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ORIGINAL ARTICLE

Hormone therapy and disease activity in Danish women with multiple sclerosis: A population-based cohort study

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Abstract

Background and purpose: Sex differences in multiple sclerosis (MS) prevalence and disease course are thought to be driven by hormones. Exogenous exposure to estrogens may affect MS disease course. Thus, our aim was to investigate the association between hormone therapy (HT) and disease activity and disability accrual among women with MS.

Methods: A register-based cohort study was conducted with prospectively enrolled cases from the Danish MS registry. Information on hormone exposure was retrieved from the National Prescription Registry. Outcomes were relapse rate, relapse rate ratio, recurrent relapses, 6-month confirmed and sustained Expanded Disability Status Scale (EDSS) milestones 4 and 6, and recurrent EDSS worsening.

Results: In all, 3325 women were eligible for analyses, of whom 333 (10%) were ever on HT at some time during follow-up. We found no association between HT and disability accrual, although a trend for increasing risk with increasing length of use was seen. The risk of reaching 6-month confirmed and sustained EDSS 4 among users was 0.6 (95% confidence interval [CI] = 0.3–1.2) after <1 year of use and 1.4 (95% CI = 0.9–2.2) after >5 years of HT compared to never use. The risk of recurrent relapse was increased by 20% (95% CI = 1.0–1.4) among current users of HT compared to nonusers. However, the risk of recurrent relapses was driven by the first calendar period (1996–2005) before the introduction of high-efficacy disease-modifying therapy.

Conclusions: Our findings from this nationwide MS population suggest that HT does not affect disability accrual in women with MS, especially if used for <5 years.

KEYWORDS
cohort study, hormone therapy, menopause, multiple sclerosis

INTRODUCTION

Sex differences in multiple sclerosis (MS) prevalence and disease course are thought to be driven by sex hormones [1]. In women, hormone-related physiological changes including puberty, pregnancy, and menopause may regulate inflammatory activity and/or neurodegeneration in MS, which again may be further affected by exogenous exposure to sex hormones.

It is well known that the frequency of relapses decreases during the second and third trimester of pregnancy, whereas during the subsequent postpartum period, the frequency of relapses increases [2]. However, improved disease control before pregnancy

appears to have a protective effect on postpartum relapses [3]. This change in relapse activity is thought to be estrogen-mediated, but studies investigating the effect of pregnancy on long-term MS disability accumulation have mostly failed to find an association [4–10] although a few studies did show some long-term protective effects of pregnancy [11–13]. In contrast to studies of MS in pregnancy, there is less evidence for disease flares during other stages of a woman's reproductive lifespan, including menopause, although some evidence for disability worsening during menopause exists, reviewed in Ysrraelit and Correale [14].

Artificial estrogen in oral contraceptive pills has been studied to evaluate possible protective and therapeutic effects in the premenopausal population with MS. Both observational and interventional studies usually, but not always, point to a likely protective effect on MS risk, relapse risk, or disease activity [15,16]. If worsening of MS symptoms during menopause is mediated by fall in estrogen production, hormone therapy (HT) might mitigate these symptoms. However, studies aiming to support this theory are sparse and inconclusive [17–19]. Therefore, larger, observational studies with longitudinal assessment of disease course and assessing the influence of HT through the menopausal transition are required.

Thus, the objective of the present study was to investigate the association between use of HT and disease activity and disability accrual among women with MS aged 40–79 years using prospectively collected, nationwide register data.

METHODS

Study cohort and data sources

The study cohort consists of women diagnosed with relapsing–remitting MS in the Danish Multiple Sclerosis Registry (DMSR) [20] who were treated with a disease-modifying therapy (DMT) and aged 40–79 years between 1 January 1996, when the first DMT became available, and 1 August 2018. All exclusion criteria are illustrated in Figure S1.

The DMSR was established in 1956 and contains demographic data on all Danish patients with MS. Since 1996, it has been mandatory for all neurological departments in Denmark to regularly report clinical data on all patients with MS receiving DMT at treatment initiation and thereafter every 6–12 months to a central registry in a standardized way, ensuring a high data completeness [20]. The study cohort was linked to the National Prescription Registry by use of the unique social security number attached to every Danish citizen, where information on HT is available from 1 January 1995 onward. The National Prescription Registry contains information on the date of the redeemed prescriptions and the specific Anatomical Therapeutic Chemical code, dose, number of packages, defined daily doses, and route of administration [21]. From the Danish Cancer Registry, information on pre-entry cancer was retrieved, and Statistic Denmark delivered information on vital status, emigration, and education.

