VI Convegno

IL CONTRIBUTO DELLE UNITÀ DI VALUTAZIONE ALZHEIMER (UVA) NELL'ASSISTENZA

DEI PAZIENTI CON DEMENZA

Un approccio *life-course* alla demenza. Una Chimera?

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Roma

Emiliano Albanese, MD, PhD – National Institute on Aging (USA)

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I have no disclosures or conflict of interests to declare

Un approccio *life-course* alla demenza. Una Chimera?

SCOPO

L'epidemiologo come **Bellerofonte**

OUTLINE

Demenza

Epidemiologia delle Demenze

L'approccio life-course

DEMENZA:
Cosa sappiamo?

Demenza

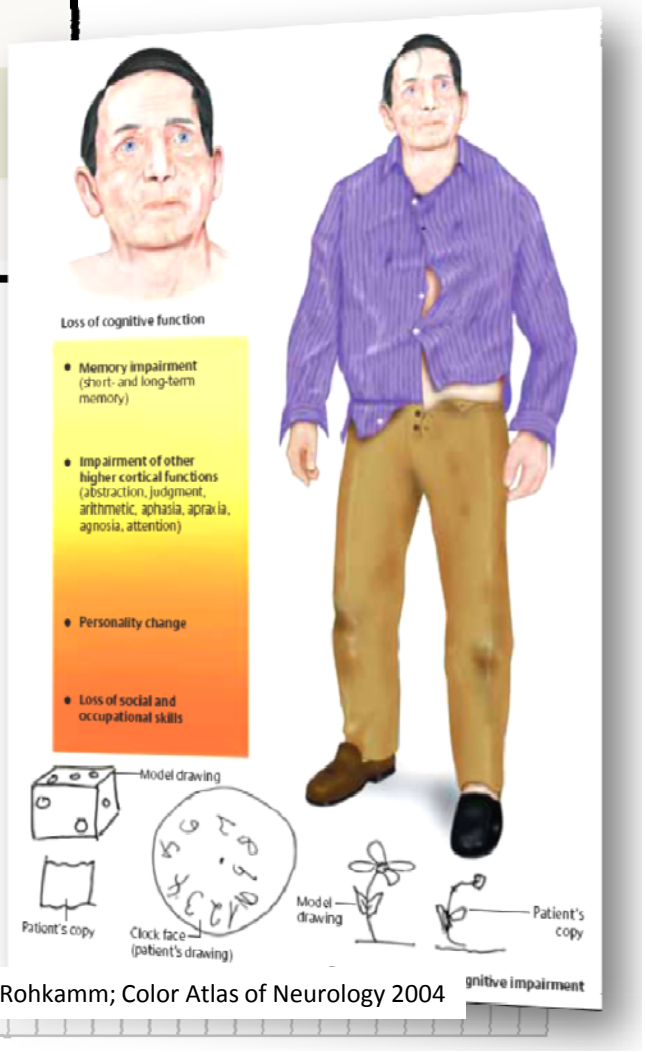
Clinica

COMMON TYPES OF DEMENTIA

There is a great deal of overlap between the symptoms of various dementias.

Dementia type	Symptoms	Neuropathology	Proportion of dementia cases
Alzheimer's disease	Impaired memory, depression, poor judgement and confusion	Amyloid plaques and neurofibrillary tangles	50–80%
Vascular dementia	Similar to Alzheimer's disease, but memory less affected	Decreased blood flow to the brain owing to a series of small strokes	20–30%
Frontotemporal dementia	Changes in personality and mood, and difficulties with language	Damage limited to frontal and temporal lobes	5–10%
Dementia with Lewy bodies	Similar to Alzheimer's disease, also hallucinations, tremors	Cortical Lewy bodies (of the protein α-synuclein) inside neurons	<5%

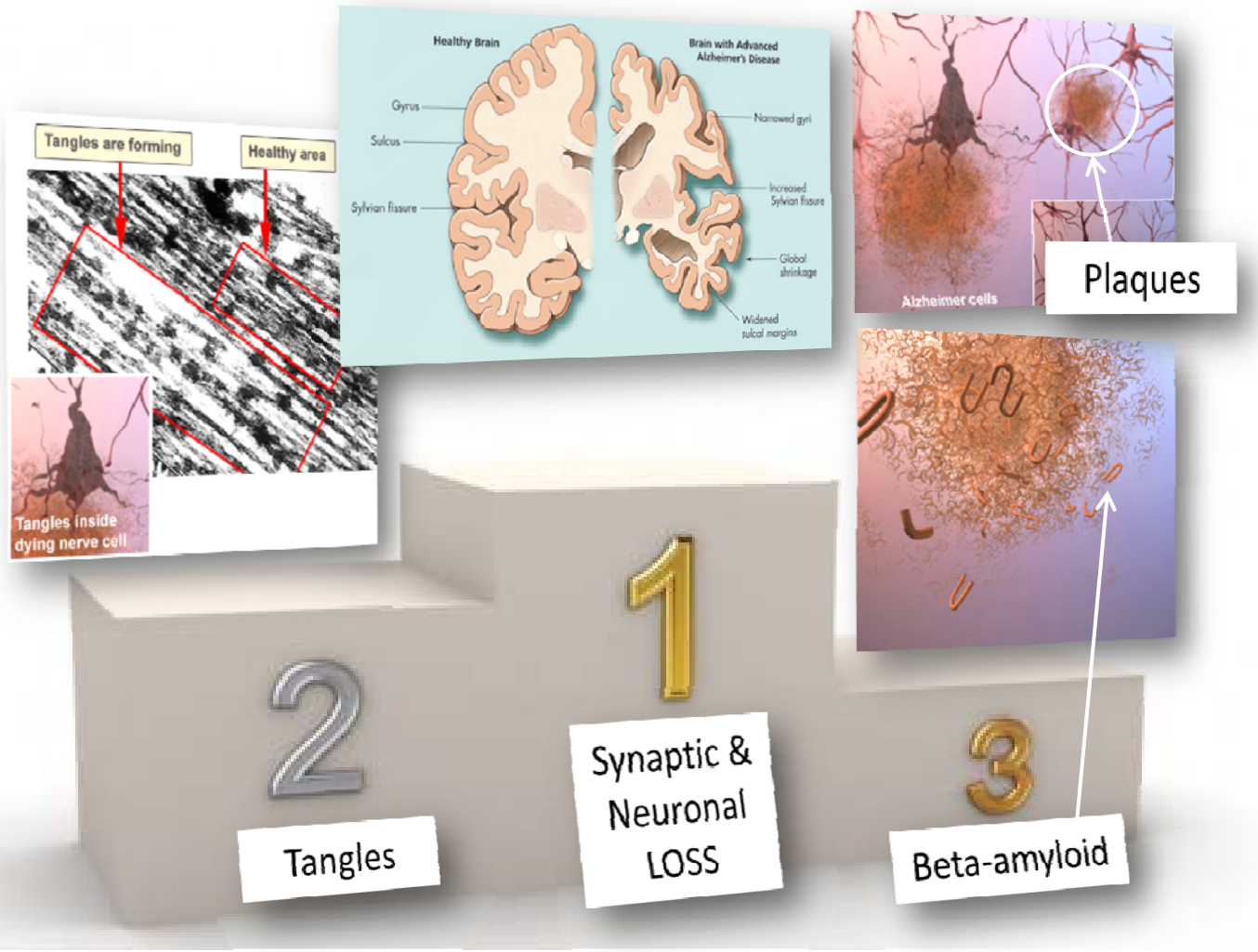
Allison Abbot 2011 – Nature Outlook



Rohkamm; Color Atlas of Neurology 2004

Neuropatologia

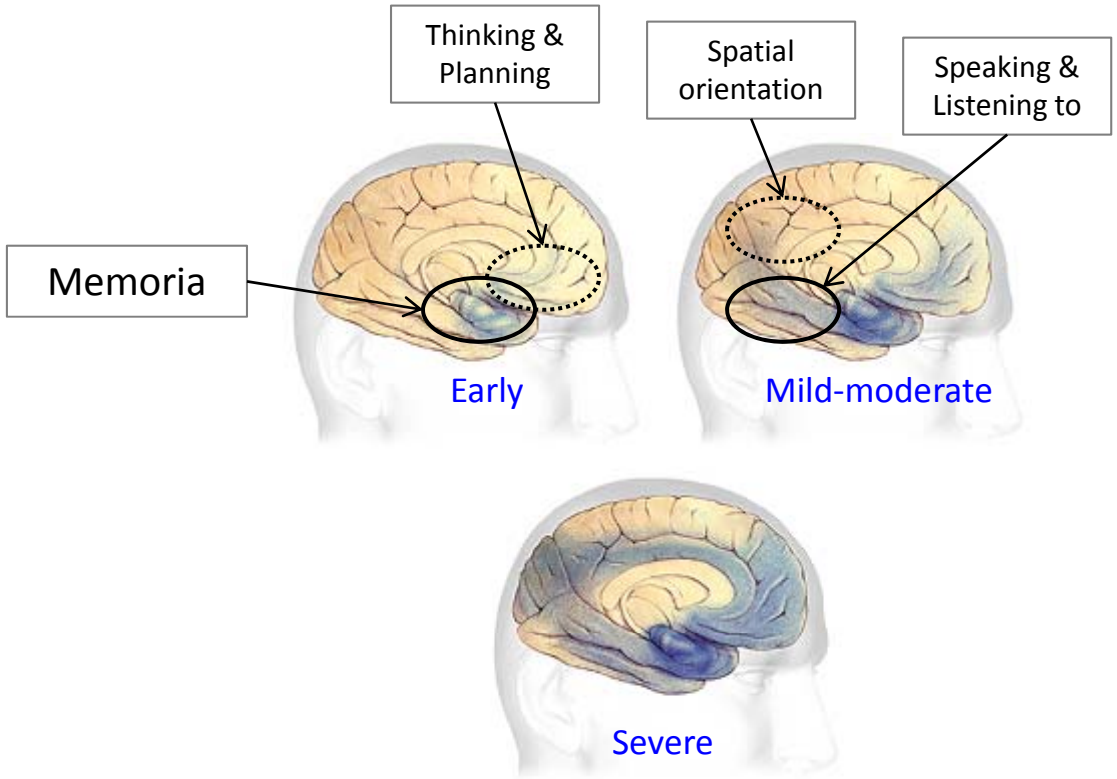
Dimunizione neuronale e sinaptica sono i correlati ‘migliori’ di sintomi e severita’, seguito dai tangles e dalle placce di amyloide.



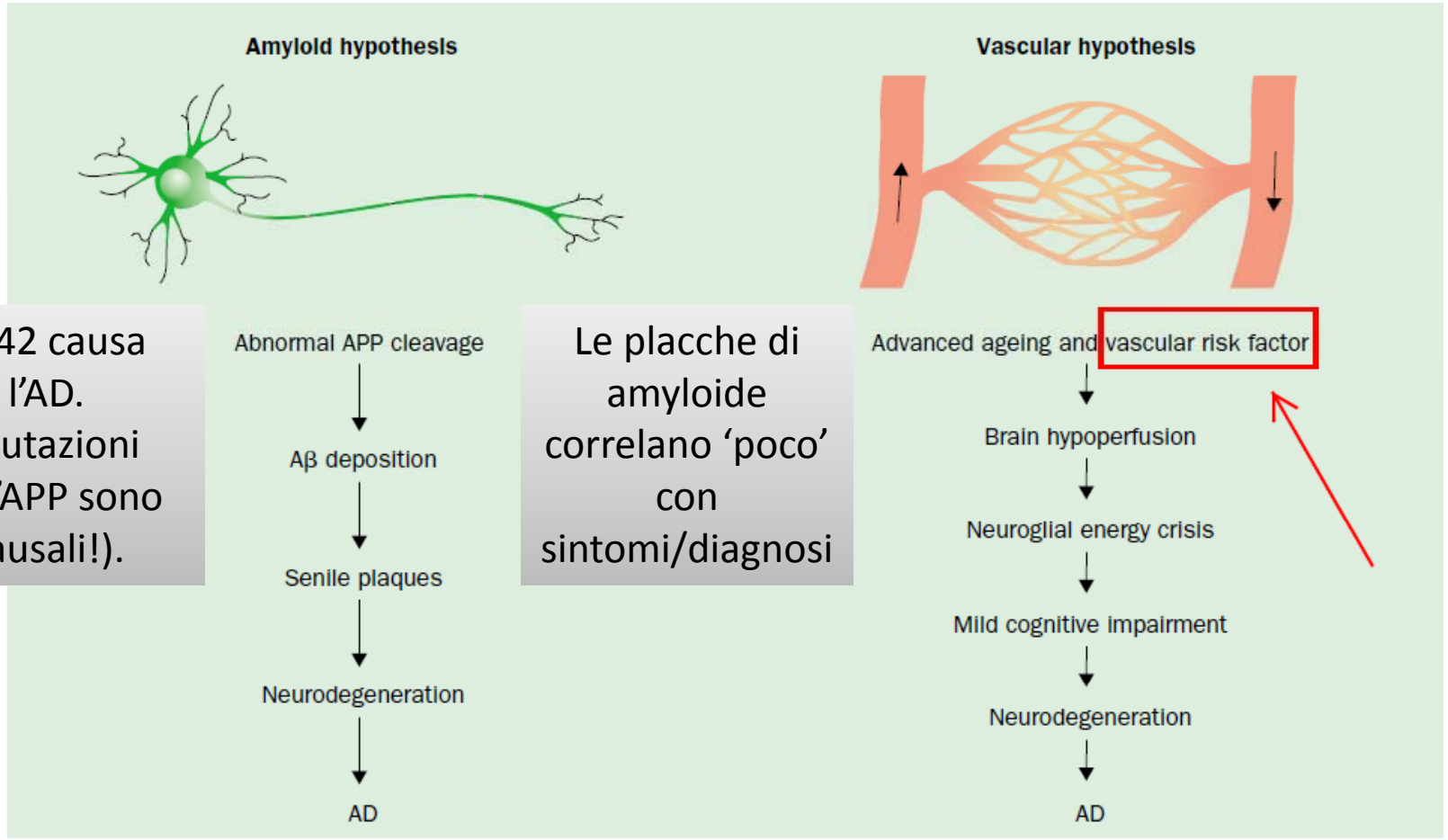
Neuropatologia e deficit cognitivo

Alta correlazione tra progressione del danno neuro-anatomica e deficit cognitivi.

Progressione e correlati neuropaologico-clinici



Ipotesi Vascolare



Aβ42 causa l'AD. (mutazioni nell'APP sono causali!).

