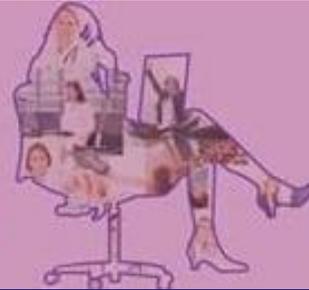


Donneⁱⁿ
Neuroscienze



LA MEDICINA DI GENERE NELLE DEMENZE

Maria Teresa Dotti

**Dipartimento di Scienze Mediche Chirurgiche e
Neuroscienze**

Università di Siena



**Azienda
Ospedaliera
Universitaria
Senese**



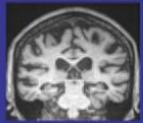
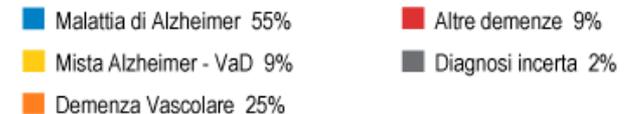
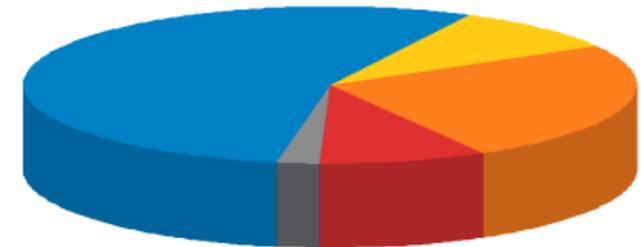
**UNIVERSITÀ
DI SIENA**
1240

Demenza

Condizione clinica dovuta a disordini cerebrali, caratterizzata dal deterioramento della memoria e di altre funzioni cognitive rispetto al livello cognitivo precedente del paziente e tale da interferire con la vita sociale e lavorativa

- Cause diverse
- Diverso profilo clinico e outcome
- Diversi fattori di rischio
- Diversa prevalenza sex-linked

FREQUENZA RELATIVA DELLE DIVERSE FORME DI DEMENZA

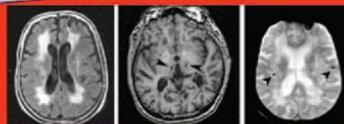


Neurodegenerative burden

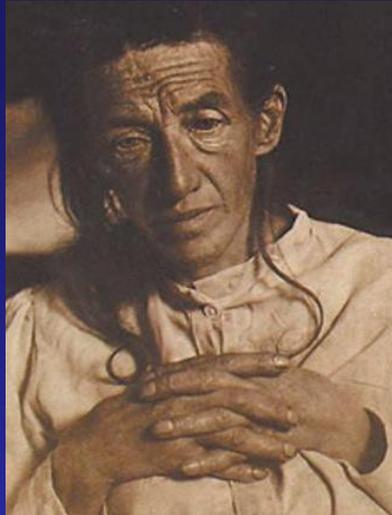
Alzheimer disease

Vascular dementia

Vascular cerebral lesion burden



Malattia di Alzheimer



Neurology, 1984 Jul;34(7):939-44.

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.

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM.

Alzheimers Dement. 2011 May ; 7(3): 263–269. doi:10.1016/j.jalz.2011.03.005.

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

Guy M. McKhann^{a,b,*}, David S. Knopman^c, Howard Chertkow^{d,e}, Bradley T. Hyman^f, Clifford

er cognitive
oratory tests,
of Alzheimer's
nd help to
e, possible,



Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria

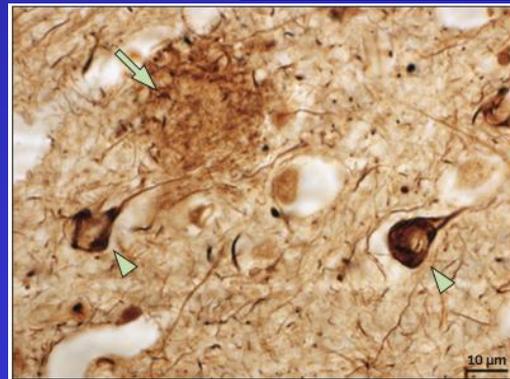
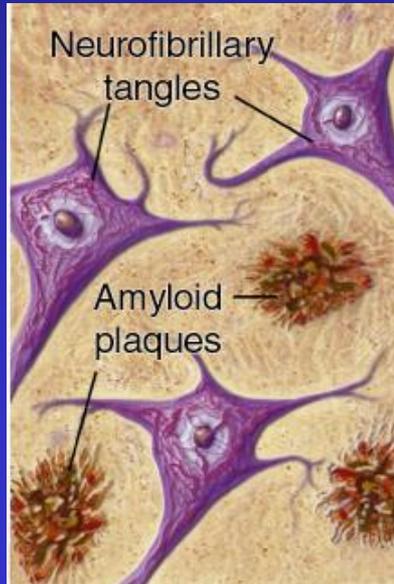
Lancet Neurol 2014; 13: 614–29



Alzheimer's & Dementia 14 (2018) 535-562

Alzheimer's
&
Dementia

2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework
NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease



AT(N) profiles	Biomarker category	
A-T-(N)-	Normal AD biomarkers	
A+T-(N)-	Alzheimer's pathologic change	Alzheimer's continuum
A+T+(N)-	Alzheimer's disease	
A+T+(N)+	Alzheimer's disease	
A+T-(N)+	Alzheimer's and concomitant suspected non Alzheimer's pathologic change	
A-T+(N)-	Non-AD pathologic change	
A-T-(N)+	Non-AD pathologic change	
A-T+(N)+	Non-AD pathologic change	

La demenza, inclusa l'AD, è una patologia multifattoriale: concorrenza di fattori genetici e ambientali

Principali fattori rischio AD: Invecchiamento, Sesso e Genotipo APOE

Invecchiamento e Demenza

Nessuna altra patologia è così strettamente legata all'invecchiamento come la demenza, la principale causa di disabilità nell'anziano

L'invecchiamento della popolazione è un fenomeno globale con un impatto profondo socio-economico e politico nell'ultimo secolo

L'età della popolazione continuerà a crescere fino a superare il numero dei nuovi nati nei prossimi 30 anni