Follow-up and censoring

The study cohort was followed from their 40th birthday or start of first DMT treatment (if after 40 years of age, and up to 60 years at entrance) until an Expanded Disability Status Scale (EDSS) milestone or end of follow-up. We used start of first DMT treatment as entry date instead of diagnosis or onset, because only patients treated with DMT have been regularly monitored by neurologists. Censoring was done at time of death, emigration, loss of follow-up (defined as a visit followed by 36 months without a subsequent visit), 80 years of age, or end of data collection for DMSR and the National Prescription Registry: 1 August 2019. We chose 1 January 1996 as start date because DMT was introduced in 1996. The study design is illustrated in Figure S2.

Exposure to HT

The prescribed defined daily doses of HT were used to determine the periods of exposure. To account for the prolonged use of those taking less than the defined daily dose we included 4 months after the expiration of the prescription in all records of hormone exposure. Gaps between prescriptions of <4 months were filled prospectively; that is, a woman was classified as exposed to the drug at a given point in time if the dispensed supply from the last redemption had not run out or if it had run out within the past 4 months [22]. We only considered systemic hormone use in the present study, as we did not expect local use to affect MS disease course. Systemic hormone use includes hormones administered orally, transdermal, or by injections. Use of progestins was included if combined with estrogen in either continuous or cyclic regimens. A detailed description of the HT groups used for this study is found in Table S1.

For the association between HT use and relapse rate, we categorized hormone exposure as either "no use" or "current use," reflecting the time spend in either exposure group (illustrated in Figure S2). For EDSS outcomes, we were interested in both contemporary and long-term associations. We therefore also categorized HT as "never use," "previous use," and "current use" for EDSS milestones 4 and 6 according to the time spent in each category. Additionally, cumulative use of HT was categorized into "<1 year," "1–4 years," and "5+ years," and regimens were stratified into "estrogen only" or "combined therapy." HT prescribed before cohort entry but within the study follow-up was included in the assessment of cumulative duration of use.

Outcomes

We examined the following outcomes: relapse rate, relapse rate ratio, recurrent relapses, 6-month confirmed and sustained (at last visit) EDSS milestones 4 and 6 (referred to as "EDSS 4 and 6"), and recurrent EDSS worsening in the absence of relapses (i.e., within 90 days following a relapse). An EDSS worsening was defined as a

1.5-point increase if the baseline EDSS was 0, 1.0-point increase if the baseline EDSS was 1.0–5.5, and 0.5-point increase if the baseline EDSS was 6.0 or more. At each worsening event, we rebaselined the EDSS score so that the next EDSS score would have to be even larger to signify a new worsening event.

Statistical methods

For illustration of baseline demographic and clinical characteristics of the cohort at entry according to use of HT, we divided the cohort into those having ever versus never used hormones during follow-up, presented as numbers with their percentages and medians with interquartile ranges.

To examine the association between HT and relapses, we used two models: (i) a negative binomial regression model with age as time scale in 5-year age bands for relapse rates and (ii) an Andersen–Gill Cox proportional hazard model for recurrent events with age as the time axis [23]. Risk of reaching EDSS 4 and 6 was evaluated by a conventional Cox proportional hazard model according to HT, whereas an Andersen–Gill model was used for investigating the association between HT and recurrent EDSS worsening in the absence of relapses.

Use of hormones was included in all models as a time-dependent variable. We used attained age as time scale in all analyses to account for decreasing MS disease activity and increasing risk of reaching EDSS milestones with increasing age.

The following covariates were included in the statistical models: disease duration (numerical, per year increment), 24-month prebaseline relapse activity (for relapse outcomes only), closest EDSS score at cohort entry (5th–95th percentile of time since cohort entry: −124 to 118 days; categorical, three categories: 0, 1–2.5, 3.0–3.5), level of education at cohort entry (university degree, yes/no), and calendar year at cohort entry (categorical, three categories: 1996–2005, 2006–2010, 2011–2018). To take into account different baseline hazards of EDSS and calendar year categories, EDSS and calendar year were placed as strata in the Cox models. Additionally, in the Andersen–Gill models, number of prior events (i.e., relapses and EDSS worsening) was included as a time-dependent variable in the models. Tests and 95% confidence intervals (CIs) were based on Wald tests.

