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Menopausal hormone therapy and long term mortality: nationwide, register based cohort study

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ABSTRACT

OBJECTIVE
To assess whether menopausal hormone therapy increases the risk of all cause mortality.

DESIGN
Nationwide, registry based cohort study.

SETTING
Denmark.

PARTICIPANTS
Danish women born between 1950 and 1977 and alive at 45 years. Follow-up began on each woman's 45th birthday and ended on 31 July 2023. Of 969 424 eligible women, 92 619 were excluded because of thrombophilia, liver disease, arterial thrombosis or venous thrombosis, breast cancer, endometrial cancer, ovarian cancer, previous use of menopausal hormone therapy, or previous bilateral oophorectomy. Systemic menopausal hormone therapy was the intervention of interest.

MAIN OUTCOME MEASURES
Death as registered in the Central Persons Register. Secondary outcomes were cause specific mortality registered in the cause of death register (cardiovascular, cancer, or other mortality). Hazard ratios were estimated using Cox regression, adjusted for age, calendar year, parity, educational degree, income group quarter (based on quartiles), country of birth, diabetes, hypercholesterolemia, hypertension, atrial fibrillation, valvular disease, heart failure, and three or more hospital contacts between 44 and 45 years of age.

RESULTS
Of 876 805 women, 104 086 (11.9%) redeemed a prescription for menopausal hormone therapy, and 47 594 (5.4%) died, with a median follow-up time of 14.3 years (interquartile range (IQR) 7.9-21.0 years). Women who used menopausal hormone therapy had an incidence rate of 54.9 deaths per 10 000 person years compared to 35.5 per 10 000 person years in the unexposed group, corresponding to an adjusted hazard ratio of 0.96 (95% confidence interval (CI) 0.93 to 0.98). Stratifying this by cumulative duration of menopausal hormone therapy use gave an adjusted hazard ratio after <1 years of menopausal hormone therapy of 1.01 (95% CI 0.98 to 1.05), after 1-2.9 years of use 0.94 (0.89 to 0.98), 3-4.9 years of use 0.90 (0.84 to 0.95), 5-9.9 years of use 0.89 (0.84 to 0.95), and over ≥10 years of use 0.98 (0.90 to 1.07). No unequivocal differences in cause-specific mortality were found between groups. Among the 703 women who underwent bilateral oophorectomy between 45-54 years, those who used menopausal hormone therapy experienced a 27-34% lower mortality hazard as compared to women who did not (median age at death for those who had taken menopausal hormone therapy 60.9 years (IQR 55.3-66.6 years) *v* 56.6 years (52.9-62.0 years) for those who had not).

CONCLUSIONS
This nationwide cohort study did not find menopausal hormone therapy was associated with increased mortality.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Starting menopausal hormone therapy a decade or more after menopause may be linked to breast cancer and cardiovascular disease

Use of menopausal hormone therapy has fallen considerably in past decades

Real world evidence regarding the effect of menopausal hormone therapy on mortality is lacking

WHAT THIS STUDY ADDS

In this large nationwide cohort study, menopausal hormone therapy was not associated with increased mortality

Among women who underwent bilateral oophorectomy between age 45-54 years, menopausal hormone therapy was associated with a 27-34% decrease in mortality

No unequivocal differences in cardiovascular specific or cancer specific mortality were found between groups

Introduction

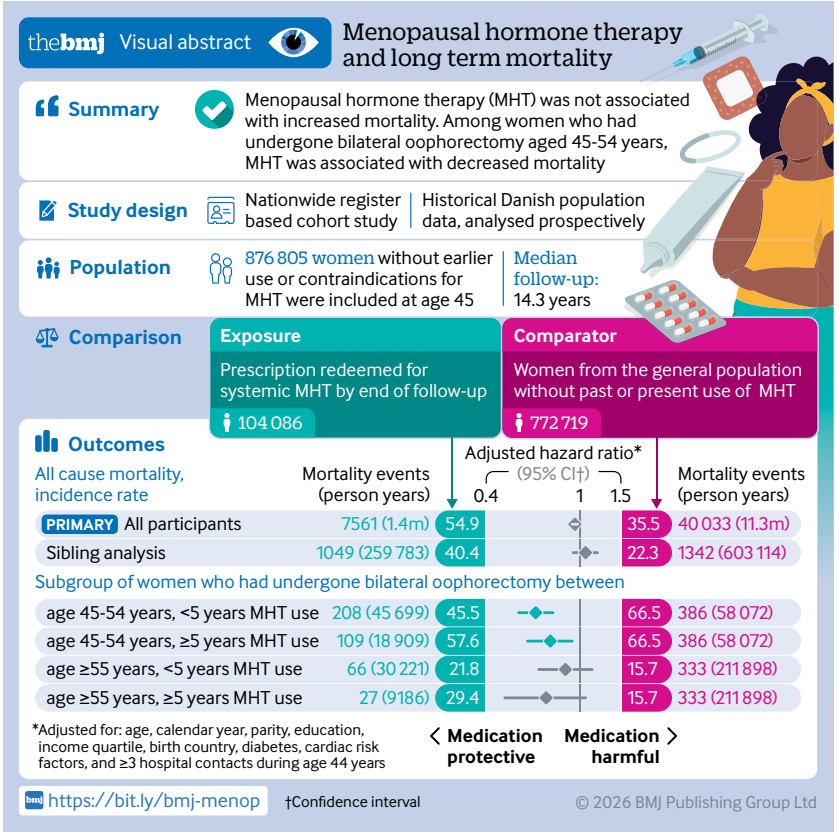
Most women enter menopause between 45 and 55 years.[1] This transition marks the end of the reproductive stage and is accompanied by a large drop in oestrogen levels in the blood.[2] Around 80% of women experience symptoms during menopause for a median time of more than seven years, most commonly hot flushes and night sweats, while many also report depressed mood, sleep disturbances, decreased concentration, vaginal dryness, or decreased libido.[3 4] In many countries, around half of women seek help from a healthcare provider and one third of women report severe or debilitating menopausal symptoms.[5-7] Unemployment due to menopausal symptoms is estimated to have an economic impact of £1.5bn (€1.7bn; $2.1bn) annually in the UK alone.[8] For many years, menopausal symptoms have been known to be effectively ameliorated by menopausal hormone therapy containing oestrogen.[9-12] Despite this, use of menopausal hormone therapy globally has steadily declined during the last two decades, mainly due to safety concerns.[13-15]

