Sex-specific reproductive and hormonal factors in relation to Alzheimer's disease-related biomarkers: A Systematic Review

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eFigure 1 Newcastle-Ottawa Scale (NOS) risk of bias assessment for cohort and cross-sectional studies included in the systematic review. Note: Figure was created by EGK in RStudio version 2026.01.0. 178
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eTable 1 Ovid Medline search strategy.

1	Menarche/
2	exp Menstrual cycle/
3	exp Menstruation Disturbances/
4	exp Reproduction/
5	exp Climacteric/
6	exp Reproductive history/
7	exp Pregnancy/
8	exp Breast Feeding/
9	exp Fertilization in Vitro/
10	exp Infertility/
11	exp Gynecologic Surgical Procedures/
12	exp Obstetric Surgical Procedures/
13	Gonadal Steroid Hormones/
14	exp Estrogens/
15	exp Progesterone/
16	exp Follicle Stimulating Hormone/
17	exp Luteinizing Hormone/
18	exp Sex Hormone-Binding Globulin/
19	exp Estradiol/
20	exp Ovarian diseases/
21	exp Female Urogenital Diseases/ and Pregnancy Complications/
22	Hyperprolactinemia/
23	(amenorrhea or climacteric* or endometrial cycle* or fertile period* or follicular phase or gravidit* or luteal phase or menarche or menopause or menstrual cycle* or menstruation or ovarian cycle* or parity or perimenopause or postmenopause or pregnan* or premenopause or reproduct* or stillbirth*).ti,ab,kf.
24	(breast fed or breastfed or breast feeding or breastfeeding or chestfeeding* or milk sharing or wet nursing).ti,ab,kf.
25	(abdominal deliver* or abortion* or c?esarean section* or c-section* or fertili#ation* in vitro or gynecologic* or hysterectom* or in vitro fertili#ation* or infertil* or obstetric* or oophorectom* or ovariectom* or steril* or sub-fertil* or subfertil* or test tube bab* or test tube fertili#ation*).ti,ab,kf.
26	(gonadal steroid hormone* or sex hormone* or sex steroid hormone*).ti,ab,kf.

27	(estradiol or estrogen* or follicle stimulating hormone or follitropin or FSH or ICSH or interstitial cell stimulating hormone or LH or luteinizing hormone or luteoziman or luteozyman or lutropin or pregnenedione or progesterone or sex steroid binding protein).ti,ab,kf.
28	(amniotic fluid embolism* or dystocia* or female genit* disease* or female urogenital disease* or fetal death* or fetal demise or fetal growth restriction or fetal growth retardation or fetal mummification or gestational diabetes or gestational hypertension or hyperemesis gravidarum or hyperprolactinemia or hypothalamus pituitary ovary axis or intrauterine growth restriction or intrauterine growth retardation or labo?r or membrane premature rupture* or ovarian disease* or ovarian failure or ovarian hyperstimulation or placental bed disorder* or polycystic ovar* syndrome or post natal depression or post natal dysphoria or post partum depression or post partum dysphoria or postnatal depression or postnatal dysphoria or postpartum depression or postpartum dysphoria or postpartum hemorrhage or postpartum seps?s or premature birth* or premature rupture of fetal membranes or premature rupture of membrane or preterm delivery or primary ovarian insufficiency or PROM or puerperal infection* or resistant ovary syndrome or urogenital tract disease*).ti,ab,kf.
29	exp Male Genital Diseases/
30	exp Androstanes/
31	Androgens/
32	Hypogonadism/
33	exp Urogenital Surgical Procedures/
34	(cryptorchidism or erectile dysfunction or impotence or male genital disease* or prostatic adenoma* or prostatic hyperplasia or prostatic hypertroph* or undescended test?s or varicocele*).ti,ab,kf.
35	(androgen* or androst* or dihydrotestosterone or eugonad* or hypogonad* or testosterone).ti,ab,kf.
36	(castration* or gonadectom* or orchidectom* or orchiectom* or urogenital surgical procedure* or Y chromosome haplotype).ti,ab,kf.
37	Sex Characteristics/
38	(sex-related or sex* characteristic* or sex difference* or gender characteristic* or gender difference* or sexual dichromatism* or gender dimorphism*).ti,ab,kf.
39	or/1-38
40	((biomarker* or marker*) adj8 (alzheimer* or cogniti* or neurodegeneration)).ti,ab,kf.
41	exp Amyloid/
42	Plaque, Amyloid/
43	(a beta peptide* or a beta protein* or abeta* or AD plaque* or alzheimer* beta-protein* or alzheimer* ABP or alzheimer* plaque* or amyloid or neuritic plaque* or Ab42 or Ab-42 or Abeta42 or Ab1-42 or Ab1-40 or Ab40).ti,ab,kf.
44	tau Proteins/
45	Neurofibrillary Tangles/
46	(tau or tau181 or tau231 or tau217).ti,ab,kf.
47	(neurofibrillary tangle* or neuro-fibrillary tangle* or neurofibrillary tautangle* or neuro-fibrillary tautangle* or NfL or NfLs or NFT or NFTs or protease nexin 2 or protease nexin II or senile plaque*).ti,ab,kf.

48	Fluorodeoxyglucose F18/
49	(18F Fluorodeoxyglucose or 18F-FDG or 18FDG or Fludeoxyglucose F 18 or Fluorine 18 fluorodeoxyglucose or Fluorodeoxyglucose F 18 or 2 Fluoro 2 deoxy D glucose or 2 Fluoro 2 deoxyglucose or F-18-deoxyglucose).ti,ab,kf.
50	(neurofilament light* or neuro-filament light* or NFL).ti,ab,kf.
51	Pittsburgh compound B.ti,ab,kf.
52	or/40-51
53	Atrophy/
54	(brain or cerebral).ti,ab,kf.
55	53 and 54
56	((brain or cerebral) adj8 atrophy).ti,ab,kf.
57	Brain Cortical Thickness/
58	(cortical thickness or cerebral cortex thickness or grey matter thickness).ti,ab,kf.
59	((hippocamp* or ventric* or brain) adj3 volume).ti,ab,kf.
60	(white matter hyperintensit* or white matter integrity or lacune* or microbleeds or infarct* or perivascular space* or superficial siderosis or small vessel disease).ti,ab,kf.
61	or/55-60
62	exp Magnetic Resonance Imaging/
63	exp Positron Emission Tomography Computed Tomography/
64	(magnetic resonance imag* or MRI or positron emission tomography computed tomography or PET).ti,ab,kf.
65	or/62-64
66	61 and 65
67	52 or 66
68	39 and 67
69	68 not (animals not humans).sh.
70	limit 69 to english language

eTable 2 Embase search strategy.

#1	'menarche'/mj
#2	'menstrual cycle'/exp/mj
#3	'menstruation disorder'/exp/mj
#4	'reproduction'/exp/mj
#5	'climacterium'/exp/mj
#6	'reproductive history'/exp/mj
#7	'pregnancy'/exp/mj
#8	'breast feeding'/exp/mj
#9	'in vitro fertilization'/exp/mj
#10	'infertility'/exp/mj
#11	'gynecologic surgery'/exp/mj
#12	'obstetric operation'/exp/mj
#13	'sex hormone'/mj
#14	'estrogen'/exp/mj
#15	'progesterone'/exp/mj
#16	'follitropin'/exp/mj
#17	'luteinizing hormone'/exp/mj
#18	'sex hormone binding globulin'/exp/mj
#19	'estradiol'/exp/mj
#20	'ovary disease'/exp/mj
#21	'urogenital tract disease'/exp/mj
#22	'hyperprolactinemia'/mj
#23	amenorrhea:ti,ab,kw OR climacteric*:ti,ab,kw OR 'endometrial cycle*':ti,ab,kw OR 'fertile period*':ti,ab,kw OR 'follicular phase':ti,ab,kw OR gravidit*:ti,ab,kw OR 'luteal phase':ti,ab,kw OR menarche:ti,ab,kw OR menopause:ti,ab,kw OR 'menstrual cycle*':ti,ab,kw OR menstruation:ti,ab,kw OR 'ovarian cycle*':ti,ab,kw OR parity:ti,ab,kw OR perimenopause:ti,ab,kw OR postmenopause:ti,ab,kw OR pregnan*:ti,ab,kw OR premenopause:ti,ab,kw OR reproduct*:ti,ab,kw OR stillbirth*:ti,ab,kw
#24	'breast fed':ti,ab,kw OR breastfed:ti,ab,kw OR 'breast feeding':ti,ab,kw OR breastfeeding:ti,ab,kw OR chestfeeding*:ti,ab,kw OR 'milk sharing':ti,ab,kw OR 'wet nursing':ti,ab,kw
#25	'abdominal deliver*':ti,ab,kw OR abortion*:ti,ab,kw OR 'cesarean section*':ti,ab,kw OR 'caesarean section*':ti,ab,kw OR 'c section*':ti,ab,kw OR 'fertili?ation* in vitro':ti,ab,kw OR gynecologic*:ti,ab,kw OR hysterectom*:ti,ab,kw OR 'in vitro fertili?ation*':ti,ab,kw OR infertil*:ti,ab,kw OR obstetric*:ti,ab,kw OR oophorectom*:ti,ab,kw OR ovariectom*:ti,ab,kw OR steril*:ti,ab,kw OR 'sub fertil*':ti,ab,kw OR subfertil*:ti,ab,kw OR 'test tube bab*':ti,ab,kw OR 'test tube fertili?ation*':ti,ab,kw
#26	'gonadal steroid hormone*':ti,ab,kw OR 'sex hormone*':ti,ab,kw OR 'sex steroid hormone*':ti,ab,kw

#27	estradiol:ti,ab,kw OR estrogen*:ti,ab,kw OR 'follicle stimulating hormone':ti,ab,kw OR follitropin:ti,ab,kw OR fsh:ti,ab,kw OR icsh:ti,ab,kw OR 'interstitial cell stimulating hormone':ti,ab,kw OR lh:ti,ab,kw OR 'luteinizing hormone':ti,ab,kw OR luteoziman:ti,ab,kw OR luteozyman:ti,ab,kw OR lutropin:ti,ab,kw OR pregnenedione:ti,ab,kw OR progesterone:ti,ab,kw OR 'sex steroid binding protein':ti,ab,kw
#28	'amniotic fluid embolism*':ti,ab,kw OR dystocia*:ti,ab,kw OR 'female genit* disease*':ti,ab,kw OR 'female urogenital disease*':ti,ab,kw OR 'fetal death*':ti,ab,kw OR 'fetal demise':ti,ab,kw OR 'fetal growth restriction':ti,ab,kw OR 'fetal growth retardation':ti,ab,kw OR 'fetal mummification':ti,ab,kw OR 'gestational diabetes':ti,ab,kw OR 'gestational hypertension':ti,ab,kw OR 'hyperemesis gravidarum':ti,ab,kw OR hyperprolactinemia:ti,ab,kw OR 'hypothalamus pituitary ovary axis':ti,ab,kw OR 'intrauterine growth restriction':ti,ab,kw OR 'intrauterine growth retardation':ti,ab,kw OR labor:ti,ab,kw OR labour:ti,ab,kw OR 'membrane premature rupture*':ti,ab,kw OR 'ovarian disease*':ti,ab,kw OR 'ovarian failure':ti,ab,kw OR 'ovarian hyperstimulation':ti,ab,kw OR 'placental bed disorder*':ti,ab,kw OR 'polycystic ovar* syndrome':ti,ab,kw OR 'post natal depression':ti,ab,kw OR 'post natal dysphoria':ti,ab,kw OR 'post partum depression':ti,ab,kw OR 'post partum dysphoria':ti,ab,kw OR 'postnatal depression':ti,ab,kw OR 'postnatal dysphoria':ti,ab,kw OR 'postpartum depression':ti,ab,kw OR 'postpartum dysphoria':ti,ab,kw OR 'postpartum hemorrhage':ti,ab,kw OR 'postpartum seps?s':ti,ab,kw OR 'premature birth*':ti,ab,kw OR 'premature rupture of fetal membranes':ti,ab,kw OR 'premature rupture of membrane':ti,ab,kw OR 'preterm delivery':ti,ab,kw OR 'primary ovarian insufficiency':ti,ab,kw OR prom:ti,ab,kw OR 'puerperal infection*':ti,ab,kw OR 'resistant ovary syndrome':ti,ab,kw OR 'urogenital tract disease*':ti,ab,kw
#29	'male genital system disease'/exp/mj
#30	'androstane derivative'/exp/mj
#31	'androgen'/mj
#32	'hypogonadism'/mj
#33	'urologic surgery'/exp/mj
#34	cryptorchidism:ti,ab,kw OR 'erectile dysfunction':ti,ab,kw OR impotence:ti,ab,kw OR 'male genital disease*':ti,ab,kw OR 'prostatic adenoma*':ti,ab,kw OR 'prostatic hyperplasia':ti,ab,kw OR 'prostatic hypertroph*':ti,ab,kw OR 'undescended test?s':ti,ab,kw OR varicocele*:ti,ab,kw
#35	androgen*:ti,ab,kw OR androst*:ti,ab,kw OR dihydrotestosterone:ti,ab,kw OR eugonad*:ti,ab,kw OR hypogonad*:ti,ab,kw OR testosterone:ti,ab,kw
#36	castration*:ti,ab,kw OR gonadectom*:ti,ab,kw OR orchidectom*:ti,ab,kw OR orchiectom*:ti,ab,kw OR 'urogenital surgical procedure*':ti,ab,kw OR 'y chromosome haplotype':ti,ab,kw
#37	'sexual characteristics'/mj
#38	'sex-related':ti,ab,kw OR 'sex* characteristic*':ti,ab,kw OR 'sex difference*':ti,ab,kw OR 'gender characteristic*':ti,ab,kw OR 'gender difference*':ti,ab,kw OR 'sexual dichromatism*':ti,ab,kw OR 'gender dimorphism*':ti,ab,kw
#39	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38
#40	((biomarker* OR marker*) NEAR/8 (alzheimer* OR cogniti* OR neurodegeneration)):ti,ab,kw
#41	'amyloid'/exp
#42	'amyloid plaque'/de
#43	'tau protein'/de
#44	'neurofibrillary tangle'/de
#45	'fluorodeoxyglucose f 18'/de
#46	'a beta peptide*':ti,ab,kw OR 'a beta protein*':ti,ab,kw OR abeta*:ti,ab,kw OR 'ad plaque*':ti,ab,kw OR 'alzheimer* beta-protein*':ti,ab,kw OR 'alzheimer* abp':ti,ab,kw OR 'alzheimer* plaque*':ti,ab,kw OR amyloid:ti,ab,kw OR 'neuritic plaque*':ti,ab,kw OR ab42:ti,ab,kw OR 'ab 42':ti,ab,kw OR abeta42:ti,ab,kw OR 'ab1 42':ti,ab,kw OR 'ab1 40':ti,ab,kw OR ab40:ti,ab,kw

#47	tau:ti,ab,kw OR tau181:ti,ab,kw OR tau231:ti,ab,kw OR tau217:ti,ab,kw
#48	'neurofibrillary tangle*':ti,ab,kw OR 'neuro-fibrillary tangle*':ti,ab,kw OR 'neurofibrillary tautangle*':ti,ab,kw OR 'neuro-fibrillary tautangle*':ti,ab,kw OR nfl:ti,ab,kw OR nfls:ti,ab,kw OR nft:ti,ab,kw OR nfts:ti,ab,kw OR 'protease nexin 2':ti,ab,kw OR 'protease nexin ii':ti,ab,kw OR 'senile plaque*':ti,ab,kw
#49	'18f fluorodeoxyglucose':ti,ab,kw OR '18f fdg':ti,ab,kw OR 18fdg:ti,ab,kw OR 'fludeoxyglucose f 18':ti,ab,kw OR 'fluorine 18 fluorodeoxyglucose':ti,ab,kw OR 'fluorodeoxyglucose f 18':ti,ab,kw OR '2 fluoro 2 deoxy d glucose':ti,ab,kw OR '2 fluoro 2 deoxyglucose':ti,ab,kw OR 'f-18-deoxyglucose':ti,ab,kw
#50	'neurofilament light*':ti,ab,kw OR 'neuro-filament light*':ti,ab,kw OR nfl:ti,ab,kw
#51	'pittsburgh compound b':ti,ab,kw
#52	#40 OR #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51
#53	'atrophy'/de
#54	brain:ti,ab,kw OR cerebral:ti,ab,kw
#55	#53 and #54
#56	((brain OR cerebral) NEAR/8 atrophy):ti,ab,kw
#57	'cortical thickness (brain)'/de
#58	'cortical thickness':ti,ab,kw OR 'cerebral cortex thickness':ti,ab,kw OR 'grey matter thickness':ti,ab,kw
#59	((hippocamp* OR ventric* OR brain) NEAR/3 volume):ti,ab,kw
#60	'white matter hyperintensit*':ti,ab,kw OR 'white matter integrity':ti,ab,kw OR lacune*:ti,ab,kw OR microbleeds:ti,ab,kw OR infarct*:ti,ab,kw OR 'perivascular space*':ti,ab,kw OR 'superficial siderosis':ti,ab,kw OR 'small vessel disease':ti,ab,kw
#61	#55 OR #56 OR #57 OR #58 OR #59 OR #60
#62	'nuclear magnetic resonance imaging'/exp
#63	'positron emission tomography-computed tomography'/exp
#64	'magnetic resonance imag*':ti,ab,kw OR mri:ti,ab,kw OR 'positron emission tomography computed tomography':ti,ab,kw OR pet:ti,ab,kw
#65	#62 OR #63 OR #64
#66	#61 AND #65
#67	#52 OR #66
#68	#39 AND #67
#69	#68 NOT ([animals]/lim NOT [humans]/lim)
#70	#69 AND ('conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it)
#71	#69 NOT #70
#72	#69 NOT #70 AND [english]/lim

eTable 3 Web of Science search strategy.

1	TS=((amenorrhea or climacteric* or "endometrial cycle*" or "fertile period*" or "follicular phase" or gravidit* or "luteal phase" or menarche or menopause or "menstrual cycle*" or menstruation or "ovarian cycle*" or parity or perimenopause or postmenopause or pregnan* or premenopause or reproduct* or stillbirth*))
2	TS=(("breast fed" or breastfed or "breast feeding" or breastfeeding or chestfeeding* or "milk sharing" or "wet nursing"))
3	TS=(("abdominal deliver*" or abortion* or "cesarean section*" or "caesarean section*" or c-section* or "fertili?ation* in vitro" or gynecologic* or hysterectom* or "in vitro fertili?ation*" or infertil* or obstetric* or oophorectom* or ovariectom* or steril* or sub-fertil* or subfertil* or "test tube bab*" or "test tube fertili?ation*"))
4	TS=(("gonadal steroid hormone*" or "sex hormone*" or "sex steroid hormone*"))
5	TS=((estradiol or estrogen* or "follicle stimulating hormone" or follitropin or FSH or ICSH or "interstitial cell stimulating hormone" or LH or "luteinizing hormone" or luteoziman or luteozyman or lutropin or pregnenedione or progesterone or "sex steroid binding protein"))
6	TS=(("amniotic fluid embolism*" or dystocia* or "female genit* disease*" or "female urogenital disease*" or "fetal death*" or "fetal demise" or "fetal growth restriction" or "fetal growth retardation" or "fetal mummification" or "gestational diabetes" or "gestational hypertension" or "hyperemesis gravidarum" or hyperprolactinemia or "hypothalamus pituitary ovary axis" or "intrauterine growth restriction" or "intrauterine growth retardation" or labo$r or "membrane premature rupture*" or "ovarian disease*" or "ovarian failure" or "ovarian hyperstimulation" or "placental bed disorder*" or "polycystic ovar* syndrome" or "post natal depression" or "post natal dysphoria" or "post partum depression" or "post partum dysphoria" or "postnatal depression" or "postnatal dysphoria" or "postpartum depression" or "postpartum dysphoria" or "postpartum hemorrhage" or "postpartum seps?s" or "premature birth*" or "premature rupture of fetal membranes" or "premature rupture of membrane" or "preterm delivery" or "primary ovarian insufficiency" or PROM or "puerperal infection*" or "resistant ovary syndrome" or "urogenital tract disease*"))
7	TS=((cryptorchidism or "erectile dysfunction" or impotence or "male genital disease*" or "prostatic adenoma*" or "prostatic hyperplasia" or "prostatic hypertroph*" or "undescended test?s" or varicocele*))
8	TS=((androgen* or androst* or dihydrotestosterone or eugonad* or hypogonad* or testosterone))
9	TS=((castration* or gonadectom* or orchidectom* or orchiectom* or "urogenital surgical procedure*" or "Y chromosome haplotype"))
10	TS=(("sex-related" or "sex* characteristic*" or "sex difference*" or "gender characteristic*" or "gender difference*" or "sexual dichromatism*" or "gender dimorphism*"))
11	#10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
12	TS=(((biomarker* or marker*) NEAR/8 (alzheimer* or cogniti* or neurodegeneration)))
13	TS=(("a beta peptide*" or "a beta protein*" or abeta* or "AD plaque*" or "alzheimer* beta-protein*" or "alzheimer* ABP" or "alzheimer* plaque*" or amyloid or "neuritic plaque*" or Ab42 or Ab-42 or Abeta42 or Ab1-42 or Ab1-40 or Ab40))
14	TS=((tau or tau181 or tau231 or tau217))
15	TS=(("neurofibrillary tangle*" or "neuro-fibrillary tangle*" or "neurofibrillary tautangle*" or "neuro-fibrillary tautangle*" or NfL or NfLs or NFT or NFTs or "protease nexin 2" or "protease nexin II" or "senile plaque*"))
16	TS=(("18F Fluorodeoxyglucose" or 18F-FDG or 18FDG or "Fludeoxyglucose F 18" or "Fluorine 18 fluorodeoxyglucose" or "Fluorodeoxyglucose F 18" or "2 Fluoro 2 deoxy D glucose" or "2 Fluoro 2 deoxyglucose" or "F-18-deoxyglucose"))
17	TS=(("neurofilament light*" or "neuro-filament light*" or NFL))
18	TS=("Pittsburgh compound B")

19	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
20	TS=(((brain or cerebral) NEAR/8 atrophy))
21	TS=(("cortical thickness" or "cerebral cortex thickness" or "grey matter thickness"))
22	TS=(((hippocamp* or ventric* or brain) NEAR/3 volume))
23	TS=(("white matter hyperintensit*" or "white matter integrity" or lacune* or microbleeds or infarct* or "perivascular space*" or "superficial siderosis" or "small vessel disease"))
24	#20 OR #21 OR #22 OR #23
25	TS=(("magnetic resonance imag*" or MRI or "positron emission tomography computed tomography" or PET))
26	#24 AND #25
27	#19 OR #26
28	#11 AND #27
29	PMID=(40055645 OR 40114204 OR 40054104 OR 40023441 OR 40089164 OR 40024019 OR 40117341 OR 39505806 OR 39609275 OR 39914657 OR 40100796 OR 39832750 OR 39639170 OR 40057971 OR 35777535 OR 39283526 OR 39999279 OR 40108996 OR 39657832 OR 39778840 OR 39814270 OR 39848022 OR 39855430 OR 39986234 OR 40067832 OR 39775669 OR 39647630 OR 39908274 OR 39829385 OR 40004200 OR 39549949 OR 39774101 OR 39521422 OR 39894567 OR 39819738 OR 39818142 OR 39824498 OR 39410659 OR 39575525 OR 39690128 OR 39780443 OR 39799553 OR 39937416 OR 40061939 OR 40119726 OR 39447490 OR 40111597 OR 39388249 OR 40093888 OR 39488949 OR 39835519 OR 39637835 OR 38365827 OR 38445838 OR 38862757 OR 39135052 OR 39334471 OR 39390478 OR 39412689 OR 39487477 OR 39684212 OR 39769435 OR 39265451 OR 39321864 OR 39349117 OR 39004128 OR 39642042 OR 39550500 OR 38375996 OR 38504469 OR 39167347 OR 39305349 OR 39389279 OR 39180888 OR 39543985 OR 39425543 OR 39526610 OR 39142510 OR 39089073 OR 39406773 OR 39354854 OR 38985243 OR 38945454 OR 39028589 OR 39350323 OR 39283977 OR 39273325 OR 39330860 OR 38636670 OR 38971132 OR 39002827 OR 39151586 OR 38869890 OR 38910516 OR 38642656 OR 38754826 OR 38754820 OR 39226781 OR 39213082 OR 39119909 OR 39164329 OR 38897347 OR 38684411 OR 39007742 OR 38423984 OR 38923164 OR 38942967 OR 39175337 OR 39201636 OR 39201705 OR 38698671 OR 38942282 OR 39098090 OR 38650574 OR 39197039 OR 38778746 OR 38922751 OR 38848313 OR 38057643 OR 38083902 OR 38994978 OR 39063104 OR 38735268 OR 38865747 OR 38395399 OR 36409648 OR 38705966 OR 38927745 OR 38519010 OR 38655691 OR 38413747 OR 38450924 OR 38669563 OR 38702895 OR 38432113 OR 38484978 OR 38643726 OR 37949403 OR 38101734 OR 38503494 OR 38294617 OR 38514467 OR 38640117 OR 38627959 OR 37926988 OR 38169182 OR 38171198 OR 38109363 OR 37542532 OR 38153668 OR 38323709 OR 38338656 OR 38379185 OR 38398879 OR 38315685 OR 39606929 OR 37852113 OR 38000775 OR 37946400 OR 37991136 OR 38091051 OR 38008208 OR 37707543 OR 38142289 OR 38758542 OR 38888777 OR 38767632 OR 39548323 OR 39736040 OR 38220437 OR 38233342 OR 38124145 OR 37926343 OR 37370108 OR 37422495 OR 37474957 OR 37587511 OR 37758709 OR 37852961 OR 38139156 OR 37806088 OR 39491237 OR 37910662 OR 37641319 OR 37641308 OR 37678770 OR 37678786 OR 37549523 OR 37641299 OR 37824601 OR 37889501 OR 37395729 OR 37458952 OR 37522293 OR 37578550 OR 37437614 OR 37834366 OR 37379587 OR 37674420 OR 37758935 OR 37541447 OR 37433937 OR 37315391 OR 37442014 OR 37759724 OR 37762358 OR 37471421 OR 37479579 OR 38008966 OR 37653057 OR 37494181 OR 37559092 OR 37195481 OR 37245852 OR 37566616 OR 37471385 OR 37030625 OR 37182890 OR 36484981 OR 36718979 OR 36794556 OR 36942377 OR 36931593 OR 36958104 OR 37296636 OR 37137264 OR 37127299 OR 37080781 OR 37268579 OR 36940724 OR 37235352 OR 37162190 OR 37067455 OR 36934584 OR 36935239 OR 37246145 OR 37567676 OR 36781020 OR 36807777 OR 36740105 OR 37108601 OR 36653292 OR 36797190 OR 36823004 OR 36977735 OR 36572179 OR 36195205 OR 36634247 OR 36529113 OR 36899916 OR 36902018 OR 36918475 OR 36634751 OR 36038084 OR 36155778 OR 36602917 OR 36592924 OR 36259728 OR 36835532 OR 35609517 OR 36190633 OR 36460494 OR 36594396 OR 36065472 OR 36194703 OR 36776065 OR 37183470 OR 37424461 OR 37855434 OR 36357210 OR 34596883 OR 35313963 OR 35364737 OR 35439990 OR 35568928 OR 35705972 OR 35906855 OR 35984596 OR 36314682 OR

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16707766 OR 16925587 OR 16951581 OR 16977382 OR 16707209 OR 16820652 OR 16909864 OR 16908960 OR 16720320 OR 16469811 OR 16452456 OR 16426607 OR 16647929 OR 16574231 OR 16406021 OR 16672354 OR 16503402 OR 16435375 OR 16533397 OR 16251743 OR 16488973 OR 15961189 OR 16293347 OR 16207835 OR 16251498 OR 16443500 OR 16274726 OR 16362882 OR 16360126 OR 16177981 OR 16271716 OR 16336227 OR 16327005 OR 17029229 OR 16391199 OR 16079305 OR 16122394 OR 16099855 OR 16295934 OR 15987823 OR 15950203 OR 16011741 OR 16261763 OR 15982524 OR 15911130 OR 15882808 OR 15919817 OR 15837589 OR 16033199 OR 15731362 OR 15890599 OR 15910780 OR 15837120 OR 15854640 OR 15788451 OR 16153145 OR 15653182 OR 15793278 OR 15850676 OR 15613779 OR 15659394 OR 15647739 OR 15813954 OR 15881674 OR 15663894 OR 15634781 OR 16024764 OR 16024766 OR 16108528 OR 15570177 OR 15457517 OR 15545013 OR 15579583 OR 15590986 OR 15560851 OR 15308615 OR 15464829 OR 15357665 OR 15307151 OR 15336519 OR 15457471 OR 15347727 OR 15308303 OR 15305149 OR 15212841 OR 15246826 OR 15246835 OR 15299068 OR 15345812 OR 15158533 OR 14973264 OR 15307897 OR 15271478 OR 15301238 OR 15007105 OR 15147569 OR 15295718 OR 14982935 OR 15039952 OR 15081593 OR 15066212 OR 15105831 OR 15073267 OR 14681234 OR 15033165 OR 15074097 OR 14975704 OR 14694435 OR 14749383 OR 14744630 OR 14697319 OR 13679318 OR 14705215 OR 15004784 OR 15254070 OR 12876404 OR 14635938 OR 14635939 OR 14635940 OR 14750653 OR 14967893 OR 14580942 OR 12855605 OR 14622134 OR 14652679 OR 14511787 OR 12826577 OR 12927766 OR 14572470 OR 12928783 OR 12914969 OR 12960202 OR 12956885 OR 12756249 OR 14967922 OR 12810569 OR 12876302 OR 12736081 OR 12817504 OR 12753077 OR 12719532 OR 12723885 OR 12726924 OR 12606392 OR 12678689 OR 12756058 OR 12471018 OR 12614681 OR 12600667 OR 12604656 OR 12614334 OR 12533434 OR 12566109 OR 14967948 OR 12627715 OR 14993045 OR 12515325 OR 12527479 OR 12515896 OR 12417753 OR 12393227 OR 12441769 OR 12882368 OR 12206872 OR 12360579 OR 12360580 OR 12423251 OR 12372566 OR 12161340 OR 12191810 OR 12090928 OR 12176677 OR 12212774 OR 12049785 OR 12513124 OR 12032347 OR 12081239 OR 12212938 OR 11916308 OR 11756436 OR 11898800 OR 11949857 OR 11821147 OR 11804954 OR 11812515 OR 12094016 OR 11689174 OR 11162193 OR 11573983 OR 11566724 OR 11578779 OR 11484079 OR 11536323 OR 11505032 OR 11418417 OR 11440193 OR 11435923 OR 11435931 OR 11319143 OR 11337197 OR 11355657 OR 11328559 OR 11238065 OR 11241181 OR 11361106 OR 11274783 OR 11207214 OR 11207217 OR 11226041 OR 11083861 OR 11159370 OR 11137887 OR 11152658 OR 11272188 OR 11479146 OR 11099491 OR 11099831 OR 11113610 OR 11106067 OR 11063323 OR 11079750 OR 11039852 OR 10998202 OR 10993862 OR 10981671 OR 10906045 OR 10869339 OR 10913358 OR 10881241 OR 10819777 OR 10842078 OR 10843766 OR 10895977 OR 10775182 OR 10858597 OR 10777685 OR 11215751 OR 10805155 OR 10762031 OR 10915920 OR 10737804 OR 10719073 OR 10708675 OR 10684803 OR 10655508 OR 10684690 OR 10611076 OR 10678751 OR 10654578 OR 10864796 OR 10818524 OR 10818545 OR 10638317 OR 11193810 OR 10569983 OR 10570008 OR 10566973 OR 10692864 OR 10692865 OR 10619630 OR 10564538 OR 10529281 OR 10735098 OR 10510453 OR 10491620 OR 10491621 OR 10501189 OR 10521559 OR 10411528 OR 10444031 OR 10587105 OR 10621945 OR 10734400 OR 10377064 OR 10626000 OR 10446751 OR 10374817 OR 10230812 OR 10206436 OR 10438325 OR 10221457 OR 9927303 OR 9854173 OR 9886868 OR 9890977 OR 9974116 OR 10341723 OR 10484288 OR 10460699 OR 11254026 OR 9883888 OR 10050945 OR 9853021 OR 10063969 OR 9719418 OR 9851691 OR 9813255 OR 9884997 OR 10457312 OR 9871483 OR 9746726 OR 9700688 OR 9687290 OR 9687291 OR 9687298 OR 9881892 OR 9679964 OR 9605127 OR 12671307 OR 9547226 OR 9603248 OR 9551399 OR 9595361 OR 9546718 OR 9569670 OR 9542153 OR 9615175 OR 9460750 OR 9522357 OR 9571566 OR 9538340 OR 9521904 OR 9832130 OR 9551254 OR 9467306 OR 9348208 OR 9348245 OR 9415454 OR 9427376 OR 9500123 OR 9396135 OR 9404063 OR 9310170 OR 9324053 OR 9376641 OR 9283000 OR 9255154 OR 9583999 OR 9192613 OR 9228295 OR 9182944 OR

	9190953 OR 9199666 OR 9143235 OR 9165109 OR 9090564 OR 9106616 OR 9138447 OR 9022585 OR 9021744 OR 9116139 OR 9225113 OR 9321870 OR 8941576 OR 8691035 OR 8816744 OR 8880461 OR 8926197 OR 8652672 OR 8652673 OR 8805095 OR 8612567 OR 8603586 OR 8695888 OR 8565321 OR 8845053 OR 8650104 OR 8920256 OR 8780008 OR 9266545 OR 7488136 OR 8562708 OR 8608654 OR 8606939 OR 7588227 OR 8522881 OR 8750877 OR 8537018 OR 8580366 OR 7478449 OR 7492688 OR 8587967 OR 7623310 OR 7623321 OR 7477655 OR 7473874 OR 7667410 OR 7593840 OR 7546244 OR 7721855 OR 7780007 OR 7628948 OR 7628952 OR 7781160 OR 7898628 OR 7539437 OR 7653112 OR 7729802 OR 7850465 OR 7827621 OR 7930760 OR 7838378 OR 8033819 OR 8126796 OR 8003804 OR 8157530 OR 8131083 OR 7861381 OR 7509640 OR 8235447 OR 7691816 OR 7903429 OR 8242340 OR 8213351 OR 8097942 OR 8322607 OR 8457241 OR 8452929 OR 7680026 OR 7678954 OR 1488050 OR 1282805 OR 1469745 OR 1453490 OR 1281203 OR 1353757 OR 1527992 OR 1456186 OR 1520040 OR 1402485 OR 1754300 OR 1939386 OR 1944725 OR 1908244 OR 1679206 OR 2046828 OR 1868374 OR 1902286 OR 1899446 OR 2085748 OR 2230953 OR 2144302 OR 1695006 OR 2113283 OR 2211293 OR 1696529 OR 2388945 OR 1691262 OR 2139536 OR 2182503 OR 2108230 OR 2817080 OR 2774586 OR 2768063 OR 2731581 OR 2498572 OR 2648649 OR 2711570 OR 2909653 OR 2717138 OR 2626668 OR 3146720 OR 3197816 OR 3241839 OR 2978293 OR 3189043 OR 3140107 OR 2968047 OR 3260365 OR 3430482 OR 3117356 OR 3501249 OR 3443430 OR 3115177 OR 3620333 OR 2438393 OR 2951644 OR 3505961 OR 3715410 OR 3747331 OR 3956662 OR 3512716 OR 3780636 OR 4085595 OR 3909974 OR 4065533 OR 4025511 OR 3990242 OR 3159702 OR 2986266 OR 3923292 OR 4000546 OR 2982527 OR 6509082 OR 6433402 OR 6513235 OR 6725634 OR 6710810 OR 6226670 OR 6685394 OR 6409477 OR 7187810 OR 6213073 OR 7058346 OR 6166709 OR 7391842 OR 7435596 OR 6991809 OR 7356053 OR 157110 OR 555061 OR 697442 OR 732262 OR 668386 OR 623207 OR 578106 OR 848292 OR 1247859 OR 946395 OR 1124644 OR 1189236 OR 1059163 OR 4279316 OR 4617929 OR 4568075 OR 4943459 OR 5564918 OR 4325690 OR 4099427 OR 5421775 OR 5494805 OR 4310548 OR 4183938 OR 5814951 OR 6011790 OR 4159062 OR 5891357 OR 5318199 OR 14121411 OR 14058705 OR 14059001 OR 14448731 OR 13826202 OR 18895387)
30	#28 NOT #29
31	#28 NOT #29 and Proceeding Paper or Meeting Abstract or Editorial Material (Exclude – Document Types)
32	#28 NOT #29 and Proceeding Paper or Meeting Abstract or Editorial Material (Exclude – Document Types) and English (Languages)

eTable 4 Reasons for full-text screening exclusions (n=79).

Author Year	DOI	Reason
Asih 2015	https://dx.doi.org/10.2174/1871527314666150429112112	Wrong population
Ballesteros 2025	https://dx.doi.org/10.1126/sciadv.adt5619	Other subgroup/natural variation
Beeri 2009	https://dx.doi.org/10.1016/j.neurobiolaging.2007.11.011	Postmortem study
Bergman 2018	https://dx.doi.org/10.1371/journal.pone.0196025	Wrong RQ
Bergman 2022	https://dx.doi.org/10.1016/j.ajog.2022.02.036	Inappropriate age grouping
Bergman 2024	https://dx.doi.org/10.1016/j.ajog.2024.10.034	Wrong RQ
Berman 2013	https://dx.doi.org/10.1016/j.jad.2012.06.038	Other subgroup/natural variation
Bjornebekk 2021	https://dx.doi.org/10.1016/j.bpsc.2021.01.001	Wrong population
Bove 2014	https://dx.doi.org/10.1212/WNL.0000000000000033	Postmortem study
Brouillard 2023	https://dx.doi.org/10.3389/fendo.2023.1228504	Wrong RQ
Brouillard 2024	https://dx.doi.org/10.1111/ejn.16509	Wrong RQ
Brown 2023	10.1007/s12035-023-03424-6	Wrong outcomes (cognitive task-based cerebral activity)
Canjels 2023	https://dx.doi.org/10.1002/uog.26172	Inappropriate age grouping
Carr 2018	https://dx.doi.org/10.3389/fnins.2018.00529	Article Retracted
Chen 2023	https://dx.doi.org/10.1002/alz.13037	Postmortem study
Chen 2025	https://dx.doi.org/10.1093/braincomms/fcaf052	Inappropriate age grouping
Choi 2012	https://dx.doi.org/10.3109/10641955.2010.507839	Inappropriate age grouping
Di 2018	https://dx.doi.org/10.1038/s41440-018-0051-3	Inappropriate age grouping
Dibiase 2018	10.1017/cts.2018.188	Abstract
Ding 2023	https://dx.doi.org/10.14283/jpad.2023.28	Wrong outcomes (incident AD and cognition)
Dubol 2022	https://dx.doi.org/10.1038/s41398-022-02017-6	Other subgroup/natural variation
Dubol 2024	https://dx.doi.org/10.1016/j.jad.2024.03.130	Other subgroup/natural variation
Evers 2018	https://dx.doi.org/10.1161/HYPERTENSIONAHA.117.10314	Inappropriate age grouping
Friis 2022	https://dx.doi.org/10.3390/cells11050789	Inappropriate age grouping
Gao 2018	https://dx.doi.org/10.1016/j.jsxm.2018.07.012	Other subgroup/natural variation
Goto 2011	https://dx.doi.org/10.1007/s12194-011-0120-7	Wrong exposure
Gu 2025	10.1016/j.preghy.2025.101265	Inappropriate age grouping
Guo 2018	https://dx.doi.org/10.1002/jmri.25808	Other subgroup/natural variation
Honea 2025	10.2139/ssrn.5375257	Preprint

Hu 2006		Unable to access
Hu 2026	10.1186/s12974-025-03657-3	Wrong RQ
Hussainali 2025	10.1161/HYPERTENSIONAHA.124.24544	Inappropriate age grouping
Jacobs 2016	10.1523/JNEUROSCI.0951-16.2016	Wrong outcomes (cognitive task-based cerebral activity)
Jayachandran 2020	https://dx.doi.org/10.1097/GME.0000000000001465	Wrong RQ
Jett 2022	10.1038/s41598-022-26573-5	Wrong outcomes
Jotwani 2025	10.1038/s42003-025-08952-6	Wrong exposure
Kaltsouni 2022	https://dx.doi.org/10.1016/j.euroneuro.2022.10.002	Other subgroup/natural variation
Kara 2025	10.1097/GME.0000000000002481	Wrong exposure
Kenna 2009	https://dx.doi.org/10.1007/s11064-008-9756-z	Wrong outcomes
Li 2021	https://dx.doi.org/10.1016/j.bbr.2021.113340	Inappropriate age grouping
Liu 2016	https://dx.doi.org/10.1002/ejp.753	Inappropriate age grouping
Liu 2018	https://dx.doi.org/10.1016/j.jad.2018.04.046	Other subgroup/natural variation
Maki 2007	https://dx.doi.org/10.1210/jc.2006-1805	Wrong outcomes
Marjanovic 2025	10.1016/j.jadr.2025.100916	Inappropriate age grouping
Martinez-Garcia 2023	https://dx.doi.org/10.1093/cercor/bhac333	Other subgroup/natural variation
Miller 2021	https://dx.doi.org/10.1080/13697137.2020.1804545	review paper
Moffat 1997	https://dx.doi.org/10.1016/s0006-8993(97)00614-8	Inappropriate age grouping
Nehls 2026	10.1016/j.ebiom.2026.106184	Inappropriate age grouping
Niu 2023	https://dx.doi.org/10.1007/s40618-023-02028-0	Wrong RQ
Ofori 2024	https://dx.doi.org/10.3390/brainsci14030276	wrong direction of relation
Panizzon 2010	https://dx.doi.org/10.1212/WNL.0b013e3181f11deb	wrong exposure, interactions - no individual association
Panizzon 2012	https://dx.doi.org/10.1016/j.neuroimage.2011.09.044	Wrong RQ
Petersen 2015	https://dx.doi.org/10.1002/hbm.22797	Inappropriate age grouping
Petersen 2021	https://dx.doi.org/10.1038/s41380-020-00990-2	Wrong RQ
Raikes 2025	10.1038/s41598-025-24136-y	Wrong comparator
Rapkin 2011	10.1016/j.biopsych.2010.09.029	Other subgroup/natural variation
Rizor 2024	https://dx.doi.org/10.1002/hbm.26785	Other subgroup/natural variation
Rosario 2011	https://dx.doi.org/10.1016/j.neurobiolaging.2009.04.008	Other subgroup/natural variation
Saxbe 2023	https://dx.doi.org/10.1111/jne.13270	Other subgroup/natural variation
Schmidt 1996	https://dx.doi.org/10.1111/j.1532-5415.1996.tb01400.x	Unable to access
Schonknecht 2001	https://dx.doi.org/10.1016/s0304-3940(01)01896-1	Wrong comparator
Servin-Barthet 2025	10.1038/s41467-025-55830-0	Other subgroup/natural variation

Silver 2018	https://dx.doi.org/10.1038/s41386-018-0023-y	Inappropriate age grouping
Smeha 2025	10.3389/fnhum.2025.1718846	Wrong outcomes (cognitive-motor task imaging)
Spets 2024	10.1093/cercor/bhae088	Wrong outcomes (default mode network)
Strozyk 2007	https://dx.doi.org/10.1016/j.neurobiolaging.2005.11.010	Postmortem study
Syan 2017	https://dx.doi.org/10.3389/fpsyt.2017.00301	Wrong population
Tang 2024	https://dx.doi.org/10.1002/alz.13889	Wrong outcomes (cognitive decline)
Than 2023	https://dx.doi.org/10.3389/frdem.2023.1098693	Wrong outcomes (cognitive decline)
Tian 2025	10.1038/s41598-025-14706-5	Inappropriate age grouping
Umar 2022	https://dx.doi.org/10.55519/JAMC-02-8478	Wrong RQ
Wang 2025	10.5534/wjmh.250060	Inappropriate age grouping
Wang 2026	10.1016/j.tjpad.2025.100475	Inappropriate age grouping
Wen 2025	10.1016/j.neuroimage.2025.121343	Wrong exposure
WoodAlexander 2025	https://dx.doi.org/10.1126/sciadv.adt0757	Postmortem study
Wrigglesworth 2023	https://dx.doi.org/10.1111/cen.14898	Wrong outcomes (brain predicted age difference)
Xing 2026	10.1017/cjn.2025.10495	Inappropriate age grouping
Yuan 2025	https://dx.doi.org/10.1002/alz.70111	Inappropriate age grouping
Zitzmann 2001	https://dx.doi.org/10.1055/s-2001-16351	Wrong outcomes (cognitive task based cerebral activity)

eTable 5 Newcastle-Ottawa Scale (NOS) risk of bias assessment for cross-sectional studies.

