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SUPPLEMENTARY INFORMATION

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Sex differences in Alzheimer disease — the gateway to precision medicine

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Supplementary box 1| The Alzheimer Precision Medicine Initiative – Working Group (APMI–WG)

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Supplementary box 2 | Hormone replacement therapy trials in Alzheimer disease – a reappraisal

Hormone replacement therapy (HRT) for the prevention of Alzheimer disease (AD) in women after the menopause has yielded inconclusive results in large interventional studies[1]. However, differences in the timing of treatment and the use of different hormones, formulations and regimes, are important variables that need to be taken into account when interpreting the results.

Timing of treatment

A vascular protective effect of HRT initiated early in menopause was clearly demonstrated in a randomized study [2] and in a Cochrane overview that reported on >40,000 women included in randomized studies [3]. In the Women Health Initiative (WHI) trial, dementia risk was increased when hormonal therapy was initiated after the age of 65[4], a worrying result that led to the halting of further studies. However, mortality associated with AD or dementia was decreased in the same WHI study when all women (including those who had recently been through the menopause) were included[5].

Optimal formulation

The oral, high-dose equine oestrogens and medroxyprogesterone acetate (MPA) used in WHI was suboptimal. The Pepi trial[6] indicated that MPA counteracts the beneficial effect of oestrogens and that natural progesterone is more neutral. In the KEEPS study[7], transdermal administration of oestrogens improved serum glucose levels and insulin sensitivity over placebo. This beneficial effect was not observed with oral preparations, which, especially at high doses (2 mg of eostradiol or 0.625 mg of equine oestrogen as compared with 1 mg or less of oral oestradiol or 0.3 mg of equine oestrogen) and later in menopausal life (in women aged 68 years or older) are known to increase the risk of thrombosis[8,9].

Long-term effects

Though short-term follow-up of the WHI[4] indicated an increase in dementia risk, an 18-year cumulative follow-up (in which data were pooled from patients who received conjugated equine oestrogens alone and patients who received these oestrogens with MPA) demonstrated a significant 15% reduction in AD or dementia risk and a significant 31% reduction in all-cause mortality among women whose hormone therapy was initiated between the ages of 50 and 59 years[5].

1 Depypere, H., Vierin, A., Weyers, S. & Sieben, A. Alzheimer's disease, apolipoprotein E and hormone replacement therapy. *Maturitas* **94**, 98-105 (2016).

2 Hodis, H. N. *et al.* Vascular Effects of Early versus Late Postmenopausal Treatment with Estradiol. *N Engl J Med* **374**, 1221-1231 (2016).

3 Boardman, H. M. *et al.* Hormone therapy for preventing cardiovascular disease in post-menopausal women. *Cochrane Database Syst Rev*, CD002229 (2015).

4 Shumaker, S. A. *et al.* Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA* **289**, 2651-2662 (2003).

5 Manson, J. E. *et al.* Menopausal Hormone Therapy and Long-term All-Cause and Cause-Specific Mortality: The Women's Health Initiative Randomized Trials. *JAMA* **318**, 927-938 (2017).

6 Valery T. Miller et al. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial. *JAMA* **273**, 199-208 (1995).

7 Harman, S. M. *et al.* Arterial imaging outcomes and cardiovascular risk factors in recently menopausal women: a randomized trial. *Annals of internal medicine* **161**, 249-260 (2014).

8 Rossouw, J. E. *et al.* Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA* **288**, 321-333 (2002).

9 Grodstein, F. *et al.* A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. *Annals of internal medicine* **133**, 933-941 (2000).