Sensitivity analyses

We examined possible cohort effects by analyzing cohorts of women entering the cohort in the first calendar period, and second and third combined, respectively. We expected that women entering the cohort in the first period had higher risk of reaching EDSS milestones and relapse rate compared to those entering the cohort later due to earlier treatment and accessibility of high-efficacy therapies since 2006. High efficacy DMTs are more effective at slowing progression compared to moderate efficacy DMTs. We restricted these analyses to recurrent events to have enough power to conduct these analyses.

RESULTS

In all, 3325 women were eligible for analyses, of whom 333 (10%) used hormones at some time during follow-up and an additional 5% had used hormones before study entry (Table 1). Median (5th–95th percentiles) follow-up was 8 years (2–8). The only notable differences among women ever on HT versus those never on HT during follow-up were calendar year of diagnosis and cohort entry. The total number of women in the cohort increased over time (Figure 1a), whereas the proportion on HT decreased from 9%–14% in 1998–2003 to 3%–4% in 2007–2018 (Figure 1b).

Current use of hormones was associated with a nonsignificant increased rate of reaching EDSS 4 (hazard ratio [HR] = 1.2, 95% CI = 0.8–1.7) and EDSS 6 (HR = 1.2, 95% CI = 0.7–1.9) compared to no use (Table 2). Risk estimates where higher for current use than for previous use when compared to never use for risk of reaching EDSS 4 (HR for current use = 1.2, 95% CI = 0.8–1.7; HR for previous use = 1.0, 95% CI = 0.8–1.4) and EDSS 6 (HR for current use = 1.1, 95% CI = 0.7–1.9; HR for previous use = 0.8, 95% CI = 0.6–1.2). Estrogen use was associated with a higher rate of reaching EDSS 4 and 6 (HR for EDSS 4 = 1.4, 95% CI = 0.8–2.5; HR for EDSS 6 = 1.3, 95% CI = 0.6–2.9) compared to combined therapy (HR for EDSS 4 = 1.1, 95% CI = 0.7–1.7; HR for EDSS 6 = 1.1, 95% CI = 0.6–2.0) compared to no use. However, these risk estimates were based on small numbers and were not significantly different from each other. The risk of reaching EDSS 4 increased from 0.6 (95% CI = 0.3–1.2) after <1 year of use to 1.4 (95% CI = 0.9–2.2) after >5 years of use compared to never use. The same pattern was seen for risk of reaching EDSS 6.

The association between HT and disability accumulation measured as hazard of recurrent EDSS worsening showed similar results to EDSS milestones 4 and 6, indicating no association between HT and disability accumulation (Table 3).

The risk of recurrent relapses increased by 20% (95% CI = 1.0–1.4) among current users of hormones compared to nonusers (Table 4). Similar risk estimates for recurrent relapses were found for use of estrogen and combined therapy compared to no HT. Mean adjusted relapse rates were 0.1 (95% CI = 0.1–0.1) for no use versus 0.2 (95% CI = 0.1–0.2) for current use, corresponding to a relapse rate ratio of 1.3 (95% CI = 0.9–1.7) for current use versus no use. The β-estimate for current use versus no use was 0.24, which translates into one additional relapse per 4 years use of hormones compared to nonuse.

Sensitivity analyses

When stratifying the cohort according to entry year, women who entered after 2005 had lower risk of recurrent EDSS worsening and

TABLE 1 Clinical and demographic characteristics at study entry among ever- and never-users of HT during follow-up ($N = 3325$)