Study ID	First author, year	Study sample selection		Assessment of exposure and outcome		Confounding factors		Total (0-9)
		Representativeness of the study sample	Sample size	Assessment of the exposure(s)	Assessment of the outcome(s)	Adjustment for confounder(s)	Assessment of confounder(s)	
61	Aleknaviciute, 2022	0	1	2	2	1	1	7
51	*Ambikairajah, 2020 [exposure: menopausal stage]	0	1	1	2	1	1	6
51	*Ambikairajah, 2020 [exposure: age at menopause, menarche & reproductive span]	0	1	2	2	1	1	7
81	*Bachmann, 2024 [exposure: age at menopause]	0	0	2	2	1	1	6
81	*Bachmann, 2024 [exposure: MHT]	0	0	1	2	1	1	5
85	*Barth, 2025 [exposure: self-reported MHT]	0	1	1	2	1	1	6
85	*Barth, 2025 [exposure: MHT from prescription/primary-care records]	0	1	2	2	1	1	7
55	Boyle, 2021	0	1	1	1	1	1	5
94	Brown, 2025	1	1	1	2	0	0	5
62	*Buckley, 2022 [exposure: age at menopause]	0	1	2	2	1	1	7
62	*Buckley, 2022 [exposure: menopause status]	0	1	1	2	1	1	6
66	*Cote, 2023 [exposure: reproductive factors include age at menarche, the number of live births (LHEParity), age at menopause, use;	0	1	2	2	1	1	7
66	*Cote, 2023 [HRT use and OC self-reported]	0	1	1	2	1	1	6
67	Coughlan, 2023	1	1	1	2	1	1	7
7	den Heijer, 2003	0	1	2	1	1	1	6
6	Eberling, 2003	1	0	2	1	0	0	4
22	Erickson, 2010	1	0	1	1	1	1	5

12	Erickson, 2005	0	0	0	2	1	1	4
4	Gillett, 2003	0	0	2	1	1	1	5
87	Giudicessi, 2025	1	0	1	2	1	1	6
16	Greenberg, 2006	0	0	1	1	1	1	4
78	Huddleston, 2024	1	1	1	2	1	1	7
14	Irie, 2006	1	1	2	1	1	1	7
91	Jauregi-Zinkuneg, 2025	0	1	1	2	1	1	6
96	Jiang, 2025	0	1	0	2	1	1	5
46	Jung, 2020	1	1	2	2	1	1	8
86	Kantarci, 2025	1	1	2	2	1	1	8
68	Kim, 2023	0	0	1	1	1	1	4
79	Kim, 2024	1	0	1	1	1	1	5
40	Kim, 2018	0	0	2	2	0	0	4
88	Kwan, 2025	1	1	1	2	0	0	5
36	Lee, 2017	1	1	1	2	2	1	8
83	Li, 2025	0	1	2	2	1	1	7
19	Liu, 2009	0	1	1	1	0	0	3
59	Lohner, 2022	1	1	1	2	1	1	7
18	Lord, 2008	1	0	1	1	1	1	5
15	Low, 2006	1	1	1	1	1	1	6
42	Lu, 2018	0	0	2	2	1	1	6
1	Luoto, 2000	1	1	1	1	1	1	6
97	McGrath, 2025	1	1	1	2	1	1	7
30	Mielke, 2016	0	1	1	2	1	1	6
75	Mielke, 2024	1	1	2	2	1	1	8
70	Moir, 2023	0	0	2	2	0	0	4
37	Mosconi, 2017	0	1	2	2	1	1	7
38	Mosconi, 2017	0	0	2	2	1	1	6
56	Mosconi, 2021	0	1	2	2	1	1	7
100	Mutee, 2026	0	1	1	2	1	1	6
54	Najar, 2021	1	0	2	2	1	1	7
65	Nerattini, 2023	0	1	2	2	1	1	7
27	Pintzka, 2015	1	1	1	2	0	0	5
50	Rahman, 2020	0	1	1	2	1	1	6
26	Ryan, 2014	1	1	1	1	1	1	6
71	Sato, 2023	1	1	2	1	1	1	7
53	*Schelbaum, 2021 [men sample]	0	0	2	2	1	1	6
53	*Schelbaum, 2021 [women - exogenous estrogen exposure]	0	0	1	2	1	1	5
53	*Schelbaum, 2021 [women sample - endogenous estrogen exposure]	0	0	2	2	1	1	6
8	Schönknecht, 2003	0	0	2	2	0	0	4

44	Seitz, 2019	1	1	2	2	1	1	8
29	Srinath, 2016	1	1	2	2	1	1	8
72	*Steventon, 2023 [exposure: HRT / menopause timing]	0	1	1	2	1	1	6
72	*Steventon, 2023 [exposure: reproductive events (menarche, age at first birth)]	0	1	2	2	1	1	7
11	Sullivan, 2005	1	0	1	1	0	0	3
47	*Sundermann, 2020 [men sample]	0	1	2	2	1	1	7
47	*Sundermann, 2020 [overall sample]	0	1	2	2	1	1	7
47	*Sundermann, 2020 [women sample]	0	0	2	2	1	1	6
52	Than, 2021	0	1	1	2	1	1	6
80	Thurston, 2024, [exposure: vasomotor symptoms]	1	1	2	1	1	1	7
73	Thurston, 2024 [exposure: reproductive hormones (E1/E2/FSH)]	1	1	2	2	1	1	8
28	Thurston, 2016	0	0	2	2	1	1	6
64	Thurston, 2023	1	1	2	2	1	1	8
17	Verdile, 2008	1	0	2	1	1	1	6
24	Verdile, 2014	0	1	2	2	1	1	7
99	Wang, 2025	0	1	2	2	1	1	7
77	*Wang, 2024 [sample: TRIAD cohort]	1	1	1	2	1	1	7
77	*Wang, 2024 [sample: ADNI cohort]	0	1	1	2	1	1	6
92	Wezel, 2025	0	1	1	2	1	1	6
57	Wisch, 2021	0	0	1	2	0	0	3
74	Wugalter, 2024	1	1	2	2	1	1	8
48	Xu, 2020	0	1	2	2	1	1	7
82	Yong, 2025	1	1	1	1	1	1	6
58	Zhang, 2021	0	0	1	2	1	1	5
102	Zuhlsdorff, 2026	0	1	1	2	1	1	6

* Duplicate studies due to multiple exposures or outcomes assessed in same study with different assessment scores; Total score assessment definition: 0-3 high risk, 4-6 moderate risk, 7-9 low risk. MHT = menopausal hormone therapy; LHE = lifetime hormonal exposure; OC = oral contraceptives; TRIAD = Translational biomarkers in aging and dementia ; ADNI= Alzheimer's Disease Neuroimaging Initiative.

eTable 6 Newcastle-Ottawa Scale (NOS) risk of bias assessment for cohort studies.

Study ID	First author, year	Selection				Comparability		Outcome			Total (0-9)
		Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Study controls for most important factor	Study controls for any additional factor	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
93	Alshikho, 2025	0	1	1	0	1	0	1	1	0	5
34	Braden, 2017	0	1	0	1	1	0	1	0	0	4
95	Buckley, 2025	1	1	1	0	1	0	1	1	0	6
3	Cook, 2002	0	1	0	1	0	0	1	0	1	4
84	Coughlan, 2025	0	1	0	1	1	1	1	0	0	5
60	Depypere, 2023	0	1	1	1	1	0	1	0	1	6
39	Elbejjani, 2017	0	0	1	0	1	1	1	1	0	5
76	Lee, 2024	1	1	1	0	1	1	1	0	0	6
13	Lessov-Schlaggar, 2005	0	1	1	1	1	0	1	1	0	6
69	Liao, 2023	0	1	1	1	1	0	1	1	1	7
43	Mosconi, 2018	0	1	1	1	1	1	1	0	0	6
2	Rasgon, 2001	1	1	0	1	0	0	1	0	0	4
10	Rasgon, 2005	0	1	0	1	1	1	1	0	0	5
9	Raz, 2004	0	1	0	1	1	0	1	1	0	5
48	Xu, 2020	0	1	1	1	1	1	1	0	1	7

Total score assessment definition: 0-3 high risk, 4-6 moderate risk, 7-9 low risk.

eTable 7 Newcastle-Ottawa Scale (NOS) risk of bias assessment for case-control studies.

Study ID	First author, year	Selection				Comparability		Exposure			
		Is the case definition adequate?	Representativeness of the cases	Selection of Controls	Definition of Controls	Study controls for the most important factor	Study controls for any additional factor	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	Total (0-9)
31	Guoqing, 2016	0	0	0	0	0	0	1	1	0	2
98	Stocker, 2025	1	1	0	1	1	0	0	1	1	6
45	Zeydan, 2019	1	1	1	1	0	0	1	1	0	6

Total score assessment definition: 0-3 high risk, 4-6 moderate risk, 7-9 low risk.

eTable 8 Amyloid and Tau pathology-related studies: Basic information and study characteristics

Study ID	First author, year	Country	Cohort	Study population	Study design	Follow-up duration in years, mean (SD)	Total analytical sample	Age, mean (SD)	% Female	Ethnicity	Cognition	APOE ε4 carrier %
4	Gillett, 2003	Australia		Community-dwelling cognitively impaired older men	Cross-sectional		28	75.4 ± 6.9	0		MMSE = 22.6 ± 5.6	
5	Baker, 2003	USA		Postmenopausal women diagnosed with probable AD	randomized, double-blind, parallel-group, placebo-controlled study; pilot trial		18	HRT naïve: Estrogen group = 81.5 (6.9) Placebo group = 79.8 (7.2) Previous HRT users: Estrogen group = 75.0 (11.1) Placebo group = 78.0	100		MMSE HRT naïve: Estrogen group = 22.2 (6.2) Placebo group = 21.8 (4.3) Previous HRT users: Estrogen group = 19.8 (6.2) Placebo group = 20.0	
17	Verdile, 2008	Australia		Cognitively normal, community-dwelling men aged ≥55 years recruited from community and Alzheimer's disease research settings.	Cross-sectional		40	70.9 ± 6.9	0		MMSE (score 0-30; ± SD) 28.08 ± 1.92	30%
24	Verdile, 2014	Australia	AIBL (Australian imaging, biomarkers and lifestyle) cohort	Men across the AD spectrum (healthy, MCI, AD); volunteer-based community/clinic recruitment.	Cross-sectional		427 overall; 118 with PiB-PET imaging	for overall sample: no single overall age provided 69.8±6.4 healthy controls, 71.1±7.0 subjective memory complaints (SMC),	0			

								75.5±7.7 MCI, 77.0±7.7 AD				
32	Kantarci, 2016.1	USA	The Kronos Early Estrogen Prevention Study (KEEPS)	Healthy recently postmenopausal women with good cardiovascular health; clinical/research center participants.	Randomized, double blinded, placebo-controlled clinical trial; Cross-sectional analysis of a follow-up study subset	PET imaging ~3 years after treatment ended (~7 years post-randomization)	68	At the time of PiB PET imaging = median age of 60 (range, 52–65)	100		Global Cognition CEE= –0.12 (–1.79, 1.67) 17β-Estradiol = 0.38 (–1.84, 1.15) Placebo = 0.08 (–1.06, 1.83)	CEE=18% 17β-Estradiol = 50% Placebo = 18%
36	Lee, 2017	South Korea	Korean Brain Aging Study for Early Diagnosis and Prediction of Alzheimer's Disease	Men and postmenopausal women (≥2 years post menopause) recruited from community or memory clinic settings.	cross-sectional		265	females: 73.1(6.1); males 72.0(7.1)	49.8			female: 30.3%; males 24.8%
38	Mosconi, 2017	USA		Clinically and cognitively normal community volunteers aged 40–60 years participating in brain imaging studies.	cross-sectional		42 (pre 15; peri 13; post 14)	PRE (control) 48(5); Peri 50(6); Post 57(2)	100	PRE 75%; Peri 71%; Post 89% White	MMSE: PRE: 29(2); Peri 29(1); Post 29(1)	PRE 57%; Peri 46%; Post 36%
43	Mosconi, 2018	USA		Community-recruited, cognitively normal women at different menopausal stages participating in brain imaging studies.	Cohort: longitudinal repeated-measures study	Pre 3 (0.5); Peri 3(0.5); Post 2(0.4)	41 (pre 15; peri 14; post 12)	Pre 47(5); Peri 53(4); Post 58(2)	100	Pre 73%; Peri 75%; Post 42%		Pre 47%; Peri 50%; Post 42%
45	Zeydan, 2019	USA	The Mayo Clinic Cohort Study of Oophorectomy and	Community-dwelling women within a medical record–linkage system enabling population-based research	nested case-control		43	The median (interquartile range [IQR]) age at imaging was 65 (62-68) years	100			BSO 9%; control 20%

			Aging-2 (MOA-2) and The Mayo Clinic Study of Aging (MCSA)					in the BSO group and 63 (60-66) years in the control group. Controls were age-matched				
46	Jung, 2020	South Korea	Korean Brain Aging Study for Early Diagnosis and Prediction of Alzheimer's Disease (KBASE)	Older women with normal cognition or MCI; community- and memory clinic–recruited.	Cross-sectional		Amyloid = 236	70.45 (7.68)	100	Korean	MMSE = 24.93 (3.55)	24.9%
47	Sundermann, 2020	USA, Canada	Alzheimer's Disease Neuroimaging Initiative (ADNI)	Adults aged 55–90 years from multicenter consortium (academic/clinical centers), including CN, MCI, and AD participants.	Cross-sectional		172	75	34.3	97% white	MMSE apoe4- = 27.1 (2.2) apoe4+ = 25.8 (2.5)	54.10%
48	Xu, 2020	China; USA/Canada	Chinese Alzheimer's Biomarker and LifestylE (CABLE) study; ADNI	ADNI: Non-demented adults from multicenter consortium (academic/clinical centers), including CN and those with MCI. CABLE: Non-demented adults from hospital-based patient samples.	CABLE (China) → cross-sectional ADNI (USA multicenter) → longitudinal	Average follow-up for mixed model not provided but "In the ADNI cohort for incident AD dementia, 199 subjects were lost to follow-up and 237 were finally included (with a follow-up duration of 3.2 ± 2.4 years), among whom 164 subjects (36%)	CABLE (cross-sectional) = 707 ADNI (longitudinal): Baseline sample: n = 448; Subset with both plasma & CSF SHBG: n = 188	CABLE: 62.5 ± 10.5 years ADNI: 74.8 ± 7.2 years	CABLE: ~59% ADNI: ~37%	CABLE: Northern Han Chinese ADNI: Predominantly non-Hispanic White (~93.3%)	MMSE CABLE: 27.1 ± 3.2 ADNI: 27.3 ± 1.8	CABLE: 16.5% ADNI: 47.5%

						developed AD dementia."						
50	Rahman, 2020	USA			cross-sectional		85	53 (6)	100	White = 89%	MMSE = 0.01 (0.11)	42%
54	Najar, 2021	Sweden	The Prospective Population Study of Women from Gothenburg (as part of the Gothenburg H70 Birth Cohort Studies)	Dementia-free women with natural menopause from a population-based cohort subsample aged ≥70 year	Cross-sectional	The mean time from baseline to lumber puncture was 20.2 years (SD 3.8). The analytical framework was cross-sectional.	75	Median (=/- IQR) Age at baseline: 52 (46, 60) Age at lumber puncture = 74 (70, 85)	100	Mainly Caucasian		
56	Mosconi, 2021	USA		Cognitively intact older women	cross-sectional		161 (pre 30; peri 57; post 74)	Pre 44(4); Peri 50(4); Post 57(4)	100	Pre 80% white; peri 77%; post 89%	MMSE: Pre 29(1); Peri 29(1); Post 29(1)	42%
57	Wisch, 2021	USA			cross-sectional		86	female HT use 70.3(8.1); no HT 68.5 (6.9)	100			HT use 4%; no HT 20%
60	Depypere, 2022	Belgium		Healthy menopausal women naïve to MHT; university-based menopause clinic recruits.	prospective longitudinal study (repeated measures; change in the two time-points)	Control group: 7.2 ± 2.4 months MHT group: 6.7 ± 1.6 month	224 Control = 31 MHT = 193	Mean age overall: 54.03 ± 4.71 years Control: 55.69 ± 4.94 MHT: 53.76 ± 4.63	100		MMSE: 29.5 ± 1.01	29.90%
62	Buckley, 2022	USA	Framingham Health Study (FHS), 2nd and 3rd generation cohorts	Community-dwelling pre-and postmenopausal women from multigenerational family cohort.	cross-sectional		161	57(10)	100	100% White		23%
65	Nerattini, 2023	USA		Cognitively normal midlife women at	Cross-sectional		191	Premenopausal = 44 (4)	100	%white Premenopa	MOCA score (unitless)	Premenopausal =

				increased risk of AD (family history and/or APOE ε4), recruited through a university-based Alzheimer's prevention program.			Premenopausal = 45 Perimenopause = 67 Postmenopause = 79	Perimenopause = 49 (4) Postmenopause = 55 (4)		usal = 75 Perimenopause = 76 Postmenopause = 82	Premenopausal = 28 (1) Perimenopause = 29 (2) Postmenopause = 29 (1)	44 Perimenopause = 39 Postmenopause = 50
67	Coughlan, 2023	USA	Wisconsin Registry for Alzheimer Prevention	Cognitively unimpaired women recruited through memory clinics (parental AD history), and community.	cross-sectional		193; N=98 HT users; 95 nonusers) By menopausal status: Regular menopause age >45y: n = 153; early menopause age 40-45y: n=18; premature menopause age <40y: n=9	HT users: 64.9(7.0); Nonusers 69.8(5.2)	100			HT users: 37%; Nonusers 37%
76	Lee, 2024	USA	Mayo Clinic Study of Aging (MCSA)	Community-dwelling women within a medical records–linkage system enabling population-based research	Prospective longitudinal study with repeated measures	They do not explicitly state it. Based on graph = longest follow-up seems to be less than around years. 263 had at least 2 scans, 103 had at least 3 scans, and 23 had 4 or more scans	389	median (range) = 71.1 years (51.1, 90.4)	100	Mostly white		30.6%
77	Wang, 2024	USA, Canada	The Translational Biomarkers in Aging	ADNI: Postmenopausal women across the Alzheimer's disease spectrum (CU and CI) from a multisite	Cross-sectional		TRIAD cohort = 201 ADNI Imaging cohort = 343	TRIAD cohort HT−: 71.4 years (± 6.7) HT+: 73.1 years (± 5.8)	100		MMSE TRIAD cohort	TRIAD cohort HT−: 33.7% HT+:

			and Dementia (TRIAD) cohort, and ADNI	consortium TRIAD: Postmenopausal women across the AD spectrum; patients from research center and community-recruited general public.			ADNI Fluid cohort = 396 Total = 940	ADNI imaging cohort HT−: 72.8 years (± 8.6) HT+: 71.5 years (± 7.9) ADNI fluid cohort HT−: 73.0 years (± 7.4) HT+: 70.5 years (± 6.4) Mean age: ~70–73 years			HT−: 26.9 (± 4.9) HT+: 29.2 (± 1.0) ADNI imaging cohort HT−: 27.8 (± 3.6) HT+: 28.1 (± 3.3) ADNI fluid cohort HT−: 27.3 (± 3.2) HT+: 28.7 (± 1.6) MMSE: ~27–29	27.3% ADNI imaging cohort HT−: 41.6% HT+: 40% ADNI fluid cohort HT−: 46.4% HT+: 34% ~27–46% across groups
80	Thurston, 2024	USA	MsBrain study	Midlife women; community-based recruitment and MsHeart cohort participants.	cross-sectional		248	59 (4.3)	100	81% white; 15% black; 3.6% Asian or mixed race and ethnicity		61%
81	Bachmann, 2024	Switzerland		Community-dwelling menopausal women.	cross-sectional		52 (focus only on women)	69(9)	100			28.8%
82	Young, 2025	Singapore	Integrated Women's Health Program	Clinic-based sample of community dwelling midlife women without dementia	Cross-sectional analysis at follow-up		743	62.9 ± 6.0 years	100	Chinese ethnicity (82.3 %)		16.70%
84	Coughlan, 2025	USA	Harvard Aging Brain Study (HABS)	Community-dwelling cognitively impaired women	Observational longitudinal cohort study with repeated measures	Aβ-PET follow-up time = 4.45 (2.1); (IQR, 1.3 to 10.4 years) Tau-PET follow-up time = 3.50 (1.5); (IQR, 1.2 to 8.1 years)	146	Baseline age years: Total = 70.8 (7.6) HT users = 70.3 (8.1) HT non-users = 71.4 (7.1)	100	Hispanic 6.8 %		27%

						women underwent at least two time points						
86	Kantarci, 2025	USA	Mayo Clinic Cohort Study of Oophorectomy and Aging-2 (MOA-2)	Community-dwelling women aged ≥60 years within a medical record–linkage system enabling population-based research	Cross-sectional		N = 231 (61 early BSO, 51 late BSO, 119 controls; MRI); control group n = 108 for PET.	Median [IQR]; current visit age; Referent group: 67 years (63–70) Early PBO: 64 years (62–68) Late PBO: 67 years (64–72)	100	Race (White): Referent: 91.5% Early PBO: 95.0% Late PBO: 93.8%	Modified Mini-Mental State Examination (3MS): Referent: 97 (94–99) Early PBO: 96 (93–99) Late PBO: 96 (94–98)	Referent: 22.9% Early PBO: 23.7% Late PBO: 22.0%
90	Kantarci, 2026	USA	KEEPS Continuation	Healthy recently postmenopausal women with good cardiovascular health	Cross-sectional analysis [Observational follow-up of a randomized, double-blind, placebo-controlled trial]	~14 years post-randomization' around 10 years post RCT completion	Aβ-PET keeps continuation = 244	whole group = 67 (2)	100			whole group = 26%
91	Jauregi-Zinkunegi, 2025	USA	Wisconsin Registry for Alzheimer's Prevention (WRAP)	Cognitively unimpaired women at higher AD risk (parental dementia history)	Cross-sectional analysis (within a longitudinal cohort)		136 [main is primary outcomes]	Age at lumbar puncture: 65.95 (6.3) Age at menopause: 50.17 (5.8) Elapsed time = 15.78 (8.2)	100	Non-Hispanic White = 96.3%		35.30%
95	Buckley, 2025	USA	FHS Third Generation	Community-dwelling men and women from a multigenerational population-based cohort	cohort	15	334; 159 men /175 women	42.5 (8.7)	52.40%	100% non-Hispanic white		24

98	Stocker, 2025	Germany	ESTHER	Community-dwelling adults recruited through primary care health screening visits.	Nested case-control		Subsample of 60 women with menopause info	Total sample 64.1(6.5)	100			Total sample: 32.8%
99	Wang, 2026	South Korea	Catholic Aging Brain Imaging (CABI) database	Postmenopausal women aged ≥60 years across the AD spectrum (cognitively normal to AD); outpatient memory clinic cohort.	Cross-sectional		Overall = 884 sample with PET = 367	overall = 76.94 (7.17) Aβ negative = 76.16 (7.05) Aβ positive = 76.88 (6.73)	100	Korean	our analytical sample = MMSE Aβ negative = 23.83 (4.94) Aβ positive = 21.04 (5.87)	for overall participants, not our analytical sample = 35.29% Aβ negative = 22.54% Aβ positive = 54.8%
101	Shadyab, 2026	USA	WHIMS	Postmenopausal women aged ≥65 years	RCT (double-masked, parallel randomized placebo controlled); repeated measures	Plasma biomarkers measured at baseline and a second assessment ~15 years later (mean follow-up 15.1 years)	2784	69.9(3.8)	100	73.1% White		

eTable 9 Amyloid and Tau pathology-related studies: Methods and Materials

Study ID	First author, year	Exposure	Exposure Ascertainment	Outcome	Outcome ascertainment	Covariates adjusted for in models	Statistical Analysis
4	Gillett, 2003	Serum: testosterone, estradiol, SHBG, DHEAS, LH derived free testosterone	Serum (blood-based); assay not specified.	Plasma: Aβ40		Age	Single and multiple linear regression
5	Baker, 2003	HRT treatment groups: 1. Intervention: 0.10 mg/day of 17b-estradiol by skin patch OR 2. Placebo patch for 8 weeks Prior trial HRT status: user vs non-user (stratification, subgroup analyses)	High-dose (0.10 mg/day) transdermal 17b-estradiol (Estraderm, Ciba-Geigy Corporation) administered for 8 weeks. Participants previously receiving HRT underwent a 2-month washout period prior to baseline assessment.	Plasma: Aβ40	Plasma: ELISA Outcome measures were obtained at baseline, after 3, 5, and 8 weeks of treatment, and again 8 weeks after treatment termination.	Baseline Aβ40 value and age	Whether Aβ40 changes over time differ between estradiol and placebo groups, controlling for baseline and age: repeated-measures analysis of covariance (ANCOVA) ; Two (Treatment group: placebo, estrogen) * three (Time: Week 3, Week 5, Week 8) ANCOVA on Ab40 plasma concentration. outset of the study: one-way ANCOVA compared baseline Aβ40 levels between HRT groups, adjusting for age. This led to examining the effect of controlled estradiol administration for the HRT-naïve subjects alone.
17	Verdile, 2008	Serum: total testosterone, SHBG levels, LH levels, DHEAS, calculated free testosterone, Estrogen E2	Serum (blood-based); assay not specified.	Plasma: Aβ40	Plasma: ELISA	Demographic factors (age, BMI), genetic status (APOE ε4), other circulating hormones and gonadotropins (testosterone, LH, SHBG, E2, DHEAS), and cognitive parameters (CAMCOG and MMSE).	Multiple linear regression, hierarchical linear regression, stepwise regression.

24	Verdile, 2014	Blood-based: total testosterone, calculated free testosterone, SHBG, FSH, LH, Estradiol E2	Blood-based; assay not specified	Plasma: Aβ40, Aβ42, Aβ42/Aβ40 PET: Aβ burden SUVR	Plasm: ELISA PET PIB: ref. cerebellar cortex	age, BMI, insulin, thyroid stimulating hormone (TSH), free thyroxine, creatinine, current smoking and having been diagnosed with diabetes mellitus.	Linear regression
32	Kantarci, 2016.1	Hormone therapy treatment groups: 1. Oral CEE 2. Transdermal 17β-Estradiol 3. Placebo [reference]	Participants were randomized to either: 1) oral conjugated equine estrogen (CEE; Premarin, 0.45 mg/day); 2) transdermal 17β-estradiol (skin patch, Climara, 50 μg/day); or 3) placebo pills and patch. Progesterone was given orally (Prometrium; micronized progesterone, 200 mg/day) for the first 12 days each month to both active treatment groups. Participants were treated for four years.	PET: Global Aβ burden SUVR	PET PIB: ref. cerebellar grey matter; Region: bilateral parietal, posterior cingulate, precuneus, temporal, prefrontal, orbitofrontal, and anterior cingulate.	Age	Performed the comparisons of PiB SUVR values across treatment and placebo groups, using proportional odds logistic regressions. Because of a difference in the proportion of APOEε4 carriers among treatment groups, and the potential impact of this variable on outcome, a stratified analysis in APOEε4 carriers and non-carriers was conducted.
36	Lee, 2017	Serum: total testosterone, calculated free testosterone, total estradiol, calculated free estradiol, LH, FSH	Serum (blood-based); total testosterone and total estradiol: chemiluminescent enzyme immunoassays; LH and FSH: sandwich immunoassays with direct chemiluminometri technology	PET: Global Aβ burden SUVR Amyloid positivity	PET PIB: ref. cerebellum; Region: frontal, lateral parietal, posterior cingulate precuneus, and lateral temporal; Amyloid positivity threshold: SUVR>1.21.	age, years of education, APOE e4, cognitive group, BMI, history of diabetes, and history of hypertension	Logistic and linear regression
38	Mosconi, 2017	Menopausal status: asymptomatic perimenopausal by age, perimenopausal, and postmenopausal	Clinical judgment, medical records, and detection of cluster symptoms according to the STRAW criteria. Asymptomatic perimenopausal women by age (e.g., regular cyclers, or premenopausal control, CNT); symptomatic perimenopausal women	PET: Regional Aβ burden SUVR	PET PiB: ref. cerebellar GM; regions: posterior cingulate cortex, precuneus, inferior and superior parietal lobule, lateral and medial temporal cortex, and medial, inferior, and prefrontal cortex; analyses	age, education, and APOE genotype	For SPM a full factorial model with post hoc t contrasts was used to test regional differences in imaging measures across sex and reproductive aging groups, accounting for modality-specific reference values. Linear regressions were used to evaluate

			(e.g., irregular cyclers, PERI); postmenopausal women (e.g., no menstrual cycles for ≥12 months, MENO). These groups were compared to each other and to 18 age- and education matched men selected on the basis of a complete imaging dataset.		restricted to a standardized GM mask.		the associations among biomarkers, lab measures, neuropsychological measures and clinical group
43	Mosconi, 2018	Menopausal status: asymptomatic perimenopausal by age, perimenopausal, and postmenopausal	Clinical judgment, medical records, and detection of cluster symptoms according to the STRAW criteria. Asymptomatic perimenopausal women by age (e.g., regular cyclers, or premenopausal control, CNT); symptomatic perimenopausal women (e.g., irregular cyclers, PERI); postmenopausal women (e.g., no menstrual cycles for ≥12 months, MENO).	PET: Regional Aβ burden SUVR	PET PiB: ref. cerebellar GM; regions: posterior cingulate cortex, and prefrontal cortex.	Age, education, APOE4 status, vascular risk measures	targeted minimum loss-based estimation (TMLE) to compute adjusted means for each group (PRE, PERI, MENO). TMLE uses a preliminary estimator of the outcome regression and propensity score to construct a doubly robust estimator that remains consistent under misspecification of either model.
45	Zeydan, 2019	Women who underwent BSO before age 50 and before reaching natural menopause and an age-matched control group who had not undergone bilateral oophorectomy before age 50 years.	Record linkage	PET: Global cortical Aβ burden SUVR	PET PiB	Intracranial volume (ICV)	Wilcoxon rank sum tests, rank regression tests adjusted for ICV to compare BSO and control groups
46	Jung, 2020	Number of deliveries (parity): 1. 0-4 parity (reference) 2. grand multiparity (>=5 births)	systematic interviews implemented by trained nurses.	PET: Global Aβ burden SUVR Amyloid positivity	PET PiB: ref. cerebellar; region: frontal, lateral parietal, posterior cingulate-precuneus, lateral temporal; Amyloid positivity threshold: SUVR > 1.4 in ≥1 cortical ROI.	Model 1: age, years of education, APOE4 positivity, and cognitive status (i.e., CN vs. MCI) Model 2: Model 1 + Vascular risk score, income level at early adulthood, level of lifetime occupation, age at menarche age,	Logistic regression analyses SA = exclusion of two nulliparous subjects

						and age at menopause.	
47	Sundermann, 2020	Plasma: total testosterone level, calculated free testosterone level	Serum (blood-based); Luminex xMAP platform; testosterone levels normalized.	CSF: P-Tau181	Roche Elecsys assay	age, sex (oversample analysis), education, BMI and self-reported history of cardiovascular events; adjustment for Aβ1-42 levels (sensitivity)	Used linear regression to examine the effect of testosterone on p-Tau levels in the overall sample and within sex. SA: adjustment for Aβ1-42 levels
48	Xu, 2020	Plasma: SHBG; categorized high vs low based on median split	Plasma (blood-based); overnight fasting; Human SHBG ELISA kit (CABLE study), Multiplex immunoassay panel on the Luminex xMAP platform (ADNI)	CSF: Aβ42 CSF: P-Tau181	CSF: ELISA for both (CABLE); INNOBIA AlzBio3 immunoassay for Aβ42 (ADNI)	CABLE: cross-sectional: CSF Aβ42 or tau levels: age, gender, education, APOE4 status, and MMSE score. ADNI data: longitudinal: age, gender, education, APOE4 status, and clinical diagnosis at baseline. Sensitivity: re-ran all analyses in men and women separately; excluding those who developed dementia whine one year since baseline; repeated all analyses after	CABLE: linear regression used to explore the cross-sectional relationships of SHBG (high vs. low with cutoff = 46.74 nmol/L) with CSF Aβ42 or tau levels. ADNI data: the longitudinal influences of plasma SHBG at baseline on CSF AD biomarkers, cognition, hippocampus volume, and brain metabolism were explored using linear mixed effects models. Included the interaction between time (continuous) and plasma SHBG (high vs low) as a predictor. SA: re-ran all analyses in men and women separately; excluding those who developed dementia whine one year since baseline; repeated all analyses after further adjusting for plasma levels of total testosterone (TT) or free testosterone index (FTI) which were calculated by dividing TT by SHBG.

						further adjusting for plasma levels of total testosterone (TT) or free testosterone index (FTI) which were calculated by dividing TT by SHBG.	
50	Rahman, 2020	Menopausal status: perimenopausal, perimenopausal, and postmenopausal HRT status: user vs non-user Hysterectomy status: yes vs no	STRAW criteria and cluster symptoms; based on clinical judgment	PET: Regional Aβ burden SUVR	PET PiB: ref. cerebellar GM uptake; regions: Anterior cingulate gyrus, Medial frontal gyrus, Orbitofrontal gyrus, Superior Frontal Gyrus		Brain biomarker differences by sex: SPM12 was used to perform voxel-wise comparisons. Full factorial models with post hoc t contrasts were used to test regional differences in MRI, PiB and FDG measures. Analyses done again with age and size matched groups, by matching the men in cohort to the women of the same age. All results were corrected for FWE and with cluster extent >=50 voxels. AD risk factors and sex-driven biomarker differences: LASSO regressions to determine menopausal status as a potential predictor. If showing a significant association it was further examined with general linear models corrected for multiple comparisons
54	Najar, 2021	Length of reproductive period, years (main exposure) Age at menarche, continuous Age at menopause, continuous	semi structured interviews; Length of reproductive period was defined as the time from age at menarche to age at menopause; Age at menarche was defined as first menstruation, and menopause as last menstruation after 1 year without menstruation.	CSF: Ab42, Ab40, Ab42/Ab40 ratio, P-tau, T-tau	CSF: Sandwich enzyme-linked immunosorbent assays; T-tau and P-tau natural log-transformed	Model 1: adjusted for birth year Covariates selected for Model 2 of Ab42 = birth year, oral contraceptives, waist-hip ratio, and education; P-tau = birth	Linear regression models; SA: excluding major outliers (ie, 3 * interquartile range) from P-tau

						year, psychological stress, smoking status, and education; T-tau = birth year and psychological stress; Ab42/Ab40 = birth year, waist-hip ratio, and psychological stress. Age of menarche and menopause as exposures - only adjusted for birth year. SA: excluding major outliers (i.e., 3 * interquartile range) from P-tau	
56	Mosconi, 2021	Menopausal status: premenopausal, perimenopausal, and postmenopausal	STRAW criteria, corroborated by means of hormone assessments; premenopausal (regular cyclers), perimenopausal (irregular cyclers), and postmenopausal (no menstrual cycles for ≥12 months).	PET: Global Aβ burden SUVR	PET PiB: ref. cerebellar gray matter uptake; regions: Frontal cortex, Temporal cortex, Parietal cortex Posterior cingulate cortex, Precuneus	Age, APOE4, modality-specific confounders	Factorial models with post hoc t contrasts; longitudinal changes (2yrs later); Voxel-based changes in GMV, WMV and CMRglc were examined by means of post hoc t-tests on baseline vs 2-yr follow-up scans and by comparing the maps of change between groups using SPM12
57	Wisch, 2021	HRT use: user vs non-user	Self-reported	PET: Global amyloid burden, regional tau accumulation	PET-PiB for amyloid: ref. cerebellar cortex; regions: lateral orbitofrontal, medial orbitofrontal, rostral middle frontal, superior frontal, superior temporal, middle temporal, and precuneus;	Age, APOE, education	Linear regression with Bonferroni correction for multiple comparisons.

					log-transformed. PET-AV1451 for tau: ref. cerebellar cortex; 35 gray matter regions evaluated for tau burden, including amygdala, entorhinal cortex, inferior temporal region, and lateral occipital cortex; log-transformed.		
60	Depypere, 2022	HT status: user vs control	menopause clinic; "MHT" arm = Women who underwent a therapeutic MHT program. "control" arm = Women who opted out for any MHT treatment. MHT was prescribed in accordance with the guidelines of international societies IMS, EMAS, NAMS, and NICE.	Plasma; Annual rate of change in biomarkers over time: Aβ1-42 Aβ1-40 p-tau231 T-tau Aβ1-42 / p-tau231 ratio	Plasma (blood-based); Single molecule array (Simoa) Tau2.0 assay (T-Tau); in-house Simoa assay (p-tau231); amyblood assay (Aβ42, Aβ40); baseline and one follow-up.	Age and APOE ε4 carrier status	>> Annual rate of change (ARC) as the difference in plasma concentration between the two visits (V1 and V2) divided by the delay in years. >> Longitudinal analyses were performed using linear models on the annual rate of change of biomarkers, comparing MHT and control groups. Subgroup analysis [not our RQ]: used a LM with an interaction term between the group (MHT arm or control arm) and APOE ε4 status (APOE ε4 status*group).
62	Buckley, 2022	Menopause status; Age at menopause	Self-reported	PET: Global Aβ burden, Global tau burden		age at PET and type of PET camera	linear regression
65	Nerattini, 2023	Blood: FSH, LH	Blood-based; electrochemiluminescence sandwich immunoassay (ELISA); overnight fast; normalized	PET: Regional Aβ burden SUVR	PET: PiB: ref. cerebellar gray matter uptake; regions: Frontal cortex Parietal cortex Temporal cortex Cingulate gyrus Precuneus Thalamus	primary model = age, menopause status, history of depression For exposures showing significant associations with outcome measures: further examined	Analyses to address the independent effects of FSH and LH levels from age and menopause status: Checked age overlap across menopause groups; tested multicollinearity (VIF); Included age and menopause as covariates; performed voxel-wise subtraction masking to remove confounder-related regions; conducted stratified analyses by menopausal

						oral contraceptive (OCP) usage status (user vs. non-user), MHT status (user vs. non-user) and menopause type (history of hysterectomy and/or oophorectomy vs. spontaneous menopause), APOE-4 status.	status (age-adjusted). Multivariate linear regressions with post-hoc t-contrasts to test voxel-based associations between exposures (FSH or LH) and biomarker outcomes. Primary analysis = adjusted for age and menopause; additional masking analysis further excluded all regional contributions of these confounders to isolate independent hormone effects. Cluster extraction (VOI) using MarsBaR 0.45. Voxel-wise results threshold at $P < 0.05$, cluster-level FWE-corrected. Additional: Analyses repeated after restricting analysis to MHT non-users. SA: associations between gonadotropin levels and hippocampal volume as an a priori selected region, using ROI approach. SA: estradiol as exposure. Subtraction masking for estradiol was performed only for GMV (not Aβ), excluding regions associated with estradiol to test whether FSH/LH effects were independent.
67	Coughlan, 2023	Age at menopause HT use (current/past vs never). HT timing: ≤5 years vs >5 years after menopause.	Self-reported	PET: Global Aβ burden DVR and regional tau burden SUVR.	PiB-PET for amyloid: regions: angular gyrus, anterior cingulate gyrus, posterior cingulate gyrus, frontal medial orbital gyrus, precuneus, supramarginal gyrus, middle temporal gyrus, and superior temporal	age at tau scan and global Aβ burden SA: education, APOE ε4 status, cardiovascular risk (FHS-CVD), menopausal	Linear regression.

					gyrus; Aβ positivity defined as DVR >1.16. 18F-MK-6240 SUVR for tau: ref. inferior cerebellar gray matter; regions: entorhinal cortex, amygdala, inferior temporal gyrus, temporooccipital gyri, superior parietal lobule, temporal fusiform gyrus, and lateral occipital cortex.	symptom severity, and reproductive surgery history.	
76	Lee, 2024	Reproductive factors and exogeneous estrogen use: 1. Age at menarche, per 1 year 2. Age at menopause, per 1 year 3. Reproductive Window, per 5-year increase 4. Number of Pregnancies>20 weeks: 0 (ref), 1, 2, 3, 4, 5+ 5. Ever HC Use: user vs non-user (ref) 6. Ever MHT Use: user vs non-user (ref) 7. Initiation of MHT use relative to menopause: non-user (ref), Before or <1 year Postmenopause, 1–5 years Postmenopause, > 5 years post menopause	Information obtained through abstraction of written and electronic medical records.	PET: Global Aβ burden, Temporal meta-ROI tau burden	PiB-PET for amyloid: ref. cerebellar crus; regions: prefrontal, orbitofrontal, parietal, temporal, anterior cingulate, posterior cingulate, and precuneus. Flortaucipir-PET for tau: regions: temporal meta-ROI.	age, and education. Sensitivity analyses: APOE genotype + cardiovascular risk factors and conditions (smoking, BMI, hypertension, dyslipidemia, diabetes, heart disease, and stroke).	Linear mixed-effect models with a random slope and intercept for each participant to examine the associations between female-specific reproductive factors (reproductive window and parity) or exogeneous estrogens (HC use, MHT use, and initiation of MHT relative to menopause), and each AD and cerebrovascular neuroimaging marker. To determine the significance of potential linear trends over time, each model included time and an interaction between time and the reproductive risk factor covariate of interest. SA: additional adjustment for covariates
77	Wang, 2024	Use of hormone therapy status: Yes or no	Current medication inventory reviewed; FDA-approved hormone therapy medications used to classify HT status (users vs non-users). Female individuals with oophorectomy were excluded. HT user: individuals who were current or previous users of estrogen alone or combination (estrogen plus progestin) HT	PET: Global Aβ burden, Braak I–II, III–IV, V–VI ROIs and temporal meta-ROI tau	[18F]AZD4694-PET for amyloid (TRIAD) / [18F]florbetapir-PET (ADNI): Global neocortical SUVR, ref. cerebellum gray matter; regions: precuneus, prefrontal, orbitofrontal, parietal, temporal, anterior and posterior cingulate	age, education, APOE carrier status and clinical diagnosis (CU or CI)	Concentration of plasma and CSF biomarkers, PET SUVRs were compared between HT and HT + females using independent t-tests or Welch's t-tests (accounting for unequal sample sizes and unequal variances) with Bonferroni correction, as appropriate. Voxel-based analyses: Welch's t-