Aumento esponenziale patologie età-correlate: demenza, cardiovascolari, tumori

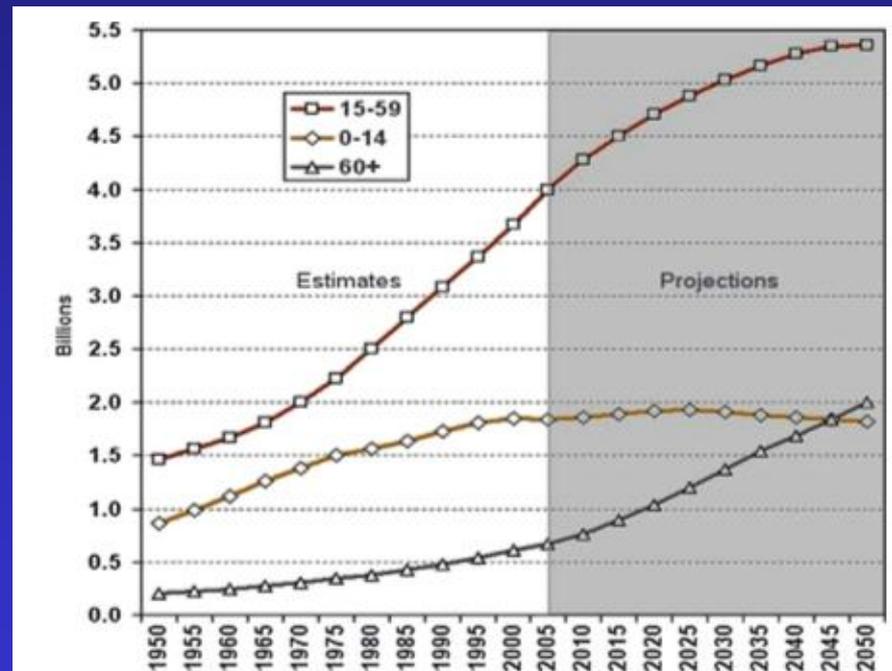


Figure 1. World population by age groups, 1950–2050. Source: World Population Prospects. Fact Sheet, Series A. Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat (7).

Invecchiamento e Demenza

- 2015: ~47 milioni di persone affette da demenza
- 2050: previsti ~115 milioni
- 50-70% Alzheimer; ~ 2/3 donne (www.dementiastatistics.org)

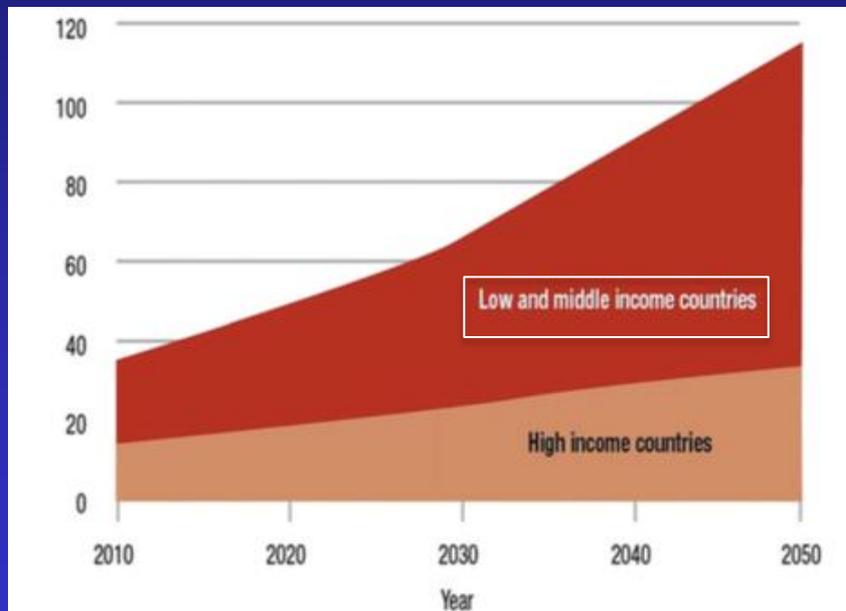


Figure 2. The growth in numbers of people with dementia (in millions) by

Il tasso di crescita della demenza aumenterà soprattutto nei paesi in via di sviluppo

