onda
Osservatorio nazionale sulla salute della donna e di genere

2° CONGRESSO NAZIONALE
Verso la medicina genere specifica

LA DONNA E LA COPPIA
DOPO L'ETA' FERTILE

La salute che cambia:
prevenzione, stili di vita, fragilità

19 - 20
settembre 2018

HOTEL MICHELANGELO
MILANO

Decadimento cognitivo lieve e differenze di genere

Vincenzo Silani

U.O. Neurologia-Stroke Unit - Laboratorio di Neuroscienze
IRCCS Istituto Auxologico Italiano
Università degli Studi di Milano

MCI (1999…..)

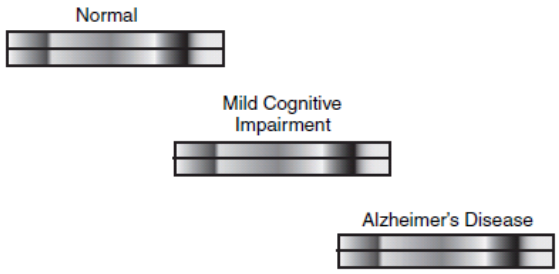
Mild Cognitive Impairment: *An Overview*

By Ronald C. Petersen, MD, PhD, and Selamawit Negash, PhD

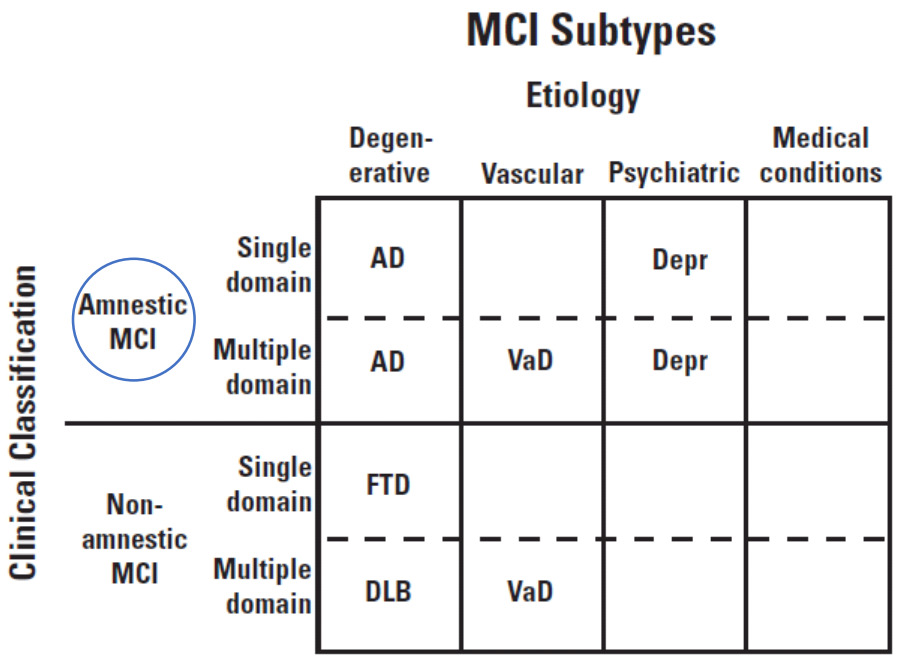
TABLE.
MCI Original Criteria

1. Memory complaint, preferably qualified by an informant
2. Memory impairment for age
3. Preserved general cognitive function
4. Intact activities of daily living
5. Not demented

Petersen R, Negash S. *CNS Spectr.* Vol 13, No 1. 2008.



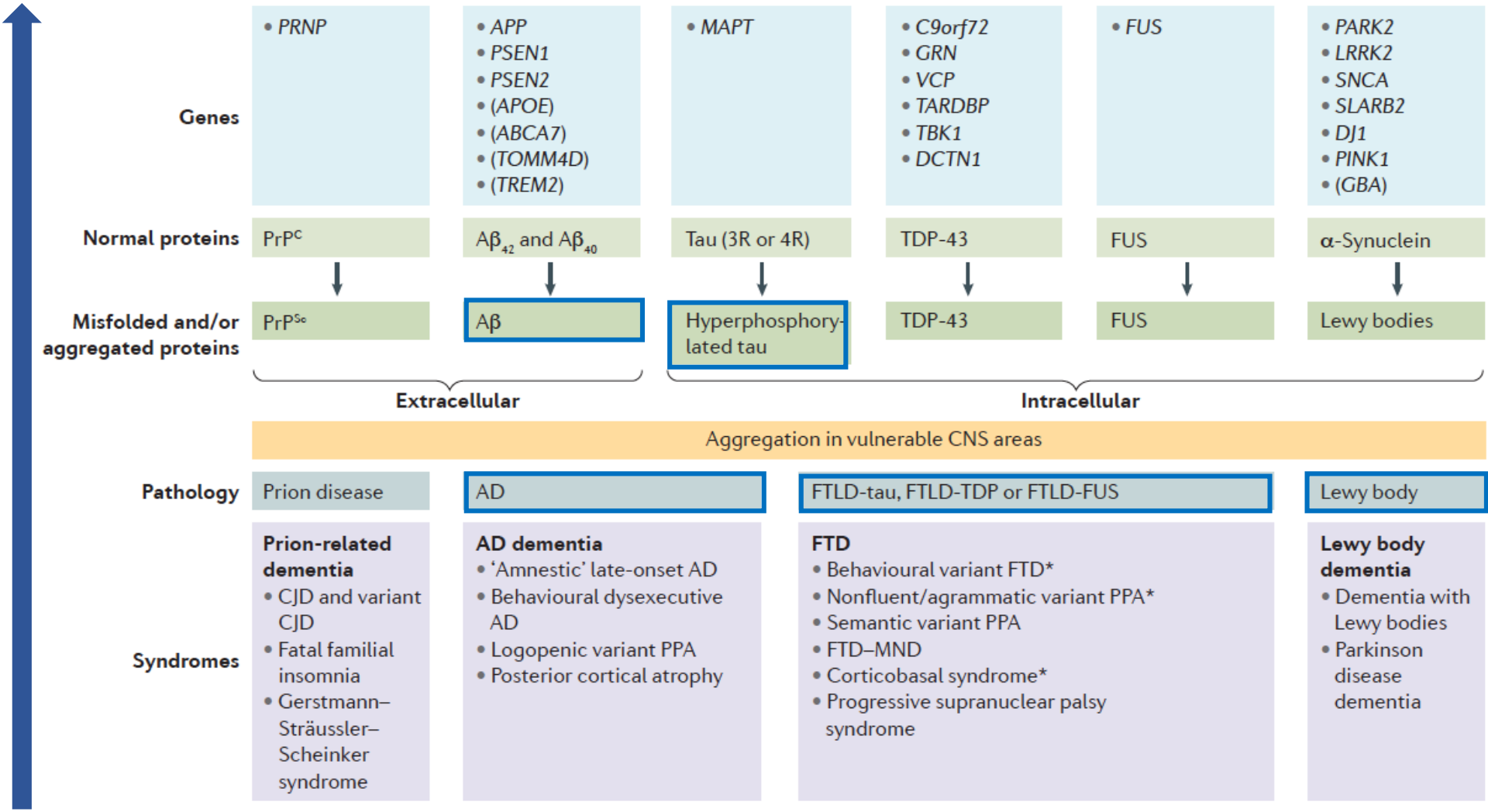
Predicted outcome of MCI subtypes according to presumed etiology



MCI=mild cognitive impairment; AD=Alzheimer's disease; Depr=depression; VaD=vascular dementia; FTD=frontotemporal dementia; DLB=dementia with Lewy bodies.

Petersen R, Negash S. *CNS Spectr.* Vol 13, No 1. 2008.

Lo scenario molecolare



Elahi et al., 2017

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 30, 2012 VOL. 367 NO. 9

Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease

Randall J. Bateman, M.D., Chengjie Xiong, Ph.D., Tammie L.S. Benzinger, M.D., Ph.D., Anne M. Fagan, Ph.D., Alison Goate, Ph.D., Nick C. Fox, M.D., Daniel S. Marcus, Ph.D., Nigel J. Cairns, Ph.D., Xianyun Xie, M.S., Tyler M. Blazey, B.S., David M. Holtzman, M.D., Anna Santacruz, B.S., Virginia Buckles, Ph.D., Angela Oliver, R.N., Krista Moulder, Ph.D., Paul S. Aisen, M.D., Bernardino Ghetti, M.D., William E. Klunk, M.D., Eric McDade, M.D., Ralph N. Martins, Ph.D., Colin L. Masters, M.D., Richard Mayeux, M.D., John M. Ringman, M.D., Martin N. Rossor, M.D., Peter R. Schofield, Ph.D., D.Sc., Reisa A. Sperling, M.D., Stephen Salloway, M.D., and John C. Morris, M.D., for the Dominantly Inherited Alzheimer Network