Le placche di amyloide correlano 'poco' con sintomi/diagnosi

...opment of Alzheimer's disease according to the amyloid[8] or vascular hypothesis.[76]

Viewpoint

Demonstrating the case that AD is a vascular disease: epidemiologic evidence

Lenore J. Launer *

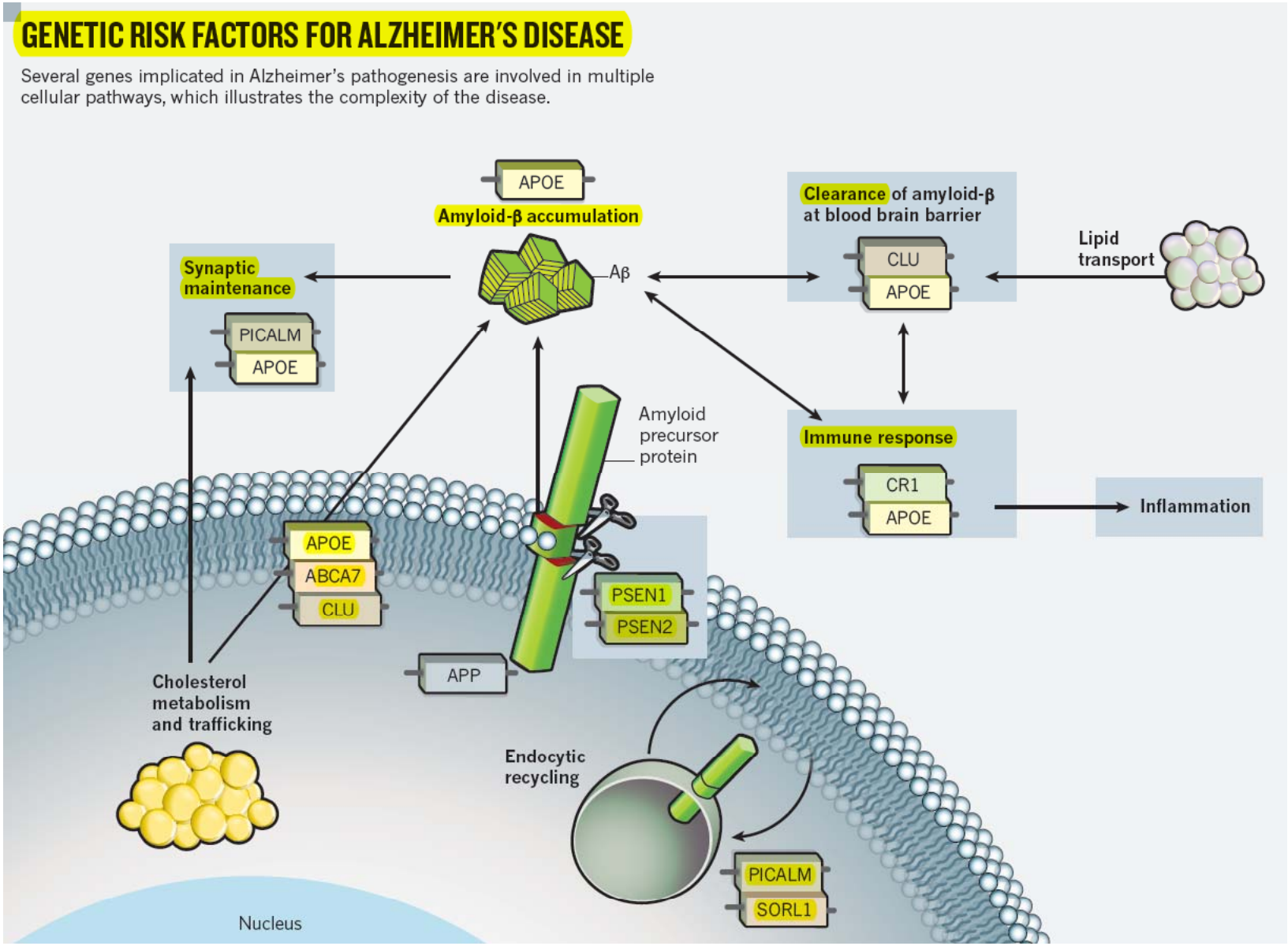
Intramural Research Program, Laboratory of Epidemiology, Demography and Biometry, Neuroepidemiology Section, National Institute on Aging, 7201 Wisconsin Avenue, Gateway Building, Suite 3C-309, Bethesda, MD 20892-9205, USA

Received 16 July 2001; received in revised form 17 July 2001; accepted 18 July 2001

Is Alzheimer's disease a neurodegenerative or a vascular disorder? Data, dogma, and dialectics

Jack C de la Torre

Genetica

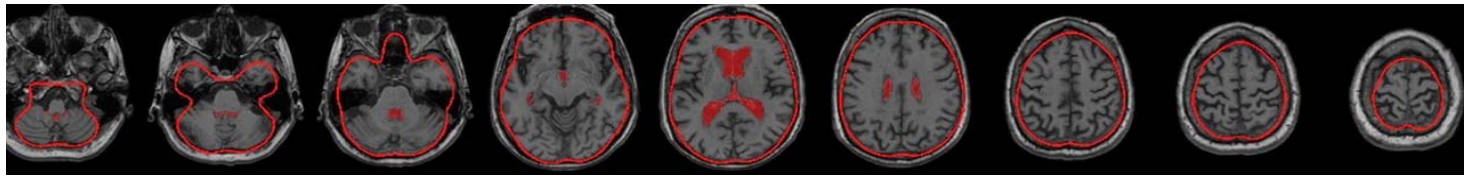


Michael Eisenstein 2011 – Nature Outlook

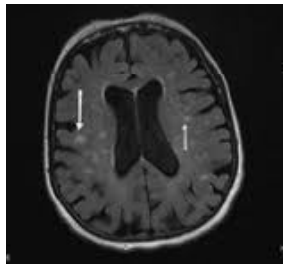
Demenza

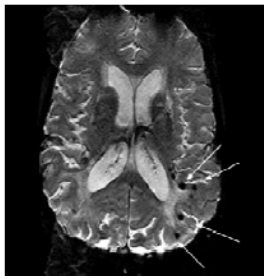
Neuroimaging

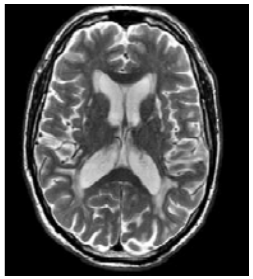
Atrofia



Lesioni vascolari







FGD-PET e C-PiB

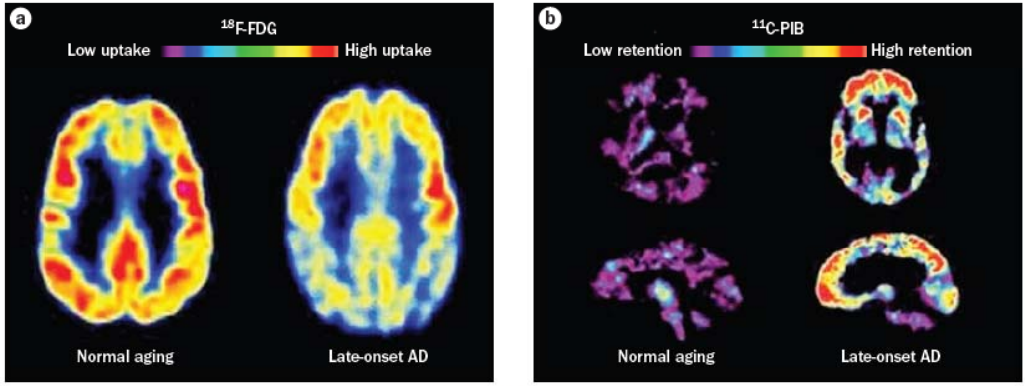


Figure 3 | Changes revealed by PET in the AD brain. **a** | ^{18}F-FDG-PET patterns characteristic of metabolic activity in cognitively normal individuals and patients with late-onset AD. In comparison with people aging normally, individuals with late-onset AD show decreased bilateral glucose metabolism, particularly in the temporal and parietal regions. **b** | ^{11}C-PIB PET images characteristic of elderly individuals without cognitive impairment and patients with late-onset AD. The high concentrations of ^{11}C-PIB in the AD brain are suggestive of high amounts of amyloid deposits. Abbreviations: AD, Alzheimer disease; FDG, 2-fluoro-2-deoxy-D-glucose; PIB, Pittsburgh compound B.

Christiane Reitz, Carol Brayne and Richard Mayeux

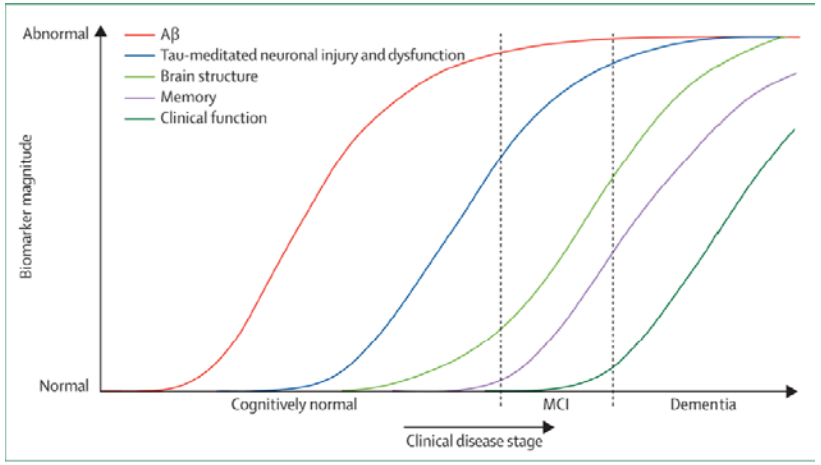


Figure 2. Dynamic biomarkers of the Alzheimer's pathological cascade
Aβ is identified by CSF $A\beta_{42}$ or PET amyloid imaging. Tau-mediated neuronal injury and dysfunction is identified by CSF tau or fluorodeoxyglucose-PET. Brain structure is measured by use of structural MRI. Aβ=β-amyloid. MCI=mild cognitive impairment.

Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade

Clifford R Jack Jr, David S Knopman, William J Jagust, Leslie M Shaw, Paul S Aisen, Michael W Weiner, Ronald C Petersen, and John Q Trojanowski

NIA-*pre-demenza* criteria & Biomarkers

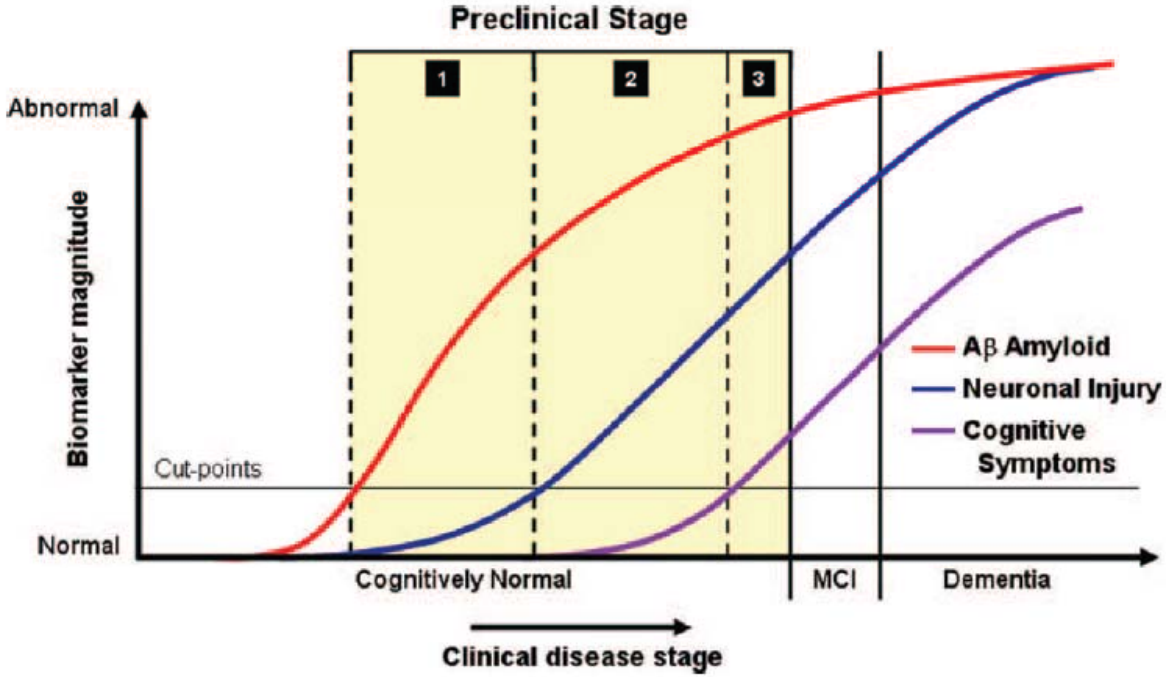


FIGURE 1: Preclinical stages 1 to 3 of Alzheimer disease (AD; indicated by the yellow highlighted section) in relation to our model of biomarkers of the AD pathological cascade. The horizontal axis indicates clinical stages of AD: cognitively normal, mildly impaired (MCI), and dementia. The vertical axis indicates the changing values of each biomarker, scaled from maximally normal (bottom) to maximally abnormal (top). The A*β* amyloid biomarker is positron emission tomography (PET) amyloid imaging (*red line*). Biomarkers of neuronal injury are fluorodeoxyglucose-PET or atrophy on magnetic resonance imaging (*blue line*). Onset or worsening of cognitive symptoms is determined from cognitive testing scores (*purple line*). The horizontal cutpoints line represents the cutpoints used to operationalize preclinical staging.

An Operational Approach to National Institute on Aging–Alzheimer's Association Criteria for Preclinical Alzheimer Disease

Clifford R. Jack, Jr, MD,[1] David S. Knopman, MD,[2,3] Stephen D. Weigand, MS,[4] Heather J. Wiste, BA,[4] Prashanthi Vemuri, PhD,[1] Val Lowe, MD,[1] Kejal Kantarci, MD,[1] Jeffrey L. Gunter, PhD,[1] Matthew L. Senjem, MS,[1] Robert J. Ivnik, PhD, LP,[5] Rosebud O. Roberts, MBBCh,[3,6] Walter A. Rocca, MD, MPH,[2,6] Bradley F. Boeve, MD,[2,7] and Ronald C. Petersen, MD, PhD[2,3,6]

(farmco)-terapia

Le molecole (per meccanismo d'azione)