Lancet 2013

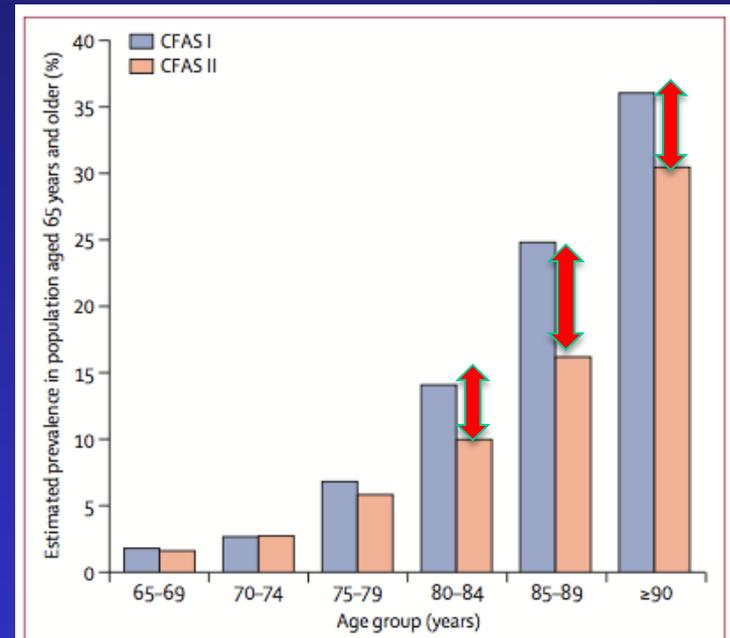
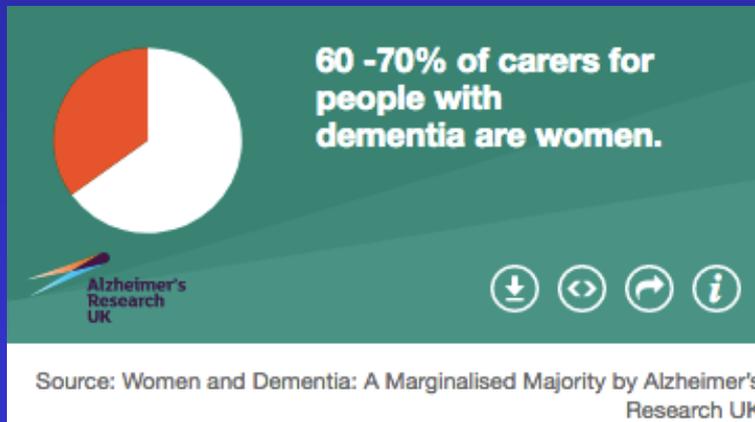
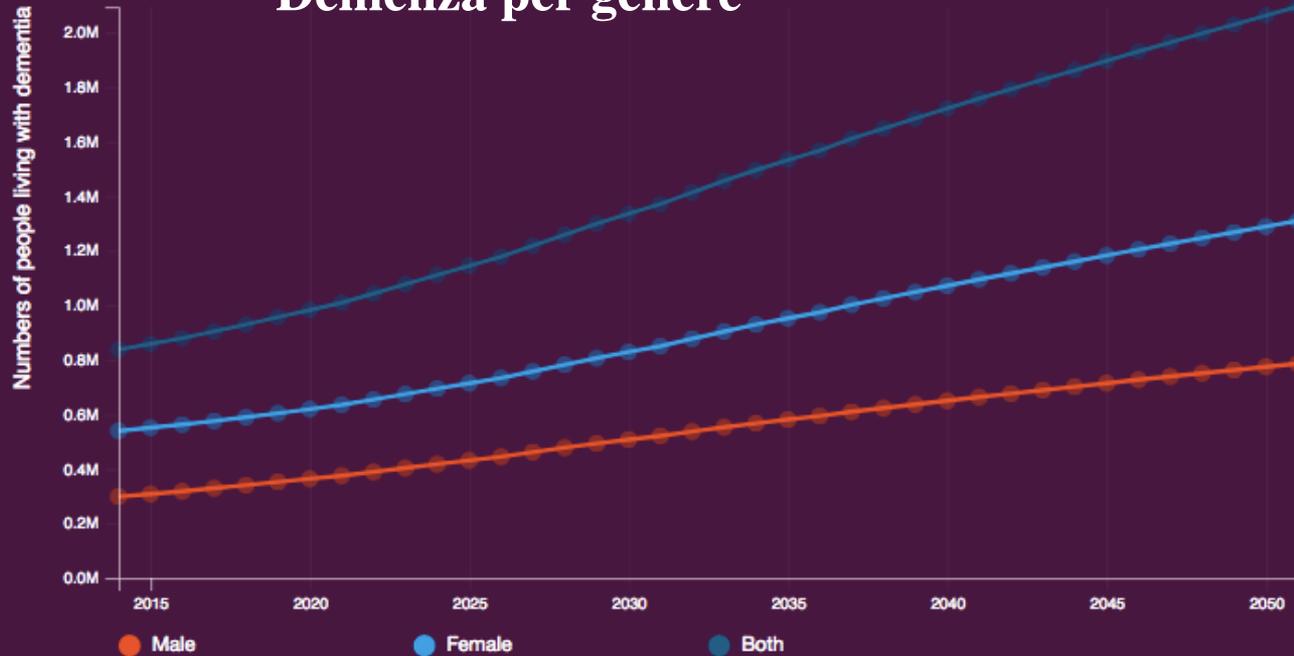


Figure 1: CFAS I and CFAS II age-specific dementia prevalence
CFAS=Cognitive Function and Ageing Study.

In occidente la prevalenza della demenza, a parità di età, si è ridotta nelle ultime due decadi negli individui nati più tardi

Demenza per genere



Carico assistenziale delle donne nella demenza

Lifetime risk of stroke and dementia: current concepts, and estimates from the Framingham Study

Sudha Seshadri, Philip A Wolf

Lancet Neurol 2007

Arruolati 2611 soggetti cognitivamente normali (1550 f 1061m), follow up 20 anni :

- ✓ maschi 65 aa rischio AD → 6.3%, demenze in generale 10.9%
- ✓ donne 65 aa rischio AD → 12% , demenze in generale 19%

Incidenza uguale
M/F precocemente,
aumenta con l'età
nella donna

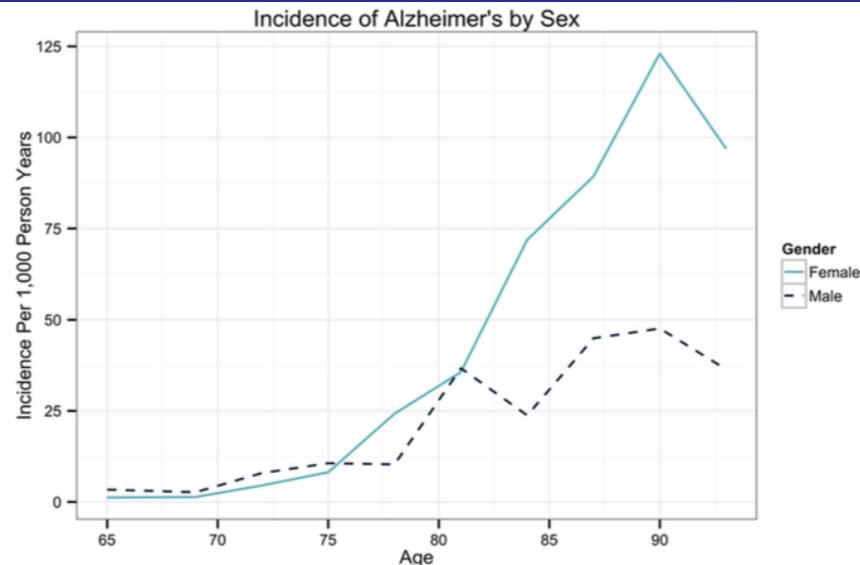


Fig. 1. Sex-specific incidence estimates of Alzheimer's per 1000 person years. Obtained with data from the Cache County Study [12]. Additional data reported in Ruitenberg et al. [13] indicate that men are at greater risk than women for developing earlier onset AD. However, this sex difference is reversed by age 75, with women at a 2 fold greater risk for AD, thereafter.