Table 1. Characteristics of the Study Participants.*

Characteristic	Carriers (N = 88)	Noncarriers (N = 40)	P Value
Age — yr	39.1±10.3	39.5±8.9	0.92
Male sex — no. (%)	36 (41)	17 (42)	0.85
Education level — yr	13.9±2.5	15.0±2.5	0.04
Cognitive status — no. (%)†			
Symptomatic	43 (49)	1 (2)	0.29
Asymptomatic	45 (51)	39 (98)	
Positive for apolipoprotein E ε4 allele — no. (%)	22 (25)	9 (22)	0.69

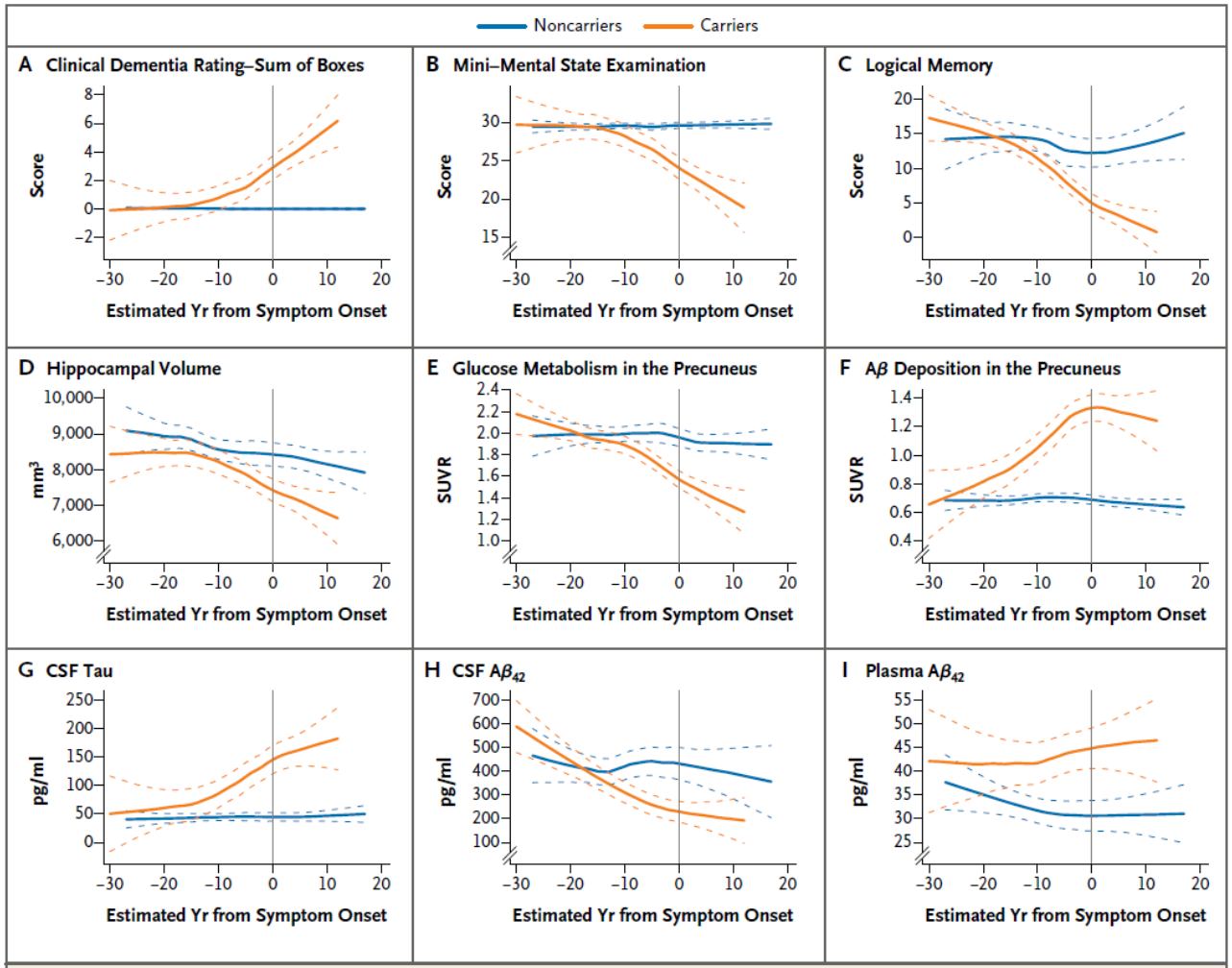


Figure 1. Cross-Sectional Analyses of Clinical, Cognitive, Structural, Metabolic, and Biochemical Changes in Autosomal Dominant Alzheimer's Disease Mutation Carriers versus Noncarriers, According to Estimated Years from Expected Symptom Onset.

The NEW ENGLAND JOURNAL of MEDICINE

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> 20 anni !!

sAD ?

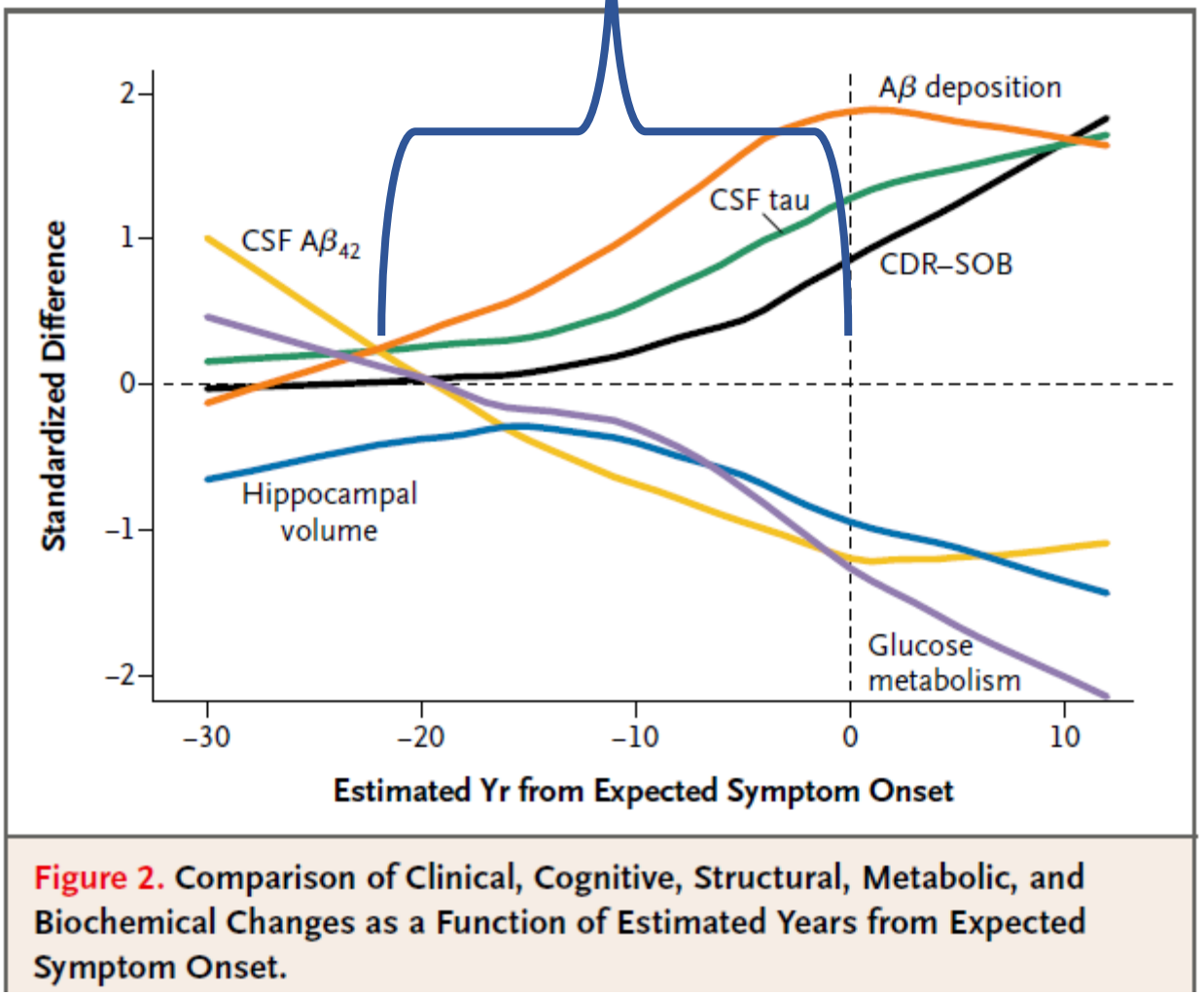


Figure 2. Comparison of Clinical, Cognitive, Structural, Metabolic, and Biochemical Changes as a Function of Estimated Years from Expected Symptom Onset.