In 2002, the Women's Health Initiative conducted a large randomised controlled trial, including more than 16 000 postmenopausal women who had not undergone hysterectomy. The trial was stopped prematurely because the safety monitoring board

identified a higher risk of breast cancer, heart attack, stroke, and blood clots among users of menopausal hormone therapy compared with placebo.[16] Subsequently, the use of menopausal hormone therapy in the US dropped by 80%.[17] Notably, the majority of women in the study were not perimenopausal, but had an average age of 63 years at enrolment, raising questions of the applicability of the results for younger perimenopausal women.

In general, previous studies have either found a reduction or no change in mortality following use of menopausal hormone therapy.[18-24] However, these studies have had methodological limitations including starting treatment many years after onset of menopause, post hoc subgroup analysis, self-reported drug use, unknown duration of drug use, and unknown follow-up time. Further, most studies have been underpowered to examine differences among types of menopausal hormone therapy and have not examined women who have undergone bilateral oophorectomy separately.

Using nationwide Danish registers, our study aimed to examine the risk of mortality following menopausal hormone therapy use in women aged 45 or older. We chose our primary endpoint of mortality because it represents the most severe outcome, captures the additive effects on different organ systems, and remains unbiased from competing risks. Secondary outcomes included mortality specific to cardiovascular problems and cancer.



Methods

Study design

This register based cohort study used data from the nationwide Danish registries which could be linked using the unique and permanent identification number assigned to all Danish citizens. Data are not openly available, however, authorised research groups can apply for access to data for research purposes.

Cohort

All Danish women born between 1950 and 1977, alive and living in Denmark at their 45th birthday, were eligible for inclusion. Immigrant people were only included if immigration occurred before they reached 25 years to ensure sufficient register based information about pregnancies and comorbidity. Women were excluded if they were diagnosed with any contraindication for menopausal hormone therapy before follow-up began, including thrombophilia, liver disease, arterial thrombosis (including stroke or myocardial infarction), venous thrombosis, breast cancer, endometrial cancer, or ovarian cancer. Furthermore, women who started using menopausal hormone therapy before age 45 years or underwent bilateral oophorectomy before 45 years were excluded to ensure women were new users and not taking the medication for premature ovarian insufficiency or early menopause. For all definitions used to extract specific diagnoses and surgical procedures, see supplemental material, supplementary table 1.

Intervention

The intervention of interest was menopausal hormone therapy identified in the Danish National Prescription Register,[25] which contains data on all prescriptions redeemed at Danish pharmacies since 1994. Menopausal hormone therapy included combined products containing oestrogen and progestogen (available in oral and transdermal formulations) and oestrogen monotherapy (available in the following formulations: oral, transdermal, nasal spray, rectal, or subcutaneous injection). Oestrogen therapy with simultaneous separate progestogen therapy was considered combined treatment and grouped as either cyclic or continuous depending on progestogen. Low dose vaginal oestrogens were not considered in the current study as the systemic uptake has been found to be clinically negligible.[26]

We ascertained the length of use of menopausal hormone therapy: for all products this was assumed to follow the defined daily dose for the medication. The cumulative number of years of menopausal hormone therapy use was determined time dependently (ie, women could move groups during follow-up) and were categorised: 0 years (no use), <1 year, 1-2.9 years, 3-4.9 years, 5-9.9 years, or ≥10 years. Women were considered to be unexposed until they redeemed a prescription for menopausal hormone therapy. As the effects of menopausal hormone therapy were expected to be long term, ever having used menopausal hormone

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therapy (intention-to-treat) was determined as the definition of use in the primary analysis. Once exposed to menopausal hormone therapy, participating women could not re-enter the unexposed group. For a full description of menopausal hormone therapy regimens in the cohort, see supplemental material, supplementary table 2.