Supplementary table 1 | Summary of sex-specific clinical manifestations in AD

	Ref.	Study design (database)	Diagnosis	n. m/w	Diagnostic criteria	Biomarker-based diagnosis?	Corrected for CVD?	Read-out	Worst in m/w?
Cognitive impairments	Pusswald et al. [1]	cohort study (PRODEM)	AD dementia	113/173	NINCDS-ADRDA	no	no	verbal learning (word list recall, delayed recall and recognition)	w
	Benke et al [2]	cohort study (PRODEM)	AD dementia	91/130	NINCDS-ADRDA	no	no	verbal learning (word list learning and recall)	w
	Gale et al[3]	cohort study, Arizona Alzheimer's disease core center	AD dementia and MCI	AD: 63/38, MCI: 46/30	NIA-AA	no	no	RAVLT total score and delayed recall (analysis performed on Z-scores separately based on male or female healthy controls)	w
	Irvine et al. [4]	Meta-analysis	AD dementia	828/1,238 (15 studies)	NINCDS-ADRDA (13 studies); DSM-III-R (1 study); no description (1 study)	no	no	mean effect size on verbal and visuospatial tasks and tests of episodic and semantic memory	w
	Pradier et al. [5]	cross sectional analysis (BNA)	AD dementia	13650/ 25800	classification by the National Federation of CMRRs in relation with the ICD10	no	no	MMSE at diagnosis	w

	Sundermann et al. [6]	Cross-sectional observational study (ADNI)	AD dementia	128/107	MMSE score between 20 and 26, a CDR of 0.5 or 1, meeting the NINCDS-ADRDA criteria	no	no	RAVLT total score and delayed recall	=
			aMCI	409/285	MMSE score between 24 and 30, CDR of 0.5, a subjective memory complaint, and objective memory loss as measured by education-adjusted scores on the Wechsler Memory Scale Logical Memory II, but without significant impairment in other cognitive domains or interference in daily life activities	no	no		m (in spite of similar hippocampal atrophy)
	Sundermann et al [7]	Cross-sectional observational study (ADNI)	AD dementia	153/101	MMSE score between 20 and 26, a CDR of 0.5 or 1, and a probable diagnosis of AD dementia by the NINCDS/ADRDA	no	no	RAVLT delayed recall	=
			aMCI	396/276	MMSE score between 24 and 30, a CDR of 0.5, a subjective memory complaint, and objective memory loss as measured by LM-II	no	no		m (in spite of similar glucose metabolism rate)

Rate of cognitive decline	Lin et al. [8]	Cross-sectional observational study (ADNI)	aMCI	257/141	MMSE from 24–30, subjective memory complaint, objective evidence of impaired memory calculated by WMS-LM-II, a score of 0.5 on the global CDR, absence of current major depressive episode	no	no	rate of decline in ADAS-Cog and CDR-Sb; mixed-effects models incorporating all follow-ups	w
	Tifratene et al. [9]	retrospective cohort study (BNA)	aMCI and naMCI	9748/ 13928	classification by the National Federation of CMRRs in relation with the ICD10	no	no	Hazard ratios of dementia due to Alzheimer disease were estimated using Cox regression model	w
	Holland et al. [10]	Cross-sectional observational study (ADNI)	aMCI	244/141	subjective memory complaint, objective memory loss measured by education-adjusted scores on WMS-LM II, a CDR of 0.5, preserved activities of daily living	no	no	Rate of decline in ADAS-Cog and CDR-Sb	w
	Gamberger et al. [11]	Cross-sectional observational study (ADNI 1 and 2)	late aMCI	344/218	subjective memory complaint, objective evidence of impaired memory calculated by WMS LM- II adjusted for education, absence of current major depressive episode, an inclusive MMSE score from 24–30, and a score of 0.5 on the global CDR.	no	n.a.	Rate of cognitive, as measured with ADAS-Cog13, in clusters of 'fast progressors' identified via multilayer clustering algorithm	w

Psychiatric symptoms	Karttunen et al. [12]	cross-sectional study (patient-caregiver dyads living in three municipalities in Finland, participating in a prospective, controlled rehabilitation study ALSOVA)	AD dementia	117/123	NINCDS-ADRDA; very mild AD (CDR 0.5) or mild AD (CDR 1)	no	no	Delusions	w
								Aberrant motor behaviour	m
	Spalletta et al. [13]	cross-sectional study (five Italian outpatient memory clinics)	AD dementia	292/723	NINCDS-ARDA	no	no	Mean scores for depression, anxiety and general neuropsychiatric score	w
	Hollingworth et al. [14]	cross-sectional study; community-dwelling individuals and those residing in nursing homes, United Kingdom and Republic of Ireland	AD dementia	334/786	NINCDS-ARDA	no	no	Behavioral dysfunction and mood component scores	w

