



ORDINE DEI MEDICI CHIRURGI  
E DEGLI ODONTOIATRI  
DELLA PROVINCIA DI BERGAMO



# **LA MEDICINA DI GENERE IN RETE**

**23 OTTOBRE ORE 9:30-13:30**  
**ORDINE DEI MEDICI DI BERGAMO**

## **L'anziano, la Demenza e il Genere**

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# Populations are getting older





# Life expectancy and gender difference



**Women tend to live longer than men but this can also mean more years spent in ill health**

HelpAge  
International

age helps

**Men have a shorter life expectancy than women, but they will enjoy a greater proportion of their lives in good health**

## + Health

Women tend to live longer than men.

### Global average for men

- Life expectancy at age 60
- Healthy life expectancy at age 60

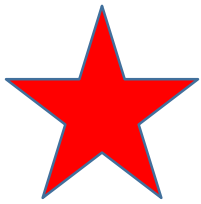


### Global average for women

- Life expectancy at age 60
- Healthy life expectancy at age 60



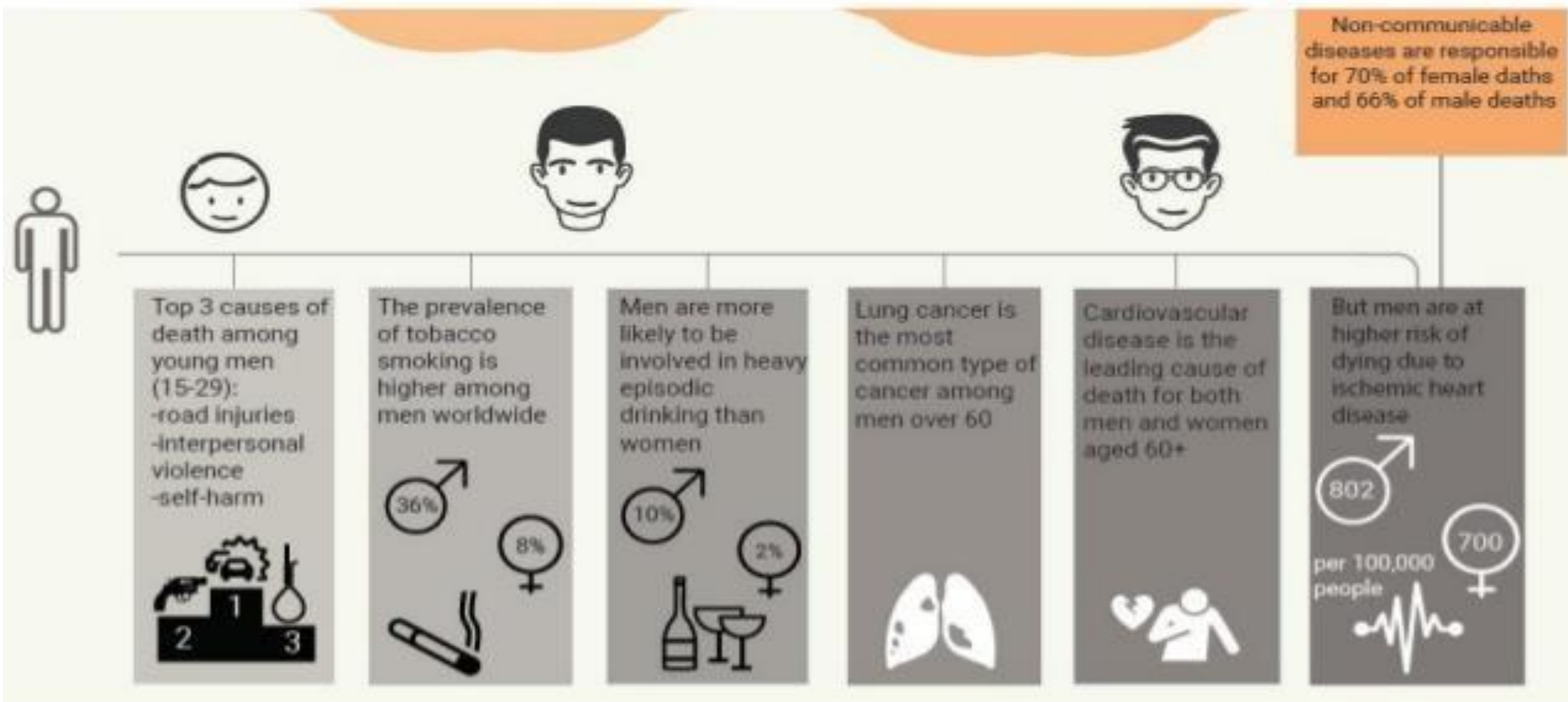
*(Global AgeWatch 2015)*



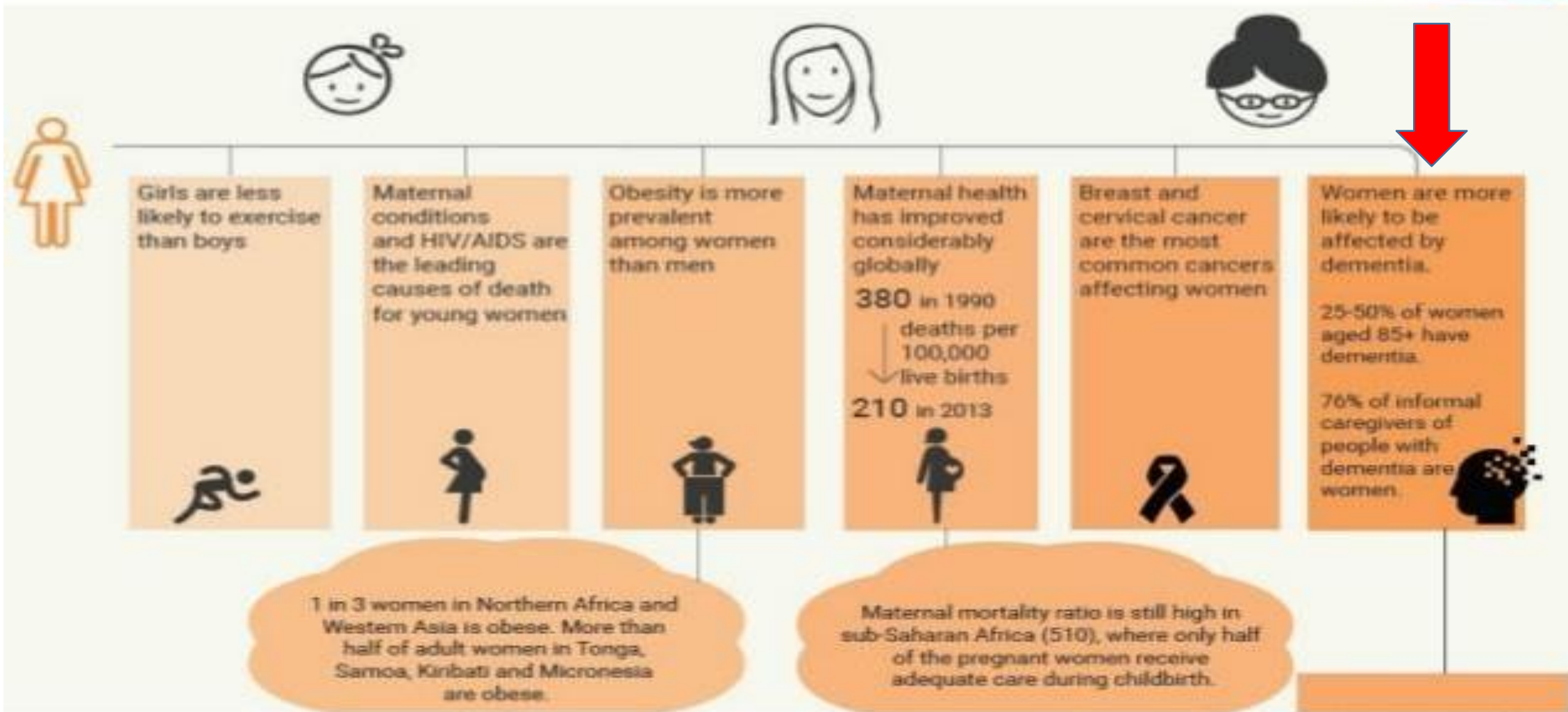
Popolazione residente per condizione di salute, malattie croniche dichiarate negli ultimi due giorni precedenti l'intervista, classe di età, sesso  
Anno 2013 (per 100 persone della stessa classe di età e sesso)

ANNI CLASSI DI ETA'	1 malattia cronica o più	2 malattie croniche o più	Diabete	Ipertensione	Malattie del cuore
2009	38,8	20,3	4,8	15,8	2,6
2010	38,6	20,1	4,9	16,0	3,7
2011	38,4	20,0	4,9	15,9	3,6
2012	38,6	20,4	5,5	16,4	3,5
<b>2013</b>	<b>37,9</b>	<b>20,0</b>	<b>5,4</b>	<b>16,7</b>	<b>3,7</b>
2013 – Per classi di età e sesso					
<b>MASCHI</b>					
60-64	<b>61,0</b>	30,4	13,0	33,0	6,9
65-74	<b>72,8</b>	42,2	16,0	45,2	11,6
75 e oltre	<b>82,8</b>	58,7	20,7	50,4	19,8
2013 – Per classi di età e sesso					
<b>FEMMINE</b>					
60-64	<b>66,4</b>	39,4	7,7	31,9	3,2
65-74	<b>78,1</b>	54,4	14,3	44,7	6,7
75 e oltre	<b>88,6</b>	73,9	20,1	57,6	14,4

Non-communicable diseases are responsible for 70% of female deaths and 66% of male deaths



(The World's Women 2015: Trends and Statistics, UN Statistics Division)

