Menopausal hormone therapy and dementia: nationwide, nested case-control study

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ABSTRACT

OBJECTIVES

To assess the association between use of menopausal hormone therapy and development of dementia according to type of hormone treatment, duration of use, and age at usage.

DESIGN

Nationwide, nested case-control study.

SETTING

Denmark through national registries.

PARTICIPANTS

5589 incident cases of dementia and 55 890 age matched controls were identified between 2000 and 2018 from a population of all Danish women aged 50-60 years in 2000 with no history of dementia or contraindications for use of menopausal hormone therapy.

MAIN OUTCOME MEASURES

Adjusted hazard ratios with 95% confidence intervals for all cause dementia defined by a first time diagnosis or first time use of dementia specific medication.

RESULTS

Compared with people who had never used treatment, people who had received oestrogen-progestin therapy had an increased rate of all cause dementia (hazard ratio 1.24 (95% confidence interval 1.17 to 1.33)). Increasing durations of use yielded higher hazard ratios, ranging from 1.21 (1.09 to 1.35) for one year or less of use to 1.74 (1.45 to 2.10) for more than 12 years of use. Oestrogen-progestin therapy was positively associated with development of dementia for both continuous (1.31 (1.18 to 1.46)) and cyclic (1.24 (1.13 to 1.35)) regimens. Associations persisted in women who received treatment at the age 55 years or younger (1.24 (1.11 to 1.40)). Findings persisted when restricted to late onset dementia (1.21 (1.12 to 1.30)) and Alzheimer's disease (1.22 (1.07 to 1.39)).

CONCLUSIONS

Menopausal hormone therapy was positively associated with development of all cause dementia and Alzheimer's disease, even in women who received treatment at the age of 55 years or younger. The increased rate of dementia was similar between continuous and cyclic treatment. Further studies are warranted to determine whether these findings represent an actual effect of menopausal hormone therapy on dementia risk, or whether they reflect an underlying predisposition in women in need of these treatments.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Large scale observational studies found long term use of menopausal hormone therapy is associated with development of dementia, confirming findings from the largest randomised, double blind, placebo controlled trial on the topic

The effect of short term use of menopausal hormone therapy around the age of menopause remains to be fully explored

Information is scarce on the effect of continuous versus cyclic combined menopausal hormone therapy on the risk of dementia

WHAT THIS STUDY ADDS

Exposure to menopausal hormone therapy was positively associated with development of all cause dementia and Alzheimer's disease, even for short term usage around the age of menopause onset

Continuous and cyclic oestrogen-progestin regimens were associated with a comparable increased rate of dementia

Introduction

Dementia affects more women than men worldwide.[1 2] Even when controlling for differences in survival rates, the incidence of dementia among women is higher compared with that of men, suggestive of risk factors related to the female sex.[1 3]

Oestrogen is known to have both neuroprotective and neurodamaging properties.[4 5] Exogenous systemic oestrogen is used in the management of menopausal vasomotor symptoms. The effect of menopausal hormone therapy on the risk of dementia is uncertain. Early meta-analyses found a protective effect of menopausal hormone therapy on the development of Alzheimer's disease, the most common cause of dementia.[6 7] Later, in 2003, a randomised, double blind, placebo controlled trial, the Women's Health Initiative Memory Study, reported that menopausal hormone therapy was associated with an increased risk of dementia.[8 9] However, the trial only included women who were 65 years or older. The contemporary standard recommendation for timing and duration of menopausal hormone therapy is use around the age of menopause, preferably for a maximum of five years.[10] As such, the primary target population of hormone therapy is around 50-55 years old and the findings from the Women's Health Initiative Memory Study less relevant in a real-world contemporary setting. Furthermore, the trial was not able to distinguish between different subtypes of dementia, and only conjugated oestrogens were examined, not oestradiol, which is the leading oestrogen contained in contemporary menopausal hormone therapy products. Following the Women's Health Initiative Memory Study, two small randomised controlled trials reported no association between oestrogen use and cognitive decline in postmenopausal women, however, the trial populations were highly selected.[11 12]

Recent, large scale observational studies have reported a positive association between use of menopausal hormone therapy and Alzheimer's disease in long term users who initiated treatment before age 60 years.[13 14] However, the studies were not able to obtain full exposure history of hormone treatment for most of their study population, especially short term use (eg, up to five years) around the age of menopause.

