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RESEARCH ARTICLE

Association between menopausal hormone therapy and risk of neurodegenerative diseases: Implications for precision hormone therapy

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Abstract

Introduction: The impact of menopausal hormone therapy (HT) on age-associated Alzheimer's and neurodegenerative diseases (NDDs) remains unresolved. To determine the effect of HT, formulation, type, and duration on risk of NDDs, a retrospective analysis was performed using a 10-year Humana claims dataset.

Methods: Study population included women aged 45 years or older with or without claim records of HT medications. Patients diagnosed with NDDs including Alzheimer's disease (AD), Parkinson's disease (PD), dementia, multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS) were identified. Relative risk (RR) ratios and 95% confidence intervals (CI) for combined NDDs, or AD, PD, dementia, MS, and ALS were determined. Cumulative hazard ratios were determined to investigate the association between HT and NDDs at different age groups.

Results: In 379,352 women with or without claim records of HT, use of HT was associated with significantly reduced risk for combined NDDs (RR 0.42, 95% CI 0.40–0.43, $P < 0.001$). Average follow-up time was 5.1 [2.3] years. Formulations containing natural steroids 17β-estradiol and/or progesterone were associated with greater reduction in NDD risk. Oral- HT users showed significantly reduced RRs (0.42, 0.41–0.44, $P < 0.001$) for combined NDDs compared to non-HT users. The RRs for transdermal-HT users were significantly decreased for all-cause dementia (0.73, 0.60–0.88, $P = 0.001$) and MS (0.55, 0.36–0.84, $P = 0.005$). Greatest reduction in risk of NDD, AD, and dementia emerged in patients aged 65 years or older. Further, the protective effect of long-term therapy (>1 year) on combined NDDs, AD, PD, and dementia was greater compared to short-term therapy (≤1 year).

Discussion: HT was associated with reduced risk of all NDDs including AD and dementia, with greater duration of therapy and natural steroid formulations associated with greater efficacy. These findings advance precision HT to prevent NDDs including AD.

KEYWORDS
age-associated neurodegenerative diseases, Alzheimer's disease, dementia, estrogen, menopausal hormone therapy, precision hormone therapy, progestin, retrospective analysis

1 | INTRODUCTION

Neurodegenerative diseases (NDDs) associated with aging are a major public health concern, as the magnitude and proportion of populations aged 65 years and older continue to increase.[1] Women are at a greater lifetime risk for Alzheimer's disease (AD) relative to men,[2] which may be associated with hormonal changes during and after menopause.[3] For decades, the association between menopausal hormone therapy (HT) and the incidence of NDDs has been debated. Findings from clinical studies have not been consistent due to different characteristics of study participants and methodological approaches for study analyses,[4–13] although preclinical studies have more clearly indicated the potential of estrogen therapy to protect against NDDs.[14–18]

Results from ancillary studies of randomized clinical trials including the Women's Health Initiative Memory Study (WHIMS), Kronos Early Estrogen Prevention Cognitive and Affective Ancillary Study (KEEPS-cog), and Early versus Late Intervention Trial with Estradiol-Cognitive Endpoints (ELITE-cog) indicated no beneficial or harmful effect of HT on cognitive function.[8,19–22] These clinical trials were conducted in postmenopausal women with no menopausal symptoms and who had aged passed the "critical window" for efficacy of hormone therapy to impact estrogenic action in brain.[23–25] By design, participants were uniformly treated with one HT formulation, dose, and duration of therapy. .[23–25] Thus, the impact of hormone therapy intervention during which menopausal symptoms occurred, for which hormone therapy was developed, was not evaluated.

In contrast to clinical trials, multiple observational studies have indicated a protective association between HT and reduced risk of NDDs.[10,26–31] Data from observational studies were based on prescription records regarding HT use. HT prescriptions were based on a clinician's counsel, based on menopausal symptoms during the menopausal transition and on best practice for dose, type, and duration based on the individual's comorbidities and could be changed based on individual response profile. However, women who receive HT are generally healthier, more educated, and more socioeconomically advantaged relative to non-users, which could influence outcomes in observational studies.

Continued controversy regarding benefits and risks of HT in clinical studies may be due to a lack of precision medicine in HT, as multiple factors can influence its efficacy and safety.[32] Previous reports have indicated a critical window for therapeutic benefit for HT within the context of the healthy cell bias of estrogen action[33] and a critical window for HT therapeutic efficacy.[14,34] Further, the progestin within a HT formulation can significantly impact the effects of and response to HT. Hormonal fluctuations during the peri- or postmenopause are also associated with changes in the peripheral and neuro-immune systems.[35–37] Moreover, genetic (polymorphisms in metabolizing enzymes and apolipoprotein E [*APOE*] status) and medical conditions are known modulate HT efficacy.[38–47] Collectively, these studies indicate the need for precision HT to increase predictive efficacy and safety.

Toward precision HT, this retrospective analysis was designed to investigate the association between HT and the risk of NDDs in pharmaceutical perspectives. The aims of this study were to evaluate the effects of: (1) the U.S. Food and Drug Administration (FDA)–approved HT medications including estrogens, progestins, and their combinations; (2) each independent HT; (3) route of administration (oral vs. transdermal administration); and (4) duration of HT, on the risk of NDDs in women.

2 | METHODS

2.1 | Study population

A retrospective analysis was performed using insurance claim records of women aged 45 years or older in the Humana dataset (Louisville, Kentucky), a U.S. health insurance company, from 2007 to 2016. Patients were included in the study if they were enrolled in medical and pharmacy insurance for a minimum of 6 months before and 2 years after defined index dates. The index dates were the first date of a prescription for HT for the treatment group, and maximum 6 months (wash-out period) after the first patient claim record in the Humana database for the control group. Patients were excluded from the study if their claim records included International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) or ICD-10-CM codes for the diagnosis of brain cancer and/or brain surgery. In addition, patients were excluded if they had any previous diagnosis of NDDs including AD, Parkinson's disease (PD), dementia, multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS) before the first date of claim records for the prescription of any type of HT (ICD codes listed in Table S1 in supporting information).

