Sex and gender differences in Alzheimer‘s and cognitive screening

WOMEN‘S BRAIN PROJECT®

Maria Teresa Ferretti, PhD

Co-founder and Chief Scientific Officer, Women’s Brain Project

October 7th 2021, MoCA free webinar

Remembering Dr Nadia Chaudhri

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Dr. Nadia Chaudhri
@DrNadiaChaudhri

I hope you found this thread helpful. Know your bodies. Pay attention to fatigue and changes in bowel/urinary tract movements. Make sure you understand all the words on a medical report. Do not dismiss your pain or malaise. Find the expert doctors.

10:49 PM · Sep 13, 2021 · Twitter for iPhone

Our agenda

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1 Gender medicine and precision medicine: the work of Women's Brain Project

Q&A

2 Sex and gender differences in Alzheimer's disease
I – risk factors, biomarkers, clinical trials

Q&A

3 Sex and gender differences in Alzheimer's disease
II – focus on cognitive assessment

Q&A

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1

Gender Medicine and Precision Medicine

The work of WBP

Women's Brain Project (WBP) – A clear purpose to transform brain and mental diseases

WOMEN'S BRAIN PROJECT®

WHO WE ARE

WBP is leading an unprecedented initiative to understand how **SEX AND GENDER FACTORS** impact brain and mental diseases to achieve precision medicine

OUR MISSION

Improve the state of medical treatments and drug development for **BRAIN AND MENTAL HEALTH** through sex and gender factors analysis as a gateway to **PRECISION MEDICINE**

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@womensbrainpro

Positioning sex differences within Precision Medicine

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nature reviews neurology

Review Article | Published: 09 July 2018

Sex differences in Alzheimer disease - the gateway to precision medicine

Maria Teresa Ferretti, Maria Florencia Iulita, Enrica Cavedo, Patrizia Andrea Chiesa, Annemarie Schumacher Dimech, Antonella Santuccione Chadha, Francesca Baracchi, Hélène Girouard, Sabina Misoch, Ezio Giacobini, Herma Depypere, Harald Hampel & for the Women's Brain Project and the Alzheimer Precision Medicine Initiative

Nature Reviews Neurology **14**, 457–469(2018) | Cite this article

european journal of neurology
the official journal of the european academy of neurology

ean

EAN REVIEW | Free Access

Sex and gender differences in Alzheimer's disease: current challenges and implications for clinical practice

Maria Teresa Ferretti, Julie Martinkova, Ewelina Biskup, Thomas Benke ... See all authors

First published:13 February 2020 | https://doi.org/10.1111/ene.14174

nature

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CORRESPONDENCE · 30 APRIL 2019

Account for sex in brain research for precision medicine

Maria Teresa Ferretti, Antonella Santuccione-Chadha & Harald Hampel

Precision medicine and breast cancer

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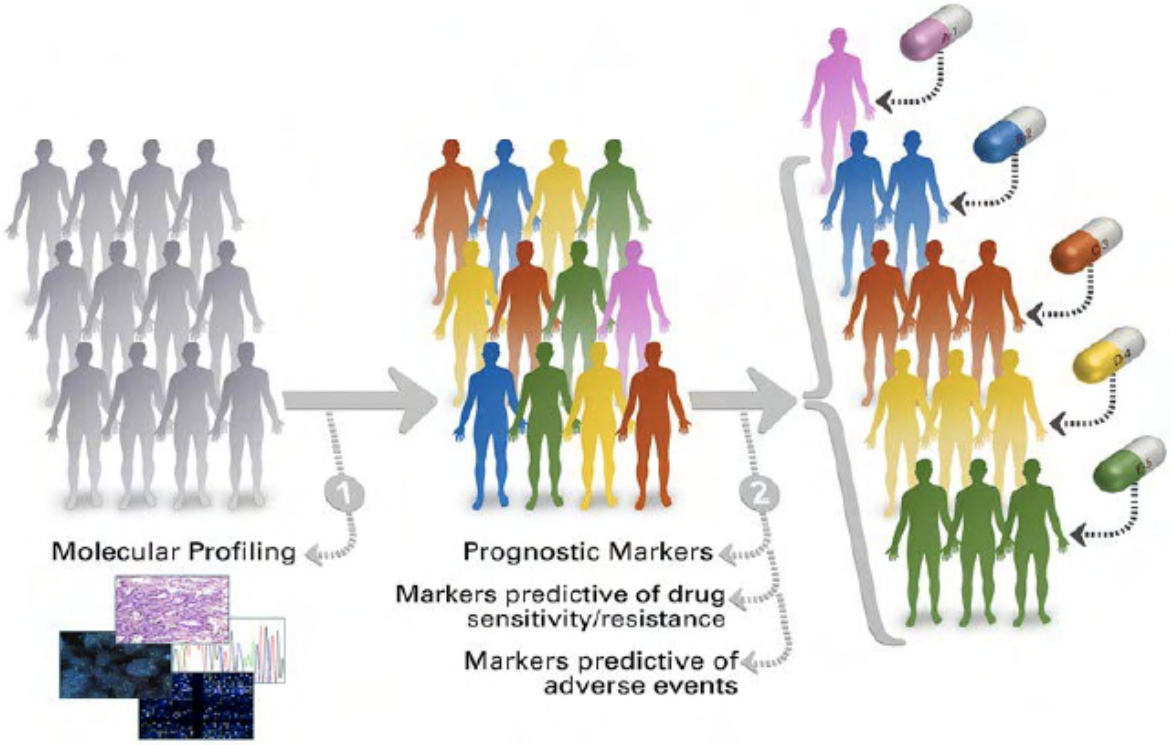

Why we need precision medicine in neurology

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1Fernandenz et al., J Neurol 2010; 2Breen et al., J Neurol 2013; 3Paganoni et al., Am Lat Scl Frontotemp Deg 2014; 4 Alzheimer Europe

- Late/no diagnosis
- Low use of biomarkers
- No treatment or
- Treatment often based on trial and error

Poll 1
Are sex and gender synonyms?