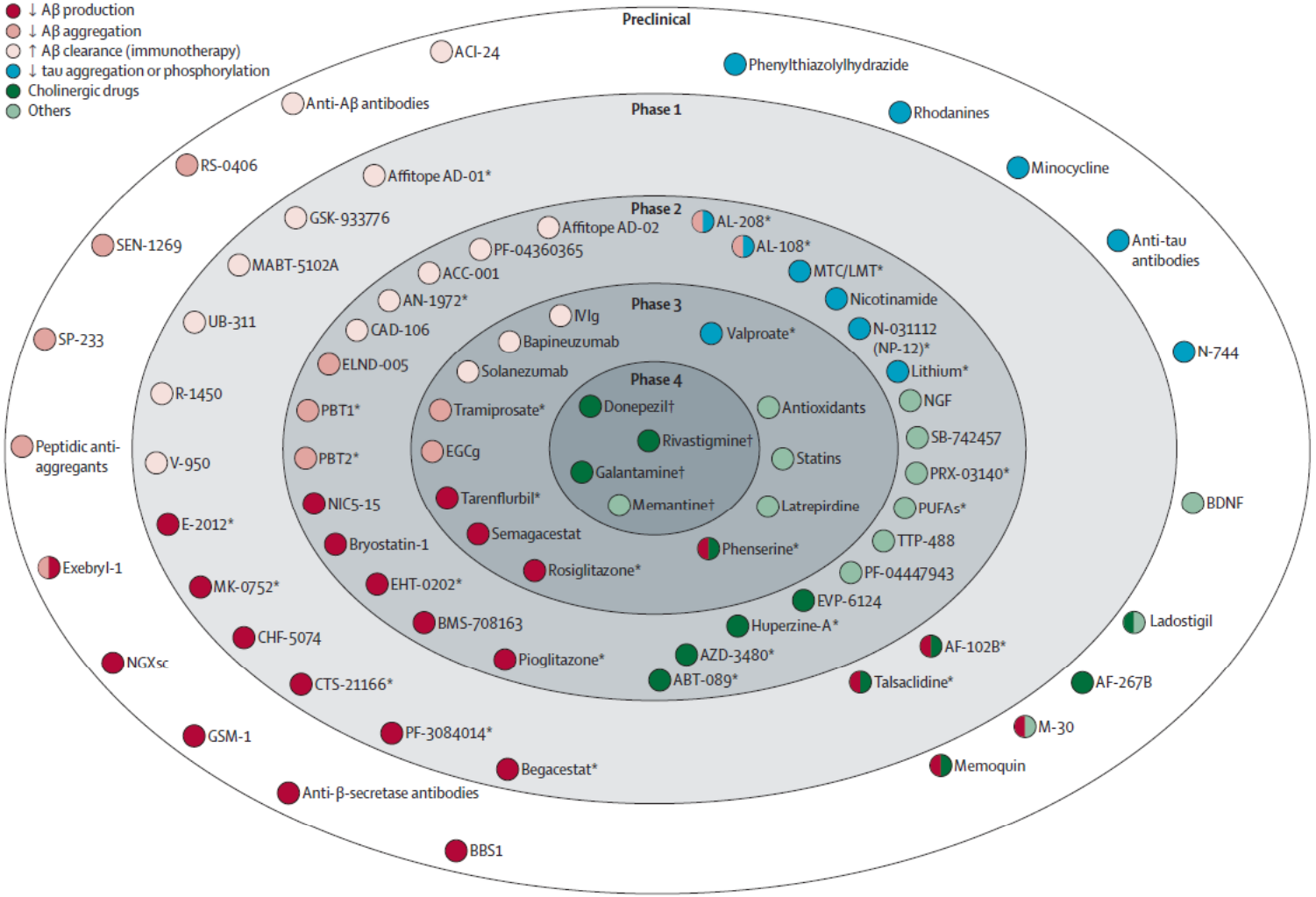


Figure: **Drug development in Alzheimer's disease**

Francesca Mangialasche, Alina Solomon, Bengt Winblad, Patrizia Mecocci, Miia Kivipelto

Drugs being investigated for Alzheimer's disease therapy, reported according to the most advanced phase of study and main therapeutic properties (including data from studies in vitro and animal models). Aβ=amyloid β. BBS1=anti-β-site antibodies. BDNF=brain-derived neurotrophic factor. EGCg=epigallocatechin-3-gallate. IVIg=intravenous immunoglobulin. LMT=leuco-methylthioninium. MTC=methylthioninium chloride. NGF=nerve growth factor. NGXsc=NGX series compounds. PUFAs=polyunsaturated fatty acids. GSM=γ-secretase modulator. RCT=randomised controlled trial. *RCTs in Alzheimer's disease not ongoing. †Drugs approved for the treatment of Alzheimer's disease.

Un approccio *life-course* alla demenza e' una Chimera?

Demenza

- Sappiamo molto, ma cause e l'eziopatogenesi sono ignote e non c'e' una terapia.
- QUINDI: L'epidemiologia e la prevenzione sono importanti.

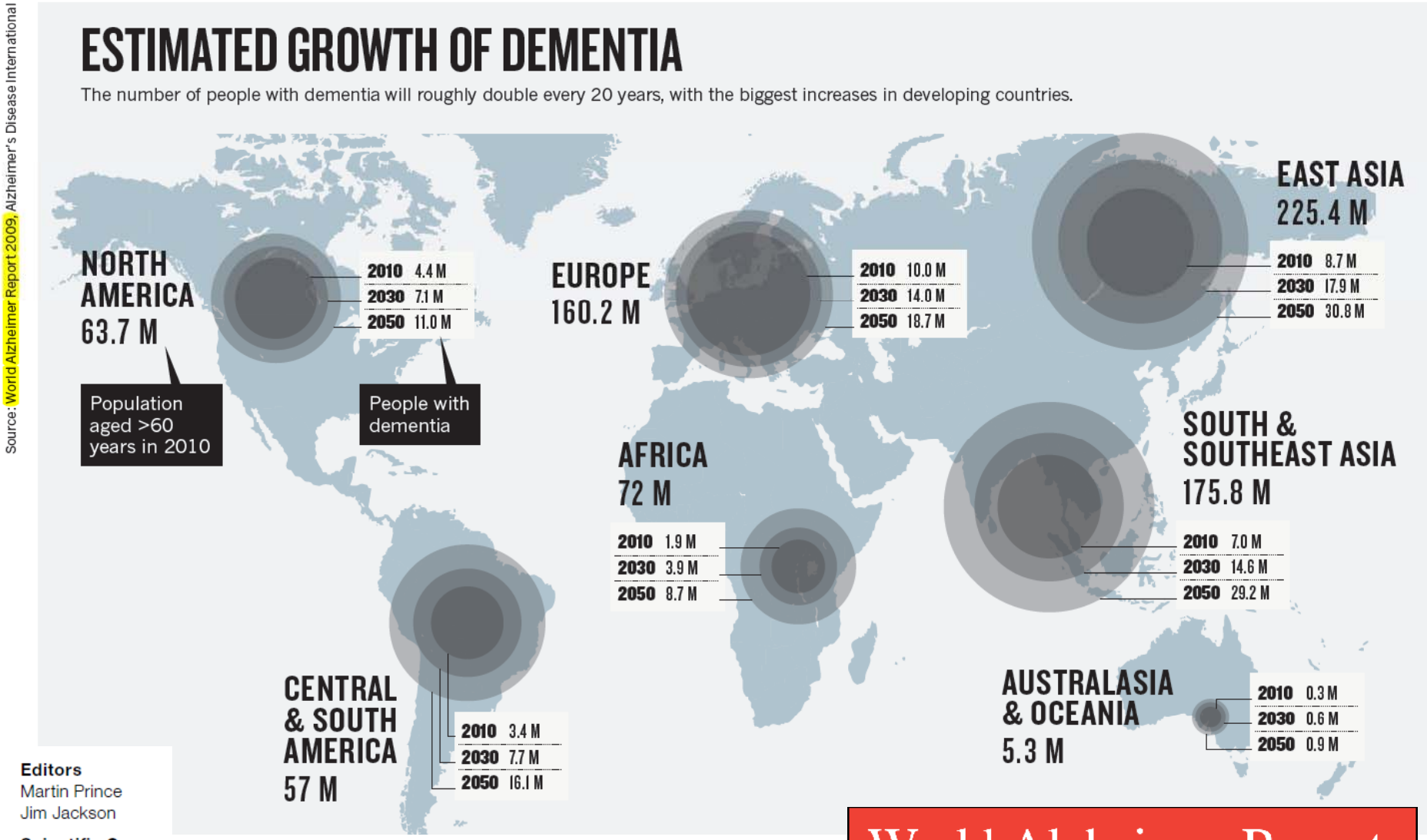
Epidemiologia delle Demenze

Un approccio A *Life-course* alla demenza

EPIDEMIOLOGIA

Gli ***usi*** *classici* dell'epidemiologia

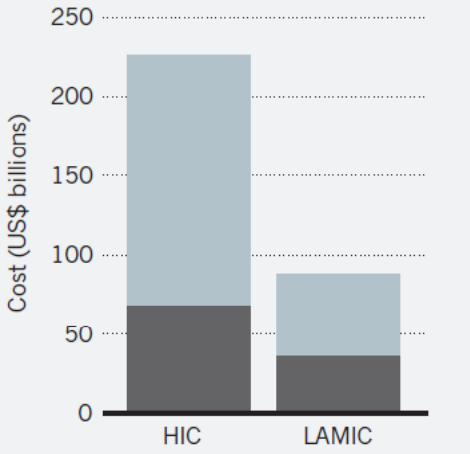
- Distribuzione e Impatto della malattia
- Fattori di Rischio e Protettivi
- Prevenzione & Nuove Ipotesi
- Valutazione dell'efficacia degli interventi


ESTIMATED GROWTH OF DEMENTIA
The number of people with dementia will roughly double every 20 years, with the biggest increases in developing countries.
Source: World Alzheimer Report 2009, Alzheimer's Disease International
NORTH AMERICA
63.7 M
2010 4.4 M
2030 7.1 M
2050 11.0 M
Population aged >60 years in 2010
People with dementia
EUROPE
160.2 M
2010 10.0 M
2030 14.0 M
2050 18.7 M
EAST ASIA
225.4 M
2010 8.7 M
2030 17.9 M
2050 30.8 M
AFRICA
72 M
2010 1.9 M
2030 3.9 M
2050 8.7 M
SOUTH & SOUTHEAST ASIA
175.8 M
2010 7.0 M
2030 14.6 M
2050 29.2 M
CENTRAL & SOUTH AMERICA
57 M
2010 3.4 M
2030 7.7 M
2050 16.1 M
AUSTRALASIA & OCEANIA
5.3 M
2010 0.3 M
2030 0.6 M
2050 0.9 M
Editors
Martin Prince
Jim Jackson
Scientific Group
Cleusa P Ferri
Renata Sousa
Emiliano Albanese
Wagner S Ribeiro
Mina Honyashiki
World Alzheimer Report
2009
Executive Summary

Impatto (ex. costi)

GLOBAL COSTS OF DEMENTIA

There is a vast difference in the cost of care per person between high-income countries (HIC) and low- and middle-income countries (LAMIC).

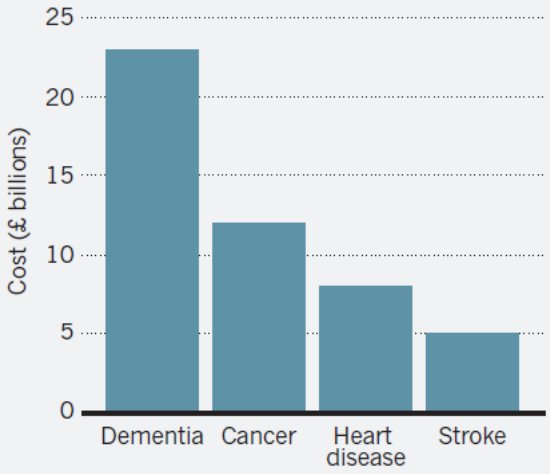


Direct costs: institutional and social/ community care, health care

Indirect costs: unpaid care by family members or others including their lost opportunity to earn income

COMPARING COSTS

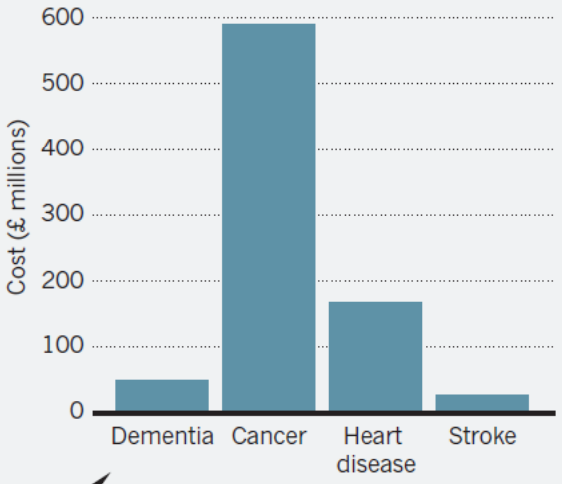
In the United Kingdom, the economic impact of dementias dwarfs the costs of other diseases.



Total costs, comprising direct and indirect costs

COMPARING INVESTMENT

In the United Kingdom, annual government and charity spend on dementia research is 12 times lower than on cancer research.



For every person in the UK with dementia just £61 is spent on research, compared to £295 for every person with cancer.

Allison Abbot 2011 – Nature Outlook

A problem for our age

As the number of Alzheimer's cases rises rapidly in an ageing global population, the need to understand this puzzling disease is growing.

The elephant in the room — healthy brains in later life, epidemiology and public health

Carol Brayne

Proiezioni e impatto della prevenzione

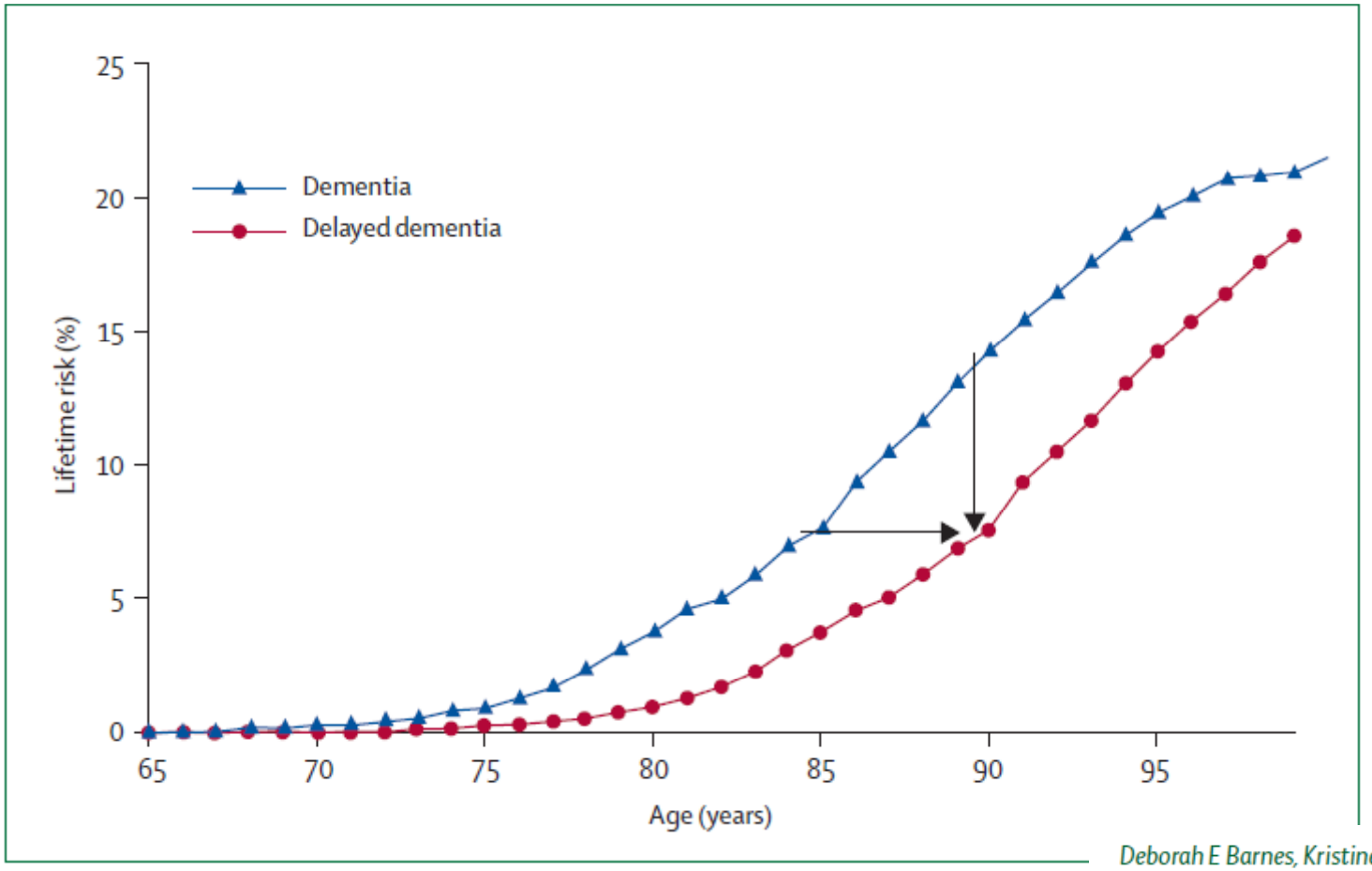


Figure 2: Lifetime risk of dementia for women aged 65 years

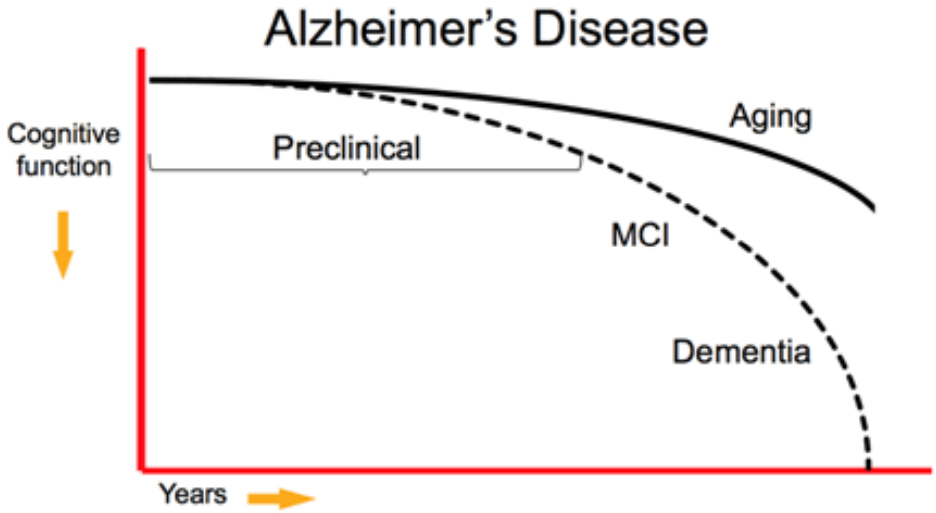
Actual (blue line) lifetime risk in 65-year-old, dementia-free women in the Framingham Heart Study[11] who were followed up throughout their remaining life compared with projected lifetime risk (red line) of incident dementia if it could be delayed in all cases by 5 years (arrows).