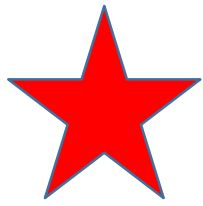


*(The World's Women 2015: Trends and Statistics, UN Statistics Division)*

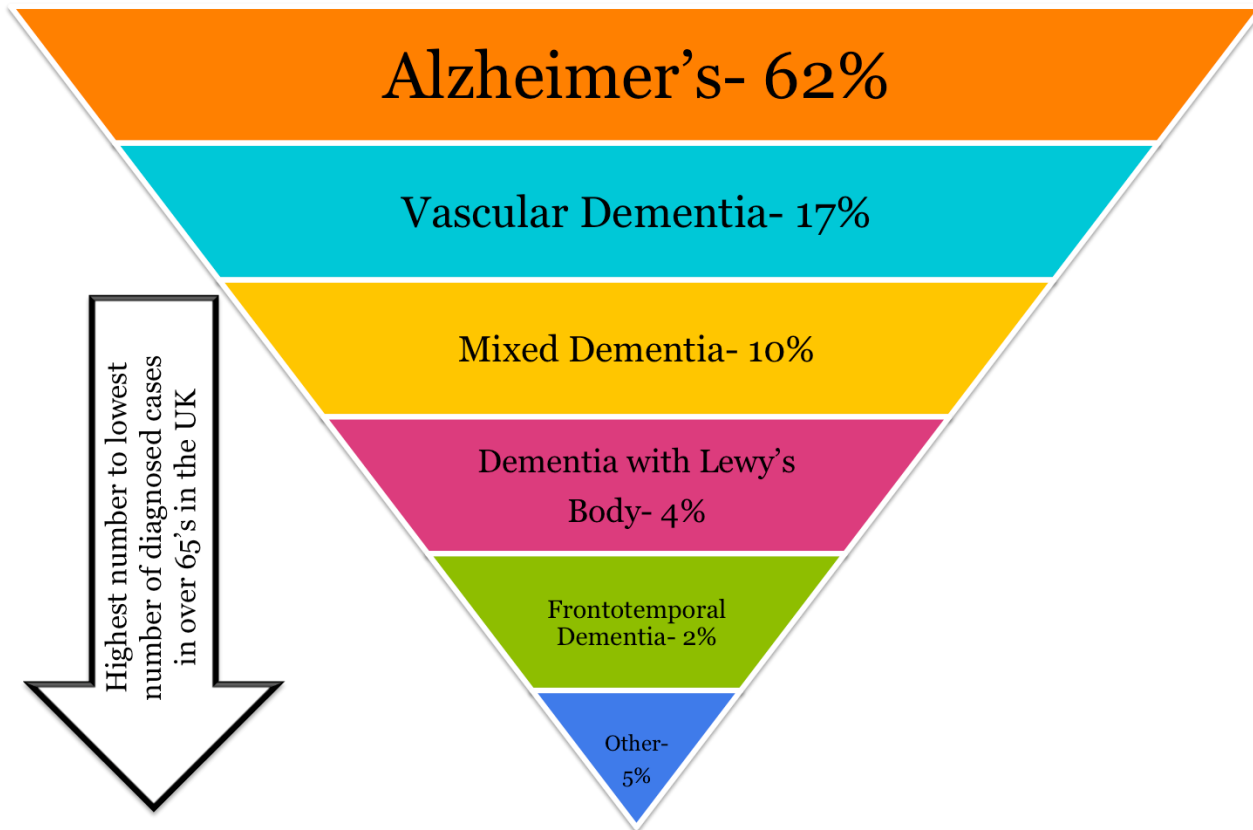
# **Il paradosso donna**

- **La donna vive più a lungo e soprattutto nei paesi più sviluppati.**
- **Ciò è dovuto a fattori di tipo biomedico, ad un sistema sanitario efficiente e alla capacità di sfruttare meglio le condizioni di vita e di prevenzione delle malattie in genere.**
- **Ma paradossalmente le donne vivono peggio rispetto agli uomini per la presenza di un maggior numero di malattie croniche, per una maggiore disabilità e fragilità, nonché per essere aggravate maggiormente dal ruolo di caregiver e quindi di isolamento e non facile accesso alle cure e alla prevenzione**
- **Il vantaggio in anni di vita spesso corrisponde ad un vissuto in disabilità**
- **Già dai 50 anni le donne sono maggiormente colpite sia sotto il profilo psicologico che sotto quello fisico.**

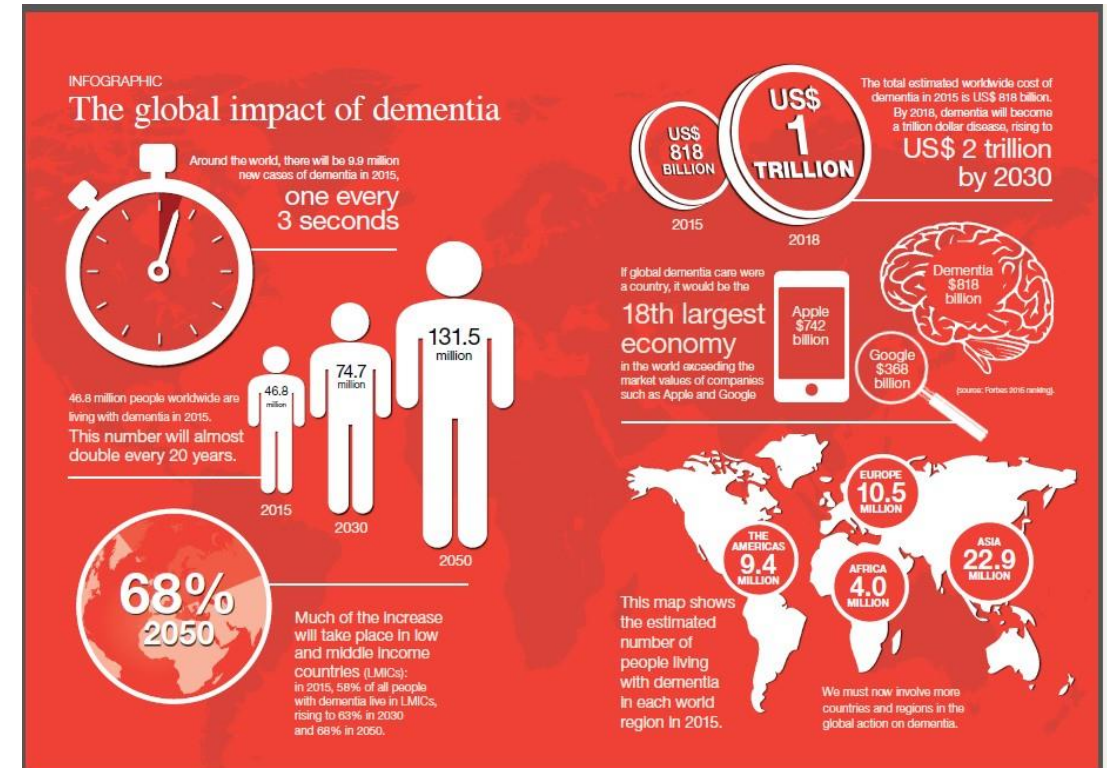
*Ridotta quality life*



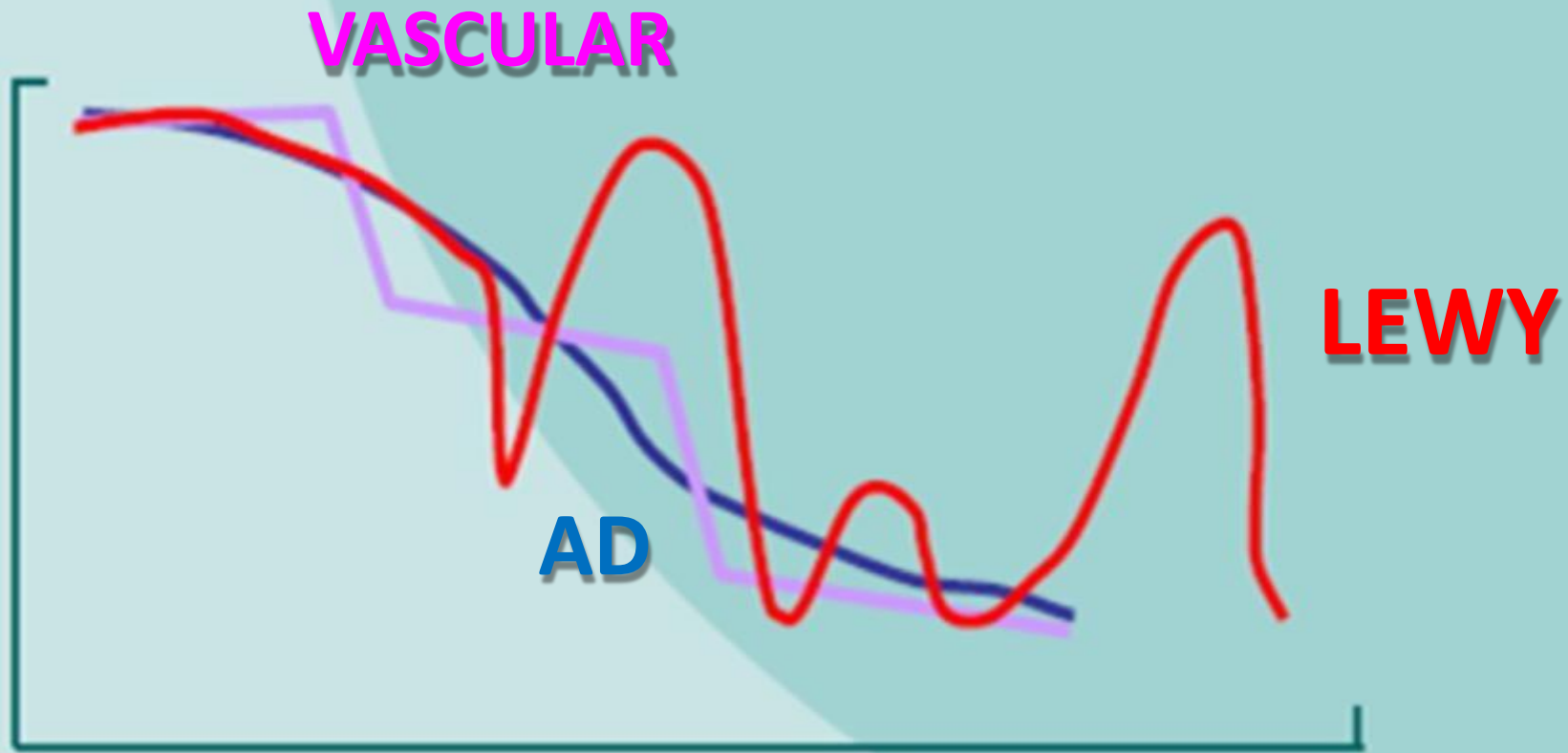
# Dementia subtypes

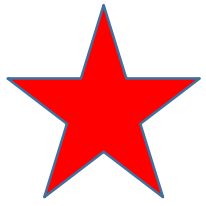


Nel mondo un caso di demenza ogni tre secondi !!!



# TIMELINE DEMENZE





## Demenza subtypes /questions

Esiste una specificità di genere?

Disorders leading to dementia	Prevalence/incidence & impact of sex/gender
Alzheimer disease	<ul style="list-style-type: none"> <li>• Accounts for 60%-80% of dementia cases.</li> <li>• Almost twofold increased risk in women versus men.<sup>1</sup></li> <li>• However, shorter life span for men after diagnosis.<sup>2</sup></li> </ul>
Vascular disease	<ul style="list-style-type: none"> <li>• Accounts for 10%-20% of dementia cases.</li> <li>• Risk factors for vascular or multi-infarct dementia are more common in males, but have greater severity of impact in females.<sup>3</sup></li> </ul>
Dementia with Lewy bodies	<ul style="list-style-type: none"> <li>• Extensive overlap with Parkinson disease dementia.</li> <li>• Incidence greater in males than females (4.8 vs 2.2).<sup>4</sup></li> <li>• Male sex is associated with more rapid cognitive decline.</li> </ul>
Parkinson disease dementia	<ul style="list-style-type: none"> <li>• Parkinson disease prevalence higher in males than females;<sup>5,6</sup></li> <li>• Earlier onset of Parkinson disease dementia in males.<sup>7</sup></li> <li>• Greater severity of cognitive decline in males.<sup>8</sup></li> </ul>
Due to multiple causes (mixed)	<ul style="list-style-type: none"> <li>• Most often a combination of vascular dementia and Alzheimer disease.<sup>9,10</sup></li> <li>• More common in males than females: 31% vs 25%.<sup>11</sup></li> </ul>
Normal pressure hydrocephalus	<ul style="list-style-type: none"> <li>• Prevalence differs greatly depending upon age and study, but is 1.3% according to a recent systematic review.<sup>12</sup></li> <li>• Almost twice as common in men than women after age 60, though other studies suggest equal frequency in males and females.<sup>13</sup></li> </ul>
Frontotemporal degeneration	<ul style="list-style-type: none"> <li>• Earlier age of onset in those with TBI and LOC.</li> <li>• May be more common in males.<sup>14,15</sup></li> <li>• Sex not associated with survival duration after diagnosis.<sup>16</sup></li> </ul>
Creutzfeldt-Jakob disease	<ul style="list-style-type: none"> <li>• Rare: 1.26 cases/million people.<sup>17</sup></li> <li>• Sex differences in prevalence and clinical course have not been reported.</li> </ul>



**Table I.** Prevalence/incidence of disorders leading to dementia and the impact of sex or gender. LOC, loss of consciousness; TBI, traumatic brain injury.