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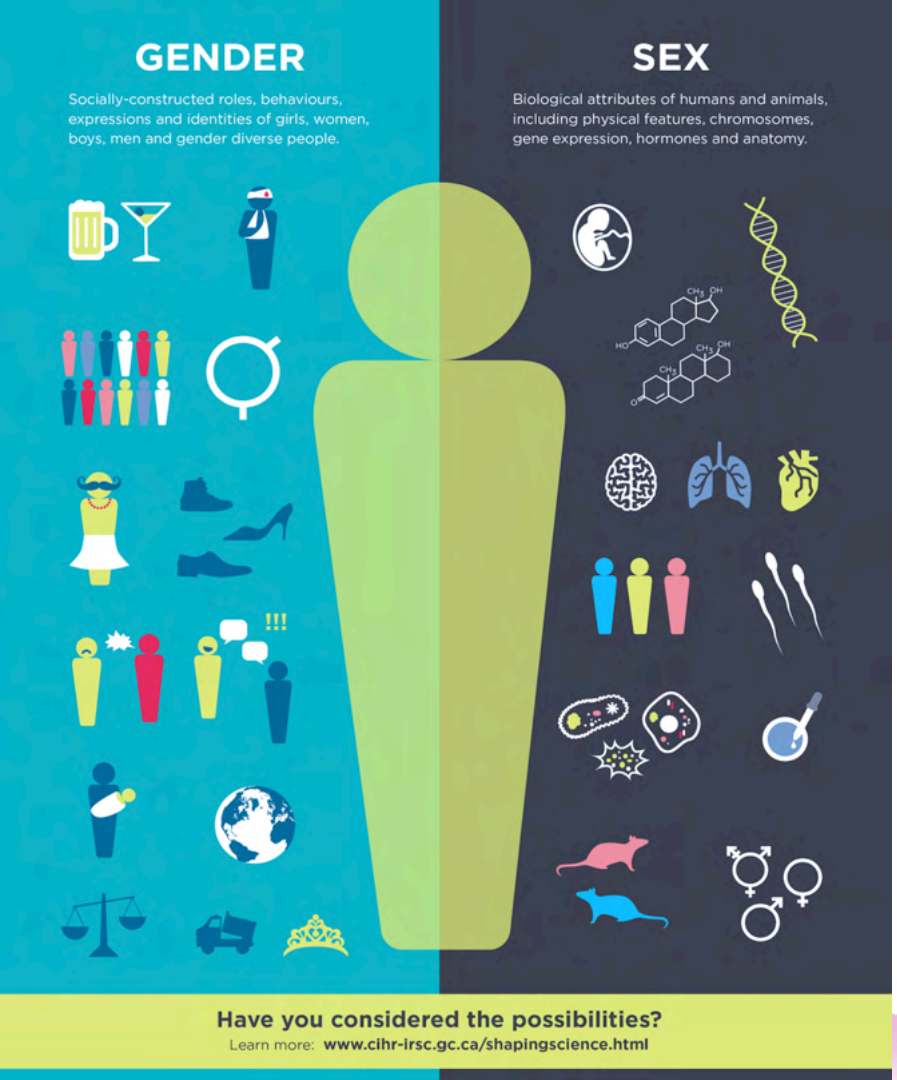

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Both sex and gender are determinants of health (source: WHO)

Image source: CIHR

Gender medicine

Women's health is not just bikini medicine

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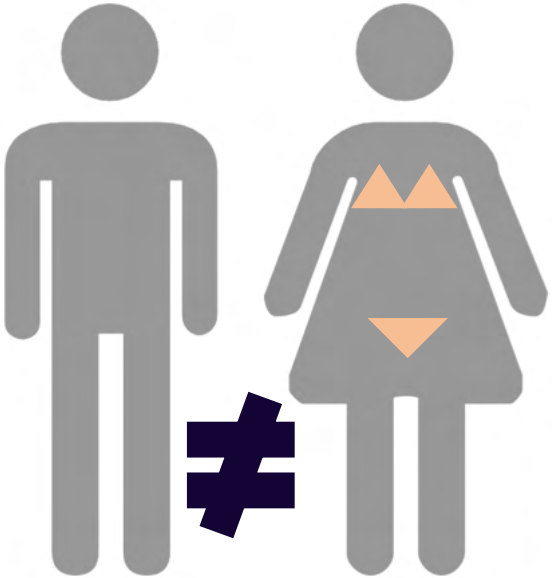

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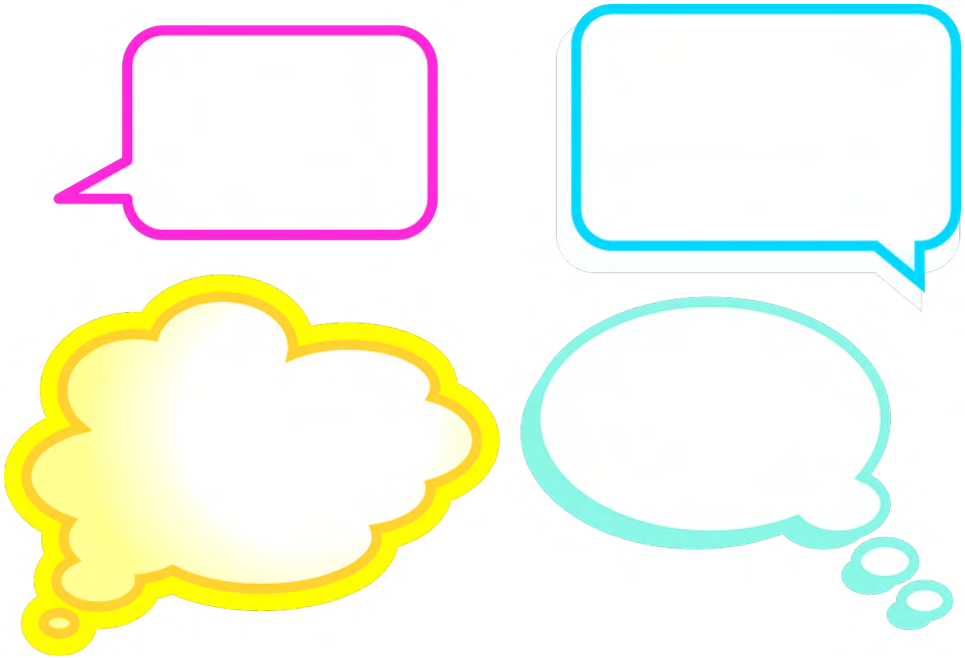