Lifetime risk of stroke and dementia: current concepts, and estimates from the Framingham Study

Sudha Seshadri, Phillip A Wolf

Lancet Neurol 2007

...if the age at onset of clinical dementia could be delayed in all cases by just 5 years, the lifetime risk of dementia could be drastically reduced

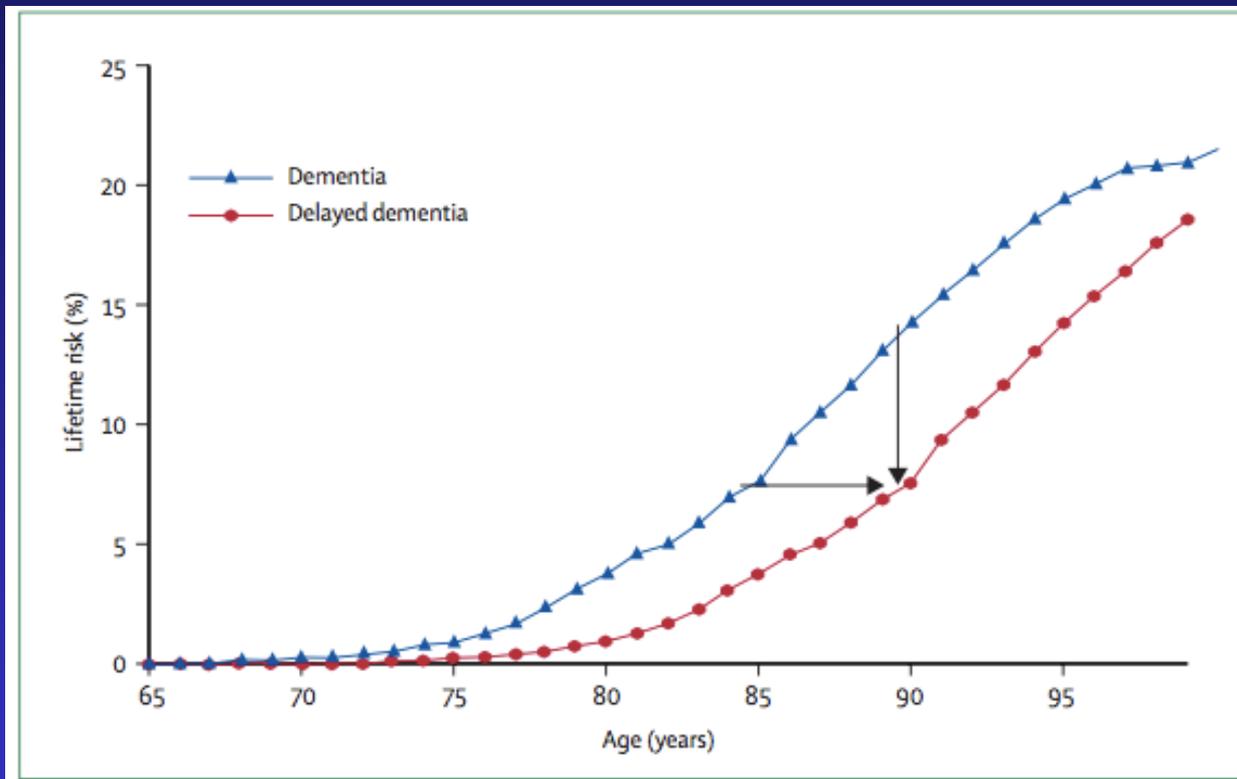


Figure 2: Lifetime risk of dementia for women aged 65 years
Actual (blue line) lifetime risk in 65-year-old, dementia-free women in the Framingham Heart Study¹¹ who were followed up throughout their remaining life compared with projected lifetime risk (red line) of incident dementia if it could be delayed in all cases by 5 years (arrows).

The risk can be refined, however, for an individual on the basis of their risk factor profile

Ormoni e AD

Il maggior rischio di AD nelle donne suggerisce l'intervento di cambiamenti fisiopatologici → riduzione livelli estrogeni, processo late-onset sesso e età specifico → menopausa

Aumento rischio AD dopo menopausa chirurgica

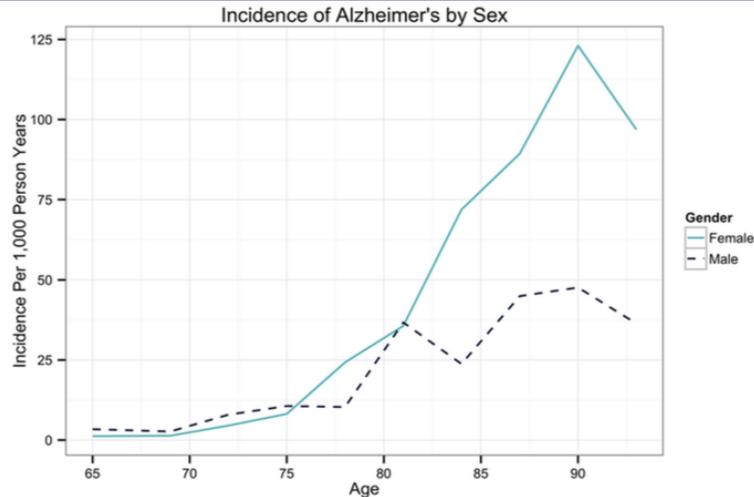


Fig. 1. Sex-specific incidence estimates of Alzheimer's per 1000 person years. Obtained with data from the Cache County Study [12]. Additional data reported in Ruitenberg et al. [13] indicate that men are at greater risk than women for developing earlier onset AD. However, this sex difference is reversed by age 75, with women at a 2 fold greater risk for AD, thereafter.

Azione neuroprotettiva degli estrogeni

- ✓ Associazione livelli estradiolo e performance cognitiva
- ✓ Attività colinergica
- ✓ Riduzione della vulnerabilità dei neuroni all'apoptosi in presenza di $A\beta$, soprattutto dell'ippocampo
- ✓ Formazione sinapsi, flusso cerebrale e metabolismo glucosio
- ✓ *Resilience*