# Un soggetto su nove ha la malattia di Alzheimer e le donne sono il doppio

(>65 anni)

## PREVALENCE



figure 3

Estimated Lifetime Risks for Alzheimer's, by Age and Sex, from the Framingham Study

Percentage

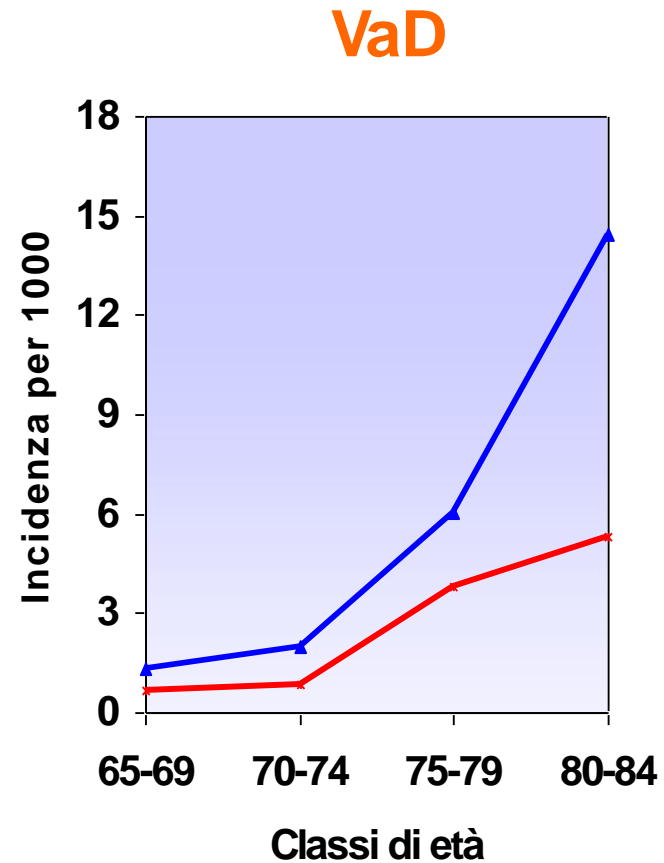
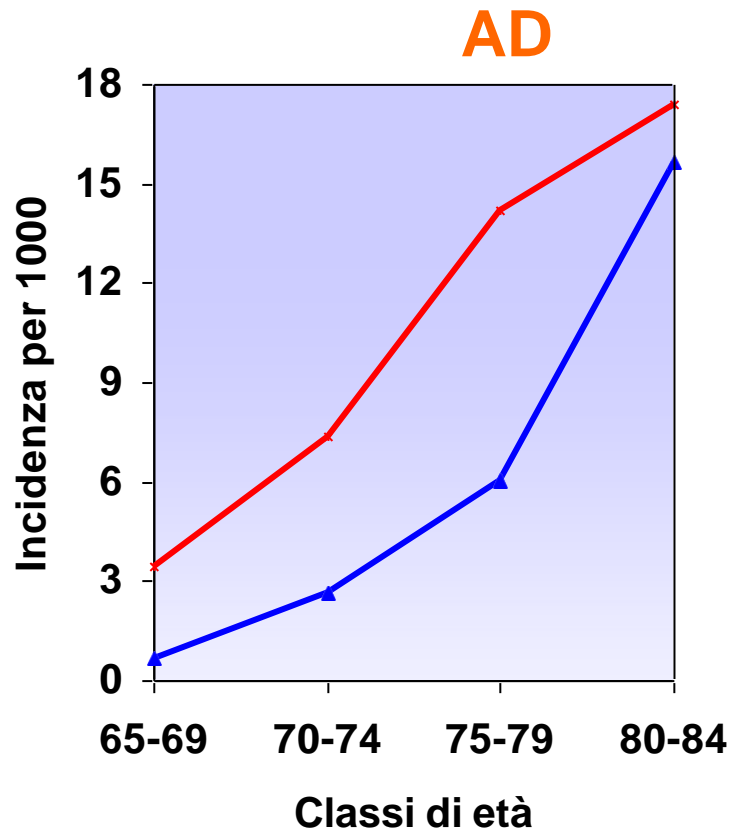
Men

Women



Created from data from Seshadri et al. <sup>(142)</sup>

# Studio ILSA: Incidenza della malattia di Alzheimer e della demenza vascolare per sesso e classi di età



—▲— Uomini —■— Donne



Published in final edited form as:

*J Neurol.* 2010 November ; 257(11): 1875–1881. doi:10.1007/s00415-010-5630-4.

## Association between male gender and cortical Lewy body pathology in large autopsy series

Table 1

Patient characteristics by gender including neuropathology and demographic data from NACC Registry and UK ADC autopsy series

	Research subjects grouped by neuropathology				Total	
	AD only	DLB Only	AD + DLB	Neither AD nor DLB		
Patients	Male	734	109	240	451	1,534
NACC	Female	883	42	230	483	1,638
	Total	1,617	151	470	934	3,172
OR, M:F (95% CI)		0.78 (0.68–0.90)	2.91 (2.02–4.18)	1.14 (0.93–1.38)	1.00 (0.85–1.16)	
Patients	Male	77	22	35	141	275
UK ADC	Female	147	11	61	164	383
	Total	224	33	96	305	658
OR, M:F (95% CI)		0.62 (0.45–0.87)	2.94 (1.40–6.17)	0.77 (0.49–1.20)	1.41 (1.03–1.92)	
Mean	Male	76.7 (75.9–77.4)	78.9 (77.3–80.4)	78.0 (76.9–79.1)	83.6 (82.8–84.4)	79.1 (78.6–79.6)
Age	Female	80.9 (80.2–81.7)	81.9 (78.8–84.9)	80.4 (79.1–81.7)	86.6 (85.7–87.4)	82.5 (82.0–83.1)
NACC	Total	79.0 (78.5–79.5)	79.7 (78.3–81.1)	79.2 (78.3–80.0)	85.1 (84.5–85.7)	80.9 (80.5–81.2)
Mean	Male	14.9 (14.6–15.1)	15.7 (15.1–16.4)	15.0 (14.5–15.4)	15.5 (15.1–15.8)	15.1 (14.9–15.3)
Education	Female	13.4 (13.2–13.6)	14.0 (12.9–15.0)	13.3 (12.9–13.7)	14.6 (14.3–14.9)	13.8 (13.6–13.9)
NACC	Total	14.1 (13.9–14.3)	15.2 (14.7–15.8)	14.1 (13.8–14.5)	15.0 (14.8–15.2)	14.4 (14.3–14.5)

# A cosa DOBBIAMO QUESTE DIFFERENZE???



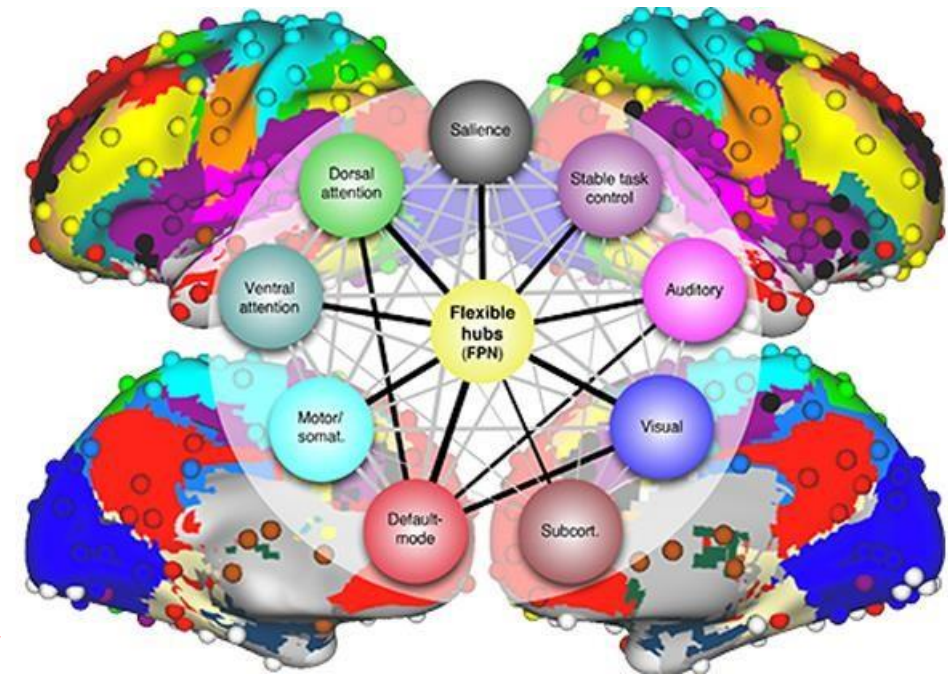
- **DIFFERENTI CONNESSIONI E NETWORK**
- **DIFFERENTE BACKGROUND ORMONALE**
- **DIFFERENTE ESPRESSIONE/ASSETTO GENETICO DIFFERENTE PESO DEI FATTORI DI RISCHIO**

# Gender differences in behavioral and cognitive functioning.

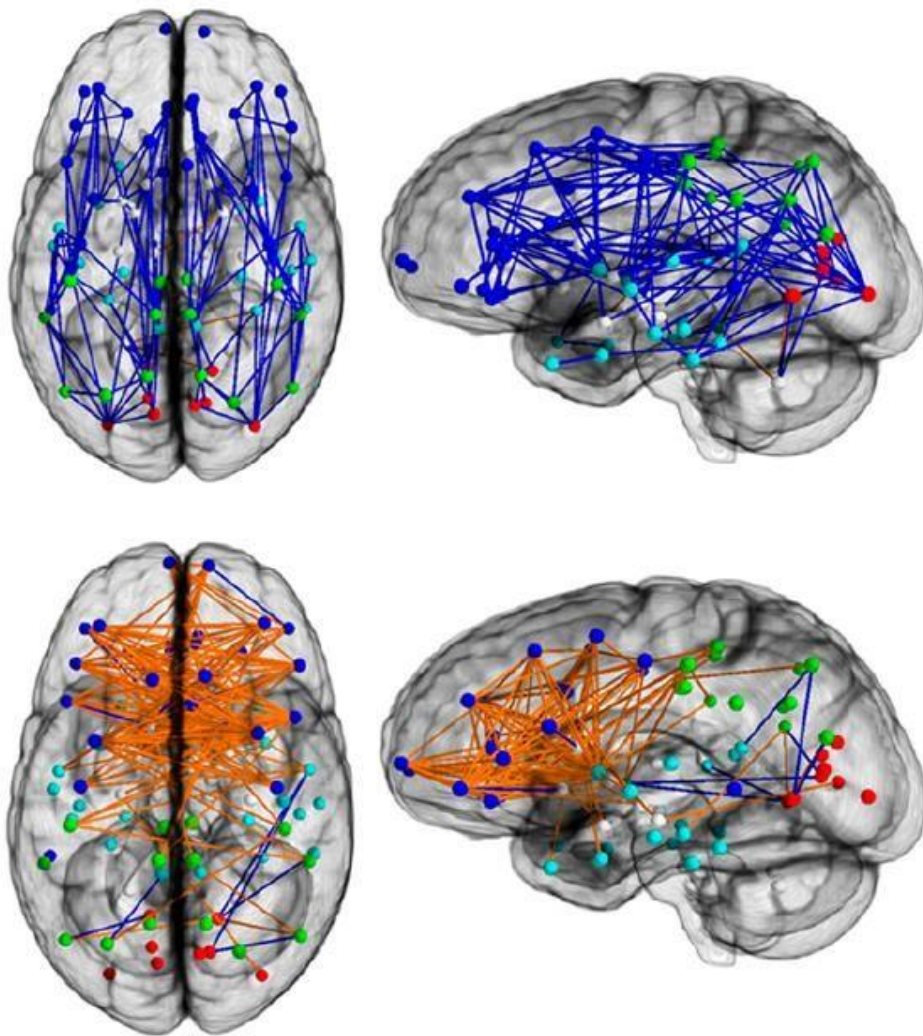
- The brain can be considered as a large-scale network of interconnected nodes within the human connectome
- Small world network (network di connessione tra nodi)



Gender differences in brain connectome may provide an important foundation to delineate the pathophysiological mechanisms underlying sex differences in neuropsychiatric disorders and to potentially guide the development of sex specific treatments.