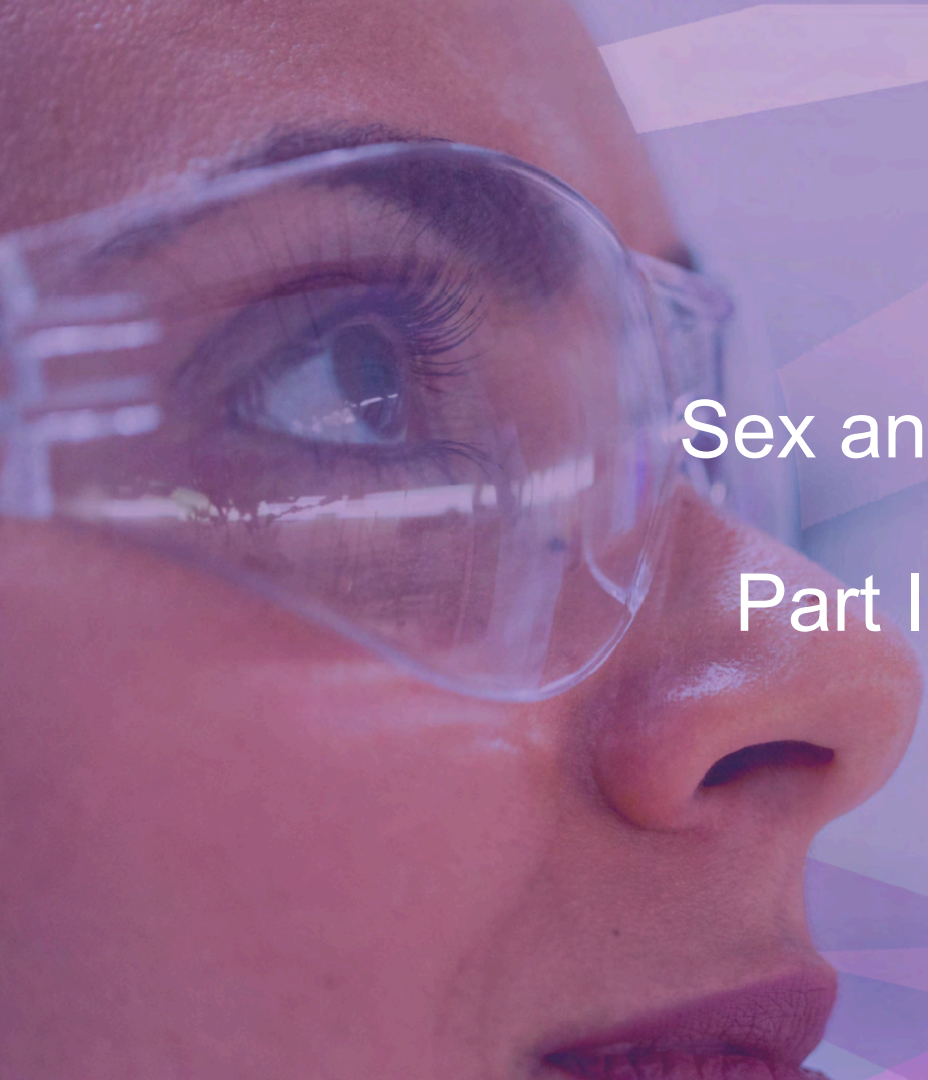

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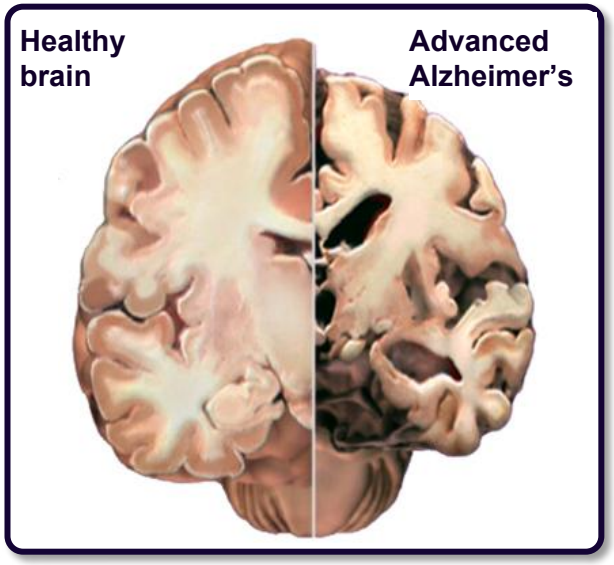
2

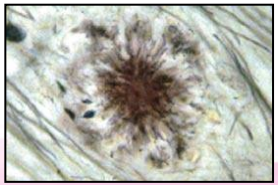
Sex and gender differences in AD

Part I: risk factors, biomarkers, clinical trials

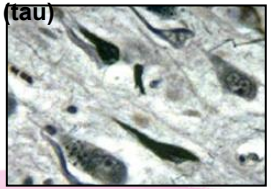
Alzheimer's - a progressive, neurodegenerative disease



Amyloid plaque

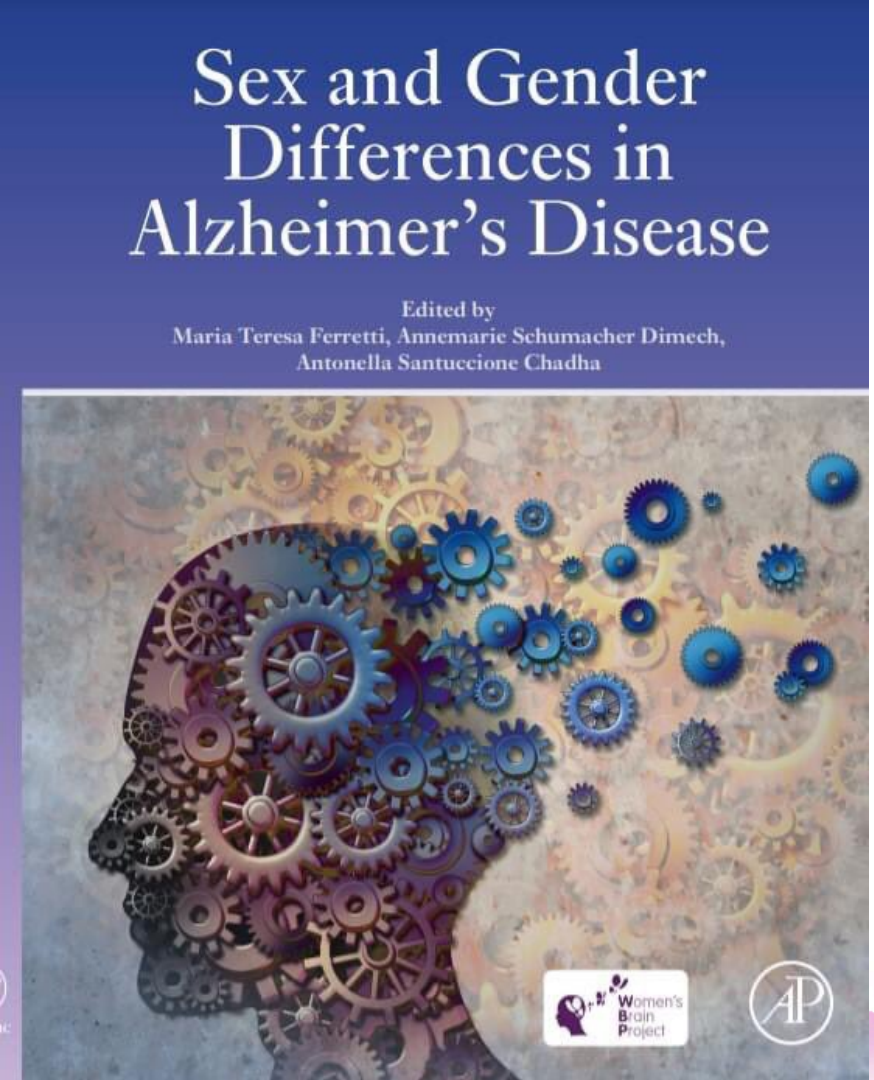


Neurofibrillary tangle (tau)