Characteristic	Ever-use during follow-up	Never-use during follow-up	Total cohort
Total, *n* (%)	333 (10)	2992 (90)	3325
Age, years, median (p5–p95)	44 (40–55)	42 (40–54)	42 (40–54)
Age at MS onset, years, median (p5–p95)	37 (22–50)	36 (22–50)	36 (22–50)
Age at MS diagnosis, years, median (p5–p95)	41 (28–53)	40 (25–53)	40 (25–53)
Disease duration, years, median (p5–p95)	7 (0–23)	6 (0–21)	6 (0–21)
Calendar year at diagnosis, median (p5–p95)	2001 (1988–2014)	2006 (1992–2015)	2006 (1992–2015)
Calendar year, median (p5–p95)	2006 (1997–2015)	2010 (2000–2016)	2010 (1999–2016)
24-month relapse activity prior to cohort entry, mean (±SD)	0.97 (±1.2)	1.02 (±1.1)	1.01 (±1.1)
EDSS score, median (p5–p95)	2.5 (0–3.5)	2.0 (0–3.5)	2.0 (0–3.5)
DMT efficacy, *n* (%)			
Moderate efficacy	304 (91)	2666 (89)	2970 (89)
High efficacy	19 (6)	249 (8)	268 (8)
No DMT[a]	10 (3)	77 (3)	87 (3)
Higher education, *n* (%)	102 (31)	1030 (34)	1132 (34)
Use of HT, *n* (%)			
Past	18 (5)	149 (5)	167 (5)
Current	83 (25)	-	83 (2)
Never	232 (70)	2843 (95)	3075 (92)
Postbaseline characteristics			
Total follow-up, years, median (p5–p95)	12 (4–21)	8 (2–18)	8 (2–18)
Age at end of follow-up, years, median (p5–p95)	57 (46–70)	52 (43–65)	52 (43–67)
Rate of visits during follow-up, median (p5–p95)	1.4 (1–3)	1.5 (1–3)	1.5 (1–3)

Abbreviations: DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; HT, hormone therapy; MS, multiple sclerosis; p5–p95, 5th–95th percentiles.

[a]Treatment pause, i.e., no DMT treatment within 3 months.

recurrent relapses for HT use versus no use (HR = 0.8, 95% CI = 0.6–1.2; HR = 1.0, 95% CI = 0.7–1.3, respectively) compared to women who entered the cohort before 2006. In this cohort of women entering from 1996 to 2005, risk estimates for recurrent EDSS worsening and recurrent relapses for HT use versus no use were higher (HR = 1.2, 95% CI = 1.0–1.5; HR = 1.2, 95% CI = 1.0–1.4, respectively; Table 5).

DISCUSSION

In this nationwide cohort study of DMT-treated women with MS with up to 22 years of follow-up and 29,588 accumulated person-years, we found no overall association between HT and disability accrual, although a trend toward increased risk of disability with longer use of hormones was observed. We also found a 20% increased risk of recurrent relapses among women currently using hormones compared to nonuse, but with minimal clinical significance. When we restricted cohort entry to the period after 2006, when the first high-efficacy DMT was introduced, we found no association with recurrent relapses and a nonsignificant decreased risk of recurrent EDSS worsening. Conversely, when we limited the analyses to women starting DMT before 2006, the risks of recurrent EDSS worsening and relapses were increased. Thus, the risk of recurrent relapses seems to be driven by the first calendar period.

Sex hormones are thought to affect the immune system through hormone receptors on immune cells [24]. Endogenous estrogens consist of estrone, 17β-estradiol (E2), and estriol (E3). E3 is mainly produced during pregnancy, whereas E2 is the predominant form in premenopausal women and is the form used in HT. E2 has been shown to have anti-inflammatory effects by both inhibition of proinflammatory cytokines and induction of anti-inflammatory cytokines, but at lower levels (i.e., nonpregnant concentrations), E2 stimulates proinflammatory cytokines, resulting in a proinflammatory environment in T cells from MS patients [25]. This is in contrast to E3, which also has anti-inflammatory properties at similar low nonpregnant levels [26]. This paradox of opposing effects on the immune system by E2 could explain the greater female prevalence of autoimmune diseases including MS as well as the reduced disease activity in MS women during pregnancy, where concentrations of both E2 and E3 are high [27]. Likewise, this could also explain the increased risk of relapses in patients on HT found in the present study. The doses

