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Cognitive health after menopause: Does menopausal hormone therapy affect it?

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Abbreviations: AD, Alzheimer's disease; EMAS, European Menopause and Andropause Society; EPT, Estrogen Progestogen Therapy; ET, Estrogen only Therapy; IMS, International Menopause Society; MHT, Menopausal Hormone Therapy; NAMS, North American Menopause Society; NICE, National Institute for Health and Care Excellence.

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Dementia is a pandemic chronic non-communicable disease. 10 in 100 women above age 65 will be diagnosed with dementia, primarily Alzheimer's disease (AD). Apart from age and hereditary risk factors, there are multiple acquired risk and protective factors. So far, Menopausal Hormone Therapy (MHT) is not recommended as preventive measure. A systematic literature search on MHT and dementia risk and MHT and cognitive performance in demented women, respectively, was performed. Two recent meta-analyses identified 18 and 16 studies analyzing the impact of MHT on dementia/AD risk. Our systematic literature search identified eight additional original articles. The majority of studies found a risk reducing impact of MHT by 11–33%. However, results may vary depending on MHT type, age at initiation and study design. For example, the Women's Health Initiative Memory Study (WHIMS) reported an approximately 2-fold increased risk of dementia/Alzheimer's disease if MHT comprising conjugated equine estrogens and medroxyprogesterone acetate was initiated in predominantly comorbid postmenopausal women above age 65. In general, MHT displays a beneficial effect on several dementia risk factors and also augments some protective factors. Accordingly, clinicians can be reassured that MHT can be safely prescribed in the context of cognition in women free of dementia. However, MHT is not indicated for cognitive improvement in demented women. International scientific guidelines on MHT and dementia should consider incorporating most recent data.

Introduction

Dementia is a pandemic chronic non-communicable disease (NCD). Dementia is characterized by impairment of cognition, mostly involving memory and at least one other cognitive domain (language, visuospatial, executive function). Until today, there is no effective single intervention for dementia prevention and treatment, respectively. Thus, the focus lies on intensive risk factor modification, especially during midlife (age 45–65 years). About 35% of dementia cases are thought to be attributable to a combination of nine potentially modifiable risk factors (low educational attainment, midlife hypertension, midlife obesity, hearing loss, late-life depression, type 2 diabetes mellitus (T2DM), physical inactivity, smoking, social isolation) [1]. Alzheimer disease (AD) is the most common cause of dementia. Without doubt, there are sex differences in AD. For example, according to a recent review, men die faster with AD, more women live with AD, and both sexes show similar risk of developing AD until advanced ages when women show increased risk, respectively [2]. In Europe, approximately 10% of women above age 65 will be diagnosed with AD at some point [3]. It is still an ongoing controversy if and to which extent the age and menopause associated decline in endogenous steroid hormone exposure has an impact on AD development and disease course, and if menopausal hormone therapy (MHT) can be used for AD prevention. As current guidelines from international scientific societies have not been updated for some time (NICE in 2015 [4], IMS in 2016 [5], EMAS in 2016 [6], NAMS in 2017 [7], the goal of this systematic review was to 1) update the scientific evidence on the impact of MHT on dementia risk, and to 2) provide a counseling tool to support daily clinical practice (personalized medicine).

Material and methods

Information sources and search strategy

Complex literature searches were designed and executed by a medical information specialist (HJ) for the following information sources to identify all potentially relevant documents on the topics: 1) Medline (Ovid) (incl. Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Medline Daily and Ovid Medline Versions (1946–February 26, 2021), 2), Embase (Ovid) (1974–February 26, 2021), 3) PsycInfo (Ovid) (1806–February 26, 2021), 4) Cochrane Library (Wiley) (1996–February 26, 2021), 5) Web of Science (Clarivate) (1900–February 26, 2021), and 6) ClinicalTrials.gov (NLM), respectively.

Initial search strategies in Medline/Ovid were drafted for four topics (1) Impact of menopause on risk for affective disorders: depression, anxiety, 2) Impact of menopause on cognition: in general, MCI risk, dementia risk, 3) Impact of MHT on affective disorders: depression, anxiety, 4) Impact of MHT on cognition: in general, risk of MCI, dementia) and tested against a list of core references to see if they were included in the search results. After refinement and consultation, complex search strategies were set up for each information source based on database-specific controlled vocabulary (thesaurus terms/subject headings) and textwords. Synonyms, acronyms and similar terms were included in the textword search. No limits have been applied in any database considering study types, languages, publication years or any other formal criteria. The searches have been run in the medical bibliographic databases Medline, Embase and the Cochrane Library, as well as PsycInfo, Web of Science and ClinicalTrials.com, a database of clinical trials. The search dates were March 2nd and 3rd, 2021. The main search concepts identified were "menopause" (including pre-, peri- and post-menopause) for topics 1 and 2, "hormone replacement therapy" for topics 3 and 4", "depression" and "anxiety" for topics 1 and 3, and "risk of dementia" and "mild cognitive impairment" for topics 2 and 4. In addition to electronic database searching, reference lists and bibliographies from relevant publications were checked for relevant studies. The final detailed search strategies are presented in supplementary file 1.

Eligibility criteria

Articles were included if women were postmenopausal and taking MHT. MHT was defined as use of systemic estrogens only (ET), systemic estrogen progestogen therapy (EPT), or tibolone at any dosing schedule and dosage. Studies on systemic androgen therapy or only vaginal estrogen therapy were excluded. All original studies, systematic reviews and meta-analyses were included, while editorials, letters, and comments were excluded.

Study selection and data collection process

All identified citations were imported into EndNote and duplicates were removed. Title and abstract screening was performed by two co-authors (AK, SB) using EndNote and tested against the inclusion criteria. In case of disagreement the fulltext article was read to allow for decision making. Then, fulltext screening of all identified abstracts was carried out by four co-authors (CH, JW, SB, WW) with each article being checked for relevance twice. Any ambiguity was discussed among all authors. Data extraction from all selected articles was performed by PS.

Data outcomes

Systematic database searches for the four topics (see 2.1) yielded a total of 18′235 hits after removing duplicates. After screening of titles and abstracts for these four topics, 387 articles remained. Reviewing the fulltext articles with respect to the topic of MHT and dementia, 54 relevant articles were identified which were included in this paper (supplementary file 2).

Table 1
Original articles on the impact of MHT on dementia risk published between September 2019 and February 2021.