A



### Significance

Sex differences are of high scientific and societal interest because of their prominence in behavior of humans and non-human species. This work is highly significant because it studies a very large population of 949 youths (8–22 y, 428 males and 521 females) using the diffusion-based structural connectome of the brain, identifying novel sex differences. The results establish that male brains are optimized for intrahemispheric and female brains for interhemispheric communication. The developmental trajectories of males and females separate at a young age, demonstrating wide differences during adolescence and adulthood. The observations suggest that male brains are structured to facilitate connectivity between perception and coordinated action, whereas female brains are designed to facilitate communication between analytical and intuitive processing modes.

**Differenti comunicazioni:**    **maschi in blu (percezione-azione coordinata)**  
**donne in arancio (analitico-intuitivo)**

## Sex differences in Alzheimer risk

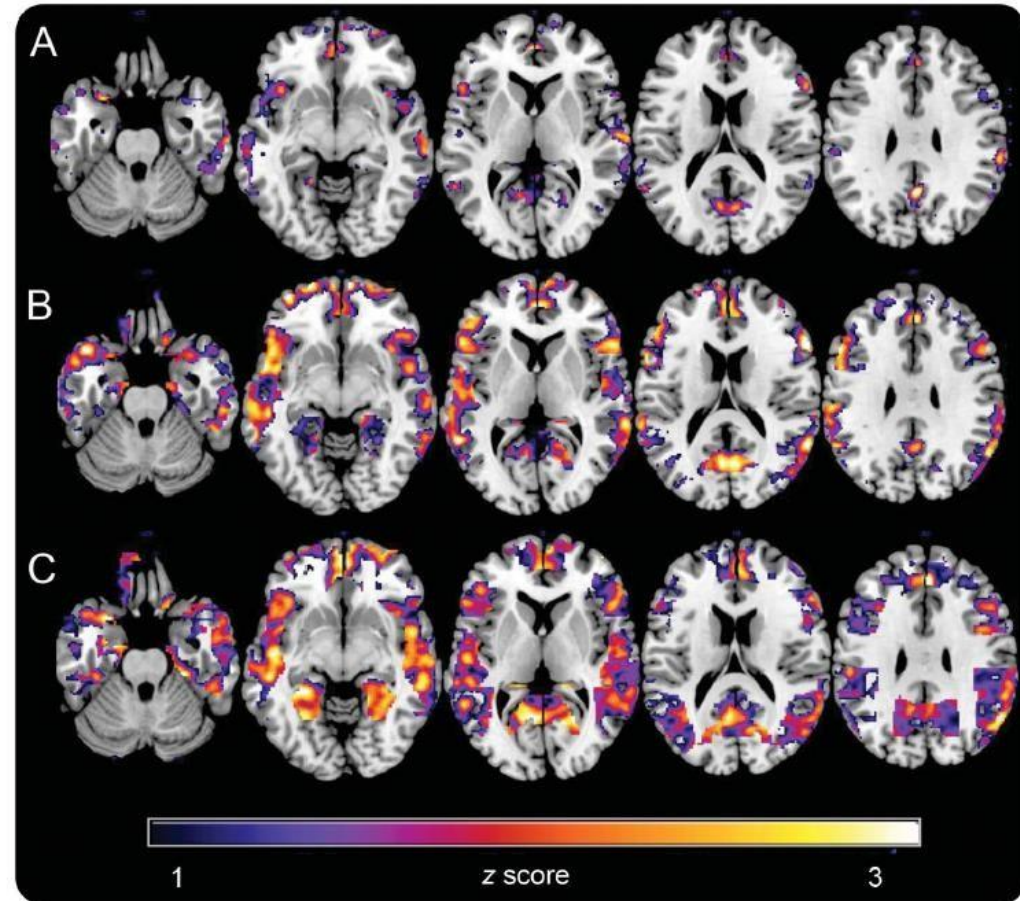
Brain imaging of endocrine vs chronologic aging

Mosconi et al Neurology 2017

Differenze ormonali

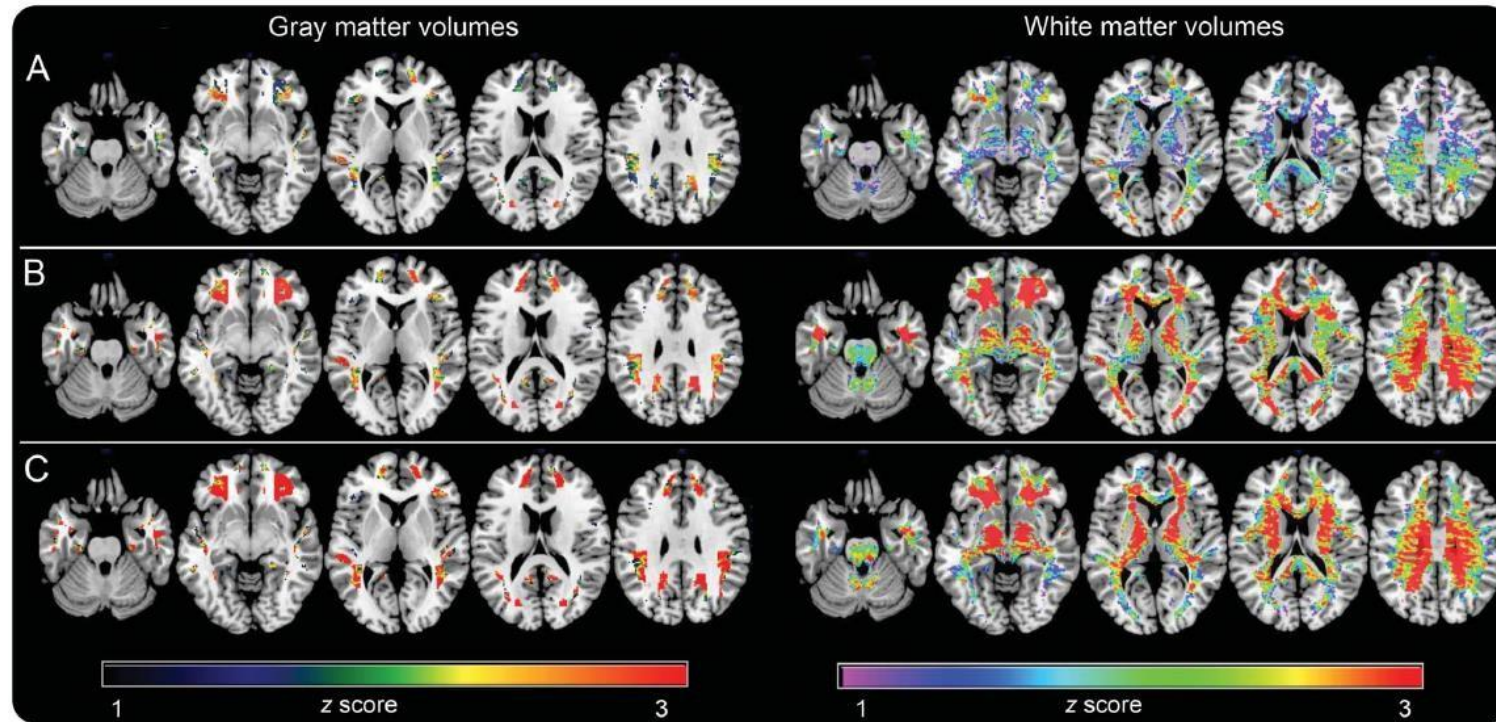
Figure 1 18F-fluoro-2-deoxyglucose (FDG)-PET brain glucose metabolism as a function of chronologic vs endocrine aging

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



Statistical parametric maps (SPMs) display increased  $^{11}\text{C}$ -PiB uptake in (A) asymptomatic perimenopausal women, (B) perimenopausal women, and (C) menopausal women vs men. SPMs are represented on a color-coded scale ( $1 < z < 3$ , where  $z > 2$  corresponds to  $p < 0.001$ ) and displayed on a standardized MRI.

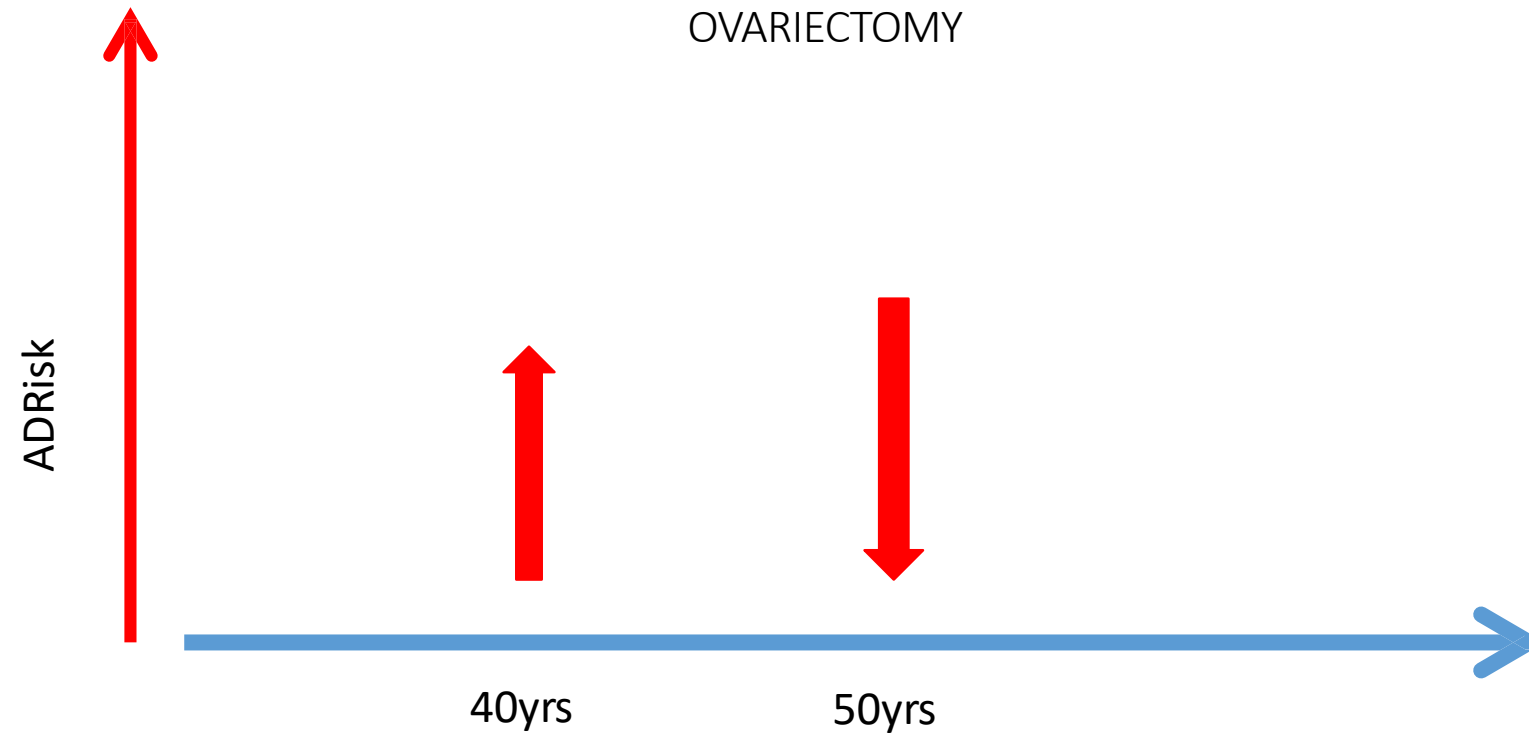
Figure 3 MRI brain volumes as a function of chronologic vs endocrine aging