- Prodromal phase: MCI= mild cognitive impairment
- High heterogeneity
- Symptomatic therapies
- Aducanumab approved by FDA as disease-modifying
- Early diagnosis is key

- **2/3 patients worldwide are women**



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First textbook on the topic

- > 400 pages
- > 60 authors
- 15 countries
- 3 sections (basic science, clinical science, socioeconomic factors)
- 16 chapters

Women representation in clinical trials

JAMA Network | Open

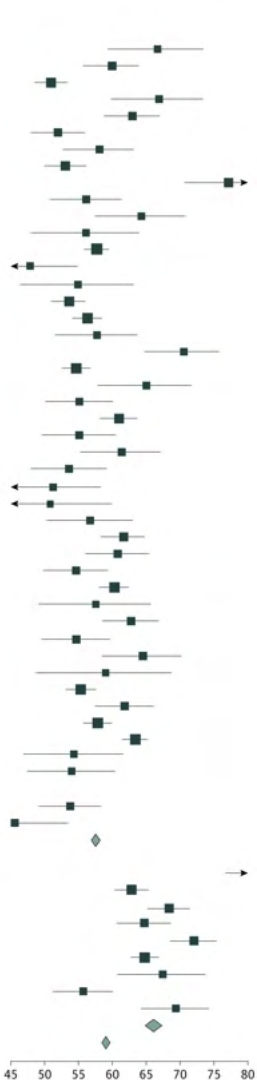
Original Investigation | Neurology

Proportion of Women and Reporting of Outcomes by Sex in Clinical Trials for Alzheimer Disease

A Systematic Review and Meta-analysis

Julie Martinkova, MD; Frances-Catherine Quevenco, PhD; Helene Karcher, PhD; Alberto Ferrari, PhD; Elsa Charlotte Sanchez, MD, PhD; Cassandra Szoeke, PhD, MBBS; Jakub Hort, MD, PhD; Reinhold Schmidt, MD; Antonella Santuccione Chadha, MD, PhD; Maria Teresa Ferretti, PhD

Study	Patients, No.	Females, % (95% CI)
Experimental drugs		
Doody et al,[26] 2008	183	66.7 (59.3-73.4)
Sevigny et al,[27] 2008	563	57.9 (53.7-62.0)
Green et al,[28] 2009	1649	50.9 (48.5-53.4)
Maher-Edwards et al,[29] 2011	196	66.8 (59.8-73.4)
Gold et al,[30] 2010	553	62.9 (58.8-67.0)
Feldman et al,[31] 2010	614	52.0 (47.9-56.0)
Maher-Edwards et al,[32] 2010	357	58.0 (52.7-63.2)
Aisen et al,[33] 2011	1005	53.0 (49.9-56.2)
Alvarez et al,[34] 2011	197	77.2 (70.7-82.8)
Salloway et al,[35] 2011	351	56.1 (50.8-61.4)
Raffi et al,[36] 2011	210	64.3 (57.4-70.8)
Vellas et al,[37] 2011	157	56.1 (47.9-64.0)
Harrington et al,[38] 2011	2822	57.7 (55.8-59.5)
Coric et al,[39] 2012	209	47.8 (40.9-54.8)
Egan et al,[40] 2012	144	54.9 (46.4-63.2)
Doody et al,[41] 2013	1534	53.5 (50.9-56.0)
Doody et al,[42] 2014	2052	56.3 (54.1-58.4)
Marek et al,[43] 2014	267	57.7 (51.5-63.7)
Wilkinson et al,[44] 2014	278	70.5 (64.8-75.8)
Salloway et al,[45] 2014	2204	53.9 (51.8-56.0)
Grove et al,[46] 2014	194	64.9 (57.8-71.6)
Galasko et al,[47] 2014	399	57.1 (52.1-62.1)
Maher-Edwards et al,[48] 2015	1231	60.9 (58.1-63.7)
Lenz et al,[49] 2015	334	55.1 (49.6-60.5)
Gault et al,[50] 2015	274	61.3 (55.3-67.1)
Wischik et al,[51] 2015	321	53.6 (48.0-59.1)
Gauthier et al,[52] 2015	203	51.2 (44.1-58.3)
Maher-Edwards et al,[53] 2015	121	50.4 (41.2-59.6)
Pasquier et al,[54] 2016	245	56.7 (50.3-63.0)
Gauthier et al,[55] 2016	885	61.6 (58.3-64.8)
Gault et al,[56] 2016	436	60.8 (56.0-65.4)
Florian et al,[57] 2016	434	54.6 (49.8-59.4)
Vandenberghe et al,[58] 2016	1917	60.3 (58.0-62.5)
Brody et al,[59] 2016	146	57.5 (49.1-65.7)
Nave et al,[60] 2017	542	62.7 (58.5-66.8)
Relkin et al,[61] 2017	390	54.6 (49.5-59.6)
Xiao et al,[62] 2017	273	64.5 (58.5-70.1)
Rinne et al,[63] 2016	100	59.0 (48.7-68.7)
Egan et al,[64] 2018	1957	55.3 (53.1-57.6)
Lawlor et al,[65] 2018	498	61.8 (57.4-66.1)
Honig et al,[66] 2018	2129	57.8 (55.7-59.9)
Atri et al,[67] 2018	2475	63.4 (61.4-65.3)
Fullerton et al,[68] 2018	186	54.3 (46.9-61.6)
Voss et al,[69] 2018	239	54.0 (47.4-60.4)
Cummings et al,[70] 2018	433	52.7 (47.8-57.4)
Schneider et al,[71] 2019	469	53.7 (49.1-58.3)
van Dyck et al,[72] 2019	159	45.3 (37.4-53.4)
Subtotal	32535	57.5 (56.9-58.0)
Approved drugs		
Burns et al,[73] 2009	407	80.8 (76.7-84.5)
Farlow et al,[74] 2010	1434	62.8 (60.3-65.3)
Nakamura et al,[75] 2011	855	68.3 (65.1-71.4)
Cummings et al,[76] 2012	567	64.7 (60.6-68.7)
Grossberg et al,[77] 2013	676	72.0 (68.5-75.4)
Hager et al,[78] 2014	2045	64.8 (62.7-66.9)
Nakamura et al,[79] 2015	215	67.4 (60.7-73.7)
Zhang et al,[80] 2016	501	55.7 (51.2-60.1)
Homma et al,[81] 2016	340	69.4 (64.2-74.3)
Subtotal	7040	66.1 (65.0-67.2)
Total	39575	59.0 (58.5-59.5)