The effect of the progestin component in menopausal hormone therapy on the risk of dementia also remains uncertain. In women with an intact uterus, systemic oestrogen for menopausal vasomotor symptoms is accompanied by progestin to protect the endometrium from the proliferative properties of the oestrogen. Based on observations of a higher risk of dementia in users of both oestrogen and progestin compared with users of systemic oestrogen only treatment,[8 9 13 14] both the Women's Health Initiative Memory Study and recent observational studies hypothesise that progestin might intensify a potential neurodamaging effect of oestrogen, thereby potentially proposing benefits of cyclic progestin treatment compared with continuous progestin treatment. However, none of the studies were able to differentiate between these types of treatments.

We report a nationwide study on the association between menopausal hormone therapy and development of dementia. We distinguish between cyclic and continuous regimens of oestrogen-progestin therapy as well as analyses in short term users aged 55 years or younger as currently recommended.

Methods

Study population

We conducted a nationwide, nested case-control study using Danish national registries. Incident dementia cases and age matched dementia-free controls were identified between 1 January 2000 and 31 December 2018 in a nationwide population of all Danish women (sex assigned at birth) aged 50-60 years on 1 January 2000 with no history of dementia, breast cancer, gynaecological cancers, thrombosis, liver disease, thrombophilia, bilateral oophorectomy, and hysterectomy (information about data sources and definitions in supplementary table A). Like bilateral oophorectomy, hysterectomy has been associated with an increased risk of menopausal vasomotor symptoms and with an increased risk of dementia, making hysterectomy a potential confounder of the association between use of menopausal hormone therapy and development of dementia.[15 16] Thus, we excluded women who had a hysterectomy to limit bias. The rest of the exclusion criteria are contraindications for menopausal hormone therapy use and thus were chosen for the study population to mimic the clinical target population. The age restriction was defined to ensure almost complete exposure history on all individuals.

Dementia

In Denmark, dementia is diagnosed and managed in a hospital setting typically on specialised memory clinics, allowing us to identify a first time diagnosis of dementia from the National Registry of Patients, which holds information on all diagnoses given in Danish hospitals since 1977 for admissions and 1995 for outpatient visitis.[17] Furthermore, drugs used in the treatment of dementia require a prescription, and since 1995, all filled prescriptions are registered in the National Prescription Registry.[18] A woman was considered a case with all cause dementia from the date (index date) of first dementia diagnosis (the 10th revision of the International Classification of Diseases (ICD-10) code F00, F01, F02, F03, G30, G31.8-9) or from the date of redeeming first prescription with drug specific to dementia (ie, Anatomical Therapeutic Chemical code N06D). On the index date, each case

Table 1 | Characteristics of the case-control population at time of index

	Cases of all cause dementia (n=5589)	Age matched controls without dementia (n=55 890)	P value
Age, years:			
Median (interquartile range)	70 (66-73)	70 (66-73)	1.00
<65	1148 (20.5)	11 476 (20.5)	
65-69	1466 (26.2)	14 672 (26.2)	
70-74	2013 (36.0)	20 097 (36.0)	
≥75	962 (17.3)	9645 (17.3)	
Highest educational level:			
Elementary school only	2598 (46.5)	22 590 (40.4)	<0.001
Secondary school only	67 (1.2)	795 (1.4)	
Skilled worker	2007 (35.9)	21 879 (39.1)	
Theoretical education	791 (14.2)	8943 (16.0)	
Theoretical and research education	126 (2.3)	1683 (3.0)	
Annual household income:			
Low	1898 (34.0)	13 472 (24.1)	<0.001
Medium	1331 (23.8)	14 038 (25.1)	
High	2360 (42.2)	28 380 (50.8)	
Cohabitation	1790 (32.0)	30 732 (55.0)	<0.001
Medical history:			
Hypertension	1707 (30.5)	16 296 (29.2)	0.03
Diabetes	623 (11.1)	4266 (7.6)	<0.001
Thyroid disease	710 (12.7)	5528 (9.9)	<0.001