Statistical parametric maps (SPMs) display (left) gray matter and (right) white matter volume reductions in (A) asymptomatic perimenopausal women, (B) perimenopausal women, and (C) menopausal women vs men. SPMs are represented on different color-coded scales ( $1 < z < 3$ , where  $z > 2$  corresponds to  $p < 0.001$ ) and displayed on a standardized MRI.

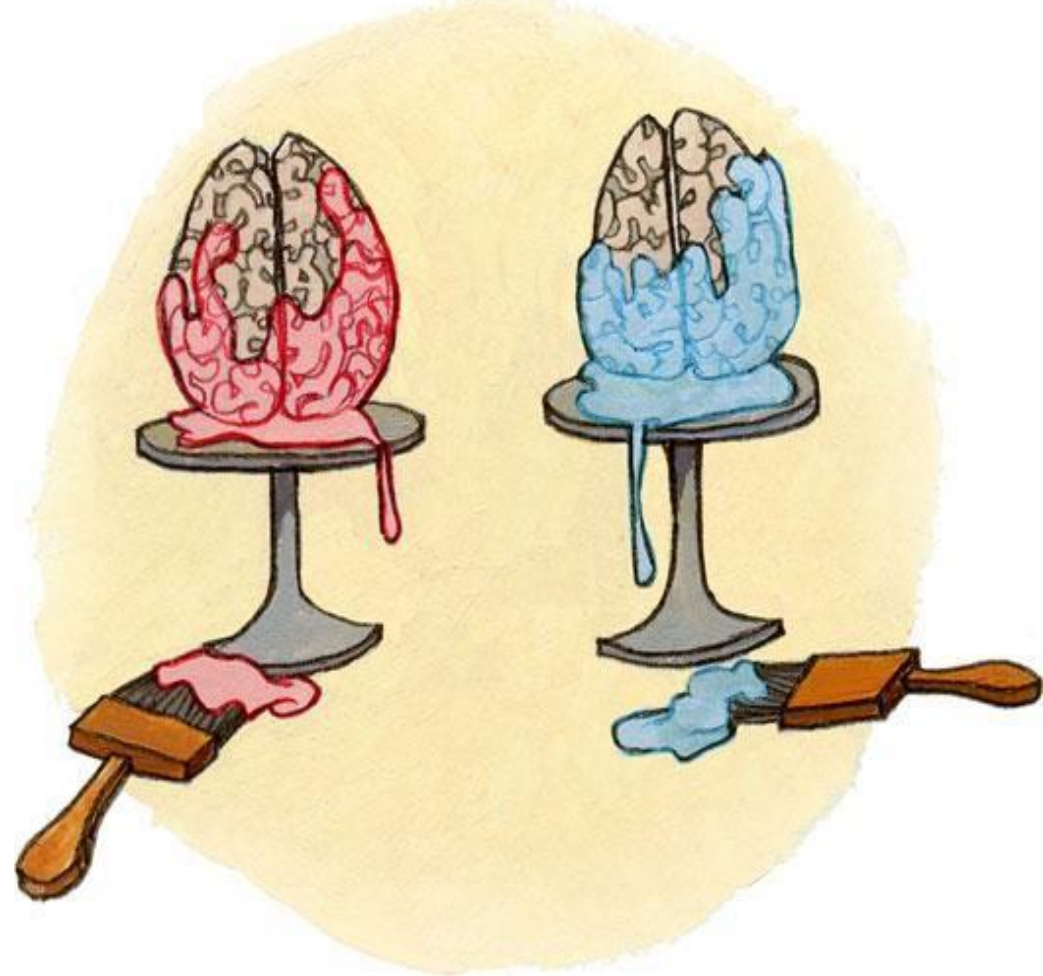
These results indicate progressively increased risk of AD as women undergo menopausal changes, suggesting that endocrine aging accelerates chronologic aging in the female brain several years, if not decades, prior to emergence of possible clinical symptoms of AD.

# Timing hypothesis



## Genes differences

Approximately 650 genes (~ 14% of all genes in mouse tissue) are expressed differentially in the brains of males and females. The morphology of the brain may be sexually differentiated because of epigenetic mechanisms



Diversa espressione dei geni nei cervelli di maschi e femmine

Yang, X. et al. (2006) Tissue-specific expression and regulation of sexually dimorphic genes in mice. *Genome Research* 16 (8): 995-1004  
Murray, E. K. et al. (2009) Epigenetic Control of Sexual Differentiation of the Bed Nucleus of the Stria Terminalis. *Endocrinology* 150 (9): 4241-4247

## **Sex differences in metabolic aging of the brain: insights into female susceptibility to Alzheimer's disease**

- Gene expression profiles revealed substantial differences in the trajectory of aging changes between female and male brains.

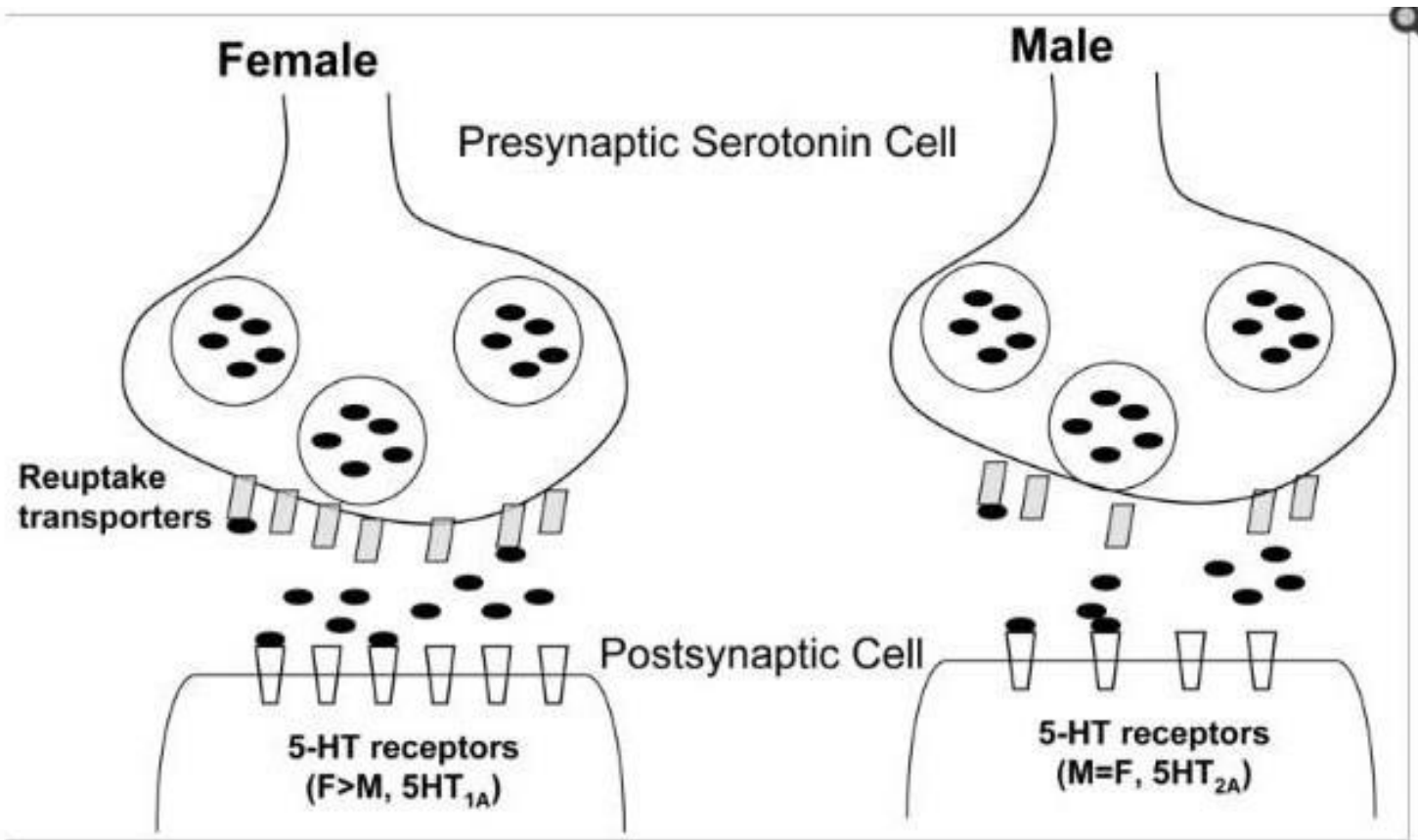
### **Conclusions:**

**female and male brains follow profoundly dissimilar trajectories as they age; female brains undergo age-related changes much earlier than male brains; early changes in female brains signal the onset of a hypometabolic phenotype at risk for AD.**

**These findings provide a mechanistic rationale for female susceptibility to AD and suggest a potential window of opportunity for AD prevention and risk reduction in women.**