Functional Independence	Benke et al. [2]	cohort study (PRODEM)	AD dementia	91/130	NINCDS-ADRDA	no	no	DAD % (total score and instrumental function)	m
	Sinforiani et al. [15]	prospective study (three Italian outpatient memory clinics)	AD dementia	214/386	NINCDS-ARDA	no	no	ADL at baseline	m
								IADL a baseline	m
								CIRS	m
								Autonomy loss at follow-up (5 years)	w

The table summarizes the main findings of the studies reported in the body of the manuscript, specifying the diagnostic criteria used, the use of biomarkers for diagnosis and whether the results where statistically corrected for CVD (cerebrovascular disease or cardiovascular risk factors). m (men), w (women).
PRODEM (Prospective Dementia Registry-Austria); BNA (French National Alzheimer databank); CMRR (Memory Center (CMRR) Paris North Ile-de-France); NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association, criteria for probable AD dementia[16]; NIA-AA (National Institute on Aging and the Alzheimer's Association criteria for probable AD dementia[17]); DSM-III (Diagnostic and Statistical Manual of Mental Disorders, third edition, American Psychiatric Association); IWG-2 (revised international working group criteria[18]); ICD 10ICD-10 (tenth Revision of the International Classification of Diseases, World Health Organization); CDR (clinical dementia rate); CDR-sb (CDR sum-of-boxes); MMSE (mini-mental state examination); RAVLT (Rey auditory verbal learning test); ADAS-Cog = Alzheimer's Disease Assessment Scale Cognitive Subscale Total Score; WMS-LM II (Wechsler Memory Scale Logical Memory II); Disability Assessment for Dementia Scale (DAD); Activities of Daily Living (ADL); Instrumental Activities of Daily Living (IADL); Cumulative Illness Rating Scale (CIRS).

1 Pusswald, G. *et al.* Gender-Specific Differences in Cognitive Profiles of Patients with Alzheimer's Disease: Results of the Prospective Dementia Registry Austria (PRODEM-Austria). *J Alzheimers Dis* **46**, 631-637 (2015).
2 Benke, T. *et al.* Cognition, gender, and functional abilities in Alzheimer's disease: how are they related? *J Alzheimers Dis* **35**, 247-252 (2013).
3 Gale, S. D., Baxter, L. & Thompson, J. Greater memory impairment in dementing females than males relative to sex-matched healthy controls. *J Clin Exp Neuropsychol* **38**, 527-533 (2016).
4 Irvine, K., Laws, K. R., Gale, T. M. & Kondel, T. K. Greater cognitive deterioration in women than men with Alzheimer's disease: a meta analysis. *J Clin Exp Neuropsychol* **34**, 989-998 (2012).
5 Pradier, C. *et al.* The mini mental state examination at the time of Alzheimer's disease and related disorders diagnosis, according to age, education, gender and place of residence: a cross-sectional study among the French National Alzheimer database. *PloS one* **9**, e103630 (2014).
6 Sundermann, E. E. *et al.* Better verbal memory in women than men in MCI despite similar levels of hippocampal atrophy. *Neurology* **86**, 1368-1376 (2016).
7 Sundermann, E. E. *et al.* Female advantage in verbal memory: Evidence of sex-specific cognitive reserve. *Neurology* **87**, 1916-1924 (2016).
8 Lin, K. A. *et al.* Marked gender differences in progression of mild cognitive impairment over 8 years. *Alzheimers Dement (N Y)* **1**, 103-110 (2015).
9 Tifratene, K., Robert, P., Metelkina, A., Pradier, C. & Dartigues, J. F. Progression of mild cognitive impairment to dementia due to AD in clinical settings. *Neurology* **85**, 331-338 (2015).
10 Holland, D., Desikan, R. S., Dale, A. M., McEvoy, L. K. & Alzheimer's Disease Neuroimaging, I. Higher rates of decline for women and apolipoprotein E epsilon4 carriers. *AJNR. American journal of neuroradiology* **34**, 2287-2293 (2013).
11 Gamberger, D., Lavrac, N., Srivatsa, S., Tanzi, R. E. & Doraiswamy, P. M. Identification of clusters of rapid and slow decliners among subjects at risk for Alzheimer's disease. *Sci Rep* **7**, 6763 (2017).
12 Karttunen, K. *et al.* Neuropsychiatric symptoms and quality of life in patients with very mild and mild Alzheimer's disease. *Int J Geriatr Psychiatry* **26**, 473-482 (2011).