Author, year of publication	Study design	Sample size	Cohort's characteristics	Intervention	Follow-up	Endpoint(s)	Method for endpoint(s) assessment	Results
Yoo, 2020 [1]	Prospective cohort study	4'696'633	Postmenopausal non-hysterectomized women from the Korean National Health Insurance System database; mean age 61.2 yrs (SD 8.6 yrs); BMI: < 18.5 (2.3%), 18.5–23 (35.6%), 23–25 (26.1%), 25–30 (31.5%), ≥30 (4.5%); mean age at menopause: 50.2 yrs (SD 4.0 yrs); MHT duration: never (81.6%), <2 yrs (8.7%), 2–5 yrs (3.4%), ≥5 yrs (3.7%), unknown (3.7%)	MHT	Median 5.74 yrs.	Incident dementia (AD, VaD, other)	Self-administered questionnaire, ICD codes for dementia, anti-dementia drug prescription database; multivariate-adjusted proportional hazards model (age at menarche, age at menopause, parity, duration of breastfeeding, duration of MHT, duration of OC use, alcohol consumption, smoking, regular exercise, income, BMI, hypertension, diabetes mellitus, dyslipidemia, cancer)	212'227 incident cases of dementia, incidence rate (per 1000 person-yrs.: 8.6); never MHT vs. 1) all MHT user: HR 0.85 (no 95% CI provided), 2) MHT <2 yrs: HR 0.86 (95% CI 0.84–0.88), 3) MHT 2–5 yrs: HR 0.81 (95% CI 0.78–0.84), 4) MHT ≥5 yrs: HR 0.87 (95% CI 0.84–0.90)
Han, 2020 [2]	Prospective cohort study	13'110	Postmenopausal women from the Korean National Health Insurance System database; no prior tibolone use, mean age of user 58.2 yrs (SD 6.2 yrs) and of nonuser 61.8 yrs (SD 7.9), mean BMI of (non)user 24.2	Tibolone	Total 9 yrs.	Incident dementia (total, AD, VaD,	ICD codes for dementia, anti-dementia drug and tibolone prescription database; multivariate-adjusted proportional hazards model (age, BMI, smoking, alcohol consumption, physical activity, systolic blood pressure, fasting blood glucose, total cholesterol Charlson comorbidity index, comedication, socioeconomic status	940 incident cases of dementia (883 AD, 206 VaD); Tibolone use vs. nonuse: 1) total dementia: HR 1.04 (95% CI 0.73–1.47), 2) AD: HR 0.95 (95% CI 0.65–1.38), 3) VaD: HR 1.25 (95% CI 0.63–2.46); cumulative dose, treatment duration and age at initiation did not have a significant impact

Table 1 (*continued*)

Author, year of publication	Study design	Sample size	Cohort's characteristics	Intervention	Follow-up	Endpoint(s)	Method for endpoint(s) assessment	Results
Paganini-Hill, 2020 [3]	Prospective cohort study	424	Postmenopausal women without dementia at baseline, mean age 68.5 yrs (SD 5.0) at enrollment in Leisure World Cohort study (when information on reproductive parameters were assessed by questionnaire), mean age 93.2 yrs (SD 2.6) at enrollment in The 90+ Study (when cognitive function was assessed prospectively)	MHT	Mean 3.4 yrs (SD 2.5)	Incident dementia	Questionnaire on reproductive factors (part of the Leisure World Cohort study), neurological examination, MMSE (if face-to-face consultation was possible), CASI-short (telephone interview with subject if face-to-face consultation was impossible), DQ (telephone interview with informant (if neither face-to-face nor telephone interview with subject was possible)	209 incident cases of dementia, never vs. ever MHT: adjusted HR 0.94 (95% CI 0.69–1.28), neither dose, duration nor time since last use was associated with dementia risk after age 90 yrs.

Abbreviations: AD = Alzheimer's disease, BMI = Body Mass Index, CASI = Cognitive Abilities Screening Instrument, CI = Confidence Interval, DQ = Dementia Questionnaire, HR = Hazard Ratio, MHT = Menopausal Hormone Therapy, MMSE = Mini-Mental State Examination, SD = Standard Deviation, VaD = Vascular Dementia, yrs. = years.

Results

Impact of MHT on dementia and Alzheimer's disease risk

Our systematic literature search identified four systematic reviews and meta-analyses [8–11], of which two were published in 2020 [8,10] including original articles published until June 2019 [10] and September 2019 [8], respectively. According to our systematic literature search three additional original articles have been published since then [12–14] (Table 1).

The first meta-analysis [8] included 18 studies of which 13 focused on AD [15–28] and five on not further specified dementia [20,29–32]. The second meta-analysis [10] included 16 studies focusing on AD [18,19,21–24,26,28,33–40]. Thus, only eight original studies were included in both meta-analyses. Furthermore, our systematic literature search identified five additional original articles not having been included in any of the two meta-analyses [41–45] (supplementary table 1 and table 2).

The first meta-analysis [8] reported a significantly increased risk for AD (OR 1.08, 95% CI 1.03–1.14) and overall dementia (OR 1.16, 95% CI 1.02–1.31) in MHT users compared to hormone-naïve women. However, this association was not found when only including cohort studies (AD: OR 0.89, 95% CI 0.76–1.04; dementia OR 1.13, 95% CI 0.97–1.33) [17,18,20,24,26,31,32,46]. The two articles from the RCT WHI reporting an increased dementia risk for MHT user only focused on women above age 65 when initiating MHT [29,30] thus not considering the hypothesized neuroprotective “critical window” [32]. However, overall, meta-regression based on baseline age of subjects did not reveal this parameter as a

source of heterogeneity for AD or dementia diagnosis, respectively. When considering type of MHT specifically combined MHT (mainly estrogens combined with the synthetic progestogen MPA) displayed a negative impact (OR 1.16, 95% CI 1.12–1.21) while progestogen only and estrogen only therapy only had a minor effect. Interestingly, the observed significant positive correlation between MHT and AD was only found for women using MHT for up to five years (Coef = 0.0477, $p < 0.001$). When MHT was used for more than five years AD risk significantly declined (Coef = −0.0932, $p < 0.001$). Accordingly, longer MHT duration displayed a protective effect on AD. The second meta-analysis [10] reported a significantly decreased risk for AD in MHT user (OR 0.672, 95% CI 0.581–0.779; $p < 0.001$) which was not significantly modified by, e.g. age (age ≤70, age 71–79, age ≥80), MHT ascertainment (oral, transdermal estrogens) and treatment duration (<5 years, 5–10 years, > 10 years). Comparable to the first meta-analysis [8], when only prospective cohort studies were included, the effect size was increased supporting the beneficial effect of MHT in cognition (OR 0.519, 95% CI 0.413–0.653; $p < 0.001$). However, the meta-analysis did not differentiate between estrogen only and combined EPT.