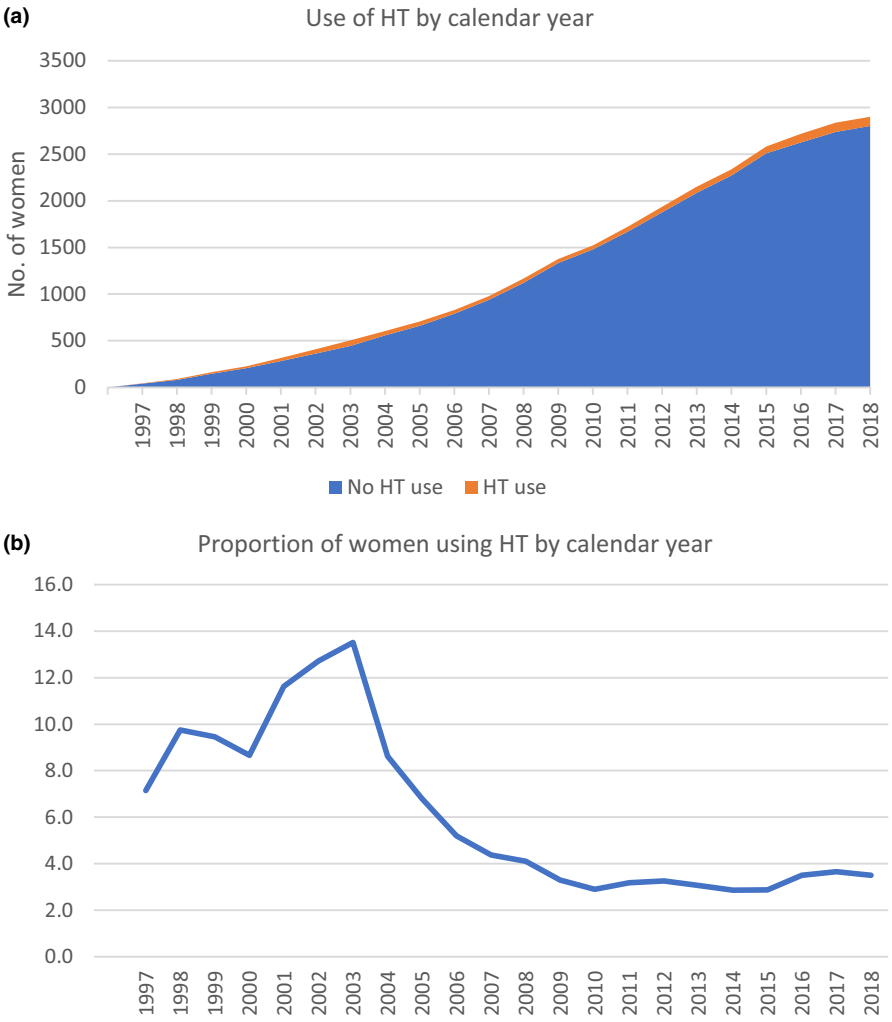

FIGURE 1 (a) Absolute number of women according to use of hormone therapy (HT) by calendar year as of 1 August. (b) Proportion of women using HT by calendar year as of 1 August [Colour figure can be viewed at wileyonlinelibrary.com]

used in HT are comparable to those seen during normal menstrual cycle and, hence, could promote a proinflammatory environment, specifically in women with MS, resulting in increased risk of relapses.

Progesterone, which is also present at high levels during pregnancy, has both anti-inflammatory and neuroprotective properties. Progesterone has shown such promising effects in promoting myelin repair in animal models [28] that a randomized clinical trial was initiated with the aim of preventing postpartum relapses [29]. Both progesterone and E2 were administered. However, the trial was prematurely halted due to lack of effect on relapse rate and the development of new lesions on magnetic resonance imaging (MRI), potentially because progesterone mainly seems to affect remyelination, not relapses [27]. This could also explain the difference in risk estimates on EDSS milestones for use of estrogen compared to combined therapy. MS patients with a high ratio of E2 to progesterone had a significantly greater number of active MRI lesions than those with a low ratio [30]. However, our results need to be confirmed in larger cohort studies.

We found no other observational study examining the association between use of hormones and MS disease activity in a population-based cohort. Three studies using self-administered questionnaires have examined the association between the influence on menopause including HT on MS disease, with conflicting results [18,19,31]. The studies included 19–513 patients, of whom 11%–17% of the study patients had ever used any hormones, systemic or local. These studies mainly focused on the age at menopause, as some studies demonstrated changes in disease severity during menopause [32,33], whereas others have failed to find such a change in disease severity related to menopause [34,35]. It has been argued that age and disease duration alone are more important independent risk factors for MS disease severity than menopause [36]. We did not focus on the age at menopause, as we did not have information about this in our register. However, the objective of this study was the overall association between HT and both long-term disability and disease activity with adjustment for age and disease duration.