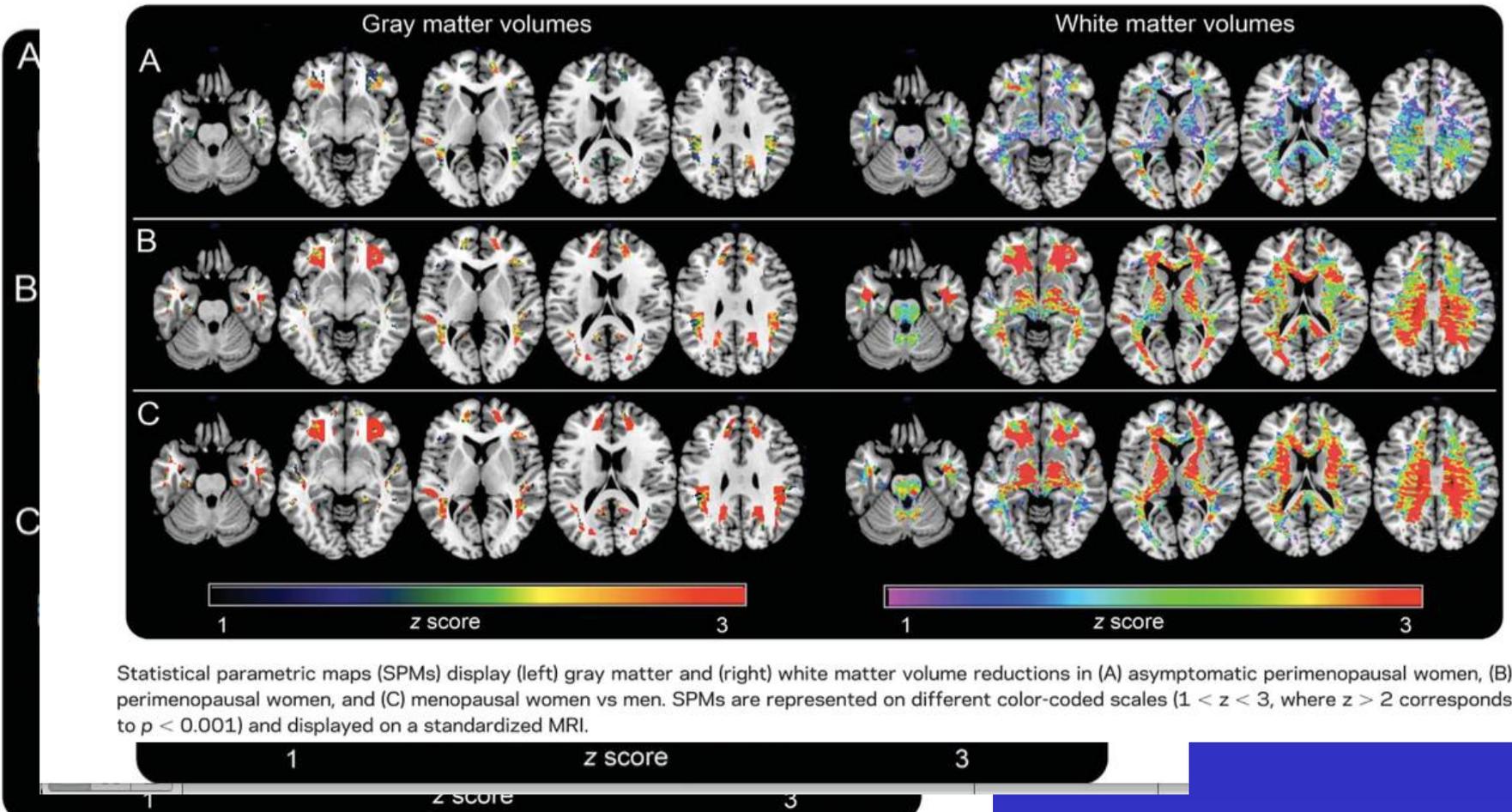
Sex steroid hormones may also drive sex differences in AD through their organizational effects during developmental sexual differentiation of the brain. Specifically, sex hormone actions during early development may confer inherent vulnerability of the female brain to development of AD in advanced age.

M

Figure 2 Pittsburgh compound B (PiB)-PET β -amyloid deposition as a function of chronologic vs endocrine aging

Figure 1

Figure 3 MRI brain volumes as a function of chronologic vs endocrine aging

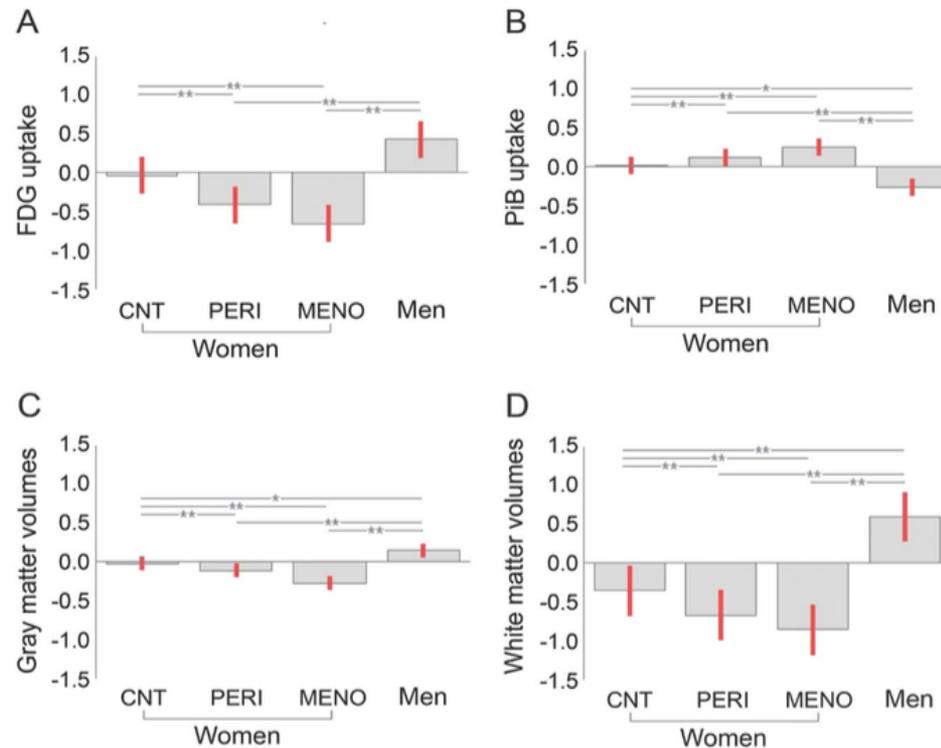


Conclusions: Multimodality brain imaging indicates sex differences in development of the AD endophenotype, suggesting that the preclinical AD phase is early in the female aging process and coincides with the endocrine transition of perimenopause. These data indicate that the optimal window of opportunity for therapeutic intervention in women is early in the endocrine aging process. *Neurology*® 2017;89:1382-1390

Sex differences in Alzheimer risk

Brain imaging of endocrine vs chronologic aging

Figure 4 Comparing Alzheimer disease (AD) biomarker abnormalities across groups



(A) ¹⁸F-fluoro-2-deoxyglucose (FDG) uptake. (B) Pittsburgh compound B (PiB) uptake. (C) Gray matter volumes. (D) White matter volumes. Biomarkers are extracted from frontal cortex clusters showing maximal statistical differences across groups and displayed on the same scale. Values are grand-mean scaled, reference-adjusted mean values, SEM. * $p < 0.05$ ** $p < 0.01$. CNT = asymptomatic perimenopausal women by age; PERI = asymptomatic perimenopausal women;