			Non-HT user: those with no record of HT use.	burden CSF: P-Tau181, P-Tau217 Plasma: P-Tau181, P-Tau217	cortices; Aβ positivity threshold: SUVR > 1.55. [18F]MK6240-PET for tau (TRIAD) / [18F]flortaucipir-PET (ADNI): Braak I–II, III–IV, V–VI ROIs and temporal meta-ROI [ref. inferior cerebellar gray matter; regions: entorhinal, amygdala, parahippocampal, fusiform, inferior temporal and medial temporal.] CSF (TRIAD): custom Simoa (P-Tau181, P-Tau217) Blood-based plasma (TRIAD): in-house Simoa methods on an HD-X Analyzer (P-Tau181), Janssen R&D Simoa assay (P-Tau217). Blood-based plasms (ADNI): P-Tau181, P-Tau217; assays not reported.		test was performed at the voxel level to assess the differences in Aβ and NFT loads between HT- and HT + females. Linear regression models were fitted with an interaction term to estimate the extent to which HT use moderated the association between cortical Aβ load and regional tau aggregation. [not our RQ]
80	Thurston, 2024	Vasomotor symptoms	Objective vasomotor symptoms: 24-hour ambulatory sternal skin conductance monitoring (within 3 days of monitoring); sleep assessed with wrist actigraphy (Actiwatch 2, nondominant wrist). Subjective vasomotor symptoms: Electronic symptom diary/self-report and event-marker button recordings.	Plasma: Aβ42/Aβ40, P-tau181, P-tau2017	Blood-based biomarkers (plasma): Simoa assays on an HD-X instrument	age, race, and ethnicity, education, BMI, and APOEe4	linear regression; additional with multiple comparisons.
81	Bachmann, 2024	Age at menopause: <51 vs ≥51 years HRT use: yes or no	Age at menopause: self-reported age at final menstruation (+1 year); categorized as <51 vs ≥51 years based on average age at menopause among	PET: Regional tau burden	[18F]flortaucipir-PET: regional neocortical SUVRs; ref. eroded inferior cerebellar gray matter;	Age and global amyloid burden (Centiloid scale)	multiple linear regression.

			women in Europe. HRT use: self-report.		regions: parahippocampal cortex, the inferior temporal cortex, and the isthmus cingulate.		
82	Young, 2025	History of hypertension during pregnancy (Yes vs No)	Self-reported using the question: "Did you develop high blood pressure during your pregnancy?"	Serum: P-Tau217	Serum: Simoa ALZpath; overnight fast	Age, MCI, hypertension, BMI, renal function, and APOE4 genetic status	General linear modelling
84	Coughlan, 2025	HRT use: yes or no	History of postmenopausal HT use self-reported	PET: Global Aβ DUVR burden, Regional Tau burden	PiB-PET for amyloid: global neocortical DVR; ref. cerebellar gray matter; regions: frontal, lateral temporal, and retrosplenial cortices ^{18}F-Flortaucipir-PET: ref. cerebellar gray matter; regions: entorhinal cortex (Braak II), temporal fusiform gyrus (Braak III), inferior temporal gyrus (Braak IV), inferior parietal lobule, superior parietal lobule, and lateral occipital cortex (Braak V).	age, BMI SA: Years of education, APOEε4 carrier status, baseline WM lesions, and the baseline office-based Framingham Heart Study Cardiovascular disease risk score.	HT non-users were **age-matched** to HT users. Linear mixed effect models - random slope and random intercept; main model a three-way interaction term to estimate the extent to which HT moderated the association between the baseline age (i.e., age at study enrollment/first Aβ-PET scan and continuous variable) and longitudinal neocortical Aβ-PET and longitudinal regional tau-PET (as separate outcomes). >>They reduced multiple testing by grouping tau regions into 2 independent factors using PCA, then applied Bonferroni correction for 2 tests ($\alpha = 0.025$). >>sensitivity for tau-PET analysis three-way interaction (significant for multiple ROIs): additional covariates adjusted one at a a time; excluding baseline BMI as a covariate; adjusting for baseline neocortical Aβ-PET over time (at first tau scan), using balanced weights for each individual's baseline Aβ burden to down weight HT users with elevated baseline Aβ; including all covariates in one

							model; in the non-age matched sample. >>age categorized <70 vs >=70 years for visualization = HT interaction with age to predict neocortical Aβ accumulation >>age groups: mean age: 64, 71, 77 = to predict regional tau accumulation >>post-hoc analysis: subgroup with HT start age and duration of use - interactions with time to predict tau accumulation, including and excluding the baseline age interaction; repeated analysis in subset sample of participants with detailed HT information, along with 58 age-matched HT non-users (HT × Age × Time + BMI × Time + APOEε4 × Time).
86	Kantarci, 2025	Premenopausal bilateral oophorectomy (PBO) before 50 years: 1. Early PBO (<46 years) vs referent (age-matched referent women who had not undergone PBO before the index date [date of matching]) 2. Late PBO (46–49 years) vs referent	Record linkage PBO was defined as complete removal of both ovaries or as second unilateral oophorectomy, with or without hysterectomy, and performed before the onset of spontaneous menopause.	PET: Global Aβ burden SUVR, Global Tau SUVR	PET-PiB: ref. cerebellar crus gray matters; regions: prefrontal, orbitofrontal, parietal, temporal, anterior cingulate, and posterior cingulate/precuneus regions; Flortaucipir-PET: ref. cerebellar crus gray matters; entorhinal, amygdala, parahippocampal,	Age at imaging, APOE4	Multivariable linear regression, stratified by early PBO (<46 years) and late PBO (46–49 years) groups. Analyses were first adjusted for age at imaging, then additionally for adjusted for APOE ε4 status; then with interaction terms included to assess effect modification by age (age × PBO). SA: most of the participants who underwent PBO were using HT

					fusiform, inferior temporal, and middle temporal regions.		(65.6% in the early PBO and 77.1% in the late PBO), SA excluding women who did not use HT through the age of 50 years. [comparable findings]
90	Kantarci, 2026	Hormone therapy groups: Oral CEE Transdermal 17β-Estradiol Placebo [reference]	Participants were randomized to either: 1) oral conjugated equine estrogen (CEE; Premarin, 0.45 mg/day); 2) transdermal 17β-estradiol (skin patch, Climara, 50 μg/day); or 3) placebo pills and patch. Progesterone was given orally (Prometrium; micronized progesterone, 200 mg/day) for the first 12 days each month to both active treatment groups. Participants were treated for four years.	PET: Global Aβ burden SUVR	PiB-PET for amyloid: ref. Cerebellar crus gray matter; regions: Prefrontal, orbitofrontal, parietal, temporal, anterior cingulate, and posterior cingulate/precuneus.	Age, site of assessment, APOE ε4 carrier status	Statistical comparisons of the oCEE versus placebo, and tE2 versus placebo groups on imaging biomarker outcomes were conducted using a multivariable linear regression model. SA: repeat analyses excluding participants who used systemic mHT after cessation of randomized treatment.
91	Jauregi-Zinkunegi, 2025	MHT use: yes or no (reference) Age at MHT initiation (secondary exposure)	MHT use assessed by self-report at baseline and follow-up visits. Current and past users were combined as "MHT users".	CSF: p-tau181/Aβ42 and Aβ42/Aβ40 (primary); p-tau181, Aβ40, and Aβ42 (secondary).	CSF biomarkers: Roche NeuroToolKit assays; Elecsys Aβ42, Aβ40, and P-tau(181) were performed on a cobas e 601 analyzer.	main analyses - MHT users vs non-users = age at most recent LP, elapsed time between menopause and lumbar puncture, years of education, race/ethnicity (non-Hispanic White as reference category), history of surgery at lumbar puncture, age at menarche, and LIBRA risk group at lumbar puncture (low as reference), APOE ε4 carrier status. secondary analyses, in	Linear models (LMs) were used to explore the association between MHT use and levels of CSF biomarkers. For all the models tested, influential data points on model outputs were inspected using Cook's distance; no data points had a Cook's distance ≥ 1. In addition, all the models were checked for multicollinearity and none of the variables had a VIF > 2.

						which only MHT users were included: covariates same as for the main analyses, along with specific MHT-related variables: MHT medication (estrogen as reference), MHT form (pill as reference), and MHT duration in years.	
95	Buckley, 2025	Plasma: Total testosterone, SHBG, Estradiol	Blood plasma; fasting; liquid-chromatography tandem mass spectrometry (LC–MS/MS) assay [total testosterone, Estradiol]; immunofluorometric assay [SHBG]	PET: Global Aβ burden SUVR, regional tau burden SUVR	PiB-PET for amyloid: ref. cerebellar grey; regions: precuneus, rostral anterior cingulate, medial orbitofrontal, superior frontal, rostral middle frontal, inferior parietal, inferior temporal, and middle temporal; Aβ quantiles (ref. highest quantile). 18F-Flortaucipir-PET for tau: regions: entorhinal, inferior temporal, rostral middle frontal, inferior parietal, superior parietal, lateral occipital.	age; age squared; camera type; latency between blood and PET collection; SA: hormone therapy use, oral contraceptive use, menopause status; BMI.	linear regression; interactions with APOEe4; no adjustment for multiple comparisons
98	Stocker, 2025	Menopause status: yes or no (secondary exposure of study)	self-administered questionnaire and/or physician reports	Plasma: P-Tau181	Blood-based biomarkers (plasma): Simoa assays on an HD-X Analyzer	age, sex, and APOE4	Linear regression
99	Wang, 2026	Serum: FSH, E2	Blood-based (serum): radioimmunoassay using GammaPro	PET: Global and regional Aβ SUVR; amyloid positivity.	18F-flutemetamol-PET: ref. pons; global and regional SUVRs (frontal, parietal, lateral temporal, anterior cingulate, posterior cingulate/precuneus,	age, education, APOE ε4 carrier status, FSH, and E2	FSH levels and cerebral Aβ positivity: Univariate logistic regression followed by multivariate logistic regression including significant predictors. APOE ε4 and FSH identified as potential factors

					striatum); Aβ positivity: gray matter uptake ≥ adjacent white matter uptake in any of the predefined regions (visual analysis).		FSH levels and global mean SUVR values: Univariate linear regression followed by multivariate linear regression including significant predictors. APOE ε4 and FSH identified as potential factors. SA: **62.2% of subjects had E2 levels below the detection limit of 4 pg./mL**. rerun analyses excluding these participants.
101	Shadyab, 2026	MHT: HT vs placebo	Estrogen-alone: CEE 0.625 mg/day vs placebo (women with hysterectomy). Estrogen-plus-progestin: CEE 0.625 mg/day + medroxyprogesterone acetate 2.5 mg/day vs placebo (women with intact uterus).	Plasma: Aβ42/Aβ40 ratio, p-tau181, p-tau217	Blood-based plasma biomarkers: Simoa Human Neurology 4-Plex E platform (Aβ40, Aβ42); Simoa p-tau181 version 2 assay (p-tau181); ALZpath Simoa pTau-217 version 2 assay (P-tau217); fasting.	Time-varying estimated glomerular filtration rate (eGFR) and weighted for the biomarker sampling design	linear mixed models with random intercepts and slopes and an unstructured covariance matrix to estimate rate of change in blood-based biomarkers by HT vs placebo.

eTable 10 Amyloid and Tau pathology-related studies: Overall findings and limitations

Study ID	First author, year	Main Finding	Direction of association	Key limitations
4	Gillett, 2003	Lower total and free testosterone and higher SHBG were independently associated with higher plasma Aβ40 levels, while LH and estradiol showed no association.	↓ Total testosterone → ↑ Aβ40 ↓ Free testosterone → ↑ Aβ40 ↑ SHBG → ↑ Aβ40 LH ↔ Aβ40 Estradiol ↔ Aβ40	Cross-sectional study design
5	Baker, 2003	Controlled estradiol administration did not have a consistent effect on plasma concentration of Ab40 for postmenopausal women with AD. In HRT-naïve women, estradiol reduced Aβ40 at Week 8 (end of treatment), but this effect was transient and disappeared by Week 16 (8 weeks after treatment cessation). Short-term estradiol administration reduces plasma Ab40 concentration for HRT-naive postmenopausal AD women.	Estradiol ↔ Aβ40 (overall) Estradiol → ↓ Aβ40 (HRT-naïve women only; Week 8, transient)	1. Small sample size 2. Retrospective analysis of prior HRT status 3. Possible confounding by prior HRT use: lower baseline Aβ40 levels in previous HRT users may reflect long-term effects of prior hormone therapy or delayed disease onset, rather than the effect of the study treatment itself.
17	Verdile, 2008	In cognitively normal elderly men, serum LH was the only hormone independently associated with higher plasma Aβ40 levels after adjustment for age, BMI, testosterone, estradiol, DHEAS, SHBG, and cognitive measures.	Higher LH → ↑ Plasma Aβ40 levels Free testosterone ↔ Plasma Aβ40 levels	Possibility that the study is underpowered to detect an independent association between testosterone and plasma Aβ levels. Testosterone assays may not be sensitive enough to distinguish between small changes in testosterone levels in a healthy cohort.
24	Verdile, 2014	Elevated LH levels are associated with increased plasma Ab levels and amyloid burden (in brain via PiB) in SMC (prior to the onset of clinical symptoms), but the association is lost with the onset and severity of clinical symptoms (that is, MCI and AD). With the onset of objective clinical symptomology (that is, MCI), the reduced levels of testosterone (calculated free - bioavailable) are associated with a greater amyloid burden.	↑ LH → ↑ Aβ40, ↑ Aβ42 (overall cohort) ↑ LH → ↑ Aβ40, ↑ Aβ42, ↑ PiB retention (Subjective Memory Complaints) ↑ LH → ↑ Aβ40 (MCI) ↓ Free testosterone → ↓ Aβ42 (MCI) [in the context of study] ↓ Free testosterone → ↑ PiB retention (MCI) No significant hormone–amyloid associations (AD)	
32	Kantarci, 2016.1	In this pilot study, transdermal 17β-estradiol therapy in recently postmenopausal women was	Transdermal 17β-estradiol → ↓ Aβ burden (↓ PiB SUVR) vs placebo	Small, single-center sample.

		associated with a reduced amyloid-β deposition, particularly in APOE ε4 carriers.	APOE ε4 carriers: Transdermal 17β-estradiol → ↓ Aβ burden vs placebo and oral CEE APOE ε4 non-carriers: ↔ Aβ burden (no association) Oral CEE → ↔ Aβ burden vs placebo (no association)	Ancillary/subsample analysis: Only a subset of the original KEEPS trial participants underwent PiB-PET imaging, introducing potential selection bias. Imbalance in APOE ε4 carrier distribution between groups.
36	Lee, 2017	In females, higher free testosterone, LH, and FSH levels were associated with greater cerebral Aβ positivity, whereas no associations were observed in males. No associations were found between sex hormones/gonadotropins and global amyloid burden (PiB SUVR) in either sex.	Females: Free testosterone → ↑ Aβ positivity Females: LH → ↑ Aβ positivity Females: FSH → ↑ Aβ positivity Females: Free estradiol ↔ Aβ positivity Males: Sex hormones/gonadotropins ↔ Aβ positivity Both sexes: Sex hormones/gonadotropins ↔ Global Aβ burden (PiB SUVR)	Peripheral hormone measurements: Serum sex hormone and gonadotropin concentrations may not accurately reflect concentrations within the brain. Free hormone estimates: Calculated free sex hormone concentrations may not correspond to actual concentrations in cerebrospinal fluid.
38	Mosconi, 2017	Both PERI and MENO groups showed increased PiB uptake in the frontal and temporal cortex compared with CNT women, with Aβ burden progressively increasing across menopausal stages (CNT < PERI < MENO). As compared to any of the female groups, no brain regions showed increased PiB uptake in men.	PERI/MENO → ↑ Aβ burden (frontal and temporal PiB uptake) vs CNT; CNT < PERI < MENO (progressively increasing amyloid burden) APOE ε4-positive MENO → further ↑ Aβ burden Men showed no regions of increased PiB uptake relative to female groups.	Menopausal status was not hormonally confirmed → potential misclassification of reproductive stage. Limited evaluation of hormone therapy effects. Highly selected healthy cohort.
43	Mosconi, 2018	MENO women showed higher rates of Aβ deposition in both posterior cingulate cortex and frontal cortex vs PRE women. PERI women showed higher rates of frontal Aβ deposition vs PRE women.	PERI → ↑ frontal Aβ burden vs PRE MENO → ↑ Aβ burden (PCC + frontal PiB uptake) vs PRE Frontal PiB uptake: MENO +6.3%, PERI +4.5%, PRE <1% change over 3 years APOE ε4 → ↑ frontal Aβ deposition over time	Small sample size, limiting power (including inability to test APOE ε4 interactions). Menopausal status not hormonally confirmed, creating potential misclassification. Highly selected healthy cohort with short (3-year) follow-up, limiting generalizability and long-term prediction of AD outcomes.
45	Zeydan, 2019	Higher cortical PiB standard uptake value ratio on PiB PET scan were observed in the BSO group compared with the control group, but not statistically significant.	No difference	Small sample size.
46	Jung, 2020	In non-demented older women (CN and MCI), grand multiparity (>=5 births) as compared with 0-4 parity showed no significant association with global Aβ deposition or Aβ positivity.	Grand multiparity (≥5 births vs. 0–4 births) ↔ Global Aβ deposition Grand multiparity (≥5 births vs. 0–4 births) ↔ Aβ positivity	Recall bias: reproductive history self-reported. Although, they reconfirmed information from reliable informants and got additional information.

				Nulliparity could not be assessed separately.
47	Sundermann, 2020	In the overall sample, there was a significant relationship between lower total testosterone levels and higher CSF p-Tau levels. In sex-stratified analyses, lower testosterone levels were associated with higher CSF p-Tau levels in both women and men.	Overall sample: Lower total testosterone → ↑ CSF p-Tau181 Women: Lower testosterone → ↑ CSF p-Tau181 Men: Lower testosterone → ↑ CSF p-Tau181	ADNI is a convenience sample of mostly white and well-educated volunteers compared with the general US population. Levels of circulating estradiol were not available, which precluded from examining whether it is testosterone or the aromatization of testosterone to estradiol that is responsible for the observed association.
48	Xu, 2020	Higher levels of plasma SHBG were associated with decreased CSF Aβ42, but not with CSF P-Tau181.	Cross-sectional: Higher plasma SHBG → ↓ CSF Aβ42 Longitudinal: Higher plasma SHBG → Faster ↓ CSF Aβ42 Cross-sectional: CSF p-tau181: Plasma SHBG ↔ CSF p-tau181	Plasma SHBG was measured in singlicate, increasing risk of measurement error. Some subgroup analyses (e.g., by sex) had limited sample size, reducing reliability. Loss to follow-up in longitudinal analyses may affect validity.
50	Rahman, 2020	Menopausal status was a predictor associated with higher PiB uptake across all regions examined. Hysterectomy status was associated with PiB uptake in the superior frontal gyrus (SFG), medial frontal gyrus; and anterior cingulate cortex regions; HRT was associated with PiB uptake in the orbitofrontal gyrus.	Menopausal status → ↑ PiB uptake (across all regions examined) Hysterectomy status → ↑ PiB uptake (superior frontal gyrus, medial frontal gyrus, anterior cingulate cortex) HRT use → ↑ PiB uptake (orbitofrontal gyrus)	Small sample size; potential misclassification of exposure groups; limited generalizability
54	Najar, 2021	In a population-based sample of women with natural menopause and free from dementia followed over 25 years, longer reproductive period was associated with preclinical CSF markers of AD (lower levels of Ab42, lower ratio of Ab42/Ab40, and higher levels of P-tau). Findings suggest a negative effect of longer exposure to endogenous estrogen on CSF biomarkers for AD in the preclinical phase of AD.	Longer reproductive period → ↓ CSF Aβ42 Longer reproductive period → ↓ CSF Aβ42/Aβ40 ratio Longer reproductive period → ↑ CSF p-tau Longer reproductive period ↔ CSF t-tau Earlier menarche → ↑ CSF p-tau Earlier menarche → ↓ CSF Aβ42/Aβ40 ratio	Small sample size Substantial attrition with a small, healthier lumber puncture subsample, this constituted only 10% of the eligible sample (selection bias). Incomplete adjustment for all hormonal factors influencing estrogen exposure. Possible influence of mortality-related bias - longer reproductive period and later age at menopause related to increased mortality rate.

56	Mosconi, 2021	There were no significant differences in PiB uptake between MT groups.	Menopausal status ↔ Global Aβ burden (PiB SUVR)	Misclassification of the exposure groups that could have reduced the effect to null. Small sample size Highly educated therefore difficult to generalize to women with different educational or socio-economical background.
57	Wisch, 2021	There was a trend level evidence to suggest that females who had a history of HT may have a small reduction in tau PET burden.	HT use ↔ Global Aβ burden HT use → ↓ Regional tau PET burden (trend-level/small reduction among women)	Self-reported HRT use
60	Depypere, 2022	Longitudinal analyses showed no significant overall differences in annual biomarker change between MHT and control groups.	MHT ↔ Longitudinal change in Aβ1-42, p-tau231, t-tau	1. Short follow-up (~6 months): limits ability to assess long-term effects of MHT on AD. 2. Non-randomized design: participants chose treatment → risk of selection bias and confounding. 3. Unbalanced group sizes: more participants in the MHT group than controls. 4. Unable to distinguish effects of: Oral vs transdermal estrogen; Role of progesterone co-treatment 5. Subset analysis (complete cases): only participants with full data were analyzed → potential bias. 6. Single-center study: limits generalizability and does not capture ethnic/genetic variability.
62	Buckley, 2022	No main effect of menopause status on global Abeta-PET or tau among women. Those who reported age at menopause below 50yrs, had higher tau in rostral middle frontal and lateral occipital regions relative to those with later age-at-menopause, but were not significant after FDR correction.	Menopause status ↔ Global Aβ-PET (no significant association) Menopause status ↔ Tau PET (no significant association) Age at menopause <50 years ↔ Regional tau PET (trend toward higher tau, not significant after FDR correction)	Did not look at impact of surgery or circulating sex hormones, so do not know which component drives the findings; 2 PET scanners used; sample is well-educated and predominantly Caucasian therefore may limit generalizability
65	Nerattini, 2023	Gonadotropin effects on biomarkers were evident at the perimenopausal stage and more pronounced at the postmenopausal stage. Associations with Ab load involved middle and superior frontal gyrus for FSH and inferior frontal gyrus for LH. Moreover, associations with Ab load were more robust with FSH than with LH.	FSH → ↑ Regional Aβ-PET (frontal cortex; strongest in postmenopausal women), whereas LH showed no independent association after adjustment.	Selected sample; partial PET; voxel limits; single hormone measure.

67	Coughlan, 2023	Age at menopause yielded no main association with regional tau PET. Females with late HT initiation, more than 5 years after age at menopause, exhibited higher tau PET in the entorhinal cortex, inferior-temporal gyrus, superior parietal, temporal fusiform, lateral occipital cortex, and the temporo-occipital lobe, relative to those who initiated near their age at menopause.	Age at menopause ↔ Regional tau burden. HT use (current/past vs never) ↔ Regional tau burden. Late HT initiation (>5 years after menopause vs <=5 years) → ↑ Regional tau burden (entorhinal cortex, inferior temporal gyrus, superior parietal cortex, temporal fusiform gyrus, lateral occipital cortex, and temporo-occipital lobe)	Potential residual confounding, as the causes of premature/early menopause and reasons for HT initiation were unavailable. Menopause and HT data were self-reported, introducing possible recall bias. Limited generalizability due to the predominantly non-Hispanic White sample.
76	Lee, 2024	Mostly no association between reproductive factors/exogenous estrogens and amyloid or tau PET	Age at menarche ↔ Global Aβ burden Age at menopause ↔ Global Aβ burden Reproductive window ↔ Global Aβ burden ≥5 pregnancies vs 0 → ↑ Global Aβ burden (greater increase in amyloid PET over time). Ever HC use vs non-user ↔ Global Aβ burden Ever MHT use vs non-user ↔ Global Aβ burden Initiation of MHT use relative to menopause vs non-user ↔ Global Aβ burden Age at menarche ↔ Temporal tau burden Age at menopause → ↓ Temporal tau burden (younger age at menopause associated with lower tau PET) Reproductive window ↔Temporal tau burden ≥5 pregnancies vs 0 ↔ Temporal tau burden Ever HC use vs non-user ↔Temporal tau burden Ever MHT use vs non-user ↔ Temporal tau burden Initiation of MHT use relative to menopause vs non-user ↔ Temporal tau burden	Potential survival bias in longitudinal cohort Insufficient power to examine specific HC and MHT types/doses
77	Wang, 2024	HT is associated with lower tau neuroimaging and fluid biomarkers in post-menopausal females. (its group differences)	HT+ vs HT− → ↓ Tau-PET burden among cognitively impaired (CI) individuals. HT+ vs HT− → ↓ Tau-PET burden (Braak I–II, III–IV, V–VI, and meta-ROI SUVRs). HT+ vs HT− → ↓ CSF p-tau181. HT+ vs HT− → ↓ Plasma p-tau181. Findings were consistent across TRIAD and ADNI cohorts.	Lack of data on menopause timing and timing of HT initiation limits detailed analysis; Small HT+ group (~10%) → reduced statistical power Inability to examine HT timing, duration, and type

			HT+ vs HT− ↔ Global Aβ burden. P-tau217 measured, but no main results reported.	
80	Thurston, 2024	Vasomotor, and specifically sleep vasomotor symptoms, were associated with the AD risk factor lower plasma Ab42-to-Ab40 ratio. Only objectively measured nighttime VMS were associated with amyloid biomarkers. No associations were observed for self-reported VMS or tau biomarkers	More objectively measured nighttime VMS → ↓ Plasma Aβ42/Aβ40 ratio (suggesting greater amyloid pathology). Objective nighttime VMS ↔ Plasma p-tau181. Objective nighttime VMS ↔ Plasma p-tau231. Subjective VMS ↔ Plasma Aβ42/Aβ40 ratio. Subjective VMS ↔ Plasma p-tau181. Subjective VMS ↔ Plasma p-tau231.	Lower rates of vasomotor symptoms.
81	Bachmann, 2024	No main association between age at menopause or HRT use and tau-PET in any of the four ROIs.	Age at menopause ↔ Regional tau burden. HRT use ↔ Regional tau burden.	small sample and smaller group with HRT cohort is highly educated therefore may not be fully representative lacked additional info on HRT use and reproductive factors, such as HRT initiation, age at menarche, or reproductive years.
82	Young, 2025	Higher serum p-tau217 levels were still observed in women with pregnancy hypertension after adjustment for age, MCI, hypertension, BMI, renal function, and APOE4 carrier status.	Pregnancy hypertension → ↑ Serum p-tau217 levels.	Latency period (time since pregnancy) was not included as a covariate due to small numbers. High proportion with MCI (~40%) could affect reporting; although adjusted for cognitive status in analysis. Latency period (time since pregnancy) was not included as a covariate due to small numbers.
84	Coughlan, 2025	Faster regional tau accumulation was associated with self-reported history of menopausal HT use in older women (~70 years), with minimal to no association present in younger women. HT associations with tau accumulation were observed in the entorhinal cortex, the inferior temporal gyri, and the temporal fusiform gyri, areas of known vulnerability in preclinical AD. HT associations with global Aβ accumulation were	HT use ↔ Global Aβ burden HT use × older age (>70 years) → ↑ Regional tau accumulation	Age vs timing confounding: Cannot distinguish whether age effects reflect biological aging or differences in HT timing (initiation relative to menopause). Long lag (~14 years): Significant time between HT initiation and PET imaging → possible intervening influences.

		notably weak and did not survive confounder adjustment in sensitivity analyses.		No precise information on age at menopause, HT initiation, duration, or formulation.
86	Kantarci, 2025	Overall, neither early PBO (<46 years) nor late PBO (46–49 years) was associated with overall amyloid or tau burden.	Early PBO (<46 years) vs age-matched referent women without PBO ↔ Aβ burden. Late PBO (46–49 years) vs age-matched referent women without PBO ↔ Aβ burden. Early PBO (<46 years) vs age-matched referent women without PBO ↔ Tau burden. Late PBO (46–49 years) vs age-matched referent women without PBO ↔ Tau burden.	Biomarker abnormalities were observed primarily at older ages, suggesting age-dependent effects; longer follow-up would likely reveal more widespread abnormalities across the entire cohort, better capturing the evolving impact of early PBO over time.
90	Kantarci, 2026	In this KEEPS Continuation imaging study, performed by recontacting the original KEEPS participants 10 years after completion of the MHT clinical trial and at an average age of 68 years, neither oCEE nor tE2 exposure was associated with brain Aβ or tau biomarkers (compared to placebo) after adjusting for age and enrollment site.	oCEE vs placebo ↔ Aβ burden tE2 vs placebo ↔ Aβ burden	High attrition due to COVID-19: Many participants declined follow-up participation (travel concerns). Selection bias (healthier participants): Included participants had lower blood pressure and BMI than non-participants.
91	Jauregi-Zinkunegi, 2025	MHT use was not significantly associated with CSF amyloid and tau biomarker levels.	MHT use ↔ CSF p-tau/Aβ42 ratio. MHT use ↔ CSF Aβ42/40 ratio. MHT use ↔ CSF Aβ42. MHT use ↔ CSF Aβ40. MHT use ↔ CSF p-tau181.	Age imbalance: MHT users were older than non-users; adjusted for statistically, but residual confounding may remain. High-risk sample: Many participants had parental AD history (enriched cohort), which may affect external validity.
95	Buckley, 2025	Higher midlife SHBG was associated with a more favorable tau biomarker profile in men, characterized by lower regional tau burden (entorhinal, inferior temporal, and rostral middle frontal regions), but was not associated with amyloid burden. No associations were observed between estradiol, total testosterone, or SHBG and amyloid or tau burden.	Overall (men): Higher SHBG → ↓ Tau burden (entorhinal cortex) Higher SHBG → ↓ Tau burden (inferior temporal cortex). Higher SHBG → ↓ Tau burden (rostral middle frontal cortex) SHBG ↔ Global Aβ burden Testosterone ↔ Global Aβ burden Testosterone ↔ Tau burden Overall (women): Estradiol ↔ Aβ burden.	Lack diversity in sample, therefore limited generalizability

			Estradiol ↔ Tau burden. Total testosterone ↔ Aβ burden. Total testosterone ↔ Tau burden. SHBG ↔ Aβ burden. SHBG ↔ Tau burden	
98	Stocker, 2025	In the secondary analysis, menopause was not associated with P-tau181.	Menopause status ↔ plasma p-tau181 levels.	Menopause analyses did not adjust for hormone therapy use.
99	Wang, 2026	Higher FSH, but not estradiol, was associated with greater cerebral amyloid burden and increased likelihood of Aβ positivity in postmenopausal women.	Higher FSH → ↑ Aβ positivity, independent of APOE ε4 status. Higher FSH → ↑ Global Aβ burden. Higher FSH → ↑ Regional Aβ burden (frontal, parietal, posterior cingulate/precuneus, lateral temporal, and anterior cingulate regions). Estradiol (E2) ↔ Aβ positivity. Estradiol (E2) ↔ Global Aβ burden. Estradiol (E2) ↔ Regional Aβ burden.	Used radioimmunoassay which restricts the precise quantification of very low E2 levels in postmenopausal women: more sensitive methods, such as mass spectrometry required. SHBG, which regulates the bioavailability of estradiol not measured. Residual confounding by unmeasured vascular or lifestyle variables: registry did not systematically capture vascular risk factors such as hypertension, diabetes, dyslipidemia, or smoking.
101	Shadyab, 2026	Rates of change in the biomarkers (p-tau217, p-tau181, Aβ42:Aβ40) over an average 15-year follow-up did not significantly differ for estrogen alone vs placebo or estrogen plus progestin vs placebo.	Estrogen alone vs placebo ↔ Change in plasma Aβ42/Aβ40 ratio. Estrogen alone vs placebo ↔ Change in plasma p-tau217. Estrogen alone vs placebo ↔ Change in plasma p-tau181. Estrogen plus progestin vs placebo ↔ Change in plasma Aβ42/Aβ40 ratio. Estrogen plus progestin vs placebo ↔ Change in plasma p-tau217. Estrogen plus progestin vs placebo ↔ Change in plasma p-tau181.	Limited generalizability to current HT regimens (lower doses, transdermal formulations, micronized progesterone) and to women initiating HT earlier in menopause. Potential selection bias (participants able/willing to provide two blood samples). Only two biomarker assessments are available. Early trial termination and declining adherence may have attenuated associations.

eTable 11 FDG-PET-related studies: Basic information and study characteristics

Study ID	First author, year	Country	Cohort	Study population	Study design	Follow-up duration in years, mean (SD)	Total analytical sample	Age, mean (SD)	% Female	Ethnicity	Cognition	APOE ε4 carrier %
37	Mosconi, 2017	USA		Community-based women volunteers, 50-60yrs old cognitively intact, participating in brain imaging studies at medical universities.	Cross-sectional		43 (Pre (control) 15; peri 14; post 14)	Pre 47(5); Peri 50(6); Post 57(2)	100	pre80%/peri71%/post86% white	MMSE: Pre 29(2); Peri 29(1); Post 29(1)	Pre46%/peri43%/post36%
56	Mosconi, 2021	USA		Women that are cognitively intact, from medical universities	Cross-sectional		161 (pre 30; peri 57; post 74)	Pre 44(4); Peri 50(4); Post 57(4)	100	Pre 80% white; peri 77%; post 89%	MMSE: Pre 29(1); Peri 29(1); Post 29(1)	42%
38	Mosconi, 2017	USA		Women 40-60yrs; Community-based volunteers who are clinically and cognitively normal who participated in brain imaging studies medical universities	Cross-sectional		42 (pre 15; peri 13; post 14)	PRE (control) 48(5); Peri 50(6); Post 57(2)	100	PRE 75%; Peri 71%; Post 89% White	MMSE: PRE: 29(2); Peri 29(1); Post 29(1)	PRE 57%; Peri 46%; Post 36%
50	Rahman, 2020	USA		Community-based women that are cognitively normal, from	Cross-sectional		85	53(6)	100	89% White	Age and education adjusted MMSE of	42%

				brain imaging studies at medical universities							0.01 (0.11)	
8	Schönknecht, 2003	Germany		Postmenopausal women with probable AD	Cross-sectional		6	70.3(7.7)	100		MMSE score mean 20.5(SD4)	
43	Mosconi, 2018	USA		Community-dwelling, cognitively normal women, who participated in brain imaging studies at medical universities	Cohort	Pre 3 (0.5); Peri 3(0.5); Post 2(0.4)	41 (pre 15; peri 14; post 12)	Pre 47(5); Peri 53(4); Post 58(2)	100	Pre 73%; Peri 75%; Post 42%	NA	Pre 47%; Peri 50%; Post 42%
2	Rasgon, 2001	USA		Postmenopausal women from community with memory complaints and/or dementia family history, but without dementia	Cohort	27.9(1.7) months	12 (Estrogen users; 8 nonusers)	users 65.5(9.5), nonusers 71.8(9.2)	100		MMSE: users 28.5(0.6); nonusers 28(1.9)	users 50%, nonusers 50%
10	Rasgon, 2005	USA		Community-recruited, Postmenopausal women with intact cognition, some with subjective memory complaints and/or family history of dementia, but	Cohort	29.9 ± 2.4 month	20 (11 Estrogen users; 9 nonusers)	65.2±9.5; users 60.4(7.3); nonusers 7171(8.7)	100	85% Caucasian	MMSE: users = 29.2 (1.3) nonusers = 28.9 (1.4)	55%

				without dementia								
48	Xu, 2020	USA/Canada	ADNI	Non-demented adults, including CN and those with MCI, recruited from medical center/university hospital	Cohort	3.2 ± 2.4 years	448	74.8 ± 7.2	approx. 37	Predominantly non-Hispanic White (~93.3%)	MMSE: 27.3 ± 1.8	47.5%

eTable 12 FDG-PET-related studies: Methods and Materials

Study ID	First author, year	Exposure	Exposure Ascertainment	Outcome	Outcome ascertainment	Covariates adjusted for in models	Statistical Analysis
37	Mosconi, 2017	Menopausal status (pre-; peri-; and postmenopause)	Clinical judgement, medical records and detection of cluster symptoms according to STRAW criteria. Groups defined by menopause status (pre = regular cycler <7days variability in cycle length (CNT); peri= irregular menstrual cycles with variation in cycle length >7 days; post = no cycle for >=12 or months), and cluster symptoms.	Pons-adjusted FDG SUVR	18F-FDG PET; normalized to pons; reported as region SUVR	Age, education, APOE	Voxel-wise SPM12 full factorial model and posthoc t-contrasts with regional/masked reporting
56	Mosconi 2021	Menopausal status (pre-; peri-; and postmenopause)	Based on the STRAW criteria and corroborated by means of hormone assessments.	Global-adjusted CMRglc	18F-FDG PET; adjusted by global-metabolic uptake	Age, APOE4, global metabolic activity	Voxel-wise SPM12 full factorial model and posthoc t-contrasts with regional/masked reporting
38	Mosconi, 2017	Menopausal status (pre-; peri-; and postmenopause)	Clinical judgement, medical records and detection of cluster symptoms according to STRAW criteria. Groups defined by menopause status (pre = regular cycler <7days variability in cycle length; peri= irregular menstrual cycles with variation in cycle length >7 days; post = no cycle for >=12 or months), and cluster symptoms.	Pons-adjusted CMRglc	18F-FDG PET; adjusted to pons; reported as reference-adjusted SUVR	Age, education, APOE	Voxel-wise SPM12 full factorial model and posthoc t-contrasts with regional/masked reporting
50	Rahman, 2020	Menopausal status (pre-; peri-; and postmenopause); HRT status (user vs nonuser); Hysterectomy status (yes, no)	Menopausal status based on the STRAW criteria and cluster symptoms and based on clinical judgement.	Global-adjusted FDG uptake	18F-FDG PET; adjusted by global-activity; reported as adjusted SUVR	Age and global activity	Voxel-wise SPM12 full factorial model and posthoc t-contrasts with regional/masked reporting. If showing a significnat. LASSO regression.
8	Schönknecht, 2003	CSF E2 levels	CSF using electro-chemiluminescence-immunoassay	Hippocampal FDG uptake	[18F] FDG PET	age and MMSE	Voxel-side SPM96 with regional/masked correlations
43	Mosconi, 2018	Menopause status (pre-; peri-; and postmenopause)	Clinical judgement, medical records and detection of cluster symptoms according to STRAW criteria.	Global-adjusted FDG SUVR	18F-FDG PET	Age, APOE4 status, and vascular risk measures	ROI/region-based analysis. Targeted minimum loss-based estimation.
2	Rasgon, 2001	Estrogen Users vs. non-users	Self-report	WB-normalized ROI CMRglc	[18F]FDG during mental rest; normalized to whole brain metabolic rate. Used 2 scanners at	age and MMSE	ROI/region-based analyses. Baseline groups compared with 3-way repetaed measrues ANOVA. Two-tailed statistical tests were

					baseline, but same at follow-up.		performed on 3 regions: lateral temporal, posterior cingulate and inferior parietal cortices.
10	Rasgon, 2005	Estrogen Users vs. non-users	self-reported + Researchers also recorded details of therapy (type + duration); Estrogen use defined as receiving hormonal preparations consisting of plant-derived estradiol or conjugated equine estrogens, sometimes in combination with progesterone or its derivatives.	WB-normalized ROI CMRglc	[18F]FDG-PET (two different scanners used). ROI metabolic rates normalized to whole-brain values.	age	ROI repeated measures ANCOVA, normalized to whole brain metabolism. Whole brain voxel-wise SPM96, normalized to global activity.
48	Xu, 2020	Plasma SHBG : categorized as High vs low (based on median split)	Cutoff is defined using the median level of plasma SHBG: > 56.23 nmol/L. Samples for each subject were obtained in the morning following an overnight fast. Experimenters were blind to the clinical information of samples. Multiplex immunoassay panel on the Luminex xMAP platform by Rules-Based Medicine	ADNI FDG metabolism	18F-FDG PET in the resting state; ADNI derived brain metabolism	Age, gender, education, APOE4 status, and clinical diagnosis of MCI at baseline.	Linear mixed effects models. SA: re-ran all analyses in men and women separately; excluding those who developed dementia whine one year since baseline; repeated all analyses after further adjusting for plasma levels of total testosterone (TT) or free testosterone index (FTI) which were calculated by dividing TT by SHBG.

eTable 13 FDG-PET-related studies: Overall findings and limitations

Study ID	First author, year	Main Finding	Direction of association	Key limitations
37	Mosconi, 2017	POST vs PRE: lower CMRgluc in AD-vulnerable areas: posterior, cingulate/precuneus, frontal cortex, parietal cortex, medial temporal cortex, and lateral temporal cortex POST vs PERI: lower CMRglc in the temporal cortex and left frontal/posterior cingulate regions PERI vs PRE: lower CMRglc in the bilateral temporal cortex, posterior cingulate, and right inferior parietal cortex PRE vs POST or PERI: no brain regions exhibited reduced CMRglc. Gradient FDG uptake lower PRE>PERI>POST.	Postmenopause ↓ FDG uptake vs premenopause Postmenopause ↓ FDG uptake vs perimenopause Perimenopause ↓ FDG uptake vs premenopause Premenopause ↔ lower FDG regions vs peri/postmenopause	Small sample; self-report
56	Mosconi, 2021	POST vs PRE or PERI: lower CMRglc throughout temporal and parietal regions PERI vs PRE: lower CMRglc in right middle temporal gyrus.	Postmenopause ↓ FDG uptake vs pre/perimenopause Perimenopause ↓ FDG uptake vs premenopause	small sample size; limited generalizability; potential misclassification of exposure groups
38	Mosconi, 2017	PERI and MENO vs PRE: showed reduced CMRglc in posterior cingulate/precuneus (PCC) and parietal cortex and temporal cortex. Gradient PRE>PERI>MENO.	Perimenopause/postmenopause ↓ FDG uptake vs premenopause	small sample size; potential misclassification of exposure groups; highly sleeted sample; unmeasured confounders; limited generalizability
50	Rahman, 2020	More advanced menopause associated with lower CMRglc. Hysterectomy status was associated with lower CMRglc. SA: HRT was also associated with higher FDG uptake.	More advanced menopause ↓ FDG metabolism Hysterectomy ↓ FDG metabolism HRT use ↑ FDG uptake	small sample size; potential misclassification of exposure groups; limited generalizability
8	Schönknecht, 2003	Estrogen associated with higher glucose metabolism in left hippocampus.	CSF estradiol ↑ hippocampal FDG uptake	small sample size
43	Mosconi, 2018	POST vs PRE and PERI: negative association (higher rates of CMRglc decline in frontal cortex compared to all other groups) POST and PERI declined in CMRglc over time in the frontal region. With faster declines in the MENO vs PERI. CMRglc did not decline over the 3-year period in PRE women.	Postmenopause ↓ frontal FDG metabolism vs pre/perimenopause Perimenopause ↓ frontal FDG metabolism over time Postmenopause ↓ frontal FDG metabolism over time Premenopause ↔ FDG change over time	Potential exposure misclassification because no hormonal confirmation; Small sample size; Limited generalizability
2	Rasgon, 2001	No difference in baseline metabolism among the 3 groups. At 2-yr follow-up a significant group difference in metabolic change in the lateral temporal cortical region. Estrogen users showed significantly increased metabolism in lateral	Estrogen use ↔ baseline FDG metabolism Estrogen users ↑ lateral temporal metabolism at follow-up Nonusers ↔ lateral temporal metabolism change	pilot study; small sample size; self-report exposure; not randomized; potential confounding factors; short follow-up

		temporal cortical region, whereas nonusers had no significant change.		
10	Rasgon, 2005	Results showed that postmenopausal estrogen users maintained stable metabolism in the posterior cingulate cortex, while non-users exhibited significant decline, suggesting a potential protective effect of estrogen in a brain region vulnerable to early Alzheimer's disease.	Estrogen users ⇔ posterior cingulate metabolism (maintained) Nonusers ↓ posterior cingulate metabolism	1. Significant difference in age between the estrogen users and non-users; 2. Non-random assignment for use or non-use of estrogen. 3. Sample size small 4. The ROI method may be limited by predefined region assumptions, while SPM may introduce errors due to differences in brain alignment. 5. Use of multiple scanners; 6. Group differences in brain metabolism may be due to underlying differences between women who choose to use estrogen and those who do not, rather than a direct effect of estrogen itself.
48	Xu, 2020	Higher levels vs low of plasma SHBG were associated with decreased brain metabolism decline. Higher plasma SHBG → faster brain metabolism decline SA barely changed results.	Higher plasma SHBG ↓ brain FDG metabolism (faster decline)	Small subgroup sizes; Attrition bias; Measurement bias: Plasma SHBG was measured in singlicate, increasing risk of measurement error.