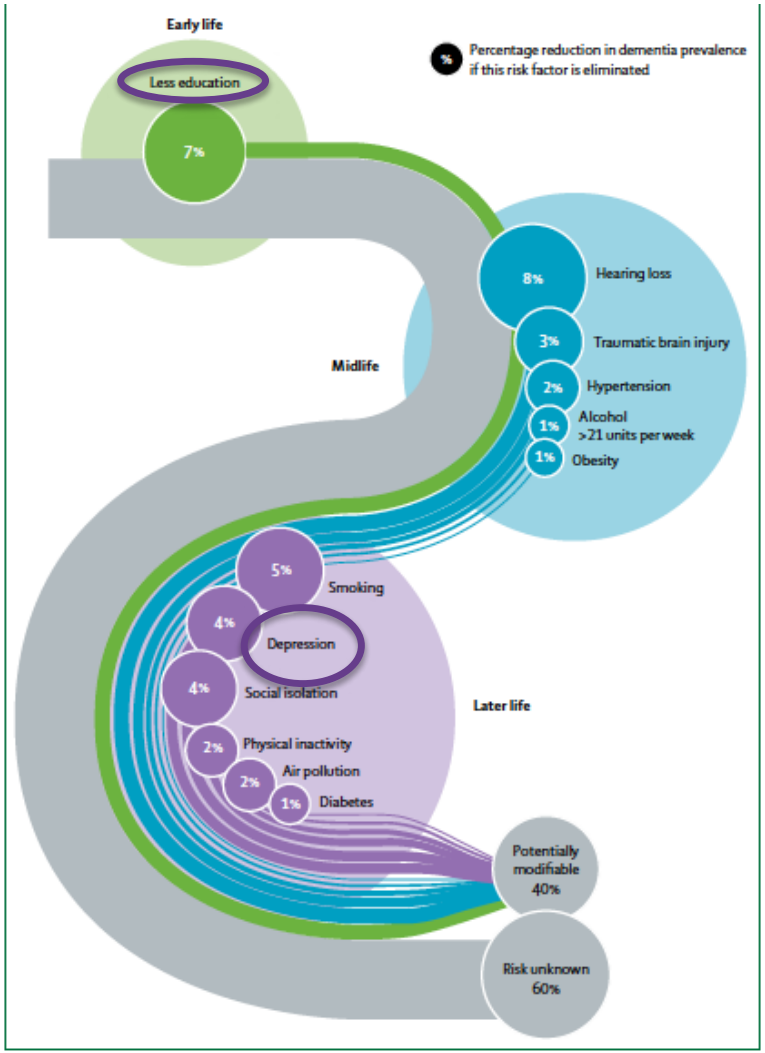


Figure 7: Population attributable fraction of potentially modifiable risk factors for dementia

Sex and gender differences in modifiable risk factors:

Opportunities for personalized strategies of risk reduction

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Livingstone et al, Lancet Commission 2020

Genetic risk prediction accuracy increases by considering sex differences

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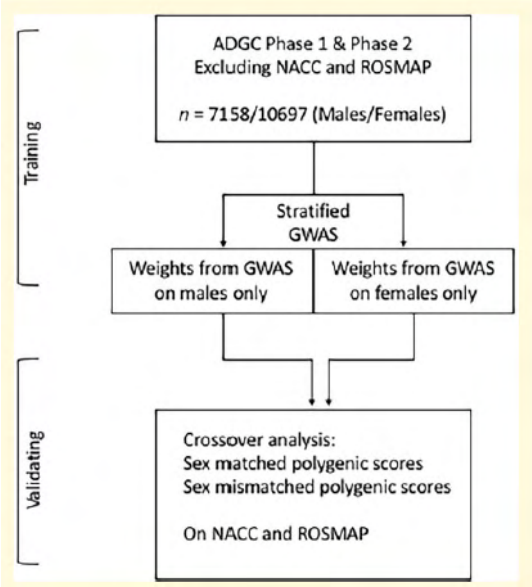

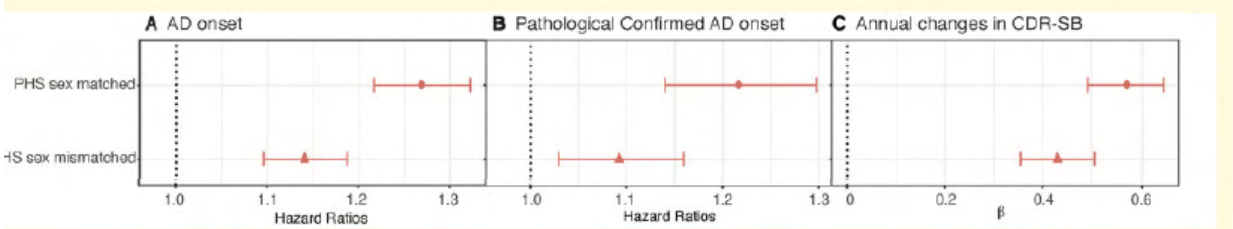

Fan et al; Brain 2020

Sex-differences in biomarkers: tau

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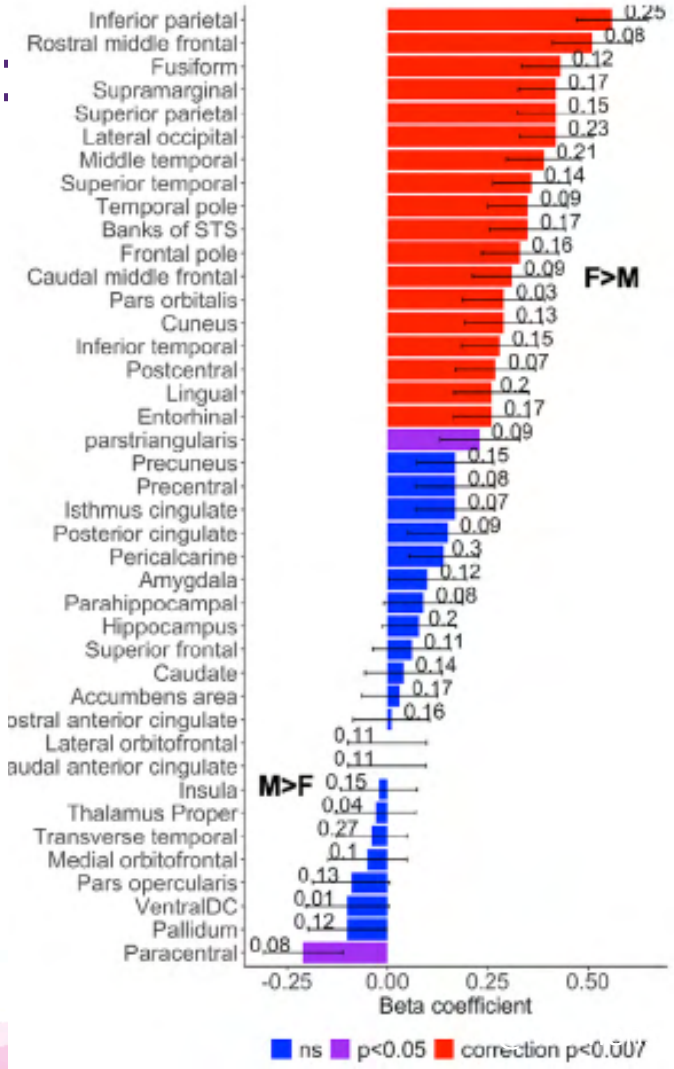
ARE August 11, 2020 ARTICLE