Outcomes

The primary outcome was death, registered in the Central Persons Register[27] which is updated daily and assumed to be virtually complete. Secondary analyses explored cause-specific mortality by identifying the primary cause of death in the Cause of Death Register[27]. Cause of death was stratified by cardiovascular mortality (which included death from ischaemic heart disease, cerebrovascular disease, hypertension, or other circulatory diseases), cancer mortality, or mortality from other causes. The Cause of Death Register[27]was available throughout 2022, therefore analyses assessing cause-specific mortality concluded on 31 December 2022.

Covariates

To minimise confounding, all statistical models used age as the underlying time-axis. Thus, the crude model and adjusted model were adjusted for age. Adjustment variables were defined prospectively in a time-dependent manner throughout follow-up. We included calendar year in the following periods: 1995-2001, 2002-2008, 2009-2015, and 2016-2023. Parity was identified in the Medical Birth Register[28] in the following categories: 0, 1-2, or ≥3. Women were categorised into the diabetes and hypercholesterolemia groups if they had redeemed a prescription for an antidiabetic or lipid lowering drug, respectively, and into the hypertension group if they had redeemed prescriptions for at least two classes of antihypertensive drugs.[29] The atrial fibrillation and valvular groups categorised women on the basis of discharge diagnosis codes, and the heart failure group comprised women with a relevant discharge diagnosis code who had redeemed a prescription for a loop diuretic.[30] We used three or more instances of hospital contact in the year leading up to inclusion in the study (between the participant age of 44 and 45 years) as a proxy for poor general health. Demographic variables were available from Statistics Denmark and included income group quarter (divided into quartiles) at the ages of 45 years and 55 years, and highest educational qualification attained (primary or lower secondary school, upper secondary school, bachelor's degree or equivalent, master's degree or equivalent, or unknown), country of birth (Denmark, other, or unknown), and civil status (unmarried, married, divorced, or unknown). For the outcome of cardiovascular mortality, analyses were not adjusted for hypercholesterolemia, hypertension, atrial fibrillation, and heart failure, as they were potential mediating variables.

Statistical analyses

Eligible women were included at their 45th birthday and followed until emigration from Denmark for over six months, end of follow-up (31 July 2023), or an event of interest. In the primary analysis, women were not censored at a contraindication for menopausal hormone therapy as the Cox model assumes non-informative censoring, and these contraindications were considered informative of the outcome (eg, cancer predicting future all cause mortality).[31]

Because women were unexposed to menopausal hormone therapy at inclusion (at 45 years), characteristics were assessed at a landmark 10 years after follow-up commenced (at 55 years) to better describe differences by menopausal hormone therapy treatment. We summarised the number of events and person-years by years of menopausal hormone therapy use, and crude and adjusted measures of association were calculated using the Cox proportional hazards model. The proportional hazards assumption was accepted after assessing plots of Schoenfeld residuals for all independent variables (supplementary material, supplementary figure 1).

To examine the robustness of the results, we conducted three sensitivity analyses: firstly, we assessed the effect of censoring at contraindications for menopausal hormone therapy (ie, thrombophilia, liver disease, arterial or venous thrombosis, breast cancer, endometrial cancer, or ovarian cancer). Secondly, a sibling design was used to minimise influence from unmeasured confounders. In this analysis, we only included sisters in the cohort with discordant use of menopausal hormone therapy at end of follow-up (ie, at least one sister was unexposed and at least one was exposed). In order for the statistical model to compare exposed versus unexposed siblings from the same family, we used a strata term on the identification number of the mother of the siblings. Thirdly, as the potential adverse effects of menopausal hormone therapy could possibly only occur during use and not as a result of past use, an 'as treated' analysis examined the effect of current menopausal hormone therapy treatment by censoring women at menopausal hormone therapy cessation. In this analysis, all prescriptions for menopausal hormone therapy were prolonged by 90 days to account for gaps in treatment.

Three subgroup analyses examined women who had undergone gynaecological surgery: hysterectomy at any age, bilateral oophorectomy between age 45 and 54 years, or bilateral oophorectomy at age 55 years or older. Hysterectomy and oophorectomy are not mutually exclusive, meaning that some women fulfilled both criteria. In these analyses, women were censored in case of breast cancer, endometrial cancer, or ovarian cancer to avoid overrepresentation in the non-user group. Three stratified analyses explored possible effect modification by form of menopausal hormone therapy given (oral, transdermal, or other), progestogen regimen of menopausal hormone therapy (oestrogen monotherapy, oestrogen+cyclic progestogen, or oestrogen+continuous progestogen),