Table 2 | Use of combined menopausal hormone therapy in cases and controls

	Cases of all cause dementia (n=5589)	Controls (n=55 890)	P value
Ever users of oestrogen-progestin	1782 (31.9)	16 154 (28.9)	
Age at initiation of use, years:			
Median (interquartile range)	53 (50-54)	53 (50-54)	
45-49	331 (18.6)	2714 (16.8)	0.31
50-54	1084 (60.8)	10 051 (62.2)	
55-59	354 (19.9)	3271 (20.2)	
≥60	13 (0.7)	118 (0.7)	
Duration of use, years:			
≤1	447 (25.1)	4043 (25.0)	<0.001
>1-4	460 (25.8)	4397 (27.2)	
>4-8	447 (25.1)	4468 (27.7)	
>8-12	282 (15.8)	2311 (14.3)	
>12	146 (8.2)	935 (5.8)	
Method of treatment:			
Continuous progestin	458 (25.7)	3919 (24.3)	0.49
Cyclic progestin	694 (38.9)	6284 (38.9)	
Continuous and cyclic oestrogen and progestin	542 (30.4)	5096 (31.5)	
Unknown	88 (4.9)	855 (5.3)	
Route of administration:			
Oral administration only	1609 (90.3)	14 391 (89.1)	0.07
Transdermal administration only	56 (3.1)	462 (2.9)	
Mixed or other administration	117 (6.6)	1301 (8.1)	
Active ingredients:			
Oestradiol+norethisterone	1488 (83.5)	13 024 (80.6)	0.004
Oestradiol+medroxyprogesterone	525 (29.5)	5134 (31.8)	0.05
Oestradiol+levonorgestrel	137 (7.7)	1557 (9.6)	0.009
Oestradiol+cyproterone	77 (4.3)	874 (5.4)	0.06
Oestradiol+dienogest	40 (2.2)	270 (1.7)	0.10

Column percentages are no of ever users of oestrogen-progestin.

was matched with 10 female controls who did not have dementia by incidence density matching per birth year.[19]

Menopausal hormone therapy

The primary exposure of interest was use of combined oestrogen and progestin treatment. Using relevant Anatomical Therapeutic Chemical codes (available in supplementary table B), individual information about timing, amount, and type (continuous *v* cyclic) of purchased menopausal hormone therapy was obtained from the National Prescription Registry from 1 January 1995 until two years before index date. Thus, for all included participants, history of menopausal hormone therapy was assessed from the age 45-55 years until two years before a dementia diagnosis or matching, the latter to reduce the likelihood of protopathic bias.[20]

Duration of oestrogen-progestin use was estimated using the program medicinMacro accessible in the tagteam/heaven R package available on Github.[21] Oestrogen-progestin treatment may be given in one combined drug formulation or as two drugs, one with oestrogen and one with progestin (supplementary table B). The dosage may be regulated up or down according to the vasomotor symptoms of the women. The program medicinMacro calculates the most probable daily dose and duration of medication use according to information about dates of prescription redemption, the amount of purchased drugs, and the prescription pattern of the women, which is highly relevant when dealing with individualised dosages. Besides prescription data, the program medicinMacro used information about recommended default, minimum, and maximum dosages acquired from the respective summaries of product characteristics.

Statistical analysis

Conditional logistic regression provided adjusted hazard rate ratios and corresponding 95% confidence intervals of all cause dementia according to type, duration, and timing of hormone treatment use. We conducted subgroup analyses for late onset dementia (all cause dementia diagnosed from age 65 years and above[22]) and Alzheimer's disease (ICD-10 codes F00 and G30). Never users of menopausal oestrogen-progestin treatment, systemic or vaginal oestrogen only treatment, and perimenopausal progestin only treatment, constituted the reference group in all analyses. All statistical models included education, income, cohabitation, hypertension, diabetes, and thyroid disease as potential confounding variables (information about data sources and definitions in supplementary table A). Sensitivity analyses were conducted with one year and eight year lag time instead of the default two year lag time window. Data were categorised and analysed using R statistical software (R Core Team, 2020).[23]

Patient and public involvement

Patients or members of the public were not involved in the study's design, analysis, or manuscript writing, since the project was carried out by a small research group without available funding or personnel to include patients or the public. Nonetheless, press