Definizioni/ concetti

‘Invecchiamento cognitivo’

Con l’**eta**’:

1. Normale riduzione delle capacita’ cognitive
2. Deficit cognitivo (non-demenza)
3. Demenza



Definizioni/ concetti

Cos'e' il RISCHIO

RISCHIO

La probabilita' futura di contrarre una malattia, in funzione dell'esposizione ad uno specifico fattore, a livello di popolazione.

1. La **stima** del rischio puo' essere fatta con:
   - **STUDI OSSERVAZIONALI**
   - **STUDI SPERIMENTALI**
2. Sono rilevanti sia:
   - Fattori **GENETICI** che
   - **AMBIENTALI**
3. I **Fattori Modificabili** modulerebbero sia
   - I processi (neuro-) **PATOLOGICI** che
   - I **SINTOMI** (brain/cognitive reserve)

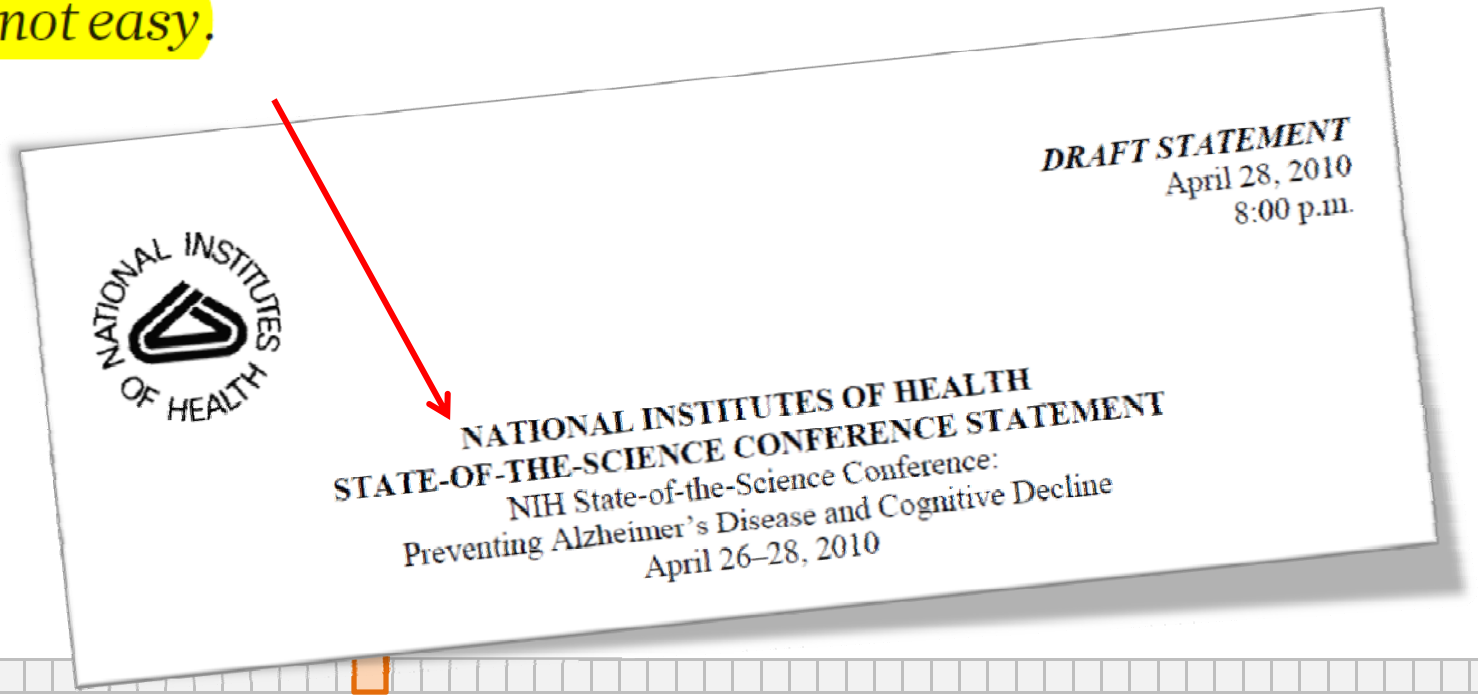
CRITICITA'

1. Confounding
2. Bias
3. **Competing-risks** (I fattori di rischio per la demenza sono spesso gli stessi per la mortalita')
2. **QUANDO**? La neuropatologia inizia molto prima dei sintomi, qundi come e quando operano i fattori di rischio e' potenzialmente cruciale… (**timing** & **duration**: *life-course*).

La demenza si puo' prevenire ? **2**

Finding risk factors

Uncovering genes that are linked with Alzheimer's disease can help researchers understand what causes the disease. But it's not easy.



Esempio: fattori VASCOLARI (modello)

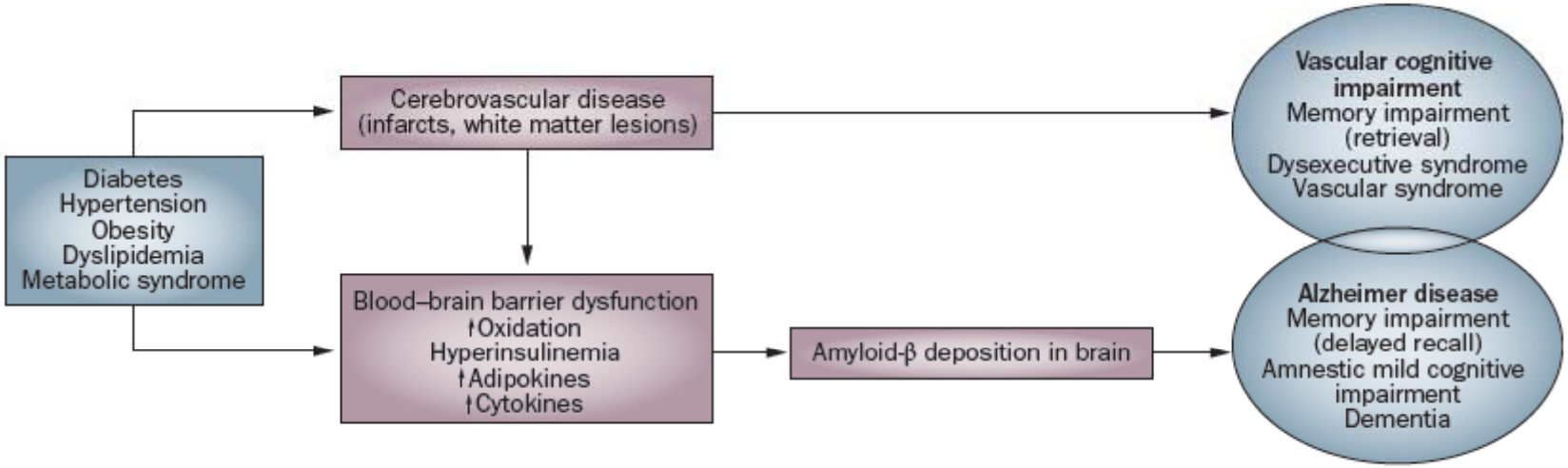


Figure 1 | Potential mechanisms linking vascular risk factors and cognitive impairment. At least two pathways exist that result in cognitive impairment and dementia: development of cerebrovascular disease may lead to vascular cognitive impairment syndromes, and deposition of amyloid-β may lead to other distinct amnestic clinical syndromes, including Alzheimer disease. In addition, these pathways may overlap and interact, resulting in mixed cognitive syndromes.

Christiane Reitz, Carol Brayne and Richard Mayeux

Timing and **duration**
dei fattori di rischio
non sono contemplati

Fattori di Rischio

La demenza si puo' prevenire? **1**

PREVENTION

Activity is the best medicine

Can exercise, social interaction and the Mediterranean diet really help to keep the cognitive decline of Alzheimer's disease at bay?

Dai PAFs al calcolo dei **casi 'evitabili'**

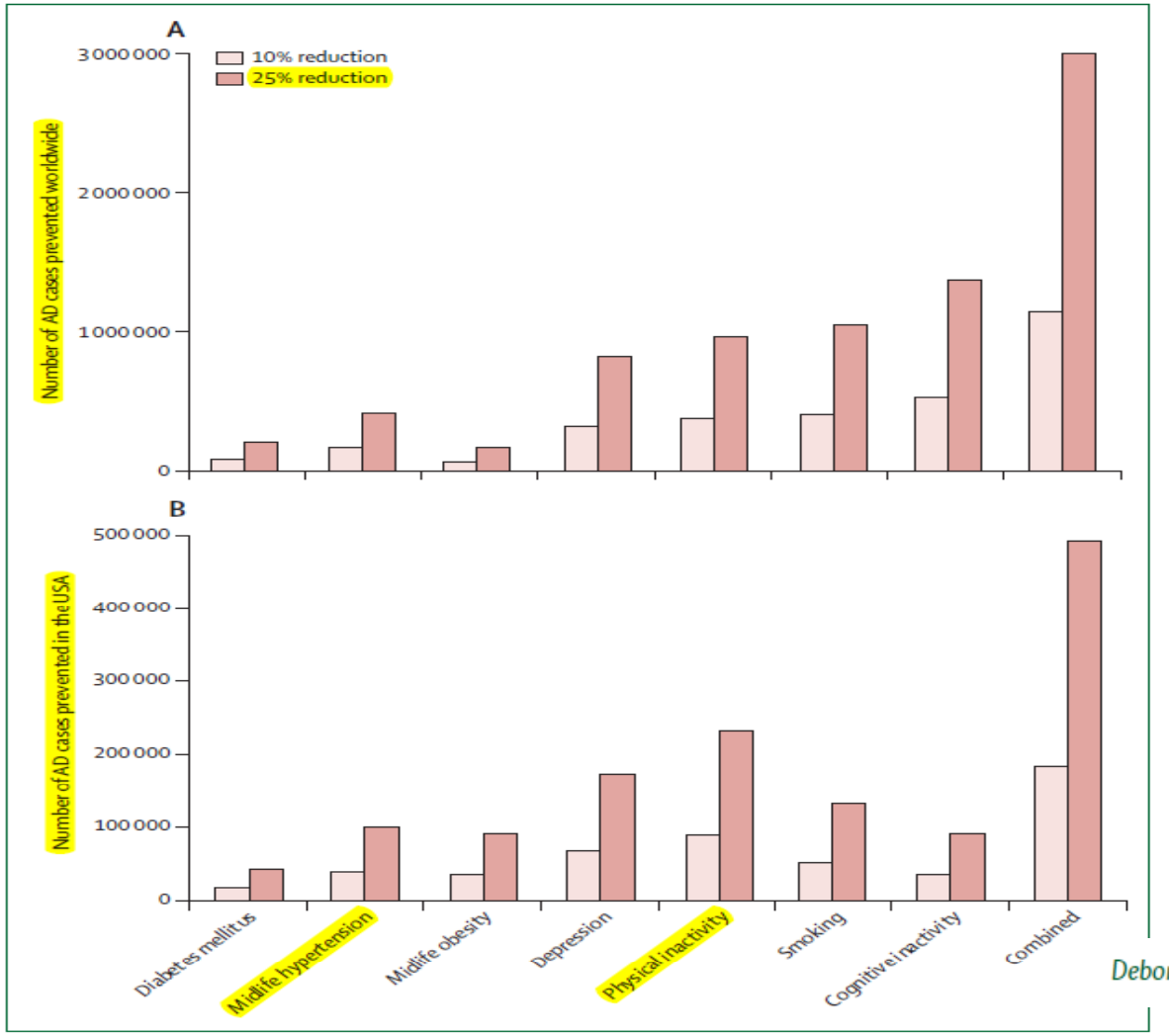


Figure: **Potential number of AD cases that could be prevented through risk factor reduction**
The numbers of AD cases that could potentially be prevented (A) worldwide and (B) in the USA through risk factor reductions of 10% or 25% were estimated by multiplying present prevalence estimates by 0·90 and 0·75, respectively, and subtracting the revised number of attributable cases from the original number. These estimates assume that a causal relation exists between the risk factor and AD and that the relative risk estimate is a good approximation of the effect of risk factor reduction. Therefore, the actual number of cases prevented could be higher or lower, depending on the extent to which these assumptions are valid. Additionally, the combined estimate assumes that the individual risk factors are independent and have an additive relationship. Because several of the risk factors examined are inter-related, the combined PAR estimates should be considered as maximums. AD=Alzheimer's disease.

Alcuni Esempi

Gli studi osservazionali non possono provare rapporti di causalita', generano ipotesi che, quando e' fattibile, vengono testate sperimentalmente (con gli RCTs).

Questo *paradigma* metodologico funziona nell'ambito della demenza?

Alcuni Esempi

1. **Cioccolata** e demenza?
2. **Obesita'** e demenza

Dagli studi osservazionali agli RCTs??