2.2 | Study design and strategy

Based on prescription records of HT, the study population was divided into untreated control and treatment groups (Figure 1). Medications considered in this study included hormone therapies approved by the FDA and administered via oral, transdermal, and injection routes for the treatment of menopausal symptoms. The control population consisted of patients for which no medical claims of HT were present in their record. Patients in the treatment group had a claim record of at least one medication prescribed for HT.

Hormone therapies were identified by Drug Codes and National Drug Codes (NDCs) by using the commercial name of the medications (Table S2 in supporting information). Hormone therapies administered via a vaginal route were not considered in this analysis, as serum estrogen levels with use of low-dose vaginal estrogen are generally below the average level for postmenopausal women.[48] Contraceptive drugs used for birth control were not included in this study. The study outcome was defined as the incidence of NDDs at least 1 year after the index date to remove other potential medical and pharmaceutical effects on NDDs prior to the initiation of HT.

The effect of each hormone therapy on the risk of NDDs was investigated by selecting 14 HTs highly prescribed for women (Figure 2B) in the Humana dataset compared to other HTs. Individual HT groups were created from the propensity score matched treatment population, and the number of NDD patients in each HT group was determined to evaluate the incidence of each NDD. To investigate the effect of route of administration on the risk of NDDs, populations within inclusion and exclusion criteria were stratified into non-HT (control), oral-HT, and transdermal-HT. To evaluate the impact of HT duration on the risk of NDDs, analyses were conducted for durations of ≤1 year, 1 to 3 years, 4 to 6 years, and ≥6 years. The relative risk (RR) ratio of NDDs was determined by comparing the number of NDD patients between short-term (≤1 year) and long-term users (1 to 3 years, 4 to 6 years, or ≥6 years).

Comorbidities considered in this analysis were cardiovascular disease (CVD), type 2 diabetes (T2DM), hypertension (HP), stroke, chronic kidney disease (CKD), and chronic obstructive pulmonary disease (COPD; Table S1).

This report follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. This study received a waiver by the University of Arizona Institutional Review Board. Requirements for informed consent were waived because the data were deidentified.

2.3 | Statistical methods

Propensity score matching was performed to balance demographic and comorbidity characteristics between control (non-HT) and treatment populations as described in Branigan et al.[49] and Torrandell-Haro et al.[50] Prior to propensity score matching, logistic regression was initially used to estimate the probability for each patient receiving HT based on confounding variables including age, race, region, Charlson Comorbidity Index (CCI), comorbidity claim records, and the year of the first patient record in the Humana dataset. Next, control and treatment populations were propensity score matched by incorporating statistically significant confounding variables identified in the regression model. Further, to investigate the effect of route of administration (oral and transdermal) on NDD risk, additional logistic regression and propensity score matching were performed between control (non-HT) and each treatment (oral or transdermal) group.

Unpaired Mann-Whitney test was performed to determine statistical significance ($P < 0.05$) between control and treatment populations comparing the demographic and clinical characteristics using GraphPad Prism 8. The RR ratio with 95% confidence interval (CI) and *P*-value was estimated by Fisher's exact test using GraphPad Prism 8.

Cumulative hazard ratios were determined using propensity score matched control and treatment populations (n = 379,352; Table 1). For this analysis, the populations were stratified by six different age groups (60–64, 65–69, 70–74, 75–79, 80–84, and 85–89 years), and cumulative hazard curves for all combined NDDs, AD, and dementia were generated in GraphPad Prism 8.

HIGHLIGHTS

- Menopausal hormone therapy reduced Alzheimer's and neurodegenerative disease risk.
- Risk reduction was greater for formulations containing natural steroids.
- Longer duration of hormone therapy was associated with greater risk reduction.
- Risk reduction became apparent in women aged 65 years or older.
- Precision medicine can be advanced by optimizing type, route, and duration of therapy.

RESEARCH IN CONTEXT

1. **Systematic review**: The effect of menopausal hormone therapy (HT) on the incidence of neurodegenerative diseases (NDDs) remains uncertain. Multiple factors could contribute to disparate findings including variance in characteristics of baseline study population (demographic and comorbidity conditions), type, route, and duration of hormone therapy and menopausal status at the time of treatment.
2. **Interpretation**: Women who received HT for menopausal symptoms had significantly reduced risk of NDDs compared to non-users after adjustment for differences in demographic and comorbidity characteristics between non- and HT-users. Regardless of route of administration, HT containing natural steroids with longest exposure exerted greatest risk reduction for NDDs.
3. **Future directions**: Precision HT can be advanced by considering type, route, and duration of therapy. Further, controlling for comorbidities may be a critical variable for detecting impact of HT on NDDs and for identifying women appropriate for HT.