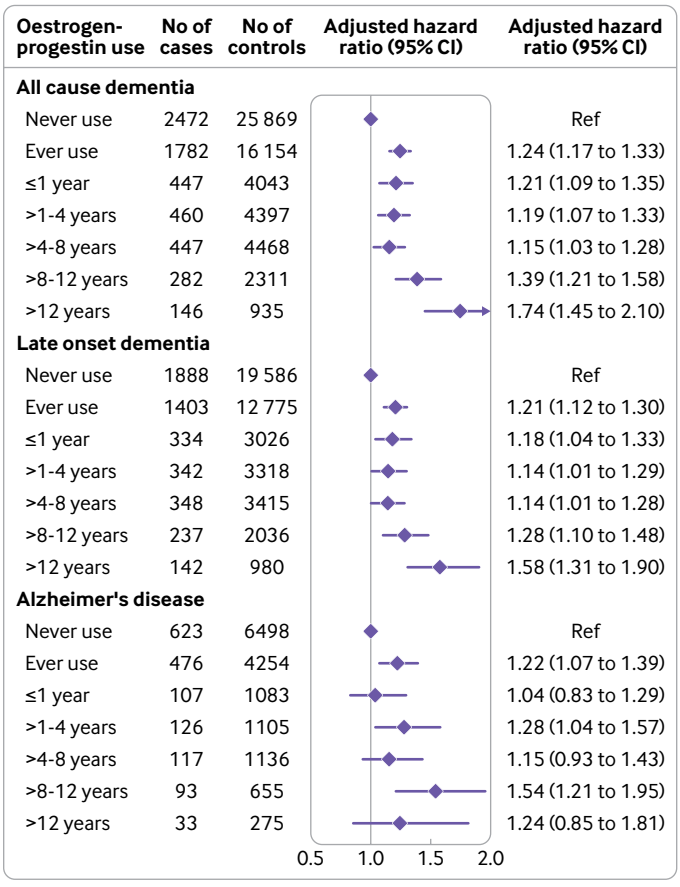

Fig 1 | Adjusted hazard rate ratios with 95% confidence intervals (CI) of all cause dementia, late onset dementia, and Alzheimer's disease according to cumulative duration of oestrogen-progestin hormone therapy use. Two regression models for each outcome (one for ever use and one for cumulative use). Adjusted for education, income, cohabitation, hypertension, diabetes, and thyroid disease at index date. Never use accounted for women who had never received oestrogen-progestin hormone treatment, systemic oestrogen only treatment, vaginal oestrogen treatment, or progestin only treatment (including the levonorgestrel releasing intrauterine device) from the ages of 45-55 years until index date. Estimates for systemic oestrogen only, vaginal oestrogen only, or progestin only treatment are not shown

releases, conference presentations, and social media posts will be used to communicate the study findings to the public and healthcare professionals.

Results

A total of 5589 incident cases of all cause dementia (1.8% of all eligible individuals in the source population) were matched to 55 890 dementia-free controls. Characteristics of the case-control population are shown in table 1. Late onset dementia incidences comprised 4436 (79.4%) cases among women with all cause dementia. A total of 1458 (26.1%) cases were registered as Alzheimer's disease.

The median age at diagnosis was 70 years (interquartile range 66-73 years). Compared with the control group, more often the case group had shorter education, lower household income, and were more likely to live alone and have hypertension, diabetes, and thyroid disease at time of index (table 1).

Before the index date, 1782 (31.9%) cases and 16 154 (28.9%) controls had received combined menopausal hormone therapy with oestrogen and progestin. Among all oestrogen-progestin users, 11 879 (66.2%) had their last treatment day more than eight years before the index date, and 1555 (8.7%) were still users at the time of diagnosis or matching. Table 2 provides information about timing, duration, and type of oestrogen and progestin exposure in cases and controls. Median age at initiation of oestrogen-progestin use was 53 years (interquartile range 50-54) for both cases and controls. The median duration of use was 3.8 years (interquartile range 1.1-7.5) for cases and 3.6 years (1.0-7.1) for controls. Among people in the cases group who used oestrogen-progestin, 25.7% received continuous progestin, 38.9% received progestin cyclically, and 30.4% had undergone both continuous and cyclic oestrogen-progestin treatment before the index date. The control group had similar proportions with 24.3% who received continuous progestin, 38.9% who received progestin cyclically, and 31.5% who had undergone both continuous and cyclic regimens (table 2). Oral administration was by far the most common route for oestrogen and progestin administration (table 2). The most used progestin in combination with oestrogen was norethisterone followed by medroxyprogesterone and levonorgestrel (table 2). Extensive details of the distribution of menopausal hormone therapy use in the study population are shown in supplementary table B.