2 Cioccolata – **studio ecologico**

Chocolate Consumption, Cognitive Function, and Nobel Laureates

Franz H. Messerli, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

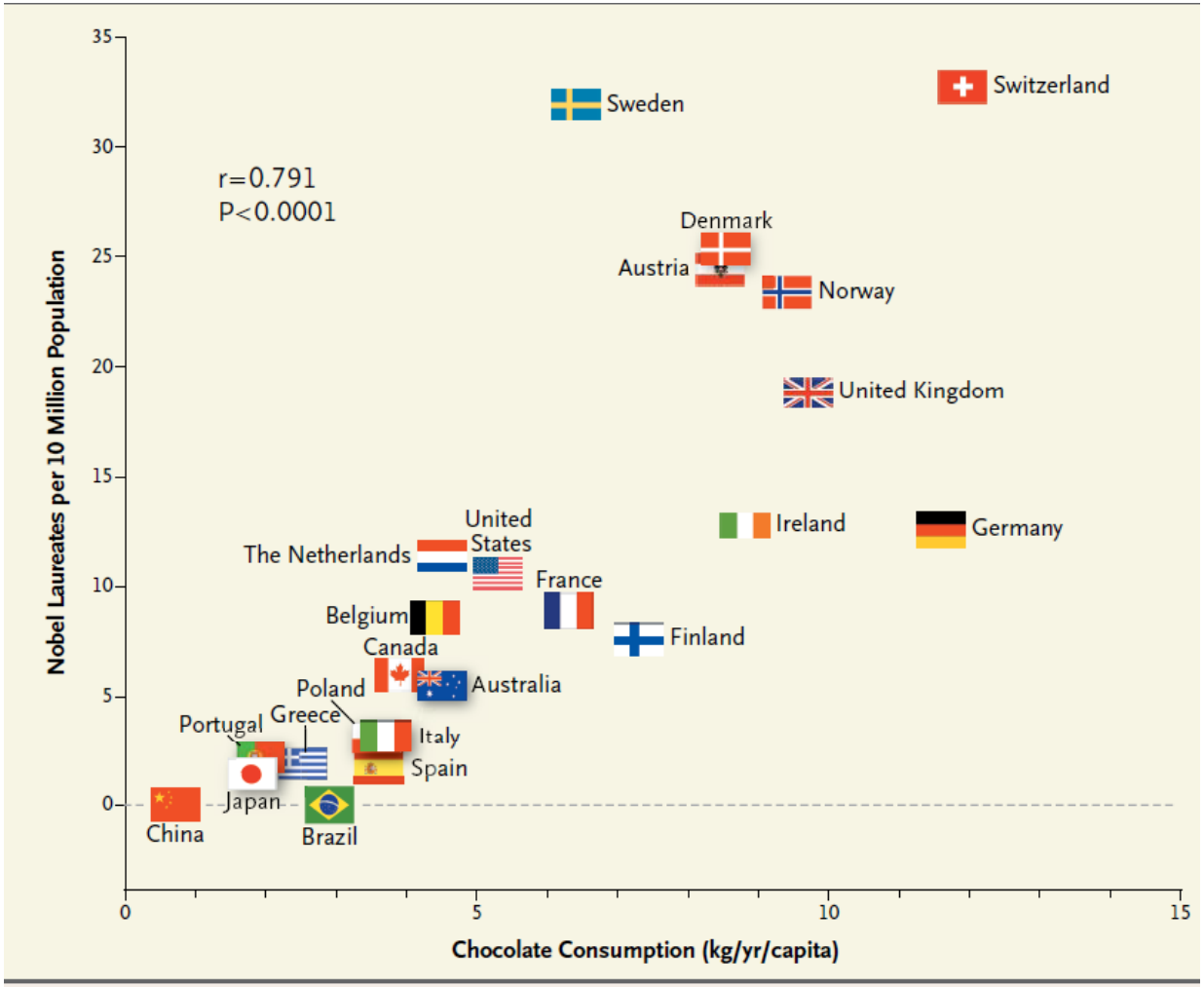


Figure 1. Correlation between Countries' Annual Per Capita Chocolate Consumption and the Number of Nobel Laureates per 10 Million Population.

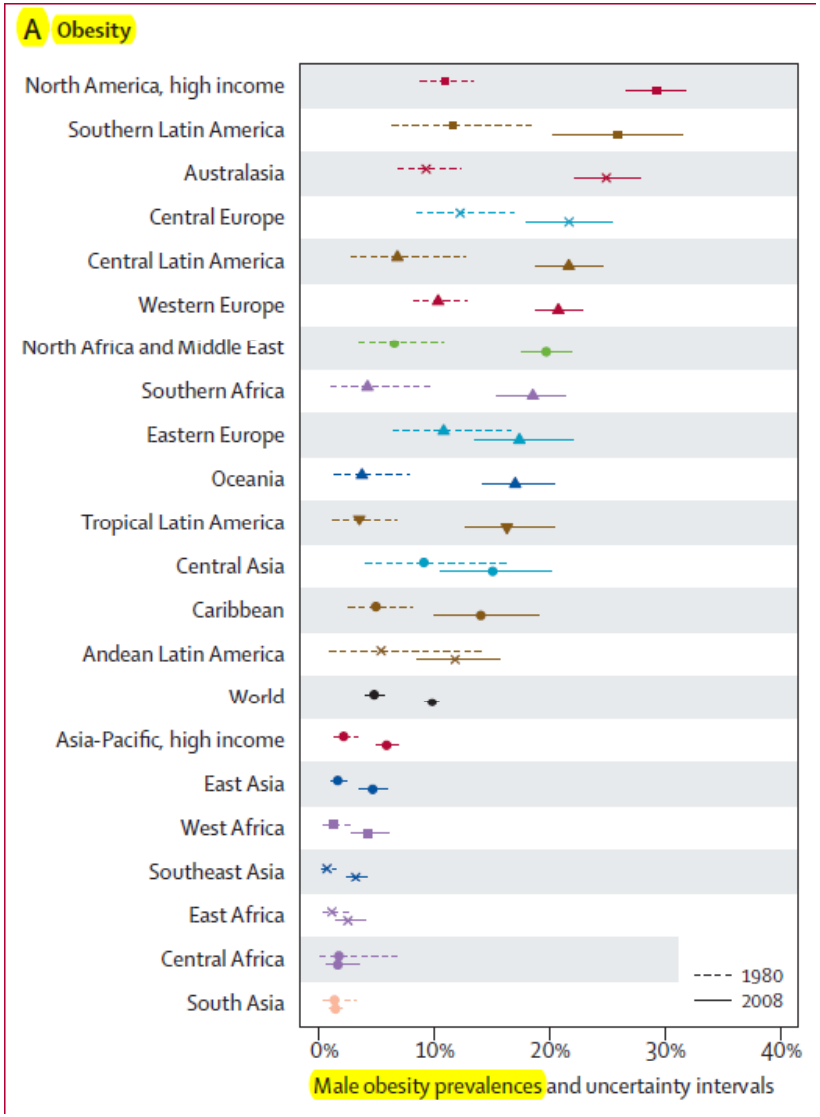
Un RCT non esiste.

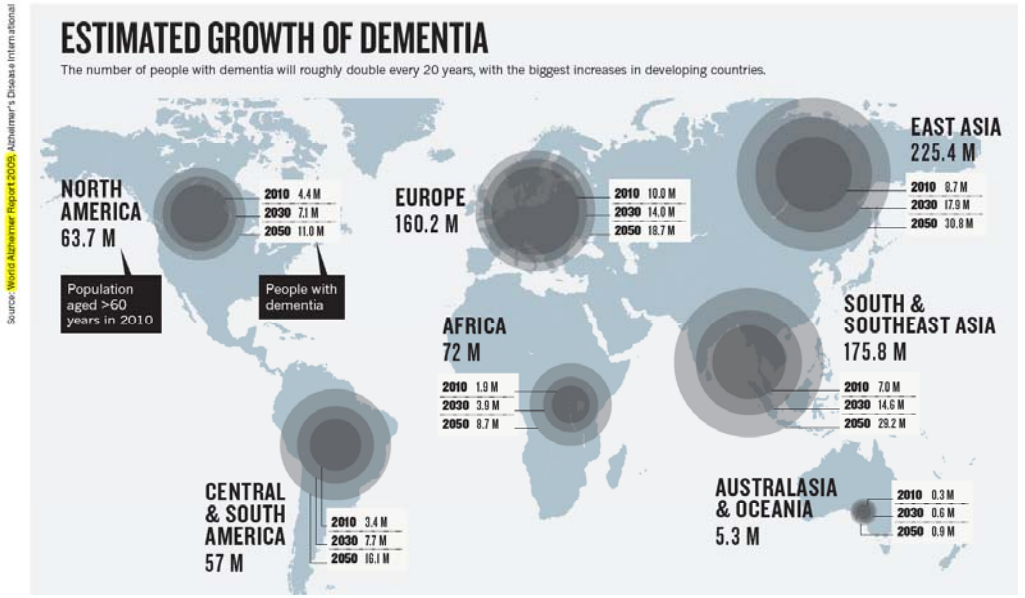
Volontari per un RCT?

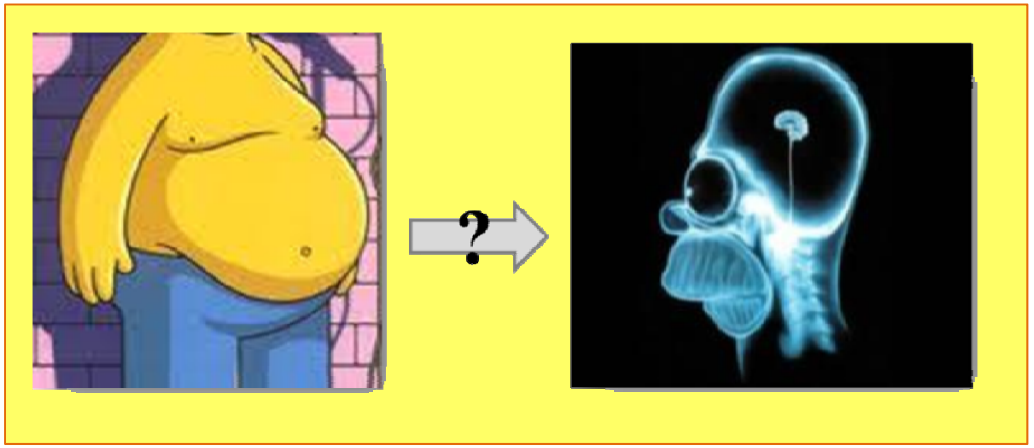
Dagli studi osservazionali agli RCTs??

3 Obesita' & Demenza - RILEVANZA

RILEVANZA



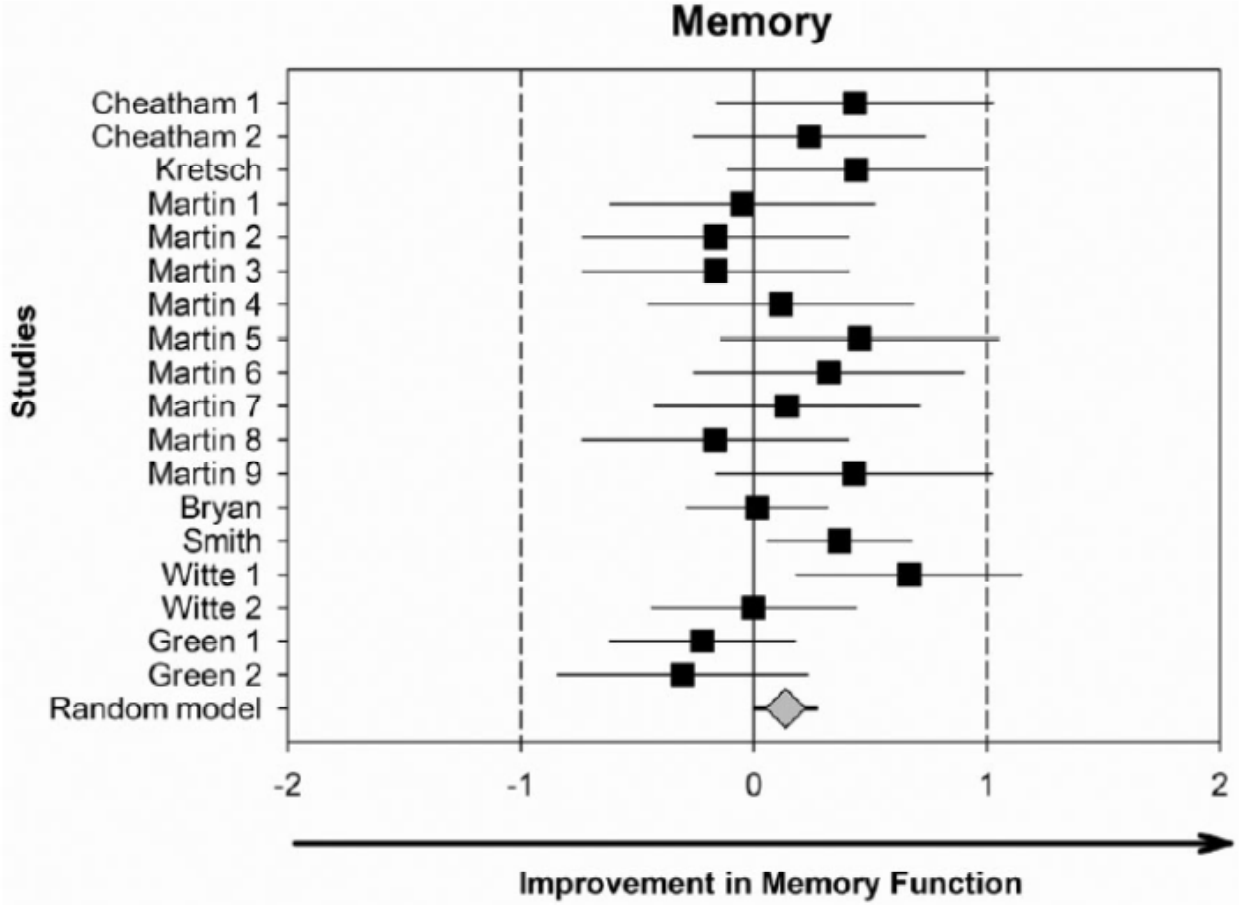




Mariel M Finucane, Gretchen A Stevens,**

Intentional weight loss in overweight and obese individuals and cognitive function: a systematic review and meta-analysis

M. Siervo[1], R. Arnold[2], J. C. K. Wells[3], A. Tagliabue[4], A. Colantuoni[1], E. Albanese[5], C. Brayne[6] and B. C. M. Stephan[6]



3 Obesita' & Demenza – *Inconsistent Results…*

Disaccordo tra studi osservazionali (e con gli RCTs)!

Incongruenze tra gli Studi

1. Quale misura di *adiposity*
2. Cohort effects
3. Diversi criteri per la demenza
4. **Eta' dell'esposizione**
5. ***Reverse causality***

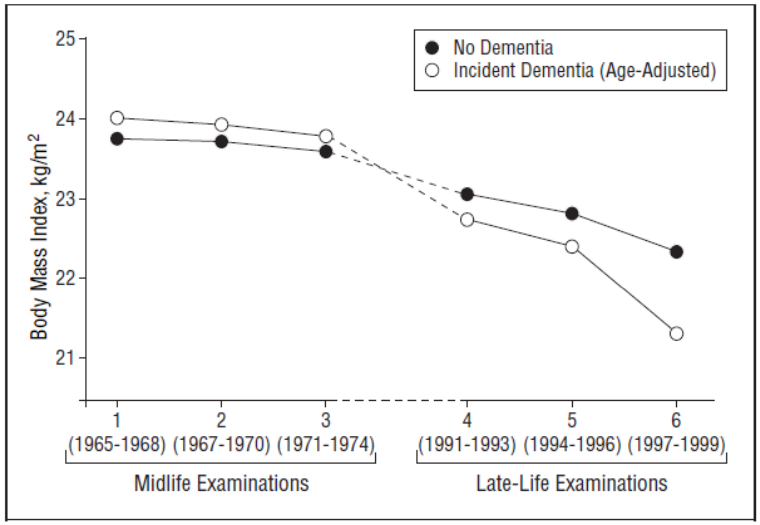


Figure 2. A graph plotting mean previous body mass index according to incident dementia at examination 6 (1997-1999).