Conclusions: Multimodality brain imaging indicates sex differences in development of the AD endophenotype, suggesting that the preclinical AD phase is early in the female aging process and coincides with the endocrine transition of perimenopause. These data indicate that the optimal window of opportunity for therapeutic intervention in women is early in the endocrine aging process. *Neurology*® 2017;89:1382-1390

Effetto neuroprotettivo degli estrogeni osservato in modelli animali, non confermato negli studi clinici

Reproductive Period and Risk of Dementia in Postmenopausal Women

Mirjam I. Geerlings, PhD
Annemieke Ruitenbergh, MD, PhD
Jacqueline C. M. Witteman, PhD
John C. van Swieten, MD, PhD
Albert Hofman, MD, PhD

Context Exogenous estrogen use may lower risk of dementia in postmenopausal women. A relationship between long-term exposure to endogenous estrogens and incident dementia has been hypothesized but not studied.

Objective To determine whether a longer reproductive period, as an indicator of longer exposure to endogenous estrogens, is associated with lower risk of dementia and Alzheimer disease (AD) in women who have natural menopause.

Conclusion Our findings do not support the hypothesis that a longer reproductive period reduces risk of dementia in women who have natural menopause.

JAMA. 2001;285:1475-1481

www.jama.com

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

Conclusions Estrogen plus progestin therapy increased the risk for probable dementia in postmenopausal women aged 65 years or older. In addition, estrogen plus progestin therapy did not prevent mild cognitive impairment in these women. These findings, coupled with previously reported WHI data, support the conclusion that the risks of estrogen plus progestin outweigh the benefits.

JAMA. 2003;289:2651-2662

www.jama.com

Postmenopausal hormone therapy and Alzheimer disease

A prospective cohort study

Results: Postmenopausal estrogen use was not associated with AD risk in register-based or self-reported data (hazard ratio/95% confidence interval 0.92/0.68-1.2, 0.99/0.75-1.3, respectively). Long-term self-reported postmenopausal HT was associated with reduced AD risk (0.53/0.31-0.91). Similar results were obtained with any dementia diagnosis in the hospital discharge register as an outcome.

Conclusions: Our results do not provide strong evidence for a protective association between postmenopausal HT use and AD or dementia, although we observed a reduced AD risk among those with long-term self-reported HT use. *Neurology*® 2017;88:1062-1068

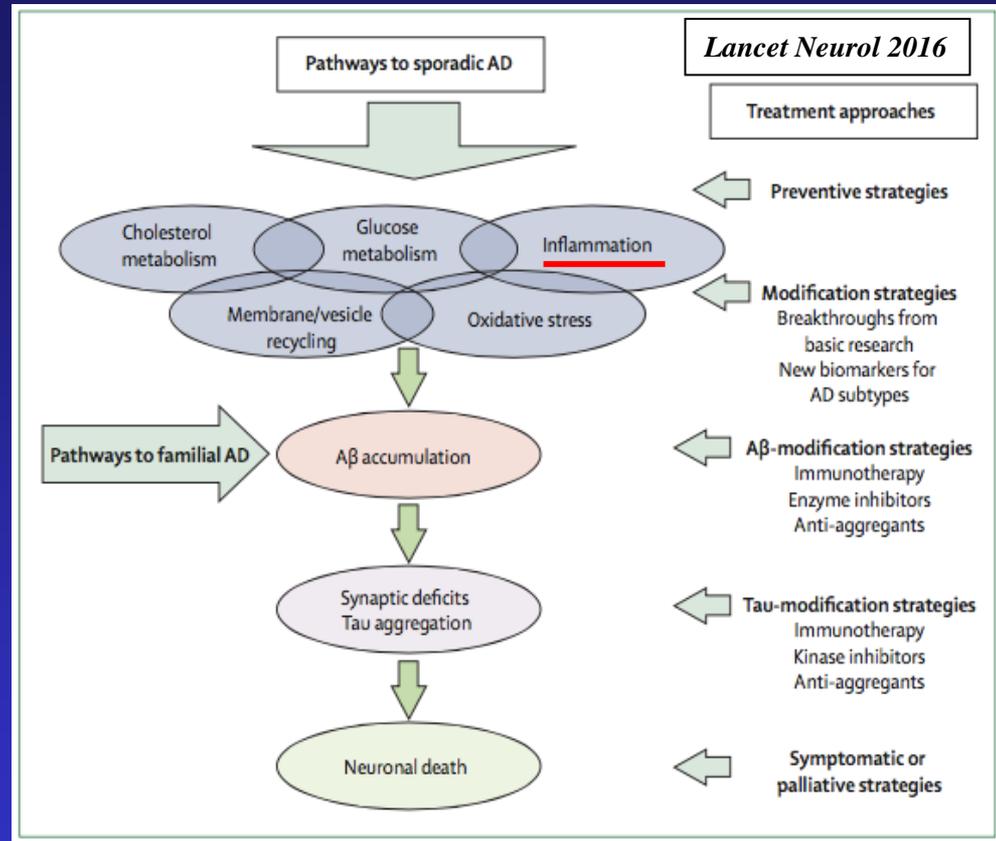
This finding indirectly favors the effectiveness of HT if started in the early postmenopausal period (critical window theory)

Interactions between inflammation, sex steroids, and Alzheimer's disease risk factors

AD patologia multifattoriale:
Infiammazione → uno dei
meccanismi principali

Vari fattori di rischio ambientali e
genetici agiscono
sull'infiammazione: obesità,
rapporto citochine pro- e anti-
APOEε4, riduzione età-correlata
ormoni sessuali

Infiammazione e malattia di Alzheimer



Differenze di sesso nella suscettibilità all'infiammazione:
ruolo degli ormoni sessuali (che hanno un'azione anti-infiammatoria) nel contributo alle
differenze di sesso nell'infiammazione

Obesità e BMI: effetti di genere sull'AD

J Alzheimers Dis. 2015;43(3):739-55. doi: 10.3233/JAD-141086.