Table 2 presents the additional five original articles identified by our systematic literature search [41–45]. Two articles were derived from the placebo-controlled randomized Women's Health Initiative Memory Study (WHIMS) [43,44] while the others either were cross-sectional [41], retrospective [42]) cohort, or case–control [45] studies. Sample size ranged from 30 [41] to 489,105 [42] women. MHT either comprised oral estrogens (CEE [43], E2 [42]) combined with a progestin (MPA only [43], mainly MPA or norethisterone acetate (NETA) [42]), estrogens only (CEE) [44], or was not further specified [41,45], respectively. Mean MHT duration ranged from four [43] to 6.8 [42] years, or was not reported [41,45]. In those studies providing details on MHT type and duration, risk of incident dementia (mainly AD) was either significantly increased by EPT in women initiating MHT at age 65+ [43] or unaffected by estrogen only therapy (ET) [44]. On the contrary, risk of death due to AD or vascular dementia was significantly reduced by MHT regardless of age at MHT initiation [42].

All three original studies published in 2020 (Table 1) were prospective cohort studies performed in South Korea [12,14] or USA [13], respectively. Sample size ranged from 424 [13] to more than 4.5 million [14] postmenopausal women. At baseline, mean age of South Korean women was approximately 58–63 years [12,14] while US-American women had a mean age of 93 years [13]. Mean follow-up was 3.4 [13] to nine years [12]. In all studies, incident dementia was the primary endpoint. Dementia cases were either identified by ICD codes in the National Health Insurance System database [12,14], and by neurological examination or telephone interviews [13], respectively. For dementia risk analysis, women using MHT were compared to MHT nonuser adjusting for several potential confounding factors. MHT was only specified in one study (tibolone) [12] while MHT type, mode of application and dosage were not reported in the remainder [13,14]. However, as the largest study only included non-hysterectomized women it can be assumed that only combined MHT was applied [14]. It was also this study [14] that reported a significant reduction of overall dementia (including AD and vascular dementia) by MHT regardless of MHT duration. The remainder did not report a significant impact of MHT on overall dementia risk. Similarly, MHT duration [12,13] and age at initiation [12] did not alter their results.

Cognitive "window of opportunity" hypothesis

The "window of opportunity" hypothesis proposes that following long-term ovarian hormone deprivation, the brain and cognition become insensitive to exogenously administered estrogens, while in contrast, if estrogens are administered during a critical period near menopause, they will exert beneficial effects [47]. Accordingly, some observational cohort studies, reviewed in 2014 [48], suggested that MHT use in the early postmenopausal years was associated with a lower risk of dementia, while later MHT use was not. In detail, the large Multi-Institutional Research on Alzheimer Genetic Epidemiology (MIRAGE) case–control study reported a reduced AD risk only in younger postmenopausal MHT user [39]. In the Kaiser Permanente integrated health care system, self-reported MHT use at midlife but not nearly 30 years later, was associated with a significant reduction in risk of all-cause dementia [31]. In the Cache County cohort study of healthy postmenopausal women age 65 years and older, self-reported initiation of MHT within five years of menopause was linked to a significant reduction in incident AD, whereas later initiation did not alter risk [19]. These observations

Table 2
Additional original articles on the impact of MHT on dementia risk identified by our systematic literature search.

Author, year of publication	Study design	Sample size	Cohort's characteristics	Intervention	Follow-up	Endpoint(s)	Method for endpoint(s) assessment	Results (selection)
Levine & Hewett, 2003 [1]	Cohort	30	Postmenopausal women with FTD, mean age at evaluation 70 yrs (range 51−91 yrs); mean age of dementia onset 64.9 yrs (range 46−87 yrs)	MHT (not further specified)	Assessment only once (cross-sectional)	Prevalence of MHT use in FTD women compared to the general population (national estimate 24%)	Chi-square analysis	Prevalence of MHT use was significantly higher in FTD women compared to the general population ($p < 0.01$).
Mikkola, 2017 [2]	Cohort	489'105	Postmenopausal women with MHT mean duration 6.8 yrs (SD 6.0); death due to AD n = 1057 resp. VaD n = 581; prevalence of myocardial infarction preceding MHT initiation was higher in MHT user (2.3%) than in reference population (1.4%)	ET and EPT; 90% oral MHT; estrogen type only E2, progestogen type mostly MPA and NETA	Observation period for deaths 1998−2009	Standardized Mortality ratio (SMR) for AD and VaD	The number of deaths as a result of VaD and AD in MHT users were compared with those that occurred in the age-standardized Finnish female Population at 5-yr intervals (expected deaths); data source of women who died from AD and VaD: nationwide prescription register, National Cause-of-Death Register, National Hospital Discharge Register	VaD death risk was significantly reduced by MHT regardless of MHT type and duration (>0 to ≤ 5 yrs. SMR 0.63, 95% CI 0.55−0.72; >5 yrs. SMR 0.61, 95% CI 0.54−0.67); AD death risk was significantly reduced by any MHT if MHT duration was >5 yrs, (SMR 0.85, 95% CI 0.79−0.92); AD and VaD death risk reduction by MHT was not affected by age at MHT initiation.
Shumaker, 2003 [3]	PC-RCT	4532	Postmenopausal women with a uterus, participants in WHI with age ≥65 yrs and no dementia at enrollment; 1−2% with history of stroke	oCEE 0.625 mg/day combined with MPA 2.5 mg/day (n = 2229), placebo (n = 2303)	EPT mean 4.01 yrs (SD 1.21), placebo mean 4.06 yrs (SD 1.18)	All-cause dementia, mild cognitive impairment, global cognitive functioning	Phase 1: 3MSE at baseline and annually Phase 2: if 3MSE score was below defined cut points > modified CERAD neuropsychological battery, standardized	During Follow-up 61 cases of dementia were identified (EPT n = 40, placebo n = 21): HR 2.05 (95% CI 1.21−3.48); dementia type:

(*continued on next page*)

Table 2 (*continued*)