eTable 14 Neurofilament light (NfL)-related studies: Basic information and study characteristics

Study ID	First author, year	Country	Cohort	Study population	Study design	Follow-up duration in years, mean (SD)	Total analytical sample	Age, mean (SD)	% Female	Ethnicity	Cognition	APOE ε4 carrier %
60	Depypere, 2022	Belgium		Healthy, MHT-naïve women during menopause recruited from university-based outpatient menopause clinic	Cohort	Control group: 7.2 ± 2.4 months MHT group: 6.7 ± 1.6 month	224; Control = 31 MHT = 193	Mean age overall: 54.03 ± 4.71 years Control: 55.69 ± 4.94 MHT: 53.76 ± 4.63	100		Mean MMSE: 29.5 ± 1.01 Control: 29.77 ± 0.56 MHT: 29.52 ± 1.07	29.9%
101	Shadyab, 2026	USA	WHIMS	Postmenopausal women volunteers from clinical centers and cognitively unimpaired	RCT (double-masked, parallel randomized placebo controlled); repeated measures	15.1(0.6)	2784	69.9(3.8)	100	0.6% American Indian/Alaskan Native, 4.7% Asian, 18.5% Black, 2.8% more than one race, 0.3% Native Hawaiian/Other Pacific Islander, 73.1% White, and 7.3% Hispanic/Latina		
98	Stocker, 2025	Germany	ESTHER	Women 50-75yrs, recruited by general practitioners	Nested case-control		Subsample of 60 women with menopause info	Total sample 64.1(6.5)	100			Total sample: 32.8%
80	Thurston, 2024	USA	MsBrain study	Community-based perimenopausal or postmenopausal	Cross-sectional		248	59 (4.3)	100	81% white; 15% black; 3.6% Asian or mixed	exclusion criteria included a reported history of stroke or cerebrovascular	61%

				women without dementia						race and ethnicity	accident, dementia, seizure disorder, brain tumor, Parkinson disease	

eTable 15 Neurofilament light (NfL)-related studies: Methods and Materials

Study ID	First author, year	Exposure	Exposure Ascertainment	Outcome	Outcome ascertainment	Covariates adjusted for in models	Statistical Analysis
60	Depypere, 2022	MHT and control arm	Clinical treatment assignment at enrollment, not randomization. Exposure was ascertained by whether the participant chose and was prescribed/placed on MHT versus choosing no MHT.	Annual rate of change in NfL biomarkers over time	NfL concentrations were measured using the Single molecule array (Simoa).	Age and APOE ε4	Annual rate of change (ARC) as the difference in plasma concentration between the two visits (V1 and V2) divided by the delay in years. Linear models.
101	Shadyab, 2026	Randomized HT vs placebo	CEE 0.625mg/d vs placebo among those with hysterectomy (estrogen alone vs placebo) or CEE combined with medroxyprogesterone acetate 2.5mg/d vs placebo (estrogen plus progestin vs placebo) for those with an intact uterus	NfL	Fasting blood samples drawn at baseline and 2012-2013. Levels of NfL were measured using the Simoa.	HT treatment arm, time, and an interaction between treatment assignment and time. Time-varying estimated glomerular filtration rate (eGFR) based on serum creatinine and were weighted to account for biomarker sampling design.	Linear mixed models with random intercepts and slopes and an unstructured covariance matrix
98	Stocker, 2025	Menopause status	Self-administered questionnaire and/or physician reports	Nfl	Automated Simoa HD-X Analyzer by Quanterix	Age, sex, APOE4	Linear regression
80	Thurston, 2024	Vasomotor symptoms	3 days of ambulatory VMS and sleep actigraphy monitoring, with a wearable VMS monitor (VU-AMS 5fs; Vrije Universiteit Amsterdam, Amsterdam, The Netherlands) quantifies VMS via sternal skin conductance, a validated objective measure of VMS and completing an electronic VMS diary and by pressing event	NfL	Plasma biomarker concentrations were measured using single-molecule array (Simoa) technology on an HD-X instrument (Quanterix, Billerica, MA).	Age, race, and ethnicity, education, BMI, and APOEe4	Linear regression; additional with multiple comparisons.

			mark buttons on the VU-AMS monitor.				

eTable 16 Neurofilament light (NfL)-related studies: Overall findings and limitations

Study ID	First author, year	Main Finding	Direction of association	Key limitations
60	Depypere, 2022	No significant overall differences in annual biomarker change between MHT and control groups.	MHT ↔ annual NfL change	Short follow-up (~6 months); Non-randomized design, thus risk of selection bias and confounding; Unbalanced group sizes; Unable to distinguish effects of: Oral vs transdermal estrogen; Role of progesterone co-treatment
101	Shadyab, 2026	NfL increased over time among all treatment groups. However, rate of change did not significantly vary for estrogen alone vs placebo or estrogen plus progesitn vs placebo.	Randomized hormone therapy ↔ rate of NfL change	WHI HT formulations may not generalize to current regimens with lower doses, transdermal preparations, or micronized progesterone; don't know if results can be generalized to HT initiated earlier in menopause. Selection bias; examined BBM at only 2 time points; the trials were stopped earlier for harm
98	Stocker, 2025	Menopause was not significantly associated with NFl levels. There was no difference by dementia status	Menopause status ↔ NfL	Potential measurement and assay variability; possibility of dementia misdiagnosis; the analysis with menopaused did not account for hormone replacement therapy; Generalizability is limited to individuals of European descent; cross-sectional; Biomarkers measured at one time point; Residual confounding
80	Thurston, 2024	Associations between VMS and other AD biomarkers were not statistically significant. Self-report VMS was not associated with AD biomarkers.	Physiologically measured VMS ↔ NfL Self-reported VMS ↔ NfL	Racial and ethnic diversity of the sample was limited; lower rates of VMS reporting; don't know if causal

eTable 17 White matter hyperintensities, cerebral small vessel disease, and white matter integrity-related studies: Basic information and study characteristics

Study ID	First author, year	Country	Cohort	Study population	Study design	Follow-up duration in years, mean (SD)	Total analytical sample	Age, mean (SD)	% Female	Ethnicity	Cognition	APOE ε4 carrier %
25	Coker, 2014	USA	WHIMS-MRI2	Postmenopausal women 65-79 treated for 4- 5.6yrs with HRT compared to placebo, previously in WHIMS-MRI	RCT (parallel randomized placebo controlled); post-trial longitudinal repeated measures MRI study	4.7 after WHMIS-MRI initiation (about 7.7yrs after termination of the treatment CEE+MPA; or 6.1yrs after CEE alone)	1403 (n=674 with only MRI1; n=729 with scans at MRI1 and MRI2)	78.5 (3.7) at MRI1 82.8 (3.5) at MRI2 [76-92 years]	100	94% white, non-Hispanic	In WHIMS-MRI1: 3MSE <90 = 8%; In WHIMS-MRI2: 3MSE <90 = 3%	
21	Espeland, 2009	USA	WHIMS & WHIMS-MRI	women recruited from clinics, free of dementia, aged between 65-79yrs, previously participating in WHIMS	Ancillary, cross-sectional analysis of a randomized, placebo-controlled clinical trial	1-4yrs after the RCT	1403 No CI: HT=664; Placebo=686; CI: HT=29; Placebo=24	Active therapies 70.6 yrs; Placebo 70.5 yrs	100		3MS score: No CI HT <90=4.7%; No CI placebo <90= 4.4%; CI HT <90= 37.9%; CI Placebo <90 = 33.3%	

89	Faubion, 2025	USA	KEEPS Continuation	Healthy recently postmenopausal women with good cardiovascular health, previously in KEEPS	Observational follow-up of an RCT	~14 years post-randomization; around 10 years post RCT completion	Overall KEEP Continuation: 266 Subsets: dMRI analysis = 243 WMH analysis = 257	Age at imaging at 14-year follow-up: mean of 67 (range 58-73 y)	100			Overall keep continuation = 26% oCEE: 30% tE2: 32% placebo: 18%
33	Kantarci, 2016	USA	The Kronos Early Estrogen Prevention Study (KEEPS); ancillary KEEPS-MRI study	Healthy postmenopausal women with good cardiovascular health [baseline], previously in KEEPS	Ancillary longitudinal analysis (with repeated measures) within a randomized double blinded, placebo-controlled clinical trial	Up to 48 months (3 follow-ups (at 18, 36, 48 months))	Overall = 95 CEE: 29 Estradiol: 30 Placebo: 36	CEE: mean 53 (95%CI 52-54) Estradiol: 53 (52-54) Placebo: 53 (52-54)	100		Global cognitive function: CEE: −0.19 (−0.48, 0.10) Estradiol: 0.16 (−0.12, 0.44) Placebo: 0.14 (−0.08, 0.36)	CEE: 15 Estradiol: 45 Placebo: 21
41	Kantarci, 2018	USA	Kronos Early Estrogen Prevention Study (KEEPS); ancillary KEEPS-MRI study	Healthy recently postmenopausal women with good cardiovascular health, previously in KEEPS	Ancillary longitudinal analysis (with repeated measures) within a randomized double	Up to 84 months	Overall = 75 oCEE: 20 tE2: 22 Placebo: 33	~53 years oCEE: 53 (±2) tE2: 53 (±3) Placebo: 53 (±2)	100		oCEE: −0.20 (0.77) tE2: 0.07 (0.79) Placebo: 0.15 (0.67)	oCEE: 15% tE2: 48% Placebo: 16%

					blinded, placebo-controlled clinical trial							
49	Kling, 2020	USA	Kronos Early Estrogen Prevention Study (KEEPS); ancillary KEEPS-MRI study	Healthy recently postmenopausal women with good cardiovascular health, previously in KEEPS	Secondary longitudinal (two–time-point change) analysis within a randomized, double-blind, placebo-controlled clinical trial	Up to 48 months	Total analyzed sample: 78 women oCEE: 23 tE2: 24 Placebo: 31	Mean age ≈ 53 years (SD ~2) across all groups	100		Global cognitive function (z scores): oCEE: -0.09 (SD 0.79) tE2: 0.03 (SD 0.75) Placebo: 0.21 (SD 0.65)	Changes in circulating pituitary ovarian hormones during 48 months of randomized HT. oCEE: 9% tE2: 46% Placebo: 23%
93	Alshikho, 2025	USA	The Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be (nuMoM2b) Heart Health Study- ancillary nuMoM2b BraiN study	Women with HDP vs controls from clinics	Cohort	Median 11 (IQR 1.0)	81 HDP (27) vs healthy pregnancy (54)	39 (SD6)	100	27.2% white, 8.6% non-Hispanic black, 51.9% hispanic, 9.9% asian/pacific islander, 2.5% multiple race		
3	Cook, 2002 (pilot study)			Community-dwelling women aged ≥60 years, cognitively normal	Cohort	3.7 (0.8) years, range 2.8–	15 (No ERT = 9; ERT= 6)	74.2 (7.2) years	100		MMSE: No ERT: 29.00 ± 1.07; ERT: 29.33 ± 1.63	

						6.1 years						
76	Lee, 2024	USA	Mayo Clinic Study of Aging (MCSA)	Community dwelling women	Cohort	Not stated	389	Median (range) = 71.1 years (51.1, 90.4)	100	Mostly white		30.6%
13	Lessov-Shlaggar, 2005	USA	WWII veteran twin men	Healthy, white WWII veteran male twins, with normal cognitive levels from community/register	Cohort	10-16yrs	566	63.1(2.9)	0	white	healthy; in age-appropriate normal range for cognition and brain measures; MMSE 27.0(2.6)	
69	Liao, 2023	UK	UKB	Dementia free women with earlier or premature menopause	Cohort	Median 8.8yrs (2.11–13.82)	11604	37-73	100	>=50yrs: 91.9% white; 40-49yrs: 90.8% W; <40yrs: 92.1%W		
61	Aleknavicute, 2022	The Netherlands	Rotterdam Study/Rotterdam Scan Study	Stroke, dementia, and cortical infarct free women aged 55+yrs	Cross-sectional		2834	65.2	100	Mainly of Caucasian descent		
85	Barth, 2025	UK	UKB		Cross-sectional		Overall = Complete data related to MHT user status = 19,846 (14,693 with APOEε4 status) Among MHT users, subsample with complete MHT-related prescription data and MRI data =	MHT user status: never = 61.6±7.1 current = 60.1±6.8 past = 67.5±6.2	100	MHT user status: White never = 96.60 current = 98.0 past = 98.2		MHT user status: never = 27.5% current = 26.3 % past = 24.6%

							538 (521 with APOEε4 data)					
66	Cote, 2023	UK	UKB	Community-based mid-life women	Cross-sectional		9163	64.21(6.81) on scan day	100	97.44% white British	no dementia	
87	Giudicessi, 2025	USA	Boston Latino Aging Study (BLAST)	Community-dwelling, postmenopausal Latina women	Cross-sectional		Overall = 95; Neuroimaging sample = 58	Overall sample = 65.6 years (SD = 6.5)	100	Latina women	Overall sample = 26.4 (3.1); Number cognitively impaired: 14 participants based on MMSE<24	
16	Greenberg, 2006	USA		Women used as controls (MHT users (for at least 10yrs and still taking); nonusers) (only look at HR users vs nonusers)	Cross-sectional		92 (Non HT = 51; HT=41)	NonMHT =71 ±6 MHT =70±6	100	NonMHT: White n=38; Black = 12; Other/unknown = 1; HT: White =40; Black = 1; Other/unknown = 0		
78	Huddleston, 2024	USA	CARDIA Brain substudy	Women with PCOS and MRI	Cross-sectional		291 PCOS = 25 No PCOS = 266	54.7(3.6) PCOS; 55.3(3.6) nonPCOS	100	PCOS: 39.% black; 61.6% white; nonPCOS 53.6% black; 46.4% white		
14	Irie, 2006	USA	Honolulu–Asia Aging Study (HAAS)	Community-based older men	Cross-sectional		452	81.6 (5.08)	0	Japanese American		
96	Jiang, 2025	USA	CARDIA	Women with a history of HDP and not	Cross-sectional		1441 (367 with MRI)	Mean age at first pregnancy 24(7.1); 55.2(3.6) at yr 30	100	No HDP 50% black; GH 68% black; preeclampsia 56.9% black		
46	Jung, 2020	South Korea	Korean Brain Aging Study for Early Diagnosis and Prediction of Alzheimer's	Non-demented older women (CN and MCI)	Cross-sectional		WMH = 210	70.45 (7.68)	100	Korean	MMSE = 24.93 (3.55)	24.9%

			Disease (KBASE)									
83	Li, 2025	UK	UKB	Community-dwelling adults	Cross-sectional		34832	64.15 (7.75); Men: 64.97 ± 7.83 yrs Women: 63.31 ± 7.58 yrs	49.1	White = 96.7%		
19	Liu, 2009	China		Postmenopausal female medical staff	Cross-sectional		182	HRT gr 66.3yr; Control 67.1yrs	100		MMSE >26 (Gp 50-59, HRT 29.26(0.18); control 29.63(3.68)); Grp 60-69, HRT 29.03(0.2); control 28.8(0.27); Grp 70-87, HRT 28.57(0.75); control 28.66(0.30)	
59	Lohner, 2022	Germany	The Rhineland Study	Community-dwelling adults	Cross-sectional		1973 (only women) HT sample of postmenopausal women n = 216	54.6 years (13.6)	100	Mainly German		
15	Low, 2006	Australia	PATH (Personality And Total Health) Through Life' project	Postmenopausal women aged 60–64 years	Cross-sectional		213	62.6 (1.5)	100			
1	Luoto, 2000	USA	CHS	Postmenopausal women	Cross-sectional		2133 (329 users; 483 past; 1321 never)	Current HRT users 73.2(0.28); past 74.4 (0.17); Never	100	current 9.8% black; past 10.5% black; never 20% black	MMSE adjusted for age and race (0-100): current estrogen 89.2 (95%CI 88.3-90.2); nonusers 87.8 (87.3-88.3); past users 89.9 (89.0-90.7)	

								75.4 (0.15)				
30	Mielke, 2016	USA	Ancillary study (GMBI) within the GENOA cohort	Community-based cohort of older women with vascular risk factors (family hypertension background)	Cross-sectional		972 Normotensive Pregnancy =796 Hypertensive Pregnancy =176	Normotensive pregnancy: 61 ± 9 years Hypertensive pregnancy: 58 ± 10 years	100	Non-Hispanic white: Normotensive pregnancy: 47% Hypertensive pregnancy: 48%		
75	Mielke, 2024	USA	The Mayo Clinic Study of Aging (MCSA)	Community-dwelling women aged 50 years and above.	Cross-sectional		1011	Age at imaging = Median (IQR)/N(%) 72.15 (64.08, 77.70	100	Mainly white		30%
70	Moir, 2023	USA		Cognitively healthy postmenopausal women	Cross-sectional		35	Age at onset of menopause early 47 ± 2; late 55 ± 2	100			
56	Mosconi 2021	USA		Women that are cognitively intact, from medical universities	Cross-sectional		161 (pre 30; peri 57; post 74)	Pre 44(4); Peri 50(4); Post 57(4)	100	Pre 80% white; peri 77%; post 89%	MMSE: Pre 29(1); Peri 29(1); Post 29(1)	42%
26	Ryan, 2014	France	ESPRIT study	Nondemented older women randomly selected from community	Cross-sectional		295	Never MHT median 71(IQR 68-75; past HT 70(68-72); current 68(67-71)	100		nondemented; MMSE <=24: Never MHT 12.1%); past MHT 10%; Current MHT 4.8%	Never MHT 24.3%; Past MHT 23.3%; current MHT 16.1%

71	Sato, 2023	Japan	Ohasama study	Community-based women >=55yrs	Cross-sectional		622	67.9(6.1)	100			
29	Srinath, 2016	USA	ARIC study (Atherosclerosis Risk in Communities)	Community-dwelling men	Cross-sectional		257		0			
52	Than, 2021	UK	UKB	Community-dwelling adults	Cross-sectional		2057 Pre/perimenopausal = 230; Postmenopausal = 1827	Median age (IQR): Pre/peri =49.9(46.2-53.6) Post = 63.9 (54.2-73.6)	100			28.5%
28	Thurston, 2016	USA		Midlife women	Cross-sectional		19	55.2 (3.5)	100	73.7% white		
64	Thurston, 2023	USA	MsBrain study	Midlife women	Cross-sectional		226; 224 for models incorporating blood-based biomarkers	59.17 (4.27)	100	81.86% white		APOE e4 positive (2/4, 3/4, 4/4) = 21.2%
73	Thurston, 2024	USA	MsBrain study	Midlife women not using HT	Cross-sectional		N=222 (E1 and FSH models) N=221 (E2 models) N=214 (models incorporating APOE))	59.20 (4.29)	100	81.89% white		22.43%
92	Wezel, 2025	UK	UKB	Community-dwelling women	Cross-sectional		9560; 674 in the PRE group, 7992 in the POST group and 894 in the SURG group (bilateral	45 -81 years old	100	White British		

							oophorectomy before natural menopause, with or without hysterectomy); (n=908 in age-matched sample)					
31	Guoqing, 2016	China		Postmenopausal women aged <60yrs, recruited through the clinic	Case-control, cross-sectional		210 (PCOS=70; without PCOS controls = 140)	PCOS: 55.04 ± 2.55 yrs Controls: 55.11 ± 2.66 yrs	100			
45	Zeydan, 2019	USA	The Mayo Clinic Cohort Study of Oophorectomy and Aging-2 (MOA-2) and The Mayo Clinic Study of Aging (MCSA)	Women with BSO before the onset of menopause vs controls	Nested case-control		43 BSO =23 Control = 20	Median age (IQR) at imaging BSO grp 65 (62-68); Control 63 (60-66)	100		13% BSO group with MCI; 5% in control group	BSO 9%; control 20%

eTable 18 White matter hyperintensities, cerebral small vessel disease, and white matter integrity-related studies: Methods and Materials

Study ID	First author, year	Exposure	Exposure Ascertainment	Outcome	Outcome ascertainment	Covariates adjusted for in models	Statistical Analysis
25	Coker, 2014	HRT treatment vs placebo: CEE + MPA for women with intact uteri; CEE alone for women with prior hysterectomy; Placebo.	Exposure was ascertained from the original WHI randomized treatment assignment at baseline: CEE 0.625 mg/day plus MPA 2.5 mg/day for women with an intact uterus, or CEE 0.625 mg/day alone after hysterectomy, versus placebo.	Total ischemic lesion volume; white matter lesion volume; gray matter lesion volume; basal ganglia lesion volume. Secondary outcomes: annual rate of change (cm^3/year) in total ischemic lesion volume and its WM, GM, and basal-ganglia constituents.	MRI	Trial, visit, clinical site, age, intracranial volume, and time from randomization to MRI scan	Longitudinal mixed-effects models
21	Espeland, 2009	HRT vs placebo control: CEE + MPA in women with a uterus; CEE alone with prior hysterectomy; Placebo	Exposure was ascertained by randomized treatment assignment in the parallel placebo-controlled WHI/WHIMS trials: CEE 0.625 mg/day plus MPA 2.5 mg/day for women with a uterus, or CEE 0.625 mg/day alone after hysterectomy, versus placebo.	Brain lesion and periventricular abnormal WM volumes (for total brain, frontal lobe, and hippocampus)	MRI	ICV	ANCOVA or logistic regression
89	Faubion, 2025	Assignment to menopausal hormone therapy (MHT) during the original KEEPS randomized trial Hormone therapy groups: Oral CEE Transdermal 17β-Estradiol Placebo [reference]	Estrogens were administered through two different routes: Oral or transdermal. Participants were randomized to either: 1) oral conjugated equine estrogen (CEE; Premarin, 0.45 mg/day); 2) transdermal 17β-estradiol (skin patch, Climara, 50 µg/day); or 3) placebo pills and patch.	Total WMH volume; cerebral infarcts (total, cortical, subcortical); regional white-matter integrity by DTI	MRI; diffusion DTI	Age, study site, and TIV for WMH	Linear regression models

			Progesterone was given orally (Prometrium; micronized progesterone, 200 mg/day) for the first 12 days each month to both active treatment groups. Participants were treated for four years.				
33	Kantarci, 2016	Hormone therapy groups: Oral CEE Transdermal 17β-Estradiol (tE2) Placebo [reference]	Estrogens were administered through two different routes: Oral or transdermal. Participants were randomized to either: 1) oral conjugated equine estrogen (CEE; Premarin, 0.45 mg/day); 2) transdermal 17β-estradiol (skin patch, Climara, 50 μg/day); or 3) placebo pills and patch. Progesterone was given orally (Prometrium; micronized progesterone, 200 mg/day) for the first 12 days each month to both active treatment groups. Participants were treated for four years.	WMHV Secondary outcome: longitudinal absolute change in total WMHV (cm^3) from baseline at each follow-up; modeled with linear mixed effects.	MRI	Time from baseline, treatment group, and time from baseline*treatment group interactions [primary interest] as fixed-effects predictors. These models incorporated random effects for subject-specific intercepts and slopes.	Linear mixed models
41	Kantarci, 2018	Hormone therapy groups: Oral CEE. Transdermal 17β-Estradiol (tE2) Placebo [reference]	Estrogens were administered through two different routes: Oral or transdermal. Participants were randomized to either: 1) oral conjugated equine estrogen (CEE; Premarin, 0.45 mg/day); 2) transdermal 17β-estradiol (skin patch, Climara, 50 μg/day); or 3) placebo pills and patch. Progesterone was given orally (Prometrium; micronized progesterone, 200 mg/day) for the first 12 days each month to both active treatment groups. Participants were treated for four years.	Annual percent change in WMH volumes	MRI		Linear mixed models
49	Kling, 2020	Main exposure: change in hormone levels over time within each treatment group (stratified)	Fasting serum. E1 and E2: high-sensitivity liquid chromatography–tandem mass	Total WMHV	MRI	TIV	Pearson partial correlations

		FSH, LH, E1, E2 Hormone therapy treatment groups: Oral CEE (0.45mg/d); tE2 (approx 50 µg/day); Placebo [reference]	spectrometry. FSH and LH: specific two-site immunoenzymatic assays.				
93	Alshikho, 2025	**HDP:** in the first or any subsequent pregnancy, defined as gestational hypertension, preeclampsia, eclampsia, or HELLP syndrome. **Control:** participants with no history of any adverse pregnancy outcomes (HDP, preterm birth, small-for gestational age infant, or stillbirth)	Index-pregnancy outcomes were collected prospectively. Outcomes were verified by maternal-fetal medicine experts. HDP in subsequent pregnancies was initially self-reported but then verified by study investigators through medical-chart review.	Total and regional (lobar) WMHV; FA RD	MRI; DTI	Age (only for FA and RD analysis)	WMH compared using Mann-Whitney U test; FA and RD: surface-based GLM, FreeSurfer 7.3.2
3	Cook, 2002 (pilot study	ERT users vs Non-ERT	Participant report or clinical history in a naturalistic setting	PVH DWMH	MRI		Progression was assessed by calculating the change in MRI measures from baseline to follow-up for each participant, and group differences in progression were compared using one-tailed independent t-tests.
76	Lee, 2024	Reproductive factors and of exogeneous estrogen use: 1. Age at menarche, per 1 year 2. Age at menopause, per 1 year 3. Reproductive Window, per 5-year increase 4. Number of Pregnancies>20 weeks: 0 (ref), 1, 2, 3, 4, 5+ 5. Ever HC Use: user vs non-user (ref) 6. Ever MHT Use: user vs non-user (ref) 7. Initiation of MHT use relative to menopause: non-user (ref), Before or < 1 year post menopause, 1–5 years	Information obtained through abstraction of written and electronic medical records within the Rochester Epidemiology Project (REP) system, including information on menarche, menopause, pregnancies, and hormone use. Reproductive window was calculated as the difference between age at menopause and age at menarche. If hormonal contraception (HC) was used post menopause, it was reclassified as MHT use. All MHT use was recorded including oral, patch, and parenteral. Vaginally administered estrogen creams were	Imaging biomarkers of cerebrovascular disease 1. GCC-FA (FA of the genu of corpus callosum) 2. CC-FA (FA of overall corpus callosum) 3. WMH volume at DTI (%)	MRI	Age, education, time. SA: additional adjustment for APOE genotype + cardiovascular risk factors and conditions (smoking, BMI, hypertension, dyslipidemia, diabetes, heart disease, and stroke).	Linear mixed-effect models with a random slope and intercept for each participant. SA: additional adjustment for covariates

		postmenopause, > 5 years post menopause	also recorded if they had a known effect on systemic estrogen levels.				
13	Lessov-Shlaggar, 2005	T, E2, estrone, SHBG	Total plasma hormone concentrations were assayed using radioimmunoassay and immunoradiometric assay.	WMHV- left and right hemispheres and 8 regional volume measures: left and right frontal, parietal, temporal, occipital lobes	MRI	Age, education, depressive symptomatology (CES-D)	Linear regression
69	Liao, 2023	Age at menopause: Earlier (age <50 years, n = 3981) vs normal menopause (≥50 years, n = 7623); Type of menopause	structured interview; report	WMHs	MRI; IDPs	Age at baseline, ethnicity, education, sedentary, smoking status, alcohol intake, healthy diet, PA, healthy diet, height, and the assessment center of the imaging, additionally adjusting for baseline-image time interval	Linear regression
61	Aleknaviciute, 2022	Parity; maternal age at first childbirth; pregnancy complications; menopause; HRT	Structured interview; Menopause and HRT was additionally verified through medical records	WMH; MD and FA; lacunar infarcts and cerebral microbleeds	MRI; DTI	Age, ICV, education, marital status, smoking, BMI	Regression analysis
85	Barth, 2025	Whole sample: MHT variables 1. user status 2. age first started using MHT, 3. age last used MHT, 4. duration of MHT use (age last used - age first used) Prescription sample: 1. MHT formulation type 2. MHT route of administration 3. Daily drug dosage (mg) 4. Duration of use (weeks) 5. Formulation further categorized = bioidentical & synthetic;	Whole sample MHT variables = self-reported In current MHT users = age at last use set to their age at the imaging assessment to calculate duration of use. Subsample of participants = MHT regimes based on prescription data were extracted from primary care records (general practice).	WMH volume	MRI	Whole sample: Age, education, lifestyle score [based on a published formula and includes data on sleep, physical activity, nutrition, smoking, and alcohol consumption], BMI, menopause status for each MHT variable analysis (i.e. MHT user status, age at first use,	Linear models

		progestins stratification by generation				age at last use, duration of use) Prescribed sample: Age, education, menopause status to retain the largest sample size possible. Additional covariates: adjusting for history of hysterectomy and/or bilateral oophorectomy [for MHT formulation and route of administration]. Estrogens-only MHTs - included surgical history as a covariate instead of excluding participants with surgical history	
66	Cote, 2023	Lifetime hormone exposure (LHE) endogenous: reproductive lifespan (LHE Cycle) and pregnancy exposure (LHE Parity). LHE Endo = LHEcycle + LHE parity LHE exogenous: oral contraceptive exposure (LHE OC); Hrt (LHE Hrt) LHE Exo = LHE OC + LHE Hrt Reproductive factors: age at menarche, number of live births (LHE parity), age at menopause, use of HRT, and OC.	Self-reported, touchscreen questionnaire, and verbal interview with a trained nurse; computed age at menopause reported across visits	total WMHV (normalized by intracranial volume)	MRI	CVRFs, sociodemographic, and age; then in later models with LHE cycle, LHE OC, and LHE HRT	Multiple linear regression
87	Giudicessi, 2025	Main: Number of term pregnancies: analyzed categorically (0 [ref], 1–2, 3–4, or 5+ term pregnancies) These were included but not the	Participants' reproductive history was obtained via a self-report comprehensive questionnaire administered by study personnel. Number of term pregnancies	White matter integrity: fiber density (FD), fiber cross-section (FC), and fiber	MRI; DTI	Age, education, and Framingham cardiovascular risk score	Linear regression; false discovery rate (FDR) corrections to the p-values

		main focus: Hormone replacement therapy (yes/no) Hysterectomy (yes/no) Oophorectomy (yes/no) Reproductive span Vasomotor symptoms	calculated by summing the total number of reported vaginal and cesarean deliveries that resulted in term births. Vasomotor symptom severity variable = captured the frequency of hot flashes and night sweats experienced in the past 2 weeks, with higher scores indicating more frequent symptoms.	density cross-section (FDC) across 11 white matter tracts			
16	Greenberg, 2006	HT (mean duration 23±7yrs) vs non-HT (never used) Subset: Drug info (in n=32 of HT) 21 used estrogen alone and 11 used estrogen plus a progestin. Dose information (in n=18; all taking CEE)	Interview	White-matter lesion volume	MRI	Age, education, ICV	Linear regression
78	Huddleston, 2024	PCOS	PCOS required NIH criteria - both oligomenorrhea and hyperandrogenism (clinical or biochemical) . Oligomenorrhea was based on recalled cycles more than 32 days apart at ages 20–30. Hyperandrogenism was defined by self-reported excess hair growth and/or year-2 stored-serum total testosterone above 53 ng/dL or calculated free testosterone above 0.38 ng/dL.	Abnormal White matter volume WM- FA	MRI; DTI	Sociodemographic (self-reports and interviewer): age, race education, and study center and intracerebral volume	Linear regressions
14	Irie, 2006	Tertiles (low [ref], middle, high) of: 1. Bioavailable testosterone 2. Bioavailable estradiol 3. SHBG	Blood-based sex hormones (standard immunoassays); bioavailable and free serum levels of hormones calculated	WML; lacunes; large infarcts	MRI	Age, education, dementia status, apoE4 genotype, mid-life SBP, DBP, and smoking status, late-life BMI, total cholesterol, diabetes, and other sex hormones.	Logistic regression

						Bioavailable testosterone as exposure: adjusted for estradiol; BioEstradiol: adjusted for testosterone; SHBG: adjusted for estradiol and testosterone as other sex hormones in model 2.	
96	Jiang, 2025	History of preeclampsia and GH	Interview- self-report	WMHs absolute volumes overall and by lobe (frontal, temporal, parietal, and occipital lobes)	MRI	Age, race, and total intracranial volume	Linear regression
46	Jung, 2020	Number of deliveries (parity): 0-4 parity or grand multiparity (>=5 births)	Reproductive history was assessed through systematic interviews implemented by trained nurses.	WMH	MRI	Age, years of education, APOE4 positivity, and cognitive status (i.e., CN vs. MCI), vascular risk score (hypertension, diabetes mellitus, dyslipidemia, coronary heart disease, transient ischemic attack, and stroke), income level at early adulthood, level of lifetime occupation, age at menarche age, and age at menopause.	Multiple linear regression analyses. SA = exclusion of two nulliparous subjects
83	Li, 2025	Serum total testosterone	Serum (blood) testosterone; competitive-binding chemiluminescent immunoassay (9.3yrs before MRI).	Total volume of WMH and microstructural injury indicators (FA, MD)	MRI; DTI	Sex, age, qualifications, smoking status, alcohol drinking status, diabetes	Linear regression

						history, High BP, frequency of physical activities, BMI, HDL-C, LDL-C.	
19	Liu, 2009	E2, P, T; HRT: estradiol valerate (Progynova 1mg/d), CEE (premarin, 03mg/d), tibolone (Livial, 2.5mg/d) and medroxyprogesterone acetate (Progevera, 2mg/d).	ELISA analysis from 10mL of fastng blood was collected by vein puncture.	DWMH and PVH	MRI		Chi-sq test
59	Lohner, 2022	1.Menopausal status: premenopausal women (age ≤59 y) (reference) vs postmenopausal women (age range 45–59 years); 2.Postmenopausal women using HT vs postmenopausal women nonusers	Menopause status self-reported. HT use in postmenopausal women: ATC code of the self-reported medication.	1. WMH volume (logit-transformed) 2. WMH load (WMH volume/WM volume)	MRI	Age (mean-centered), sex, and vascular risk factors (hypertension, diabetes, prevalent cardiovascular disease, smoking, body mass load index, and use of lipid-lowering medication), age-squared	Linear multivariable regression
15	Low, 2006	HRT use status: current users, previous users, never users	Self-reported	Severity of WMH (Total brain, right/left periventricular, Deep white matter, Deep grey matter); WMH % density of total brain	MRI	Controlling for education and ICV, as appropriate.	Chi2, ANOVA or ANCOVA.
1	Luoto, 2000	Current HRT users, past users/never	self-reported or with prescription bottle with them	WMHs-total volume of periventricular and subcortical; Infarcts- lesions with abnormal signal in the vascular distribution and no mass effect. Perivascular spaces.	MRI	Age, race, parity, education, age at natural menopause and/or hysterectomy and oophorectomy, smoking, BMI, blood pressure, and alcohol use	ANCOVA (continuous) or logistic regression (categorical)

30	Mielke, 2016	History of HPD: Normotensive Pregnancy, Hypertensive Pregnancy	Standardized, previously validated questionnaire administered by trained interviewers	WML volume	MRI	Age, body mass index, smoking, hypertension, family history of hypertension, total intracranial volume, and accounted for familial clustering, duration of hypertension	Linear models fit with generalized estimating equations, accounting for sibship clustering
75	Mielke, 2024	Age at Premenopausal bilateral oophorectomy Referent: All women who did not undergo PBO before the age of 50. Age at PBO: 40 years, Age at PBO: 40-45 years, and Age at PBO: 46-49 years	Medical records-linkage	Percent brain white matter hyperintensity volume; Z-scored FA and MD regions: Anterior corona radiata Anterior limb of internal capsule Angular WM Body of corpus callosum Cingulum cingulate gyrus Cingulum hippocampus Corticospinal tract External Capsule Entorhinal area Fornix (column and body) Fornix (cres) stria terminals Genu of corpus callosum Inferior fronto–occipital fasciculus Inferior frontal WM	MRI	Age Sensitivity analyses: additional adjusted for the presence of an APOE ε4 or for cardiovascular risk factors (i.e., hypertension, diabetes mellitus, dyslipidemia, myocardial infarction, and BMI), ERT use, number of pregnancies, or use of hormonal contraception.	Linear regression SA: additional adjustment, excluding referent women who underwent premature menopause

				Interior occipital WM Inferior temporal WM Lateral fronto orbital WM Middle fronto orbibal MW Middle frontal MW Middle occipital WM Middle temporal WM Posterior corona radiata Posterior limb of internal capsule Posterior thalamic radiation Postcentral WM Precentral WM Retrolenticular part of internal capsule Splenium of corpus callosum Superior corona radiata Superior frontal WM Superior longitudinal fasciculus Supramarginal WM Superior occipital WM Superior parietal WM			

				Sagittal stratum Superior temporal WM			
70	Moir, 2023	Age at natural menopause Early group (<=49 yr of age at onset of menopause) or the Late group (>=53 yr of age at onset of menopause),	Self-reported	Total WMH lesion volume	MRI		ttest or Mann-Whitney tests
56	Mosconi 2021	Menopausal status (pre-; peri-; and postmenopause)	Based on the STRAW criteria and corroborated by means of hormone assessments.	WM-FA	MRI; DTI	Age, APOE4, TIV SA: adjusted for MHT use and hysterectomy	Voxel-wise SPM12 full factorial model and posthoc t-contrasts with regional/masked reporting
26	Ryan, 2014	Current and past HT; type of treatment; duration of current HT and timing of initiation of first treatment in relation to menopause	self-report; validated with the prescription of medication itself, and past user were shown photos to aid with recall.	WM lesions	MRI	Age, education, history of CVD, hypertension, diabetes, and number of medications currently used, low cognitive function, lifetime major depressive disorder, hyperchloremia, and APOE e4, total WMV	Linear regression
71	Sato, 2023	Reproductive events: delivery, gravidity, age at menarche, menopause	Self-administered questionnaire	WMH, lacunae and excessive IMT or plaque	MRI	Age, smoking, alcohol consumption, BMI, home measured SBP and DBP, fasting blood glucose, hemoglobin A1c, total cholesterol levels, antihypertensive drug use, hyperchloremia, diabetes mellitus, and any history of CVD.	Linear trend using Cochran-Armitage trend time; logistic regression
29	Srinath, 2016	Testosterone Tertiles: Tertile 1, Tertile 2 [reference], Tertile 3	Blood samples: Plasma total testosterone was performed by liquid chromatography mass spectrophotometry	MRI: Cortical Infarct; Subcortical Infarct; Any Infarct; WMH	MRI	Age, race/center, BMI, waist circumference, smoking status, diabetes mellitus, hypertension, low-density lipoprotein, and high-density lipoprotein	Linear and logistic regression

52	Than, 2021	Menopause status: Pre/perimenopausal (reference); Postmenopausal	Self-reported using the question: "Have you had your menopause (periods stopped)?" Pre/perimenopausal = answering "No" Postmenopausal = answering "Yes" (Participants aged >60 years and/or with a history of bilateral oophorectomy were classified grouped as postmenopausal regardless of survey response.) MHT use determined via nurse-led interview and classified using UK Biobank treatment/medication codes, including current and prior use.	WMHV	MRI	APOE ε4 status, Secondary/exploratory adjustments: cardiometabolic conditions, ethnicity, MHT use	Linear regression analyses
28	Thurston, 2016	Physiologic hot flashes: 24h, wake, sleep Self-reported hot flashes: 24h, wake, sleep	Ambulatory sternal skin conductance monitor (24 h; VU University Ambulatory Monitoring System monitor) and electronic hot flash diary (3 days). Wrist actigraph (Minimitter Actiwatch-2); 1-minute epochs; + sleep diary for 3 days	WMHV (normalized by total brain volume)	MRI	Age, race/ethnicity, BMI Sleep characteristics (including actigraphy-assessed sleep time, waking after sleep onset, sleep efficiency, and fragmentation) and questionnaire assessed sleep apnea, sleep quality, or daytime sleepiness.	Linear regression
64	Thurston, 2023	Physiologic hot flashes: 24h, wake, sleep Self-reported hot flashes: 24h, wake, sleep	Ambulatory sternal skin conductance monitor (24 h; VU University Ambulatory Monitoring System monitor) and electronic hot flash diary (3 days). Wrist actigraph (Minimitter Actiwatch-2); 1-minute epochs; + sleep diary for 3 days	Total WMHV [whole brain]; Regional WMHV: periventricular, deep, and frontal, temporal,	MRI	Age, race, and education, CVD risk factors (BMI, smoking, SBP, antihypertensive medications, HOMA, HDL-C, triglycerides) Secondary models: WASO, hormones (E1,	Linear regression

				parietal, and occipital lobes.		E2, FSH), depressive symptoms, hsCRP, and carotid IMT as additional covariates and mean arterial pressure (MAP) as an alternate covariate to BP	
73	Thurston, 2024	E1, E2, FSH	Phlebotomy after overnight fasting. E1 and E2 measured by LC-MS/MS. FSH measured via a commercially available enzyme-linked immunosorbent assay (ELISA; Cayman Chemical Company)	Total WMHV [whole brain]; Regional WMHV: periventricular, deep, and frontal, temporal, parietal, and occipital lobes.	MRI	Age, race, education, CVD risk factors (BMI, SBP, anti-hypertensive medication, smoking, HDL, triglycerides, HOMA)	Linear regression models Tested associations between reproductive hormones and regional WMHV via MANCOVA.
92	Wezel, 2025	Menopausal status/type: PRE (premenopausal women), POST (women who underwent natural menopause), SURG (women who underwent surgical menopause) Seconday analysis: age at menopause and MHT use	Self-reported	Total WMHV	MRI	Age as second-order polynomial, household income, MHT use, MRI site. Additional models controlled for 17 cardiometabolic and lifestyle factors, in the categories of alcohol consumption, blood pressure, body size, diabetes, physical activity and smoking) When looking at MHT: models adjusted for menopausal group, age, age at menopause, income, and MRI site.	Multiple linear mixed effects models
31	Guoqing, 2016	PCOS	Diagnosis by a trained obstetrician-gynecologist according to the National Institutes of Health criteria, and defined by the presence of	WMLs: periventricular (PV-WMLs) and deep	MRI	Through matching: age and prevalent hypertension	Chi-square tests for categorical; Two-tailed Student's t test (for normally distributed continuous),

			oligoanovulation (≤6 menstrual periods per year) and symptoms or clinical or signs of hyperandrogenism or biochemical hyperandrogenemia reported in medical records at reproductive age. Investigators reviewed clinical and serological records from the women's reproductive years. Controls were selected randomly from postmenopausal women attending the same gynecological health-examination clinic. Each PCOS participant was matched to two controls based on age, within one year, and presence of hypertension.	subcortical (D-WMLs); SCIs (subcortical lacunar infarcts)			Mann-Whitney U test (for skewed continuous)
45	Zeydan, 2019	BSO vs control	record linkage	WMH; Cerebral infarcts; WM-FA	MRI; DTI	ICV	Rank regression tests

eTable 19 White matter hyperintensities, cerebral small vessel disease, and white matter integrity-related studies: Overall findings and limitations