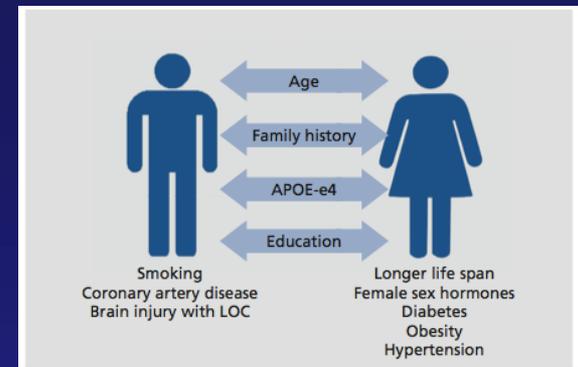
2003-2013: a decade of body mass index, Alzheimer's disease, and dementia.

Emmerzaal TL¹, Kiliaan AJ¹, Gustafson DR².

Studies investigating the association between midlife BMI and risk for dementia demonstrated generally an increased risk among overweight and obese adults. When measured in late-life, elevated BMI has been associated with lower risk

Recente studio FDG-PET (Perani et al 2018) in donne AD evidenziato un forte effetto di genere della BMI e dell'obesità che si riflette in una maggiore vulnerabilità dei sistemi neuronali coinvolti selettivamente nei meccanismi compensatori dell'AD → ridotti meccanismi di riserva cerebrale

Riserva cognitiva/educazione



Riserva cognitiva: ammontare di danno che è possibile tollerare senza che si manifestino deficit cognitivi

RC: Altro fattore critico nelle differenze di sesso nelle manifestazioni cliniche

>RC nell'uomo

< livelli di educazione nella donna → fattore di rischio AD > declino cognitivo nella donna

Education and occupation levels correlate with brain hypometabolism differently for men and women with Alzheimer's disease – with a posterior temporoparietal association in males and a frontal and limbic association in females [5^{***}]. The authors suggest that correlations of education and occupation with brain hypometabolism in Alzheimer's disease might reflect different effects coping with neurodegeneration. This proposal is consistent with

Genotipo APOE e Rischio AD sex-linked

APOE: carrier del colesterolo nel cervello
Gene APOE normalmente espresso in tre forme alleliche: E2, E3 (più frequente) ed E4

Circa 60% dei pz AD ha almeno un allele APOE ϵ 4 (15% nei NC)

Allele ϵ 4: maggiore fattore rischio genetico dell'AD sporadico

Effetto protettivo dell'allele ϵ 2 \rightarrow \gg longevità $<$ rischio AD

APOE ϵ 4 fattore di rischio sex-dipendente $>$ nelle donne anche per MCI e conversione in AD

Generalmente ritenuto rischio AD $>$ nelle donne APOE- ϵ 4, particolarmente nella condizione di eterozigosi

Key Points

Question Are female carriers of the apolipoprotein E ϵ 4 allele at greater risk of developing Alzheimer disease than men?

Findings In this meta-analysis of 27 independent research studies with 58 000 participants, women and men with 1 copy of apolipoprotein E ϵ 4 did not show a difference in risk of Alzheimer disease from age 55 to 85 years. However, these women were at increased risk vs men between ages 65 and 75 years.

Meaning Sex-specific treatments for cognitive decline and Alzheimer disease may need to be initiated a younger age, especially in those who carry an apolipoprotein E ϵ 4 allele.

CONCLUSIONS AND RELEVANCE Contrary to long-standing views, men and women with the APOE ϵ 3/ ϵ 4 genotype have nearly the same odds of developing AD from age 55 to 85 years, but women have an increased risk at younger ages.

Rapporto estrogeni/APOE



HHS Public Access

Author manuscript

J Steroid Biochem Mol Biol. Author manuscript; available in PMC 2017 June 01

Published in final edited form as:

J Steroid Biochem Mol Biol. 2016 June ; 160: 134–147. doi:10.1016/j.jsbmb.2016.03.012.

Age, APOE and Sex: Triad of Risk of Alzheimer's Disease

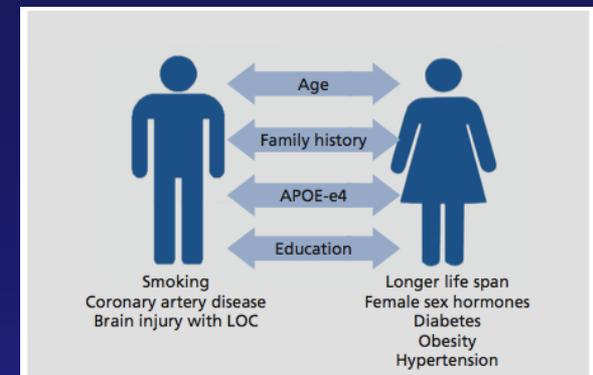
Brandalyn C. Riedel¹, Paul M. Thompson², and Roberta Diaz Brinton³

The impact of estrogen therapy in postmenopausal women is complex...

ApoE ϵ 4 negative women receiving estrogen or hormone therapy had the highest level of cognitive performance, whereas women positive for ApoE ϵ 4 receiving estrogen or hormone therapy performed worse than ApoE ϵ 4 carriers not receiving therapy.

Notably, treatment with tamoxifen, a selective estrogen receptor modulator and estrogen receptor antagonist, ameliorated cognitive deficits observed during the menopausal transition, especially in ApoE ϵ 4 women. The contradictory effects of estrogenic agonists and an estrogen receptor antagonist in ApoE ϵ 4 carriers suggest that the female ApoE ϵ 4 brain is different than the ApoE 3 carriers

Differenze di sesso rilevanti nel profilo clinico, decorso, prognosi



- Sul ruolo dei possibili determinanti e fattori rischio, risultati spesso non omogenei
- Fattori neurobiologici: maggiore longevità femminile 4,5 anni in media. Non giustifica il bias F/M nell'AD
- Maggior percentuale di progressione dell'MCI → demenza nelle donne
- Progressione clinica più rapida nella donna
- Ma... sopravvivenza dopo la diagnosi minore per l'uomo
- Prevalenza dei disturbi affettivi e disabilità nella donna
- Studi post-mortem e di neuroimaging: patologia AD diversa nei due sessi, più grave nella donna (es. ippocampo più atrofico)

Trattamento AD

Non ancora disponibili trattamenti adeguati

L'identificazione di fattori di rischio modificabili → focus di molti studi

Sfortunatamente i due maggiori “predittori” di demenza, età e sesso, non appartengono a questa categoria

Fattori genetici e ormonali potrebbero influenzare diversa risposta ai farmaci e indirizzare la ricerca

Sex and gender differences in the treatment of Alzheimer's disease: A systematic review of randomized controlled trials 2017



The present study is aimed at systematically retrieve, review and discuss data coming from **available randomized placebo-controlled trials** (RCTs) on currently marketed treatments for AD (i.e., cholinesterase inhibitors [ChEIs] and memantine) in order to describe possible sex and gender differences in their efficacy, safety and tolerability..... None of the retrieved studies reported data on the efficacy, safety and tolerability of considered medications separately in male and female patients with AD.