NIA-AA 2011: MCI dovuto ad AD

ELSEVIER

Alzheimer's & Dementia 7 (2011) 270–279

Alzheimer's & Dementia

The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease

Marilyn S. Albert[a,*], Steven T. DeKosky[b,c], Dennis Dickson[d], Bruno Dubois[e], Howard H. Feldman[f], Nick C. Fox[g], Anthony Gamst[h], David M. Holtzman[i,j], William J. Jagust[k], Ronald C. Petersen[l], Peter J. Snyder[m,n], Maria C. Carrillo[o], Bill Thies[o], Creighton H. Phelps[p]

La sindrome clinica è sovrapponibile a quella descritta da Petersen

Summary of clinical and cognitive evaluation for MCI due to AD

Establish clinical and cognitive criteria

Cognitive concern reflecting a change in cognition reported by patient or informant or clinician (i.e., historical or observed evidence of decline over time)

Objective evidence of Impairment in one or more cognitive domains, typically including memory (i.e., formal or bedside testing to establish level of cognitive function in multiple domains)

Preservation of independence in functional abilities

Not demented

Examine etiology of MCI consistent with AD pathophysiological process

Rule out vascular, traumatic, medical causes of cognitive decline, where possible

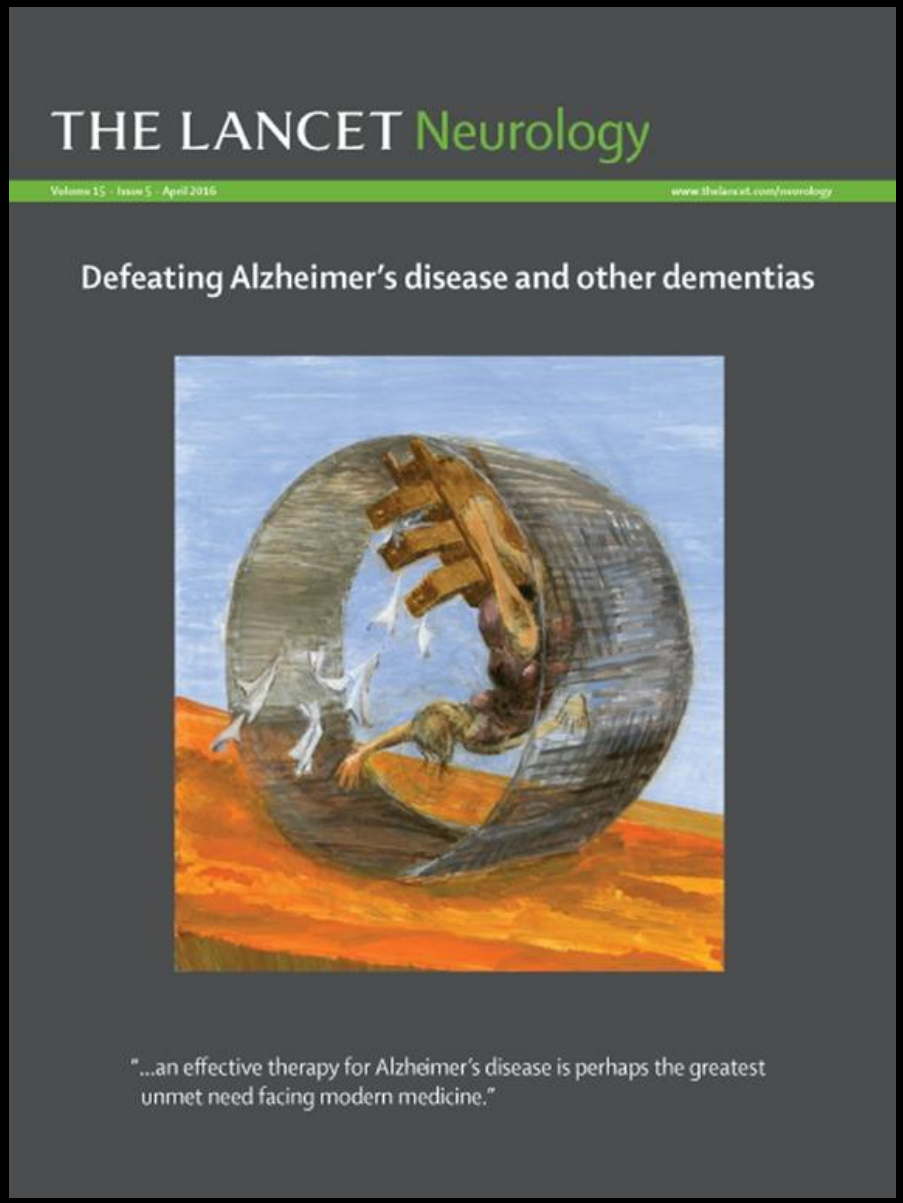
Provide evidence of longitudinal decline in cognition, when feasible

Report history consistent with AD genetic factors, where relevant

MCI – Criteri di Ricerca che includono i biomarkers

MCI criteria incorporating biomarkers

Diagnostic category	Biomarker probability of AD etiology	Aβ (PET or CSF)	Neuronal injury (tau, FDG, sMRI)
MCI–core clinical criteria	Uninformative	Conflicting/indeterminant/untested	Conflicting/indeterminant/untested
MCI due to AD—intermediate likelihood	Intermediate	Positive	Untested
		Untested	Positive
MCI due to AD—high likelihood	Highest	Positive	Positive
MCI—unlikely due to AD	Lowest	Negative	Negative



"The occurrence of AD and other dementia is higher in woman than in man, particularly in most elderly, and woman provide most caregiving for people with dementia"

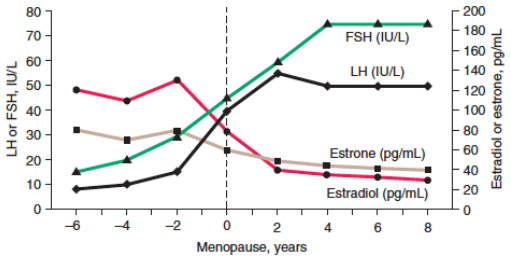
The *Lancet Neurology* Commission, 2016

Journal of Alzheimer's Disease xx (20xx) x–xx
DOI 10.3233/JAD-170432
IOS Press

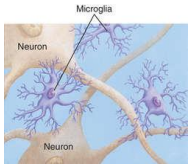
Gender-Based Cerebral Perfusion Differences in 46,034 Functional Neuroimaging Scans

Daniel G. Amen[a,*], Manuel Trujillo[b], David Keator[c], Derek V. Taylor[a], Kristen Willeumier[a], Somayeh Meysami[d] and Cyrus A. Raji[e]