13 Spalletta, G. *et al.* Neuropsychiatric symptoms and syndromes in a large cohort of newly diagnosed, untreated patients with Alzheimer disease. *Am J Geriatr Psychiatry* **18**, 1026-1035 (2010).
14 Hollingworth, P. *et al.* Four components describe behavioral symptoms in 1,120 individuals with late-onset Alzheimer's disease. *J Am Geriatr Soc* **54**, 1348-1354 (2006).
15 Sinforiani, E. *et al.* Impact of gender differences on the outcome of Alzheimer's disease. *Dementia and geriatric cognitive disorders* **30**, 147-154 (2010).
16 McKhann, G. *et al.* Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* **34**, 939-944 (1984).
17 McKhann, G. M. *et al.* The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 263-269 (2011).
18 Dubois, B. *et al.* Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. *Lancet Neurol* **13**, 614-629 (2014).

Supplementary table 2 | Summary of sex-effects on diagnostic biomarkers in the elderly and AD

	Ref.	Study design (database)	Diagnosis	n. m/w	Average age m/w (y)	Diagnostic criteria	Biomarker-based diagnosis?	Corrected for CVD?	Read-out	Worst in m/w?
β-Amyloid	Barnes et al. [1]	Cohort study (ROS)	AD dementia	64/77	83.5/86.2	NINCDS-ADRDA plus post-mortem neuropathological confirmation	no	yes	Amyloid plaques (modified Bielschowsky silver stain)	=
	Shinohara et al. [2]	Cohort study (Mayo Clinic biobank)	AD dementia	182/243	79.5/82	Neuropathologically confirmed AD	no	no	CAA (Thioflavin-S)	m
	Mattsson et al. [3]	review	AD, prodromal AD,NCI	n.a.	n.a.	IWG-2 criteria	yes	no	Aβ42 CSF	=
	Holland et al. [4]	Cohort study (ADNI)	AD dementia	55/50	75.5/76.8	CDR of 0.5 or 1.0 NINCDS-ADRDA criteria	no	no	Aβ42 CSF	=
			MCI	244/141	77.1/76	Subjective memory complaint, objective memory loss measured by WMS-LM-II, a CDR of 0.5,	no	no	Aβ42 CSF	=
			NCI	96/93	76.2/76.2	-	no	no	Aβ42 CSF	=
	Gottesman et al. [5]	Community based study (Atherosclerosis Risk in Communities)	NCI and MCI	137/185	52.2	NIA-AA	no	yes	Florbetapir PET	w
	Jansen et al. [6]	meta-analysis	SCI	349/348	64.2	Cognitive complaint with presentation at a health care facility but normal cognition on tests.	n.a.	no	PET amyloid tracers	=
			MCI	2133/1839	70.2	Petersen's criteria	no	no	PET amyloid tracers	=
			NCI	1259/1537	66.8	-	-	-	PET amyloid tracers	=
	Jack et al. [7]	Cross-sectional observational study (MCSA)	NCI	637/572	72	-	-	no	PiB-PET	=
	Scheinin et al. [8]	Cross-sectional study	NCI	24/40	71.1/72.4	-	-	no	PiB-PET	m
	Jack et al. [9]	Cross-sectional study (MCSA)	NCI	236/199	74.9	-	-	no	prevalence of amyloid abnormal (A+) individuals, SUVR>1.42 PiB-PET	=