The management and treatment options for MS have changed considerably since 1996, which most likely explains the cohort effect found in the present study. DMTs are primarily directed against the inflammatory processes in MS, aiming at preventing relapses, and with the introduction of the first high-efficacy treatment, natalizumab, in Denmark in 2006, management of disease activity has

TABLE 2 Association between HT and cumulative disability in women with multiple sclerosis: Risk of reaching confirmed and sustained EDSS 4 and 6

			Risk of reaching 6-month confirmed and sustained EDDS					
			Hazard ratio EDSS 4 (95% CI)				Hazard ratio EDSS 6 (95% CI)	
HT	Person-years[a]	Events	Crude[b]	Adjusted[c]	Person-years[a]	Events	Crude[b]	Adjusted[c]
Non use	24,827	573	1.0	1.0 (ref.)	26,985	262	1.0	1.0 (ref.)
Current	961	34	1.4	1.2 (0.8–1.7)	1069	17	1.4	1.2 (0.7–1.9)
Never	22,660	515	1.0	1.0 (ref.)	24,488	233	1.0	1.0 (ref.)
Previous	2167	58	1.1	1.0 (0.8–1.4)	2498	29	0.9	0.8 (0.6–1.2)
Current	961	34	1.4	1.2 (0.8–1.7)	1069	17	1.3	1.1 (0.7–1.9)
Regimen								
Non use	24,827	573	1.0	1.0 (ref.)	26,985	262	1.0	1.0 (ref.)
Estrogen	307	13	1.6	1.4 (0.8–2.5)	356	7	1.6	1.3 (0.6–2.9)
Combined	654	21	1.2	1.1 (0.7–1.7)	713	10	1.2	1.1 (0.6–2.0)
Length								
Never	23,738	546	1.0	1.0 (ref.)	25,683	243	1.0	1.0 (ref.)
<1 year	593	10	0.7	0.6 (0.3–1.2)	650	4	0.9	0.8 (0.2–3.3)
1–4 years	927	30	1.3	1.1 (0.8–1.6)	1064	18	1.1	0.9 (0.4–2.0)
5+ years	530	21	1.5	1.4 (0.9–2.2)	657	14	1.8	1.6 (0.8–3.2)

Abbreviations: CI, confidence interval; EDSS, Expanded Disability Status Scale; HT, hormone therapy

[a]Person-years is the cumulative number of years for all women while belonging to the given exposure category. "Non use" is person-time not exposed regardless of past exposure, "previous" HT refers to person-time where the women was not exposed, but had been exposed in the past, and "current" HT is person-time when the women was exposed.

[b]Adjusted for age.

[c]Additionally, adjusted for disease duration, education, EDSS and calendar year at cohort entry.

TABLE 3 Association between exposure to HT and cumulative disability in women with multiple sclerosis

			Hazard ratio of recurrent EDSS worsening in the absence of relapses (95% CI)		
HT use	Person-years[a]	No. of events	Crude[b]	Adjusted[c]	Fully adjusted[d]
Non use	28,435	2766	1.0 (ref)	1.0 (ref)	1.0 (ref)
Current	1153	114	1.1 (0.9–1.3)	1.1 (0.9–1.3)	1.1 (0.9–1.3)
Never	25,663	253	1.0 (ref)	1.0 (ref)	1.0 (ref)
Previous	2773	236	0.9 (0.8–1.1)	0.9 (0.8–1.1)	0.9 (0.8–1.1)
Current	1153	114	1.1 (0.9–1.3)	1.1 (0.9–1.3)	1.1 (0.9–1.3)
Regimen					
Non use	28,435	2766	1.0 (ref)	1.0 (ref)	1.0 (ref)
Estrogen	378	42	1.2 (0.9–1.7)	1.2 (0.9–1.7)	1.2 (0.9–1.7)
Combined	775	72	1.0 (0.8–1.3)	1.0 (0.8–1.3)	1.0 (0.8–1.3)

Abbreviations: CI, confidence interval; HT, hormone therapy.