Author, year of publication	Study design	Sample size	Cohort's characteristics	Intervention	Follow-up	Endpoint(s)	Method for endpoint(s) assessment	Results (selection)
							interview by certified technician, standardized questionnaire (patient, informant) Phase 3: results from phase 1 + 2 were reviewed by clinician and diagnosis was made (no dementia/ MCI/dementia) Phase 4: if dementia was diagnosed > brain computed tomography scan, blood sampling	mostly AD (EPT 50%, placebo 57.1%); EPT without impact on MCI risk
Shumaker, 2004 [4]	PC-RCT	2947	Postmenopausal women without uterus, participants in WHI with age ≥65 yrs and no dementia at enrollment; 1.8−2.1% with history of stroke	oCEE 0.625 mg/day (n = 1464), placebo (n = 1483)	ET mean 5.16 yrs (SD 1.77), placebo mean 5.20 yrs (SD 1.71)	All-cause dementia, mild cognitive impairment, global cognitive functioning	Phase 1: 3MSE at baseline and annually Phase 2: if 3MSE score was below defined cut points > modified CERAD neuropsychological battery, standardized interview by certified technician, standardized questionnaire (patient, informant) Phase 3: results from phase 1 + 2 were reviewed by clinician and diagnosis was made (no dementia/ MCI/dementia) Phase 4: if dementia was diagnosed > brain computed tomography scan, blood sampling	During Follow-up 47 cases of dementia were identified (ET n = 28, placebo n = 19): HR 1.49 (95% CI 0.83−2.66); dementia type: mostly AD (ET 46.4%, placebo 47.4.1%); ET without impact on MCI risk; HR for dementia in pooled trials (ET + EPT) 2.19 (95% CI 1.25 −3.84, p = 0.006)

Zucchella, 2012 [5]	Case-control	AD patients n = 275, controls n = 276	Postmenopausal women, mean age 76.7–77.6 yrs, mean AD duration in AD patients 2.9 yrs (SD1.6)	MHT (not further specified)	Assessment only once (cross-sectional)	Cases and controls • Personal history including major reproductive life events and exogenous sex hormone exposure • Global cognitive evaluation Cases only • Basic everyday activities • More complex everyday activities • Behavioral disturbances • Dementia severity	Cases and controls • Structured interview • MMSE Cases only • ADL • ISDL • NPI • CDR	MHT prevalence in AD patients was significantly lower than in controls ($p < 0.0001$)

Abbreviations: AD = Alzheimer's disease, ADL = Activities of Daily Living, CDR = Clinical Dementia Rating, CEE = conjugated equine estrogens, CERAD = Consortium to Establish a Registry for AD, CI = Confidence Interval, ET = estrogen therapy, EPT = estrogen progestogen therapy, FTD = frontotemporal dementia, HR = Hazard Ratio, IADL = Instrumental Activities of Daily Living, MCI = mild cognitive impairment, MHT = Menopausal Hormone Therapy, (3)MMSE = (modified) Mini-Mental State Examination, MPA = medroxyprogesterone acetate, NETA = norethisterone acetate, NPI = Neuropsychiatric Inventory, o = oral, PC-RCT = placebo-controlled randomized trial, SD = Standard Deviation, VaD = Vascular Dementia, WHI = Women's Health Initiative, yrs. = years.

seem to be supported by the Kronos Early Estrogen Prevention Study (KEEPS) trial showing that transdermal E2 therapy was associated with a decrease in amyloid-beta deposition on neuroimaging studies, particularly in apolipoprotein E (APOE) E4 carriers [49], and by the WHIMS reporting an increased risk of dementia in women older than 65 years when initiating EPT (no younger cohort to compare with) [43].

However, the critical timing hypothesis was not supported by the two most recent meta-analyses showing no impact of age at MHT initiation and MHT duration [8,10]. Similarly, the three studies published in 2020, did not find an impact of MHT duration [12–14] and age at initiation [12] on incident dementia risk. Furthermore, the large Finnish cohort study did not find an age-modifying effect on risk reduction for death due to AD or vascular dementia by MHT [42].

Impact of MHT in women with Alzheimer's disease and dementia

Our systematic literature search identified 14 original articles [50–63] (Table 3) and one meta-analysis [64] on the impact of MHT on cognitive function in postmenopausal women with dementia. While case–control [54], cross-sectional [55,58,62], and prospective cohort studies [52,53,60] mostly reported a beneficial effect of estrogens on cognitive function in AD females, the meta-analysis comprising of RCTs only did not [64]. The latter argued that due to different MHT regimens applied and study designs chosen it was not possible to combine more than two studies in any analysis. Accordingly, the authors concluded that MHT was not indicated for cognitive improvement or maintenance for women with AD.

Counseling tool for daily practice

Healthy ageing includes survival to old age, delay in the onset of NCD and optimal functioning for a maximal period at individual levels of body systems and cells. In 2016, EMAS published

The conceptual framework of Healthy Menopause, a holistic model of care covering physical, psychological and social functioning and incorporating disease and disability. It encompasses women as a whole, beyond their hormonal, reproductive and physiological health [65]. Accordingly, cognitive aging and dementia prevention should be part of counselling in midlife women. Apart from age, there are several hereditary (disposition) and acquired (exposition) risk factors for developing dementia and AD, respectively. Hereditary AD risk factors comprise a family history of dementia, rare dominantly inherited mutations in genes that impact amyloid in the brain, and the APOE epsilon 4 allele. A recent meta-umbrella systematic review of umbrella reviews put together risk and protective factors of non-communicable neurological disorders including (vascular) dementia and AD [66]. The most prominent risk factors were T2DM, high midlife BMI, hypertension, smoking, low-frequency electromagnetic fields, mild traumatic brain injury, depression, low level of education and frequency of social contacts, respectively (Table 4). The most prominent protective factors were lifestyle (Mediterranean diet, high fish intake, coffee consumption, light or moderate alcohol intake, high physical activity, micronutrients (vitamin C and E), some drugs (e.g., statins, antihypertensive drugs, aspirin, NSAIDS), and personality (e.g. openness) (Table 5). In this meta-umbrella systematic review, MHT is neither mentioned as risk nor as protective factor for developing dementia and AD, respectively. However, this may be due to not differentiating risk/protective factors for sex. According to our and other previous systematic literature searches and meta-analyses, MHT is not indicated in already demented women for cognitive improvement (section Impact of MHT in women with Alzheimer's disease and dementia). However, MHT may be a protective factor for developing AD in (healthy) menopausal women (section Impact of MHT on dementia and Alzheimer's disease risk). In fact, the RCT WHIMS only including MHT starters at age 65+ has been the only study so far, showing a negative impact of combined EPT on dementia risk [43]. However, this may also be due to the participants' higher age, other prevalent risk factors, or the applied EPT containing MPA. MPA exerts glucocorticoid effects supporting fluid retention and thus blood pressure increase, causes an impairment of glucose tolerance, and stimulates the pro-coagulatory activity in the vessel wall [67], all of which may have a detrimental effect on the brain. In contrast, many studies have been published demonstrating a direct beneficial effect of estrogens on brain tissue [68]. Furthermore, estrogens display a beneficial impact on most risk and protective factors

Table 3
Original articles on the impact of MHT in women with dementia.