Study ID	First author, year	Main Finding	Direction of association	Key limitations
25	Coker, 2014	Lesion volumes increased significantly across scans within treatment arms, except those in the basal ganglia, but there were no treatment-related differences in overall lesion volumes. Treatment-related effects on rates of change did not differ across subgroups of women defined by age, 3MSE scores, prior HT, and CEE regimen.	Treatment↔ishcemic lesion volumes	underrepresented participants because of selective attrition over a 12yr period, thus a healthier follow-up cohort. High nonparticipation, about 1/3 didn't participate.
21	Espeland, 2009	Those with placebo and developed cognitive impairment had greater ischemic lesion volumes in the frontal lobe and overall, but not different from CEE-based therapies	Treatment↔ishcemic lesion volumes	Small sample size; The volunteers do not closely represent the population of elderly women at large
89	Faubion, 2025	The present study did not find any evidence of long-term benefit or risk on white matter integrity and cerebrovascular lesions in women exposed to 4 years of mHTs (oCEE or tE2 and cyclic progesterone) compared to placebo after correcting for multiple comparisons. Neither WMH volume nor number of infarcts differed significantly between treatment groups and öNo difference between treatment arms. Within arm changes: FSH decreased during transdermal estradiol. Estrone increased during oral CEE. Estrone during transdermal estradiol was borderline positive. LH and estradiol had no association.	MHT↔ WM integrity, cerebrovascular lesions, WMHV, or number of infarcts after 4yrs of MHT compared to placebo.	High attrition; Potential selection bias (recruitment also occurred during COVID); Use of differing MRI scanners across the multiple sites of the study; Follow-up participants had lower baseline blood pressure than non-participants; Limited generalizability
33	Kantarci, 2016	WMH increased within both active-treatment groups over 48 months, but the prespecified mixed-model treatment-vs-placebo differences were not statistically significant.	Treatment↔WMHV	Limited generalizability; Small sample size; Short follow-up duration (4 years); Baseline imbalance: Higher WMH volume in CEE group Randomization imbalance due to small sample size

41	Kantarci, 2018	WMH volume increased in the oCEE compared placebo, but not in the tE2 grp compared to the placebo.	WMH ↑ : oCEE vs placebo WMH ↔ : oCEE vs placebo	Small sample size; Healthy, low-risk population; Follow-up still limited for dementia outcomes; Inability to assess risk modifiers; Potential imbalance in baseline characteristics (Higher APOE ε4 prevalence in tE2 group)
49	Kling, 2020	No difference between treatment arms. Within arm changes: FSH decreased during transdermal estradiol. Estrone increased during oral CEE. Estrone during transdermal estradiol was borderline positive. LH and estradiol had no association.	FSH, E1, E2, LH change by treatment arm ↔ WMHV Within arms changes: ↓FSH in tE2 ↓ WMHV FSH in OCEE ↔ WMHV FSH in placebo ↔ WMHV ↑E1 in oCEE ↓ WMHV E1 in tE2 ↔ WMHV LH in any arm ↔ WMHV E2 in any arm ↔ WMHV	Limited generalizability; Incomplete hormone assessment; Measured serum levels reflect total hormones only, not the free (biologically active) fraction: small sample size
93	Alshikho, 2025	No difference in total or regional WMHV between groups. Those with prior HDP had lower FA in the left superior frontal lobe, right lateral occipital lobe, and right precuneus. Those with prior HDP had higher RD in the bilateral medial orbitofrontal lobes. In subgroup analysis, among those with preeclampsia vs healthy results were similar. Lower FA and higher radial diffusivity were seen in the preeclampsia group in multiple regions.	HDP ↓ regional FA HDP ↑ RD HDP ↔ WMH volume	Lack neuroimaging prior to first pregnancy, small sample size; unmeasured confounding;
3	Cook, 2002 (pilot study	In the posterior region there was a trend toward lower PVH in the estrogen group, but was not statistically significant, while anterior PVH showed no relationship with ERT use. Changes in DWMH volume were not different between the groups.	Whole brain: ERT ↔ PVH ERT ↔ posterior PVH progression ERT ↔ anterior PVH progression ERT ↔ DWMH progression	Sample size limited (pilot study); ERT was not randomized; variability in follow-up intervals; information on ERT exposure (dose, duration, details) was limited
76	Lee, 2024	History of HC use was associated longitudinally with higher FA across the corpus callosum, lower WMH volume. Ever MHT use was not associated with any	History of hormonal contraception ↑ corpus callosum FA History of hormonal contraception ↓ WMH volume	Limited generalizability; Possible missing/incomplete data from medical records or migration history; insufficient power; Potential survival bias; Possible confounding by indication

		neuroimaging outcome. Initiation of MHT 5 or more years post menopause was associated with increasing WMH volume (harmful effect). Age at menarche and length of reproductive window were not associated with changes in neuroimaging measures 3. Other reproductive factors → no clear association	Ever MHT use ↔ neuroimaging outcomes MHT initiation ≥5 years after menopause ↑ WMH volume Age at menarche/reproductive window ↔ neuroimaging outcomes Other reproductive factors ↔ neuroimaging outcomes	
13	Lessov-Shlaggar, 2005	None of the hormones (T, T+SHBG, E2, E2+SHBG, Estrone, SHBG) were associated with WMHS 10-16yrs later.	T, E2, estrone, and SHBG ↔ later WMH volume	
69	Liao, 2023	Earlier menopause vs normal menopause was positively associated with WMH	Earlier menopause ↑ WMH burden	Unmeasured confounding; low response rate; health volunteer bias; dementia might be misdiagnosed and more likely to be lost to follow-up, so some dementia maybe were not caught; self-reported questions; could not ensure that menopause lasted more than 12 months; limited generalizability
61	Aleknaviciute, 2022	MD was lower in parous women. No relationship between parity and FA. No relationship between parity and markers of cerebral small vessel disease, expect with an increase in microbleeds in multiparous women compared to nulliparous.	Parity ↓ MD Parity ↔ FA Parity ↔ lacunar infarcts Multiparity ↑ microbleeds	no info on infertility and gravidity; residual and unmeasured confounders (infertility, gravidity, time varying covariates); small sample; limited generalizability; selection bias
85	Barth, 2025	Among MHT user: -age at MHT initiation, alone or in relation to age at menopause = no associations -older age at last use after age at menopause, longer duration of MHT use associated with higher WMHV. Subsample with prescription data: No associations.	Age at MHT initiation ↔ WMH volume Older age at last MHT use ↑ WMH volume Longer MHT duration ↑ WMH volume Prescription-data subsample ↔ WMH volume	Residual confounding; Participants may switch between MHT regimes thus exposure inconsistent across individuals; Prescription data limitations; generalizability limitations; healthy volunteer bias; self-reported menopause; survivor bias
66	Cote, 2023	Lifetime hormone exposure (LHE) endo (LHE parity and LHE cycle) was negatively associated with WMHV. LHEexo was positively associated with WMHV (but not statistically sig). Similar	Endogenous lifetime hormone exposure ↓ WMH volume Exogenous lifetime hormone exposure ↔ WMH	Do not know the exact cerebral location of the WMH; LHE parity and LHE cycles may have localized effects; Recall bias of reproductive events that occur in early in life; Lack of

		results when controlling for self-reported migraine and HIV diagnosis and educational attainment. HRT was not significantly related to WMHV.	volume HRT ↔ WMH volume	accurate measure of OC an HRT use; No measure of breastfeeding, chronic alcohol use, or recreational drug use; low generalizability.
87	Giudicessi, 2025	Number of term pregnancies was not significantly associated with white matter integrity after false discovery rate correction.	Number of pregnancies ↔ white matter integrity	Small sample size; Self-reported reproductive history; Missing key variables (e.g, breastfeeding, sleep, or detailed hormone therapy timing/duration); Unmeasured psychosocial factors
16	Greenberg, 2006	No significant effect of HT use on WML volume.	HT ↔ WML volume	Small sample; nonrandomized; no MRI measurements before HT began; not sufficient info on hysterectomies, date and duration of menopause or childbearing history
78	Huddleston, 2024	Abnormal white matter volume did not differ between women with and without PCOS, but WM FA was lower in PCOS.	PCOS ↔ abnormal white matter volume PCOS ↓ WM-FA	1. Hypertensive pregnancy disorders pooled together (cannot assess specific types): preeclamptic or eclamptic pregnancies, gestational hypertension. 2. Cortical infarctions excluded (may bias results toward null) 3. Selected sample (families with hypertension) →high risk sample - limited generalizability 4. Survival bias (participants assessed decades later) 5. Cross-sectional design (cannot infer causality) 6. Cannot distinguish between: Shared risk factors vs Underlying vascular mechanism 7. Self-reported pregnancy history (possible misclassification)
14	Irie, 2006	One or more lacunes were associated with higher levels of bioavailable estradiol. Significant inverse association of SHBG level and lacunes is not independent from testosterone, estradiol, cardiovascular risk factors, and other brain lesions. There were no associations of sex hormone tertile to WML or large infarctions.	Bioavailable estradiol ↑ lacunes SHBG ↓ lacunes Sex hormone tertiles ↔ WML and large infarcts	imprecise estimation of low estradiol concentrations; potential selection/survivor bias; and generalizability

96	Jiang, 2025	Women with gestational hypertension (GH) and preeclampsia had greater WMHs in the parietal and frontal lobes after adjustment. The differences in WMHs between women with GH and those without HDP were more pronounced than those between women with preeclampsia and those without HDP.	Gestational hypertension ↑ frontal/parietal WMH Preeclampsia ↑ frontal/parietal WMH	self-report of HDP; small sample size in the MRI; other types of small vessel disease may contribute but did not include; specific types of preeclampsia, HDP severity and labor induced was not available. Lack of generalizability as focused mainly on black and white women.
46	Jung, 2020	Grand multiparity (>=5 births) compared with 0-4 parity had no association with WMHs.	Grand multiparity ↔ WMH	Recall bias; nulliparity could not be separately assessed.
83	Li, 2025	In females, STT was found to be linearly negatively related to WMH volume, but not associated with FA and MD, after adjustment. In males, STT was not associated with WMH, FA, or MD.	Females: testosterone ↓ WMH volume Females: testosterone ↔ FA Females: testosterone ↔ MD Males: testosterone ↔ WMH volume Males: testosterone ↔ FA Males: testosterone ↔ MD	Not region specific; Time interval from the measurement of WMH volume around 9.33 years; Testosterone was assayed using a competitive binding chemiluminescent immunoassay, which may not be a reliable measurement; Residual confounding; Limited generalizability
19	Liu, 2009	No difference in DWMH imaging between HRT and control group in 50-59 grp. In 60-69 group the incidence of severe change was higher in the HRT grp than in the controls, but not statistically significant. In 70-87 age, the DWMH the was much higher in the control group than the HRT grp. No significant differences were observed in PVH between the 2 groups for all age subgroups.	HRT ↔ DWMH (ages 50–59) HRT ↔ DWMH (ages 60–69) HRT ↓ DWMH (ages 70–87) HRT ↔ PVH (all age groups)	Limited generalizability; non-random allocation to HRT
59	Lohner, 2022	Postmenopausal women have a higher WMH load compared with premenopausal women of the same age range. No difference in WMH load between postmenopausal women using HT and postmenopausal women who did not.	Postmenopause ↑ WMH load HT ↔ WMH load	Menopause data self-reported; no data on age of menopause and perimenopause status; excluded women <45 years with postmenopause (early menopause); limited sample size for HT; Participants healthier and more educated than the German population; select MRI sample (smaller sample and healthier)
15	Low, 2006	No significant differences between HRT current, previous or never users in WMH severity.	HRT ↔ WMH severity	'Healthy volunteer' bias; HRT use self-reported without data on dose; moderate participation rate and different characteristics between groups

1	Luoto, 2000	No difference in MRI infarcts, perivascular spaces, WM changes by ERT use, and duration of current or past ERT use.	ERT ↔ MRI infarcts, perivascular spaces, and WM changes	Healthy volunteer effect; self-report; nonrandom assignment of ERT
30	Mielke, 2016	Compared with women with history of normotensive pregnancies, women with histories of a HPD had a trend toward a greater degree of WML volume, but not significant.	History of hypertensive pregnancy ↔ WML volume	HPD, cortical infarctions excluded; selected sample of families with hypertension, thus limited generalizability; survival bias (participants assessed decades later); self-reported pregnancy history
75	Mielke, 2024	Women who undergo PBO, compared to women who do not, have worse white matter integrity across multiple brain regions. No association per se with WMHV. Females who underwent PBO, especially before the age of 40 years, had worse WM integrity in multiple brain regions, including the anterior corona radiata, genu of the corpus collosum, inferior fronto-occipital fasciculus, superior occipital, and superior temporal white matter. **PBO <40 years vs referent - strongest and widespread association** >>lower FA in the anterior corona radiata, genu of the corpus collosum, inferior fronto-occipital fasciculus, inferior frontal white matter, superior occipital, superior temporal white matter. >>higher MD in the corona radiata, genu of the corpus collosum, inferior fronto-occipital fasciculus, posterior thalamic radiation, superior occipital, and superior temporal white matter **PBO 40-44 - no association** **PBO 45-49 - milder but still effect present** >>lower FA in the interior occipital, middle frontal, posterior thalamic radiation, supramarginal, superior occipital white matter regions. >>higher MD middle frontal, retrolenticular, part of the internal capsule, superior occipital, and superior temporal, white matter regions. >>findings not explained by estrogen replacement	PBO ↔ WMH volume PBO before age 40 ↓ FA PBO before age 40 ↑ MD PBO age 40–44 ↔ WM integrity PBO age 45–49 ↓ FA PBO age 45–49 ↑ MD	Selection bias; Limited generalizability; Exploratory analysis; Confounding by indication: underlying conditions leading to PBO may have altered prior hormone exposure, influencing both surgery and outcomes; Missing info: hot flashes

		therapy. might not protect the brain. notably prescribed conjugated equine estrogens based on the years of PBO Could be in part due to loss of testosterone.		
70	Moir, 2023	The Early group demonstrated greater WMH fraction compared with the late group. There was an inverse relationship between age at onset of menopause and WMH fraction. No association was observed between yrs since menopause and WMH fraction.	Early menopause ↑ WMH fraction Age at menopause ↓ WMH fraction Years since menopause ↔ WMH fraction	The definition of age of menopause may not align with other studies; the lab and MRI visits were complete on separate days with about on average 4 months apart
56	Mosconi 2021	POST < PERI: lower FA in the right external capsule Results were substantially unchanged after accounting for hormone therapy and hysterectomy.	Postmenopause ↓ WM-FA vs perimenopause Postmenopause ↔ WM-FA vs premenopause Perimenopause ↔ WM-FA vs premenopause	small sample size; limited generalizability; potential misclassification of exposure groups
26	Ryan, 2014	No significant group differences for white matter lesion volume in women. Did not differ by duration use, type of treatment and age at initiation	HT ↔ WML volume	limited generalizability; data on HT is subject to recall errors; small sample size
71	Sato, 2023	The quartiles of gravidity were linearly associated with the proportions of WMH. The quartiles of delivery were linearly associated with proportions of lacunar and WMH. The quartiles of age at menarche were linearly associated with the proportions of WMH. The numbers of gravidity and delivery were higher in those with lacunar infarcts than those without and those with WMHs than in those without. Age at menarche was older in those with WMHs than in those without.	Gravidity ↑ WMH Number of deliveries ↑ WMH Age at menarche ↑ WMH Gravidity/number of deliveries ↑ lacunes	limited generalizability; did not consider age at surgical menopause; did not include maternal info on pregnancy complications; unmeasured confounders
29	Srinath, 2016	No association of testosterone was found with WMHs, cortical infarcts, or subcortical infarcts.	Testosterone ↔ WMH and cortical/subcortical infarcts	Testosterone was measured only once and free testosterone/SHBG were not assessed; long time gap (~15 years) between testosterone measurement and MRI
52	Than, 2021	Postmenopausal women → higher WMH burden compared to pre/perimenopausal women	Postmenopause ↑ WMH burden	Menopause measurement: Self-reported; Survival bias; Residual explanation
28	Thurston, 2016	More physiologically monitored hot flashes during sleep were associated with greater WMH burden among midlife women without clinical	Physiologic sleep hot flashes ↑ WMH burden Self-reported hot flashes ↔ WMH	small sample size

		cardiovascular or cerebrovascular disease. Independent of demographic factors, CVD risk factors, sleep, E2, or other potential confounding factors. No significant associations between self-reported hot flashes and WMH.		
64	Thurston, 2023	Those with more physiologically detected VMS, particularly VMS occurring during sleep, had greater brain WMHV (both deep and periventricular), and most pronounced in the frontal lobe (for total, wake, sleep). These relationships were not explained by CVD risk factors or by sleep (WASO) nor by endogenous E2 levels or depressive symptoms. No associations observed for self-reported VMS	Physiologic VMS ↑ WMH burden Self-reported VMS ↔ WMH	Limited racial/ethnic diversity; few perimenopausal women
73	Thurston, 2024	Higher E1 was associated with fewer whole-brain, deep, frontal, and temporal WMHV. Higher FSH was associated with greater whole-brain, periventricular, and frontal WMHV. These associations persisted with adjustment for a range of demographic factors and CVD risk factors. Higher E2 was associated with fewer WMHV (whole-brain) in models adjusted for demographic factors, but these associations were explained by CVD risk factors, particularly BMI. E2 was not significantly associated with regional WMHV in multivariable models.	E1 ↓ WMH volume FSH ↑ WMH volume E2 ↔ WMH volume	Hormones measured once; limited generalizability; limited racial/ethnic diversity; limited applicability to higher-risk populations
92	Wezel, 2025	POST vs PRE: No association on WMHV in nearest neighbor age-matched analysis. In unmatched or more-than 5-yrs-since menopause analyses showed lower WMH in POST women. SURG vs PRE: no association in nearest neighbor age-matched. Lower WMHV in SURG in some	POST vs PRE ↔ WMH volume SURG vs PRE ↔ WMH volume SURG vs POST ↔ WMH volume Age at menopause ↔ WMH volume	absence of a perimenopause category; self-reported menopause and age at menopause, lack of detailed information on MHT; limited ethnic diversity

		alternative analyses. SURG vs POST: No association Neither age at menopause or MHT were associated with WMHV.	MHT ↔ WMH volume	
31	Guoqing, 2016	PCOS group had higher prevalence of any WMLs, especially D-WMLs compared to the control group. PCOS had a higher prevalence of SCI than control group. No association with periventricular WMLs.	PCOS↑ Any WMLs PCOS↑ D-WMLs PCOS↑ Any SCI PCOS↔PV-WMLs	Residual confounding; Controls based on exposure instead of outcome
45	Zeydan, 2019	The entorhinal WM FA was lower in the BSO group compared with the control group. WMH volume and the frequency of infarctions did not differ between the groups.	BSO ↓ entorhinal WM FA BSO ↔ WMH volume and infarct frequency	small sample size

eTable 20 Brain volumes-related studies: Basic information and study characteristics

Study ID	First author, year	Country	Cohort	Study population	Study design	Follow-up duration in years, mean (SD)	Total analytical sample	Age, mean (SD)	% Female	Ethnicity	Cognition	APOE ε4 carrier %
93	Alshikho, 2025	USA	The Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be (nuMoM2b) Heart Health Study- ancillary nuMoM2b BraiN study	Women with HDP vs controls from clinics	Cohort	Median 11 (IQR 1.0)	81 HDP (27) vs healthy pregnancy (54)	39 (SD6)	100	27.2% white, 8.6% nonhispanic black, 51.9% hispanic, 9.9% asian/pacific islander, 2.5% multiple race		
3	Cook, 2002			Community-dwelling women aged ≥60 years, cognitively normal	Cohort	3.7 (0.8) years, range 2.8–6.1 years	15 (No ERT = 9; ERT= 6)	74.2 (7.2) years	100		MMSE: No ERT: 29.00 ± 1.07; ERT: 29.33 ± 1.63	
39	Elbejjani, 2017	USA	CARDIA (substudies CARDIA Male Hormone Study; CARDIA Brain MRI)	Middle-aged men	Cohort	10-15yrs	267	50(3.53)	0	64.8% white		30.1%
76	Lee, 2024	USA	Mayo Clinic Study of Aging (MCSA)	Community-dwelling women within a medical records–linkage system enabling population-based research	Cohort	Not explicitly reported (up to 8ys)	389	median (range) = 71.1 years (51.1, 90.4)	100	Mostly white		30.6%
13	Lessov-Shlaggar, 2005	USA	WWII veteran twin men	Healthy, white WWII veteran male twins, with normal cognitive levels form	Cohort	10–16	566	63.1(2.9)	0	white	MMSE 27.0(2.6)	

				community/register								
69	Liao, 2023	UK	UKB	Dementia free women with earlier or premature menopause	Cohort	Median 8.8yrs (2.11–13.82)	11604; Menopause <50 =3981 Menopause ≥50= 7623	37-73	100	>=50yrs: 91.9% white; 40-49yrs: 90.8% W; <40yrs: 92.1%W		
9	Raz, 2004	USA		Healthy educated women	Cohort	5	24; MHT =12; Age- and education-matched controls = 12 (SA: 9 persistent users throughout folow-up)	MHT= 63.6; Contrls =61.7	100	100% Caucasians	MMSE 29.42 controls vs 28.92 MHT users	
25	Coker, 2014	USA	WHIMS-MRI2	Postmenopausal women 65-79y treated for 4ys with CEE with MPA or 5.6yrs with CEE alone compared to placebo	RCT (parallel randomized placebo controlled); post-trial longitudinal repeated measures MRI study	Mean 4.7 between MRI scans; ~6.1–7.7 after treatment ended	1403 (n=674 with only MRI1; n=729 with scans at MRI1 and MRI2)	82.8 (3.5) at scan	100	94% white, nonhispanic	In WHIMS-MRI1: 3MSE <90 = 8%; In WHIMS-MRI2: 3MSE <90 = 3%	
21	Espeland, 2009	USA	WHIMS & WHIMS-MRI	Women recruited from clinics, free of dementia, aged between 65-79yrs, previously participating in WHIMS	Ancillary, cross-sectional analysis of a randomized, placebo-controlled clinical trial	1-4yrs after the RCT	1403 No CI: HT=664; Placebo=686; CI: HT=29; Placebo=24	Active therapies 70.6 yrs; Placebo 70.5 yrs	100		3MS score: No CI HT <90=4.7%; No CI placebo <90= 4.4%; CI HT <90= 37.9%; CI Placebo <90 = 33.3%	
20	Resnick, 2009	USA	WHIMS & WHIMS-MRI	Postmenopausal women >=65yrs	Ancillary, cross-sectional	MRI approximately 8 after	1403 CEE+MPA	78.5(3.7)	100	>85% white,	Baseline 3MS categories <90/90–94/95–100: CEE+MPA	

					analysis of a randomized, placebo-controlled clinical trial	enrollment; treatment lasted 4.0–5.6	n=436; its placebo n=447; CEE alone n=257; its placebo n=263			non-Hispanic	5.1%/15.2%/79.8%; corresponding placebo 4.3%/18.1%/77.6%; CEE alone 7.8%/19.6%/72.6%; corresponding placebo 7.3%/22.2%/70.5%	
33	Kantarci, 2016	USA	The Kronos Early Estrogen Prevention Study (KEEPS); ancillary KEEPS-MRI study	Healthy postmenopausal women with good cardiovascular health [baseline], previously in KEEPS	Ancillary, longitudinal analysis from a randomized, double-blinded, placebo-controlled clinical trial	Up to 48 months (3 follow-ups (at 18, 36, 48 months))	Overall = 95 CEE: 29 Estradiol (tE2): 30 Placebo: 36	CEE: mean 53 (95% CI 52-54) tE2: 53 (52-54) Placebo: 53 (52-54)	100		Global cognitive function: CEE: −0.19 (−0.48, 0.10) Estradiol: 0.16 (−0.12, 0.44) Placebo: 0.14 (−0.08, 0.36)	CEE: 15% tE2: 45 % Placebo: 21%
41	Kantarci, 2018	USA	Kronos Early Estrogen Prevention Study (KEEPS); ancillary KEEPS-MRI study Ancillary longitudinal analysis (with repeated measures) within a randomized double blinded, placebo-controlled clinical trial	Healthy recently postmenopausal women with good cardiovascular health, previously in KEEPS	Ancillary, longitudinal analysis from a randomized, double-blinded, placebo-controlled clinical trial	Up to 84 months	Overall = 75 oCEE: 20 tE2: 22 Placebo: 33	~53 years oCEE: 53 (±2) tE2: 53 (±3) Placebo: 53 (±2)	100		oCEE: −0.20 (0.77) tE2: 0.07 (0.79) Placebo: 0.15 (0.67)	oCEE: 15% tE2: 48% Placebo: 16%
90	Kantarci, 2026	USA	KEEPS Continuation	Healthy recently postmenopausal women with good	Cross-sectional analysis		266; oCEE n=77;	whole group	100			whole group = 26%

				cardiovascular health	[Observational follow-up of a randomized, double-blind, placebo-controlled trial]		tE2 n=88; placebo n=101	= 67 (2)				
61	Aleknaviciute, 2022	The Netherlands	Rotterdam Study/Rotterdam Scan Study	Community-based, dementia free women	Cross-sectional		2834 (Pregnancy-complications subset n=894)	65.2	100	mainly of Caucasian descent	stroke, dementia, and cortical infarct free women	
51	Ambikairajah, 2020	UK	UKB	Menopausal women	Cross-sectional		5072	60.32(7.11)	100			
55	Boyle, 2021	USA	CHS; CHS memory study	Community-dwelling women with present or past estrogen use with mixed cognitive status	Cross-sectional		562	79.4(4.2)	100	86.8% White	24% diagnosis of AD or MCI	27.1%
94	Brown, 2025	Canada		BSO vs BSO + ET vs controls	Cross-sectional		85	AMC 43.8(3.6); BSO+ ET 45.2(4.5); BSP 46(5.9)	100			
12	Erickson, 2005	USA	-	Postmenopausal women	Cross-sectional		43	Current 68.9(5.5); past 66..2(6.2); never 68.4(5.5)	100		modified MMSE <51; non demented but could be in preclinical state	
22	Erickson, 2010	USA		Postmenopausal women	Cross-sectional		102 overall sample; but for main	66.84 (5.7)	100			

							analyses - primary aim = 62 women who had used HT					
16	Greenberg, 2006	USA		Elderly females currently using MHT and nonusers	Cross-sectional		92 Current MHT users for ≥10yrs =41; Nonusers = 51	NonMHT users =71 (6) MHT users = 70 (6)	100		NonMHT: White n=38; Black = 12; Other/unknown = 1; HT: White =40; Black = 1; Other/unknown = 0		
78	Huddleston, 2024	USA	CARDIA (focus on the MRI- from yrs 25 and 30 as part of CARDIA Brain substudy)	Women with PCOS and MRI	Cross-sectional		291 PCOS = 25 No PCOS = 266	54.7(3.6) PCOS; 55.3(3.6)nonPCOS	100		PCOS: 39.% black; 61.6% white; nonPCOS 53.6% black; 46.4% white		
14	Irie, 2006	USA	Honolulu–Asia Aging Study (HAAS)	Old men	Cross-sectional		452	81.6 (5.08)	0		Japanese-American		
46	Jung, 2020	South Korea	Korean Brain Aging Study for Early Diagnosis and Prediction of Alzheimer's Disease (KBASE)	Non-demented older women (CN and MCI)	Cross-sectional		Overall = 237 Other imaging =233	70.45 (7.68)	100		Korean	MMSE = 24.93 (3.55)	24.9%
86	Kantarci, 2025	USA	Mayo Clinic Cohort Study of Oophorectomy	Community-dwelling women aged ≥ 60 years	Cross-sectional		231 (61 early PBO (before age 46), 51 late PBO (at	Median [IQR]; curre	100		Race (White): Referent: 91.5%	Referent: 97 (94–99) Early PBO: 96 (93–99) Late PBO: 96 (94–98)	Referent: 22.9% Early PBO:

			and Aging-2 (MOA-2)				aes 46-49), 119 controls [MRI])	nt visit age; Referent group: 67 years (63–70) Early PBO: 64 years (62–68) Late PBO: 67 years (64–72)		Early PBO: 95.0% Late PBO: 93.8%		23.7% Late PBO: 22.0%
40	Kim, 2018	Not stated in text; South Korea based on affiliation		Women across menopausal status	Cross-sectional		40 (20 pre-menopausal women; 20 post-menopausal women)	pre-menopausal = 39.9 ± 8.1 post-menopausal = 55.7 ± 2.4 (on ag 5.5yrs past menopasue)	100	Korean		
68	Kim, 2023	Korea		Clinic-recruited menopausal women	Cross-sectional		41 No MHT = 21;	57.2(4.2)	100			

							Current MHT = 20	No MHT = 56.6 (3.8) Current MHT = 57.2 (4.2)				
79	Kim, 2024	Korea		Community-dwelling pre and postmenopausal women	Cross-sectional		42 Premenopausal = 21 Postmenopausal = 21	Premenopausal 39.8 (7.6) Postmenopausal 55.3(2.5) (on avg 4.8 yrs past menopause)	100			
88	Kwan, 2025	Australia	Women's Healthy Ageing Project	Cognitively healthy older women from population-based random sampling, and from long-term cohort with MRI	Cross-sectional		124 HT+ = 62 HT- = 62 (age- and education-matched)	MHT users: 70.97 (SD 2.97) MHT non-users: 70.14 (SD 2.62)	100	Caucasian Australian		
18	Lord, 2008	Canada		Community-dwelling adults	Cross-sectional		41; n=16 ET users;	ET users: 58.9 ± 6.4 years	100			

							n=10 Past users; n=15 never users	Past users: 65.9 ± 5.5 years Never users: 59.9 ± 7.6 years				
15	Low, 2006	Australia	PATH (Personality And Total Health) Through Life' project	Postmenopausal women aged 60–64 years	Cross-sectional		213	62.6 (1.5)	100			
42	Lu, 2018	China		Hosptial recruited premenopausal and perimenopausal women aged 45-55	Cross-sectional		Total = 57 Premenopausal women=32 Perimenopausal women=25	Premenopausal women=47.75 ± 1.55 Perimenopausal women=51.60 ± 1.63	100			
1	Luoto, 2000	USA	CHS	Postmenopausal women	Cross-sectional		2133 ERT = 329; Past ERT = 483; Never ERT = 1321		100		Age-and race-adjusted scores on the study's 100-pt MMS/Modified MMSE: ERT = 89.2; past ERT = 89.9 Never ERT = 87.8	
97	McGrath, 2025	USA	FHS Offspring cohort	Women cognitively healthy	Cross-sectional		MRI subsample = 1165	MRI subsample = 60.4 (9.4)	100		Without dementia	22.9%

30	Mielke, 2016	USA	Ancillary study (GMBI) within the GENOA cohort	Community-based cohort of older women with vascular risk factors (family hypertension background)	Cross-sectional		972 Normotensive Pregnancy=796 Hypertensive Pregnancy=176	Normotensive pregnancy: 61 ± 9 years Hypertensive pregnancy: 58 ± 10 years	100	Non-hispanic white: Normotensive pregnancy: 47% Hypertensive pregnancy: 48%		
70	Moir, 2023	USA		Healthy postmenopausal women	Cross-sectional		35 earlier natural menopause at 49 or younger =19; later natural menopause at age 53 or older = 16	Earlier menopause = 47(2); Later menopause = 55(2)	100			
38	Mosconi, 2017	USA		Clinically and cognitively normal community volunteers aged 40–60 years participating in brain imaging studies.	Cross-sectional		42 (pre 15; peri 13; post 14)	PRE (control) 48(5); Peri 50(6); Post 57(2)	100	PRE 75%; Peri 71%; Post 89% White	MMSE: PRE: 29(2); Peri 29(1); Post 29(1)	PRE 57%; Peri 46%; Post 36%
56	Mosconi, 2021	USA		Cognitively intact older women	Cross-sectional		161 (pre 30; peri 57; post 74)	Pre 44(4); Peri 50(4); Post 57(4)	100	Pre 80% white; peri 77%; post 89%	MMSE: Pre 29(1); Peri 29(1); Post 29(1)	42%
100	Mutee, 2026	USA/Canada	ADNI	Adults across the Alzheimer's	Cross-sectional		439 CN = 50	CN: 76.0 ± 5.6	CN: 46.0% MCI: 34.2% AD: 47.1%		CN: 29.02 ± 1.23 MCI: 26.27 ± 2.91 AD: 21.06 ± 4.74	CN: 8.0% MCI: 48.7%

				disease spectrum (CN, MCI, AD)			MCI = 304 AD = 85	MCI: 75.6 ± 7.2 AD: 75.5 ± 7.9				AD: 57.6%
50	Rahman, 2020	USA		Cognitively intact women 40-65yrs	Cross-sectional		85	53(6)	100		MMSE = 0.01 (0.11)	42%
26	Ryan, 2014	France	ESPRIT study	nondemented older women	Cross-sectional		295	Never MHT median 71(IQR 68-75; past HT 70(68-72); current 68(67-71)	100		nondemented; MMSE <=24: Never MHT 12.1%); past MHT 10%; Current MHT 4.8%	never MHT 24.3%; Past MHT 23.3%; current MHT 16.1%
53	Schelbaum, 2021	USA		Cognitively normal men and women in 40-65yrs at risk of AD	Cross-sectional		Women = 99 Men = 29	Women = 52 (6) Men = 52 (7)	77.3	Women = 80% White Men =76% White	Global cognition score: Women = −0.01 (0.06) Men = −0.06 (0.12)	47% in each subsample
44	Seitz, 2019	USA	New England Family Study	men and women in early midlife	Cross-sectional		94; n=33 pre; n = 29 peri; n=32 post	Pre 49.2± 1.7; Peri 49.8± 1.9; Post 50.6± 2.2	100	Pre: 3% Afro-American, 90.9% white, non-hispanic; Peri: 10.3% Afro-American, 86.2% white, non-Hispanic;		

										Post: 18.8% Afro-American, 81.3% white, non-Hispanic		
72	Steventon, 2023	UK	UKB	postmenopausal women	Cross-sectional		10924	63.41(6.65)	100	British/Irish ancestry		
11	Sullivan, 2005	USA		Healthy women	Cross-sectional		Subsample = 44 Premenopausal = 17; post-menopausal = 27 (MHT users = 11 MHT nonusers = 16)		Subsample = 100%		MMSE ≥25	
52	Than, 2021	UK	UKB	Community-dwelling adults	Cross-sectional		2057 Pre/perimenopausal = 230; Postmenopausal = 1827	Median age (IQR): Pre/peri =49.9(46.2-53.6) Post = 63.9 (54.2-73.6)	100			28.5%
74	Wugalter, 2024	USA	MsBrain	Postmenopausal women from MsHeart study	Cross-sectional		171	59.4 (4.03)	100	82.5% White	MoCA score = 26.9 (2.61)	23.4%
45	Zeydan, 2019	USA	The Mayo Clinic Cohort Study of Oophorectomy and Aging-2 (MOA-2) and The	women with BSO vs controls	Nest case-control		43	The median (interquarti	100		13% in BSO group had MCI, and 5% in control group	BSO 9%; control 20%

			Mayo Clinic Study of Aging (MCSA)					le range [IQR]) age at imaging was 65 (62-68) years in the BSO group and 63 (60-66) years in the control group. Controls were age-matched				
58	Zhang, 2021	China		early menopausal women with naturally low endogenous estradiol levels and age-matched premenopausal women	Cross-sectional		45 (early menopausal); 54 (premenopausal control women)	47.4(1.65), 46.9(1.7)	100			
102	Zuhlsdorf, 2026	UK	UKB	Community-dwelling women	Cross-sectional		10873(only the brain imaging)	65.53(7.22)	100			

eTable 21 Brain volumes-related studies: Methods and Materials

Study ID	First author, year	Exposure	Exposure Ascertainment	Outcome	Outcome ascertainment	Covariates adjusted for in models	Statistical Analysis
93	Alshikho, 2025	**HDP:** in the first or any subsequent pregnancy, defined as gestational hypertension, preeclampsia, eclampsia, or HELLP syndrome. **Control:** participants with no history of any adverse pregnancy outcomes (HDP, preterm birth, small-for gestational age infant, or stillbirth)	Index-pregnancy outcomes were collected prospectively. Outcomes were verified by maternal-fetal medicine experts. HDP in subsequent pregnancies was initially self-reported but then verified by study investigators through medical-chart review.	Regional gray matter volume; regional cortical thickness	MRI	Age	FreeSurfer to compare surface-based outcomes; GLM. Corrected for multiple comparisons
3	Cook, 2002	ERT users vs Non-ERT	Participant report or clinical history in a naturalistic setting	Progression of ventricular CSF volume (central brain atrophy)	MRI		Group differences were analyzed with independent t-tests. The Levene test was used to determine whether each t-test should be calculated with assumptions of equal or unequal variance. It appears that group differences in SSBD by ERT status were done separately for baseline and progression from baseline [meaning at follow-up]. Progression was assessed by calculating the change in MRI measures from baseline to follow-up for each participant, and group differences in progression were compared using independent t-tests on these change scores. //they were not that explicit.
39	Elbejjani, 2017	Total-T, bio-T, and SHBG serum concentrations	Morning blood collected at years 2, 7, and 10 (at ages about 27, 32, and	Total brain, gray matter, white matter,	MRI	Age, race, education, TIV,	Multivariable linear regression

			35yrs). Total testosterone measured by radioimmunoassay. Bioavailable T was calculated. SHBG was measured by chemiluminescent enzyme immunometric assay. Took average concentration over 8yrs.	and lobar tissue volumes		and study center and APOE, BMI, fasting insulin, hypercholesterolemia, smoking status, hypertension, diabetes mellitus, vascular disorders (e.g., heart attack, stroke, etc.), depressive symptoms	
76	Lee, 2024	Reproductive factors and of exogeneous estrogen use: 1. Age at menarche, per 1 year 2. Age at menopause, per 1 year 3. Reproductive Window, per 5-year increase 4. Number of Pregnancies>20 weeks: 0 (ref), 1, 2, 3, 4, 5+ 5. Age at first pregnancy 6. Ever HC Use: user vs non-user (ref) 7. Ever MHT Use: user vs non-user (ref) 8. Initiation of MHT use relative to menopause: non-user (ref), Before or < 1-year postmenopause, 1–5 years postmenopause, > 5 years post menopause	Information obtained through abstraction, by trained nurses, of written and electronic medical records.	Longitudinal cortical thickness in an Alzheimer disease temporal meta-ROI	MRI	Age and education. SA: Additionally, for APOE genotype + cardiovascular risk factors and conditions (smoking, BMI, hypertension, dyslipidemia, diabetes, heart disease, and stroke).	Linear mixed-effect models with a random slope and intercept. SA: additional adjustment for covariates
13	Lessov-Shlaggar, 2005	T, E2; estrone, and SHBG	Blood samples collected. Total plasma hormone concentrations were assayed using radioimmunoassay and immunoradiometric assay.	Total brain volume; bilateral hemispheric, frontal, parietal, temporal and occipital volumes	MRI; Regional volumes were normalized to total cranial volume.	Age, education, depressive symptomatology (assessed by the CES-D), SHBG	Linear regression

69	Liao, 2023	Age at menopause: Earlier (age <50 years, n = 3981) vs normal menopause (≥50 years, n = 7623); Type of menopause	Structured interview; report	Global gray and white matter volume; regional cortical and subcortical volume and thickness	MRI; IDPs	Age at baseline, ethnicity, education, socioeconomic deprivation, smoking status, alcohol intake, PA, healthy diet	Linear regression
9	Raz, 2004	MHT use	self-reported use	Regional GMV, WMV	MRI; All regional volumes were adjusted for the ICV	Age, hypertension status, time	Ordinary least-squares model with repeated measures. Interaction with time and MHT
25	Coker, 2014	CEE 0.625 mg 1 MPA 2.5 mg/d for women with intact uteri, or CEE alone for women with prior hysterectomy; vs placebo		Annual change in total brain, frontal lobe, and ventricular volumes	MRI	Trial, visit, clinical site, age, intracranial volume, and time from randomization to MRI scan	Longitudinal mixed-effects models
21	Espeland, 2009	HRT vs placebo control: CEE + MPA in women with a uterus; CEE alone with prior hysterectomy; Placebo	Exposure was ascertained by randomized treatment assignment in the parallel placebo-controlled WHI/WHIMS trials: CEE 0.625 mg/day plus MPA 2.5 mg/day for women with a uterus, or CEE 0.625 mg/day alone after hysterectomy, versus placebo.	Total brain volumes and frontal lobe volume	MRI	ICV	ANCOVA or logistic regression
20	Resnick, 2009	HRT vs placebo control: CEE + MPA in women with a uterus ; CEE alone with prior hysterectomy; Placebo	Exposure was ascertained by randomized treatment assignment in the parallel placebo-controlled WHI/WHIMS trials: CEE 0.625 mg/day plus MPA 2.5 mg/day for women with a uterus, or CEE 0.625 mg/day alone after hysterectomy, versus placebo.	Total brain (GM+WM), frontal lobe, and ventricular volumes	MRI	age at enrollment, time between enrollment and scanning, ICV, clinical center site, other baseline dementia risk factors (education, ethnicity,	analyses of covariance

						smoking status, BMI, hypertension, prior CVD, diabetes, prior HT, and baseline 3MS score)	
33	Kantarci, 2016	Hormone therapy groups: Oral CEE Transdermal 17β-Estradiol (tE2) Placebo [reference]	Estrogens were administered through two different routes: Oral or transdermal. Participants were randomized to either: 1) oral conjugated equine estrogen (CEE; Premarin, 0.45 mg/day); 2) transdermal 17β-estradiol (skin patch, Climara, 50 μg/day); or 3) placebo pills and patch. Progesterone was given orally (Prometrium; micronized progesterone, 200 mg/day) for the first 12 days each month to both active treatment groups. Participants were treated for four years.	Longitudinal whole-brain and ventricular volume change	MRI		Linear mixed models as planned a priori, with each model containing time from baseline, treatment group, and time from baseline*treatment group interactions [primary interest] as fixed-effects predictors. These models incorporated random effects for subject-specific intercepts and slopes.
41	Kantarci, 2018	Hormone therapy groups: Oral CEE. Transdermal 17β-Estradiol (tE2) Placebo [reference]	Estrogens were administered through two different routes: Oral or transdermal. Participants were randomized to either: 1) oral conjugated equine estrogen (CEE; Premarin, 0.45 mg/day); 2) transdermal 17β-estradiol (skin patch, Climara, 50 μg/day); or 3) placebo pills and patch. Progesterone was given orally (Prometrium; micronized progesterone, 200 mg/day) for the first 12 days each month to both active treatment groups.	Longitudinal whole-brain, ventricular, and regional cortical volume change at 18, 36, 48, and 84 months	MRI		Linear mixed models and including random subject-specific intercepts, slopes, and treatment × time interactions. Regional cortical volume changes in each of the oCEE and tE2 groups were compared to placebo using area under the ROC curve analysis for 21 ROIs combining the right and left hemispheric regions. Because 21 ROIs were compared to placebo, the analyses were corrected for multiple comparisons by using the false discovery rate.