Robert Stewart, MD; K Lenore J. Launer, PhD

Central Obesity in the Elderly is Related to Late-onset Alzheimer Disease

José A. Luchsinger, MD, MPH,† ‡§ Derek Cheng, MPH,* Ming Xin Tang, PhD,† ‡‖ Nicole Schupf, PhD,*† ‡ and Richard Mayeux, MD*† ‡¶#*

Problema: Discrepanza tra evidenza osservazionale e sperimentale

Non e' un problema nuovo

Those confounded vitamins: what can we learn from the differences between observational versus randomised trial evidence?

Debbie A Lawlor, George Davey Smith, K Richard Bruckdorfer, Devi Kundu, Shah Ebrahim

Problema: Discrepanza tra evidenza osservazionale e sperimentale

E' colpa di come noi epidemiologi?

Lost in Translation

Epidemiology, Risk, and Alzheimer Disease

Mary Ganguli, MD, MPH; Walter A. Kukull, PhD

cepts, for which we epidemiologists must shoulder some of the blame.

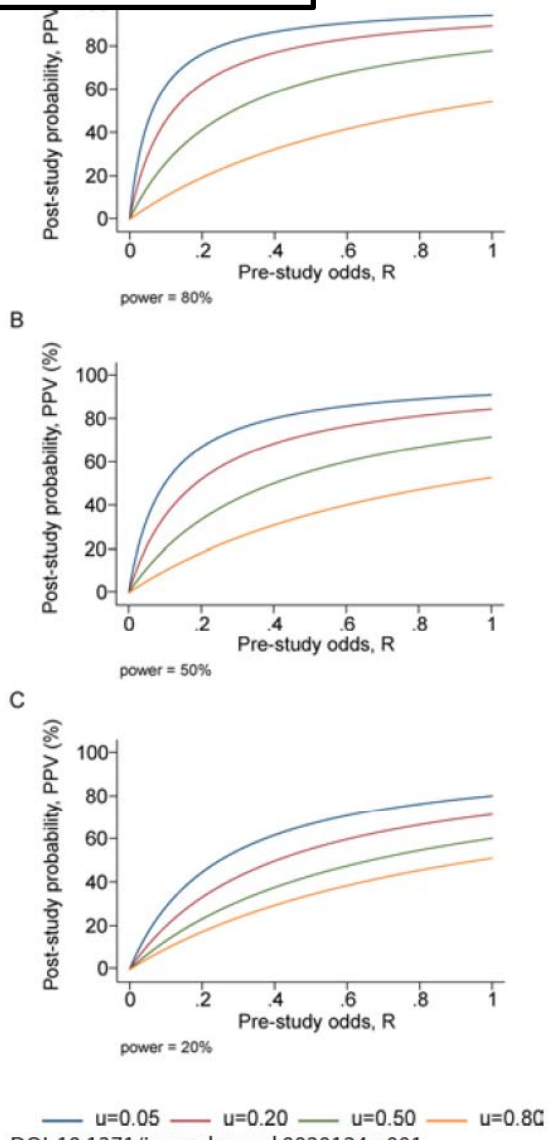
Problema: Discrepanza tra evidenza osservazionale e sperimentale

Non c'e' speranza?

Why Most Published Research Findings Are False

John P. A. Ioannidis

It can be proven that most claimed research findings are false.



DOI: 10.1371/journal.pmed.0020124.g001

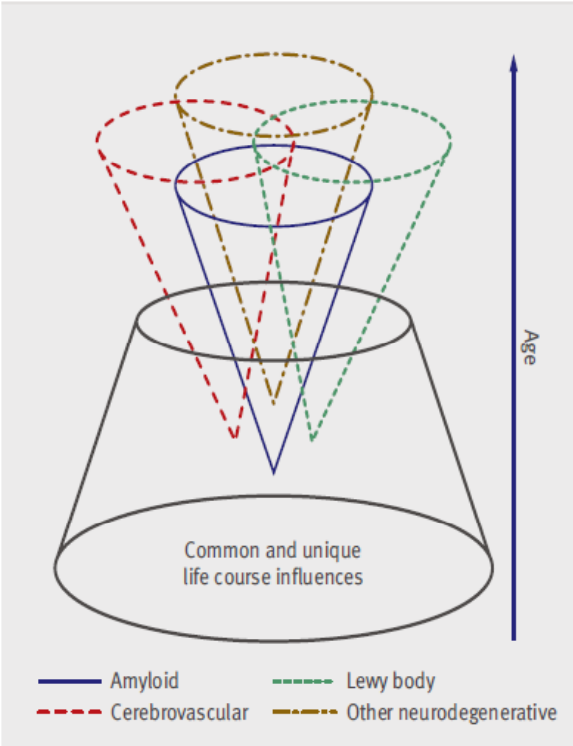
Figure 1. PPV (Probability That a Research Finding Is True) as a Function of the Pre-Study Odds for Various Levels of Bias, *u*

Panels correspond to power of 0.20, 0.50, and 0.80.

Soluzione: La prospettiva epidemiologica

1. Ridefinire la malattia

What do we mean by Alzheimer's disease?



Dementia as a diffuse multiform syndrome

strategy should also recognise that risk of Alzheimer's disease evolves throughout life.[18] This

Soluzione: La prospettiva epidemiologica

2. Ripensare il nostro APPROCCIO

Next Steps in Alzheimer's Disease Research: Interaction between Epidemiology and Basic Science

Lenore J. Launer*

The epidemiologic study of dementia: a life-long quest?

L.J. Launer*

cognitive impairment and dementia. Our understanding the contribution of cardiovascular risk factors to late age brain disease has been helped tremendously by prospective studies with long follow-up. To better understand which risk factors lead to disease initiation, progression and prognosis, a life course approach to the epidemiologic study of dementia is needed.

Un approccio *life-course* alla demenza e' una Chimera?

Demenza

- Sappiamo molto, ma cause e l'eziopatogenesi sono ignote e non c'e' una terapia.
- QUINDI: L'epidemiologia e la prevenzione sono importanti.

Epidemiologia delle Demenze

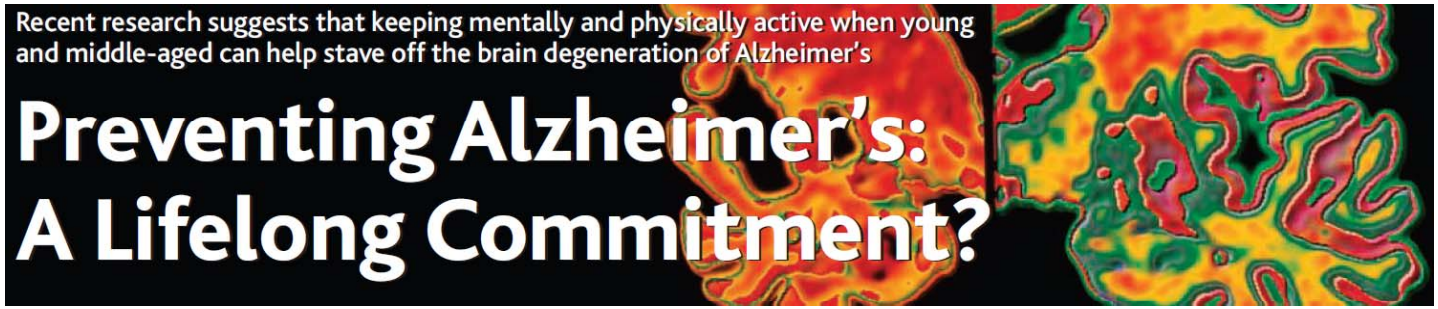
- La demenza e' in aumento e ha un grande impatto (e costi)
- Lo studio dei fattori di rischio (e protettivi) e' importante per la prevenzione ma anche..
- Per comprendere la mallattia

Un approccio A *Life-course* alla demenza

Un approccio A *Life-course* alla demenza

Soluzione: La prospettiva epidemiologica

3. Uno sforzo collettivo e concertato



Modifiable Midlife Risk Factors for Late-Life Cognitive Impairment and Dementia

Tiffany F. Hughes* and **Mary Ganguli**

FUTURE DIRECTIONS: CHALLENGES AND RECOMMENDATIONS

As demonstrated by this review, few studies have examined risk factors more than a few years prior to dementia onset, which does not permit discrimination between a true independent risk factor and a prodromal or early symptom. In order to accomplish this, a life course approach needs to be taken. Life course epidemiology presents challenges in terms of both design and analysis. First, it entails more than collecting exposure data across the life span; temporal associations and inter-relationships must also be examined. Second, obtaining data at birth and

Risk Factors

How to address the gap (NIH/ Dukes just dig)?

4. Obbiettivi chiari

DRAFT STATEMENT
April 28, 2010
8:00 p.m.

NATIONAL INSTITUTES OF HEALTH
STATE-OF-THE-SCIENCE CONFERENCE STATEMENT
NIH State-of-the-Science Conference:
Preventing Alzheimer's Disease and Cognitive Decline
April 26–28, 2010

Key Question 6: If recommendations for interventions cannot be made currently, what studies need to be done that could provide the quality and strength of evidence necessary to make such recommendations to individuals?

Addressing the gap. Observational studies need to assess exposures initially years prior to expected onset of symptoms. The collection of exposure data should continue over an extended period of time because it is not known whether exposures with a protective effect or those with a detrimental effect may still be influential even after the pathological process has begun. It is also important to collect longitudinal exposure data to examine whether the timing of the exposure makes a difference, and whether changes in exposure over time alter risk of cognitive decline. Prospectively collecting this exposure information for decades prior to onset of clinical disease is costly and logistically challenging. Realistically, intermediate or shorter-term outcomes may need to be integrated into such a life course approach to make the studies viable. Some of the

Un approccio A *Life-course* alla demenza

Concetti base

Studi & Risorse

Metodi & Analisi

Concetti | ***Life-course* e' piu' che *longitudinale***

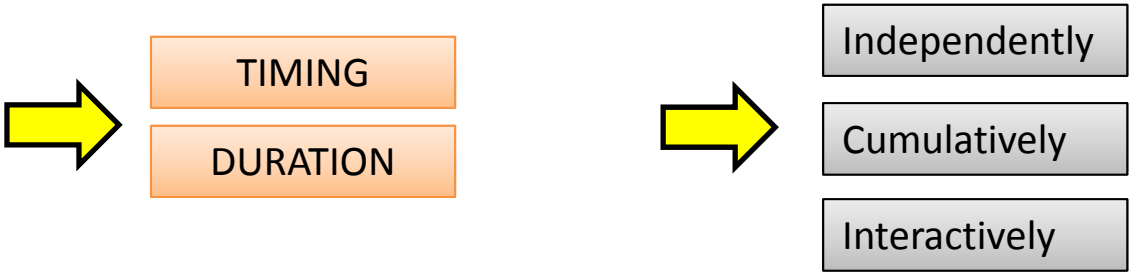
Life course epidemiology

D Kuh, Y Ben-Shlomo, J Lynch, J Hallqvist, C Power

Origini | Contrapposizione tra fattori in eta' adulta e FOAD.

Definizione | E' un **MODELLO TEORICO** per studiare gli effetti di fattori di rischio lungo tutto il ciclo di vita, su malattie in eta' adulta/ anziana, che da' indizi sull'EZIOLOGIA. E' diverso da uno studio longitudinale che e' solo un disegno sperimentale.

Focus | **Timing** e **Duration** dei fattori di rischio e lor interazioni



Scopo | Costruire e testare modelli teorici di **PATHWAYS** tra fattori di esposizione (lungo il ciclo di vita) e malattie (croniche) in eta' adulta/ anziana.

Concetti

MODELLI di relazione exposure-outcome

Indipendenti

Cumulativi

Interattivi

Cumulaitivi & Indipendenti

Cumulativi a ‘cluster’

Catena di Eventi (probabilistici)

Catena di Rischi a ’trigger’

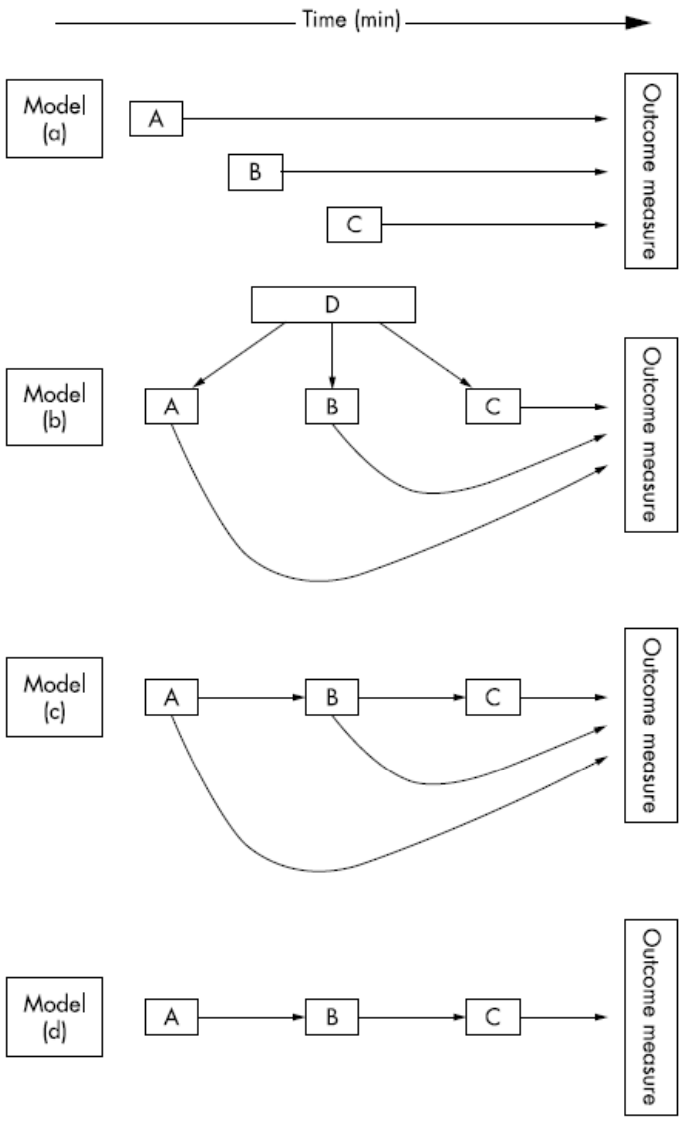


Figure 1 Life course causal models.

D Kuh, Y Ben-Shlomo, J Lynch, J Hallqvist, C Power

Concetti

Terminologia – il glossari epidemiologico illustra i concetti

PATHWAYS

Accumulo del danno in sistemi biologici in funzione del numero, intensita' e durata dell'esposizione

Catena di Rischi aSequenza di fattori *correlati* che aumenta il rischio generale di malattia (mediatori o modificatori)

Traiettorie di una dimensione nel corso della vita (implica traiettorie *normali* intorno alle quali gli individui deviano)

TIMING

Tempo E' sia l'eta' che il momento storico.

Birth Cohort Ubicazione e Epoca definito dall'anno di nascita.

Periodi *Sensibili* Finestra temporale durante la quale l'effetto dell'esposizione e' maggiore (FOAD + mis-match?)

Induzione Intervallo di tempo tra l'esposizione e l'inizio del processo patologico.

Latenza Intervallo tra inizio e osservazione della malattia

MECCANISMI

Mediatore che sta sulla *pathway* tra fattore di esposizione e outcome.