Author, year of publication	Study design	Sample size	Cohort's characteristics	Intervention	Intervention (post-intervention Follow-up)	Endpoint(a)	Method for endpoint(s) assessment	Results (selection)
Asthana, 1999 [1]	Pilot PC-RCT	12	AD women without other significant medical, neurological or psychiatric diseases; no MHT or psychoactive medication during past 2 months; mean age 79.5 (SD 7.7.9) and 77.6 (SD 6.6) yrs.	tE2 50 mcg/day, placebo	8 wks (5 wks)	• Cognitive domains memory, attention and language • Dementia severity • Mood • Serum estrogens, catecholamines, IGF system	• Neuropsychological test battery at baseline and wk 1,3, 5, 8, 9, 10, 11, 13: 1) memory (Buschke Selective Reminding Test, Paragraph Recall Test, Visual Reproduction Test), 2) attention (Stroop Color Word Interference Test, Trail-Making Test), 3) language (Verbal Fluency Test, Token Test); • MMSE, BMICT • BPRS • Blood sample	E2 improved verbal memory (significant) and visual memory (borderline significant), E2 significantly improved attention. After treatment discontinuation the E2 effect vanished. E2 without effect on other neuropsychological tests.
Asthana, 2001 [2]	PC-RCT	20	AD women without other significant medical, neurological or psychiatric diseases; no MHT or psychoactive medication during past 2 months; mean age 79.0 (SD 9.7) and 80.2 (SD 6.7) yrs., n = 8 with hysterectomy	tE2 100 mcg/day, placebo	8 wks (8 wks)	• Cognitive domains attention and memory • Dementia severity • Mood • Relative change in subject's global cognitive and behavioral status (physician) • Physical function • Serum estrogens, catecholamines, IGF system	• Neuropsychological test battery at baseline and wk 3, 5, 8 and 16: 1) attention (Stroop Color Word Interference Test, Trail-Making Test, Treisman Visual Search), 2) recent verbal memory (Buschke Selective Reminding Test, Story Recall), 3) Recent visual memory (Figure Copy/Memory, Visual Paired-Associates, Oculomotor Delayed Response), 4) semantic memory (Boston Naming Test); • MMSE, BMICT • BPRS • CIBIC • IADL, PSMS • Blood sample	E2 significantly improved attention (Stroop Color Word Interference Test) ($p = 0.02$), verbal memory (Buschke Selective Reminding Test) ($p = 0.049$) and visual memory (Figure Copy/Memory) ($p = 0.02$); E2 without effect on other neuropsychological tests

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Table 3 (*continued*)

Author, year of publication	Study design	Sample size	Cohort's characteristics	Intervention	Intervention (post-intervention Follow-up)	Endpoint(a)	Method for endpoint(s) assessment	Results (selection)
Fillit, 1986 [4]	Cohort	7	AD women without other significant medical diseases	oE2 2 mg/day	6 wks (3 wks)	Not further specifed	Neuropsychological test battery: • Global deterioration Scale • Blessed Dementia Scale • Ham-D • Wechsler Adult Intelligence Scale • MMSE • Hachinski Ischemic Score • Randt Memory Test • Mattis Dementia Rating Scale	3 in 4 AD women were responders defined as improvement of MMSE, Ham-D and Randt Memory test; responders were older at AD onset und had less severe dementia at baseline
Fillit, 1994 [5]	Case report	1	78 yr old woman with AD	oE2 2.5 mg/d	4 wks (3 wks)	Not further specified	• MMSE • Paired associated learning • Bradburn Affect Balance Scale	E2 improved MMSE and paired associated learning with only little change of mood.
Henderson, 1994 [6]	Case-control	235 (AD n = 143, controls n = 92)	Age of AD women 76.0 yrs (SD 8.9) and of controls 76.3 (SD 8.5) yrs.; no significant intergroup difference for education and symptom duration	ET in 10 (7%) AD cases and in 17 (18%) controls; mainly CEE	Assessment only once (cross-sectional)	Global dementia severity	MMSE	AD cases with ET performed significantly better than AD controls (p = 0.02)
Henderson, 1996 [7]	Cohort	63	AD women with MHT (n = 9), AD women without MHT (n = 27), AD men (n = 26), mean age 74.3–75.3 yrs.	oCEE 0.3–1.25 mg/day (n = 8), E1 0.625 mg/day (n = 1), ET combined with MPA (n = 3)	Assessment only once (cross-sectional)	• global dementia severity • semantic memory • other language tasks • visuospatial memory • verbal episodic memory • verbal short-term memory	Neuropsychological test battery: • MMSE, OMC • BNT, fluency semantic retrieval • Fluency: FAS, comprehension: Token Test • Clock and house drawings, CERAD drawings • Immediate/delayed recall • DSF, DSB • VMSF, VMSB • GDS	AD women with MHT scored significantly better than women without MHT on semantic memory test (BNT), verbal short-term memory (DSF, DSB), visuospatial memory (clock and house drawings); non-significant trend for AD women with MHT to score better on semantic

						• nonverbal short-term memory • depression		retrieval task and language comprehension (Token Test); no significant difference between AD women with MHT compared to AD men; no significant intergroup difference for depression
Henderson, 2000 [8]	PC-RCT	42 (36 completed the trial)	Mean age 77 −78 yrs, mean BMI 35−38, prior use of estrogen therapy 19 −23%	oCEE 1.25 mg/day, placebo	16 wks.	• Variety of cognitive skills • Global change • Function • Mood	• ADAS-cog • CGIC • ADL/IADL • Collateral Source Geriatric Depression Scale, Montgomery -Asberg Depression Rating Scale	• No significant group differences for ADAS-cog, CGIC, ADL/IADL, mood; heterogenous results for function
Kyomen, 2002 [10]	PC-RCT	16	Women (n = 14) and men (n = 2) with dementia but without other acute major affective or psychotic diseases; no MHT during past 1 month; mean age 83.4 (SD 6.9) yrs.	oCEE 0.625 −1.25 mg−1.875 mg −2.5 mg/day (weekly dose increase), placebo	4 wks.	• Dementia Signs and Symptoms	• Dementia Signs and Symptoms scale • Modified Overt Aggression Scale, MMSE, physical examinations At baseline, then weekly.	• CEE significantly improved total score and subscores of Dementia Signs and Symptoms scale (also after exclusion of men)
Levine, 2004 [11]	Cohort	99	AD women with ET (n = 20) and without ET (n = 79); age 77.5−78.8 yrs.	ET not specified	Assessment only once (cross-sectional)	• Daily functioning • Global dementia severity • Independent cognitive areas • Depression • Overall level of functioning	• BRDRS (informant) • MMSE, OMC • NCSE • CSDD, GDS • NRS	No significant difference on global dementia severity (MMSE, OMC), overall level of (cognitive) functioning (NCSE, NRS), depression (CSDD, GDS); significant difference of course of disease (BRDRS): AD women without ET had more “non-memory” problems as initial symptoms (p = 0.046) and a greater degree of overall behavioral deficit in activities of daily living at the time of evaluation (p = 0.033)