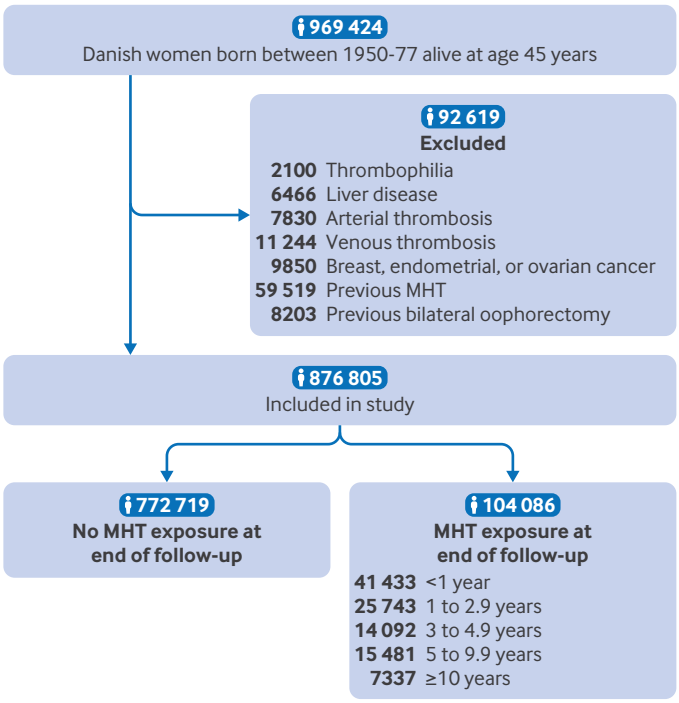

Fig 1 | Flowchart of cohort selection for study on relationship between menopausal hormone therapy and long term, all cause mortality. Sum of exclusions does not equal the total because women could fulfil multiple exclusion criteria. MHT=menopausal hormone therapy

and age of initiation of menopausal hormone therapy (45-51 years, 52-56 years, or ≥57 years). In analyses investigating different menopausal hormone therapy forms and progestogen regimens, women were grouped according to where they had contributed most defined daily dose cumulatively at a given time during follow-up (ie, if a woman initially used oral therapy for one year and then changed to transdermal therapy, she would be considered exposed to transdermal therapy after more than more year of use).

Information about educational qualification, marriage status, country of birth, and income was missing for 1.0%, 0.2%, 0.2%, and 0.2% of the cohort, respectively. As the proportion of participants with missing data was very low, missing data was handled by using mode imputation assigning missing values to the most frequent group.[32] A two sided P<0.05 was determined a priori to be statistically significant.

Patient and public involvement

Patients were not directly involved in formulating the research question, choosing the study design, or in interpretation of results. The authors fully support involving patients and members of the public in conducting medical research, and although no funding was available for this purpose in our study, the authors will pursue patient and public involvement in future studies.

Results

Of 969 424 Danish women born between 1950 and 1977 alive at 45 years, 876 805 were eligible for inclusion (fig 1), and 92 619 were excluded because of contraindications for menopausal hormone therapy, earlier use of menopausal hormone therapy, or bilateral oophorectomy. The median follow-up time was 14.3 years (interquartile range (IQR) 7.9-21.0 years). Of the included women, 104 086 (11.9%) had redeemed at least one prescription for menopausal hormone therapy by the end of follow-up. This percentage was markedly higher for the eldest women in the cohort: 29.5% of those born in 1950, 11.2% of those born in 1960, and 7.7% of those born in 1970 had redeemed at least one prescription. Correspondingly, the proportion of 55 year old women with past or present use of menopausal hormone therapy decreased over time, from 27.0% of women reporting current or past use between 2004 and 2006, to 9.7% between 2021 and 2023. The most common type of menopausal hormone therapy used was tablets containing oestradiol and continuous norethisteronacetat, accounting for 32.3% of all menopausal hormone therapy used, followed by oestradiol monotherapy tablets (18.1%), and tablets with oestradiol and cyclic norethisteronacetat (17.2%). By the end of the follow-up period, the median duration of menopausal hormone therapy use was 1.7 years (IQR 0.5-4.4 years), with 41 433 (4.7%) women using menopausal hormone therapy for less than one year, and only 7337 (0.8%) women reporting ≥10 years of use.

On average, women aged 55 years who had past or present menopausal hormone therapy use had delivered slightly fewer children, were more often divorced, had hypertension, had three or more hospital contacts between age 44 and 45, and had previously undergone hysterectomy and/or bilateral oophorectomy, as compared with women without registered use of menopausal hormone therapy. We observed only minor differences in educational or income level between these groups (table 1).

The first sensitivity analysis explored the effect of censoring women at contraindications for menopausal hormone therapy: this did not change the results materially. The second sensitivity analysis used a sibling design which reduced the size of the cohort to 57 773 women (6.6% of the cohort). In this analysis, menopausal hormone therapy was not significantly associated with an increased risk of mortality (adjusted hazard ratio 1.06 (95% CI 0.94 to 1.19); table 2), as compared with never having used of menopausal hormone therapy. The third sensitivity analysis used an 'as treated' study design, censoring women at menopausal hormone therapy cessation, and found a significantly reduced adjusted hazard ratio of mortality of 0.83 (95% CI 0.76 to 0.89).