[a]Person-years is the cumulative number of years for all women while belonging to the given exposure category. "Non use" is person-time not exposed regardless of past exposure, "previous" HT use refers to person-time where the women was not exposed, but had been exposed in the past, and "current" HT use is person-time when the women was exposed.

[b]Adjusted for age.

[c]Additionally, adjusted for disease duration, education, EDSS and calendar year at cohort entry.

[d]Additionally, adjusted for number of prior EDSS worsening events.

TABLE 4 Association between exposure to HT and disease activity in women with multiple sclerosis

HT use	Person-years[a]	No. of events	Hazard ratio of recurrent relapses (95% CI)		
			Crude[b]	Adjusted[c]	Fully adjusted[d]
Non use	28,435	4882	1.0 (ref)	1.0 (ref)	1.0 (ref)
Current	1153	229	1.4 (1.3–1.6)	1.4 (1.2–1.6)	1.2 (1.0–1.4)
Regimen					
Non use	28,435	4882	1.0 (ref)	1.0 (ref)	1.0 (ref)
Estrogen	378	84	1.7 (1.4–2.1)	1.6 (1.3–2.0)	1.2 (1.0–1.5)
Combined	775	145	1.3 (1.1–1.6)	1.3 (1.1–1.5)	1.2 (1.0–1.4)

			Adjusted[c] mean relapse rates (95% CI)	Adjusted[c] relapse rate ratio (95%CI)	Adjusted[c] β-estimates (95%CI)
Non use	28,361	4882	0.1 (0.1–0.1)	1.0 (ref)	0.00 (ref)
Current	115	229	0.2 (0.1–0.2)	1.3 (0.9–1.7)	0.24 (−0.07;0.55)
Regimen					
Non use	28,361	4882	0.1 (0.1–0.1)	1.0 (ref)	0.00 (ref)
Estrogen	375	84	0.2 (0.1–0.2)	1.4 (0.9–2.1)	0.31 (−0.09;0.72)
Combined	775	145	0.1 (0.1–0.2)	1.2 (0.8–1.8)	0.21 (−0.19;0.61)

Note: In the negative binomial regression model, the age-group 70-75 is removed from analyses because none of the women in this age group experienced an event. The number of person-years are therefore lower in these analyses compared to the Andersen-Gill models.

Abbreviations: CI, confidence interval; HT, hormone therapy.

[a]Person-years is the cumulative number of years for all women while belonging to the given exposure category. "Non use" is person-time not exposed regardless of past exposure, "previous" HT use refers to person-time where the women was not exposed, but had been exposed in the past, and "current" HT use is person-time when the women was exposed.

[b]Adjusted for age.

[c]Additionally, adjusted for disease duration, education, pre-baseline relapse activity and calendar year at cohort entry.

[d]Additionally, adjusted for number of prior relapses.

TABLE 5 Subgroup and sensitivity analyses

Description of analysis	Person-years, use/no use	Events, *n*, use/no use	Fully adjusted estimate (95% CI)
Women entering the cohort 2006–2018:			
HR for recurrent EDSS worsening for current use of HT vs. no use (ref.)	407/17,141	30/1666	0.8 (0.6–1.2)
HR for recurrent relapses for current use of HT vs. no use (ref.)	407/17,141	48/2751	1.0 (0.7–1.3)
Women entering the cohort 1996–2005:			
HR for recurrent EDSS worsening for current use of HT vs. no use (ref.)	746/11,294	84/1100	1.2 (1.0–1.5)
HR for recurrent relapses for current use of HT vs. no use (ref.)	746/11,294	181/2131	1.2 (1.0–1.4)

Abbreviations: CI, confidence interval; EDSS, Expanded Disability Status Scale; HR, hazard ratio; HT, hormone therapy; ref., reference.

improved [37]. Also, early escalation and intensive treatment start have resulted in reduced disease activity as well as postponing MS disability accrual in recent years [38,39]. Lastly, the revised 2010 [40] and 2017 [41] McDonald diagnostic criteria for MS have resulted in both earlier diagnosis and in diagnosis of patients with a more benign disease course [42]. We therefore assume that even if HT promotes a proinflammatory environment in MS patients, as seen in women entering the cohort from 1996 to 2006, this effect could potentially be alleviated with early and more aggressive treatment of MS.