	Vemuri et al. [10]	Cohort study, prospective analysis (MCSA)	737 NCI, 174 MCI, 18 AD dementia, 1 Parkinson disease, 1 AD with vascular dementia, 1 progressive supranuclear palsy, 3 dementia hard to classify, and 7 missing clinical diagnosis	519/423	80/79.4	DSM-IV criteria for dementia	no	yes	PiB-PET	w
Tau	Barnes et al. [1]	Cohort study (ROS)	AD dementia	64/77	83.5/86.2	NINCDS-ADRDA plus post-mortem neuropathological confirmation	no	yes	NFT (modified Bielschowsky silver stain)	w
	Holland et al. [4]	Cohort study (ADNI)	AD dementia	55/50	75.5/76.8	NINCDS-ADRDA CDR of 0.5 or 1.0	no	no	tau CSF	=
			MCI	244/141	77.1/76	Subjective memory complaint, objective memory loss measured by WMS-LM-II, a CDR of 0.5				= (p=0.06 for higher tau concentration in women)
			NCI	96/93	76.2/76.2	n.a.	no	no		=
	Mattsson et al. [3]	Review	AD, prodromal AD,NCI	n.a.	n.a.	IWG-2 criteria	yes	n.a.	tau CSF	=
	Johnson et al. [11]	Cohort study (Harvard Aging Brain Study)	AD dementia, MCI and NCI	32/43	73	NIA-AA	no	no	18F T807 PET	=
	Jack et al. [9]	Cross-sectional study (MCSA)	NCI	(236/199)	74.9	-	-	no	prevalence of tau abnormal (T+) individuals, SUVR>1.23, AV1451 - PET	=

The table summarizes the main findings of the studies reported in the body of the manuscript, specifying the diagnostic criteria, the use of biomarkers for diagnosis and whether the results where statistically corrected for CVD (cerebrovascular disease or cardiovascular risk factors). m(men), w (women).
ROS (Religious Order Study); MCSA (Mayo Clinic Study of Aging), ADNI (Alzheimer's Disease Neuroimaging Initiative); NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association, criteria for probable AD dementia [12]); NIA-AA (National Institute on Aging and the Alzheimer's Association criteria for probable AD dementia [13]); DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, forth edition, American

Psychiatric Association); IWG-2 (revised international working group criteria [14]); Petersen's criteria [15]; CDR (clinical dementia rate); MMSE (mini-mental state examination); CAA (cerebral amyloid angiopathy); NFT (neurofibrillary tangles); WMS-LM-II (Wechsler Memory Scale Logical Memory II)
n.a. not available

1 Barnes, L. L. *et al.* Sex differences in the clinical manifestations of Alzheimer disease pathology. *Arch Gen Psychiatry* **62**, 685-691 (2005).
2 Shinohara, M. *et al.* Impact of sex and APOE4 on cerebral amyloid angiopathy in Alzheimer's disease. *Acta Neuropathol* **132**, 225-234 (2016).
3 Mattsson, N. *et al.* Clinical validity of cerebrospinal fluid Abeta42, tau, and phospho-tau as biomarkers for Alzheimer's disease in the context of a structured 5-phase development framework. *Neurobiol Aging* **52**, 196-213 (2017).
4 Holland, D., Desikan, R. S., Dale, A. M., McEvoy, L. K. & Alzheimer's Disease Neuroimaging, I. Higher rates of decline for women and apolipoprotein E epsilon4 carriers. *AJNR. American journal of neuroradiology* **34**, 2287-2293 (2013).
5 Gottesman, R. F. *et al.* The ARIC-PET amyloid imaging study: Brain amyloid differences by age, race, sex, and APOE. *Neurology* **87**, 473-480 (2016).
6 Jansen, W. J. *et al.* Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. *JAMA* **313**, 1924-1938 (2015).
7 Jack, C. R., Jr. *et al.* Age, Sex, and APOE epsilon4 Effects on Memory, Brain Structure, and beta-Amyloid Across the Adult Life Span. *JAMA Neurol* **72**, 511-519 (2015).
8 Scheinin, N. M. *et al.* Cortical (1)(1)C-PIB uptake is associated with age, APOE genotype, and gender in "healthy aging". *J Alzheimers Dis* **41**, 193-202 (2014).
9 Jack, C. R., Jr. *et al.* Age-specific and sex-specific prevalence of cerebral beta-amyloidosis, tauopathy, and neurodegeneration in cognitively unimpaired individuals aged 50-95 years: a cross-sectional study. *Lancet Neurol* **16**, 435-444 (2017).
10 Vemuri, P. *et al.* Evaluation of Amyloid Protective Factors and Alzheimer Disease Neurodegeneration Protective Factors in Elderly Individuals. *JAMA Neurol* (2017).
11 Johnson, K. A. *et al.* Tau positron emission tomographic imaging in aging and early Alzheimer disease. *Annals of neurology* **79**, 110-119 (2016).
12 McKhann, G. *et al.* Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* **34**, 939-944 (1984).
13 McKhann, G. M. *et al.* The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 263-269 (2011).
14 Dubois, B. *et al.* Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. *Lancet Neurol* **13**, 614-629 (2014).
15 Petersen, R. C. Mild cognitive impairment as a diagnostic entity. *J Intern Med* **256**, 183-194 (2004).