Subgroup analyses examined women who had undergone hysterectomy and/or bilateral oophorectomy at 55 years or older. These analyses found no significant increase in mortality among groups. However, among women who had undergone bilateral oophorectomy between age 45 and 54 years, use of menopausal hormone therapy was associated with a significant 27-34% reduction in mortality

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Table 1 | Cohort characteristics of women in the study at age 55. Data are number (%) unless otherwise specified

Characteristic	Past or present MHT use at 55 years	
	Yes (n=79 466)	No (n=512 004)
Birthplace:		
Denmark	76 896 (96.8)	495 443 (96.8)
Other	2564 (3.2)	15 547 (3.0)
Unknown	6 (<0.1)	1014 (0.2)
Mean parity (SD)	1.60 (0.99)	1.77 (1.07)
Parity category:		
0	11 496 (14.5)	72 699 (14.2)
1-2	55 744 (70.1)	332 543 (64.9)
≥3	12 226 (15.4)	106 762 (20.9)
Marriage status:		
Unmarried	9404 (11.8)	80 469 (15.7)
Married	52 677 (66.3)	336 821 (65.8)
Divorced	17 290 (21.8)	93 245 (18.2)
Unknown	95 (0.1)	1469 (0.3)
Highest completed educational degree:		
Primary or lower secondary school	19 935 (25.1)	116 930 (22.8)
Upper secondary school	34 494 (43.4)	232 557 (45.4)
Bachelor's degree or equivalent	18 991 (23.9)	123 158 (24.1)
Master's degree or equivalent	5341 (6.7)	33 579 (6.6)
Unknown	705 (0.9)	5780 (1.1)
Income quartile*		
1st	17 112 (21.5)	99 870 (19.5)
2nd	17 364 (21.9)	110 166 (21.5)
3rd	19 893 (25.0)	133 495 (26.1)
4th	25 097 (31.6)	168 473 (32.9)
Year of 55th birthday:		
2002-2008	29 833 (37.5)	95 074 (18.6)
2009-2015	25 508 (32.1)	188 795 (36.9)
2016-2023	24 125 (30.4)	228 135 (44.6)
Diabetes	3258 (4.1)	24 793 (4.8)
Hypertension	16 761 (21.1)	93 983 (18.4)
Hypercholesterolemia	10 719 (13.5)	66 997 (13.1)
Atrial fibrillation	758 (1.0)	4544 (0.9)
Heart failure	210 (0.3)	1605 (0.3)
Valvular disease	404 (0.5)	2828 (0.6)
Three or more hospital contacts between age 44 and 45 years	7343 (9.2)	37 489 (7.3)
Earlier hysterectomy	15 103 (19.0)	45 079 (8.8)
Earlier bilateral oophorectomy	4383 (5.5)	6948 (1.4)

MHT=menopausal hormone therapy; SD=standard deviation.
*Missing group masked by presenting mode imputed variables due to rules by Statistics Denmark stating cells with under three persons cannot be presented.
The unadjusted absolute risk of all cause mortality for women with past or present use of menopausal hormone therapy was 54.9 deaths per 10 000 person years, as compared with 35.5 deaths per 10 000 person years for women who had never used menopausal hormone therapy. This corresponded to an adjusted hazard ratio of all cause mortality of 0.96 (95% CI 0.93 to 0.98). Stratifying this by cumulative duration of menopausal hormone therapy use gave an adjusted hazard ratio after <1 years of menopausal hormone therapy of 1.01 (95% CI 0.98 to 1.05), after 1-2.9 years of use 0.94 (0.89 to 0.98), 3-4.9 years of use 0.90 (0.84 to 0.95), 5-9.9 years of use 0.89 (0.84 to 0.95), and ≥10 years of use 0.98 (0.90 to 1.07) (table 2).

hazard depending on duration of use. Among the 703 women who underwent bilateral oophorectomy between 45-54 years and had subsequently died during follow-up, the median age at death for those who had taken menopausal hormone therapy was 60.9 years (IQR 55.3-66.6 years) as compared with 56.6 years (IQR 52.9-62.0 years) for those who had not.

Stratifying by form of menopausal hormone therapy given found that women who mostly used transdermal menopausal hormone therapy formulations (ie, plaster or gel) were associated with a significantly lower hazard of mortality (adjusted hazard ratio 0.85 (95% CI 0.80 to 0.90)), as compared with women who had never used menopausal hormone therapy. Stratifying analyses by progestogen regimen found that women who mostly used oestrogen monotherapy or oestrogen with cyclic progestogen were associated with a marginally lower mortality as compared with women who had never used menopausal hormone therapy. Stratifying by age of therapy initiation revealed that starting menopausal hormone therapy at age 52 or older was associated with the lowest mortality, as compared with never having used menopausal hormone therapy.

Separate analyses explored outcomes of cause-specific mortality. Few deaths were registered as primarily caused by cardiovascular disease (11.6%), compared with deaths caused by cancer (48.3%), and death from other causes (40.0%). Short term use to menopausal hormone therapy (<5 years) was associated with a slight reduction in hazard of mortality from cardiovascular disease and a minor increased hazard of mortality from cancer. However,