(*continued on next page*)

Table 3 (*continued*)

Author, year of publication	Study design	Sample size	Cohort's characteristics	Intervention	Intervention (post-intervention Follow-up)	Endpoint(a)	Method for endpoint(s) assessment	Results (selection)
Mulnard, 2000 [12]	PC-RCT	120 (97 completed the trial)	AD women without uterus; age 74.1 −76.8 yrs; prior oophorectomy 50% −69%; prior ET use 31%−41%	oCEE 0.625 mg/d (n = 42), oCEE 1.25 mg/day (n = 39), placebo (n = 39)	12 months (3 months)	• Global score • Mood • Memory • Attention • Language • Motor • Activities of Daily Living	• MMSE, ADAS-cog, CDRS • Ham-D • Emotional Face Recognition Test, New Dot Test • Letter Cancellation, Trail-Making Test, Digit Symbol • Category Fluency, Letter Fluency • Grooved Pegboard Test, Finger Tapping Test • Blessed Dementia Rating Scale, Dependency Scale	After 12 months of treatment no significant group differences but on CDRS and Finger Tapping Test (each favoring placebo)
Ohkura, 1994 [13]	Cohort	30	AD women; age 71.2 −71.9 yrs.	oCEE 1.25 mg/day (n = 15), control (n = 15)	6 wks (3 wks)	• Global score • Dementia syndrome (motor, intellectual, emotional functions, different symptoms) • Depression • Regional blood flow • Brain activity • Serum steroid levels	• MMSE, HDS • GBSS • Ham-D • SPECT • Quantitative EEG • Blood sample	Significant improvement with ET on MMSE ($p < 0.001$), HDS ($p < 0.01$), GBSS ($p < 0.02$ resp. $p < 0.01$) but return to baseline values after ET discontinuation; significant and sustained improvement with ET on Ham-D ($p < 0.001$)
Schneider, 1997 [14]	PC-RCT (post-hoc analysis)	118 (per protocol analysis)	AD women: placebo (n = 53), placebo + ET (n = 7), tacrine (n = 50), tacrine + ET (n = 8)	oCEE (86%), oE2 (12%), E1-sulfate (2%); mean ET duration 11 yrs; concomitant MPA (n = 8)	30 wks.	• Global score • Relative change in subject's global cognitive and behavioral status (physician) • Relative change in subject's global cognitive and behavioral status (caregiver)	• MMSE, ADAS-cog • CIBIC • CIC	Significant improvement with tacrine + ET on ADAS-cog (vs. placebo, $p = 0.009$); significant improvement with placebo + ET on CIC (vs. placebo, $p = 0.005$)
Sundermann, 2006 [15]	Cohort	101	AD women with ever ET for at least	Not specified	Assessment only once (cross-sectional)	• Odor threshold	• Two-alternative, forced-choice, ascending	No significant differences in hit rate

			1 yr (n = 24) and with never ET (n = 77); mean age 74 yrs.			• Recognition memory	method of limits with the odorant butanol • Standardized test with 15 household odors, 15 pictures with faces and 15 abstract symbols, assessment of number of hits and false-positive errors	(odors, faces, symbols) between ET user and nonuser; however, ET nonuser committed significantly more false-positive errors for olfactory stimuli than ET user (not found for visual stimuli)
Wang, 2000 [16]	PC-RCT	50	Mean age 71 −72.6 yrs.	oCEE 1.25 mg/day, placebo	12 wks.	• Cognitive performance • Dementia severity • General clinical status • Common behavioral problems in AD patients • Affective condition • Regional cerebral blood flow	• CASI • CDR • CIBIC-plus • BEHAVE-AD • HARS, Ham-D • SPECT	No meaningful differences for any outcome.

Abbreviations: AD = Alzheimer's disease, ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive, BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease, BMI = Body Mass Index, BMICT = Blessed Memory Information and Concentration Test, BNT = Boston Naming Test, BPRS = Brief Psychiatric Rating Scale, BRDRS = Blessed Roth Dementia Rating Scale, CASI = Cognitive Ability Screening Instrument, CDRS = Clinical Dementia Rating Scale, CEE = conjugated equine estrogens, CERAD = Consortium to Establish a Registry for AD, CGIC = Clinical Global Impression of Change, CIBIC = Clinician-rated, Interview-based Impression of Change, CIC = Caregiver's Impression of Change, CSDD = Cornell Scale of Depression in Dementia, DSB = digit span backward, DSF = digit span forward, E1 = estrone, E2 = 17beta-estradiol, EEG = quantitative electroencepahologram, ET = estrogen therapy, GBS = Gottfries–Brane–Steen Scale, GDS = Geriatric Depression Scale, HARS = Hamilton Anxiety Rating Scale, Ham-D = Hamilton Depression Rating Scale, HDS = Hasegawa Dementia Scale, IADL = Instrumental Activities of Daily Living, MHT = Menopausal Hormone Therapy, MMSE = Mini-Mental State Examination, MPA = medroxyprogesterone acetate, NCSE = Neurocognitive Status Exam, NRS = Neuropsychological Rating Scale, o = oral, OMC = Orientation-memory-concentration test, PC-RCT = Placebo-controlled randomized trial, PSMS = Physical Self–Maintenance Scale, SD = Standard Deviation, SPECT = Single Photon Emission Computed Tomography, t = transdermal, VMSB = visual memory span backward, VMSF = visual memory span forward, wk = week, yrs. = years.

Table 4
Risk factors for dementia (only statistically significant risk factors that appeared in more than two studies were included; modified according to [1]).