# Sex-specific differences in neuromediators

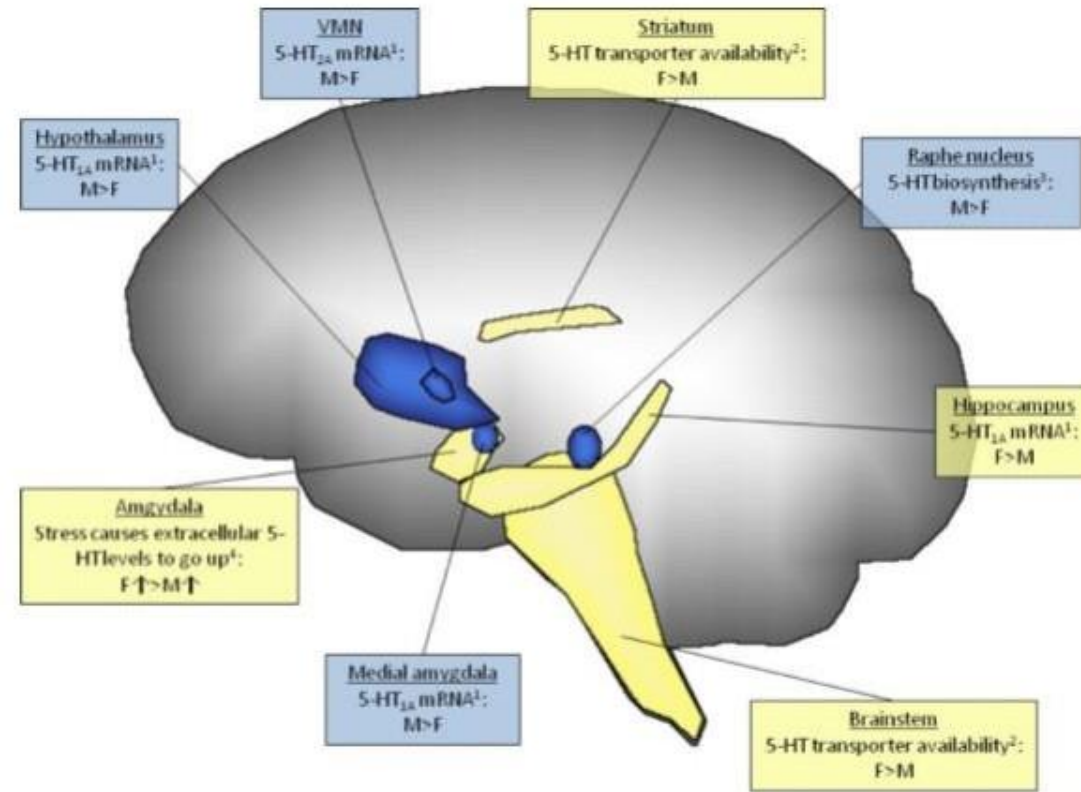


Proposed sex differences in a 5-HT synapse, with higher 5-HT reuptake transporters, neurotransmission, and 5HT<sub>1A</sub> receptors in women versus men.

Male and female brains are neurochemically distinct concerning **dopaminergic, serotonergic, and gamma-aminobutyric acid (GABA)ergic markers**



# Serotonin sexually differentiated @ multiple levels



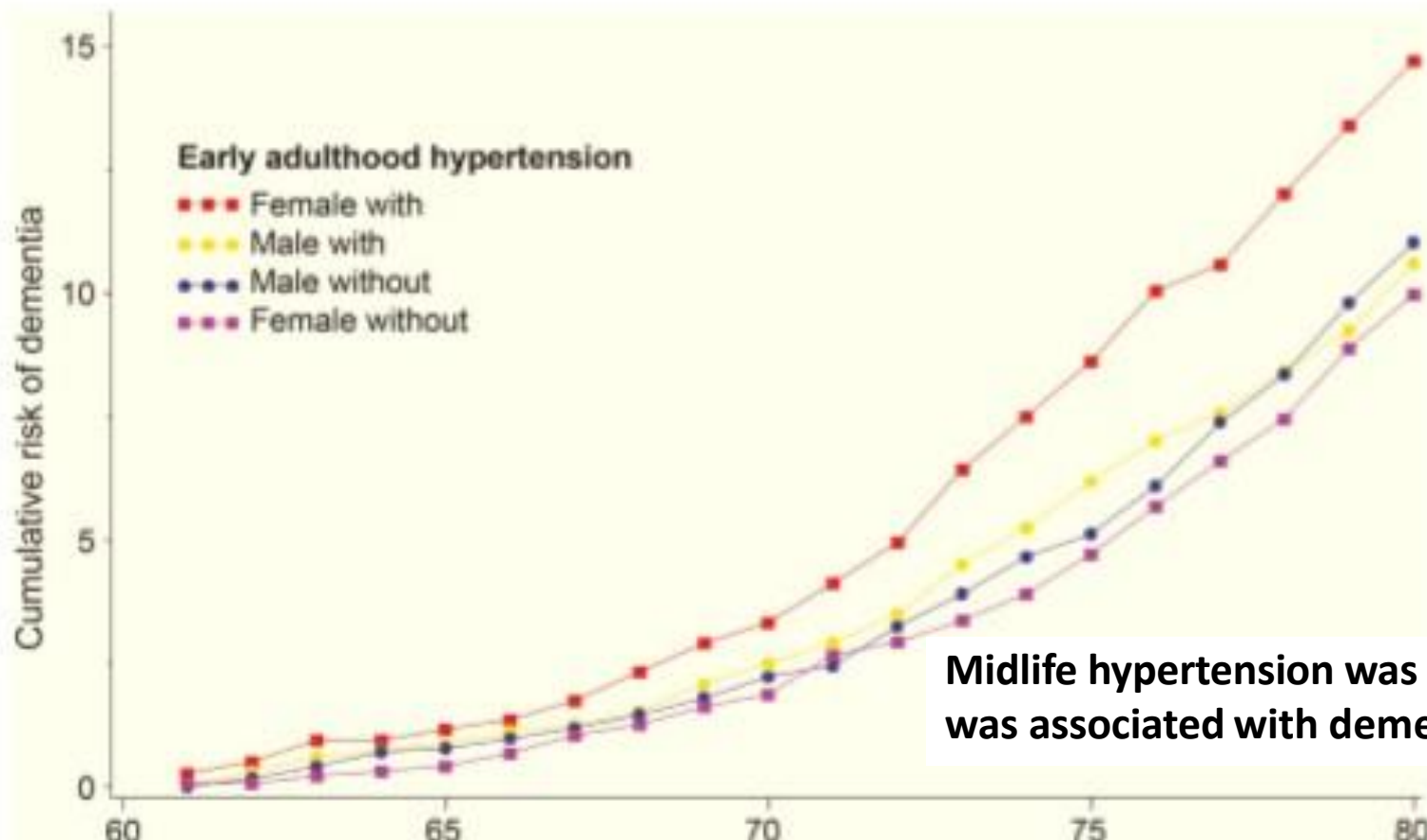
**Figure 2.**

Serotonin (5-HT) is sexually differentiated on multiple levels. In addition to the differences illustrated above, some of the loci that influence 5-HT levels in the blood are also sexually dimorphic [66]. References: 1 - [67], 2 - [68], 3 - [65], 4 - [69].



# Female sex, early-onset hypertension, and risk of dementia

**Figure** Estimates of the cumulative risk of dementia by sex and early adulthood hypertension status, conditional on survival dementia-free until age 60 and incorporating death rates



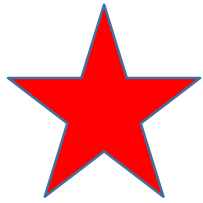
**Mid-adulthood hypertension was associated with 65% (95% confidence interval [CI] 1.25–2.18) increased dementia risk among women but not men.**

**Onset of hypertension in mid-adulthood predicted 73% higher dementia risk in women (95% CI 1.24–2.40) compared to stable normotensive**

**Midlife hypertension was more common in men, however it was associated with dementia risk only in women**

APOE4 effect is more pronounced in women than in men

**FARRER ET AL 1997**



Fattori di rischio genetici  
hanno pesi diversi

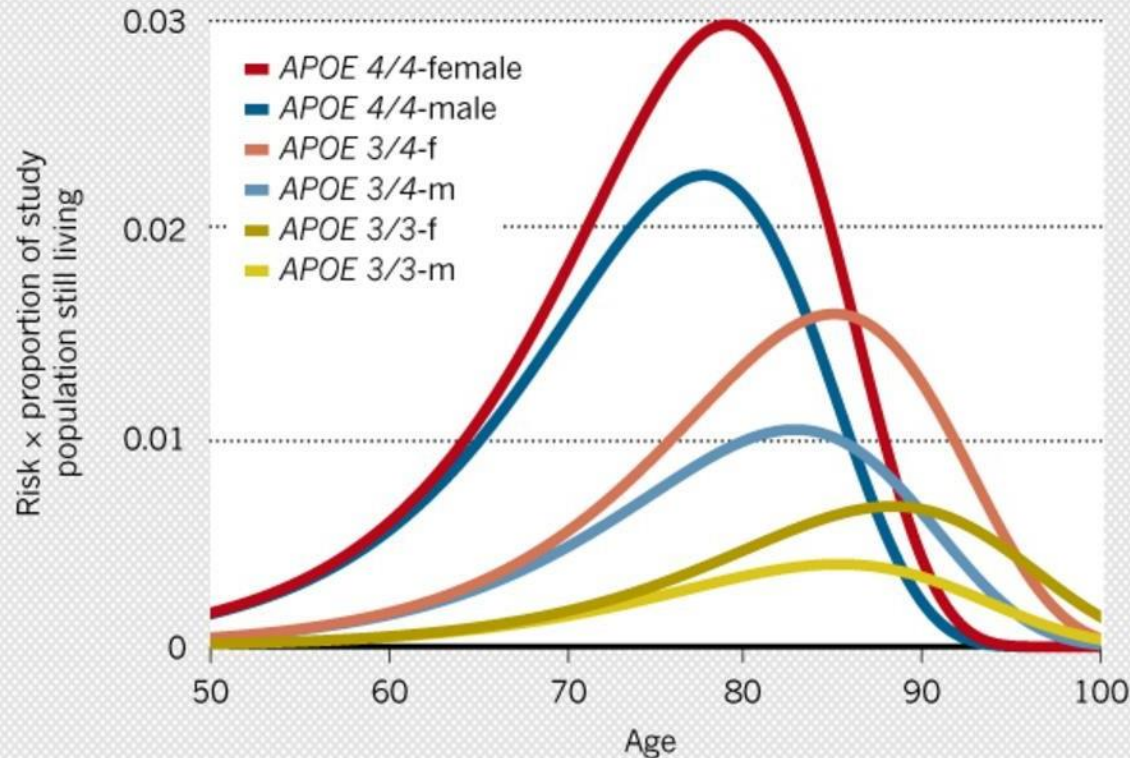
AD.<sup>89</sup> The majority of studies, including a large meta-analysis of 8,607 controls and 5,930 AD cases,<sup>90</sup> have reported that the effects of the ε4 genotype are more pronounced in women than in men.<sup>90</sup> Three studies reported that women with one ε4 allele had about a four-fold risk of AD, whereas men with one ε4 allele showed little increased risk.<sup>90-92</sup> The *APOE* ε4



# ApoE4 strongly promotes amyloid- $\beta$ deposition in the brain

## RISKY INHERITANCE

People who carry the gene variant *APOE4* tend to develop Alzheimer's at a younger age than those with two copies of *APOE3*.