Supplementary table 3 | Summary of evidence for sex-effects on brain atrophy in the elderly and AD

	Ref.	Study design (database)	Diagnosis	n. m/w	Age m/w (y)	Diagnostic criteria	Biomarker-based diagnosis?	Corrected for CVD?	MRI measurement	Worst in m/w?
Brain atrophy	Sundermann et al. [1]	Cross-sectional (ADNI)	AD dementia	128/107	74.7/74.3	MMSE score between 20 and 26, a CDR of 0.5 or 1, NINCDS-ADRDA	no	no	Hippocampal volume calculated using the formula hippocampal/intracranial volume x 10^3	m
			aMCI	409/285	73.3/71.2	MMSE score between 24 and 30, CDR of 0.5, a subjective memory complaint, and objective memory loss by WMS-LM II	no	no		m
			NCI	192/187	74.6/73.7	-	-	no		m
	Apostolova et al. [2]	Prospective longitudinal cohort study (UCLA)	AD dementia	15/19	76.2	NINCDS/ADRDA	no	no	hippocampal thickness measured via surface-based analytic technique	w
			aMCI	15/16	73.7	DSM-IV criteria	no	no		
	Jack et al. [3]	Cross-sectional (MCSA)	NCI	655/591	72	n.a.	no	no	adjusted hippocampal volume (the difference, in cubic centimeters, compared to the expected hippocampal volume given a person's head size)	m
	Vemuri et al. [4]	Cohort study, prospective analysis (MCSA)	737 NCI, 174 MCI, 18 AD dementia, 1 Parkinson disease, 1 AD with vascular dementia, 1 progressive supranuclear palsy, 3 dementia hard to classify, and 7 had a missing clinical diagnosis	519/423	80/79.4	DSM-IV criteria for dementia	no	yes	cortical thickness	m

	Jack et al. [5]	Cross-sectional (MCSA)	NCI	236/199	74.9	-	-	no	prevalence of abnormal neurodegeneration (N+) individuals, cortical thickness < 2.67mm	=
									prevalence of abnormal neurodegeneration (N+) individuals, hippocampal volume adjusted for total intracranial volume of less than –1·15 mL	m
Brain atrophy rates	Hua et al. [6]	Longitudinal (ADNI)	AD dementia	114	76.5	NINCDS-ADRDA	no	no	tensor-based morphometry (TBM), temporal lobes	=
			aMCI	238	76	Petersen Criteria	no	no		w
			NCI	202	77	-	no	no		=
	Ardekani et al. [7]	Longitudinal (MIRIAD)	AD dementia	18/25	69/69.5	NINCDS-ADRDA	no	no	hippocampal atrophy progression measured via Hippocampal volumetric integrity (HI) . HI was defined as the fraction of tissue (non-CSF) found in a region that is expected to encompass a normal hippocampus.	w
			NCI	11/11	72.9/65.8	-	no	no		=
	Holland et al. [8]	Longitudinal (ADNI)	AD dementia	55/50	75.5/76.8	NINCDS-ADRDA CDR of 0.5 or 1.0	no	no	rate of atrophy of all regions except the hippocampus and amygdala (quantification anatomical regional change, Quarc)	w
			aMCI	244/141	77.1/76	subjective memory complaint, objective memory loss measured by WMS-LM II, a CDR of 0.5	no	no	rate of atrophy all regions except the hippocampus (quantification anatomical regional change, Quarc)	w