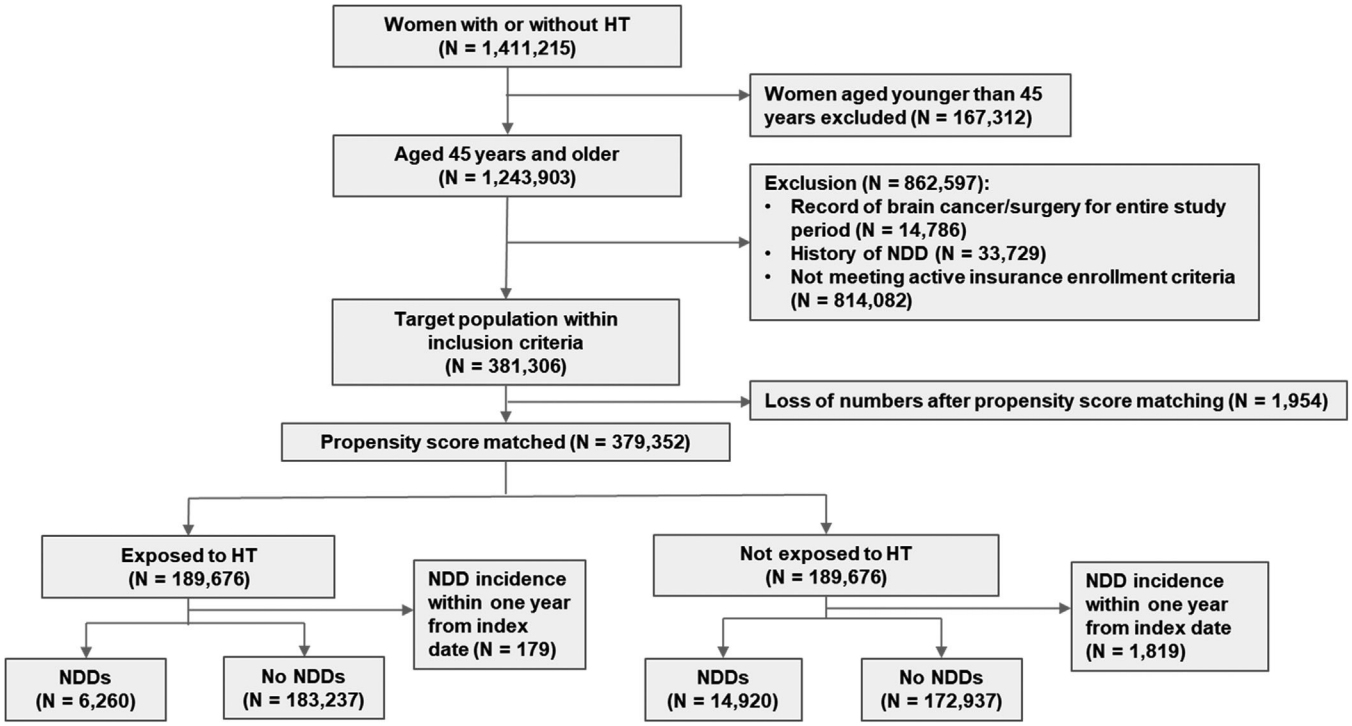
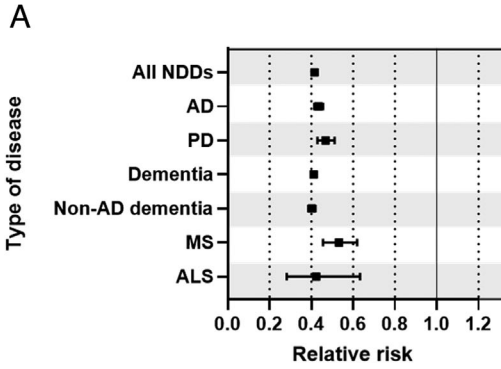


FIGURE 1 Study design for a retrospective analysis for the association between menopausal hormone therapy (HT) and risk of neurodegenerative diseases (NDDs). Propensity score matching was performed to balance demographic and comorbidity characteristics between untreated control and treatment populations prior to the identification of the number of NDD patients in control and treatment groups

A

Type of disease	Control, No. (%) (N=189,676)	Treatment, No. (%) (N=189,676)	RR (95% CI)	NNT	P-value
All NDDs	14,920 (7.87)	6,260 (3.30)	0.42 (0.40 to 0.43)	21.56	<0.001
AD	5,414 (2.85)	2,361 (1.24)	0.43 (0.41 to 0.46)	61.81	<0.001
PD	1,574 (0.83)	739 (0.39)	0.47 (0.43 to 0.51)	226.3	<0.001
Dementia	12,711 (6.70)	5,263 (2.77)	0.41 (0.40 to 0.43)	25.22	<0.001
Non-AD dementia	7,896 (4.16)	3,192 (1.68)	0.40 (0.39 to 0.42)	40.01	<0.001
MS	473 (0.25)	252 (0.13)	0.53 (0.46 to 0.62)	855.9	<0.001
ALS	78 (0.04)	33 (0.02)	0.42 (0.28 to 0.63)	4,215	<0.001



B

Type of hormone therapy	Active ingredient	Mode of administration/type of dosage form	Number of HT users	RR (95% CI)	P-value
Estrace	Estradiol	PO tablet	63,164	0.45 (0.43 to 0.46)	<0.001
Vivelle/Vivelle-dot	Estradiol	TD patch	6,553	0.19 (0.16 to 0.23)	<0.001
Climara	Estradiol	TD patch	613	0.23 (0.13 to 0.40)	<0.001
Estraderm	Estradiol	TD patch	349	0.54 (0.33 to 0.88)	0.010
Estrogel	Estradiol	TD gel	877	0.16 (0.09 to 0.28)	<0.001
Divigel	Estradiol	TD gel	847	0.22 (0.14 to 0.37)	<0.001
Evamist	Estradiol	TD spray	796	0.21 (0.12 to 0.35)	<0.001
Premarin	Conjugated estrogen	PO tablet or IM injection	123,982	0.42 (0.40 to 0.43)	<0.001
Enjuvia	Synthetic conjugated estrogens	PO tablet	898	0.43 (0.31 to 0.61)	<0.001
Cenestin	Synthetic conjugated estrogen	PO tablet	524	0.26 (0.15 to 0.46)	<0.001
Menest	Esterified estrogen	PO tablet	480	0.42 (0.26 to 0.67)	<0.001
Delestrogen	Estradiol valerate	IM injection	319	0.51 (0.30 to 0.86)	0.009
Prempro	Conjugated estrogen/medroxyprogesterone acetate	PO tablet	6,197	0.30 (0.26 to 0.36)	<0.001
ET+Prometrium	Progesterone	PO capsule	4,865	0.19 (0.15 to 0.23)	<0.001

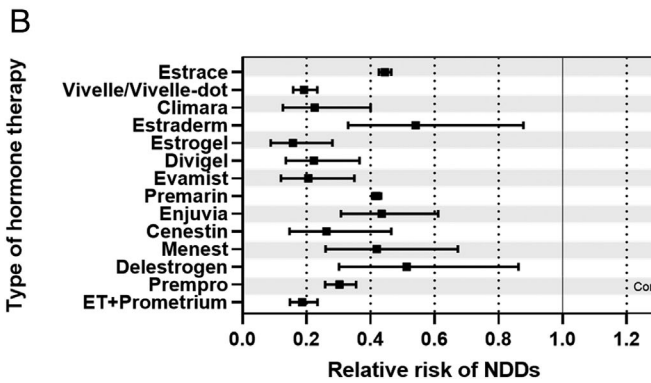


FIGURE 2 A, Relative risk (RR) of combined neurodegenerative diseases (NDDs), Alzheimer's disease (AD), Parkinson's disease (PD), dementia, multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS) in menopausal hormone therapy (HT) users, and (B) RR of combined NDDs in women receiving different type of HT; (A) indicates that the use of HT was associated with significantly reduced risk of NDDs. The magnitude of risk reduction for combined NDDs varied by composition of HT as presented in (B)