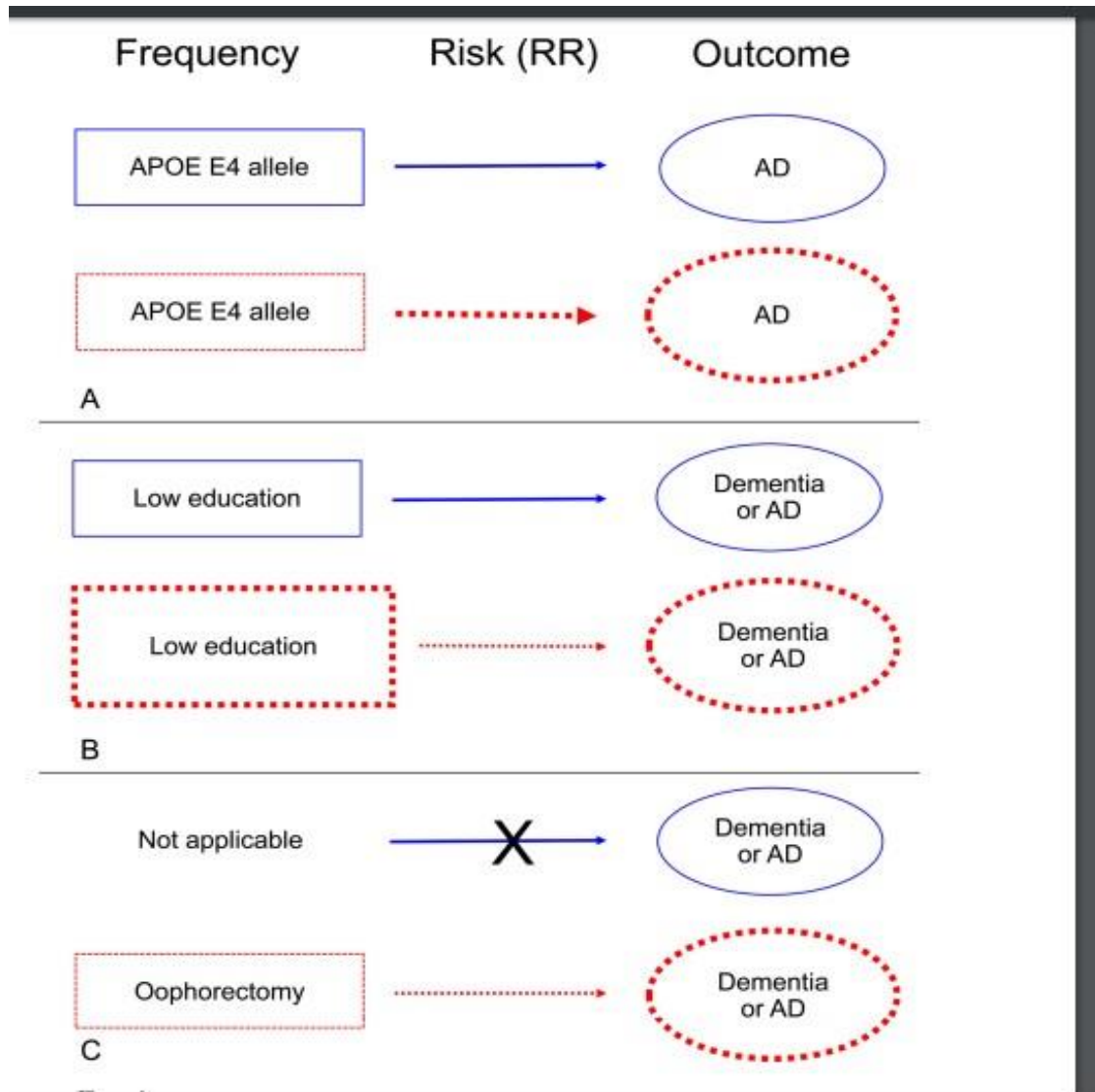


	Isoform-specific amino acid difference		Allele frequency	
	112	158	General	AD
<i>APOE2</i>	Cys	Cys	8.4%	3.9%
<i>APOE3</i>	Cys	Arg	77.9%	59.4%
<i>APOE4</i>	Arg	Arg	13.7%	36.7%

	<i>APOE4</i>		
	Non-carrier	Heterozygous	Homozygous
AD frequency	20%	47%	91%
Mean age of clinical onset	84-yr	76-yr	68-yr

# Risk gender for dementia or AD

Men blue  
Women red



- In all three examples, women experienced a higher risk of dementia or AD attributable to the specific risk factors (bigger red oval).
- Panel A: APOE E4 allele is equally frequent in men and women (equal boxes) but has a stronger effect in women (thicker red arrow).
- Panel B: low education has the same effect on the risk of dementia or AD in both men and women (equal strength of the blue and red

# ★ APOE Meta analysis

Increased risk in women  
between 65-75 yrs

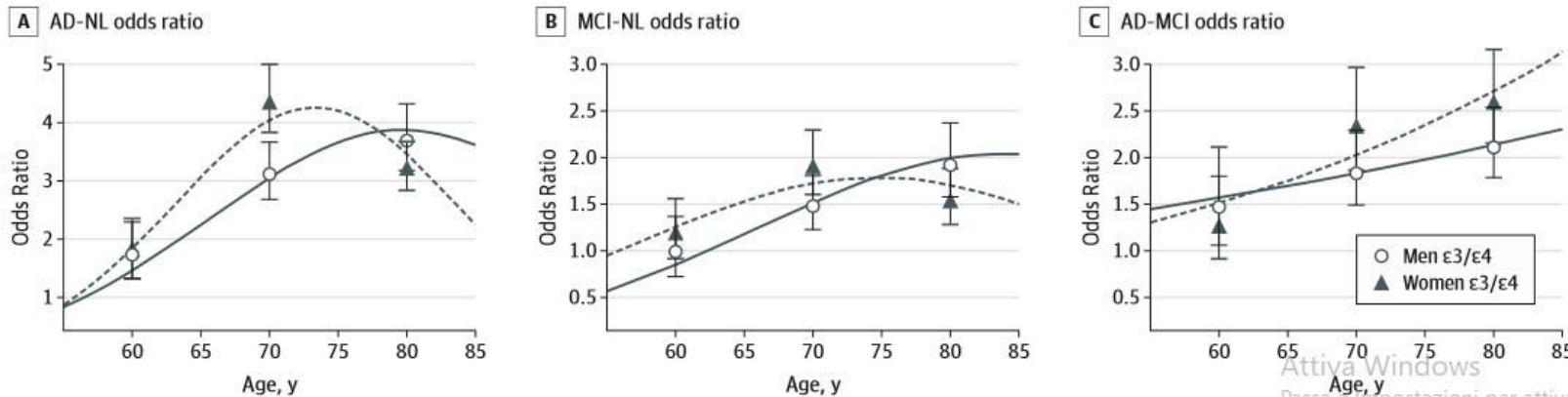
## Key Points

**Question** Are female carriers of the apolipoprotein E  $\epsilon 4$  allele at greater risk of developing Alzheimer disease than men?

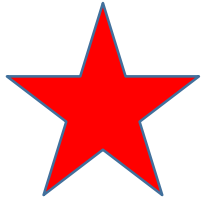
**Findings** In this meta-analysis of 27 independent research studies with 58 000 participants, women and men with 1 copy of apolipoprotein E  $\epsilon 4$  did not show a difference in risk of Alzheimer disease from age 55 to 85 years. However, these women were at increased risk vs men between ages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

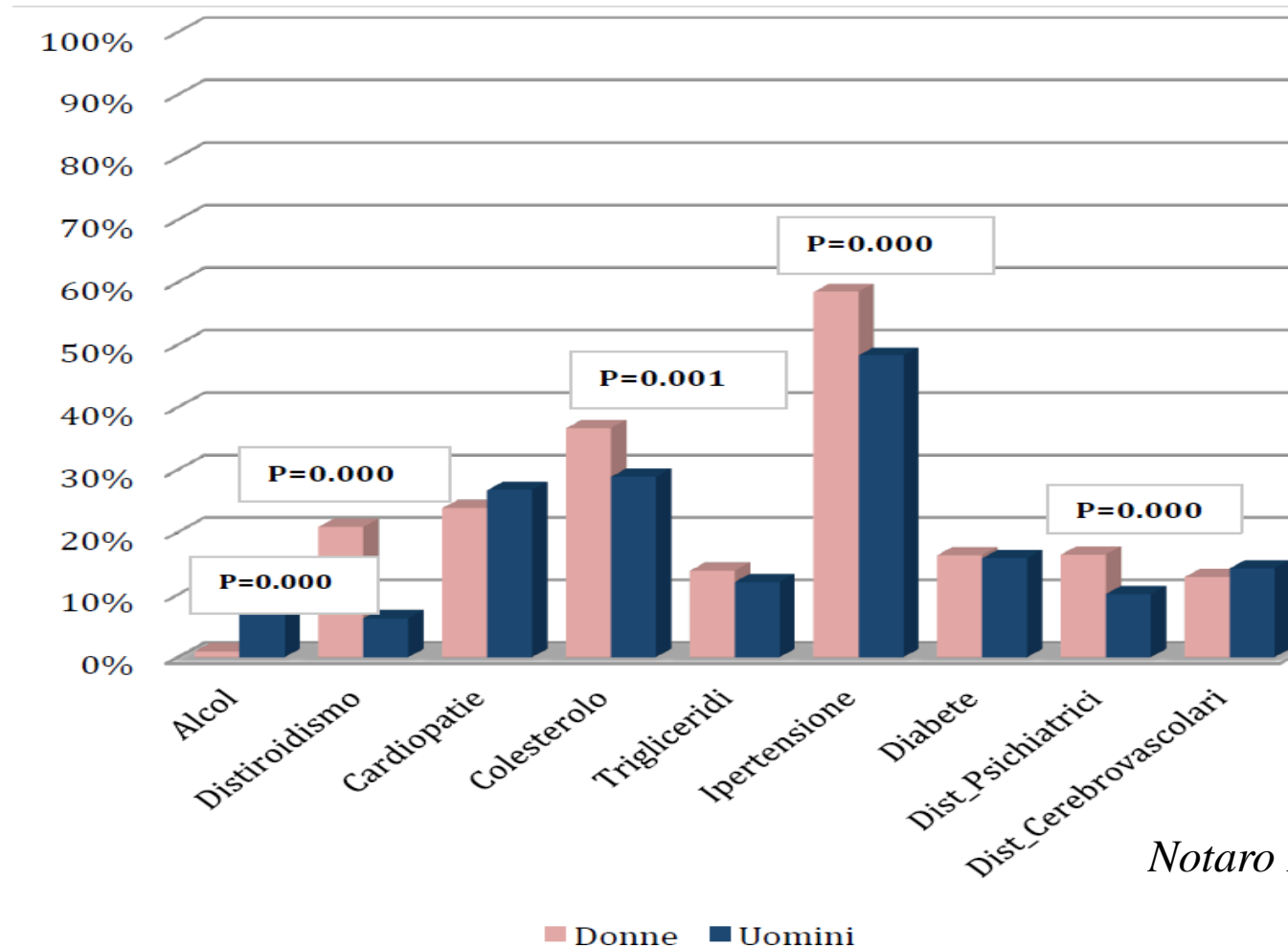
Figure 1. Alzheimer Disease (AD) and Mild Cognitive Impairment (MCI) Odds Ratios for Men and Women With APOE  $\epsilon 3/\epsilon 4$  Genotypes Between the Ages of 55 and 85 Years



JAMANEurol.[doi:10.1001/jamaneurol.2017.2188](https://doi.org/10.1001/jamaneurol.2017.2188)  
Published online August 28, 2017.