Compared with never users of menopausal oestrogen-progestin therapy, systemic or vaginal oestrogen only treatment, and perimenopausal progestin only therapy, ever users of menopausal oestrogen-progestin treatment were more likely to develop all cause dementia (adjusted hazard ratio 1.24 (95% confidence interval 1.17 to 1.33)). The association persisted when restricting to late onset dementia (1.21 (1.12 to 1.30)) and Alzheimer's disease (1.22 (1.07 to 1.39)) (fig 1). Longer durations of use were associated with increasing hazard ratios, which, for all cause dementia, ranged from 1.21 (1.09 to 1.35) for one year or less of use to 1.74 (1.45 to 2.10) with more than 12 years of use (fig 1). The increased rate of all cause dementia was similar between continuous and cyclic regimens (fig 2).

The adjusted hazard ratio for all cause dementia was 1.26 (1.13 to 1.41) in women who initiated oestrogen-progestin therapy at age 45-50 years and 1.21 (1.12 to 1.29) in women who initiated it at age 51-60 years.

The increased rate of all cause dementia persisted in women who only received combined menopausal hormone therapy at age 55 years or younger (fig 3).

Associations for progestin only therapy did not reach statistical significance; all cause dementia (1.14 (0.97 to 1.34)), late onset dementia (1.01 (0.83 to 1.22)), and Alzheimer's disease (1.27 (0.93 to 1.73)). Similarly, no association was found between use of vaginal oestrogen only treatment and all cause dementia (1.08 (0.99 to 1.16)), late onset dementia (1.05 (0.97 to 1.15)), or Alzheimer's disease (1.00 (0.86 to 1.17)).

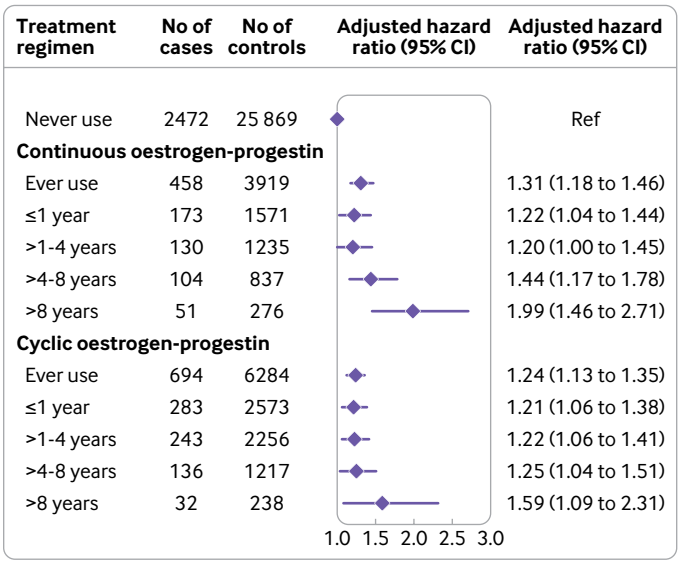

Fig 2 | Adjusted hazard rate ratios with 95% confidence intervals (CI) of all cause dementia according to regimen of oestrogen-progestin treatment and duration of use. Two regression models (one for ever use and one for cumulative use). Adjusted for education, income, cohabitation, hypertension, diabetes and thyroid disease at index date. Never use accounted for women who had never received oestrogen-progestin hormone treatment, systemic oestrogen only treatment, vaginal oestrogen treatment, and progestin only therapy (including the levonorgestrel releasing intrauterine device from the ages 45-55 years until index date. Estimates for women having used both continuous and cyclic combined menopausal hormone therapy before index date (31.4% of all who received treatment) are not shown nor for women with unidentifiable method of treatment (5.3%). Estimates for systemic oestrogen only, vaginal oestrogen only, or progestin only therapy are not shown

All associations were unchanged in sensitivity analyses with one year lag time and with eight year lag time instead of two year lag time before index date.