TABLE 1 Characteristics of study population prior to or after propensity score matching (PSM)

Variable	Control (not adjusted by PSM), no. (%)	Treatment (not adjusted by PSM), no. (%)	*P*-value	Control (PSM-adjusted), no. (%)	Treatment (PSM-adjusted), no. (%)	*P*-value
Total	190,945	190,361		189,676	189,676	
Age						
45–49	11,559 (6.05)	8364 (4.39)	0.912	11,442 (6.03)	8264 (4.36)	0.912
50–54	10,874 (5.69)	12,597 (6.62)		10,753 (5.67)	12,578 (6.63)	
55–59	12,156 (6.37)	11,907 (6.25)		12,028 (6.34)	11,869 (6.26)	
60–64	13,000 (6.81)	10,283 (5.40)		12,898 (6.80)	10,223 (5.39)	
65–69	45,219 (23.68)	47,754 (25.09)		44,946 (23.70)	47,629 (25.11)	
70–74	39,245 (20.55)	39,690 (20.85)		39,034 (20.58)	39,546 (20.85)	
75–79	27,128 (14.21)	27,649 (14.52)		26,971 (14.22)	27,554 (14.53)	
80–84	17,438 (9.13)	16,865 (8.86)		17,345 (9.14)	16,796 (8.86)	
85–89	4746 (2.49)	4222 (2.22)		4724 (2.49)	4210 (2.22)	
90 and over	9580 (5.02)	11,030 (5.79)		9535 (5.03)	11,007 (5.80)	
Race						
Unknown	32,097 (16.81)	22,027 (11.57)	0.620	31,743 (16.74)	21,713 (11.45)	0.620
White	147,855 (77.43)	153,125 (80.44)		147,018 (77.51)	152,763 (80.54)	
Black	7361 (3.86)	8634 (4.54)		7307 (3.85)	8627 (4.55)	
Other	1110 (0.58)	1615 (0.85)		1101 (0.58)	1613 (0.85)	
Asian	598 (0.31)	1484 (0.78)		593 (0.31)	1484 (0.78)	
Hispanic	1765 (0.92)	2862 (1.50)		1755 (0.93)	2862 (1.51)	
North American Native	159 (0.08)	614 (0.32)		159 (0.08)	614 (0.32)	
Comorbidities						
CVD	10,540 (5.52)	3092 (1.62)	0.132	10,476 (5.52)	2931 (1.55)	0.132
T2DM	36,480 (19.10)	13,639 (7.16)		36,265 (19.12)	13,259 (6.99)	
HP	101,196 (53.00)	39,430 (20.71)		100,588 (53.03)	38,891 (20.50)	
Stroke	7601 (3.98)	2373 (1.25)		7566 (3.99)	2236 (1.18)	
CKD	17,053 (8.93)	4591 (2.41)		16,968 (8.95)	4331 (2.28)	
COPD	5711 (2.99)	1883 (0.99)		5671 (2.99)	1811 (0.95)	
Charlson Comorbidity Index						
0–4	169,291 (88.66)	183,981 (96.65)	>0.999	168,161 (88.66)	183,817 (96.91)	>0.999
5–9	18,919 (9.91)	5711 (3.00)		18,796 (9.91)	5472 (2.88)	
>9	2735 (1.43)	669 (0.35)		2719 (1.43)	387 (0.20)	

Abbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; HP, hypertension; T2DM, type 2 diabetes.

3 | RESULTS

Of 1,411,215 women, 381,306 met inclusion and exclusion criteria, and were subsequently categorized as control (non-HT users, n = 189,676; mean [standard deviation (SD)] age, 67.5 [3.7] years) and treatment (HT users, n = 189,676, 68.0 [3.9] years) groups depending on their prescription records of HT medication (Figure 1). Average follow-up time was mean [SD] 5.1 [2.3] years.

There were no significant differences in age, race, comorbidities, and CCI between control and treatment groups (Table 1). In the study population, 58.50% (110,951 of 189,676) and 60.49% (114,729 of 189,676) were women aged between 65 and 79 years in control and treatment groups, respectively. The race distribution indicated that a majority of study population in this analysis were White women (77.51% [147,018 of 189,676] in control and 80.54% [152,763 of 189,676] in treatment).

Significant decreases in the risk of NDDs were observed in the treatment group compared to control: AD (RR 0.43, 95% CI 0.41–0.46, $P < 0.001$), PD (0.47, 0.43–0.51, $P < 0.001$), dementia (0.41, 0.40–0.43, $P < 0.001$), non-AD dementia (0.40, 0.39–0.42, $P < 0.001$), MS (0.53, 0.46–0.62, $P < 0.001$), ALS (0.42, 0.28–0.63, $P < 0.001$), and combined NDDs (0.42, 0.40–0.43, $P < 0.001$; Figure 2A).

All 14 HTs indicated reduced risk for NDDs combined compared to the risk in non-HT users (Figure 2B). The magnitude of risk reduction for all combined NDDs differed by composition of HT (Figure 2B). Formulations containing natural steroids 17β-estradiol and/or progesterone were associated with greater reduction in NDD risk (Figure 2B). Comparing HT medications containing natural or synthetic progesterone, the RR ratio for Prometrium (0.19, 0.15–0.23, $P < 0.001$) was lower than that of Prempro (0.30, 0.26–0.36, $P < 0.001$). These data suggest a potentially protective effect of a progesterone-based medication (Prometrium) compared to a medication (Prempro) containing a synthetic progestin (medroxyprogesterone acetate) on all combined NDDs.

Premarin (n = 123,982), Estrace (n = 63,164), Vivelle/Vivelle-dot (n = 6553), Prempro (n = 6197), and estrogen therapy (ET)+Prometrium (n = 4865) were further investigated for their effects on the risk of each NDD (Figure S1 in supporting information). Decreased risk of AD, PD, and dementia was observed in patients who received one of the five above HTs. Risk of MS was significantly decreased in Premarin and Estrace users. There was no significant association between the risk of MS and Vivelle/Vivelle-dot, Prometrium, or Prempro users. The data suggested that the protective effect of estrogen therapy was modestly reduced in progestin-combined HTs.

