Type of Progestogen. *Stroke* 2016;47:1734-41. doi:10.1161/STROKEAHA.116.013052
- 39 Johansson T, Karlsson T, Bliuc D, et al. Contemporary menopausal hormone therapy and risk of cardiovascular disease: Swedish nationwide register based emulated target trial. *BMJ* 2024; : e078784. doi:10.1136/bmj-2023-078784
- 40 Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA* 2013;310:1353-68. doi:10.1001/jama.2013.278040
- 41 Cherry N. Oestrogen therapy for prevention of reinfarction in postmenopausal women: A randomised placebo controlled trial. *Lancet* 2002; 360: 2001-8. doi:10.1016/s0140-6736(02)12001-0
- 42 Hall G, Pripp U, Schenck-Gustafsson K, et al. Long-term effects of hormone replacement therapy on symptoms of angina pectoris, quality of life and compliance in women with coronary artery disease. *Maturitas* 1998;28:235-42. doi:10.1016/s0378-5122(97)00080-7
- 43 Hulley S. Randomized Trial of Estrogen Plus Progestin for Secondary Prevention of Coronary Heart Disease in Postmenopausal Women. *JAMA* 1998;280:605. doi:10.1001/jama.280.7.605
- 44 Løkkegaard E, Andreasen AH, Jacobsen RK, et al. Hormone therapy and risk of myocardial infarction: a national register study. *Eur Heart J* 2008;29:2660-8. doi:10.1093/eurheartj/ehn408
- 45 Kim J, Evans S, Smeeth L, et al. Hormone replacement therapy and acute myocardial infarction: a large observational study exploring the influence of age. *Int J Epidemiol* 2006;35:731-8. doi:10.1093/ije/dyi285
- 46 Lemaitre RN, Weiss NS, Smith NL, et al. Esterified estrogen and conjugated equine estrogen and the risk of incident myocardial infarction and stroke. *Arch Intern Med* 2006;166:399-404. doi:10.1001/archinte.166.4.399
- 47 Scarabin PY, Hemker HC, Clément C, et al. Increased thrombin generation among postmenopausal women using hormone therapy: importance of the route of estrogen administration and progestogens. *Menopause* 2011;18:873-9. doi:10.1097/gme.0b013e31820eee88
- 48 Sriprasert I, Hodis HN, Karim R, et al. Differential Effect of Plasma Estradiol on Subclinical Atherosclerosis Progression in Early vs Late Postmenopause. *Journal of Clinical Endocrinology and Metabolism* . 2018;104:293-300. doi:10.1210/je.2018-01600
- 49 Goodman MP. Are All Estrogens Created Equal? A Review of Oral vs. Transdermal Therapy. *Journal of Women's Health* 2012;21:161-9. doi:10.1089/jwh.2011.2839

Web appendix: Supplementary appendix