Discussion

Principal findings

In this nationwide, nested case-control study, exposure to menopausal hormone therapy with oestrogen and progestin was associated with an increased rate of all cause dementia, late onset dementia, and Alzheimer's disease. Increasing duration of treatment was associated with increasing hazard rates of developing dementia. Continuous and cyclic oestrogen-progestin regimens were similarly associated with development of all cause dementia. The increased rate of dementia persisted in short term users who had treatment exclusively at 55 years or younger. Treatments of progestin only and vaginal oestrogen were not associated with development of dementia.[24]

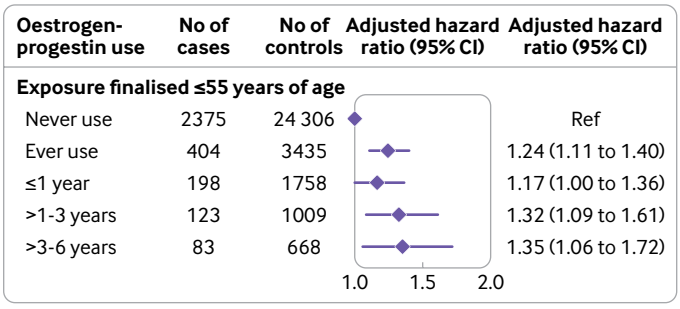

Fig 3 | Adjusted hazard rate ratios with 95% confidence intervals (CI) of all cause dementia according to hormone therapy use exclusively for women 55 years and younger. Two regression models (one for ever use and one for cumulative use). Adjusted for education, income, cohabitation, hypertension, diabetes and thyroid disease at index date. All cases and controls either never received treatment or finalised their oestrogen-progestin treatment at 55 years of age or before. Estimates for systemic oestrogen only, vaginal oestrogen only, or progestin only treatment are not shown

Comparison with other studies

The Women's Health Initiative Memory Study, the largest, randomised, double blind, placebo controlled trial on this topic, reported an increased risk of dementia in postmenopausal women treated with oestrogen and progestin after one year of use.[8 9] Furthermore, brain MRI scans of a subset of the trial population showed that menopausal hormone therapy was associated with brain atrophy,[25] a radiological finding strongly associated with cognitive decline and dementia.[26] These results align with the observations of our study that show the positive association between oestrogen-progestin exposure and development of dementia, even in short term users.

Recent large scale observational studies have also reported a positive association between use of menopausal hormone therapy and development of Alzheimer's disease, but only with long term use.[13 14] However, because of these studies included women 80 years and older, the information about potential treatment (especially short term treatment) to menopausal hormone therapy was not available for almost all of the cases. As such, misclassification of people who had treatment as people who did not have treatment is likely and thereby diluting a potential association between menopausal hormone therapy use and dementia. For example, in the study by Savolainen-Peltonen and colleagues, more than 50% of cases were of women who were at least 80 years at the time of diagnosis.[13] If, at best, these women were diagnosed at the end of the study period (year 2013), these cases of women would have been about 61 years of age at the time of initiation of exposure assessment (year 1994). Considering that the mean age of menopausal hormone therapy initiation in that study was found to be 56 years, use of menopausal hormone therapy for less than five years would not have been detectable for most cases, causing an inevitable misclassification of received treatment as did not receive treatment and thereby diluting the actual association with dementia. Similarly, in the study by Vinogradova and colleagues,[14] about 50% of cases were older than 80 years, causing the same bias towards the null, especially for short term usage of menopausal hormone therapy around the age of onset of menopause.

Strengths and weaknesses in relation to other studies

Strengths of the study included the large, nationwide, unselected study population; a highly valid method of identification of dementia cases (positive predictive

value of all cause dementia diagnoses of 86%[27]); almost complete history of treatment; the inclusion of a clinically relevant study population; and the ability to distinguish between combined continuous and cyclic menopausal hormone therapy. The Danish prescription registry provided complete data for redeemed prescriptions of menopausal hormone therapy from the year of 1995, therefore, we included only women aged 50-60 years in 2000. These data enhanced our ability to detect exposure to hormone treatment around the age of expected menopause and thereby diminishing the potential bias towards the null observed in previous observational studies. However, our age restriction has led to a lower median age of dementia onset (70 years) compared with that observed in the entire Danish population (around 80 years[1]). Nevertheless, our findings persisted when only considering late onset dementia.