The age distribution for HT users indicated that the use of Premarin and Estrace was greatest in women aged 65 to 69 years (Figure S2 in supporting information). Vivelle/Vivelle-dot, Prempro, and ET+Prometrium users were greatest in women aged 45 to 54 years and 65 to 69 years (Figure S2).

Age was a modifier of NDD risk. Within the age group with low risk of developing NDDs, women aged 60 to 64 years, there was no significant difference in the risk of AD, dementia, or combined NDDs between control and treatment populations. In women not receiving HT, the risk of NDD increased with age, which was consistent with known literature.[51] Impact of HT on risk of NDDs emerged with age such that significant reduction in risk of combined NDDs, AD, and dementia was apparent in women aged 65 years and older (Figure 3). As patient age increased, the cumulative hazard plots indicated greater divergence between women receiving HT exhibiting lower incidence of NDDs relative to untreated controls (Figure 3).

3.1 | Effect of route of administration on the risk of NDDs: oral or transdermal

Age distribution was different between oral-HT (mean [SD]) 68.3 [3.8] years and transdermal-HT populations 58.4 [1.1] years. Transdermal-HT users were younger than oral-HT users as 59.43% (8916 of 15,002) of transdermal-HT users were 45 to 64 years of age. In contrast, 61.25% (10, 910 of 174,546) of oral-HT users were distributed in the age range of 65 to 79 years. Because the age distribution was different, the propensity score–matched model was modified to include age for each population: control for oral-HT users 67.6 [3.7] years and transdermal-HT users 58.2 [1.2] years (Table S3 in supporting information).

Risk of all types of NDDs was reduced in women receiving oral-HT (Figure 4). Proportions of patients diagnosed with AD, PD, dementia, MS, and ALS in the oral-HT group were decreased approximately two-fold, compared to those in control, with significantly decreased RR (95% CI, *P*-value) for all combined NDDs: 0.42 (0.41–0.44, $P < 0.001$), AD: 0.42 (0.40–0.44, $P < 0.001$), PD: 0.47 (0.43–0.52, $P < 0.001$), dementia: 0.42 (0.41–0.43, $P < 0.001$), non-AD dementia: 0.42 (0.41–0.44, $P < 0.001$), MS: 0.51 (0.44–0.60, $P < 0.001$), and ALS: 0.40 (0.26–0.61, $P < 0.001$; Figure 4).

Transdermal HT reduced risk of combined NDDs (0.68 [0.58 to 0.80, $P < 0.001$]) including dementia with AD: 0.73 [0.60 to 0.88, $P = 0.001$], non-AD dementia: 0.64 [0.50 to 0.82, $P < 0.001$], MS: 0.55 [0.36 to 0.84, $P = 0.005$] (Figure 4). Transdermal HT had no significant effect on risk of AD (0.86, 0.66 to 1.12, $P = 0.273$) or PD (0.67, 0.44 to 1.03, $P = 0.069$) (Figure 4). Due to a low number of ALS patients in transdermal-HT users, the RR ratio was not calculated.

3.2 | Effect of duration of therapy on the risk of NDDs

In the treatment population, 60.04% (114,299 of 190,361) received HT for 1 year or less, 21.09% (40,150 of 190,361) for 1 to 3 years, 14.15% (26,928 of 190,361) for 3 to 6 years, and 4.73% (8998 of 190,361) for longer than 6 years (Table 2). These data indicated that a majority of HT users in our dataset were prescribed HT for 1 year or less.

Increased duration of therapy was associated with greater reduction of risk for all combined NDDs, AD, PD, and dementia (Table 2). HT for 1 to 3 years reduced risk for all combined NDDs: RR 0.62 (0.58–0.66, $P < 0.001$), AD: 0.57 (0.51–0.64, $P < 0.001$), PD: 0.62 (0.51–0.75, $P < 0.001$), dementia: 0.64 (0.59–0.69, $P < 0.001$), and non-AD dementia: 0.69 (0.63–0.75, $P < 0.001$). In patients prescribed HT for 6 years and longer relative risk reduction for all combined NDDs: 0.23 (0.18–0.28, $P < 0.001$), AD: 0.21 (0.15– 0.30, $P < 0.001$), PD: 0.24 (0.14–0.44, $P < 0.001$), dementia: 0.25 (0.20–0.31, $P < 0.001$), and non-AD dementia: 0.27 (0.21–0.36, $P < 0.001$) was maximal.

4 | DISCUSSION

Outcomes of this retrospective analysis indicate that use of HT was associated with significantly reduced risk for all combined NDDs. Although the benefits and risks of HT are still debated,[12,19–21,26–29,33,52–58] our results are consistent with multiple observational studies reporting an association between HT and reduced risk of AD[28,52,59,60] or maintaining cognitive function.[61]