Modificatore (interazione) in base ai suoi livelli il rapporto tra fattore di esposizione e outcome varia.

Resilenza adattamento positivo alle avversita' adversities

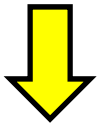
Suscettibilita' Maggiore predisposizione all'effetto di una seconda causa

Vulnerabilita' E' l'opposto della resilienza.

Embodiment

Concetti	**E’ un approccio complesso (e complicato?)**

Metodo	Misure ripetute; Modelli Gerarchici; *Latent Models*; Effetti interattivi multipli…
Statistica	Multi-level models; Latent growth models; Markov & Graphic Chains; Path Analysis & SEM…
Criticita’	Missing data (o poche misure ripetute); Measurement errors; colinearita’ e tracking…



I modelli statistici ottimali sono ancora dibattuti.

Statistica | In fieri

Confronto/ conferma di piu' modelli

Statistical Issues in Life Course Epidemiology

Bianca L. De Stavola[1], Dorothea Nitsch[1], Isabel dos Santos Silva[1], Valerie McCormack[1], Rebecca Hardy[2], Vera Mann[1], Tim J. Cole[3], Susan Morton[1], and David A. Leon[1]

two cohorts in the United Kingdom are used to illustrate alternative modeling strategies. The authors conclude that more than one analytical approach should be adopted to gain more insight into the underlying mechanisms.

A structured approach to modelling the effects of binary exposure variables over the life course

Gita Mishra,[1*†] Dorothea Nitsch,[2†] Stephanie Black,[1] Bianca De Stavola,[2] Diana Kuh[1] and Rebecca Hardy[1]

- We recommend comparing a set of nested models—each corresponding to the accumulation, critical period and effect modification hypotheses—to an all-inclusive (saturated) model.

MODELLO CONCETTUALE (per la demenza)

Oltre le FOAD

Non e' solo *early life* vs. *adult life*

Early-Life Risk Factors for Alzheimer Disease

Amy R. Borenstein, PhD, Cathleen I. Copenhaver, BS,* and James A. Mortimer, PhD**

ature reviewed suggests that risk of Alzheimer disease is probably not determined in any single time period but results from the complex interplay between genetic and environmental exposures throughout the life course. Enhancement or preservation of brain or cognitive

il **MODELLO**

Esiste GIA' un modello concettuale

I fattori di rischio sono ora intesi all'interno di un quadro complessivo piu' articolato

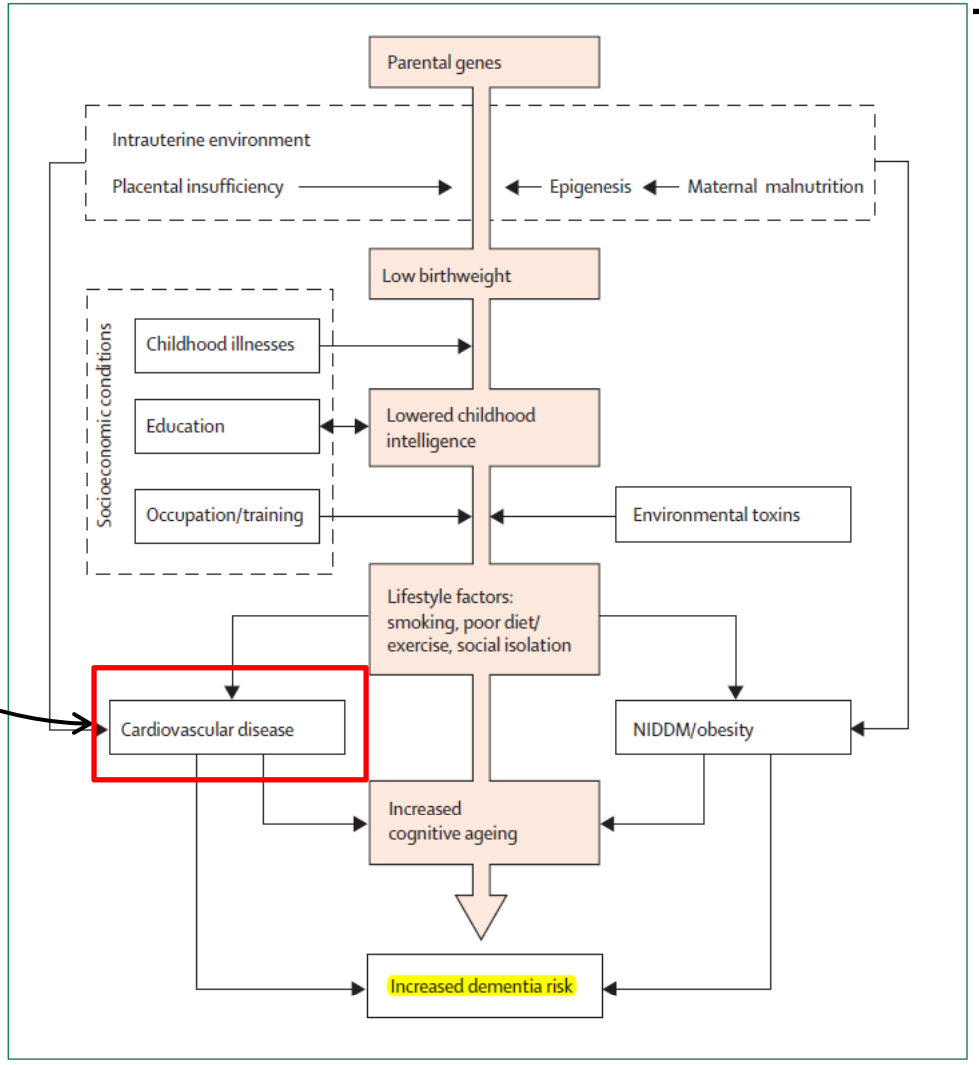


***Figure 3*: Summary of possible associations between adult diseases and the risk of dementia**
Pathways are shown by directional arrows between a malnourished intrauterine environment and an increased risk of cognitive ageing and progression to dementia. Factors present from early life (figure 1) are shown in the upper part of this figure. These contribute to the risk of suboptimum cognitive development, fewer learning ...ities, and poor lifestyle choices. These factors precede the clinical onset of cardiovascular disease, non-...ependent diabetes mellitus (NIDDM), and the metabolic syndrome. The risk of these diseases is associated directly with impaired fetal nutrition. There are alternate pathways from fetal malnutrition to increased cognitive ageing and dementia. Low average childhood intelligence is a major influence on lifestyle choices, educational attainments, and occupational opportunities, and, downstream from these, on morbidity and mortality from cardiovascular disease, NIDDM, and metabolic syndrome.

Lawrence J Whalley, Finlay D Dick, Geraldine McNeill

Il MODELLO

A Life-course approach to dementia is...

Necessario

Nonostante I grandi progressi degli anni recenti, non esistono **MODELLI CAUSALI ESAUSTIVI**.
Vi e' accordo sulla necessita di un modello *life course* nella comunita' scientifica, non solo tra gli epidemiologi.

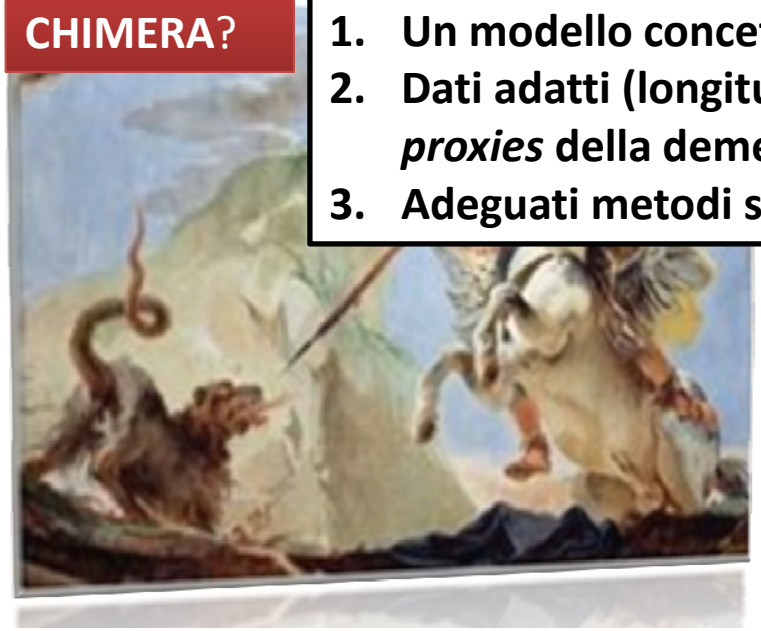
Non e' FOAD

L'ipotesi "FOAD" applicata alla demenza e' SOLO uno degli aspetti del modello *life course* – il **timing** e la **durata** dei fattori di esposizione e le loro interazioni devono essere ipotizzati e testati formalmente.

E' una **CHIMERA**?

Ci sono 3 condizioni necessarie per condrre studi *life* course:

1. **Un modello concettuale di riferimento e ipotesi specifiche**
2. **Dati adatti (longitudinali, con misure ripetute, e *outcomes* prospettici e/o *proxies* della demenza)**
3. **Adeguati metodi statistici**



Ad oggi, un vero studio di life-course epidemiology sulle demenze NON e' stato condotto

Un approccio A *Life-course* alla demenza

Modelli concettuali

Esempio – *obesita' & demenza*

Esempio

'A life course of adiposity and dementia'

3 CONDIZIONI

1. ~~Un modello concettuale di riferimento e~~ **OK!**
2. Ipotesi (e domande) specifiche **OK!**
3. Dati
4. Adeguati metodi statistici

IPOTESI

Sovrappeso/ obesita' durante tutto l'arco della vita sono associati ad un maggior rischio di demenza/ deterioramente cognitivo

DOMANDE

- C'e' un *cumulative effet?*
- Esistono periodi sensibili?

A life course of adiposity and dementia☆

Deborah Gustafson*

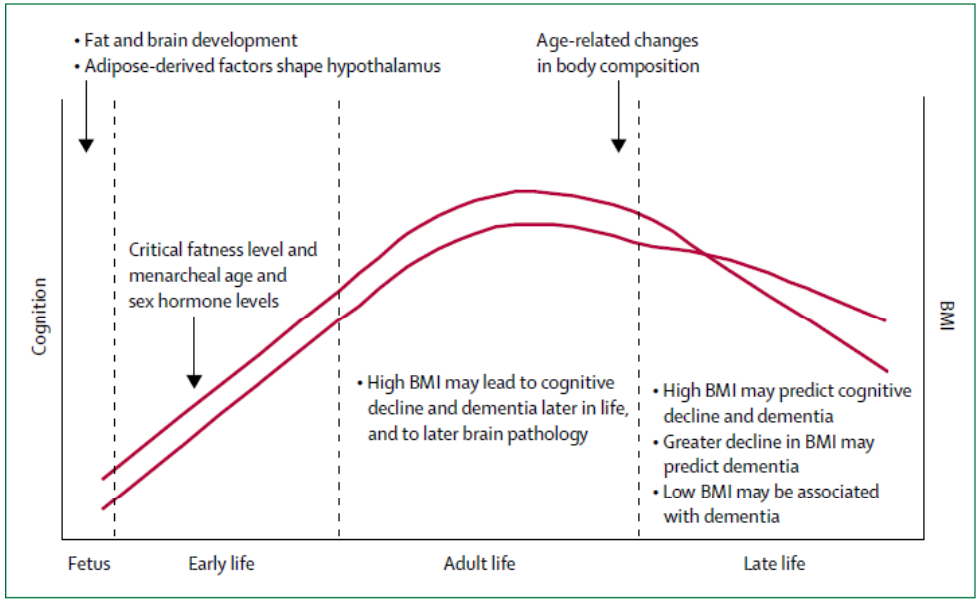


Figure 1: Potential trajectories of cognition associated with adipose tissue and stage of life

Esempio | *'A life course of adiposity and dementia'*

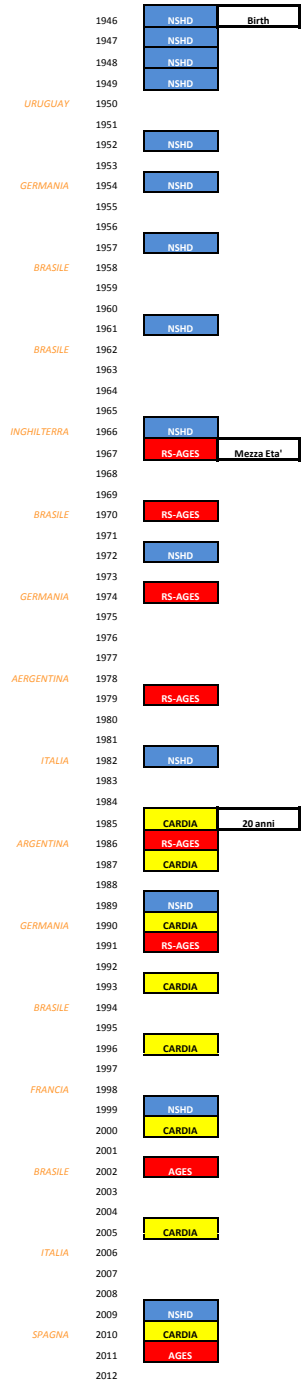
3 CONDIZIONI

1. ~~Un modello concettuale di riferimento e ipotesi specifiche~~ **OK!**
2. Dati
   - Longitudinali
   - misure ripetute
   - outcomes prospettici e/o proxies della demenza
3. Adeguati metodi statistici

NSHD — *birth cohort study* iniziato nel 1946 - 2010

RS-AGES — Studio di coorte di CVD 'trasformato' in un aging study

CARDIA — Uno studio su giovani seguiti per CVD e ora MRI (in mid-life!)