donna

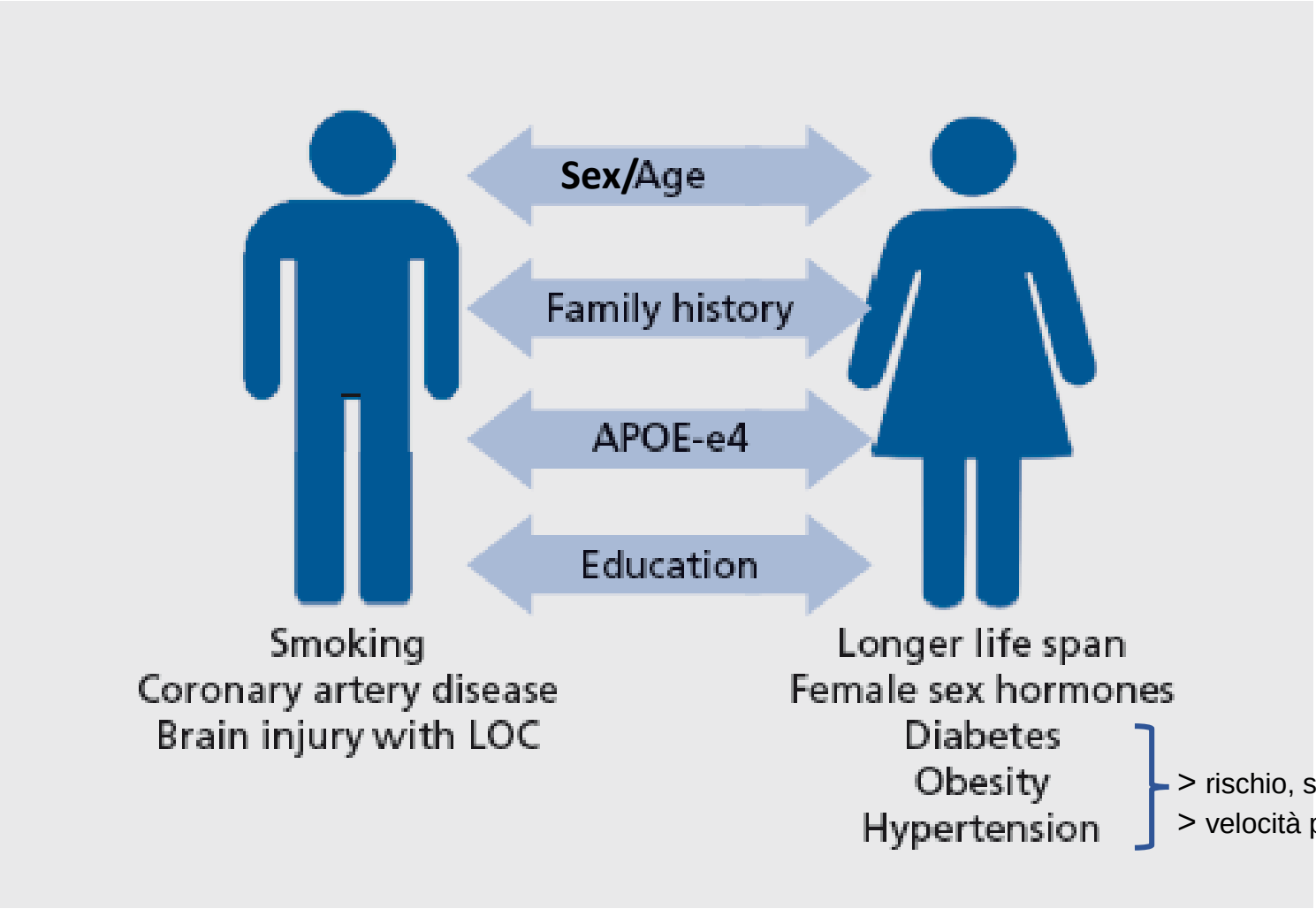


> disregolazione nella neuroinfiammazione



uomo

Fattori di rischio



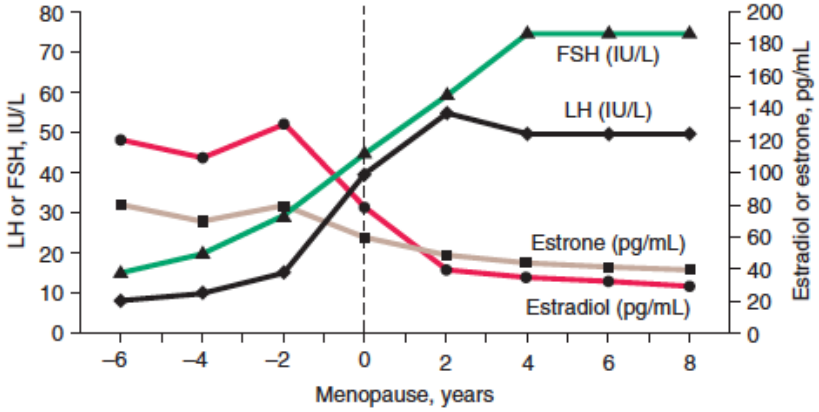
Podcasy and Epperson, 2016

Climaterio

Dal greco κλιματήρ «gradino», complesso delle modificazioni organiche e psichiche che si manifestano nel periodo di transizione, da prima della menopausa, fino alla completa cessazione del ciclo mestruale.

Menarche — FMP (0)

Stage	–5	–4	–3b	–3a	–2	–1	+1a	+1b	+1c	+2
Terminology	Reproductive				Menopausal transition		Postmenopause			
	Early	Peak	Late		Early	Late	Early			Late
					Perimenopause					
Duration	*Variable*				*Variable*	1–3 years	2 years (1+1)		3–6 years	*Remaining lifespan*
Principal criteria										
Menstrual cycle	Variable to regular	Regular	Regular	Subtle changes in flow/ length	*Variable Length* Persistent ≥7-day difference in length of consecutive cycles	Interval of amenorrhea of ≥60 days				
Supportive criteria										
Endocrine FSH AMH Inhibin B			Low Low	Variable* Low Low	↑ Variable* Low Low	↑ >25 IU/L** Low Low	↑ Variable Low Low		Stabilizes Very low Very low	
Antral follicle count			Low	Low	Low	Low	Very low		Very low	
Descriptive characteristics										
Symptoms						Vasomotor symptoms *Likely*	Vasomotor symptoms *Most likely*			*Increasing* symptoms of urogenital atrophy



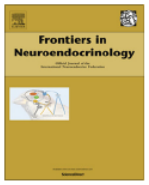
Harrison, 2015

Frontiers in Neuroendocrinology 35 (2014) 385–403

Contents lists available at ScienceDirect

Frontiers in Neuroendocrinology

journal homepage: www.elsevier.com/locate/yfrne



Review

Sex differences in cognitive impairment and Alzheimer's disease

Rena Li [a,*], Meharvan Singh [b]

[a] Center for Hormone Advanced Science and Education (CHASE), Roskamp Institute, Sarasota, FL 34243, United States
[b] Department of Pharmacology and Neuroscience, Institute for Aging and Alzheimer's Disease Research (IAADR), Center FOR HER, University of North Texas, Health Science Center, Fort Worth, TX 76107, United States

Le donne con > rischio AD e declino cognitivo età-relato più rapido e consistente vs uomini

Prevalenza: donne 0.7% (65-69 anni) a 23,6% (ultranovantenni) vs 0,6% a 17,6 uomini
Incidenza: donne 2,2 casi anno 1000 persone (65-69) a 69,7 vs 0,9 – 20 casi uomini

L'influenza di genere ed invecchiamento sui cambiamenti cerebrali, in particolare a carico dell'ippocampo, è modulata dai cambiamenti ormonali e dai loro effetti sul cervello, particolarmente consistenti per periodo post-menopausale.

Front Neuroendocrinol. 2014 January ; 35(1): 8–30. doi:10.1016/j.yfrne.2013.08.001.

Estrogen: A master regulator of bioenergetic systems in the brain and body

Jamaica R Rettberg[a], **Jia Yao**[b], and **Roberta Diaz Brinton**[a,b,c]

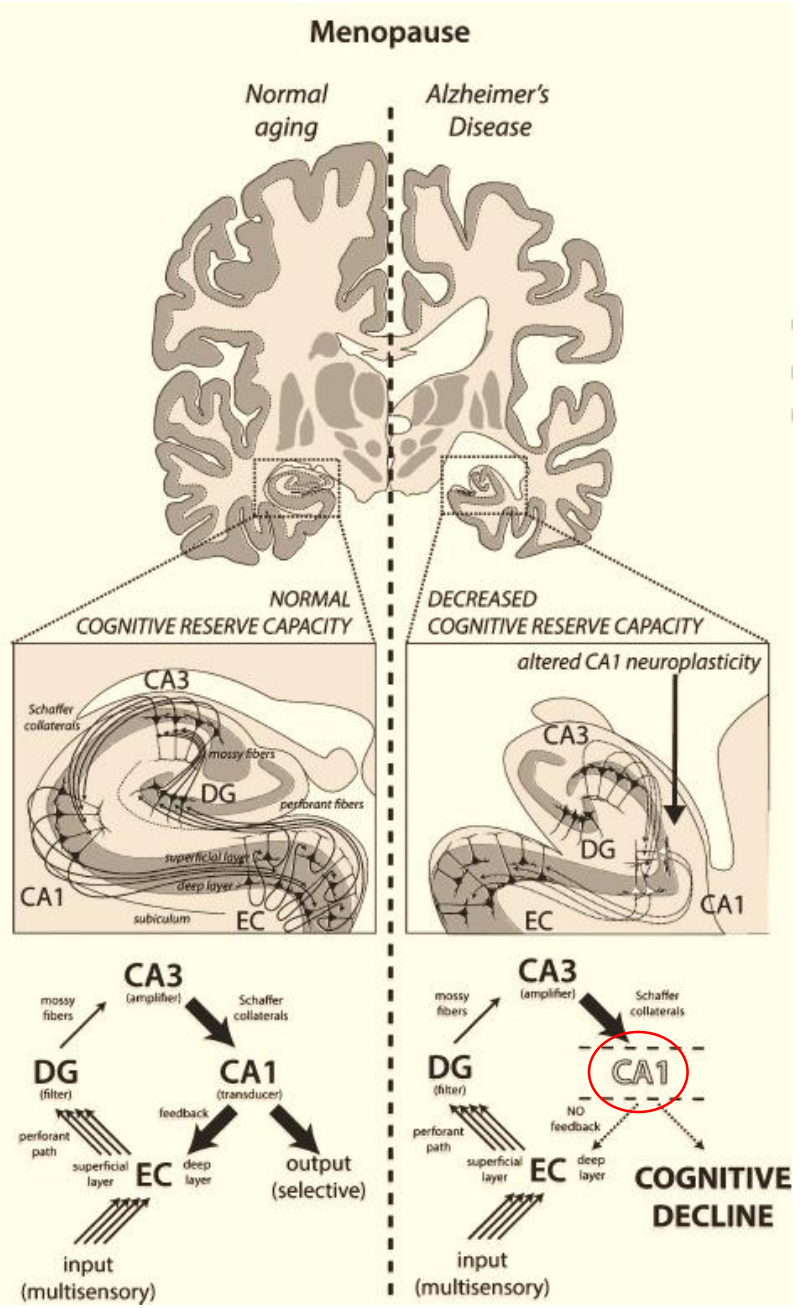
Journal of Alzheimer's Disease xx (20xx) x–xx
DOI 10.3233/JAD-160812
IOS Press

Review

Gender-Specific Degeneration of Dementia-Related Subcortical Structures Throughout the Lifespan

Il periodo post-menopausale e la relativa perdita di estrogeni appare associata a cambiamenti nella capacità neuroplastica di regioni particolarmente vulnerabili dell'ippocampo, come la regione CA1.

In concomitanza di ulteriori fattori interni ed esterni e di una ridotta riserva cognitiva, tali cambiamenti possono rappresentare una finestra temporale di vulnerabilità per il declino strutturale e funzionale dell'ippocampo, ed il conseguente declino cognitivo.