Sex differences in CSF biomarkers vary by Alzheimer's disease stage and APOE ε4 genotype

Rosha Babapour Mofrad, Betty M Tijms, Philip Scheltens, Frederik Barkhof, Wiesje M van der Flier, Sietske AM Sikkes, Charlotte E Teunissen

First published August 11, 2020, DOI: https://doi.org/10.1212/WNL.0000000000010629



Buckley et al., Annals of Neurology 2020

Sex as modifier of tau accumulation rate

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BRAIN
A JOURNAL OF NEUROLOGY

The accumulation rate of tau aggregates is higher in females and younger amyloid-positive subjects

Ruben Smith,[1,2] Olof Strandberg,[1] Niklas Mattsson-Carlgren,[1,2,3] Antoine Leuzy,[1] Sebastian Palmqvist,[1,4] Michael J. Pontecorvo,[5] Michael D. Devous Sr,[5] Rik Ossenkoppele[1,6] and Oskar Hansson[1,4]

Table 2 Results of linear models for tau accumulation

Coefficient	Estimate ± SE	T-value	P-value
Temporal meta-region of interest			
APOE ε4 status	−0.0027 ± 0.0085	−0.315	0.753
Amyloid-β status	0.0298 ± 0.0107	**2.785**	**0.006****
Age	−0.0012 ± 0.0005	**−2.494**	**0.013***
Sex	0.0220 ± 0.0077	**2.855**	**0.005****
Baseline tau	0.0577 ± 0.0151	**3.827**	**<0.001*****
Study Avid 05	0.015 ± 0.010	1.472	0.141
Study Exp 3	0.008 ± 0.017	0.465	0.642
Study BF	0.020 ± 0.013	1.551	0.122
CU	0.009 ± 0.017	0.530	0.596
MCI	0.016 ± 0.016	1.011	0.312
Neocortical region of interest			
APOE ε4 status	−0.0025 ± 0.0062	−0.398	0.691
Amyloid-β status	0.0145 ± 0.0062	1.865	0.062
Age	−0.0005 ± 0.0004	−1.501	0.134
Sex	0.0164 ± 0.0057	**2.903**	**0.004****
Baseline tau	0.0801 ± 0.0160	**5.014**	**<0.001*****
Study Avid 05	0.012 ± 0.008	1.604	0.109
Study Exp 3	0.009 ± 0.013	0.727	0.468
Study BF	0.015 ± 0.010	1.549	0.122
CU	−0.003 ± 0.012	−0.259	0.796
MCI	0.001 ± 0.011	0.073	0.942

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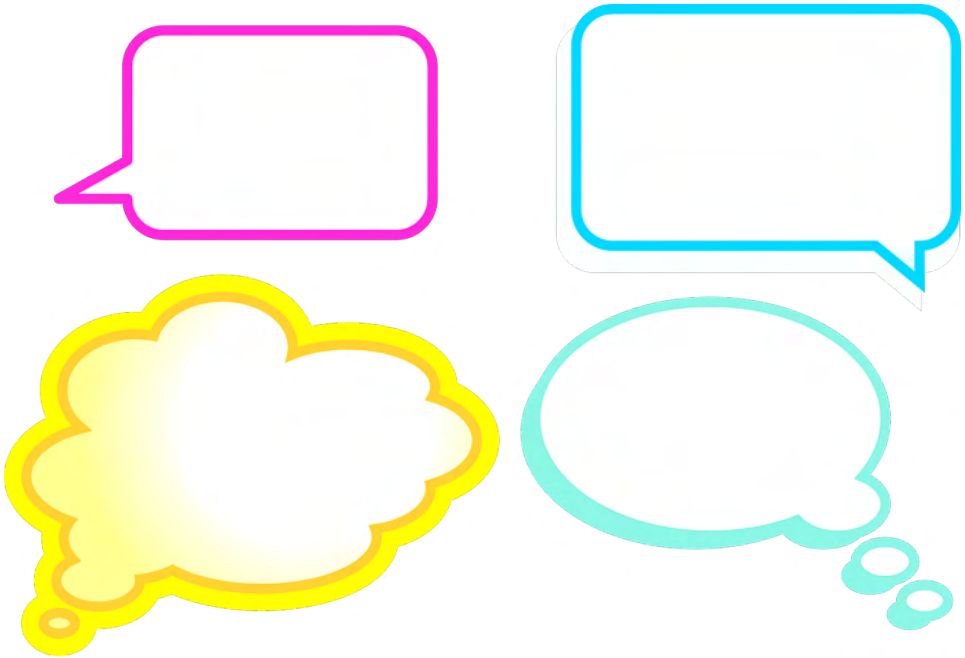

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3

Sex and gender differences in Alzheimer‘s disease

Part II – focus on cognitive assessment

The clinical continuum of Alzheimer's

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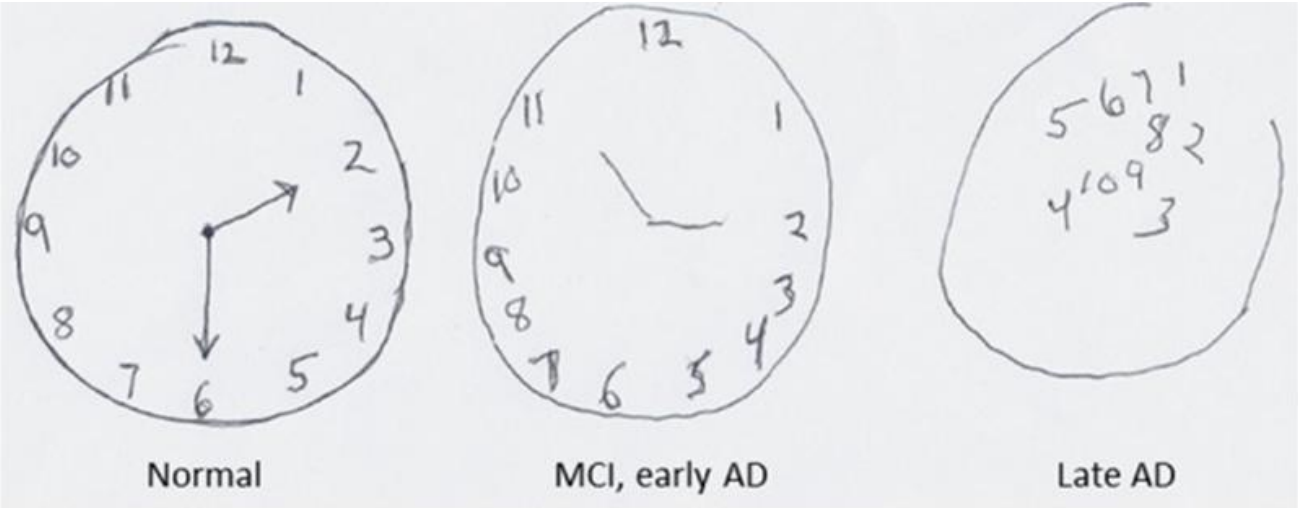