Factor	Metric	Effect size (95% CI)	Neurological condition	Level of Evidence
Type 2 diabetes mellitus	RR	1.54 (1.39–1.72)	AD	Convincig
	RR	1.60 (1.43–1.79)	Dementia	Highly suggestive
	RR	2.28 (1.94–2.66)	Vascular dementia	Convincing
Hypertension	HR	1.59 (1.20–2.11)	Vascular dementia	Weak
Smoking	RR	1.26 (1.05–1.50)	Vascular dementia	Weak
	RR	1.13 (1.05–1.22)	Dementia	Weak
Low-frequency electromagnetic fields	RR	1.74 (1.37–2.21)	AD	Suggestive
Midlife BMI (obese versus normal weight)	RR	1.81 (1.22–2.69)	AD	Weak
	RR	1.91 (1.40–2.62)	Dementia	Suggestive
Mild traumatic brain injury	OR	1.35 (1.01–1.78)	Dementia	Weak
	OR	1.40 (1.03–1.90)	AD	Weak
Depression at any age/stage	RR	1.99 (1.84–2.16)	Dementia	Convincing
	RR	2.92 (1.87–4.56)	Vascular dementia	Weak
	RR	1.77 (1.48–2.13)	AD	Highly suggestive
Early life depression	RR	1.63 (1.27–2.11)	Dementia	Suggestive
Late life depression	RR	1.85 (1.67–2.05)	Dementia	Convincing
	OR	2.52 (1.77–3.59)	Vascular dementia	Weak
	RR	1.65 (1.42–1.92)	AD	Convincing
Low level of education (versus high level)	RR	1.88 (1.51–2.33)	Dementia	Suggestive
	RR	2.75 (2.19–3.45)	Vascular dementia	Weak
	RR	1.82 (1.36–2.43)	AD	Suggestive
Frequency of social contacts (low versus high level)	RR	1.57 (1.32–1.85)	Dementia	Convincing
Loneliness	RR	1.58 (1.19–2.09)	Dementia	Weak
Neuroticism (high versus low level)	HR	1.33 (1.21–1.45)	AD	Weak
Aluminium (exposed versus not exposed)	OR	1.72 (1.33–2.21)	AD	Suggestive

Definitions: “convincing” = statistical significance according to random-effects model at $P < 10–6$; based on more than 1000 cases; without large between-study heterogeneity (I2< 50%); 95% PI excluding the null value; and no evidence of small-study effects and excess significance; “highly suggestive” = associations with >1000 cases, $P < 10–6$, and largest study presenting a statistically significant effect; “suggestive” = associations with >1000 cases and a significant effect at $P < 10–3$; “weak” = remaining nominally significant associations.
Abbreviations: AD = Alzheimer's disease, BMI = Body Mass Index, CI = confidence interval, HR = hazard ratio, OR = odds ratio, RR = relative risk.

Table 5
Protective factors for dementia (only statistically significant risk factors that appeared in more than two studies were included; modified according to [1]).

Factor	Metric	Effect size (95% CI)	Neurological condition	Level of Evidence
Mediterranean diet	RR	0.60 (0.48–0.77)	AD	IV
	RR	0.69 (0.57–0.84)	Dementia	Convincing
Coffee consumption	RR	0.73 (0.55–0.97)	AD	Possible
Alcohol intake (light or moderate versus never	RR	0.74 (0.61–0.91)	Dementia	Weak
	RR	0.75 (0.57–0.98)	Vascular dementia	Weak
	RR	0.72 (0.61–0.86)	AD	Weak
Physical activity (high level versus low level)	RR	0.76 (0.66–0.86)	Dementia	Suggestive
	RR	0.62 (0.42–0.92)	Vascular dementia	Weak
	HR	0.62 (0.52–0.72)	AD	Highly suggestive
Vitamin E dietary intake (high versus low)	RR	0.80 (0.67–0.95)	AD	Weak
Vitamin C dietary intake (high versus low)	RR	0.85 (0.74–0.96)	AD	Weak
Statins (ever versus never use)	RR	0.83 (0.76–0.91)	Dementia	Sugegstive
	RR	0.72 (0.59–0.89)	AD	Weak
Antihypertensive drugs (ever versus never use)	HR	0.84 (0.75–0.94)	Dementia	Weak
	RR	0.64 (0.42–0.98)	Vascular dementia	Weak
Aspirin (ever versus never use)	RR	0.77 (0.63–0.95)	AD	Weak
NSAIDS (ever versus never use)	RR	0.74 (0.64–0.86)	AD	Suggestive
Fish intake (high versus low)	RR	0.88 (0.79–0.98)	AD	Weak

Table 5 (*continued*)

Factor	Metric	Effect size (95% CI)	Neurological condition	Level of Evidence
Openness (high versus low level)	RR	0.86 (0.77–0.96)	AD	Weak

Definitions: "convincing" = statistical significance according to random-effects model at P < 10−6; based on more than 1000 cases; without large between-study heterogeneity (I2< 50%); 95% PI excluding the null value; and no evidence of small-study effects and excess significance; "highly suggestive" = associations with >1000 cases, P < 10−6, and largest study presenting a statistically significant effect; "suggestive" = associations with >1000 cases and a significant effect at P < 10−3; "weak" = remaining nominally significant associations.
Abbreviations: AD = Alzheimer's disease, CI = confidence interval, HR = hazard ratio, NSAIDS = Non-steroidal anti-inflammatory drugs, RR = relative risk.

Table 6
Impact of estrogens on risk and protective factors for AD/dementia.