			Participants were treated for four years.				The superior and middle frontal gyri were combined as the DLPFC outcome
90	Kantarci, 2026	Assignment to menopausal hormone therapy (MHT) during the original KEEPS randomized trial Hormone therapy groups: Oral CEE Transdermal 17β-Estradiol Placebo [reference]	Estrogens were administered through two different routes: Oral or transdermal. Participants were randomized to either: 1) oral conjugated equine estrogen (CEE; Premarin, 0.45 mg/day); 2) transdermal 17β-estradiol (skin patch, Climara, 50 μg/day); or 3) placebo pills and patch. Progesterone was given orally (Prometrium; micronized progesterone, 200 mg/day) for the first 12 days each month to both active treatment groups. Participants were treated for four years.	Dorsolateral prefrontal cortical thickness	MRI	Mean-centered age at assessment and site of assessment + APOE ε4 carrier status	Multivariable linear regression model.
61	Aleknaviciute, 2022	Parity (nulliparous, one, 2–3, or ≥4 births); Pregnancy complications	structured interview; menopause and MHT were additionally verified through medical records	Global and regional gray matter volume; white matter volume	MRI	Age, ICV, education, marital status, smoking, and BMI	regression analysis
51	Ambikairajah, 2020	Menstruation history-menopausal status, age of menopause, age of menarche, and duration of reproductive stage	self-report	Total brain volume	MRI	Age, smoking history, waist circumference, educational attainment, physical activity, frequency of alcohol intake, and number of children, vascular/heart problems, and diabetes	Multiple linear hierarchical regression; propensity matching in sensitivity analysis for age and nearest neighbor smoking history, waist circumference, educational attainment, physical activity, alcohol intake, number of children, vascular/heart problems, and diabetes, to prove not driven by confounding
55	Boyle, 2021	Past and present MHT use (have taken Premarin or other	Recorded by medical inventory, regardless of self-reported past use	MRI	Regional brain volume —	BMI and physical	Voxel-wise linear regressions

		estrogens for hot flashes or other symptoms of menopause and not having a current prescription);			voxel-wise gray and white matter volume, plus ventricular volume.	activity; site of data acquisition, age at year 11, ethnicity, yrs of education, clinical diagnosis, heart disease, T2DM, hypertension, WML, BMI yr 9, PA yr 10, APOE e4 status, and estrogen use yr 11	
94	Brown, 2025	BSO; hormone therapy (exploratory analysis, specifically 17beta-estradiol therapy	clinical history and participant recruitment from medical settings; HT. from self-report combined with structured data collection procedures	Medial temporal lobe volumes: entorhinal and perirhinal cortex	MRI; corrected for ICV	ROI and hemisphere, scanner site	Two-way repeated-measures ANCOVA
12	Erickson, 2005	MHT, age, duration of therapy		Global and regional gray matter and white matter volumes; atrophy	MRI	SES, education, and Jacobian determinants (differences in spatial transformations on differential tissue volume between MHT uses and nonusers)	multiple regression; ROI approach
22	Erickson, 2010	MHT timing relative to menopause = Interval D = Time between age at menopause and age at HT initiation (continuous) Categorical exposure: 3 groups: 1. Never used HT 2. HT coincident with	All information pertaining to HT treatment was acquired through self report by a questionnaire and interactions with an experimenter. If women reported receiving HT during the 12-months after the last menstrual cycle, this was categorized as	Amygdala, and caudate volumes	MRI; adjusted for ICV	For D interval = Age, years of education, age at menopause, duration of HT, hormone status (current or past HT use) and hormone	Multiple regression was used to examine whether regional brain volumes were associated with the interval between menopause and hormone therapy initiation (D), adjusting for confounders. Secondary analyses used t-tests to compare brain volumes across HT

		menopause (those that initiated HT near the time of menopause) 3. HT 1-18 years post-menopause	receiving HT coincidentally with menopause. Age at menopause could be defined by three events: (a) 12 months of amenorrhea, (b) age at HT initiation for women who had not yet experienced amenorrhea, and (c) age at bilateral oophorectomy or hysterectomy.			type (unopposed CEE, CEE with MPA, or PE) secondary analysis = age, years of education, and age at menopause	timing groups (never, early, and late initiation), adjusted for covariates. [it might be ANCOVA as cannot adjusted in ttest] SA: = removed those receiving PE as treatment of menopausal symptoms and reran analyses.
16	Greenberg, 2006	MHT use: Current or long-term MHT users vs nonusers	interview; Drug and dose information in a subset (n=32; of whom 21 were taking estrogens alone and 18 were taking Premarin, and 3 taking Estraderm; 11 taking estrogends and progestin; 4 Prempro, 4 taking premarin and Provera, 2 taking Estrace and Provera; 1 Ogen and Provera). Dose for 18 women (6 taking Premarin alone, two of these women were taking 0.3mg/day, while 14 were taking 0.625/2.5mg dose). Therefore, all these women were taking conjugated equine estrogens (CEE).	Gray matter volume; white matter volume; ventricular CSF, nonventricular CSF, caudate volume, and putamen volume	MRI	Age, education, ICV	Regression; adjust for multiple comparisons (Bonferroni)
78	Huddleston, 2024	PCOS	NIH criteria- both hyperandrogenism (clinical or biochemical) and oligomenorrhea were required. Androgens were assayed by the obstetrics/genecology Research and Diagnostic Lab. Total testosterone was measured by direct chemiluminescent-competitive immunoassay. Free testosterone was calculated form total testosterone and SHBG; biochemical hyperandrogenism was defined as serum androgens about the 75th percentile; clinical	White matter volume	MRI	Sociodemographic (self-reports and interviewer): age, race education, and study center and intracerebral volume	linear regressions

			hyperandrogenism was defined as self-reported excess body hair growth between 20 and 30yrs.oligomenorrhea was determined by questions about recalling irregular cycles between 20 and 30yrs, with >32 apart considered to fulfill the criterion				
14	Irie, 2006	Tertiles (low [ref], middle, high) of: 1. Bioavailable testosterone 2. Bioavailable estradiol 3. SHBG	Blood-based sex hormones (standard immunoassays) When: On average 3 years prior to the MRI, at a mean time of 8:48 a.m. (S.D.: 0.9 h) Total estradiol and testosterone measured; low estradiol values estimated via calibration curve; bioavailable and free serum levels of hormones calculated (mass action formula using total hormone, SHBG and albumin).	Cerebral atrophy (ventricular enlargement)	MRI	Model 1: age, education, dementia status, apoE4 genotype Model 2: model 1 + mid-life SBP, DBP, and smoking status, late-life BMI, total cholesterol, diabetes, and other sex hormones. Bioavailable testosterone as exposure: adjusted for estradiol; BioEstradiol: adjusted for testosterone; SHBG: adjusted for estradiol and testosterone as other sex hormones in model 2.	Logistic regression Missing data - used mean value of the variable in the analysis Additional analyses stratified by: dementia (yes or no) and AD (yes or no); other dementias were excluded because of low numbers.
46	Jung, 2020	Number of deliveries (parity): Two groups: 0-4 parity grand multiparity (>=5 births)	Reproductive history was assessed through systematic interviews implemented by trained nurses.	SPARE-AD and SPARE-BA atrophy-pattern indices	MRI; SPARE-AD (spatial patterns of	Model 1: age, years of education, APOE4	Multiple linear regression analyses

		[did not classify nulliparity as an independent group due to low numbers]			abnormality for recognition of early AD): sum of volumes from ROIs: hippocampus, inferior temporal gyrus, parahippocampal gyrus, posterior cingulate, precuneus, entorhinal cortex, and middle temporal gyrus; adjusted by ICV SPARE-BA (spatial pattern of atrophy for recognition of brain again): sum of the insular cortex, thalamus proper, cingulate cortex (anterior and middle), frontal, inferior parietal, and superior temporal gyrus; ICV-adjusted	positivity, and cognitive status (i.e., CN vs. MCI) Model 2: Model 1 + Vascular risk score, income level at early adulthood, level of lifetime occupation, age at menarche age, and age at menopause. Vascular risk score = percentage of the number of vascular risk factors present (hypertension, diabetes mellitus, dyslipidemia, coronary heart disease, transient ischemic attack, and stroke,)	
86	Kantarci, 2025	Premenopausal bilateral oophorectomy (PBO) before 50 years:	All women resided in a geographically defined population of the Rochester Epidemiology Project (REP) medical records–	Entorhinal cortex thickness; Temporal lobe cortical thickness (containing	MRI	Age at imaging; APOE ε4 carrier status when	Multivariable linear regression, stratified by early PBO (<46 years) and late PBO (46–49 years) groups.

		1. Early PBO (<46 years) vs referent (age-matched referent women who had not undergone PBO before the index date [date of matching]) 2. Late PBO (46–49 years) vs referent	linkage system. PBO was defined as complete removal of both ovaries or as second unilateral oophorectomy, with or without hysterectomy, and performed before the onset of spontaneous menopause.	the entorhinal, fusiform, parahippocampal, middle temporal, inferior temporal, and angular gyri)		interaction with age	Analyses were first adjusted for age at imaging, then additionally for adjusted for APOE ε4 status; then with interaction terms included to assess effect modification by age (age × PBO).
40	Kim, 2018	Menopausal status (pre-menopausal women vs post-menopausal) Sex hormones: Total estrogen Estradiol Estriol Free testosterone SHBG FSH LH	Menopausal status = Based on: STRAW +10, amenorrhea for more than one year, and FSH above 30 mIU/mL. The levels of total estrogen, estriol, free testosterone, and SHBG were measured by radioimmunoassay using a gamma counter. The levels of E2, FSH, and LH were measured by chemiluminescent immunoassay using ADVIA Centaur System.	Global and regional gray and white matter volume	MRI	Age	ANCOVA adjusting for age were used to compare GMV between pre-menopausal and post-menopausal women. The cluster size included more than 50 contiguous voxels. A partial correlation adjusting for age was used to evaluate the correlation between the levels of sexual hormones and mean GMV in each brain area.
68	Kim, 2023	Sex hormone levels: oral administration for MHT of only estrogen or combination hormone replacement treatment as Premina; angeliq, Livial, Progynova, and Duavive. Measured sex hormones: anti-Müllerian hormone, serum estradiol, testosterone, FSH, LH and progesterone	Treatment status was established through gynecologic evaluation and medication history; Sex hormones were measured with chemiluminoimmunoassay and electrochemiluminescence immunoassay	Global and regional gray matter	MRI	Age and TIV	t-test; simple regression
79	Kim, 2024	Menopausal status; Serum estrogen, estradion, FSH, LH, estriol (E3), free testosterone, and SHBG	Menopausal status was assigned using STRAW+10 criteria: regular cycling in the premenopausal group and at least one year without menstruation in the postmenopausal group. Women with hysterectomy, bilateral oophorectomy, neurological illness, or recent hormone/steroid treatment were excluded.; Sex hormones measured by	Cortical surface areas and subcortical volumes; Thalamic volume	MRI	Age and whole brain volume	Multivariate analysis

			chemiluminescent immunoassays or by radioimmunoassay				
88	Kwan, 2025	MHT users and MHT non-users [matched on age and education]	Appears to be self-reported. Not explicitly stated. MHT users = Participants that had used HT at any time point throughout the study since enrollment were identified. MHT non-users = Participants that had not engaged in HT were also identified and were manually age- and education matched to the MHT group. Individuals who had experienced a hysterectomy or ovariectomy were excluded from the analysis.	Gray matter volume	MRI		Voxel-based morphometry (VBM) was used to examine the relationship between gray matter volume on a voxel-by-voxel basis and measurement of interest. VBM with voxel-wise GLM with permutation-based nonparametric testing; Examined differences in gray matter volume between the MHT and non-MHT groups using t-tests. The analyses examine the relationship across each voxel in the brain; therefore, all analyses were corrected for multiple comparisons across space with threshold free cluster enhancement.
18	Lord, 2008	ET users, past users, never users	not explicitly stated; self-reported implied	Amygdala volumes	MRI	Age	A mixed-design ANCOVA was used to compare amygdala volumes across groups, with hemisphere as a repeated measure and age included as a covariate.
15	Low, 2006	MHT use status: current users, previous users, never users	Self-reported Have you ever had hormone replacement therapy'? 'Are you still having hormone replacement therapy'? 'Which hormone replacement medications are you taking/have you taken'? 'How long have you had hormone replacement therapy'? Women taking natural or alternative treatment for menopause were coded as non-MHT users.	Total gray and white matter volume; amygdala volumes; global and regional atrophy measures	MRI	controlling for education and ICV, as appropriate. ICV not controlled for atrophy measures, WMH% density of total brain; education not included as a covariate for	Differences between MHT groups were tested with chi2, ANOVA or ANCOVA.

						Visual atrophy ratings [chi2].	
42	Lu, 2018	Reproductive stage; Sex hormone levels: prolactin (PRL), FSH, LH, E2, free-T, P	Reproductive state assigned using STRAW 10+; Serum sex hormone levels measured from venous blood samples using a chemiluminescence immunoassay method.	Voxel-wise regional gray matter volume	MRI	Age, TIV	VBM analysis. whole-brain, voxel-wise analysis GLM in spm12. FDR corrected; Spearman partial correlation analysis was then conducted to evaluate the relationship between the mean grey matter volume of these regions and sex hormone levels
1	Luoto, 2000	ERT use	Current ERT from prescription-bottle inventories and participant report; past use and duration for self-report	Focal and sulcal brain atrophy (cortical atrophy); bifrontal distance; ventricular size (central atrophy)	MRI	Age and other covariates: race, parity, education, age at natural menopause and/or hysterectomy and oophorectomy, smoking, BMI, blood pressure, and alcohol use	ANCOVA or logistic regression
97	McGrath, 2025	Reproductive factors: age at menarche, type of menopause (natural, surgical, and chemotherapy or radiation-induced); reproductive lifespan (age of menopause minus age at menarche); number of live births; postmenopausal MHT was defined as previous or current use of MHT at or after the individual's age at menopause	self-reported	Total cerebral brain volume; MRI ADRD signature score (measure of cortical atrophy in typically affected regions in patients with AD; lower scores indicate greater atrophy)	MRI	Age, age squared, education status, time between baseline and MRI brain, intracranial volume	Multivariable linear regression Subgroup analysis: stratified by baseline age (<60 vs ≥60y)
30	Mielke, 2016	History of Hypertensive Pregnancy Disorders: Normotensive Pregnancy Hypertensive Pregnancy	Standardized, previously validated questionnaire administered by trained interviewers to determine whether a woman had a history of hypertension in pregnancy.	Brain atrophy; Ventricular volume	MRI; Brain atrophy =ICV-retained volume	Age, body mass index, smoking, hypertension, family history	Linear models fit with generalized estimating equations, accounting for sibship clustering.

			Women were classified as exposed when they reported that a physician had diagnosed high blood pressure or hypertension during a pregnancy lasting more than six months.			of hypertension, total intracranial volume, and accounted for familial clustering, duration of hypertension (assessed for women with current hypertension). Only covariates that differed between women with and without histories of hypertensive pregnancies (or nulliparous women) were included in the GEE models. The variables: Age Race Education Body mass index (BMI) Smoking history Kidney function (eGFR <60) Diabetes mellitus Hypertension Duration of	

						hypertension Dyslipidemia Family history of hypertension Family history of coronary heart disease	
70	Moir, 2023	Age at natural menopause	self-reported	Total brain (GM + WM), gray matter, white matter, intracranial volume (GM+WM+CSF)	MRI; adjusted for ICV		ttest or Mann-Whitney tests
38	Mosconi, 2017	Menopausal status: asymptomatic perimenopausal by age, perimenopausal, and postmenopausal	Clinical judgment, medical records, and detection of cluster symptoms according to the STRAW criteria. Asymptomatic perimenopausal women by age (e.g., regular cyclers, or premenopausal control, CNT); symptomatic perimenopausal women (e.g., irregular cyclers, PERI); postmenopausal women (e.g., no menstrual cycles for ≥12 months, MENO).	Gray matter and white matter volumes	MRI	Age, education, APOE, TIV	For SPM a full factorial model with post hoc t contrasts was used to test for regional differences in imaging measures. Linear regressions.
56	Mosconi, 2021	Menopausal status: premenopausal, perimenopausal, and postmenopausal	Based on the STRAW criteria and corroborated by means of hormone assessments.	Regional gray matter and white matter volumes	MRI	Age, APOE4, TIV SA: control for MHT use and hysterectomy	Voxel-wise SPM12 full factorial model and posthoc t-contrasts with regional/masked reporting
100	Mutee, 2026	Plasma SHBG Level	Multiplex immunoassay platform provided by Rules-Based Medicine (RBM). At RBM, SHBG concentrations were quantified using the Human DiscoveryMAP® panel, which employs Luminex xMAP® technology on Luminex 100™ or 200™ systems.	Temporal lobe volume	MRI	Age, gender, education, handedness, ApoE ε4	Multiple linear regression analyses

50	Rahman, 2020	Menopausal status (premenopausal, perimenopausal, and postmenopausal), MHT status (user vs nonuser); hysterectomy status (yes, no)	STRAW criteria and cluster symptoms. Based on clinical judgement.	Regional and global gray matter and white matter volumes	MRI	Age and TIV	Brain biomarker differences by sex: SPM12 was used to perform voxel-wise comparisons. Full factorial models with post hoc t contrasts were used to test regional differences in MRI. Analyses done again with age and size matched groups, by matching the men in cohort to the women of the same age. All results were corrected for FWE and with cluster extent >=50 voxels. AD risk factors and sex-driven biomarker differences: LASSO regressions to determine menopausal status as a potential predictor. If showing a significant association, it was further examined with general linear models corrected for multiple comparisons
26	Ryan, 2014	Current and past HT; type of treatment; duration of current HT and timing of initiation of first treatment in relation to menopause	self-report; validated with the prescription of medication itself, and past user were shown photos to aid with recall.	Gray and white matter volumes; corpus callosum area; atrophy	MRI; adjusted for ICV; atrophy = CSF/ICV ratio	Age, education, history of CVD, hypertension, and number of medications currently used, low cognitive function, lifetime major depressive disorder, diabetes, hypercholesterolemia, anticholinergic medication, current use of ≥3 medications, smoking history, living	Linear regression

						along, alcohol consumption, APOE e4 allele	
53	Schelbaum, 2021	WOMEN: Endogenous estrogen exposures 1. Menopausal status: Categorical: (pre-, peri-, postmenopausal) 2. Menopause type: Categorical (spontaneous or induced) 3. Age at menarche: Continuous and categorical (<13 and >13 years) 4. Age at menopause: Continuous and categorical (<51 and >51 years) 5. Number of children: Continuous and categorical (0, 1, >2) 6. Number of pregnancies: Continuous 7. Age at first birth: Continuous 8. Reproductive span: Continuous and categorical (<39 and >39 years) Exogenous estrogen exposures 1. HT usage: Categorical (never users, past users, current users) 2. Duration of HT usage: continuous 3. Hormonal Contraceptives (HC) usage: Categorical (never users, past users, current users) 4. Duration of HC usage: continuous Men: Number of children: Continuous and categorical (0, 1, >2)	WOMEN: Menopause status: questionnaire, clinical evaluation based on the STRAW criteria, and hormone laboratory assessments. Menopause type: Semi-structured Interviews and Questionnaire All other factors: questionnaires and semi-structured interviews MEN: questionnaire	Gray matter volume in Alzheimer-vulnerable cortical, medial temporal, parietal, frontal, and basal-ganglia regions	MRI	All analyses Model 1: age and TIV For exposures showing significant associations with outcome measures: model 1 + APOE e4 status, and midlife health variables (smoking, waist-to-hip ratios, and hypertension diagnosis) exposure-specific confounders: (1) hysterectomy status and HT use in analysis of menopausal status and reproductive span; (2) age at firstborn in analysis of number of children; (3) hysterectomy status and duration of use	Voxel-based general linear models with post-hoc t-contrasts in SPM12 to assess associations between exposures and GMV; analysis restricted to AD-vulnerable regions using an Automated Anatomical Labeling atlas mask with cluster-level small-volume correction and GM mask; significant clusters reported in Montreal Neurological Institute coordinates space, with GMV extracted from peak VOIs using Marsbar 0.44. GMV measures are extracted from the peak association cluster for each exposure, e.g., inferior temporal gyrus for menopause status, precuneus for reproductive span and HC use, inferior frontal gyrus for number of children, and superior frontal gyrus for HT use. For each exposure, they selected the most significant brain region and used its GMV value for further statistical analysis. Multiple linear regressions to examine associations. SA 1: Analyses of menopausal status, age at menopause, and duration of reproductive span were repeated after the exclusion of participants with hysterectomy. SA 2: focused on the predefined MTL region by extracting and averaging GMV from MTL clusters

						in analysis of HT effects; and (4) duration of use in analysis of HC effects.	identified in the main analysis and testing associations using regression.
44	Seitz, 2019	Menopausal staging	reproductive histories (structured clinical interview) and serologic hormonal validation (blood samples) were used to determine the reproductive stage following STRAW 10+ criteria.	Regional gray matter volumes	MRI; corrected for ICV	Age	Group comparisons were done using ANCOVA. Structural relationships were analyzed with structural covariance analysis and Box M's test. When group differences were found they compared pairwise correlations between brain regions
72	Steventon, 2023	postmenopausal status; age at menopause; MHT status; duration of MHT use, years from previous MHT use, age at MHT initiation, age at menarche, menopause onset age, and age at first live birth	self-report questions	Total gray matter; temporal, parahippocampal, perirhinal, entorhinal, amygdala	MRI	age at the time of MRI scan, education, socioeconomic status, hemispheres, normalized grey matter volume, MRI scan site, head motion from resting fMRI, and z-table position in the scanner, height and weight.	Multiple regression.
11	Sullivan, 2005	Menopause status: 1. Premenopausal women 2. Postmenopausal women not using HRT 3. Postmenopausal women using HRT	Not clearly stated.	Temporal lobe gray and white matter volumes (left and right) [excluding hippocampus]	MRI; corrected for ICV		One-way ANOVA
52	Than, 2021	Menopause status: 1. Pre/perimenopausal (reference) 2. Postmenopausal	Self-reported using the question: "Have you had your menopause (periods stopped)?" Pre/perimenopausal = answering "No" Postmenopausal = answering	Global and regional gray matter volume; white matter volume; regional cortical and subcortical volumes	MRI	APOE ε4 status Secondary/exploratory adjustments = Cardiometabolic conditions,	Linear regression analyses.

			"Yes" (Participants aged >60 years and/or with a history of bilateral oophorectomy were classified grouped as postmenopausal regardless of survey response.) MHT use determined via nurse-led interview and classified using UK Biobank treatment/medication codes, including current and prior use.			ethnicity, MHT use	
74	Wugalter, 2024	Serum E1 and E2	Assessed via liquid chromatography–tandem mass spectrometry	Frontal and temporal regional brain volumes	MRI	Age, years of education, race, and BMI	Multiple linear regressions.
45	Zeydan, 2019	BSO vs control	record linkage	Amygdala volumes; parahippocampal-entorhinal cortical thickness	MRI	ICV	Wilcoxon rank sum tests, rank regression tests adjusted for ICV to compare BSO and control groups
58	Zhang, 2021	FSH and E2 levels	Fasting Serum assessed	Selected cortical and subcortical volumes	MRI	Age and education	two-sample ttests, with multiple comparisons using FDR approach
102	Zuhlsdorff, 2026	menopause status; age at menopause; time since menopause; MHT status, age started MHT, duration of MHT	touchscreen questionnaire	Gray matter volumes of entorhinal cortex, and anterior cingulate cortex	MRI	age, household income, level of education, smoking status, BMI, time since menopause onset, and MHT duration, insomnia, sleep duration, tiredness, and cognitive task analyses, a history of depression, TIV	linear models

eTable 22 Brain volumes-related studies: Overall findings and limitations

Study ID	First author, year	Main Finding	Direction of association	Key limitations
93	Alshikho, 2025	At a median 11-year follow-up after pregnancy, women with prior HDP or preeclampsia did not differ from controls in regional gray matter volume or cortical thickness.	Prior HDP ↔ regional GMV Prior HDP ↔ cortical thickness	Lack neuroimaging prior to first pregnancy, small sample size; unmeasured confounding;
3	Cook, 2002	Over approximately 3.7 years, ERT users had significantly less increase in total, anterior, and posterior ventricular CSF, indicating less progression of central brain atrophy than nonusers.	ERT ↓ ventricular CSF progression/central atrophy ERT ↓ anterior ventricular CSF progression ERT ↓ posterior ventricular CSF progression	Small sample size; ERT was not randomized; There was variability in follow-up intervals, which could influence measured progression; Information on ERT exposure (dose, duration, details) was limited; The study may be underpowered because pilot study
39	Elbejjani, 2017	Hormone levels measured in young adulthood predicted selected midlife brain volumes: higher SHBG was associated with smaller parietal gray matter volume but greater total white matter volume. Total brain and most other regional volumes were not associated with sex hormones.	Higher SHBG ↓ parietal GMV Higher SHBG ↑ total WMV Total/Bio-T ↔ total/regional brain volume Sex hormones ↔ total brain volume Sex hormones ↔ most other regional volumes	Our study lacked information on estrogen concentrations; Bio-T levels were not measured directly (i.e., by equilibrium dialysis), which might have resulted in measurement error.
76	Lee, 2024	Prior hormonal contraception use was associated with greater longitudinal cortical thickness in an Alzheimer disease temporal meta-ROI. MHT started before or within one year after menopause was associated with greater cortical thickness at the index assessment compared with nonuse, but it was not associated with slower subsequent thinning. Ever MHT use, age at menarche, reproductive-window length, and other reproductive factors were not associated with cortical-thickness change.	Ever HC use vs never-users ↑ AD meta-ROI cortical thickness Ever MHT use ↔ cortical thickness change MHT before or within 1yr ↑ cortical thickness Age at menarche/reproductive window ↔ cortical thickness Other reproductive factors ↔ cortical thickness	1. Predominantly White female sample → limited generalizability 2. Possible missing/incomplete data from medical records or migration history 3. Insufficient power to examine specific HC and MHT types/doses 4. Potential survival bias in longitudinal cohort 5. Possible confounding by indication (e.g., women with menopausal symptoms more likely to use MHT, and these symptoms are associated with atrophy)
13	Lessov-Shlaggar, 2005	Midlife testosterone was associated with larger later bilateral hemispheric, frontal, and parietal volumes but smaller left occipital volume. Higher estradiol and estrone predicted smaller	Higher testosterone ↑ bilateral hemispheric/frontal/parietal volumes Higher testosterone ↓ left occipital volume	limited generalizability; MRI participants were somewhat younger than nonparticipants; multiple comparisons not formally corrected therefore some results may be by chance;

		occipital volumes, while total brain and temporal volumes showed no association. SHBG had no independent association with the eligible volume measures.	Higher E2/estrone ↓ occipital volumes Sex hormones ↔ total brain and temporal volumes SHBG ↔ regional brain volumes	bioavailable hormones not measured directly; only 1 MRI measure
69	Liao, 2023	Earlier menopause was associated with lower global gray and white matter volumes and lower measures across most cortical and subcortical regions, including frontal, parietal, temporal, hippocampal, thalamic, and basal-ganglia structures.	Earlier menopause ↓ global GMV Earlier menopause ↓ global WMV Earlier menopause ↓ most regional volumes/thickness particularly	unmeasured confounding; low response rate and health volunteer bias; dementia might be misdiagnosed and more likely to be lost to follow-up, so some dementia maybe were not caught; self-reported questions thus may lead to recall bias; could not ensure that menopause lasted more than 12 months; limited generalizability
9	Raz, 2004	Over five years, controls showed shrinkage in the lateral prefrontal cortex, fusiform cortex, and prefrontal white matter. MHT duration was not associated with regional volume change.	Controls had greater↓ regional brain shrinkage (LPFC, FF, PFw) vs MHT MHT duration ↔ regional volume change	sample size; limited information on establishment of menopausal status, the exact time of therapy initiation, and assessment of the individual hormonal levels and therapeutic doses. Lack of uniformity of types of treatment; therefore
25	Coker, 2014	Over a mean 4.7 years between MRI scans, prior MHT did not accelerate annual total or regional brain-volume loss. MHT-assigned women had smaller frontal lobe volumes overall; ventricular volumes did not differ by treatment.	MHT ↔ annual total brain volume loss MHT ↔ annual regional volume change MHT ↓ frontal lobe volume MHT ↔ ventricular volume	Underrepresented participants because of selective attrition over a 12yr period, thus a healthier follow-up cohort. High nonparticipation, about 1/3 didn't participate.
21	Espeland, 2009	Among women assigned to CEE-based therapy, development of cognitive impairment was associated with smaller total brain volumes. This pattern was not observed in the placebo group, although the analysis was conditional on cognitive-impairment status rather than an overall treatment effect. Across both treatment arms there was no difference with frontal lobe volume.	CEE therapy + cognitive impairment ↓ total brain volume CEE therapy + cognitive impairment ↔ frontal lobe volume	small sample size; the volunteers do not closely represent the population of elderly women at large;
20	Resnick, 2009	Women previously assigned to CEE-based hormone therapy had lower frontal lobe volumes and slightly lower total brain volumes than placebo-treated women. Ventricular volumes were unaffected.	Pooled MHT ↓ frontal lobe volume Pooled MHT ↓ total brain volume Pooled MHT ↔ ventricular volume	did not test effects in young postmenopausal women; MRI scans were conducted post-trial on average 3 and 1.4 yrs post-trial and no MRI pretreatment scans were obtained, so no comparison to baseline.
33	Kantarci, 2016	Over four years, oral CEE was associated with greater ventricular expansion than placebo. Transdermal estradiol did not significantly alter	CEE/tE2 ↔ whole-brain volume change Oral CEE ↑ ventricular expansion	Healthy, well-educated sample → limits generalizability to broader populations; Small sample size → limited statistical power;

		ventricular expansion, and no significant whole-brain volume effect was reported; later CEE initiation was linked to greater early ventricular expansion.	tE2 ↔ ventricular expansion Later CEE initiation ↑ ventricular expansion	Small magnitude of MRI changes → harder to detect significant differences; Estradiol findings may be underpowered (could become significant with longer follow-up); Short follow-up duration (4 years) → may not capture full effects; Randomization imbalance due to small sample size; Post hoc analyses performed → risk of bias
41	Kantarci, 2018	Seven years after treatment ended, whole-brain volume change did not differ between either MHT group and placebo. Transdermal estradiol was associated with preservation of dorsolateral, superior, and middle frontal cortical volumes.	tE2/oCEE vs placebo ↔ global brain volume change Oral CEE vs placebo ↔ cortical region volume change tE2 vs placebo less ↓ dorsolateral prefrontal cortical volume loss	Small sample size; Healthy, low-risk population; Follow-up still limited for dementia outcomes; Inability to assess risk modifiers; Potential imbalance in baseline characteristics (Higher APOE ε4 prevalence in tE2 group)
90	Kantarci, 2026	Neither original hormone-therapy assignment was associated with DLPFC thickness approximately 10 years after the trial ended	Prior oCEE/tE2 ↔DLPFC thickness	High attrition due to COVID-19: Many participants declined follow-up participation (travel concerns) Selection bias (healthier participants): Included participants had lower blood pressure and BMI than non-participants Limited generalizability: Original cohort is healthy, low cardiovascular risk, mostly non-Hispanic White women Limited applicability to broader populations; Post-trial hormone therapy use (confounding): Some participants continued/started MHT after trial (~14–15%)
61	Aleknaviciute, 2022	Parity was associated with larger global gray matter volume across temporal, frontal, occipital, and parietal regions. Parity was not associated with white matter volume after full adjustment.	Parity vs nulliparity ↑ global/regional GMV Parity ↔ WMV	missing information on infertility and gravidity (unmeasured confounding); lack of available info on time-varying CVRFs; small sample of women with pregnancy related complications; predominantly middle-class Caucasian descent therefore restricts generalizability; selection bias; no external validation of data therefore may be recall bias, can't distinguish between effects of pregnancy, parity, and parenting
51	Ambikairajah, 2020	Within postmenopausal women, later menopause and longer reproductive duration were associated with smaller total brain volume.	Later menopause ↓ total brain Later menarche ↑ total brain volume Longer reproductive span ↓ total brain volume	perimenopausal women were not included; self-report exposures; imaging data available at

		Later menarche was associated with larger total brain volume.		only 1 time point; healthy participant bias in the UKB;
55	Boyle, 2021	Estrogen use was associated with significantly higher regional brain volume across the whole brain after full adjustment. Frontal regions showed higher volume in users, as well as parietal and occipital regions. Secondary analyses: Age of menopause, had effect on brain volume. No effects of "window of opportunity" on brain volume.	Estrogen use was self-reported; selection bias for estrogen use and combined estrogen-progestin use; design was limited; lack info on dosage	MHT use vs non-use ↑ whole brain volume MHT use vs non-use ↑ frontal lobe, parietal, occipital volume
94	Brown, 2025	Medial temporal cortical regions did not differ.	BSO ↔ medial temporal cortical volumes	Limited control of hormonal factors; small sample; unmeasured confounders; imaging and segmentation challenges
12	Erickson, 2005	MHT users had greater gray matter volume, particularly in frontal, prefrontal, temporal, and parietal regions, and regional white matter sparing in the medial temporal lobe. Longer treatment was associated with greater regional tissue sparing.	MHT ↑ regional GMV MHT ↑ medial temporal WMV Longer MHT ↑ regional tissue sparing	ROI approach might have been a better approach to assess impact of hormones. Findings are limited to unopposed estrogen replacement therapy and cannot generalize to an opposed estrogen replacement regimen.
22	Erickson, 2010	Amygdala and caudate volumes were not associated.	HT timing ↔ amygdala/caudate volume	Possible third variables that may covary with MHT or the timing of MHT initiation. Confounding by indication or severity, selection biases, and a healthy-user bias, may explain some of the relationships described. Self-report measurements of when MHT
16	Greenberg, 2006	Current MHT users had smaller gray matter volumes and larger nonventricular CSF volumes than nonusers. White-matter volume and ventricular CSF did not differ between the two female groups. Caudate and putamen differences did not survive the study's multiple-comparison threshold.	Current MHT ↓ vs nonusers gray matter volume Current MHT vs nonusers ↑ nonventricular CSF Current MHT vs nonusers ↔ white matter ventricular CSF, caudate and putamen volume	Healthy volunteer effect; bias from self-report, nonrandom assignment of ERT
78	Huddleston, 2024	Women with PCOS did not differ from women without PCOS in white matter volume	PCOS ↔ white matter volume	cross-sectional; unable to account for the degree of to which unmeasured confounders may have contributed; PCOS diagnosis was not made by a physician but on serum androgen levels and self-report, therefore could be some misclassification; didn't allow for assessment of ovarian markers therefore may not be generalizable to those with PCOS who do not meet NIH criteria; unable to assess the degree to which these findings represent a clinically important deficit

14	Irie, 2006	Higher bioavailable testosterone was associated with cerebral atrophy; higher bioavailable estradiol also showed a positive association that weakened after testosterone adjustment.	Higher bioavailable testosterone ↑ cerebral atrophy Higher bioavailable estradiol ↑ cerebral atrophy	imprecise estimation of low estradiol concentrations; potential selection/survivor bias; and generalizability
46	Jung, 2020	Grand multiparity (≥5 births) was associated with lower SPARE-AD volume and SPARE-BA volume, compared with 0–4 births.	Grand multiparity ↓SPARE-AD and SPARE-BA volume	1. Cross-sectional 2. Recall bias: reproductive history self-reported. Although, they reconfirmed information from reliable informants and got additional information. 3. Nulliparity could not be separately assessed.
86	Kantarci, 2025	PBO before age 46 was associated with thinner entorhinal cortex and age-dependent reductions in temporal lobe cortical thickness. Late PBO at ages 46–49 showed no associations from referents. SA: most of the participants who underwent PBO were using HT (65.6% in the early PBO and 77.1% in the late PBO), SA excluding women who did not use HT through the age of 50 years. [comparable findings]	Early PBO ↓ entorhinal cortical thickness Early PBO ↓ temporal cortical thickness at older ages Late PBO ↔ cortical thickness	Small sample size; highly educated; limiting generalizability; misclassification of the exposure groups that could have reduced the effect to null
40	Kim, 2018	Postmenopausal women had lower total gray-matter volume, and lower white-matter volume. Total intracranial volume did not differ. After age adjustment, the regional differences remaining were lower gray-matter volume in the supplementary motor area, inferior frontal gyrus, olfactory cortex, and superior temporal gyrus. Estradiol was positively associated with gray-matter volume in the supplementary motor, inferior frontal, and superior temporal regions; FSH was inversely associated with these regions and the olfactory cortex. Time since menopause was inversely related to supplementary motor area volume. The approximately 16-year age difference between groups remains an important residual-confounding concern despite statistical adjustment.	Postmenopause ↓ total GMV & WMV Postmenopause ↓ regional GMV (supplementary motor area, inferior frontal gyrus, olfactory cortex, and superior temporal gyrus) Higher estradiol ↑ regional GMV (supplementary motor, inferior frontal, and superior temporal regions) Higher FSH ↓ regional GMV (supplementary motor, inferior frontal, superior temporal regions, and olfactory cortex) Longer time since menopause ↓ GMV (supplementary motor area volume)	cross-sectional; small sample size; could not confirm hormonal status in all the participants, so there may have been some error in classification; underpowered to look at specific symptom clusters; limited generalizability; age difference between groups
68	Kim, 2023	No significant global tissue-volume differences. MHT users had greater regional gray matter volumes than nonusers. Positive association between MHT and larger regional gray-matter volumes in frontal regions including superior	MHT ↔ global tissue volume MHT ↑ regional GMV Longer MHT ↑ angular gyrus/hypothalamus volume	Low sample size: unpowered; non-specific MRI marker: GMV reflects brain aging but is not specific to AD;

		middle and inferior frontal gyri, supplementary motor and precentral areas; inferior temporal and parahippocampal gyri; postcentral cortex, precuneus and angular gyrus; superior occipital cortex; cerebellar cortex; and hypothalamus. Longer MHT duration correlated positively with angular-gyrus and hypothalamic gray-matter volume. FSH, LH, and progesterone showed negative associations with selected regional volumes.	Higher FSH/LH/progesterone ↓ selected regional GMV	Healthy midlife sample: Participants were cognitively normal (40–65 years) → low pathology burden, limiting insight into later disease stages; Underrepresentation of diverse populations; Limited generalizability
79	Kim, 2024	Postmenopausal women had significantly smaller surface areas in the left medial orbitofrontal cortex, right lateral orbitofrontal cortex, and right superior temporal cortex. No other examined cortical region survived Bonferroni correction. They also had a smaller right anterior pulvinar, in premenopausal women, after correction; the whole right thalamus was not significant after correction. Estrogen and estradiol levels were positively correlated with several of these measures.	Postmenopause ↓ surface area of the left medial orbitofrontal cortex (mOFC), right lateral orbitofrontal cortex (lOFC), and right superior temporal cortex (STC) Postmenopause ↓ right pulvinar anterior (PuA) Postmenopause ↔ right thalamus Higher estrogen ↑ left medial orbitofrontal cortex, right STC, and right lOFC and volume of the right PuA Higher E2 ↑ left mOFC and right lOFC,adn right PuA	Potential unmeasured confounders; limited diversity, predominantly Caucasian; subgroups were small; uncertainty about long term complications
88	Kwan, 2025	Gray matter volume did not differ significantly between MHT users and nonusers; a nonsignificant trend favored greater posterior GMV in nonusers.	MHT ↔ GMV	Menopause measurement: Self-reported → risk of misclassification; Timing, duration, or indication of HT use not considered
18	Lord, 2008	Amygdala volume did not differ between groups.	ET status ↔ amygdala volume	Potential residual confounding from unmeasured factors (e.g., fitness, personality, menopausal symptoms). Potential selection bias, with ET users potentially representing a distinct subgroup that differed from non-users in demographic or behavioral characteristics. Possible treatment-seeking bias.
15	Low, 2006	Current, past, and never MHT users did not differ in total GMV, WMV, regional amygdala volumes, or indices of brain atrophy (atrophy ratio, anterior	MHT ↔ GMV/WMV, regional volumes, and atrophy	1. cross-sectional design did not allow evaluation of lifespan influences on brain structure and pathology 2. 'Healthy volunteer' bias, and a relatively

		horn ventricular brain ratio, mid-ventricular brain ratio, visual atrophy ratings).		young sample in terms of brain ageing, may have resulted in less overall neuropathology, decreasing any observable effect. 3. MHT use self-reported without data on dose. 4. Sample not completely representative: moderate participation rate and participant characteristics - Never MHT users had the highest education and verbal intelligence, while current users had the lowest. This contrasts with other studies and may reflect that more educated women in this sample discontinued MHT after menopause, while less educated women continued.
42	Lu, 2018	Perimenopausal women had lower GMV in the putamen, pallidum, inferior parietal, superior frontal, and postcentral regions than premenopausal women. FSH/LH not associated with right pallidum GMV after multiple-comparison correction.	Perimenopause ↓ regional GMV (left putamen, right pallidum, right inferior parietal gyrus, orbital portion of the right superior frontal gyrus, and right postcentral gyrus) Higher FSH/LH ↔ right pallidum GMV	Lack of clinical measures; Symptom variability: Mostly mild/moderate perimenopausal symptoms may have weakened observable brain effects; Moderate sample size; need larger and better-characterized groups (e.g., symptom stratification).
1	Luoto, 2000	Current ERT users showed less focal atrophy than past or never users, but the difference was not significant, and sulcal atrophy scores were similar. Current users had larger bifrontal distance and ventricular size than never users. Duration of ERT was unrelated to any atrophy measure.	Current ERT ↔ focal/sulcal atrophy Current ERT ↑ bifrontal distance/ventricular size Duration ERT ↔ any atrophy measure	Confounding by indication; healthy volunteer effect; bias from self-report, nonrandom assignment of ERT
97	McGrath, 2025	Having ≥3 live births was associated with greater total cerebral brain volume, and MRI ADRD signature score, compared to no live births. Earlier menarche, postmenopausal MHT use, and higher estrone were associated with lower total cerebral brain volume. Postmenopausal MHT use was associated with lower MRI ADRD signature score. In subgroup analysis; the association between postmenopausal MHT/higher serum estrone and greater brain atrophy (lower total cerebral brain volume and MRI ADRD signature score) was only among women ≥60y.	Live births ↑ total cerebral brain volume Live births ↑ MRI ADRD signature score (greater brain volume) Earlier menarche/postmenopausal MHT/higher estrone ↓ total cerebral brain volume Postmenopausal MHT↓ MRI ADRD signature score	Data were not available for some important reproductive factors, such as gestational diabetes mellitus or hypertension, preeclampsia/eclampsia, prior miscarriages or breastfeeding history. Data on serum estradiol and estrone levels were available at a single-time pt only; unmeasured confounding; sample is mainly non-Hispanic white therefore limits generalizability