# Risk factors in 1925 AD patients





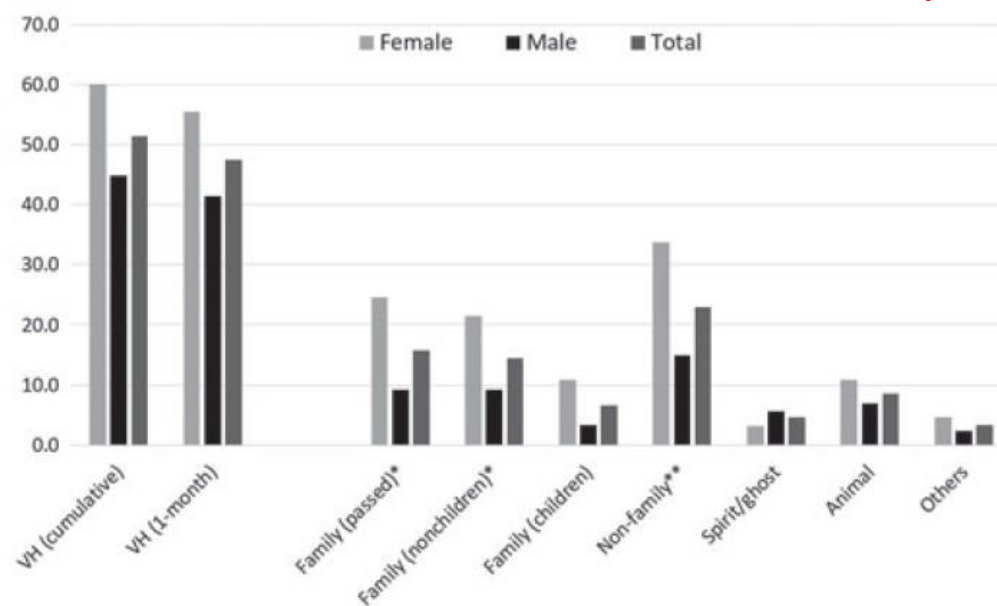
Le demenze sono molto variabili nei loro fenotipi

**Esiste una variabilità  
di espressione clinica  
gender related ??**

# Lewy Body Dementia

4

female patients with DLB having a higher frequency of VH symptoms



Females compared with males, \* $p < 0.05$ ; \*\* $p < 0.005$ .

**Figure 1** Percentage frequency of the contents of visual hallucinations (VHs) of women, men, and total patients with dementia with Lewy bodies.

Females compared with males, \* $p < 0.05$ ; \*\* $p < 0.005$ .

## Better verbal memory in women than men in MCI despite similar levels of hippocampal atrophy

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### ABSTRACT

**Objective:** To examine sex differences in the relationship between clinical symptoms related to Alzheimer disease (AD) (verbal memory deficits) and neurodegeneration (hippocampal volume/intracranial volume ratio [HpVR]) across AD stages.

**Methods:** The sample included 379 healthy participants, 694 participants with amnesic mild cognitive impairment (aMCI), and 235 participants with AD and dementia from the Alzheimer's Disease Neuroimaging Initiative who completed the Rey Auditory Verbal Learning Test (RAVLT). Cross-sectional analyses were conducted using linear regression to examine the interaction between sex and HpVR on RAVLT across and within diagnostic groups adjusting for age, education, and APOE  $\epsilon$ 4 status.

**Results:** Across groups, there were significant sex  $\times$  HpVR interactions for immediate and delayed recall ( $p < 0.01$ ). Women outperformed men among individuals with moderate to larger HpVR, but not among individuals with smaller HpVR. In diagnosis-stratified analyses, the HpVR  $\times$  sex interaction was significant in the aMCI group, but not in the control or AD dementia groups, for immediate and delayed recall ( $p < 0.01$ ). Among controls, women outperformed men on both outcomes irrespective of HpVR ( $p < 0.001$ ). In AD dementia, better RAVLT performance was independently associated with female sex (immediate,  $p = 0.04$ ) and larger HpVR (delayed,  $p = 0.001$ ).

At  
Pat

Cognitive reserve?

l'analisi dei gruppi evidenzia  
che queste donne hanno più di 15 anni di  
scolarità!!!!

Women show an advantage in verbal memory despite evidence of moderate hippocampal atrophy. This advantage may represent a sex-specific form of cognitive reserve delaying verbal memory decline until more advanced disease stages





## **Take home messages**

- **Le differenze di genere osservate nelle demenze ( per tipo, sintomi ed espressione fenotipica) originano dalle profonde differenze cerebrali (genetiche, ormonali e di connessioni) che esistono tra i due sessi.**
- **La consapevolezza e la ricerca in questa direzione potrebbero portare in futuro ad avere trattamenti genere - specifici non solo per gli aspetti cognitivi ma ancora di più per quelli comportamentali**
- **Inoltre la demenza colpisce di più le donne perché sono anche i principali caregiver formali e informali nei setting di cura, per cui anche indirettamente sono coinvolte nella demenza in questo ruolo.**

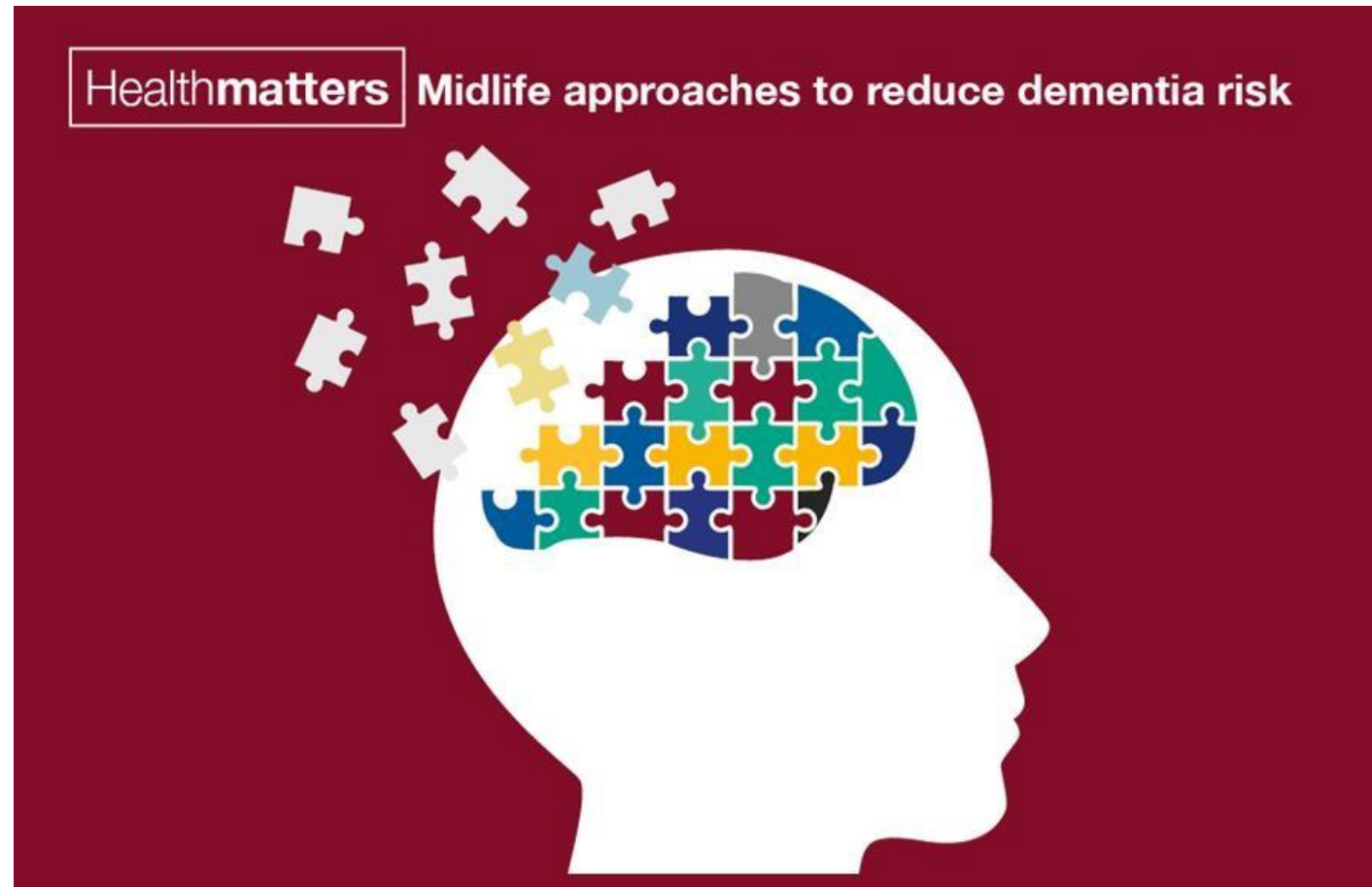
# Il cervello migliora con l'età!

- Sebbene rallentino le connessioni neuronali, la mente impara a gestire meglio le proprie capacità
- La velocità delle nostre connessioni neurali effettivamente rallenta, ma il cervello inizia a compensare utilizzando di più se stesso.
- Il dottor Bruce Yankner, professore di genetica presso la Harvard Medical School nel suo studio spiega che le risonanze magnetiche fatte a un adolescente che sta affrontando un problema mostrano molta attività su un lato della corteccia prefrontale. Si tratta della regione che usiamo per il ragionamento cosciente. Nelle persone di mezza età, l'altro lato del cervello tende a prevalere. Negli anziani, entrambi i lati del cervello condividono equamente il compito.
- Diversi studi suggeriscono che gli anziani possono attivare entrambi i lati del cervello e, di conseguenza, svolgono meglio i compiti assegnati.

# Esperienza e vita attiva

- Ancora più importante, la ricchezza di conoscenze di decenni di apprendimento ed esperienza di vita consente di valutare meglio le nuove situazioni. In tarda età, la maggior parte delle persone è più abile nel prendere decisioni finanziarie e nell'andare al cuore dei problemi rispetto a quando era più giovane
- Il direttore del Medical College della George Washington University, il picco dell'attività intellettuale umana si verifica a circa 70 anni. Superata quell'età media, infatti, il cervello impara a ottimizzare il consumo di energie, e a ottenere il massimo dalla propria condizione.
- Su Nature, infatti, un paio d'anni fa è comparso uno studio che ha chiarito una volta per tutte che quella che i neuroni siano le uniche cellule che non si rigenerano è solo una leggenda. Anzi, si rigenerano a ritmo sostenuto fino ai 90 anni e oltre.
- Per conservare le proprie capacità cognitive, però, è necessario tenerle sempre in allenamento. Dobbiamo avere una vita attiva ed equilibrata. Avere relazioni emotive soddisfacenti, mangiare bene, andare a teatro e danzare. Vedere i nostri familiari, soprattutto quelli più giovani e in grado di trasmetterci gioia e speranza nel futuro.

In ogni caso il futuro è disegnato... studiare di più, avere una maggiore vita sociale, fare attività fisica, combattere le malattie, contrastare la cronicità.....



# Contrastare la Solitudine

**Prima ancora che mangiare bene, fare attività fisica, è necessario agire contrastando la solitudine, avere relazioni significative.**

**E su questo perno far ruotare il tutto.**

**Fare i nonni**

**Iscriversi all'Università**

**Fare attività fisica insieme con altri**

**Mangiare bene e in compagnia**

**E noi donne per fare queste cose siamo un**

***FENOMENO!***





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Giri il collo, alzi le braccia  
pieghi le ginocchia e senti:  
crik, crok, crak...tranquilla,  
non stai invecchiando,



stai diventando croccante!!!