J Steroid Biochem Mol Biol. 2014 July ; 0: 90–98. doi:10.1016/j.jsbmb.2013.06.001.

Cognition and mood in perimenopause: A systematic review and meta-analysis

Miriam T. Weber, PhD[1], **Pauline M. Maki, PhD**[2,3], and **Michael P. McDermott, PhD**[1,4]

Variable	Comparison	Estimated SES	95% CI	P-value
Working Memory	Peri – Pre	−0.147	(−0.308, 0.013)	0.07
	Post – Pre	−0.122	(−0.310, 0.067)	0.21
	Post – Peri	0.028	(−0.094, 0.150)	0.66
Processing Speed	Peri – Pre	−0.022	(−0.185, 0.142)	0.80
	Post – Pre	−0.125	(−0.317, 0.066)	0.20
	Post – Peri	−0.087	(−0.210, 0.035)	0.16
Phonemic Verbal Fluency	Peri – Pre	0.146	(−0.087, 0.379)	0.22
	Post – Pre	−0.185	(−0.439, 0.068)	0.15
	Post – Peri	−0.333	(−0.612, −0.054)	0.02
Semantic Verbal Fluency	Peri – Pre	0.092	(−0.259, 0.442)	0.61
	Post – Pre	−0.217	(−0.635, 0.202)	0.31
	Post – Peri	−0.302	(−0.727, 0.123)	0.16
Immediate Verbal Memory	Peri – Pre	−0.018	(−0.179, 0.143)	0.83
	Post – Pre	−0.148	(−0.337, 0.040)	0.12
	Post – Peri	−0.118	(−0.240, 0.004)	0.06
Delayed Verbal Memory	Peri – Pre	−0.042	(−0.199, 0.114)	0.60
	Post – Pre	−0.224	(−0.404, −0.045)	0.01
	Post – Peri	−0.174	(−0.294, −0.054)	0.004

Variable	Comparison	Summary Odds Ratio	95% CI	P-value
Depressive	Early Peri – Pre	1.34	(1.14, 1.57)	0.0004
Symptoms	Late Peri – Pre	1.82	(1.38, 2.41)	< 0.0001
	Post – Pre	1.54	(1.14, 2.10)	0.006
Depression	Peri – Pre	1.92	(1.23, 2.98)	0.004
Diagnosis	Post – Pre[a]	4.32	(1.54, 12.12)	0.005

Post-menopausa: peggiori performance a test di memoria verbale a lungo termine (lobi temporali) vs pre- e peri-menopausa e a test di fluenza verbale fonemica (lobi frontali) vs peri-menopausa.

Peri- e post-menopausa a maggior rischio di depressione vs pre-menopausa.

Medicine • Volume 95, Number 6, February 2016

Medicine

OBSERVATIONAL STUDY

OPEN

Risk of Psychiatric Disorders Following Symptomatic Menopausal Transition

A Nationwide Population-Based Retrospective Cohort Study

Li-Yu Hu, MD, Cheng-Che Shen, MD, Jeng-Hsiu Hung, MD, Pan-Ming Chen, MD, Chun-Hsien Wen, MD, Yung-Yen Chiang, PhD, and Ti Lu, MD

Il periodo di transizione del climaterio è associato ad un maggior rischio di prima insorgenza del disturbo bipolare e depressivo, di disturbi d'ansia e del sonno (in assenza di condizioni psichiatriche pre-morbose e comparate a donne di pari età non in periodo menopausale).

TABLE 3. Hazard Ratios of Time Until Psychiatric Disorders Between Women With Symptomatic Menopausal Transition and Control Subjects During a 10-year Follow-Up Period

	Crude HR (95% CI)	Adjusted HR (95% CI)†
Schizophrenia	0.81 (0.51–1.27)	0.77 (0.48–1.23)
Bipolar disorder	1.75 (1.06–2.89)*	1.68 (1.01–2.79)*
Depressive disorder	2.18 (1.94–2.45)*	2.17 (1.93–2.45)*
Anxiety disorder	2.09 (1.83–2.38)*	2.11 (1.84–2.41)*
Sleep disorder	2.02 (1.74–2.35)*	2.01 (1.73–2.34)*

CI = confidence interval, HR = hazard ratio.

* Statistical significance.

† Adjusted for age, hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, congestive heart failure, cerebrovascular disease, chronic pulmonary disease, malignancy, income, and urbanization.

JAGS 59:57–66, 2011

Depressive Symptoms and Incidence of Mild Cognitive Impairment and Probable Dementia in Elderly Women: The Women's Health Initiative Memory Study

Joseph S. Goveas, MD, Mark A. Espeland, PhD,† Nancy F. Woods, PhD,‡ Sylvia Wassertheil-Smoller, PhD,§ and Jane M. Kotchen, MD, MPH‖*

At baseline

Table 2. Hazard of Developing Mild Cognitive Impairment (MCI), Probable Dementia, and MCI or Probable Dementia According to Depressive Disorder Status

	n, Unadjusted Hazard Ratio (95% Confidence Interval) *P*-Value		
Depressive Disorder	**Developed MCI (n = 216, 3.4%)**	**Developed Dementia (n = 102, 1.6%)**	**Developed MCI or Dementia (n = 285, 4.5%)**
Yes (n = 508)	33, 2.14 (1.47–3.09) <.001	16, 2.18 (1.28–3.71) .004	41, 2.01 (1.44–2.80) <.001
No (n = 5,868)	183, 1.00	86, 1.00	244, 1.00

In the history

Table 5. Adjusted Hazard of Developing Mild Cognitive Impairment (MCI), Probable Dementia, and MCI or Probable Dementia According to Current Depressive Symptoms and History of Depressive Symptoms at Baseline

	Adjusted Hazard Ratio (95% Confidence Interval) P-Value		
Depressive Symptoms	**MCI**	**Dementia**	**MCI or Dementia**
Current	1.33 (1.01–1.77) .049	1.39 (0.92–2.11) .12	1.34 (1.05–1.72) .02
History	1.38 (1.03–1.85) .03	1.98 (1.31–3.01) .001	1.62 (1.26–2.08) <.001

Alzheimer Dis Assoc Disord. 2010 ; 24(3): 248–255. doi:10.1097/WAD.0b013e3181d715d5.

Subtypes of Mild Cognitive Impairment in Older Postmenopausal Women: The Women's Health Initiative Memory Study

Stephen R. Rapp, PhD[1], Claudine Legault, PhD[2], Victor W. Henderson, MD, MS[3], Robert L. Brunner, PhD[4], Kamal Masaki, MD[5], Beverly Jones, MD[1], John Absher, MD[1], and Leon Thal, MD[6]

MCI classification (meeting all criteria)	No Impairment	MCI					Total
		a-MCI-sd	na-MCI-sd	a-MCI-md	na-MCI-md	All	
Overall N	73	14	72	143	91	320	393
N (%) [% of Total]	32 (43.8) [8.1]	7 (50.0) [1.8]	27 (37.5) [6.9]	48 (33.6) [12.2]	30 (33.0) [7.6]	112 (35.0) [28.5]	144 (36.6)
% of MCI cases		6.3	24.1	42.9	26.8		

Età media: 72.5 aa

Maggior prevalenza di *amnestic-MCI multiple domain,* seguita da *non amnestic-MCI multiple domain.*

Ageing Research Reviews 35 (2017) 176–199

Contents lists available at ScienceDirect

Ageing Research Reviews

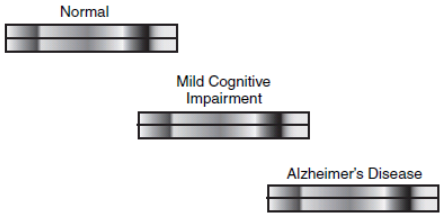
journal homepage: www.elsevier.com/locate/arr

Review

Sex differences in the prevalence and incidence of mild cognitive impairment: A meta-analysis

Bonnie Au (MSc.)[a], Sydney Dale-McGrath (MA)[a], Mary C. Tierney (Ph.D.)[a,b,c,*]

[a] Primary Care Research Unit, Sunnybrook Health Sciences Centre, Toronto, Canada
[b] Department of Family and Community Medicine, Sunnybrook Health Sciences Centre, Toronto, Canada
[c] Department of Family and Community Medicine, University of Toronto, Toronto, Canada



- **Non emerge una differenza legata al genere nella incidenza e prevalenza di MCI amnesico.**

- **Risultato in contrasto con maggior numero di donne con AD vs uomini** (MCI amnesico come precursore di AD).

- Possibile spiegazione: le **donne proseguono più rapidamente verso la diagnosi di AD** e pertanto permangono più brevemente nello stadio precursore di MCI amnesico.