Table 2 | Association between menopausal hormone therapy and all cause mortality

Years of MHT use	No of mortality events	No of person years	IR*	Crude HR (95% CI)	Adjusted HR (95% CI)†
Primary analysis					
Never used	40 033	11 285 883	35.5	1	1
Past or present use	7561	1 377 023	54.9	1.04 (1.01 to 1.06)	0.96 (0.93 to 0.98)
Primary analysis stratified by duration of use					
0 years	40 033	11 285 883	35.5	1	1
<1 year	3107	569 091	54.6	1.12 (1.08 to 1.16)	1.01 (0.98 to 1.05)
1-2.9 years	1804	369 244	48.9	0.98 (0.93 to 1.03)	0.94 (0.89 to 0.98)
3-4.9 years	979	190 191	51.5	0.94 (0.88 to 1.00)	0.90 (0.84 to 0.95)
5-9.9 years	1120	186 955	59.9	0.98 (0.92 to 1.04)	0.89 (0.84 to 0.95)
≥10 years	551	61 542	89.5	1.12 (1.03 to 1.22)	0.98 (0.90 to 1.07)
Sensitivity analysis: censored at MHT contraindication‡					
Never used	25 197	10 698 290	23.6	1	1
Past or present use	4519	1 258 033	35.9	1.04 (1.01 to 1.08)	0.97 (0.93 to 1.00)
Sensitivity analysis: sibling analysis					
Never used	1342	603 114	22.3	1	1
Past or present use	1049	259 783	40.4	1.15 (1.05 to 1.25)	1.06 (0.94 to 1.19)
Sensitivity analysis: 'as treated' analysis (censored at MHT cessation)					
Never used	40 033	11 285 883	35.5	1	1
Past or present use	618	239 921	25.8	0.87 (0.80 to 0.94)	0.83 (0.76 to 0.89)
Subgroup of women who had undergone hysterectomy§					
0 years	2915	835 825	34.9	1	1
<5 years	907	195 203	46.5	1.08 (1.00 to 1.17)	1.02 (0.94 to 1.10)
≥5 years	339	59 683	56.8	1.02 (0.91 to 1.14)	0.94 (0.84 to 1.05)
Subgroup of women who had undergone bilateral oophorectomy between age 45-54 years§					
0 years	386	58 072	66.5	1	1
<5 years	208	45 699	45.5	0.65 (0.55 to 0.77)	0.66 (0.56 to 0.79)
≥5 years	109	18 909	57.6	0.75 (0.60 to 0.93)	0.73 (0.58 to 0.91)
Subgroup of women who had undergone bilateral oophorectomy at age 55 years or older§					
0 years	333	211 898	15.7	1	1
<5 years	66	30 221	21.8	0.87 (0.67 to 1.13)	0.88 (0.67 to 1.15)
≥5 years	27	9186	29.4	0.72 (0.48 to 1.06)	0.72 (0.48 to 1.07)
Stratified analysis: by treatment form most used					
Never used	40 033	11 285 883	35.5	1	1
Oral	6457	1 119 600	57.7	1.08 (1.05 to 1.11)	0.98 (0.95 to 1.01)
Transdermal	1098	256 122	42.9	0.85 (0.80 to 0.90)	0.85 (0.80 to 0.90)
Other formulation	6	1302	46.1	0.81 (0.36 to 1.79)	0.68 (0.30 to 1.50)
Stratified analysis: by progestogen regimen most used					
Never used	40 033	11 285 883	35.5	1	1
Oestrogen monotherapy	2034	392 901	51.8	1.02 (0.97 to 1.06)	0.92 (0.88 to 0.97)
Oestrogen+cyclic progestogen	3315	597 528	55.5	1.06 (1.02 to 1.09)	0.96 (0.92 to 0.99)
Oestrogen+continuous progestogen	2212	386 594	57.2	1.03 (0.99 to 1.07)	0.99 (0.95 to 1.04)
Stratified analysis: by age of initiation					
Never use	40 033	11 285 883	35.5	1	1
45-51 years	6504	1 106 853	58.8	1.14 (1.11 to 1.18)	1.02 (1.00 to 1.05)
52-56 years	933	244 818	38.1	0.65 (0.61 to 0.70)	0.69 (0.65 to 0.74)
≥57 years	124	25 352	48.9	0.66 (0.55 to 0.78)	0.69 (0.58 to 0.83)

CI=confidence interval; IR=incidence rate; HR=hazard ratio; MHT=menopausal hormone therapy.
*Incidence rate per 10 000 person years.
†Adjusted for age, calendar year, parity, educational degree, income quarter (based on quartiles), country of birth, diabetes, hypercholesterolemia, hypertension, atrial fibrillation, valvular disease, heart failure, and three or more hospital contacts between age 44 and 45 years.
‡MHT contraindications: thrombophilia, liver disease, arterial or venous thrombosis, breast cancer, endometrial cancer, or ovarian cancer.
§Censored at breast cancer, endometrial cancer, or ovarian cancer.

these findings were not amplified nor significant for long term menopausal hormone therapy use (≥5 years), as seen in table 3.