Only 26% of our cases were registered with Alzheimer's disease compared with an expected proportion of around 70%.[28] Despite the under-registration of Alzheimer's disease, mainly due to use of unspecific dementia diagnoses in Danish hospital registries, the diagnoses of Alzheimer's disease have shown to have a positive predictive value of 81%, making these diagnoses appropriate for epidemiological research.[27] We do not expect the potential proportion of false positive diagnoses of all cause dementia or Alzheimer's disease to be differentially distributed among women who received or did not receive hormone treatment because most women who had treatment had their last treatment day more than eight years before the index date. As such, this means that exposure status would not have been likely to have affected the likelihood of dementia diagnosis.

Our study had limitations. We were not able to isolate vascular dementia from other types of dementia due to low validity of vascular dementia diagnosis.[27] Use of oral menopausal hormone therapy is an acknowledged risk factor for stroke and could explain the positive association between menopausal hormone therapy use and dementia.[29] However, we excluded women with stroke events, therefore our findings are unlikely to represent any association between systemic hormone therapy and stroke. Furthermore, the increased rate of dementia persisted when only assessing Alzheimer's disease, the most common neurodegenerative cause of dementia.

Most women who received combined hormone therapy in this study used orally administrated drug formulations, including the progestin drug norethisterone. Thus, as a result of the prescription pattern of menopausal hormone therapy in Denmark during the study period, we were not able to distinguish between modes of administration of menopausal hormone therapy as well as types of progestin. We did not have information on progesterone, as opposed to synthetic progestins.

Data for time of menopause were unavailable. However, this study was able to analyse the effect of exposure to hormone therapy restricted to the ages 45-55 years, which has not been done before, to our knowledge. Furthermore, we were able to report findings on use of hormone treatment around menopause by being able to isolate the association between use of cyclic hormone therapy and dementia risk. Cyclic hormone treatment causes regular bleeding and thus is primarily prescribed to perimenopausal women who are expected to have menstrual bleeding.

This study is of an observational design, therefore, we cannot exclude residual bias such as residual confounding by indication (ie, that women using hormone therapy have a predisposition to both menopausal vasomotor symptoms and dementia). Further studies are warranted to explore if the observed association in this study between menopausal hormone therapy use and increased risk of dementia illustrates a causal effect.

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Contributors: AM initiated the study. NP, AM, LM, and CTP contributed to the study design and methods. NP, AM, and CTP conducted the data management and analyses. NP, AM, and CTP had access to and verified the data. All authors contributed to interpretation. NP wrote the original manuscript draft, and all authors contributed to review and editing. All authors had access to statistically analysed data, approved the final version of the manuscript and agreed with submission for publication. NP is the guarantor of the study, takes full responsibility for the content and conduct of the study and controlled the decision to publish. The corresponding author attests that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted.

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Declarations of interest: All authors have completed the ICMJE uniform disclosure form at https://www.icmje.org/disclosure-of-interest/ and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years. NP, EAH, and AM declare no competing interests. LSM reports receiving grants from health insurance "Danmark", The Danish Cancer Society's Scientific Committee, and Novo Nordisk for research unrelated to the present study. LSM reports being Vice Chair of Danish Society for PharmacoEpidemiology and representative for Nordic PharmacoEpidemiological Network. CT-P reports receiving grants from Bayer and Novo Nordisk for research unrelated to the present study.

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: We plan to disseminate results to relevant medical societies and in the form of press releases from the authors' departments in accordance with the principles of the Danish Society for PharmacoEpidemiology.[30]

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

Ethical approval: According to Danish law, studies based on the national Danish registries are not required to gain patient consent or ethical approval. 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: This study was based on raw data only available with approval from the Danish Health Data Board and the Danish Data Protection Agency. Because the data were accessible at the individual level, data sharing is restricted by the General Data Protection Regulation of European Union law. The protocol and program code for the study can be accessed on request from the corresponding author.

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Web appendix: Online appendix