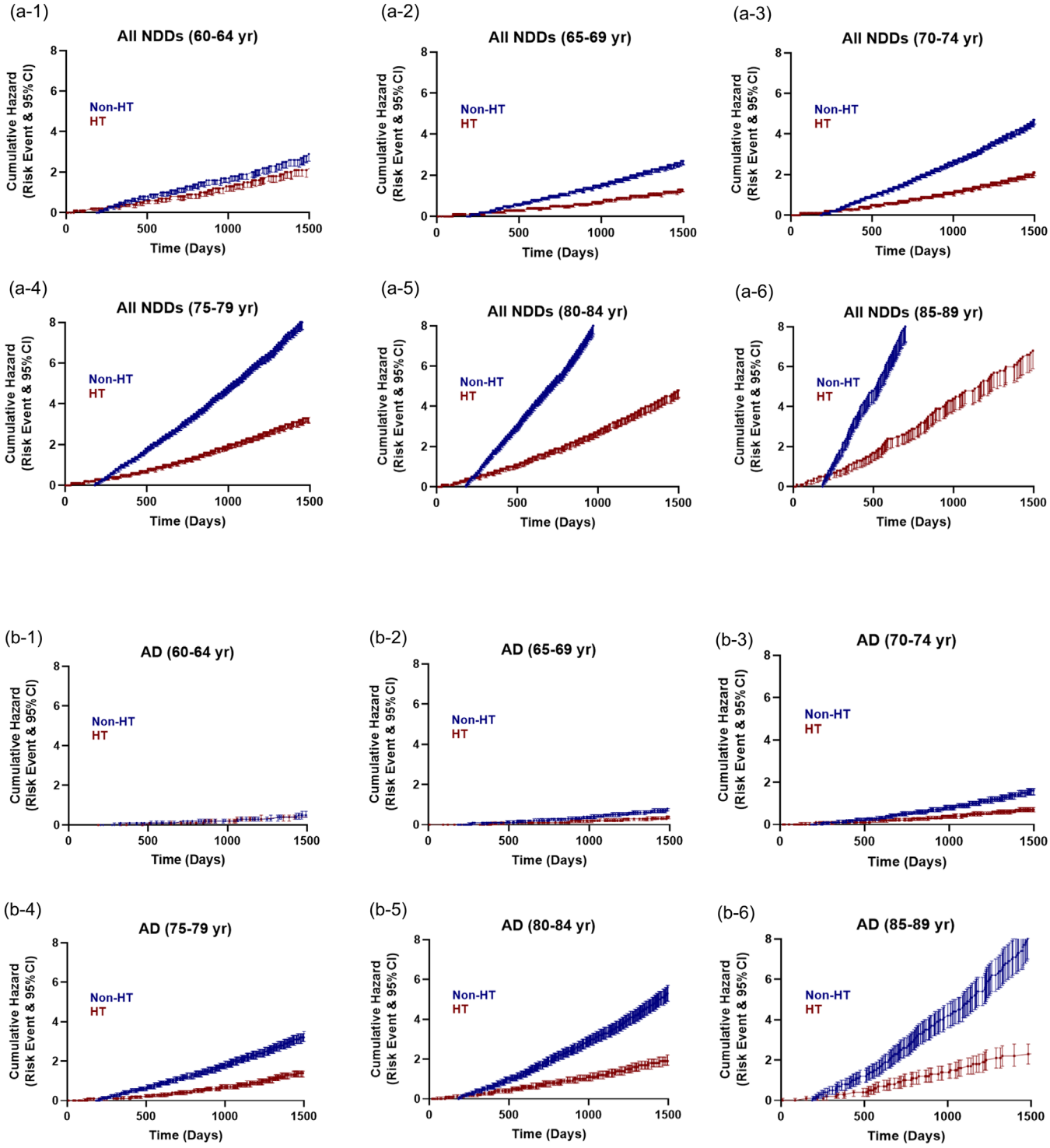


FIGURE 3 Hazard ratios by age indicating reduced risk of neurodegenerative diseases (NDDs, A), Alzheimer's disease (AD, B) and dementia (C) in women prescribed at least one FDA-approved hormone therapy (HT, red lines) compared to women not prescribed HT (blue lines) in six different age groups: (1) 60 to 64, (2) 65 to 69, (3) 70 to 74, (4) 75 to 79, (5) 80 to 84, and (6) 85 to 89 years. Reduction in the risk of NDDs, AD, and dementia became apparent in women aged 65 years or older. CI, confidence interval