30	Mielke, 2016	Women with a history of hypertensive pregnancy disorders had greater brain atrophy than women with normotensive pregnancies. Ventricular volume did not differ significantly.	History of hypertensive pregnancy ↑ brain atrophy History of hypertensive pregnancy ↔ Ventricular volume	Hypertensive pregnancy disorders pooled together (cannot assess specific types); Cortical infarctions excluded (may bias results toward null); Selected sample (families with hypertension); Survival bias (participants assessed decades later) Self-reported pregnancy history (possible misclassification)
70	Moir, 2023	Total brain volume and intracranial volume did not differ between earlier- and later-menopause groups.	Earlier vs later menopause ↔ total brain volume/ICV	The definition of age of menopause may not align with other studies; the lab and MRI visits were complete on separate days with about on average 4 months apart;
38	Mosconi, 2017	Perimenopausal and postmenopausal women had lower frontal gray and white matter volumes than premenopausal controls, with a gradient of control > perimenopause > postmenopause.	Perimenopause vs CNT ↓ frontal GMV/WMV Postmenopause vs PERI & CNT ↓ frontal GMV/WMV CNT > PERI > MENO gradient in frontal GMV/WMV	Menopausal status was not hormonally confirmed → potential misclassification of reproductive stage. Limited evaluation of hormone therapy effects. Highly selected healthy cohort.
56	Mosconi, 2021	Postmenopausal women had lower inferior temporal GMV than premenopausal women and lower anterior/posterior corona radiata WMV than pre- and perimenopausal women. Perimenopausal women had lower precuneus and fusiform GMV than postmenopausal women. Results were substantially unchanged after accounting for hormone therapy and hysterectomy.	Postmenopause vs PRE ↓ inferior temporal GMV Postmenopause vs PRE & PERI ↓ anterior/posterior corona radiata WMV Perimenopause vs POST ↓ precuneus/fusiform GMV	Small sample size; limited generalizability; potential misclassification of exposure groups
100	Mutee, 2026	Higher SHBG was associated with lower temporal lobe volume in participants with MCI, but not in cognitively normal or Alzheimer disease groups.	Higher SHBG ↓ temporal lobe volume (MCI) SHBG ↔ temporal lobe volume (CN/AD)	Unbalanced group sizes; Possible residual confounding; Uncertain validity of SHBG as a biomarker; Scanner variability (1.5T vs 3T); SHBG measured only in serum, thus may not reflect activity in the brain (no CSF data)
50	Rahman, 2020	Menopausal status was associated with the GMV and WMV differences, with a gradient of increasing biomarker abnormality from premenopausal, perimenopausal, and postmenopausal women. MHT users showed nonsignificant trends toward larger GMV and WMV, while women with hysterectomy showed nonsignificant trends toward smaller volumes.	Menopausal status ↓ regional GMV/WMV (PRE > PERI >POST gradient) INS/C = insula/caudate, WM, amygdala, parahippocampalgyrus, MHT ↔ GMV/WMV Hysterectomy ↔ GMV/WMV	small sample size; could not confirm hormonal status in all the participants, so there may have been some error in classification; underpowered to look at specific symptom clusters; limited generalizability

26	Ryan, 2014	Current MHT users had lower gray matter volume relative to ICV and greater atrophy than never users. White matter volume, and corpus callosum area did not differ by MHT status.	Current MHT vs never users↓ GMV/ICV Current MHT vs never users ↑ atrophy MHT ↔ WMV, and corpus callosum area	those who agreed to participate were younger and overall better health; therefore, limited generalizability; data on HT was gathered retrospectively and is subject to recall errors; study size may have been inadequate to study in detail differential associations; did not investigate brain volumes within given structures except HC and CC, no longitudinal structural data
53	Schelbaum, 2021	Indicators of longer estrogen exposure were generally associated with larger regional GMV. Peri/postmenopausal status vs premenopausal was associated with lower inferior temporal GMV, while longer reproductive span, more children or pregnancies, and MHT or hormonal-contraceptive use were associated with larger GMV in selected frontal, temporal, parietal, precuneus, and fusiform regions. There were no significant associations between hysterectomy and age at menarche on GMV. In men, there was no significant association between number of children and GMV.	Peri/postmenopause vs PRE ↓ inferior temporal GMV Longer reproductive span ↑ parietal/precuneus GMV More children/pregnancies ↑ frontal/temporal GMV Having at least 2 children vs none ↑ GMV peak MHT use ↑ regional GMV (superior-frontal, supramarginal, middle/inferior-temporal, fusiform, frontal-pole, and medial-frontal regions) Hormonal contraceptive use ↑ regional GMV (precuneus, superior-parietal, angular, fusiform, and inferior-frontal) Hysterectomy ↔ GMV Age at menarche ↔ GMV Number of children (in men) ↔ GMV	Small sample size; Self-reported reproductive history; Missing key variables
44	Seitz, 2019	Overall regional brain volumes (inferior parietal cortex, anterior cingulate cortex, DLPFC) did not differ by menopause stage.	Menopause stage ↔ regional GMV	Potential unmeasured confounders; limited diversity, predominantly Caucasian; subgroups were small; uncertainty about long term complications
72	Steventon, 2023	Longer MHT use was associated with larger parahippocampal volume. Earlier menopause was associated with lower parahippocampal, perirhinal, and amygdala volumes, while longer reproductive span was associated with larger volumes in these regions.	Longer MHT ↑ parahippocampal volume Earlier menopause ↓ medial temporal volumes Longer reproductive span ↑ medial temporal volumes	both the ages at menarche and menopause were reliant on self-reported recall of past events that could not be verified with medical records; unmeasured confounders (e.g. blood pressure, historical and current lifestyle factors, such as smoking and exercise behaviors); not

				possible to assess the nature or route of MHT administration; biased towards European individuals, especially women of British/Irish ancestry, limiting the generalizability
11	Sullivan, 2005	There were no significant group effects for any of the brain volumes	Menopause stage ↔ temporal lobe volumes	Healthy volunteer sample
52	Than, 2021	Postmenopausal women had smaller total brain, gray matter, and white matter volumes and steeper age-related decline across global and multiple cortical regions (frontal, temporoparietal, occipital, opercular, and paracingulate cortices) than pre/perimenopausal women. MHT use did not modify the age–brain-volume association. SA: adjusting for secondary - did not alter findings.	Postmenopause vs pre/peri ↓ total brain, GMV, and WMV Postmenopause ↑ age-related volume decline	Menopause measurement is self-reported; Survival bias; Residual explanation; Large age separation between the menopause groups
74	Wugalter, 2024	Endogenous estrogens were not consistently associated with regional brain volumes. Isolated positive associations were observed between E2 and left caudal middle frontal volume and between E1 and left caudal middle frontal and fusiform volumes. However, estrogen associations depended on plasma AD biomarker profiles. Higher E2 was more positively associated with volume when the AD biomarker ratio was lower in the right frontal pole, left lateral orbitofrontal cortex, left pars orbitalis, left pars triangularis, left rostral-middle-frontal cortex, left transverse-temporal cortex, right caudal anterior cingulate, and left caudal-middle-frontal cortex. E1 showed a similar interaction pattern, additionally involving left pars opercularis and right rostral anterior cingulate. These estrogen–AD-biomarker interactions occurred mainly among APOE ε4 noncarriers and were not significant among carriers.	Endogenous E1/E2 ↔ most regional volumes Higher E2 ↑ left caudal middle frontal volume Higher E1 ↑ left caudal middle frontal/fusiform volume	Did not control for multiple comparisons but a priori limited our analyses to 21 ROIs in the temporal and prefrontal cortex, regions with higher densities of estrogen receptors. Some of the findings may be chance findings.
45	Zeydan, 2019	Women with BSO had smaller amygdala volume and thinner parahippocampal-entorhinal cortex than controls.	BSO ↓ amygdala volume BSO ↓ parahippocampal-entorhinal cortex thickness	small sample size;
58	Zhang, 2021	Early menopausal women had smaller left and right amygdala volumes.	Early menopause ↓ bilateral amygdala volume	cross-sectional study; incomplete hormone measurement (especially estradiol) because too low to detect; hormones measured in hospital setting, not a specialized lab thus

				limited sensitivity for low hormone levels; did not include women receiving HT this prevents testing whether estradiol replacement reverses brain changes
102	Zuhlsdorff, 2026	Postmenopausal women had lower entorhinal, and anterior cingulate gray matter volumes than premenopausal women. Within postmenopausal women, MHT users had lower anterior cingulate cortex volumes than nonusers.	Postmenopause ↓ EC/ACC GMV MHT ↓ ACC GMV vs non-MHT	cross-sectional study, possible reverse causation; population is healthier and less ethnically diverse than the general UK population; pre and postmenopausal groups were not separated based on STRAW criteria; self-report were used for grouping;

eTable 23 Hippocampal volume: Basic information and study characteristics

Study ID	First author, year	Country	Cohort	Study population	Study design	Follow-up duration in years, mean (SD)	Total analytical sample	Age, mean (SD)	% Female	Ethnicity	Cognition	APOE ε4 carrier %
6	Eberling, 2003	USA	Sacramento Area Latino Study of Aging (SALSA)	Community-dwelling cognitively normal and cognitively impaired older adults	Cross-sectional		59	ERT+ = 67.00 (60–77) (5.06) ERT- = 69.43 (60–83) (6.59)	100	Mexican American	3MS: ERT+ = 83.53 (9.58) ERT- = 82.43 (11.60)	
7	den Heijer, 2003	The Netherlands	Rotterdam Scan Study	Older men and women without dementia	Cross-sectional		563 (412 for total estradiol and 311 for bioavailable and free estradiol)	Women 70(8); Men 69(8)	50		Non-demented (MMSE mean 27.6 women; 27.8 men)	27% women; 32% men
9	Raz, 2004	USA		Healthy educated women	Cohort study with repeated measures	5 years	24	MHT users = 63.6 MHT non-users = 61.7	100	100% Caucasians	MMSE: Controls = 29.42 controls MHT user = 28.92	
11	Sullivan, 2005	USA		Healthy community-dwelling volunteer women	Cross-sectional		Subsample = 44		Subsample = 100%		MMSE ≥25	
15	Low, 2006	Australia	PATH (Personality And Total Health) Through Life' project	Postmenopausal women aged 60–64 years	Cross-sectional		213	62.6 (1.5)	100			
14	Irie, 2006	USA	Honolulu–Asia Aging Study (HAAS)	Japanese-American World War II–era older men	Cross-sectional		452	81.6 (5.08)	0	Japanese-American		
18	Lord, 2008	Canada		Community-dwelling adults	Cross-sectional		41 n=16 ET users;	ET users: 58.9 ± 6.4 years	100			

							n=10 Past users; n=15 never users	Past users: 65.9 ± 5.5 years Never users: 59.9 ± 7.6 years				
20	Resnick, 2009	USA	WHIMS & WHIMS-MRI	Postmenopausal women aged 65 years and older	RCT (double-masked, parallel randomized placebo controlled); post-trial cross-sectional MRI analysis	Scans were performed, on average, 3.0 years post-trial cessation for the CEE + MPA trial and 1.4 years post-trial cessation for the CEE-Alone trial; average on-trial follow-up intervals were 4.0 years for CEE + MPA and 5.6 years for CEE-Alone; MRI took place on average 8 years after WHI enrollment.	1403 CEE+MPA n=436; its placebo n=447; CEE alone n=257; its placebo n=263	78.5 (3.7)	100	>85% white, non-hispanic	Baseline 3MS categories <90/90–94/95–100: CEE+MPA 5.1%/15.2%/79.8%; corresponding placebo 4.3%/18.1%/77.6%; CEE alone 7.8%/19.6%/72.6%; corresponding placebo 7.3%/22.2%/70.5%	
22	Erickson, 2010	USA		postmenopausal women	Cross-Sectional Study		102 overall sample; but for main analyses - primary aim = 62 women	66.84 (5.7)	100			

							who had used HT					
25	Coker, 2014	USA	WHIMS-MRI2	Postmenopausal older women	RCT (parallel randomized placebo controlled); post-trial longitudinal repeated measures MRI study	4.7 after initial MRI scab (about 7.7yrs after termination of the treatment CEE+ MPA; or 6.1yrs after CEE alone)	1403 (n=674 with only MRI1; n=729 with scans at MRI1 and MRI2)	78.5 (3.7) at MRI1 82.8 (3.5) at MRI2 [76-92 years]	100	94% white, nonhispanic	In WHIMS-MRI1: 3MSE <90 = 8%; In WHIMS-MRI2: 3MSE <90 = 3%	
26	Ryan, 2014	France	ESPRIT study	Community-dwelling non-demented older women	cross-sectional		295	Never MHT median 7 1(IQR 68-75; past MHT 70(68-72); current 68(67-71)	100		nondemented; MMSE <=24: Never MHT 12.1%); past MHT 10%; Curent MHT 4.8%	295
27	Pintzka, 2015	Norway	HUNT MRI (substudy after HUNT3)	Postmenopausal women and controls between 50-65yrs	cross-sectional		160	51-66	100			
34	Braden, 2017	USA		Cognitively normal older adults	Cross-sectional study, with a small longitudinal subset.	Small longitudinal subset (n = 20) followed for ~3 years.	Overall = 94 (current =32; past =41; never =21) Longitudinal sample = 20 (n=7 current; 8 past; 5 never)	Overall: Current 71.7(10.5); Past 70.7(7.7); Never 72.4(11.7)	100	Overall sample = Caucasian (80%)		Overall: Current n=8; Past n=9; Never n=5
35	Albert, 2017	USA		Cognitively healthy postmenopausal women	Pooled RCT; Prospective intervention study	3 months of treatment	75	58.19 (5.42)	100		Cognitively unimpaired	

43	Mosconi, 2018	USA		Community-recruited, cognitively normal women at different menopausal stages participating in brain imaging studies.	Cohort	Pre 3 (0.5); Peri 3(0.5); Post 2(0.4)	41 (pre 15; peri 14; post 12)	Pre 47(5); Peri 53(4); Post 58(2)	100	Pre 73%; Peri 75%; Post 42%		Pre 47%; Peri 50%; Post 42%
45	Zeydan, 2019	USA	The Mayo Clinic Cohort Study of Oophorectomy and Aging-2 (MOA-2) and The Mayo Clinic Study of Aging (MCSA)	Community-dwelling women within a medical records–linkage system enabling population-based research	Nest case-control		43	The median (interquartile range [IQR]) age at imaging was 65 (62-68) years in the BSO group and 63 (60-66) years in the control group. Controls were age-matched	100			BSO 9%; control 20%
48	Xu, 2020	China; USA/Canada	Chinese Alzheimer's Biomarker and LifestylE (CABLE) study; ADNI	ADNI: Non-demented adults from multicenter consortium (academic/clinical centers), including CN and those with MCI.	ADNI (USA multicenter) → longitudinal	Average follow-up for mixed model not provided but "In the ADNI cohort for incident AD dementia, 199 subjects were lost to follow-up and 237 were finally	ADNI (longitudinal): Baseline sample: n = 448; Subset with both plasma & CSF SHBG: n = 188	ADNI: 74.8 ± 7.2 years	ADNI: ~37%	ADNI: Predominantly non-Hispanic White (~93.3%)	MMSE ADNI: 27.3 ± 1.8	ADNI: 47.5%

						included (with a follow-up duration of 3.2 ± 2.4 years), among whom 164 subjects (36%) developed AD dementia."						
51	Ambikairajah, 2020	UK	UKB	Community-dwelling premenopausal and postmenopausal women	Cross-sectional		Overall = 5072 Premenopausal = 735 Postmenopausal = 4337	60.32 (7.11)	100	mainly white		
46	Jung, 2020	South Korea	Korean Brain Aging Study for Early Diagnosis and Prediction of Alzheimer's Disease (KBASE)	Older women with normal cognition or MCI; community- and memory clinic–recruited.	Cross-sectional		Overall = 237 other imaging =233	70.45 (7.68)	100	Korean	MMSE = 24.93 (3.55)	24.9%
51	Ambikairajah, 2020	UK	UKB	Community-dwelling premenopausal and postmenopausal women	Cross-sectional		Overall = 5072 Premenopausal = 735 Postmenopausal = 4337	60.32 (7.11)	100	mainly white		
72	Steventon, 2023	UK	UKB	Community-dwelling postmenopausal women	Cross-sectional		10924	63.41(6.65)	100	British/Irish ancestry		
72	Steventon, 2023	UK	UKB	Community-dwelling postmenopausal women	Cross-sectional		10924	63.41 (6.65)	100	British/Irish ancestry		
85	Barth, 2025	UK	UKB	Community-dwelling women	Cross-sectional		Overall = Complete	MHT user status:	100	MHT user status:		MHT user status:

							data related to MHT user status = 19,846 (14,693 with APOEε4 status) Among MHT users, subsample with complete MHT-related prescription data and MRI data = 538 (521 with APOEε4 data)	never = 61.6±7.1 current = 60.1±6.8 past = 67.5±6.2		White never = 96.60 current = 98.0 past = 98.2		never = 27.5 current = 26.2 past = 24.7
97	McGrath, 2025	USA	FHS Offspring cohort		Cross-sectional		MRI subsample = 1165	MRI subsample = 60.4 (9.4)	100		Without dementia	22.9
97	McGrath, 2025	USA	FHS Offspring cohort	Cognitively healthy women	Cross-sectional		MRI subsample = 1165	MRI subsample = 60.4 (9.4)	100		Without dementia	22.9
97	McGrath, 2025	USA	FHS Offspring cohort	Cognitively healthy women	Cross-sectional		MRI subsample = 1165	MRI subsample = 60.4 (9.4)	100		Without dementia	22.9
90	Kantarci, 2026	USA	KEEPS Continuation	Healthy recently postmenopausal women with good cardiovascular health	Cross-sectional analysis [Observational follow-up of a randomized, double-blind, placebo-controlled trial]	~14 years post-randomization' around 10 years post RCT completion	whole group = MRI keep continuation = 266	whole group = 67 (2)	100			whole group = 26%
102	Zuhlsdorff, 2026	UK	UKB	Community-dwelling women	cross-sectional		Imaging subsample = 10873	65.53 (7.22)	100		Without dementia	

eTable 24 Hippocampal volume: Methods and Materials

Study ID	First author, year	Exposure	Exposure ascertainment	Outcome	Outcome ascertainment	Covariates adjusted for in models	Statistical Analysis
6	Eberling, 2003	ERT: current user or not	participant interview and verified using current medication prescriptions	Hippocampal volumes (total, by hemisphere [left, right], and by subregion [anterior, posterior])	MRI; The term "hippocampus" includes the dentate gyrus, the hippocampus proper (CA3, CA2, and CA1), the subiculum, and the pre- and parasubiculum; normalized by dividing by ICV.		Group differences in hippocampal volume by MHT status were assessed using t-tests.
7	den Heijer, 2003	Plasma: estradiol (total, bioavailable, and free)	blood-based (plasma): double antibody radioimmunoassays	Total hippocampal volume	MRI; bilateral sum; Assessment performed a median of 2.9 years after blood collection.	age at time of venipuncture, midsagittal area to account for ICV, BMI, educational level, smoking, alcohol use, CES-D score, APOE genotype, and for women, age at menopause, type of menopause, and ever taking HRT.	ANCOVA-adjusted mean comparing hippocampal volumes across tertiles of total, bioavailable, and free estradiol. Multivariable linear regression to estimate the association between total estradiol levels (per 1 SD increase) and hippocampal volume. SA: Age-stratified analyses (<70 vs ≥70 years), APOE ε4 stratified analyses, repeated analyses excluding women with a history of MHT use.
9	Raz, 2004	HRT users vs Control (age- and education matched women who did not take hormonal replacements)	Self-reported	Hippocampal volume	MRI; adjusted for the ICV via a formula based on the analysis of covariance approach; measured twice over 5 years.	age (centered at sample mean), hypertension status, and time	ordinary least-squares model with repeated measures. Interaction with time and HRT.
11	Sullivan, 2005	Menopausal status:	Not clearly stated.	Total hippocampal volume (left, right)	MRI; Only main body and head included,		One-way ANOVA

		1. Pre-menopausal 2. Postmenopausal and using HRT 3. Postmenopausal and not using HRT			while unclear anterior and posterior portions excluded; uncorrected volumes and corrected for ICV-volume.		
15	Low, 2006	HRT use status: current users, previous users, never users (ref)	Self-reported	Hippocampal volume (left, right)	MRI	controlling for education and ICV.	ANCOVA
14	Irie, 2006	Tertiles (low [ref], middle, high) of: 1. Bioavailable testosterone 2. Bioavailable estradiol 3. SHBG	blood-based (serum): standard immunoassays; measured approximately 3 years before MRI.	Hippocampal atrophy: (yes or no); defined as the lowest quartile of total hippocampal volume measured on MRI.	MRI; adjusted for head size.	Age, education, dementia status, apoE4 genotype, mid-life SBP, DBP, and smoking status, late-life BMI, total cholesterol, diabetes, and other sex hormones. Bioavailable testosterone as exposure: adjusted for estradiol; BioEstradiol: adjusted for testosterone; SHBG: adjusted for estradiol and testosterone as other sex hormones in model 2. For hippocampal atrophy - adjusted for brain lesion; results changed; so not shown.	Logistic regression.
18	Lord, 2008	ET users, past users, never users	not explicitly stated; self-reported implied	Hippocampal volume (left, right)	MRI	Age	A mixed-design ANCOVA was used to compare hippocampal volumes across groups, with

							hemisphere as a repeated measure.
20	Resnick, 2009	Women randomized to: CEE + MPA, CEE alone or placebo.	0.625mg/d CEE therapy alone in women after hysterectomy and in combination with 2.5mg/d MPA in women with uterus vs placebo controlled	Total hippocampal volume	MRI	Age at enrollment, time between enrollment and scanning, ICV, clinical center site, other baseline dementia risk factors (education, ethnicity, smoking status, BMI, hypertension, prior CVD, diabetes, prior HT, and baseline 3MS score)	ANCOVA SA/subgroup analysis: Interaction by baseline 3MS cognitive score strata (<90, 90–94, 95–100). Stratified by ischemic lesion burden (<2 cm^3 vs ≥2 cm^3). Propensity-score adjusted analyses.
22	Erickson, 2010	Timing of HT relative to menopause, continuous Timing of HT relative to menopause, 3 categories: 1. Never HT user 2. HT initiated with menopause (approx. near the time of menopause) 3. HT initiated 1-18 years post-menopause	Self-reported HT history. HT initiation within 12 months of the final menstrual period was classified as coincident with menopause. Age at menopause could be defined by three events: (a) 12 months of amenorrhea, (b) age at HT initiation for women who had not yet experienced amenorrhea, and (c) age at bilateral oophorectomy or hysterectomy.	Hippocampal volume (left, right)	MRI; ICV used to adjust hippocampus volumes using a regression-based approach; hippocampus volume comprised the dentate gyrus, the ammonic subfields (CA1-4), the prosubiculum, and the subiculum and did not include the fimbria/fornix behind the posterior commissure.	Age, years of education, age at menopause, duration of HT, hormone status (current or past HT use) and hormone type (unopposed CEE, CEE with MPA, or phytoestrogens).	Multiple linear regression examining the association between the interval from menopause to HT initiation (Δ) and hippocampal volume. ANCOVA/adjusted group comparisons to compare brain volumes across HT timing groups. SA: = removed those receiving phytoestrogens as treatment of menopausal symptoms and reran analyses.
25	Coker, 2014	Women randomized to: CEE + MPA, CEE alone or placebo.	0.625mg/d CEE therapy alone in women after hysterectomy and in combination with 2.5mg/d MPA in women with uterus vs placebo controlled	Rates of change in hippocampal volume.	MRI	Trial (CEE-alone vs CEE+MPA), visit, clinical site, age, ICV, and time from randomization to MRI scan.	Longitudinal mixed-effects models; compound symmetry model was used for intrasubject correlations; An interaction term for time between scans and treatment assignment was

							used to compare study arms. Subgroup analyses: Interactions by age, baseline 3MSE scores, prior HT, and history of cardiovascular disease. SA: Propensity score analysis to assess potential bias from loss to follow-up.
26	Ryan, 2014	HT use status: women never HT users (ref), women past HT users, and women current HT users.	Self-reported; Medication use verified by prescription or medication packaging when available; Past users were shown photographs to aid recall.	Total hippocampal volume	MRI; expressed as a ratio of ICV.	Age, education level, history of cardiovascular disease, hypertension, and number of medications currently used.	Linear regression SA: Additional adjustment for other health and cognitive variables. Analyses repeated excluding participants with MMSE ≤24
27	Pintzka, 2015	HT use status: HT initiated before menopause and continued through menopause for ≥3 years (current and past users) vs. never HT users (controls: matched on age [±1 year] and ICV [±5%]).	Self-reported; mean HT duration: 7.8 ± 3.4 years (range 3–15 years).	Total hippocampal volume (left, right); Hippocampal shape (vertex analysis/subfield-level localization)	MRI; corrected for ICV.		Mixed ANOVA for total hippocampal volume. Separate ANOVAs for right and left hippocampi. Vertex-based shape analysis (FIRST/FSL).
34	Braden, 2017	HT use status: Current HT users, past HT users, and never users.	Self-reported; When possible, women were asked to bring in their prescriptions to confirm accuracy and reliability of self-report. All participants maintained their HT status during the time from baseline to follow-up.	Left and right hippocampal volume (% total brain volume).	MRI	Age, education, and time between visits (for longitudinal).	ANCOVA for group differences; Repeated measures ANCOVA was used to assess longitudinal hippocampal volume loss; interaction between time and HT use. Time (baseline vs follow-up) Group (current HT, past HT, never HT)
35	Albert, 2017	Pooled from two clinical trials: Estradiol (E2) treatment:	Estradiol treatment groups: Participants received placebo, 1 mg/day estradiol (double-	Hippocampal gray matter volume (left, right); voxel-wise gray	MRI; volumes were normalized to intracranial volume; modulated voxel-	Age	Univariate ANCOVAs comparing placebo, 1 mg estradiol, and 2 mg estradiol groups on pre–post changes

		Placebo, Estradiol 1 mg/day, Estradiol 2 mg/day.	blind), or 2 mg/day estradiol following dose titration from 1 mg/day during the first month (open-label). The two active treatment arms came from different protocols (double-blind placebo-controlled vs open-label dose-escalation),	matter within the hippocampus	based morphometry to identify regional gray-matter changes within the hippocampus.		in left and right hippocampal volume and voxel-wise hippocampal gray-matter volume (mVBM); adjusted for age and intracranial volume.
43	Mosconi, 2018	Menopausal status: asymptomatic perimenopausal by age, perimenopausal, and postmenopausal	Clinical judgment, medical records, and detection of cluster symptoms according to the STRAW criteria. Asymptomatic perimenopausal women by age (e.g., regular cyclers, or premenopausal control, CNT); symptomatic perimenopausal women (e.g., irregular cyclers, PERI); postmenopausal women (e.g., no menstrual cycles for ≥12 months, MENO).	Hippocampal volume	MRI	Age, education, APOE e4 status, vascular risk measures, TIV	Targeted minimum loss-based estimation (TMLE) to compute adjusted means for each group. TMLE uses a preliminary estimator of the outcome regression and propensity score to construct a doubly robust estimator that remains consistent under misspecification of either model.
45	Zeydan, 2019	Women who underwent BSO before age 50 and before reaching natural menopause and and an age-matched control group who had not undergone bilateral oophorectomy before age 50 years.	Record linkage	Hippocampal volume Amygdala volume		ICV	Wilcoxon rank sum tests, rank regression tests adjusted for ICV to compare BSO and control groups
48	Xu, 2020	Plasma: SHBG; categorized high vs	Plasma (blood-based); overnight fasting; Human SHBG ELISA kit (CABLE	Change in hippocampal volume over time (hippocampal atrophy)	MRI. Multiple scanners.	Age, gender, education, APOE ε4	Linear mixed-effects models. Models included random

		low based on median split	study), Multiplex immunoassay panel on the Luminex xMAP platform (ADNI)			status, and baseline clinical diagnosis.	intercepts and slopes for time and tested the interaction between time × plasma SHBG. SA: excluding those who developed dementia whine one year since baseline; repeated all analyses after further adjusting for plasma levels of total testosterone (TT) or free testosterone index (FTI) which were calculated by dividing TT by SHBG.
51	Ambikairajah, 2020	Menopausal status 1. Premenopausal women 2. Postmenopausal women	self-reported	Total hippocampal volume	MRI; bilateral sum; adjusted for head-size.	Age, smoking history, waist circumference, educational attainment, physical activity, frequency of alcohol intake, number of children, vascular/heart problems, and diabetes	Multiple linear hierarchical regression. SA: Propensity score matching (age, smoking, waist circumference, education, physical activity, alcohol intake, number of children, vascular/heart problems, and diabetes), followed by linear regression to compare total brain and hippocampal volumes between matched menopausal-status groups.
46	Jung, 2020	Number of deliveries (parity): 1. 0-4 parity (reference) 2. grand multiparity (>=5 births)	systematic interviews implemented by trained nurses.	Hippocampal volume	MRI; bilateral sum; ICV-adjusted hippocampal volume (residual from linear regression using young cognitively normal as reference)	Model 1: age, years of education, APOE4 positivity, and cognitive status (i.e., CN vs. MCI) Model 2: Model 1 + Vascular risk score, income level at early adulthood, level of lifetime occupation, age at menarche age, and age at menopause.	Linear regression

51	Ambikairajah, 2020	Age of menopause (centered at 45 years) Age of menarche Duration of reproductive stage	Self-reported	Total hippocampal volume	MRI; bilateral sum; adjusted for head-size.	Age, smoking history, waist circumference, educational attainment, physical activity, frequency of alcohol intake, number of children, vascular/heart problems, and diabetes	Multiple linear hierarchical regression.
72	Steventon, 2023	HRT duration. HRT initiation age (relative to menopause). Years since last HRT use	Self-reported	Total hippocampal volume (primary) Hippocampal subfield volumes (secondary): CA1 CA2/3 CA4 Dentate gyrus (DG)	MRI; bilateral sum.	Age at the time of MRI scan, education, socioeconomic status, hemispheres, normalized grey matter volume, MRI scan site, head motion from resting fMRI, and z-table position in the scanner, height and weight. Also adjusted for other reproductive and HRT-related predictors. All predictors entered together except for reproductive span (not including age at menarche and age at menopause). Additional predictors included HRT duration, years since last HRT use, age at HRT initiation.	Multiple linear regression; corrected for multiple comparisons.
72	Steventon, 2023	Age of menopause Age of menarche Reproductive span	Self-reported	Total hippocampal volume (primary) Hippocampal subfield volumes (secondary):	MRI; bilateral sum.	Age at the time of MRI scan, education, socioeconomic status, hemispheres, normalized grey	Multiple linear regression; corrected for multiple comparisons.

		Age at first live birth		CA1 CA2/3 CA4 Dentate gyrus (DG)		matter volume, MRI scan site, head motion from resting fMRI, and z-table position in the scanner, height and weight. Also adjusted for other reproductive and HRT-related predictors. All predictors entered together except for reproductive span (not including age at menarche and age at menopause). Additional predictors included HRT duration, years since last HRT use, age at HRT initiation.	
85	Barth, 2025	Whole sample: MHT variables 1. user status 2. age first started using MHT, 3. age last used MHT, 4. duration of MHT use (age last used - age first used) Prescription sample: 1. MHT formulation type 2. MHT route of administration 3. Daily drug dosage (mg) 4. Duration of use (weeks) 5. Formulation further	Self-reported; In current MHT users, the age at last use set to their age at the imaging assessment to calculate duration of use; In subsample of participants, MHT regimes based on prescription data were extracted from primary care records (general practice).	Hippocampal volume (left, right)	MRI; ICV-adjusted using revisualization using linear models; standardized.	Whole sample: Model 1 = age, education, lifestyle score [based on a published formula and includes data on sleep, physical activity, nutrition, smoking, and alcohol consumption], BMI, menopause status for each MHT variable analysis (i.e. MHT user status, age at first use, age at last use, duration of use) Prescribed sample: Model 2: adjusted for	linear models; p-values corrected for multiple comparisons FDR Whole sample: General MHT analyses on brain measures 1. Effect of MHT user status: User vs never-user; Never-user vs current-or past user 2. Effect of MHT variables: Age at first MHT use; Age at last MHT use; Duration of MHT use 2.1 Among postmenopausal MHT users - age started MHT – age at menopause; age last use MHT – age at menopause [these models not adjusted for menopause] 3. Effect of proxied indication

		categorized = bioidentical & synthetic; progestins stratification by generation				age, education, menopause status to retain the largest sample size possible. Additionally, covariates: adjusting for history of hysterectomy and/or bilateral oophorectomy [for MHT formulation and route of administration]. Estrogens-only MHTs - included surgical history as a covariate instead of excluding participants with surgical history	of MHT use: user with bilateral oophorectomy vs. user with no such surgery; user with hysterectomy vs. MHT user with no such surgery. 4. Interaction effect APOE e4 status by MHT measures. Excluded participants with a history of hysterectomy and/or bilateral oophorectomy were excluded from the main MHT analyses. SA for whole sample: exclusion ICD-10 diagnosis; addition of age2 as a covariate; exclusion extreme values [data-driven approach MAD method using default setting], additional covariates Prescription sample: Detailed MHT analyses on brain measures 1. Effect of MHT formulation type: never-use (ref) vs estrogens-only or estrogens + progestins 2. Effect of MHT route of administration: never-use vs oral or transdermal or vaginal or injections or mixed 3. In estrogens-only users = 3.1. Estrogen-only forms: never-user vs bioidentical or synthetic 3.2. Estrogen-only, active ingredient: estradiol or estradiol valerate or estradiol

							hemihydrate or CEE or mixed vs none 3.3. Estrogens-only, Dosage (mg) 3.4. Estrogens-only, Duration of Use (weeks) 4. In estrogens + progestin users: 4.1. form = never-user vs Bioidentical or Synthetic or Bioidentical & Synthetic 4.2. active ingredient = never-user vs estradiol hemihydrate & norethisterone acetate or estradiol hemihydrate & dydrogesterone or estradiol hemihydrate & norethisterone or CEE & norgestrel or CEE & medroxyprogesterone acetate or tibolone or mixed 4.3. Progestin Generation = never-user vs 1stGen or 2ndGen 4.4. Estrogens + Progestins, Dosage (mg): Estrogens and Progestins in same model 4.5. Estrogens + Progestins, Duration of use (weeks): Estrogens and Progestins in same model 5. Interaction effect APOE e4 status by MHT measures SA: exclusion ICD-10 diagnosis; match never-user group [genetic matching without replacement; matched based on model 2]; additional covariates
97	McGrath, 2025	Postmenopausal hormone replacement	self-reported	Total hippocampal volume	MRI	Age, age squared, time between baseline	Age, age squared, education status, time between

		therapy (pmHRT) use (current or prior use after menopause; yes/no)				and MRI brain, ICV. In a secondary model, additionally adjusted for prevalent CVD, diabetes mellitus, age at menopause (for the model with pmHRT as the predictor), menopausal status and pmHRT use (for models with serum estradiol and estrone as predictors) and cause of menopause (for the model with age at menopause as the predictor).	baseline and MRI brain, intracranial volume
97	McGrath, 2025	Serum: estradiol, estrone	Blood-based (serum): LC-MS/MS (estradiol, estrone); overnight fast; log-transformed.	Total hippocampal volume	MRI.	Age, age squared, time between baseline and MRI brain, ICV. In a secondary model, additionally adjusted for prevalent CVD, diabetes mellitus, age at menopause (for the model with pmHRT as the predictor), menopausal status and pmHRT use (for models with serum estradiol and estrone as predictors) and cause of menopause (for the model with age at menopause as the predictor).	Linear regression. SA: (1) including those with natural menopause and excluding those with surgical, radiation or chemotherapy-induced menopause, (2) excluding those with extremely early menarche (≤9y) or very delayed menarche (≥16y), and (3) excluding those on pmHRT for the model evaluating age at menopause (as women with very early menopause may be started on pmHRT, confounding the association).
97	McGrath, 2025	Age at menarche: ≤11y, 12–13y (reference), and ≥14y. Age at menopause:	Self-reported; Age at menopause was self-reported by participants as the age at which periods had stopped for ≥1 year.	Hippocampal volume	MRI	Age, age squared, time between baseline and MRI brain, ICV. In a secondary model,	Linear regression. SA: (1) including those with natural menopause and excluding those with

		≤49y, 50–51y (reference), and ≥52y. Reproductive lifespan Number of live births: 0 (reference), 1–2, and ≥3.	Use of pmHRT was defined as previous or current use of HRT at or after the individual's age at menopause.			additionally adjusted for prevalent CVD, diabetes mellitus, age at menopause (for the model with pmHRT as the predictor), menopausal status and pmHRT use (for models with serum estradiol and estrone as predictors) and cause of menopause (for the model with age at menopause as the predictor). For MRI outcomes, we performed a post-hoc exploratory subgroup analysis by age (<60y versus ≥60y at baseline).	surgical, radiation or chemotherapy-induced menopause, (2) excluding those with extremely early menarche (≤9y) or very delayed menarche (≥16y), and (3) excluding those on pmHRT for the model evaluating age at menopause (as women with very early menopause may be started on pmHRT, confounding the association).
90	Kantarci, 2026	Hormone therapy groups: Oral CEE Transdermal 17β-Estradiol Placebo [reference]	Participants were randomized to either: 1) oral conjugated equine estrogen (CEE; Premarin, 0.45 mg/day); 2) transdermal 17β-estradiol (skin patch, Climara, 50 µg/day); or 3) placebo pills and patch. Progesterone was given orally (Prometrium; micronized progesterone, 200 mg/day) for the first 12 days each month to both active treatment groups. Participants were treated for four years.	Hippocampal volume	MRI	Age, site of assessment, APOE ε4 carrier status, ICV	Statistical comparisons of the oCEE versus placebo, and tE2 versus placebo groups on imaging biomarker outcomes were conducted using a multivariable linear regression model. SA: repeat analyses excluding participants who used systemic MHT after cessation of randomized treatment.
102	Zuhlsdorff, 2026	Menopausal status: 1. Pre-menopausal (reference)	Self-reported	Hippocampal gray matter volume	MRI	Age, household income, level of education, smoking status, BMI, time	Linear models.

		2. Postmenopausal and using HRT 3. Postmenopausal and not using HRT				since menopause onset, and HRT duration, insomnia, sleep duration, tiredness, and cognitive task analyses, a history of depression, TIV	

eTable 25 Hippocampal volume: Overall findings and limitations

Study ID	First author, year	Main Finding	Direction of association	Key limitations
6	Eberling, 2003	ERT users had larger right and anterior hippocampal volumes than non-users; no differences were observed for left or posterior hippocampal volumes.	**Group differences:** ERT+ women vs MHT- women → ↑ right hippocampal volume. ERT+ women vs ERT- women ↔ left hippocampal volume. ERT+ women vs ERT- women → ↑ anterior hippocampal volume. ERT+ women vs ERT- women ↔ posterior hippocampal volume.	Sample limited to elderly Mexican American individuals with varied health conditions and lower education levels, potentially affecting brain measures and limiting generalizability to other populations. No information on ERT duration and whether the women currently not taking ERT ever took ERT.
7	den Heijer, 2003	In women, ANCOVA analyses showed that those in the highest tertiles of total, bioavailable, and free estradiol had smaller total hippocampal volumes than those in the lowest tertiles, whereas no significant associations were observed in men. However, in multivariable linear regression analyses, continuous total estradiol was not significantly associated with total hippocampal volume after full adjustment. The inverse association between estradiol levels and total hippocampal volume was strongest among women aged ≥70 years. Exclusion of women with previous MHT/HRT use (n = 17); findings were unchanged. APOE ε4-stratified analyses suggested a stronger inverse association between estradiol levels and hippocampal volume among APOE ε4 carriers; however, no significant interaction with APOE ε4 status was observed.	Women: Highest vs lowest tertile of total estradiol → ↓ total hippocampal volume. Highest vs lowest tertile of bioavailable estradiol → ↓ total hippocampal volume. Highest vs lowest tertile of free estradiol → ↓ total hippocampal volume. Total Estradiol ↔ total hippocampal volume. Men: Highest vs lowest tertile of total estradiol ↔ total hippocampal volume. Highest vs lowest tertile of bioavailable estradiol ↔ total hippocampal volume. Highest vs lowest tertile of free estradiol ↔ total hippocampal volume. Total Estradiol ↔ total hippocampal volume.	Substantial missing data were present for bioavailable and free estradiol because insufficient plasma was available for these measurements in a proportion of participants. Blood samples for estradiol assessment were collected a median of 2.9 years before MRI, making it difficult to determine whether estradiol levels at the time of blood collection accurately reflected hormone exposure at the time hippocampal volume was measured. The findings may have limited generalizability, as current HRT users were excluded and HRT use was relatively uncommon in the Netherlands in 1990-1993 compared with countries such as the USA.
9	Raz, 2004	Both HRT users and non-users showed significant hippocampal shrinkage over 5 years. The magnitude of hippocampal shrinkage was comparable between groups, indicating no protective effect of HRT on hippocampal volume.	HRT use vs age- and education matched controls ↔ hippocampal volume decline.	Limited information on menopausal status. Exact timing of HRT initiation was unavailable. Individual hormone levels and therapeutic doses were not assessed. HRT regimens were heterogeneous (different hormone formulations and combinations).