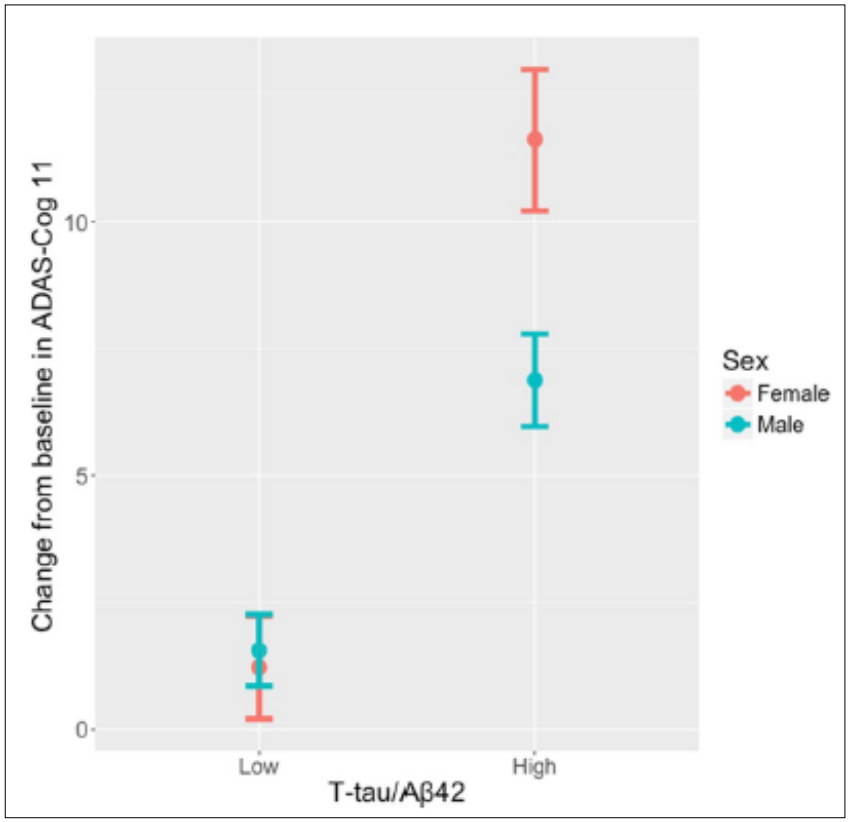
Sex Differences in Cognitive Decline in Subjects with High Likelihood of Mild Cognitive Impairment due to Alzheimer's disease

SCIENTIFIC REPORTS

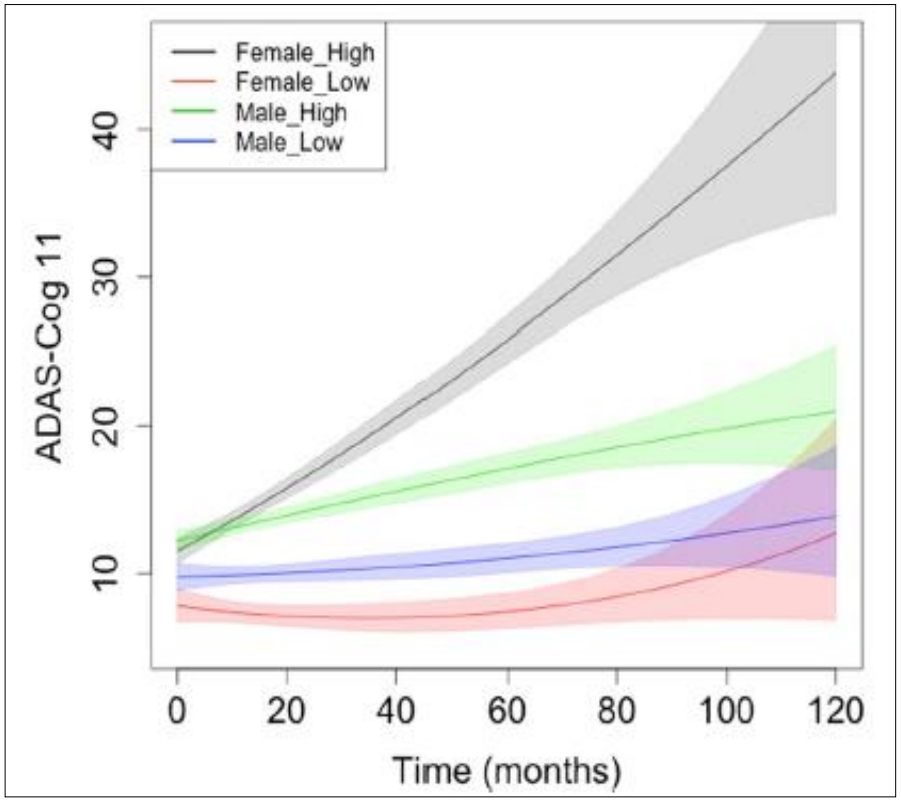
Dongwha Sohn[1,2], Katie Shpanskaya[3], Joseph E. Lucas[4], Jeffrey R. Petrella[5], Andrew J. Saykin[6], Rudolph E. Tanzi[7], Nagiza F. Samatova[1,2] & P. Murali Doraiswamy[8]

- Nel campione generale di pazienti con MCI, **peggioramento nei punteggi all'ADAS-Cog maggiore nelle donne rispetto agli uomini.**
- Soggetti con alta o bassa probabilità di avere MCI dovuto ad AD (esame liquor): nei **soggetti con alta probabilità, il peggioramento nei punteggi all' ADAS-Cog è maggiore nelle donne rispetto agli uomini.**
- Nei pazienti portatori di **gene ApoEε4, le donne peggiorano più rapidamente degli uomini.**

Entità del peggioramento nelle **donne** con '**alta probabilità di MCI dovuto ad AD'**



Rapidità del peggioramento nelle **donne** con '**alta probabilità di MCI dovuto ad AD'**



ELSEVIER

Alzheimer's & Dementia: Translational Research & Clinical Interventions 1 (2015) 103-110

Alzheimer's & Dementia

Featured Article

Marked gender differences in progression of mild cognitive impairment over 8 years

Katherine A. Lin[a,b], Kingshuk Roy Choudhury[c], Bharath G. Rathakrishnan[a], David M. Marks[a], Jeffrey R. Petrella[c], P. Murali Doraiswamy[a,b,*], and for the Alzheimer's Disease Neuroimaging Initiative

[a]*Department of Psychiatry, Duke University Medical Center, Durham, NC, USA*
[b]*Duke Institute for Brain Sciences, Duke University, Durham, NC, USA*
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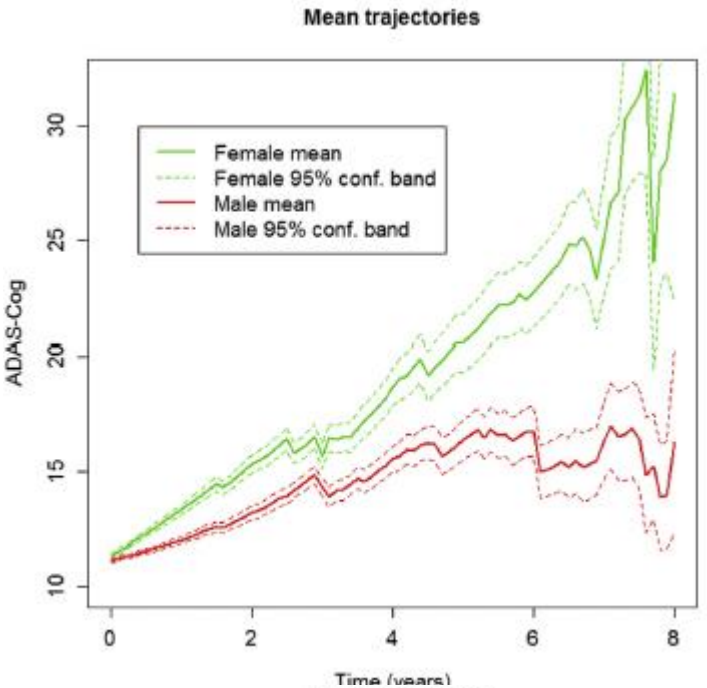
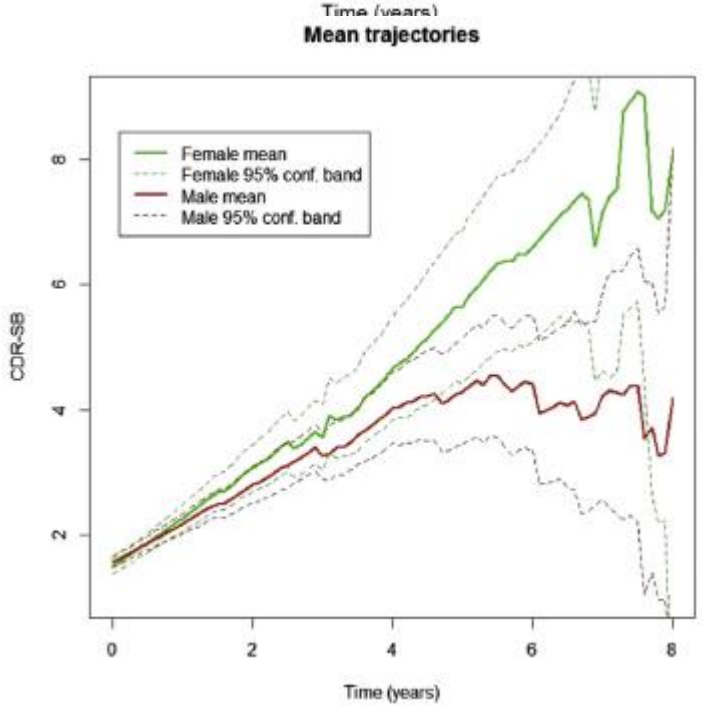


Donne affette da MCI **peggiorano più rapidamente** degli uomini **sia sul piano cognitivo (ADAS-Cog) che funzionale /gravità di malattia (CDR).**

La presenza di gene ApoEε4 influenza l'andamento della malattia in entrambi i sessi. **Nelle donne maggior peggioramento anche in assenza di genotipo ApoEε4** .