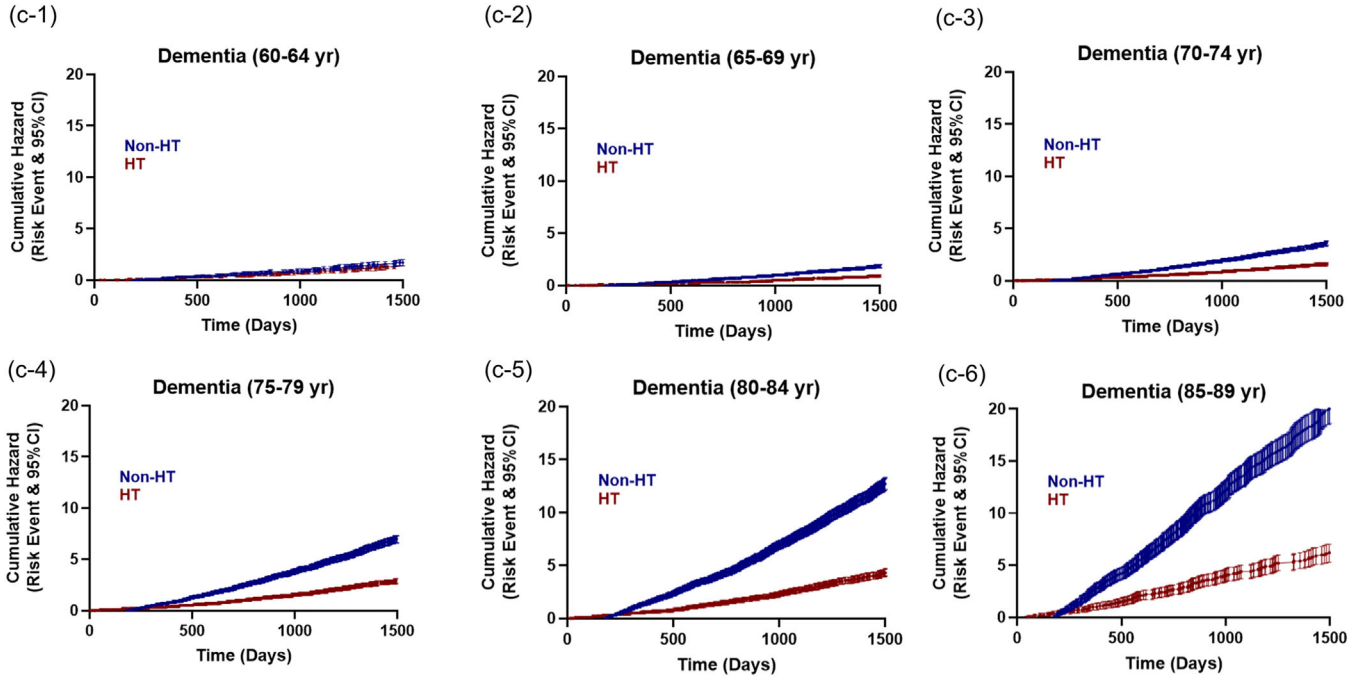


FIGURE 3 Continued

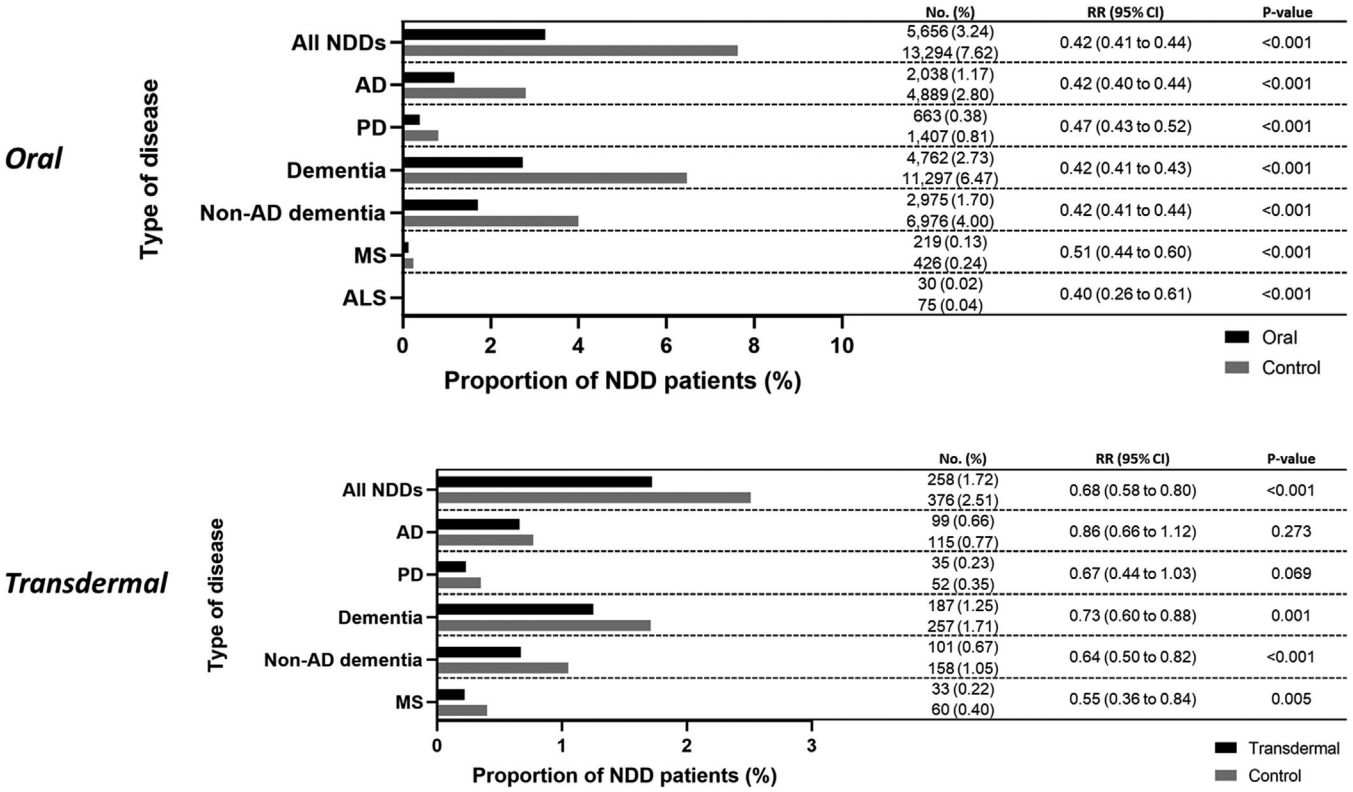


FIGURE 4 Route of administration of hormone therapy (HT) and risk of neurodegenerative diseases (NDDs): (A) oral and (B) transdermal. Significantly reduced risk of NDDs was observed in women who received oral HT. The risk reduction was significant for all-cause dementia and multiple sclerosis (MS) in women who received transdermal HT. AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; CI, confidence interval; PD, Parkinson's disease; RR, relative risk

TABLE 2 Impact of hormone therapy duration on risk of neurodegenerative diseases (NDDs)

	All NDDs			AD			PD			Dementia			Non-AD Dementia			MS		
Duration	No. (%)	RR (95% CI)	*P*-value	No. (%)	RR (95% CI)	*P*-value	No. (%)	RR (95% CI)	*P*-value	No. (%)	RR (95% CI)	*P*-value	No. (%)	RR (95% CI)	*P*-value	No. (%)	RR (95% CI)	*P*-value
1 y or less (N = 114,299)	4726 (4.13)	1.00		1819 (1.59)	1.00		570 (0.50)	1.00		3941 (3.45)	1.00		2341 (2.05)	1.00		202 (0.18)	1.00	
1–3 y (N = 40,150)	1034 (2.58)	0.62 (0.58 to 0.66)	<0.001	363 (0.90)	0.57 (0.51 to 0.64)	<0.001	124 (0.31)	0.62 (0.51 to 0.75)	<0.001	886 (2.21)	0.64 (0.59 to 0.69)	<0.001	566 (1.41)	0.69 (0.63 to 0.75)	<0.001	39 (0.10)	0.55 (0.39 to 0.77)	<0.001
3–6 y (N = 26,928)	489 (1.82)	0.44 (0.40 to 0.48)	<0.001	171 (0.64)	0.40 (0.34 to 0.47)	<0.001	51 (0.19)	0.38 (0.29 to 0.50)	<0.001	419 (1.56)	0.45 (0.41 to 0.50)	<0.001	278 (1.03)	0.50 (0.45 to 0.57)	<0.001	12 (0.04)	0.25 (0.14 to 0.45)	<0.001
6 y and longer (N = 8998)	84 (0.93)	0.23 (0.18 to 0.28)	<0.001	30 (0.33)	0.21 (0.15 to 0.30)	<0.001	<11 (< 0.12)	0.24 (0.14 to 0.44)	<0.001	77 (0.86)	0.25 (0.20 to 0.31)	<0.001	50 (0.56)	0.27 (0.21 to 0.36)	<0.001	<11 (<0.12)	0.69 (0.38 to 1.26)	0.290

Notes: Relative risk (RR) ratios for each NDD for longer-term therapies (1–3 years, 3–6 years, and 6 years and longer) were estimated compared to the risk observed in short-term therapy (1 year and less) users.
No. (%) is number of patients diagnosed with each NDD and its percentage.
Abbreviations: AD, Alzheimer's disease; MS, multiple sclerosis; PD, Parkinson's disease.