Protective Factors for developing dementia/ AD	Role of estrogens (examples)
Mediterranean diet	Possibly synergistic effect with estrogens as mediterranean diet may improve vasomotor symptoms, cardiovascular risk factors, mood and symptoms of depression. Long-term adherence may improve cardiovascular risk, bone mineral density and prevent cognitive decline [1].
Coffee consumption	Possibly synergistic effect with estrogens as bioactive substances from coffee have been shown to enhance glucose uptake in muscle cells in a dose-dependent manner in vitro, suggesting a preventive effect on T2DM in coffee drinkers [2].
Alcohol intake	Higher alcohol intake has been shown to be associated with higher serum E2 levels (post-hoc analysis of the RCT ELITE) [83].
Physical activity	Women with premature ovarian insufficiency experience significant deterioration in musculoskeletal health due to the loss of protective effects of estrogen [4]. Estrogens may regulate muscle mass and strength [5]. Decreased estrogen level occurring at menopause is linked to decreased energy expenditure [6]. Spontaneous physical activity has been shown to be reduced in OVX mice [6].
Vitamin E and C dietary intake	Positive associations between serum antioxidants (including vitamin E and C) and endogenous hormones (E2, progesterone, testosterone) have been reported in healthy premenopausal women supporting the hypothesis that concentrations of serum vitamins affect steroidogenesis [7].
Statins	Synergistic effect with estrogens also lowering serum lipids [8].
Antihypertensive drugs	Synergistic effect with estrogens as transdermal estrogens have been shown to have a beneficial effect on blood pressure in normotensive women and, at most, a neutral effect on hypertensive women. Oral estrogens had a neutral effect on blood pressure in hypertensive women [9].
Fish intake	Possibly synergistic effect with estrogens: the essential fatty acid ALA) is converted into longer-chain fatty acids including EPA, DPA and DHA. Women have been shown to reach greater increases in EPA status after ALA supplementation than men, supporting animal studies that have identified mechanisms by which sex hormones such as estrogen and progesterone interact with the synthesis of EPA and DHA [10].
Openness (high versus low level)	Possibly synergistic effect with estrogens as estrogens may reduce risk of depression in perimenopausal women [11].
Risk Factors for developing dementia/AD	**Effect of estrogens (examples)**
T2DM	Significant risk reduction for developing T2DM [12].
Hypertension	See section above on „antihypertensive drugs"
Midlife BMI	MHT has a neutral or beneficial effect on BMI [13].
Mild traumatic brain injury	E2 has a neuroprotective role in brain injury [84,85].
Depression	MHT may reduce risk of depression in perimenopausal women [11].
Frequency of social contacts	In rodents, estrogens have been shown to play an important role in the regulation of social behavior, from the production and detection of social signals to the expression of social preferences, social recognition, social learning and aggression [16].
Loneliness	As MHT may reduce risk of depression in perimenopausal women [11] the feeling of loneliness may also decrease.
Neuroticism	Estrogens have psychotropic properties such as increase in extraversion and decrease in neuroticism according to the Eysenck Personality Model [17].

Abbreviations:AD = Alzheimer's disease, ALA = α-linolenic acid, BMI = Body Mass Index, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, E2 = estradiol, ELITE = Early versus Late Intervention Trial with Estradiol, EPA = eicosapentaenoic acid, MHT = Menopausal Hormone Therapy, OVX = ovariectomy, RCT = randomized controlled trial, T2DM = type 2 diabetes mellitus.

Dementia is a chronic non-communicable disease (NCD). Alzheimer's disease (AD) is the most common cause of dementia.

Lifetime risk for developing AD is **10 in 100** women aged **65+**.

Risk factors: age, disposition (family history, genetic mutations, polymorphism of APOE gene) and exposition (behaviour, environment).

Menopausal Hormone Therapy

reduces risk for dementia / AD by

11%[1] - 33%[2].

Menopausal Hormone Therapy

has a beneficial / supporting effect on

some risk / protective factors

(marked by **).

Acquired risk factors	Acquired protective factors
Type 2 diabetes mellitus**	Mediterranean diet**
Hypertension**	Coffee consumption**
Smoking	Light/moderate alcohol intake
Low-frequency electromagnetic fields	Physical activity (high level)**
Midlife obesity**	Vitamin E dietary intake**
Mild traumatic brain injury**	Vitamin C dietary intake**
Depression**	Drugs: Statins, antihypertensive drugs, Aspirin, NSAIDS**, Menopausal Hormone Therapy
Low level of education	Fish intake**
Low frequency of social contacts, loneliness**	Openness**

[1]Wu, M., et al., Postmenopausal hormone therapy and Alzheimer's disease, dementia, and Parkinson's disease: A systematic review and time-response meta-analysis. Pharmacol Res, 2020. (prospective studies only)
[2]Song, Y.J., et al., The Effect of Estrogen Replacement Therapy on Alzheimer's Disease and Parkinson's Disease in Postmenopausal Women: A Meta-Analysis. Front Neurosci, 2020.

Fig. 1. Counseling tool for daily practice.

mentioned before (Table 6). For example, estrogens may have synergistically protective effects with certain lifestyle factors (Mediterranean diet [69], coffee consumption [70]), and drugs (micronutrients [71,72], statins [73], antihypertensive drugs [74]). Furthermore, estrogens may maintain or support physical activity [75–77] and personality traits [78]. Similarly, estrogens may counteract risk factors for AD and dementia, e.g. T2DM [79], hypertension [74], overweight/obesity [80], affective disorders [78,81,82]. Fig. 1 summarizes the above mentioned data and provides a counseling tool for daily practice.

Practice points

- 10 in 100 women above age 65 will be diagnosed with dementia/Alzheimer's disease.
- Apart from age and hereditary risk factors, there are multiple acquired risk and protective factors.
- Overall, menopausal hormone therapy may reduce the risk of dementia/Alzheimer's disease by about 11–33%. However, risk may vary depending on MHT type and age at initiation.
- Menopausal hormone therapy also displays a beneficial effect on some dementia risk factors and also augments some protective factors.
- Menopausal hormone therapy is not indicated for cognitive improvement in demented women.

Research agenda

- Impact of different hormone types, regimens and dosages on dementia/AD risk, e.g. bio-identical hormones (estradiol, micronized progesterone, dehydroepiandrosterone, testosterone), transdermal versus oral application, ultralow-dose versus standard-dose MHT.
- Defining the optimal age for MHT initiation and optimal MHT duration.
- Clarification, if there is a cognitive "window of opportunity" or not.
- Update of international scientific guidelines on MHT.

Summary

Dementia is a pandemic chronic non-communicable disease. 10 in 100 women above age 65 will be diagnosed with dementia, primarily Alzheimer's disease (AD). Apart from age and hereditary risk factors, there are multiple acquired risk and protective factors. Menopausal hormone therapy (MHT) reduces the risk of dementia/AD by about 11–33%. However, results may vary depending on MHT type, age at initiation and study design. For example, the Women's Health Initiative Memory Study (WHIMS) reported an approximately 2-fold increased risk of dementia/Alzheimer's disease if MHT comprising conjugated equine estrogens and medroxyprogesterone acetate was initiated in predominantly co-morbid postmenopausal women above age 65. MHT also displays a beneficial effect on some dementia risk factors and also supports some protective factors. MHT is not indicated for cognitive improvement in demented women. International scientific guidelines on MHT and dementia should acknowledge most recent data, including systematic reviews and meta-analyses.

Declaration of competing interest

The authors declare to have no conflict of interest in respect to the content of this publication.

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Appendix A. Supplementary data

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