Discussion

Principal findings

This large nationwide cohort study including over 800 000 women and 12 million person years of follow-up, did not find epidemiological evidence of excess mortality following menopausal hormone therapy use. The results showed a large decrease in menopausal hormone therapy use in the Danish population in the years following the publication of the results from the Women's Health Initiative study in 2002. Women who had undergone bilateral oophorectomy between age 45 and 54 years, were associated with a significant survival benefit when using menopausal hormone therapy, corresponding to a 27-34% decrease in mortality hazard. Stratified analyses found the lowest mortality among women predominantly using transdermal menopausal hormone therapy formulations, oestrogen monotherapy, cyclic progestogen regimens, and among women initiating menopausal hormone therapy aged 52 years or older, although these findings should be

Table 3 | Association between menopausal hormone therapy and cause-specific mortality

Years of MHT use	No of mortality events	No of person years	IR*	Crude HR (95% CI)	Adjusted HR (95% CI)
Cardiovascular mortality†					
0 years	4495	10 919 435	4.1	1	1
<5 years	570	1 086 597	5.2	0.91 (0.83 to 0.99)	0.84 (0.77 to 0.92)
≥5 years	180	236 475	7.6	0.99 (0.85 to 1.15)	0.91 (0.78 to 1.05)
Cancer mortality‡					
0 years	18 145	10 919 435	16.6	1	1
<5 years	2873	1 086 597	26.4	1.11 (1.06 to 1.15)	1.04 (1.00 to 1.09)
≥5 years	781	236 475	33.0	1.05 (0.98 to 1.13)	0.98 (0.91 to 1.05)
Other mortality‡					
0 years	15 310	10 919 435	14.0	1	1
<5 years	2152	1 086 597	19.8	1.01 (0.97 to 1.06)	0.88 (0.67 to 1.15)
≥5 years	597	236 475	25.2	0.98 (0.90 to 1.07)	0.72 (0.48 to 1.07)

CI=confidence interval; IR=incidence rate; HR=hazard ratio; MHT=menopausal hormone therapy.
*Incidence rate per 10 000 person years.
†Adjusted for age, calendar year, parity, educational degree, income quartile, country of birth, diabetes, and three or more hospital contacts between age 44 and 45 years.
‡Adjusted for age, calendar year, parity, educational degree, income quartile, country of birth, diabetes, hypercholesterolemia, hypertension, atrial fibrillation, valvular disease, heart failure, and three or more hospital contacts between age 44 and 45 years.

interpreted with caution and await scrutiny in future studies. No unambiguous changes in cause-specific mortality were found between groups.

Comparison with other studies

The primary result from the current study is very close to that found by Manson et al[23]in the assessment of all cause mortality following the Women's Health Initiative randomised trials. Here, 16 608 women who had not undergone a hysterectomy were randomised to conjugated equine oestrogen and medroxyprogesterone or placebo, and 10 739 women who had undergone a hysterectomy to conjugated equine oestrogen or placebo. The median age at inclusion was 63.4 years (standard deviation (SD) 7.2 years) and the pooled results from these two trials found a hazard ratio of mortality of 0.99 (95% CI 0.94 to 1.03) after 18 years of follow-up.[23] We further assessed the effect of different durations of menopausal hormone therapy use, different forms of treatment, different progestogen regimens, and the effect of menopausal hormone therapy in women who had undergone oophorectomy in a much larger cohort. Multiple observational studies have demonstrated a large decrease in all cause mortality after menopausal hormone therapy use. These historical studies are often based on self-reported data and/or limited sample size which may introduce recall bias and imprecision in estimates.[19 35 36]

A few large scale Swedish, register based studies have examined adverse effects of menopausal hormone therapy. An emulated target trial by Johansson et al[37] found oral menopausal hormone therapy was associated with an increased risk of heart disease contrasting with the slight reduction in cardiovascular mortality after menopausal hormone therapy found in our study. These differences could be explained by differences in outcome definition, study design, age groups examined, and calendar year.[37] A study by Simin et al[38] examined the risk of all cause mortality after ever having used menopausal hormone therapy. Although the study did not explore differences in mortality by duration of menopausal hormone therapy use, or earlier gynaecological surgery, results were mostly in line with those found in our study, finding an odds ratio of all cause mortality of 0.97 (95% CI 0.95 to 0.98). However, the study also found a very large reduction in cancer related mortality following ever having used menopausal hormone therapy (odds ratio 0.70, 95% CI 0.68 to 0.72), which contrasts with our findings. The difference in results could be because of left censoring in the study by Simin et al, because the Swedish prescription register did not start until 2005, which could lead to misclassification of duration of use.[38] A Danish cohort study of 29 243 women used self-reported data on menopausal hormone therapy and found no significant association with later all cause mortality.[20]

Policy implications

Current guidelines from the Endocrine Society recommend menopausal hormone therapy for women who have recently begun menopause who have moderate to severe symptoms and no contraindications.[39] Our findings support these guidelines and add that transdermal menopausal hormone therapy is associated with the lowest all cause mortality and we found no increased mortality among women who begin treatment at or older than 52 or 57 years.

Women have surgery to remove their ovaries for various reasons, including ovarian cysts, benign tumours, ovarian torsion, predisposition to cancer, gynaecological cancer, surgeon preference during a hysterectomy, or other gynaecological disease. In our study, women who had undergone bilateral oophorectomy between the ages of 45 and 54 years and had used menopausal hormone therapy, had a significantly reduced mortality compared with women who had undergone bilateral oophorectomy between the ages of 45 and 54 years and had never used menopausal hormone therapy. An earlier study

corroborated these findings: the investigators found increased mortality among women who underwent bilateral oophorectomy before 45 years and did not use oestrogen therapy up to at least age 45 years.[40] Another study found increased mortality if ovaries and fallopian tubes are removed during hysterectomies before age 50 years.[41] Our results suggest that among women who undergo bilateral oophorectomy between age 45 and 54 years old, menopausal hormone therapy is associated with a significant increase in survival, as compared to no menopausal hormone therapy, and a trend towards a survival benefit in in women who had undergone bilateral oophorectomy and were aged 55 years or older. Current guidelines from the Royal College of Obstetricians and Gynaecologists recommend offering hormone therapy to all women who undergo bilateral oophorectomy before menopause, until the average age of natural menopause is reached (about 51 years), provided there are no contraindications.[42] The magnitude of survival difference found in our study should prompt further discussion as to whether more women should be offered systemic menopausal hormone therapy after undergoing bilateral oophorectomy. Future studies should assess the optimal timing, duration, and type of menopausal hormone therapy for these women.