Our study did not take into account the alleviating effect of hormones on symptoms related to menopause unrelated to MS symptoms. Interestingly, a small survey study ($N = 95$), reported that systemic use of HT was associated with better physical quality of life in postmenopausal women with MS [43]. It is therefore important to weigh the risk associated with HT with the overall quality of life considering both MS-related symptoms and those related specifically to menopause. Our finding that the risk of disability was increased with >5 years of hormone use is in line with

the recommendation for HT by the Danish Health Authority; HT is relevant primarily within the first 10 years from menopause, and at the lowest possible dosage, for the shortest possible length of use (maximum = 5 years), and should generally not be used after age 60 years [44].

Only 15% of our MS population had ever used systemic HT (of whom 10% used systemic HT during study follow-up), which is nearly half the prevalence of what other Danish cohort studies have shown [45–49]. This is first of all because our study mainly represents hormone exposure during the years after 2003, when the proportion of women on HT started to decline markedly [50] as we were also able to show. Conversely, the other mentioned studies represent exposure windows from the years prior to 2003. Second, the age span in our study cohort was small, and we included women from 40 years of age instead of 50 years of age as in the other referenced studies. According to a population-based study describing HT in Denmark in the years 1996–2004, the largest prevalence of women on HT in Denmark was in women aged 55–59 years [50]. As the median age at end of follow-up in the present study among nonexposed subjects was 52 years, we thereby most likely miss HT among some women starting on HT in their mid to late fifties (i.e., after end of follow-up). Third, the other studies were population-based, whereas our study is limited to a very small population of women with a chronic disease. The MS survey studies had similar prevalence of HT in their cohorts [18,19,31]. We found a similar distribution, with one third of the follow-up time on estrogen therapy and two thirds on combined regimens, as in the other Danish cohort studies [45,46,49,50].

It is possible that the association between HT and relapses was influenced by women being more prone to take hormones during episodes with relapses. In addition, we cannot exclude the possibility of unmeasured confounding due to the observational design used. Also, there is a risk of misclassification if a woman stops taking HT even though the prescription length indicates she is still a user. The direction of such bias would be toward the null and hence underestimate our results. The strength of our study is the unselected and homogenous population of all Danish women with MS treated with DMT with up to 22 years of follow-up of prospectively collected data. In Denmark, health care is free to all citizens. Therefore, our registries are not biased by inclusion of specific hospitals, age groups, insurance policies, or social or financial status.

In conclusion, our findings from this nationwide MS population suggest that HT does not affect disability accrual or disease activity in women with MS treated with DMT, especially in recent years and if used for <5 years as recommended by the Danish health authorities. Together with the possible association between HT and relapses, this is information to take into account in handling MS women with menopausal complains.

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CONFLICT OF INTEREST

T.I.K. has served on a scientific advisory board for Novartis and has received support for congress participation from Biogen. M.M. has served on scientific advisory boards for Biogen, Sanofi, Roche, Novartis, Merck, Abbvie, and Alexion; has received honoraria for lecturing from Biogen, Merck, Novartis, Sanofi, and Genzyme; and has received research support and support for congress participation from Biogen, Genzyme, Roche, Merck, and Novartis. Ø.L. has nothing to disclose.

AUTHOR CONTRIBUTIONS

Tine Iskov Kopp: Conceptualization (equal), data curation (equal), formal analysis (lead), methodology (lead), visualization (lead), writing–original draft (lead). **Øjvind Lidegaard:** Conceptualization (equal), data curation (equal), methodology (equal), writing–review & editing (equal). **Melinda Magyari:** Conceptualization (equal), data curation (equal), funding acquisition (lead), methodology (equal), writing–review & editing (equal).

ETHICAL STATEMENT

Ethics approval and informed consent are not required in Denmark for studies based on national health registries. Approval to store and analyze data was given by the Danish Data Protection Agency.

DATA AVAILABILITY STATEMENT

Because of data protection regulation, data cannot be shared directly by the authors. Data are accessible to authorized researchers after application to the Danish Data Protection Agency, the Danish Health Data Authority, and the board of the Danish Multiple Sclerosis Group.

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