			NCI	96/93	76.2/76.2	n.a.	no	no	rate of atrophy in hippocampus, enthorinal cortex and amygdala (quantification anatomical regional change, Quarc)	w
	Skup et al. [9]	Longitudinal (ADNI)	AD dementia	101/96	76.5	AD dementia: MMSE scores between 20 and 26 inclusive, a CDR-sob between 1 and 9, NINCDS/ADRDA	no	no	rate of atrophy in Left insula-bilateral thalamus-Right middle temporal gyrus (RAVENS maps)	m
			aMCI	176/90	74.9	MMSE scores between 24 and 30 inclusive, a memory complaint, objective memory loss measured by WMS-LM II			rate of atrophy in bilateral thalamus-bilateral Caudate Nuclesu-Right middle temporal gyrus (RAVENS maps)	m
									rate of atrophy in Bilateral Precuneus-Left Middle Temporal gyrus (RAVENS maps)	w
			NCI	114/110	76	-			rate of atrophy in Right Amygdala (RAVENS maps)	w
									rate of atrophy in Left Thalamus-Right Caudate Nucleus - Right Precuneus (RAVENS maps)	m

The table summarizes the main findings of the studies reported in the body of the manuscript, specifying the diagnostic criteria, the use of biomarkers for diagnosis and whether the results were statistically corrected for CVD (cerebrovascular disease or cardiovascular risk factors). m(men); w (women).
MCSA (Mayo Clinic Study of Aging); ADNI (Alzheimer's disease neuroimaging initiative); NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association, criteria for probable AD dementia[10]); NIA-AA (National Institute on Aging and the Alzheimer's Association criteria for probable AD dementia[11]); DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, forth edition, American Psychiatric Association); CDR (clinical dementia rate); CDR-sob (CDR sum-of-boxes); MMSE (mini-mental state examination); UCLA (University of California–Los Angeles Alzheimer's Disease Research Center); WMS-LM II (Wechsler Memory Scale Logical Memory II).
n.a. (not available)

1 Sundermann, E. E. *et al.* Better verbal memory in women than men in MCI despite similar levels of hippocampal atrophy. *Neurology* **86**, 1368-1376 (2016).

2 Apostolova, L. G. *et al.* 3D comparison of hippocampal atrophy in amnestic mild cognitive impairment and Alzheimer's disease. *Brain : a journal of neurology* **129**, 2867-2873 (2006).

3 Jack, C. R., Jr. *et al.* Age, Sex, and APOE epsilon4 Effects on Memory, Brain Structure, and beta-Amyloid Across the Adult Life Span. *JAMA Neurol* **72**, 511-519 (2015).
4 Vemuri, P. *et al.* Evaluation of Amyloid Protective Factors and Alzheimer Disease Neurodegeneration Protective Factors in Elderly Individuals. *JAMA Neurol* (2017).
5 Jack, C. R., Jr. *et al.* Age-specific and sex-specific prevalence of cerebral beta-amyloidosis, tauopathy, and neurodegeneration in cognitively unimpaired individuals aged 50-95 years: a cross-sectional study. *Lancet Neurol* **16**, 435-444 (2017).
6 Hua, X. *et al.* Sex and age differences in atrophic rates: an ADNI study with n=1368 MRI scans. *Neurobiol Aging* **31**, 1463-1480 (2010).
7 Ardekani, B. A., Convit, A. & Bachman, A. H. Analysis of the MIRIAD Data Shows Sex Differences in Hippocampal Atrophy Progression. *J Alzheimers Dis* **50**, 847-857 (2016).
8 Holland, D., Desikan, R. S., Dale, A. M., McEvoy, L. K. & Alzheimer's Disease Neuroimaging, I. Higher rates of decline for women and apolipoprotein E epsilon4 carriers. *AJNR. American journal of neuroradiology* **34**, 2287-2293 (2013).
9 Skup, M. *et al.* Sex differences in grey matter atrophy patterns among AD and aMCI patients: results from ADNI. *Neuroimage* **56**, 890-906 (2011).
10 McKhann, G. *et al.* Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* **34**, 939-944 (1984).
11 McKhann, G. M. *et al.* The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 263-269 (2011).