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Sex Differences in the Association between AD Biomarkers and Cognitive Decline

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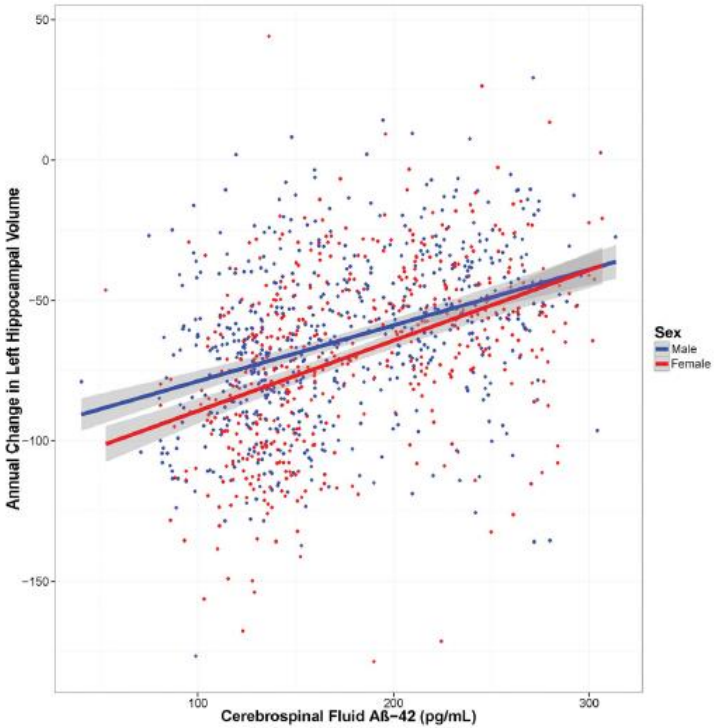
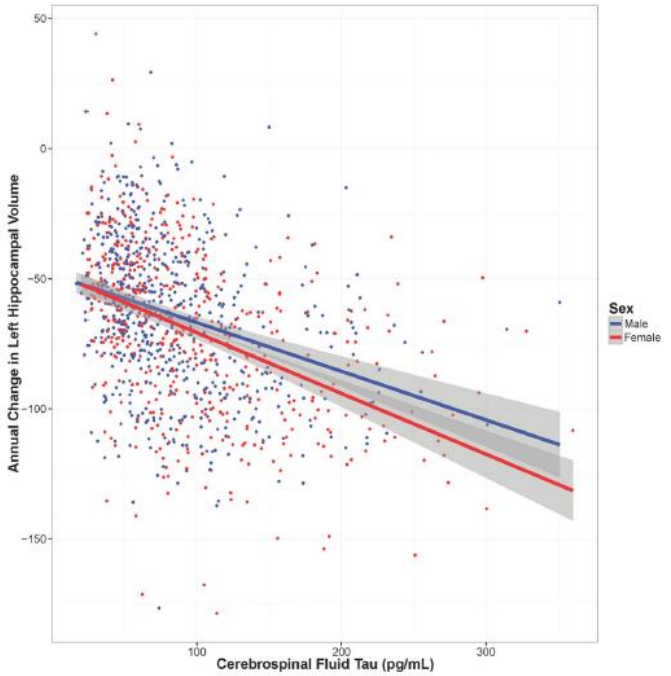
Le donne mostrano un più rapido incremento di atrofia ippocampale/declino cognitivo in presenza di aumentati livelli di biomarker di AD.





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Gender differences in risk factors for transition from mild cognitive impairment to Alzheimer's disease: A CREDOS study

Sangha Kim[a], Min Ji Kim[b], Seonwoo Kim[b], Hyo Shin Kang[c], Shin Won Lim[d], Woojae Myung[a], Yunhwan Lee[e], Chang Hyung Hong[f], Seong Hye Choi[g], Duk L. Na[h], Sang Won Seo[h], Bon D. Ku[i], Seong Yoon Kim[j], Sang Yun Kim[k], Jee Hyang Jeong[l], Sun Ah Park[m], Bernard J. Carroll[n], Doh Kwan Kim[a,*]

Fattori di rischio per **conversione da MCI ad AD** differiscono in uomini e donne:

- **Donne**: la presenza di gene **ApoEε4, età** più avanzata e **sintomi depressivi** alla baseline;
- **Uomini: iperintensità periventricolari** nella sostanza bianca ed un **peggior funzionamento cognitivo (baseline).**

Gender specific risk factors for progression to Alzheimer's disease.

	Men (n = 101)		Women (n = 193)	
	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
Age, years	1.06 (0.99–1.14)	0.091	1.10 (1.03–1.17)	0.005
Education, years	1.03 (0.91–1.16)	0.700	1.09 (1.00–1.19)	0.063
K-MMSE	0.77 (0.63–0.95)	0.012	0.94 (0.84–1.06)	0.299
CDR-SB	1.97 (1.11–3.50)	0.021	1.24 (0.79–1.95)	0.359
HIS score	0.84 (0.63–1.13)	0.242	0.94 (0.70–1.24)	0.641
Depression[a]	0.98 (0.26–3.77)	0.980	3.11 (1.40–6.91)	0.005
Hypertension	0.60 (0.22–1.62)	0.311	0.70 (0.34–1.45)	0.332
Diabetes mellitus	0.22 (0.06–0.87)	0.030	1.81 (0.77–4.26)	0.174
Hyperlipidemia	1.84 (0.42–8.04)	0.418	0.51 (0.19–1.24)	0.180
Past clinical stroke history	0.93 (0.07–12.67)	0.957	1.22 (0.25–5.84)	0.808
Anemia	1.02 (0.29–3.59)	0.976	0.60 (0.14–2.66)	0.504
APOE ε4 carrier	1.90 (0.68–5.34)	0.224	2.90 (1.44–5.81)	0.003
WMH severity[b]				
PWMH ≥ 10 mm	7.92 (2.36–26.55)	<0.001	1.36 (0.63–2.93)	0.430
DWMH ≥ 10 mm	0.08 (0.02–0.38)	0.002	0.63 (0.26–1.51)	0.299

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OXFORD

Special Article

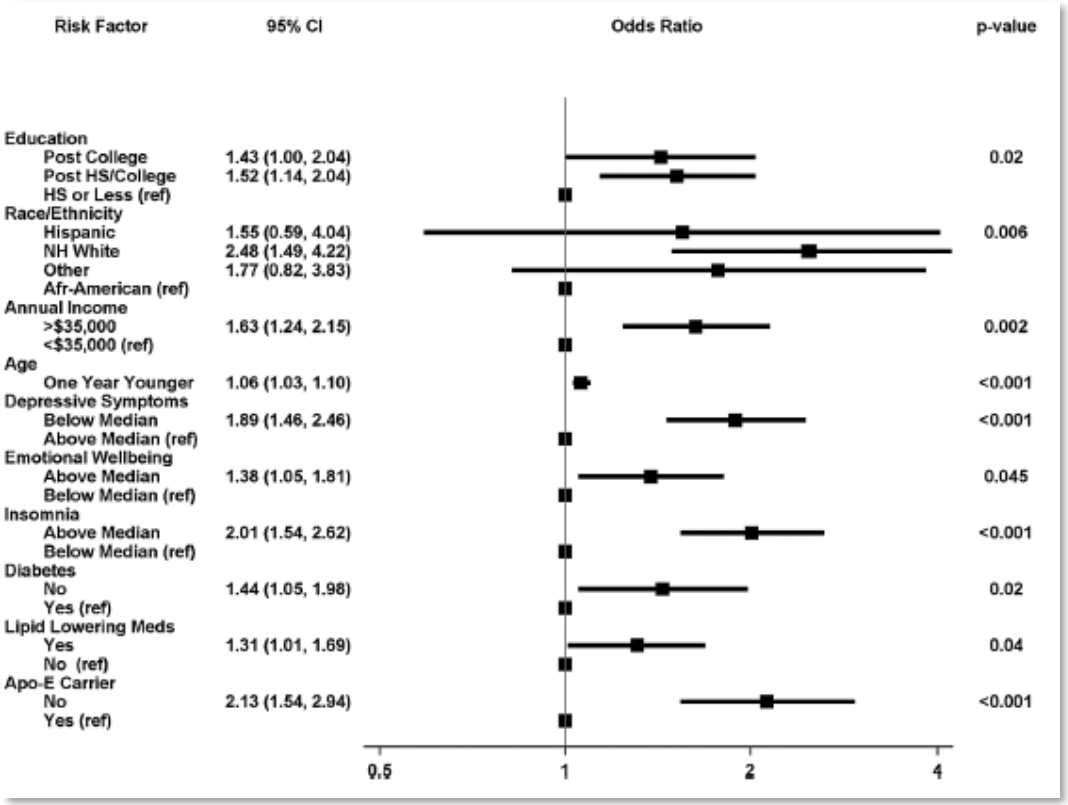
Predictors of Optimal Cognitive Aging in 80+ Women: The Women's Health Initiative Memory Study