Importantly, our analysis indicated that magnitude of risk reduction of NDDs varied depending on the compositions of HT, route of administration, and duration of therapy.

Analysis of HT formulations indicated that all formulations containing estrogen reduced risk of NDDs. A differentiating factor for efficacy of estrogen was the progestin in the formulation. Estrogen with natural progesterone (Prometrium) exerted greater reduction in risk for combined NDDs. Estrogen in combination with the synthetic progestin medroxyprogesterone acetate reduced the protective efficacy of estrogen, which is consistent with previous findings.[62,63]

Multiple factors impact biological and pharmacokinetic properties of natural versus synthetic progestins. Orally administered progesterone and medroxyprogesterone acetate have different pharmacokinetics including bioavailability and half-life,[64] which could be responsible for different effects of progestins. Progesterone and medroxyprogesterone acetate also differ in their chemical structure[64] and their binding affinities to steroid receptors including androgen, glucocorticoid, and mineralocorticoid receptors, which could be related to different risk profiles.[64,65] Moreover, progesterone stimulates oligodendrocyte and myelin repair in preclinical in vitro and in vivo studies whereas medroxyprogesterone acetate has potential adverse outcomes for neural regeneration.[66–68] In addition, polymorphisms in metabolizing enzymes[69] and steroid receptors[70] relevant to the mechanisms of progesterone and medroxyprogesterone acetate may exert interindividual variations on therapeutic effects of HT.

Route of administration is one of the critical determinants influencing therapeutic outcomes of HT.[71-74] Different absorption and permeation of drugs through intestinal or skin membranes influence time to reach systemic circulation of drugs and their concentration levels in plasma, resulting in different pharmacokinetics and pharmacological outcomes.[75] To date, a majority of hormone therapies are orally administered. Results reported herein indicate that oral-HT use significantly reduced risks of AD, PD, dementia, MS, and ALS, compared to non-HT users.

Although the risks of dementia, MS, and all combined NDDs were significantly reduced in transdermal HT users, risk reduction of AD and PD was not statistically significant, which may be due to the younger age of the majority of transdermal-HT users. Late onset AD becomes apparent at 65 years or older[76] and slightly earlier for PD (60 years).[77] In our dataset, 59.43% (8916 of 15,002) of transdermal-HT users were of younger age, 45 to 65 years. Although 58.44% (111,592 of 190,945, prior to propensity score matching) of women in the control group were 65 to 79 years, a large number of these older women were excluded after performing propensity score matching between control and transdermal-HT populations, due to relatively younger age of transdermal-HT users. Only 4.83% (5390 of 190,945) of women aged 65 to 79 years remained in the transdermal-control group after propensity score matching (106,202 records were excluded). The exclusion of a large number of women aged 65 to 79 years in the control group after propensity score matching with transdermal-HT users may explain a lack of significant difference in the risks of AD and PD between control and transdermal groups.

The data indicate that long-term use of HT exerted greater reduction in risk than short-term use (1 year or less) for AD, PD, and dementia. Although the benefits and risks of long-term HT use remain controversial,[27,29,52,57,78] findings reported herein are consistent with earlier studies indicating reduced risk of AD with longer duration of therapy.[29,52] Further, our results are consistent with a protective effect of long-term therapy (10 or more years) on AD when HT is initiated near the age of menopause.[27] The outcomes of our analysis indicating reduced risk of NDDs in HT users in a relatively healthy population of aged women are consistent with hormone therapy, especially estrogen therapy, to prevent—not treat—neurological diseases.[79,80]

In observational studies an unpredicted bias could be introduced in that women who received HT may be healthier, more highly educated, and of higher socioeconomic status relative to non-users. However, the non-user and HT-user populations contributing to this retrospective analysis were both relatively healthy with CCI score of 0 to 4 (88.66% of non-HT users and 96.65% of HT-users). Further, to minimize a potential bias, propensity score matching was performed by balancing both demographic and comorbidity characteristics between non- and HT-users. After propensity score matching, the percentage of patients diagnosed with comorbidities was slightly higher in non-HT users; however, differences in the CCI score ($P > 0.999$) and the number of patients diagnosed with comorbidities ($P = 0.132$) were not statistically significant between non- and HT-users. Because neither the CCI score nor the number of patients diagnosed with comorbidities was statistically different, non- and HT-users were statistically comparable.

Because this retrospective analysis was conducted using claims datasets entered by clinicians, HT prescriptions were likely personalized based on the presence and severity of menopausal symptoms and medical records on comorbidities. A more personalized approach may be one of the reasons for the protective effect of HT against NDDs determined in this study. Further, women generally initiate HT in response to menopausal symptoms that occur at the time of the menopausal transition. As the prevalence of NDDs becomes more apparent at older ages, our results imply that women who initiate HT for symptoms at the time of the menopausal transition and who are in a relatively healthy state have a reduced risk of NDDs at older ages. The greater risk reduction of NDD with longer HT use is consistent with sustaining brain health for a longer-term period.[79–81]

This study had several limitations. First, age at initiation and type of menopause (natural, surgical, or pharmacological) were not included in this analysis. Second, this study was limited to a 10-year analysis of claims datasets (2007–2016). Third, a portion of patients could use multiple HT medications between 2007 and 2016, such as changing from oral estrogen to transdermal estrogen, or the same oral estrogen but a different product. The potential cross-effect of different HTs was not considered in this analysis. Fourth, the claims datasets did not contain information regarding patients' *APOE* genotype or family history of NDDs. Last, there is emerging evidence indicating that the presence and severity of certain menopausal symptoms may be associated with the onset of age-associated disorders.[82] Thus, the severity of menopausal symptoms could be a critical determinant influencing the pathogenesis of age-associated neurodegeneration and the efficacy of HT to impact risk of NDDs.

In conclusion, outcomes of this retrospective analysis of medical claims data indicate reduced risk of age-associated NDDs in HT users. Reduction of NDD risk varied by type and route of HT administration. Longer duration of HT use was associated with greater reduction of NDD risk. These results support further development of precision HT to reduce risk of age-associated NDDs.

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CONFLICTS OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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