The existence of sex and gender differences in the efficacy and tolerability of ChEIs and memantine in AD has, to date, drawn limited to no attention

Review

Aging without Dementia is Achievable: Current Evidence from Epidemiological Research

Chengxuan Qiu^{a,b,*} and Laura Fratiglioni^{b,c}

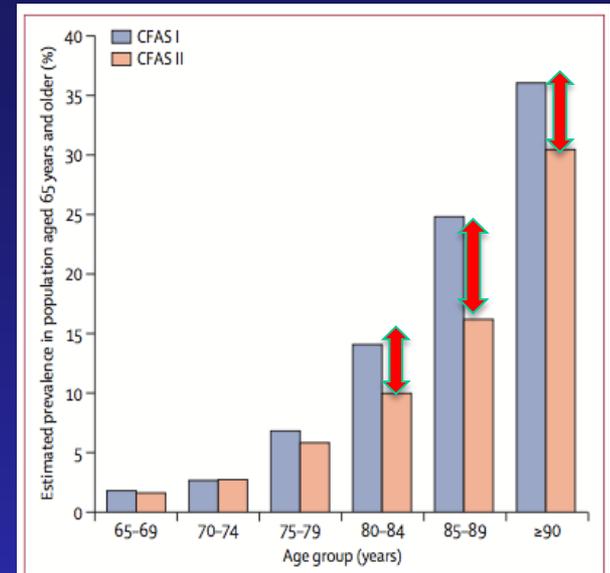


Figure 1: CFAS I and CFAS II age-specific dementia prevalence
CFAS=Cognitive Function and Ageing Study.

In occidente nelle ultime due decenni riduzione di prevalenza della demenza negli individui nati più tardi → 25% di “mancati dementi”

Possibili fattori che spiegano la riduzione dell'incidenza osservata negli ultimi anni:

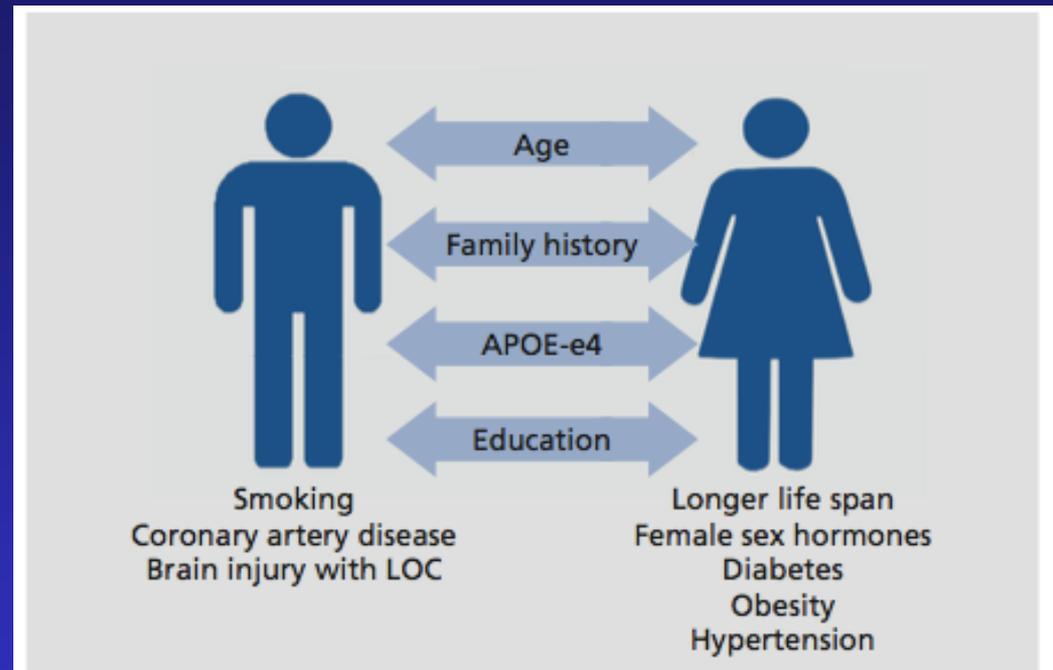
- Aumento della scolarizzazione
- Riduzione del rischio vascolare
- Migliore stile di vita



Demenza: fattori di rischio per Sesso

Possibili fattori rischio di demenza nell' uomo e nella donna

Importante la conoscenza dei diversi fattori di rischio/sexo per prevenzione, trattamento, prognosi **negli studi del normal cognitive aging, MCI, e demenza**



Fattori di rischio quali fumo, malattia coronarica, trauma cerebrale con perdita di coscienza → più frequenti nel M. Altri diabete, obesità, e ipertensione sempre più comuni nel M, ma molto più legati a rischio demenza per la donna

Ruolo delle alterazioni della WM (leucoaraiosi) > nell'uomo

Conclusioni

- Dati epidemiologici: evidente vulnerabilità nella donna → sesso femminile fattore fondamentale nell'AD
- Tuttavia meccanismi biologici alla base ancora largamente indefiniti
- Focus sull'effetto del sesso nell'AD essenziale per lo sviluppo di strategie preventive e terapie sesso-specifiche

- Differenze nelle lesioni cerebrali: **atrofia ippocampo** più rapida nella donna; peso delle lesioni della **WM** > nell'uomo
- Differenze nella clinica: nella donna prevalenza dei **disturbi** affettivi e disabilità, ma **sopravvivenza** maggiore; nell'uomo prevalenza dei comportamenti aggressivi, maggiori comorbidità e minore sopravvivenza
- Differenze nei livelli di educazione e occupazionali → conseguenze nella **RC**
- Differenze nella **penetranza di fattori di rischio** genetici (APOE) e ambientali
- Ruolo degli estrogeni: deplezione età-correlata
- Azione degli ormoni steroidei nello sviluppo cerebrale: maggiore vulnerabilità del cervello femminile nella patogenesi dell'AD?