11	Sullivan, 2005	There were no significant differences in brain volumes between premenopausal women, postmenopausal women not using HRT, and postmenopausal women using HRT.	No group differences.	Healthy volunteer sample
15	Low, 2006	No significant group differences in right or left hippocampal volume were observed between current, previous, and never HRT users.	Group differences: Current HRT users vs never users ↔ right hippocampal volume. Current HRT users vs never users ↔ left hippocampal volume. Previous HRT users vs never users ↔ right hippocampal volume. Previous HRT users vs never users ↔ left hippocampal volume.	'Healthy volunteer' bias, and a relatively young sample in terms of brain ageing, may have resulted in less overall neuropathology, decreasing any observable effect. HRT use self-reported without data on dose. Potential selection bias: The sample was not fully representative. Never HRT users had higher education and verbal intelligence than current users, suggesting systematic differences between the three groups.
14	Irie, 2006	No association between serum bioavailable testosterone, serum bioavailable estradiol, or serum SHBG and hippocampal atrophy.	Serum bioavailable testosterone ↔ hippocampal atrophy Serum bioavailable estradiol ↔ hippocampal atrophy Serum SHBG ↔ hippocampal atrophy	
18	Lord, 2008	Current ET users, past ET users, and never users did not differ significantly in left or right hippocampal volume after correction for multiple comparisons.	Group differences: ET use ↔ left and right hippocampal volume (after multiple-comparison correction).	Potential residual confounding from unmeasured factors (e.g., fitness, personality, menopausal symptoms). Potential selection bias, with ET users potentially representing a distinct subgroup that differed from non-users in demographic or behavioral characteristics. Possible treatment-seeking bias.
20	Resnick, 2009	Mean hippocampal volume was lower in women assigned to HT than placebo, with similar effects observed for both CEE+MPA and CEE-alone. HT-associated reductions in hippocampal volume were greatest among women with lower baseline cognitive function (3MS <90) and among those with greater ischemic lesion burden (≥2 cm^3). Propensity score adjustment to account for differential enrollment in WHIMS-MRI did not materially alter the results.	Group differences: HT (CEE ± MPA) vs placebo → ↓ total hippocampal volume.	Limited generalizability to older women initiating HT at ≥65 years; effects in younger postmenopausal women were not examined. MRI scans were obtained post-trial (mean 3.0 years after CEE+MPA and 1.4 years after CEE-alone), with no pretreatment MRI, preventing assessment of change from baseline. Automated image-processing methods may be susceptible to registration errors, particularly in small brain regions.

				More refined regional analyses (e.g., voxel-based approaches) may detect effects not captured by the current methodology.
22	Erickson, 2010	Shorter intervals between menopause and hormone initiation are associated with larger hippocampi. Women who initiated HT at the time of menopause had larger left and right hippocampal volumes than women who had never used HT and women who initiated HT 1–18 years after menopause. In contrast, women who initiated HT more than 1 year after menopause did not differ from never users in hippocampal volume.	Longer interval between menopause and HT initiation → ↓ left hippocampal volume. Longer interval between menopause and HT initiation → ↓ right hippocampal volume. HT initiation at menopause vs never HT use → ↑ left hippocampal volume. HT initiation at menopause vs never HT use → ↑ right hippocampal volume. HT initiation at menopause vs HT initiation 1–18 years postmenopause → ↑ hippocampal volume. HT initiation >1 year postmenopause vs never HT use ↔ hippocampal volume	Potential residual confounding from unmeasured factors that may covary with MHT use or timing of MHT initiation. Possible confounding by indication, selection bias, and healthy-user bias, which may partly explain the observed associations.
25	Coker, 2014	No evidence that women assigned to HT had faster hippocampal atrophy between MRI1 and MRI2 than placebo. Women assigned to HT continued to show a trend toward smaller hippocampal volumes than placebo at follow-up. HT-associated hippocampal volume reductions were greatest among women with the lowest baseline cognitive function (<90). [mean volume difference] Propensity score analysis; results unchanged.	HT (CEE ± MPA) vs placebo ↔ rate of hippocampal volume decline over 4.7 years.	
26	Ryan, 2014	No significant differences in hippocampal volume were observed for past HT users or current HT users relative to women who never used HT.	Past HT users vs never HT users ↔ hippocampal volume Current HT users vs never HT users ↔ hippocampal volume	Participants who agreed to participate were generally younger and in better health, limiting generalizability to the broader older population. HT exposure was assessed retrospectively, making the data susceptible to recall bias and misclassification.

				The sample size may have been insufficient to examine detailed associations according to specific HT characteristics (e.g., formulation, duration, timing).
27	Pintzka, 2015	Perimenopausal HT users had larger right hippocampal volumes than matched never-users and showed relative sparing of the right CA1/subiculum region. No significant difference was observed in left hippocampal volume.	Group differences: HT users vs never users → ↑ right hippocampal volume HT users vs never users ↔ left hippocampal volume HT users → regional sparing of the right CA1 subfield and part of the subiculum (shape analysis)	No distinction between current and past HT users, preventing assessment of persistent versus transient effects. No direct hippocampal subfield measurements; CA1/subiculum findings were inferred from shape analysis rather than subfield segmentation. Potential selection bias, as HUNT MRI participants were somewhat healthier and more educated than non-participants. No individual-level information on HT formulation or dose; HT exposure was not precisely characterized.
34	Braden, 2017	Longitudinal analyses compared all three groups (current, past, never HT users) and found no significant time × group interaction, indicating that hippocampal volume decline over time did not differ between groups. No evidence was found that postmenopausal HT use impacts longitudinal age-related hippocampal volume loss or age-related volumetric differences in cross-sectional analysis.	Cross-sectional: no group differences. Longitudinal repeat measures ANCOVA: Current HT users vs past HT users vs never HT users ↔ rate of hippocampal volume decline.	Small longitudinal sample with substantial attrition, likely underpowered to detect differences in hippocampal volume change. Potential residual confounding due to limited data on other health factors that may influence brain outcomes. Methodological heterogeneity, including use of different MRI scanners.
35	Albert, 2017	The main finding of the present study was that daily 2 mg 17b-estradiol administered over 3 months was associated with increased bilateral posterior hippocampal gray-matter volume. This effect was seen primarily in women who received 2 mg daily 17-b estradiol with no significant change in hippocampal gray-matter volume in women who received placebo or 1 mg daily 17-b estradiol. They did not observe any effects of E2 administration on total hippocampal gray-matter volume.	ROI-analysis: group differences Estradiol dose (placebo vs 1 mg vs 2 mg) ↔ left hippocampal volume change (pre to post). Estradiol dose (placebo vs 1 mg vs 2 mg) ↔ right hippocampal volume change (pre to post). mVBM: 2 mg estradiol vs placebo → ↑ bilateral posterior hippocampal gray-matter volume. 2 mg estradiol vs 1 mg estradiol → ↑ bilateral posterior	

			hippocampal gray-matter volume. Placebo vs 1 mg estradiol ↔ posterior hippocampal gray-matter volume. Higher estradiol dose → ↑ bilateral posterior hippocampal gray-matter volume (positive dose-effect in the voxel-wise analysis)	
43	Mosconi, 2018	MENO group exhibited the highest rate of hippocampal volume loss compared to all groups. Hippocampal volumes decreased in the MENO group and showed minimal to no decline in the other groups.	MENO vs PERI/PRE ↓ hippocampal volume	Small sample size, limiting power; Menopausal status not hormonally confirmed, creating potential misclassification. Highly selected healthy cohort with short (3-year) follow-up, limiting generalizability and long-term prediction of AD outcomes.
45	Zeydan, 2019	Women who underwent bilateral salpingo-oophorectomy (BSO) before age 50 and before natural menopause had a smaller hippocampal volume than age-matched controls; however, the difference did not reach statistical significance. Women who underwent bilateral salpingo-oophorectomy (BSO) before age 50 and before natural menopause had significantly smaller amygdala volumes than age-matched controls.	premenopausal BSO vs age-matched controls ↔ no hippocampal volume difference premenopausal BSO vs age-matched controls → ↓ smaller amygdala volume in BSO	Small sample size
48	Xu, 2020	Higher levels of plasma SHBG were associated with faster hippocampus atrophy. SA barely changed results.	Higher plasma SHBG → ↑ hippocampal atrophy (↓ hippocampal volume over time).	Plasma SHBG was measured in singlicate, increasing risk of measurement error. Some subgroup analyses (e.g., by sex) had limited sample size, reducing reliability. Loss to follow-up in longitudinal analyses may affect validity.
51	Ambikairajah, 2020	Postmenopausal women had larger total hippocampal volumes than premenopausal women, and the association persisted after propensity score matching.	Postmenopausal status (vs. premenopausal status) → ↑ hippocampal volume	Self-reported exposures. Healthy participant bias. Perimenopausal women not included.
46	Jung, 2020	In non-demented older women (CN and MCI), grand multiparity (>=5 births) as compared with 0-4 parity was associated with lower hippocampal volume.	Grand multiparity (≥5 births vs. 0–4 births) → ↓ hippocampal volume	Recall bias: reproductive history self-reported. Although, they reconfirmed information from reliable informants and got additional information.

				Nulliparity could not be separately assessed.
51	Ambikairajah, 2020	For postmenopausal women, after adjusting for all covariates, age of menopause was significantly associated with hippocampal volume, indicating that every 1 year delay in menopause after 45 was associated with 0.31% smaller hippocampal volume. Age of menarche and duration of reproductive stage were not associated with hippocampal volume.	Delayed age at menopause → ↓ hippocampal volume Age at menarche ↔ hippocampal volume Reproductive stage duration ↔ hippocampal volume	Self-reported exposures. Healthy participant bias. Perimenopausal women not included.
72	Steventon, 2023	No associations were observed between HRT duration, HRT initiation timing, or years since last HRT use and hippocampal volume or hippocampal subfield volumes.	HRT duration ↔ hippocampal volume. Age at HRT initiation ↔ hippocampal volume. Years since last HRT use ↔ hippocampal volume. HRT duration ↔ hippocampal subfield volumes HRT initiation timing ↔ hippocampal subfield volumes Years since last HRT use ↔ hippocampal subfield volumes	
72	Steventon, 2023	Findings suggest that reproductive factors associated with longer endogenous hormone exposure (later menopause and longer reproductive span) were related to slightly larger hippocampal volumes, with the associations appearing to be driven particularly by the CA4 and dentate gyrus subfields rather than by CA1 or CA2/3.	Earlier menopause → ↓total hippocampal volume Age of menopause ↔ CA1 volume Age of menopause ↔ CA2/3 volume Earlier menopause → ↓ CA4 volume Earlier menopause → ↓ Dentate gyrus volume Longer reproductive span → ↑ total hippocampal volume reproductive span ↔ CA1 volume reproductive span ↔ CA2/3 volume Longer reproductive span → ↑ CA4 volume Longer reproductive span → ↑ Dentate gyrus volume Age at menarche ↔ total hippocampal volume Age at first live birth ↔ total hippocampal volume	Automatic segmentation of 1×1×1 mm^3 T1-weighted MRI images may not accurately delineate hippocampal subfields (e.g., CA1, CA2/3, CA4, dentate gyrus). Residual/unmeasured confounding — some potentially important factors were not fully accounted for, including blood pressure and historical or current lifestyle factors such as smoking and physical activity. Although statistically significant, menopause age and reproductive span explained less than 1% of the variance in medial temporal lobe volumes, suggesting limited clinical impact.
85	Barth, 2025	Whole sample: MHT users - current users, but not in past years, vs never-users === smaller left and right hippocampus Among MHT user - >> age at MHT initiation, along or in relation to age at menopause = no associations >> older age at last use after age at menopause, longer	User status: Current MHT users vs never-users → ↓ left hippocampal volume. Current MHT users vs never-users → ↓ right hippocampal volume. Past MHT users vs never-users ↔ left hippocampal volume. Past MHT users vs never-users ↔ right hippocampal volume. Duration and timing:	Participants may switch between MHT regimes = differences in formulation, dose, duration = makes exposure inconsistent across individuals. Prescription data limitations: no unified UK system for primary care date; data may vary in availability. Completeness, quality across

		duration of MHT use associated with lower left and right hippocampal volumes. Among MHT users, hysterectomy without bilateral oophorectomy was associated with larger bilateral hippocampal volumes, whereas bilateral oophorectomy (with or without hysterectomy) was not associated with hippocampal volume. Subsample with prescription data: No associations after FDR corrections. Before FDR: some preliminary Hippocampus → lower volumes with longer duration of estrogen use (combined MHT) (trend-level significance only) APOE ε4 modification: No significant effect modification by APOE ε4 status for hippocampal volume outcomes.	Longer duration of MHT use → ↓ bilateral hippocampal volume. Older age at last MHT use (particularly relative to menopause) → ↓ bilateral hippocampal volume. Age at MHT initiation, along or in relation to age at menopause ↔ bilateral hippocampal volume. Surgical history: MHT users with hysterectomy (without bilateral oophorectomy) vs MHT users without surgical history → ↑ left hippocampal volume. MHT users with hysterectomy (without bilateral oophorectomy) vs MHT users without surgical history → ↑ right hippocampal volume. MHT users with bilateral oophorectomy (± hysterectomy) ↔ left hippocampal volume. MHT users with bilateral oophorectomy (± hysterectomy) ↔ right hippocampal volume. Prescription-data analyses: MHT formulation ↔ hippocampal volume. Route of administration ↔ hippocampal volume. MHT type (bioidentical vs synthetic) ↔ hippocampal volume. Active ingredient ↔ hippocampal volume. Dosage ↔ hippocampal volume. APOE ε4 × MHT ↔ hippocampal volume	sources and time; data comes from an interim subset - results may not generalize to full cohort; prescription does not equal to actual use - medications may not have been dispensed or taken. Potential survivor/healthy volunteer bias, including age-related underrepresentation of APOE ε4 carriers in older UK Biobank participants.
97	McGrath, 2025	Postmenopausal hormone replacement therapy (pmHRT) use was not associated with hippocampal volume.	Postmenopausal HRT use vs no HRT ↔ hippocampal volume.	
97	McGrath, 2025	Neither serum estradiol nor serum estrone concentrations were significantly associated with total hippocampal volume.	Serum estradiol ↔ total hippocampal volume Serum estrone ↔ total hippocampal volume	Data were unavailable for several important reproductive factors, including gestational diabetes, gestational hypertension, preeclampsia/eclampsia, miscarriage history, and breastfeeding history. The cohort was predominantly non-Hispanic White, potentially limiting generalizability to other populations.
97	McGrath, 2025	Age at menarche, reproductive lifespan, and number of	Age at menarche ↔ total hippocampal volume	Data were not available for some important reproductive factors, such as gestational

		live births showed no significant associations with hippocampal volume. However, women who experienced menopause at ≤49 years had significantly lower total hippocampal volume compared with those whose menopause occurred at 50–51 years, whereas menopause at ≥52 years was not associated with hippocampal volume. Overall, earlier menopause was the only reproductive factor linked to smaller hippocampal volume.	Earlier menopause onset (≤49y versus 50–51y) → ↓ hippocampal volume Earlier menopause onset (≥52y versus 50–51y) ↔ total hippocampal volume Reproductive lifespan ↔ total hippocampal volume Number of live births ↔ total hippocampal volume	diabetes mellitus or hypertension, preeclampsia/eclampsia, prior miscarriages or breastfeeding history.
90	Kantarci, 2026	In this KEEPS Continuation imaging study, performed by recontacting the original KEEPS participants 10 years after completion of the mHT clinical trial and at an average age of 68 years, neither oCEE nor tE2 exposure was associated with hippocampal volume (compared to placebo) after adjusting for age and enrollment site.	oCEE vs placebo ↔ Total hippocampal volume tE2 vs placebo ↔ Total hippocampal volume	High attrition due to COVID-19: Many participants declined follow-up participation (travel concerns). Selection bias (healthier participants): Included participants had lower blood pressure and BMI than non-participants.
102	Zuhlsdorff, 2026	Hippocampal volumes significantly decreased in both postmenopausal groups compared to the pre-menopausal group.	Postmenopausal status (no HRT) vs premenopausal status → ↓ hippocampal gray matter volume Postmenopausal status + HRT vs premenopausal status → ↓ hippocampal gray matter volume	Menopausal status was not classified using STRAW criteria, which may have resulted in less precise categorization of reproductive stage. Potential confounding by indication, as women who later initiated HRT reported higher levels of pre-existing psychiatric symptoms, making it difficult to determine whether lower hippocampal volumes were related to HRT use or underlying differences between women prescribed and not prescribed HRT.

eTable 26 Magnetic resonance imaging specifications for included studies.

Study ID	First author, year	Tesla	Scanner type	Scan type	Software	Atlas / manual approach	ROI/whole brain
35	Albert, 2017	3	Philips Achieva	T1-weighted	FreeSurfer; SPM12	Automated hippocampal ROI segmentation; SPM segmentation	Whole brain
61	Aleknaviciute, 2022	1.5	GE signa Excite	T1, PD, FLAIR, T2* and DTI echo-planar imaging	kNN/Elastix/N3; FSL-DTI	Lobar template-based; visual QC/manual edits	Both
93	Alshikho, 2025	3	Siemens Prisma with 64-channel head coil	; diffusion MRI; PCASL/ASL perfusion MRI	FreeSurfer v7.3.2	FreeSurfer standard pipelines; atlas not named in row	ROI
51	Ambikairajah, 2020	3	Siemens Skyra VD13ASP4; T1 3D MPRAGE	T1-weighted 3D MPRAGE	UK Biobank imaging pipeline; FSL FAST	Automated tissue segmentation	ROI
85	Barth, 2025	3	Siemens Skyra; 32-channel head coil	T1w MPRAGE; two-shell dMRI-EPI; T2-FLAIR SPACE	FreeSurfer 5.3; diffusion/YTTRIUM; BIANCA FSL 6.0; XGBoost	Glasser cortical + JHU WM atlases; automated segmentation	Both
55	Boyle, 2021	1.5	Multisite scanners at 4 CHS centres; manufacturer/model not reported	High-resolution 3D T1w SPGR; axial T1w, PDw and T2w	Tensor-based morphometry pipeline; FSL Cluster/FSLeyes; Talairach Daemon	Visual determination of WMH	ROI
34	Braden, 2017	1.5 or 3	GE scanner	3D SPGR	ANALYZE v7.5; SPM8 VBM toolbox for TIV	Manual hippocampal tracing using Machulda/Jack boundaries	Whole brain
94	Brown, 2025	3	Siemens MAGNETOM Prisma and Prisma-Fit	Whole-brain T1w 3D MPRAGE for ICV/slice placement; high-resolution oblique-coronal T2w for segmentation	ASHS; ITK-SNAP v4.0.0	Custom manually labelled MTL atlas based on the Olsen–Amaral–Palombo protocol; automated ASHS segmentation with visual QC; manual correction of MTL cortical ROIs only	ROI
62	Buckley, 2022	3	Philips Achieva	T1	FreeSurfer 6.0	FreeSurfer automated processing	Both
25	Coker, 2014	1.5	Multisite scanners across 14 centres; manufacturer/model not specified	3D T1w spoiled GRE; dual-echo PD/T2w spin echo; T2-FLAIR spin echo	Custom UPenn pipeline; HAMMER template warping; SVM lesion classifier	Automated digital-atlas warping; SVM trained on expert-defined lesions and validated against manual segmentation; no routine manual tracing reported	Both
3	Cook, 2002	1.5	GE Signa	Dual-echo transaxial ; 3-mm contiguous slices	MRX; Sun SPARCStation	No atlas; operator-created brain mask and selected tissue samples, followed by automated voxel classification, visual QC and manual correction	Both

66	Cote, 2023	3	Siemens Skyra, 32-channel coil	T2-FLAIR WMH MRI	BIANCA (Brain Intensity AbNormality Classification Algorithm)	Fully automated WMH classification	ROI
7	den Heijer, 2003	1.5	Siemens VISION MR	T1/T2/proton-density MRI; 3D HASTE	Siemens Magic View 1000	Duvernoy atlas-guided manual bilateral hippocampal tracing by blinded raters; manual midsagittal ICV proxy	ROI
6	Eberling, 2003	1.5	GE Signa Horizon LX NV/I	Coronal 3D IR-prepared SPGR T1w; 1.6-mm contiguous slices	In-house tracing program	Manual blinded tracing using anatomical landmarks; ICV-normalized	ROI
39	Elbejjani, 2017	3	Siemens Tim Trio/VB15 and Philips Achieva/2.6.3.6	Sagittal 3D T1w MPRAGE; 1-mm slices	UPenn MRI Reading Center pipeline; multi-atlas skull stripping, N3 bias correction and MICO tissue segmentation	Jakob atlas; expert ROI labels transferred from template to subject space by nonlinear registration; manual visual QC, no routine manual tracing	Both
12	Erickson, 2005	1.5 and 3	General Electric, Milwaukee, WI & Siemens Allegra, Germany	T1-weighted 3D SPGR/MPRAGE	FSL; optimized VBM	Automated segmentation	ROI
22	Erickson, 2010	3	Siemens Allegra scanner.	T1-weighted 3D MPRAGE	FSL FIRST v4.0	Semi-automated segmentation with manual quality control	ROI
21	Espeland, 2009	1.5	Multisite scanners across 14 centres; manufacturer/model not specified	Spin-density/T2 MRI; FLAIR; 3D T1 gradient-echo	Automated computer-based template warping	Automated template-warping regional volumetry	Both
89	Faubion, 2025	3	Siemens Prisma, Skyra, Vida and GE Discovery MR750	MPRAGE ; diffusion MRI/NODDI; T1-derived WMH/infarct imaging	In-house dMRI pipeline; NODDI; ANTs-SyN; SPM12; MCALT; in-house WMH segmentation	JHU Eve atlas and MCALT; automated with trained analyst QC; radiologist-confirmed infarcts	Both
87	Giudicessi, 2025	Not reported	Not reported; scanned at Massachusetts General Hospital	Single-shell diffusion-weighted single-shot spin-echo EPI	MRtrix3; fixel-based analysis	JHU White-Matter Tractography Atlas	ROI
16	Greenberg, 2006	1.5	GE Signa whole-body scanner	Axial T1w; double-echo spin echo; axial and oblique-coronal dual-echo FSE for hippocampal morphometry	GRID in-house program; modified MrX (GE)	Analyst-seeded semi-automated tissue segmentation plus manual tracing/point-counting of ROIs	Both
31	Guoqing, 2016	3	Siemens scanner	T1/T2/FLAIR	Not reported	Fazekas classification; visual lesion assessment implied	Whole brain

78	Huddleston, 2024	3	Three different 3T scanners: Siemens Tim Trio/VB15 at Minneapolis and Oakland; Philips Achieva/2.6.3.6 at Birmingham	T1/T2/3D-FLAIR structural/lesion MRI; DTI	CARDIA/UPenn automated MRI pipeline; specific software package not reported	Automated tissue classification and DTI processing with quality control	Both
14	Irie, 2006	1.5	GE Signa Advantage	T1-weighted 3D SPGR; proton density-weighted fast spin-echo; T2-weighted fast spin-echo	MEDx v3.41 for hippocampus	Visual ratings for atrophy/WM lesions/infarcts; manual hippocampal tracing	Both
96	Jiang, 2025	3	MR scanners at 3 sites: Siemens Tim Trio/VB15 at Minneapolis and Oakland; Philips Achieva/2.6.3.6 at Birmingham	3D FLAIR/T2 WMH; sagittal 3D T1	UPenn MRI Reading Center automated processing/QC pipeline; specific package not reported	Jakob atlas; automated classification of normal and abnormal WM	Both
46	Jung, 2020	3	Siemens Biograph mMR	3D T1	FreeSurfer 5.3; AAL atlas; SPARE-AD/SPARE-BA; WMH segmentation	AAL-defined Aβ ROIs; Desikan–Killiany/FreeSurfer hippocampal segmentation; semiautomated WMH	Both
33	Kantarci, 2016.2	1.5	GE Healthcare	T1-weighted 3D MPRAGE; FLAIR	Automated volume/WMH algorithms	Automated volumetry and FLAIR WMH segmentation with blinded manual review/correction	Both
41	Kantarci, 2018	1.5	GE Healthcare	T1-weighted 3D MPRAGE; FLAIR	TBM; automated WMH segmentation	Automated segmentation with manual WMH review; in-house modified 21-region atlas	Both
86	Kantarci, 2025	3	Siemens Prisma MRI	MPRAGE	SPM12 Unified Segmentation; ANTs-SyN; MCALT template	MCALT atlas/template; automated tissue	Whole brain
90	Kantarci, 2025	3	Siemens Prisma, Skyra, Vida and GE Discovery MR750	T1-weighted MPRAGE	SPM12 Unified Segmentation; MCALT template	MCALT atlas-defined hippocampus/DLPFC	Both
40	Kim, 2018	3	Siemens Magnetom Tim Trio	T1-weighted	SPM8; DARTEL; VBM	Automated segmentation using ICBM East Asian template and MNI normalization	Whole brain
68	Kim, 2023	3	Philips Ingenia Elition	3D T1-weighted TFE	SPM12; DARTEL; VBM	Automated VBM segmentation	ROI
79	Kim, 2024	3	Siemens Magnetom Tim Trio	T1-weighted 3D MPRAGE	FreeSurfer	Automatic segmentation	ROI
49	Kling, 2020	1.5	Single GE Healthcare system	T1-weighted 3D MPRAGE; T2-FLAIR	Semiautomated WMH segmentation algorithm	Semiautomated FLAIR WMH segmentation by blinded analyst	Whole brain
88	Kwan, 2025	3	Siemens Tim/Trim Trio	T1-weighted MPRAGE	FSL v6.0.5.2; FSL-VBM	MNI152 standardized-space registration; automated VBM	Both

36	Lee, 2017	3	Siemens Biograph	3D T1	FreeSurfer 5.3	Automated hippocampal segmentation with minor manual correction	ROI
76	Lee, 2024	3	GE scanners	MPRAG ; DTI/FLAIR	FreeSurfer 5.3; ANTs-SyN; SPM-based segmentations; semiautomated WMH	JHU Eve atlas; temporal meta-ROI; semiautomated WMH with analyst editing	Whole brain
13	Lessov-Shlaggar, 2005	1.5	GE Signa	T1-weighted spin-echo	Custom-written program	Semi-automated segmentation with operator-guided removal of nonbrain tissue	Both
83	Li, 2025	3	Siemens Skyra	T2-FLAIR WMH MRI; diffusion MRI/DTI-NODDI	UKB/FSL pipeline: BIANCA, DTIFIT, AMICO-NODDI and AutoPtx	Automated BIANCA WMH segmentation and AutoPtx standard-space tract masks for 27 WM tracts	Both
69	Liao, 2023	3	Siemens Skyra, software VD13	T1w 3D MPRAGE; T2-FLAIR 3D SPACE	UK Biobank automated pipeline: FSL FAST/SIENAX; BIANCA for WMH; FreeSurfer/Fischl-derived regional IDPs	Desikan–Killiany cortical atlas; automated Fischl/FreeSurfer subcortical segmentation	Both
19	Liu, 2009	3	GE system; model reported as “Sigma VHIEXITE3”	T2W/FLAIR/T1WI plus 3D whole-brain MRI	Not reported	Fazekas visual rating scale	Whole brain
59	Lohner, 2022	3	Siemens MAGNETOM Prisma	T1/T2/FLAIR MRI	FreeSurfer; DeepMedic	DeepMedic trained and tested on manual WMH segmentations, with visual QC and manual review of a subset	Whole brain
18	Lord, 2008	1.5	Siemens Magnetom Vision	volumetry	Preprocessing algorithms; software not named	Manual hippocampal/amygdala segmentation; Talairach registration	Both
15	Low, 2006	1.5	Philips Gyroscan ACS-NT	T1-weighted 3D ; T2-FLAIR	ANALYZE 5.0; SPM99	Manual hippocampus/amygdala ROI; Fazekas visual WMH ratings plus automated WMH quantification	ROI
42	Lu, 2018	3	GE Discovery MR750	T1-weighted	CAT12; SPM12; DARTEL; VBM	Automated segmentation/QC with manual verification; MNI registration	ROI
1	Luoto, 2000	1.5 at 3 centres; 0.35 at 1 centre	General Electric or Picker 1.5T scanners; 0.35T Toshiba at fourth centre	T1w, spin-density/PDw and T2w	Not reported; PDS-4 digital workstation from Vortech for image interpretation	Manual / visual CHS grading: WM changes graded 0–9; infarcts visually defined	Whole brain
97	McGrath, 2025	1 or 1.5	Siemens Magnetom	3D T1w MPRAGE	IDeA in-house pipeline; DiReCT	Automated tissue segmentation; atlas-based hippocampal	Both

						segmentation; data-driven ADRD cortical signature	
30	Mielke, 2016	1.5	GE Signa scanners	Axial FLAIR lesion/brain-volume MRI	Fully automated segmentation algorithm	Automated voxel classification into brain tissue/CSF/white-matter lesions	Both
75	Mielke, 2024	3	GE scanner	T1-weighted 3D MPRAGE; 2D FLAIR; diffusion MRI	ANTs-SyN; connected-component WMH clustering	JHU Eve atlas for diffusion regions; WMH manually edited by analysts	ROI
70	Moir, 2023	3	GE MR750	T1 BRAV ; T2-FLAIR	SPM12	Automated tissue-class segmentation; WMH method not named	Both
38	Mosconi, 2017	1.5	MRI scanner not specified in row	Volumetric T1-weighted fast gradient echo	SPM12; DARTEL	Automated VBM; MNI normalisation, Talairach coordinates; predefined AD-related mask	ROI
43	Mosconi, 2018	3	MRI: MPRAGE	T1-weighted MPRAGE; amyloid	FreeSurfer 5.3 longitudinal pipeline	FreeSurfer hippocampal segmentations	ROI
56	Mosconi, 2021	3	GE Discovery MR750	T1 BRAVO; DTI; ASL; 31P-MRS	SPM12; MATLAB 7.8; FreeSurfer 6.0	Fully automated pipeline; Desikan–Killiany atlas cortical ROIs	Both
100	Mutee, 2026	1.5 and 3	GE Healthcare, Philips and Siemens scanners	; tensor-based morphometry	BrainSuite; tensor-based morphometry	Minimum deformation template; anatomically defined temporal-lobe ROI	Whole brain
27	Pintzka, 2015	1.5	GE Signa HDx	T1-weighted MPRAGE	FreeSurfer 4.5	Automated hippocampal segmentation with visual inspection	Whole brain
50	Rahman, 2020	3	Not reported	T1-weighted MPRAGE	SPM12 (DARTEL, VBM)	Automated pipeline	Whole brain
9	Raz, 2004	1.5	GE Signa	T1-weighted 3D SPGR	Not reported	Manual ROI tracing	ROI
20	Resnick, 2009	1.5	Multisite scanners across 14 centres; manufacturer/model not specified	Spin-density/T2 MRI; FLAIR; 3D T1 gradient-echo	Automated computer-based template warping	Automated template-warping regional volumetry	Both
26	Ryan, 2014	1.5	GE Signa	T1 SPGR volumetric MRI; double-echo T2 MRI	SPM5; ANALYZE 9.0; semiautomatic WML method	Automated tissue segmentation; manual CC and hippocampal ROI; semiautomated WML	Both
71	Sato, 2023	0.5	Not reported	T1- and T2-weighted axial	Not reported	Visual/subjective Fazekas grading; lacune signal/size criteria	Whole brain
53	Schelbaum, 2021	3	GE Discovery MR750	3D T1-weighted	SPM12/MATLAB; DARTEL; VBM	Automated VBM; AAL atlas-defined AD-vulnerable regions	Both
44	Seitz, 2019	3	Siemens Tim Trio	T1-weighted 3D MPRAGE	FreeSurfer 5.3	Automated segmentation with visual QC	ROI

29	Srinath, 2016	3	Siemens scanners	FLAIR lesion imaging; MPRAGE	FreeSurfer 5.1 for TIV	Defined/visual infarct criteria; WMH burden corrected for total brain volume	Both
72	Steventon, 2023	3	Siemens Skyra	T1-weighted 3D MPRAGE	UK Biobank pipeline; BET, FLIRT, FNIRT, FAST; FreeSurfer v6.0.0	Automated atlas-based segmentation (FreeSurfer IDPs)	ROI
11	Sullivan, 2005	1.5	GE Signa	Dual-echo spin-echo	Custom software	Manual outlining + semi-automated edge detection + automated tissue segmentation	ROI
52	Than, 2021	3	Siemens Skyra	T1-weighted; T2-FLAIR	UK Biobank imaging pipeline	Automated imaging-derived phenotype pipeline	ROI
28	Thurston, 2016	3	Siemens Tim Trio	T1-weighted MPRAGE; T2-FLAIR	Fuzzy-connected algorithm	Automated WMH quantification/localization	Whole brain
64	Thurston, 2023	3	Siemens Tim Trio	T1 MPRAGE; T2w-FLAIR	SPM12; FreeSurfer 7.1.1	Desikan–Killiany atlas for lobar WMH; automated WMH pipeline with manual inspection	Both
73	Thurston, 2024	3	Siemens Prisma	T1 MPRAGE; T2w-FLAIR	SPM12; FreeSurfer 7.1.1	Desikan–Killiany atlas; automated WMH pipeline with manual inspection	Both
92	Wezel, 2025	3	Siemens Skyra	T1-weighted MRI; FLAIR; diffusion-weighted MRI	BISON and UKB/BIANCA segmentation pipelines	Automated segmentation pipelines; native-space WMH extraction	Whole brain
57	Wisch, 2021	3	Siemens Trio	T1-weighted MPRAGE (ADNI protocol)	FreeSurfer	Automated atlas-based parcellation (35 FreeSurfer grey-matter regions)	ROI
74	Wugalter, 2024	3	Siemens Tim Trio	T1-weighted MPRAGE	FreeSurfer	Desikan–Killiany atlas; automated cortical segmentation/parcellation	ROI
48	Xu, 2020	1.5	ADNI multi-site GE/Philips/Siemens	T1-weighted MP-RAGE	Not reported	Not reported	ROI
45	Zeydan, 2019	3	GE Healthcare	T1-weighted structural, FLAIR, DTI	FreeSurfer v5.3; validated in-house Mayo pipelines	Automated atlas-based (FreeSurfer; JHU white-matter atlas) + semi-automated FLAIR segmentation	Both
58	Zhang, 2021	3	GE	T1-weighted 3D SPGR	FreeSurfer 6.0	Automated FreeSurfer segmentation with minimal manual edits	Whole brain
102	Zuhlsdorff, 2026	3	Siemens Skyra	T1-weighted MPRAGE; T2-FLAIR	FreeSurfer v6.0.1	Automated atlas	ROI

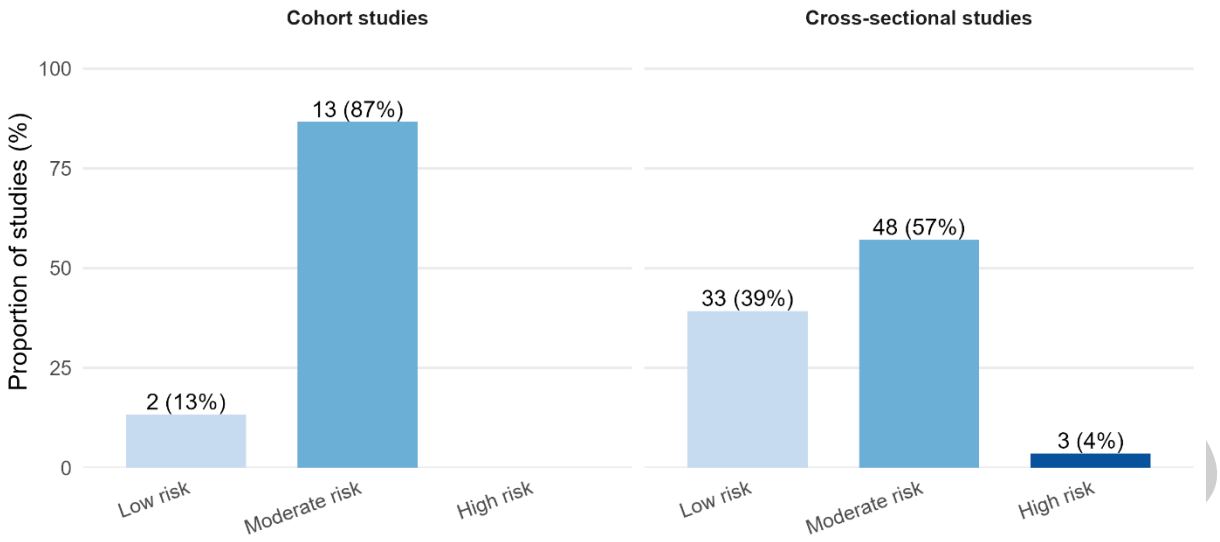
eTable 27 Abbreviations defined from eTable 26.

Abbreviation	Meaning
AAL	Automated Anatomical Labeling atlas
ACC	Anterior cingulate cortex
ACR	Anterior corona radiata
ADNI	Alzheimer's Disease Neuroimaging Initiative
ADRD	Alzheimer's disease and related dementias
ALIC	Anterior limb of the internal capsule
ARIC	Atherosclerosis Risk in Communities
ASHS	Automatic Segmentation of Hippocampal Subfields
ASL	Arterial spin labeling
AWM	Angular white matter
BA	Brodmann area
BCC	Body of the corpus callosum
BET	Brain Extraction Tool
BIANCA	Brain Intensity AbNormality Classification Algorithm
BISON	Automated brain tissue/lesion segmentation tool; expansion not stated in the source
BRAVO	Brain Volume Imaging
CAT12	Computational Anatomy Toolbox 12
CBF	Cerebral blood flow
CC	Corpus callosum
CC-FA	Corpus callosum fractional anisotropy
CEE	Conjugated equine estrogens
CGC	Cingulum, cingulate gyrus portion
CGH	Cingulum, hippocampal portion
CHS	Cardiovascular Health Study
CSF	Cerebrospinal fluid
CST	Corticospinal tract
CT	Computed tomography
DARTEL	Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra
DG	Dentate gyrus
DLPF / DLPFC	Dorsolateral prefrontal cortex
dMRI	Diffusion magnetic resonance imaging
DTI	Diffusion tensor imaging
DWMH	Deep white matter hyperintensity
EC	Entorhinal cortex; in tract lists, external capsule
EHR	Electronic health record
ELISA	Enzyme-linked immunosorbent assay

ENT	Entorhinal area
FA	Fractional anisotropy
FAST	FMRIB's Automated Segmentation Tool
FC	Fiber cross-section
FD	Fiber density
FDC	Fiber density and cross-section
FDG-PET	Fluorodeoxyglucose positron emission tomography
FDR	False discovery rate
FF	Fusiform cortex or fusiform gyrus
FIRST	FMRIB's Integrated Registration and Segmentation Tool
FLAIR	Fluid-attenuated inversion recovery
FLIRT	FMRIB's Linear Image Registration Tool
FNIRT	FMRIB's Nonlinear Image Registration Tool
FMRIB	Functional Magnetic Resonance Imaging of the Brain Centre
FSL	FMRIB Software Library
FSL-VBM	FSL voxel-based morphometry pipeline
Fx	Fornix
Fx/ST	Fornix/stria terminalis
GCC	Genu of the corpus callosum
GCC-FA	Genu of the corpus callosum fractional anisotropy
GE	General Electric
GM	Gray matter
GMV	Gray matter volume
GRID	In-house MRI image-analysis program; expansion not reported
HASTE	Half-Fourier acquisition single-shot turbo spin echo
HC	Hippocampus
HT	Hormone therapy
HUNT	Trøndelag Health Study, formerly the Nord-Trøndelag Health Study
ICBM	International Consortium for Brain Mapping
ICV	Intracranial volume
ICVF	Intracellular volume fraction
IFO	Inferior fronto-occipital fasciculus
IFWM	Inferior frontal white matter
IOWM	Inferior occipital white matter
IPG	Inferior parietal gyrus
ISOVF	Isotropic volume fraction
ITWM	Inferior temporal white matter
JHU	Johns Hopkins University
LFOWM	Lateral fronto-orbital white matter
LPFC	Lateral prefrontal cortex
MATLAB	Matrix Laboratory
MCALT	Mayo Clinic Adult Lifespan Template

MD	Mean diffusivity
meta-ROI	Composite or meta region of interest
MFOWM	Middle fronto-orbital white matter
MFWM	Middle frontal white matter
MNI	Montreal Neurological Institute
MOWM	Middle occipital white matter
MPRAGE	Magnetization-prepared rapid gradient echo
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
MRX	Semi-automated MRI segmentation software; expansion not reported
MTL	Medial temporal lobe
MTWM	Middle temporal white matter
NDI	Neurite density index
NODDI	Neurite orientation dispersion and density imaging
ODI	Orientation dispersion index
P-MRS	Phosphorus magnetic resonance spectroscopy, typically 31P-MRS
PCASL	Pseudo-continuous arterial spin labeling
PCR	Posterior corona radiata
PD	Proton density
PDS-4	Digital image-analysis workstation/model; expansion not reported
PET	Positron emission tomography
PFw	Prefrontal white matter
PiB-PET	Pittsburgh Compound B positron emission tomography
PLIC	Posterior limb of the internal capsule
PoCWM	Postcentral white matter
PrCWM	Precentral white matter
PTR	Posterior thalamic radiation
PVH	Periventricular hyperintensity
QC	Quality control
RLIC	Retrolenticular part of the internal capsule
ROI	Region of interest
RWM	Rectus white matter
SCC	Splenium of the corpus callosum
SCI	Silent cerebral infarct
SCR	Superior corona radiata
SFG	Superior frontal gyrus
SFO	Superior fronto-occipital fasciculus
SFWM	Superior frontal white matter
SHBG	Sex hormone-binding globulin
SLF	Superior longitudinal fasciculus
SMWM	Supramarginal white matter
SOWM	Superior occipital white matter

SPARE-AD	Spatial Pattern of Abnormality for Recognition of Early Alzheimer's Disease
SPARE-BA	Spatial Pattern of Atrophy for Recognition of Brain Aging
SPGR	Spoiled gradient-recalled echo
SPM	Statistical Parametric Mapping
SPWM	Superior parietal white matter
SS	Sagittal stratum
STWM	Superior temporal white matter
SUVR	Standardized uptake value ratio
T	Tesla
T1	T1-weighted or longitudinal-relaxation MRI contrast
T1WI	T1-weighted imaging
T1W-TFE	T1-weighted turbo field echo
T2	T2-weighted or transverse-relaxation MRI contrast
T2WI	T2-weighted imaging
TFE	Turbo field echo
TIV	Total intracranial volume
tNDI	Tissue-weighted neurite density index
UNC	Uncinate fasciculus
VBM	Voxel-based morphometry
VC	Visual cortex
WM	White matter
WMH	White matter hyperintensity
WMHV	White matter hyperintensity volume
WML	White matter lesion
WMV	White matter volume



eFigure 1 Newcastle-Ottawa Scale (NOS) risk of bias assessment for cohort and cross-sectional studies included in the systematic review. Note: Figure was created by EGK in RStudio version 2026.01.0.

DOMAIN

Study	First author, year	D1 Randomisation process	D2 Deviations from intended interventions	D3 Missing data outcome	D4 Measurement of the outcome	D5 Selection of the reported results	Overall judgement
35	Albert, 2017	x	!	!	✓	x	x
5	Baker, 2003	!	✓	✓	✓	!	!
25	Coker, 2014	✓	✓	x	✓	!	!
21	Espeland, 2009	✓	✓	x	✓	!	!
89	Faubion, 2025	✓	!	x	✓	x	x
32	Kantarci, 2016	✓	x	!	✓	!	!
33	Kantarci, 2016	✓	✓	x	✓	!	!
41	Kantarci, 2018	✓	!	✓	✓	!	!
90	Kantarci, 2025	✓	x	x	✓	!	x
49	Kling, 2020	✓	!	!	✓	x	x
20	Resnick, 2009	✓	✓	x	✓	x	!
101	Shadyab, 2026	✓	✓	x	✓	x	!

✓ Low risk ! Some concerns x High risk

eFigure 2. ROB2 risk of bias assessment for randomized controlled trials. Note: Figure created by EGK in Canva.com.