Joseph S. Goveas,[1] Stephen R. Rapp,[2] Patricia E. Hogan,[3] Ira Driscoll,[4] Hilary A. Tindle,[5] J. Carson Smith,[6] Shelli R. Kesler,[7] Oleg Zaslavsky,[8] Rebecca C. Rossom,[9] Judith K. Ockene,[10] Kristine Yaffe,[11] JoAnn E. Manson,[12] Susan M. Resnick,[13] and Mark A. Espeland[3]

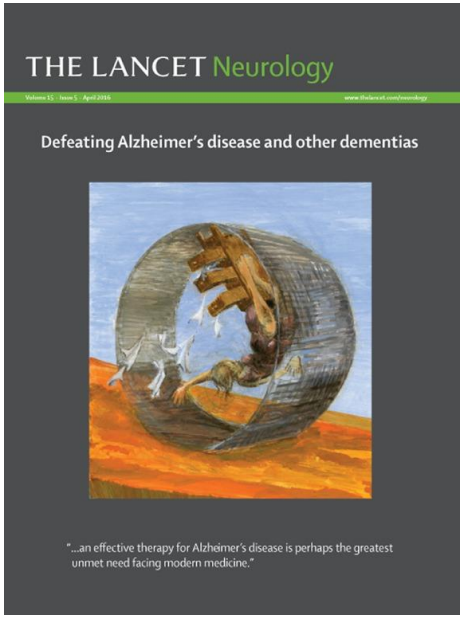
In assenza di declino cognitivo, fattori protettivi in parte sovrapponibili a quelli associati alla conversione da MCI ad AD.

I fattori protettivi per il mantenimento di un buon funzionamento cognitivo sono:

-Ridotti/assenti livelli di depressione
-Maggior scolarizzazione
-Etnia non ispanica
-Reddito economico
-Minore età
- Miglior benessere emotivo
-Presenza di insonnia???
-Assenza di diabete
-Assunzione di statine
- Attività fisica
- Non essere portatori ApoEε4



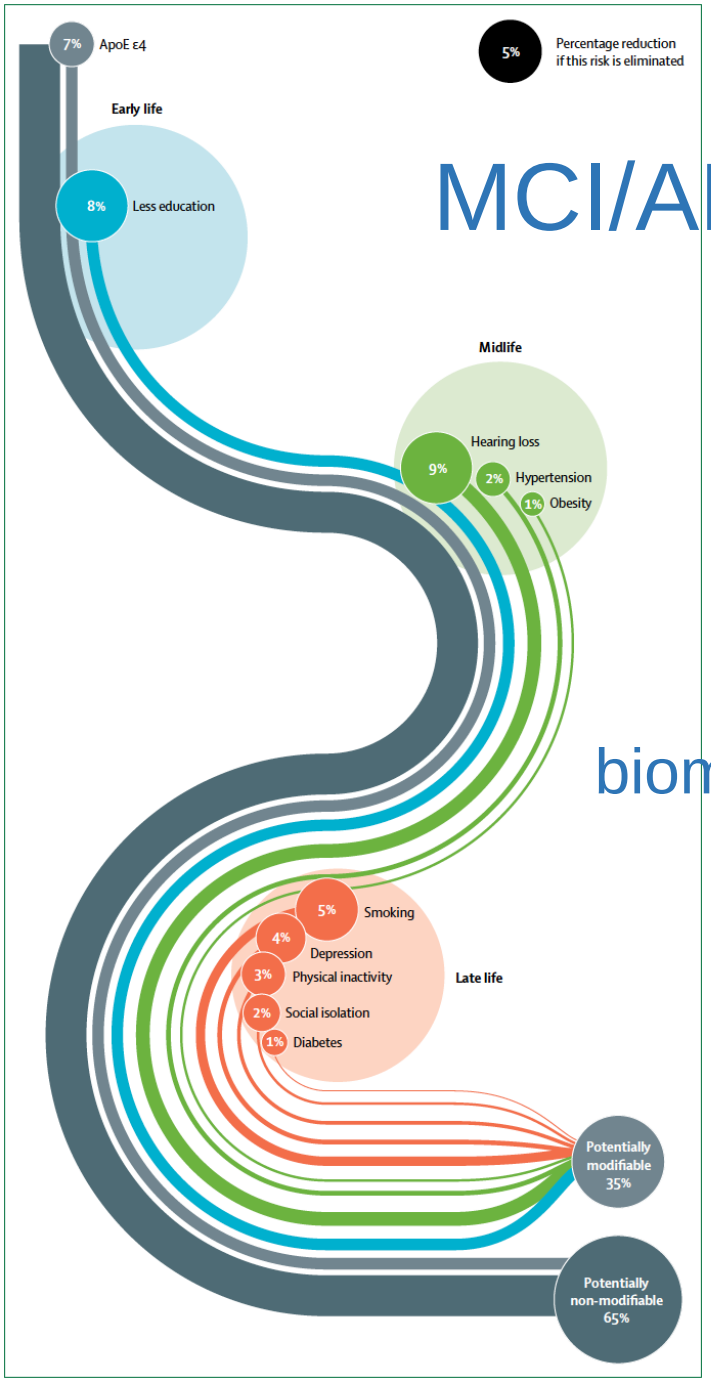
Conclusioni



Conclusion and future European perspectives

AD is the leading cause of dementia, and because the primary risk factor for AD is old age, the prevalence of the disease is increasing dramatically as life expectancy increases worldwide. The explosion in care costs and associated societal burdens of AD and other dementias threatens to become overwhelming, even in resource-rich countries. However, AD is not an inevitable consequence of ageing, and further work is needed to identify modifiable risk factors and protective factors—including a range of lifestyle factors—that could form the basis of effective, feasible preventive interventions. Although no cure for AD exists and no therapeutic option is available to delay the inevitable progression of the disease, an emphasis on early detection and integrated, team-oriented, evidence-based care—with a focus on the physical, psychosocial, and existential health needs of the patient and support for informal caregivers—has the potential to improve the quality of life of patients and their families.

FTD
LBD
CVD
.....



MCI/AD

biomarcatori di genere ?

Livingston et al., 2017, The Lancet

Panel 4: Putative risk and protective factors for late-onset dementia and Alzheimer's disease

Risk factors

Older age

Genetic factors

- Familial aggregation (two or more family members with the disease)
- *APOE* ε4 allele
- Other susceptibility genes (eg, *CR1*, *PICALM*, *CLU*, *TREM2*, *TOMM40*)

Vascular risk and metabolic factors

- Atherosclerosis
- Cerebral macrovascular and microvascular lesions
- Cardiovascular diseases
- Diabetes mellitus and pre-diabetes
- Midlife hypertension
- Midlife overweight and obesity
- Midlife high serum cholesterol

Lifestyle factors

- Sedentary lifestyle
- Smoking
- Heavy alcohol consumption

Diet and nutritional factors

- Saturated fats
- Hyperhomocysteinaemia
- Deficiencies in vitamin B6, B12, and folate

Other factors

- Depression
- Traumatic brain injury
- Occupational exposure (eg, heavy metals, extremely-low-frequency electromagnetic fields)
- Infectious agents (eg, herpes simplex virus type I, *Chlamydophila pneumoniae*, spirochetes)

Protective factors in MCI correlati a biomarcatori di genere

Genetic factors

- Some genes proposed (eg, *APP*, *APOE* ε2 allele)

Psychosocial factors

- High education and socioeconomic status
- High work complexity
- Rich social network and social engagement
- Mentally stimulating activity

Lifestyle factors

- Physical activity
- Light-to-moderate alcohol intake

Diet and nutritional factors

- Mediterranean diet
- Polyunsaturated fatty acid and fish-related fats
- Vitamin B6, vitamin B12, and folate
- Antioxidant vitamins (A, C, E)
- Vitamin D

Drugs

- Antihypertensive drugs
- Statins
- Hormone replacement therapy
- Non-steroidal anti-inflammatory drugs

Many risk and protective factors for dementia and Alzheimer's disease have been proposed and investigated; however, the evidence to support the factors listed here is variable, and the relevance of several proposed factors is open to debate. The most pronounced risk factors are advancing age and carrying one or two *APOE* ε4 alleles.

APOE=apolipoprotein E. *CR1*=complement component receptor 1. *PICALM*=phosphatidylinositol-binding clathrin assembly protein. *CLU*=clusterin. *TREM2*=triggering receptor expressed on myeloid cells 2. *TOMM40*=translocase of outer mitochondrial membrane 40 homologue. *APP*=amyloid precursor protein.

The *Lancet Neurology* Commission, 2016

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