Poll 2
In your experience, do women and men generally perform differently on neuropsychological tests?

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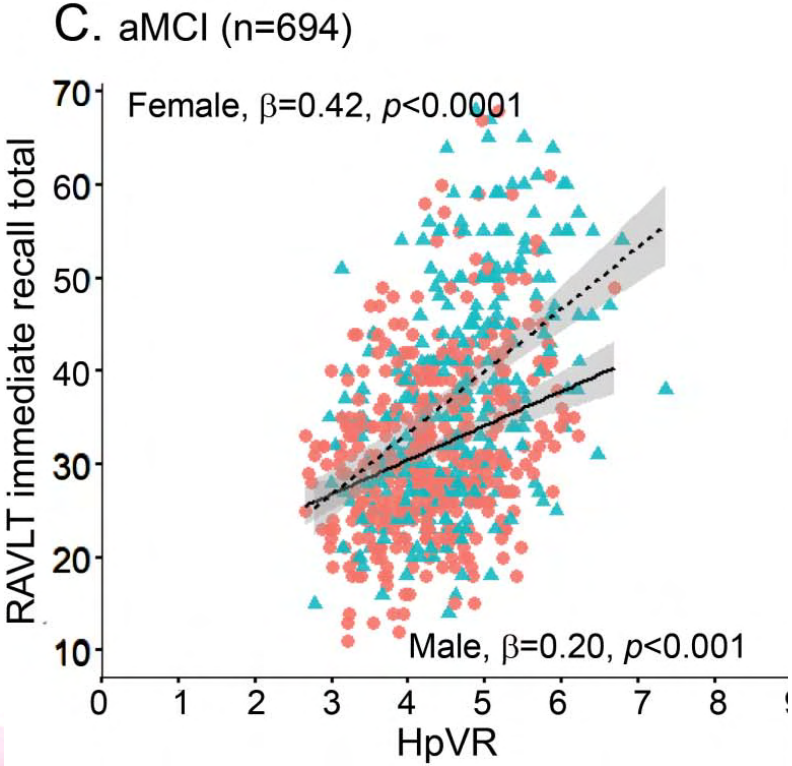
Differences in verbal memory (aMCI)



RAVLT: Rey Auditory Verbal Learning test, immediate recall

HpVR: normalized hippocampal volume

Women
Men

(Sundermann et al., Neurology 2016)

Verbal memory *Ability to learn, retain, recall, or recognize verbal information*	Language *Production, repetition, comprehension, naming, reading, and writing*	Executive function *Broad abilities associated with complex, higher-level cognitive functions*
Healthy controls • Women outperform men across learning, immediate and delayed free verbal recall • Women's advantage in semantic clustering suggests better self-initiating categorization during learning and retrieval	**Laterality** • Language representation is lateralized asymmetrically; degree of left lateralization is a function of hand dominance • The semantic system has components of bilateral neural representation • The semantic network is reliant on within-hemisphere and cross-hemisphere interconnectivity	**Source of executive disruption in AD** • Executive functions are susceptible, earliest and sensitive cognitive symptoms of AD • Dysfunction may reflect executive dysfunction direct from frontal regions, or regions with cortico-cortical networks as well as frontal cortical-subcortical networks
Mild cognitive impairment (MCI) • Women outperform men on total verbal scores at learning and at delay recall • With their verbal memory advantage, women's diagnosis of MCI may be *clinically* detected only with more advanced disease load • Verbal memory advantage in women may also reflect availability of alternate neural substrates to compensate for disease	**Semantic dysfunction in AD** • In AD, the semantic network is affected, but syntactic and phonological systems remain intact • The semantic network in AD is the most sensitive marker of disease development	**Sex/gender differences in AD** • Sex/gender performance on executive function tasks can appear "equivalent," however the strategies employed may be mediated by alternate networks resulting in sex/gender-specific advantage • Disease risk may be predicated on the vulnerability of the network disrupted during the disease course
Alzheimer's disease (AD) • Men outperform women on verbal memory recall • With clear clinical manifestation of AD, women lose their verbal memory advantage and perform worse than the men	**Sex/gender differences in language in AD** • Sex-specific language networks differ in men and women in AD • Women's ability to retain linguistic and verbal memory may rely on alternate spared semantic mechanisms • Women's semantic skills may be preserved, because of their compensatory strategy or networks	**Cognitive compensation** • Sex differences may depend on ability to reorganize to mask underlying cognitive decline • Compensatory upregulation of skill, but it may mask underlying cognitive decline • Compensatory reorganization by recruiting skills to manage novel tasks • Women's sex-specific verbal memory advantage may be associated with recruitment of frontal regions

Gammaga, Foldi and Au;
in Sex and Gender difference sin Alzheimer's Disease, Elsevier, 2021

Do women miss early diagnosis?

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October 09, 2019 ARTICLE

Sex-specific norms for verbal memory tests may improve diagnostic accuracy of amnestic MCI

Erin E. Sundermann, Pauline Maki, Anat Biegon, Richard B. Lipton, Michelle M. Mielke, Mary Machulda, Mark W. Bondi, for the Alzheimer's Disease Neuroimaging Initiative

First published October 9, 2019, DOI: https://doi.org/10.1212/WNL.0000000000008467

	Women with aMCI, n (%)	Men with aMCI, n (%)	χ^2 Test, *p* value
aMCI classified via conventional diagnostic criteria	120 (26)	239 (45)	38.5, <0.001
aMCI classified via sex-specific diagnostic criteria	165 (36)	184 (35)	0.25, 0.66

Abbreviation: aMCI = amnestic mild cognitive impairment.