Strengths and limitations of this study

The major strength of the current study is the large study population, evaluating almost a complete generation of women in the Danish population whose characteristics, hospital diagnoses, and pharmaceutical prescription purchases have been electronically registered. Registration of this information was mandatory and opting out was not possible, ensuring a near complete record and follow-up of these women, maximising external data validity, minimising recall bias, and ensuring a large sample size. However, the study also has limitations: firstly, menopausal hormone therapy was not prescribed at random (which is possible in a controlled setting), so careful confounder adjustment was used to minimise confounding bias. Because residual confounding could nonetheless have persisted, we performed a sibling analysis, because siblings are often more comparable in terms of lifestyle factors than the general population. This analysis minimised residual confounding but the reduced sample size increased the imprecision of results. However, the results were materially unchanged.

Censoring which is informative of the study outcome (ie, strongly indicative of future all cause mortality) can lead to bias, and contraindications for menopausal hormone therapy are some of the most common causes of mortality and preceded 37.6% of deaths in the cohort. Therefore, in the primary analysis women were not censored if they developed contraindications for menopausal hormone therapy during follow-up. To assess if this decision skewed the menopausal hormone therapy group into a healthy user group, in which people with comorbidity were underrepresented, we conducted a sensitivity analysis which censored women who developed contraindications for menopausal hormone therapy. We found that this did not change the results meaningfully. The effects of menopausal hormone therapy were a priori expected to be long term, persisting even after cessation, so the main analysis used an intention-to-treat design. However, short term adverse effects only apparent during treatment and ceasing upon ending menopausal hormone therapy could nevertheless not be excluded. Therefore, we conducted another sensitivity analysis exploring an 'as treated' design, censoring women at the end of menopausal hormone therapy use. The result was a vastly reduced number of person years at risk in the user group and, therefore, increased imprecision. In this analysis, menopausal hormone therapy was associated with a significantly reduced mortality, which could be explained by possible beneficial effects of menopausal hormone therapy during use that cease after cessation. However, this effect could also be caused by bias towards healthy users during treatment. The study design allowed a near complete register based history of menopausal hormone therapy among women in the cohort, however, this also meant that the median age at end of follow-up was relatively young (59.4 years). If menopausal hormone therapy only was associated with an increased mortality at old age, it could be hard to detect with the current design, although other studies do not point to this being the case.

The focus of the study was systemic menopausal hormone therapy, thus the results are not necessarily applicable to localised menopausal hormone therapy such as vaginal suppositories with low dose oestrogen, non-hormonal menopausal hormone therapy therapies such as neurokinin-3 receptor antagonist, or tibolone which is an agonist for oestrogen, progesterone, and androgen receptors. Examining these drugs was beyond the scope of the study.

Contributors: AM conceptualised the study; contributed to data curation, formal analysis, funding acquisition, methodology, project administration, resources, and writing of initial draft; and was the guarantor. TB supervised the study, and reviewed and edited the manuscript. ØL supervised the study, and contributed to data curation, project administration, reviewing and editing of the manuscript. NMS was responsible for the methodology, supervision, and reviewing and editing of the manuscript. 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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Competing interests: All authors have completed the ICMJE uniform disclosure form at https://www.icmje.org/disclosure-of-interest/ and declare: support from Copenhagen University Hospital Herlev for the submitted work; ØL reports that outside the submitted work an institutional grant from Exeltis to conduct an EMA requested post authorisation safety study on a new progestin-only contraceptive pill; ØL has not and will not receive any personal payment for my primary investigator role of this study. ØL reports honorariums for pregraduate and postgraduate speeches from the Danish Health Board and from Gedeon Richter. The authors report no other conflicts of interest.

Ethical approval: No approval by an ethics committee is necessary for register based studies in Denmark. Permission from the Danish Health Data Authority to access data was ensured. We reported our

results using the strengthening the reporting of observational studies (STROBE) guidelines for cohort studies.[33] Analyses were conducted using R version 4.4.1 (R Core Team, 2024) and packages data.table version 1.16.2 and survival version 3.7-0.[34] The study adhered to the Declaration of Helsinki.

Data sharing: Data used in the current study cannot be made openly available by the authors due to rules from the Danish Health Data Authority and Statistics Denmark. Aggregated data can be made available upon reasonable request to the corresponding author. The code used to analyse the data in the paper can be found in the supplementary materials.

Transparency: The lead author (the manuscript's guarantor) 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 (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: Findings from the current study will be disseminated to media through a press release.

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

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Web appendix: Supplemental Material