See also: Stricker et al, 2020

Faster decline in women with MCI

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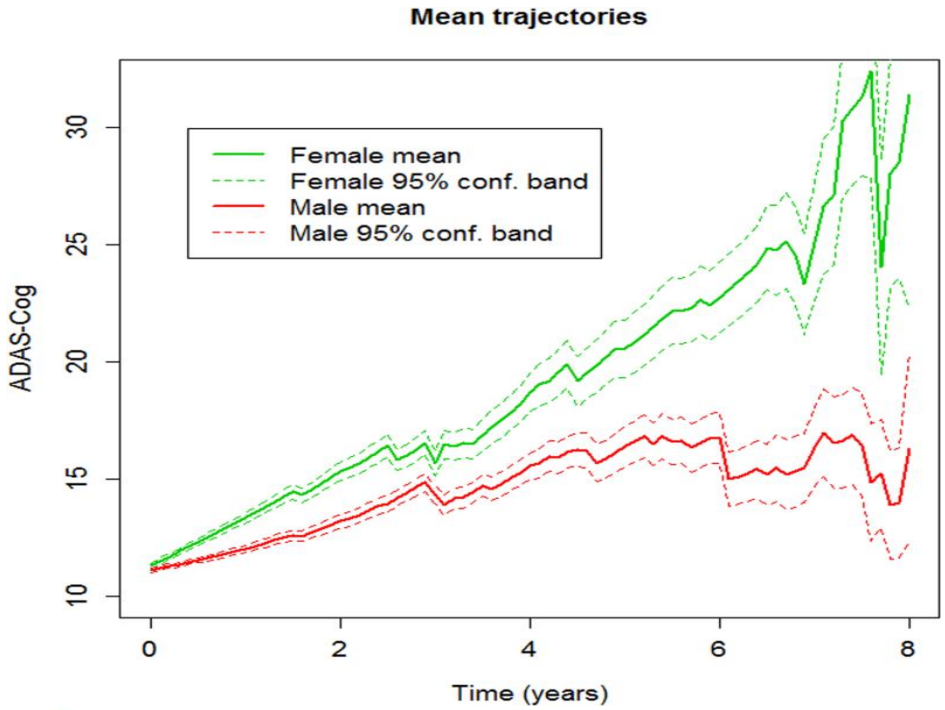

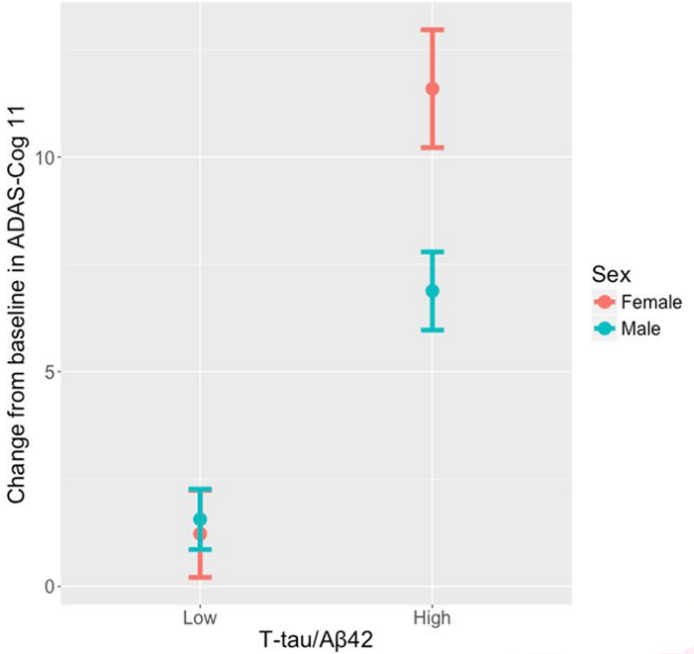

Lin et al., 2015, A&D Sohn et al., Scientific Reports 2018

The MoCA test

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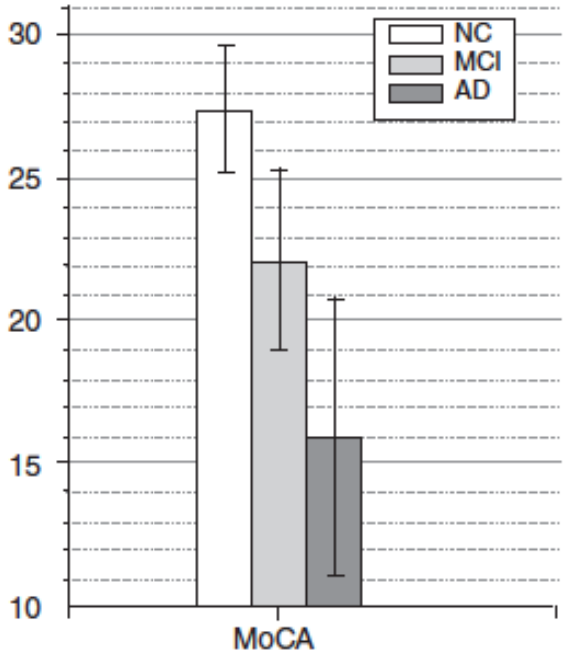
- Short term memory
- Visuospatial abilities
- Executive function
- Attention, concentration, working memory
- Language
- Orientation in time and space



Nasreddine et al, 2005

Variables that affect MoCA

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- Age
- Education

1 point is added to the test-taker's score if they have 12 years or less of formal education

How about gender?

Conti et al., 2015; Freitas et al., 2011; Kenny et al., 2013; Narazaki et al., 2013; Oren et al., 2015; Rosetti et al., 2011; Santangelo et al., 2014

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Examples of papers that found no sex differences

- Luis CA, et al 2009
- Freitas et al., 2011
- Bernstein IH, et al. 2011
- Rosetti et al., 2011
- Freitas et al. 2012
- Narazaki et al., 2013
- Santangelo et al., 2014
- Conti et al., 2015

Examples of papers that found sex differences

- Kaya et al. 2014
- Engedat, et al. 2021
- Borland et al, 2017
- Konstantopoulos et al., 2016
- Thomann et al., 2018

MoCA – paper that found sex differences

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	population	community dwelling	NCI	MCI	AD dementia
Kaya et al. 2014	Turkish				F<M
Engedat, et al. 2021	Norwegian	F>M			
Borland et al, 2017	Swedish	F>M			
Konstantopoulos et al., 2016	Greek		F>M		

Looking forward
Sex and gender differences in cognitive assessment

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- Direct comparison of scores vs multivariate regression
- In 'healthy' individuals we have no info on **biomarker status** (some might be AD +ve!)
- Sex differences might depend on **disease stage** and differ **by domain**
- Even when absolute values are equal, sex differences might exist in the diagnostic or **predictive value**

Conclusions

- Sex and gender differences have been found in fundamental clinical features of AD, including biomarkers and neuropsychological scores
- Such differences might be leveraged for more precise diagnostic tools (with new tests or sex-adjusted cut offs)
- From ‘one size fits all’ to precision medicine

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