Esempio | *'A life course of adiposity and dementia'*

3 CONDIZIONI

1. ~~Un modello concettuale di riferimento e ipotesi specifiche~~ **OK!**
2. ~~Dati~~ **OK!**
   - ~~Longitudinali~~
   - ~~misure ripetute~~
   - ~~outcomes prospettici e/o proxies della demenza~~
3. Adeguati metodi statistici **quasi OK?**

2 STEPS

1. **Ispezione dei DATI**
   - Life course z-scores
   - Regressioni seriali (ad ogni follow-up) [Life course plot]
2. **Analisi dell'associazione tra traiettorie di BMI e outcome (funzione cognitiva/ demenza)**

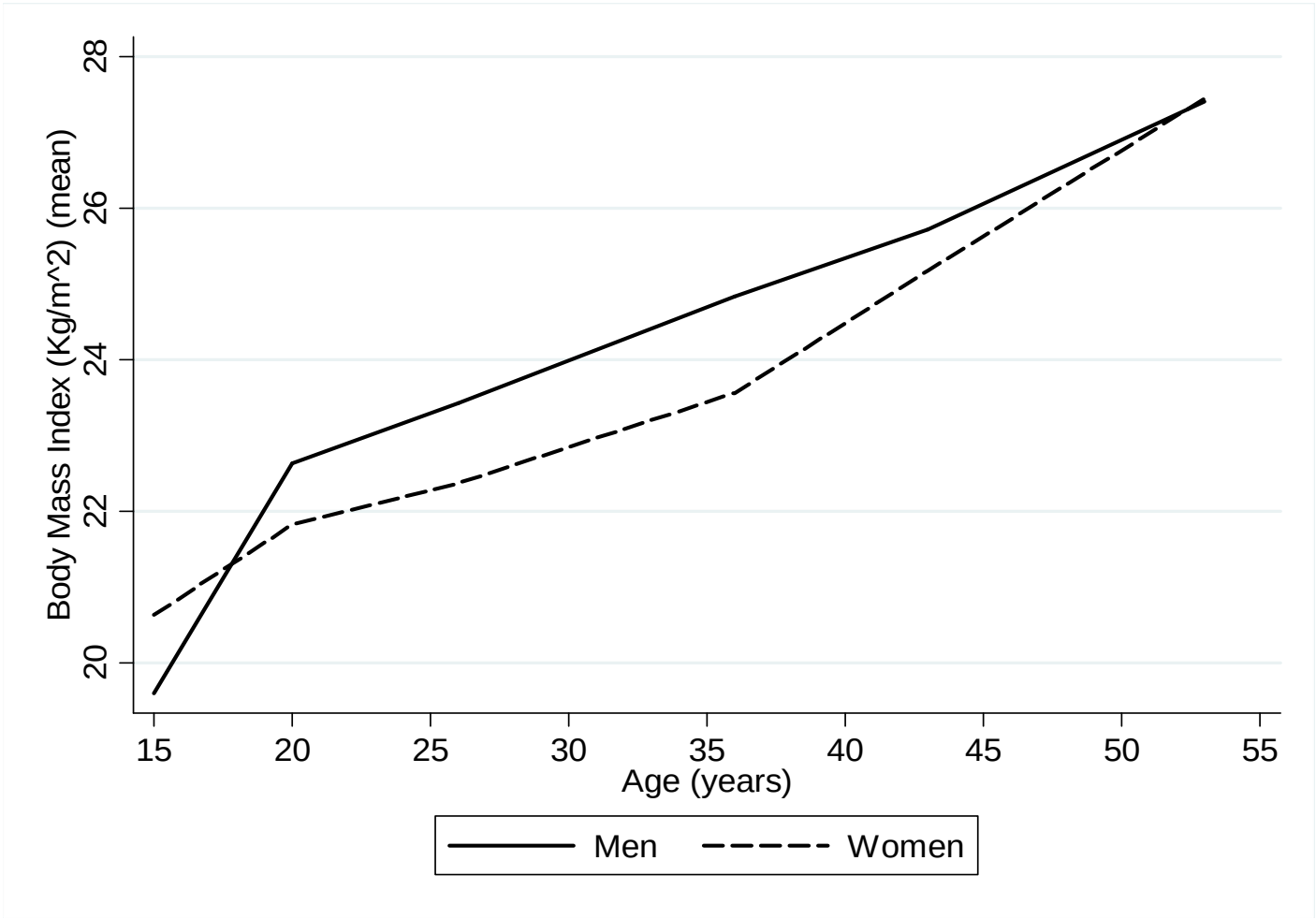
Esempio

'A life course of adiposity and dementia'

NSHD

1. Ispezione dei DATI

a) Aumento del BMI dai 15 ai 55 anni



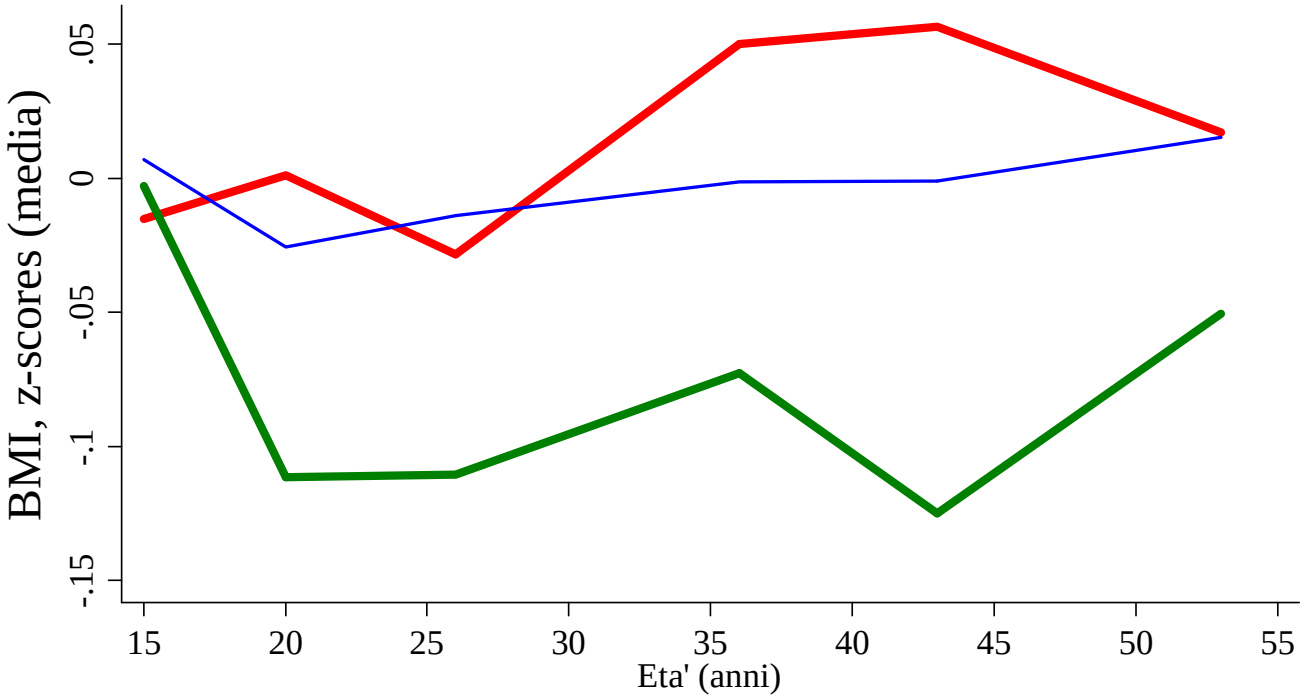
Esempio

'A life course of adiposity and dementia'

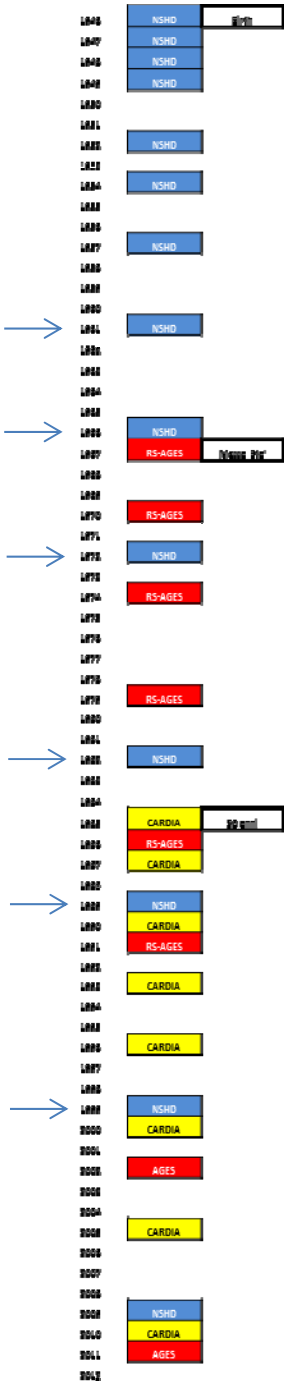
NSHD

2. Life course z-scores

b) Traiettorie di BMI per deficit mnesico tra i 45 e i 55 anni*



*Terzili della diminuzione dello score al RAVLT nell'arco di 10 anni



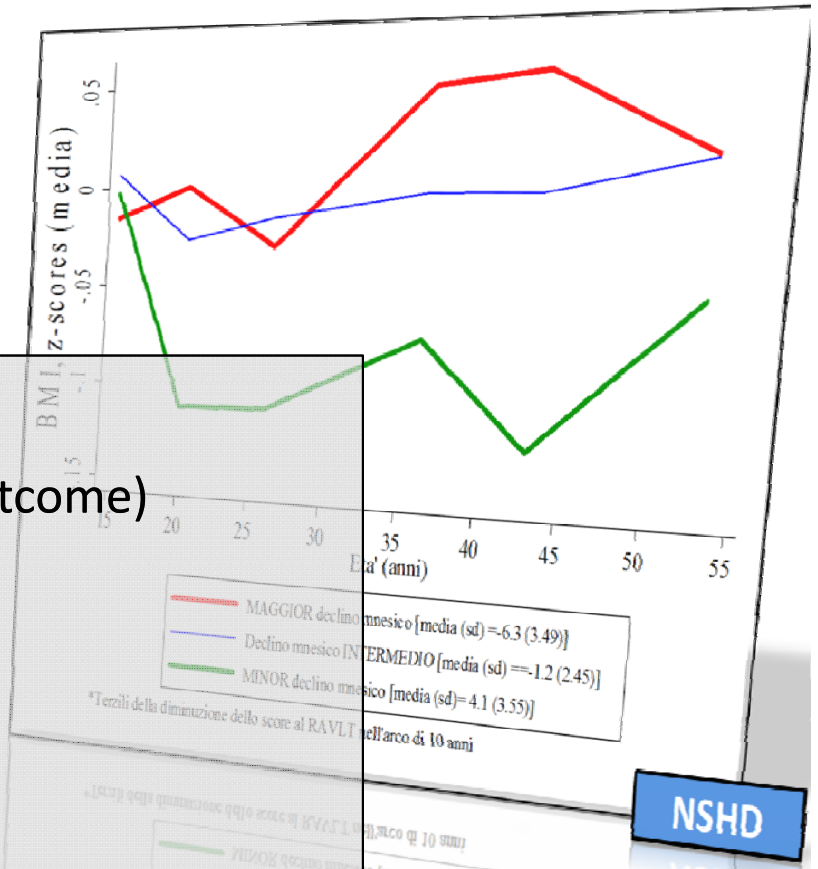
Albanese et al. Unpublished – NON CITARE

Esempio

'A life course of adiposity and dementia'

2 STEPS

1. **Ispezione dei DATI**
   - Life course means (z-scores)
2. **Analisi**



VANTAGGI:

- Mostrano le traiettorie (del BMI rispetto all'outcome)
- Facili da interpretare

SVANTAGGI:

- Non c'e' inferenza statistica
- Categorizzazione delle variabili continue
- Le traiettorie non sono *aggiustate* per covariate
- Missing data (non e' lo stesso campione ad ogni follow-up)
- Regressione verso la media?

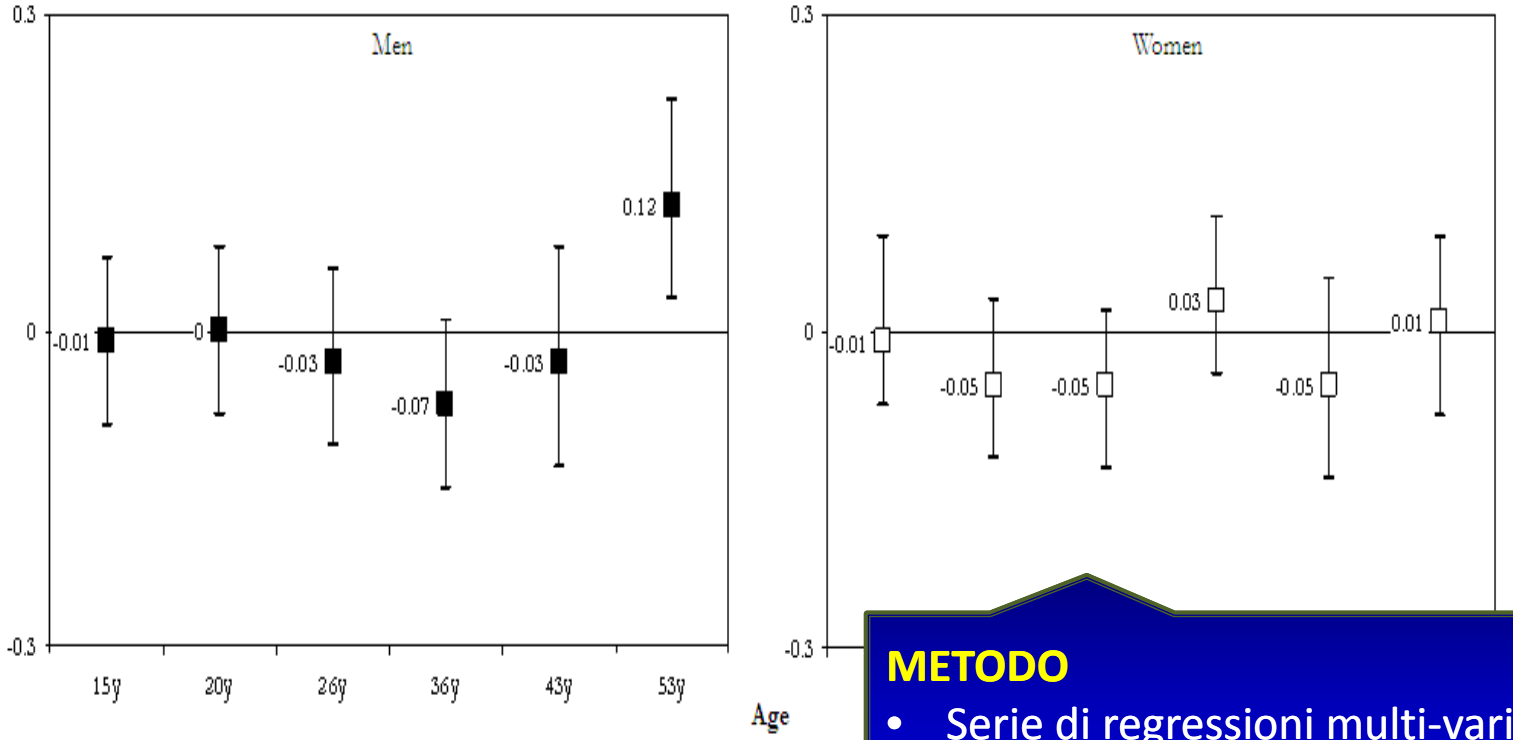
Esempio

'A life course of adiposity and dementia'

NSHD

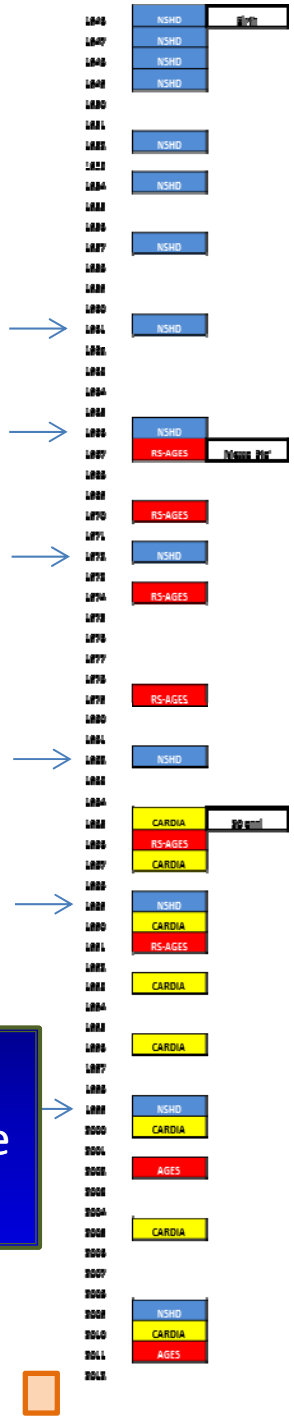
2. Regressioni seriali

c) Associazione tra BMI (15-55 anni) e declino mnesico (45-55 anni)



METODO

- Serie di regressioni multi-variate
- Grafico dei coefficienti β



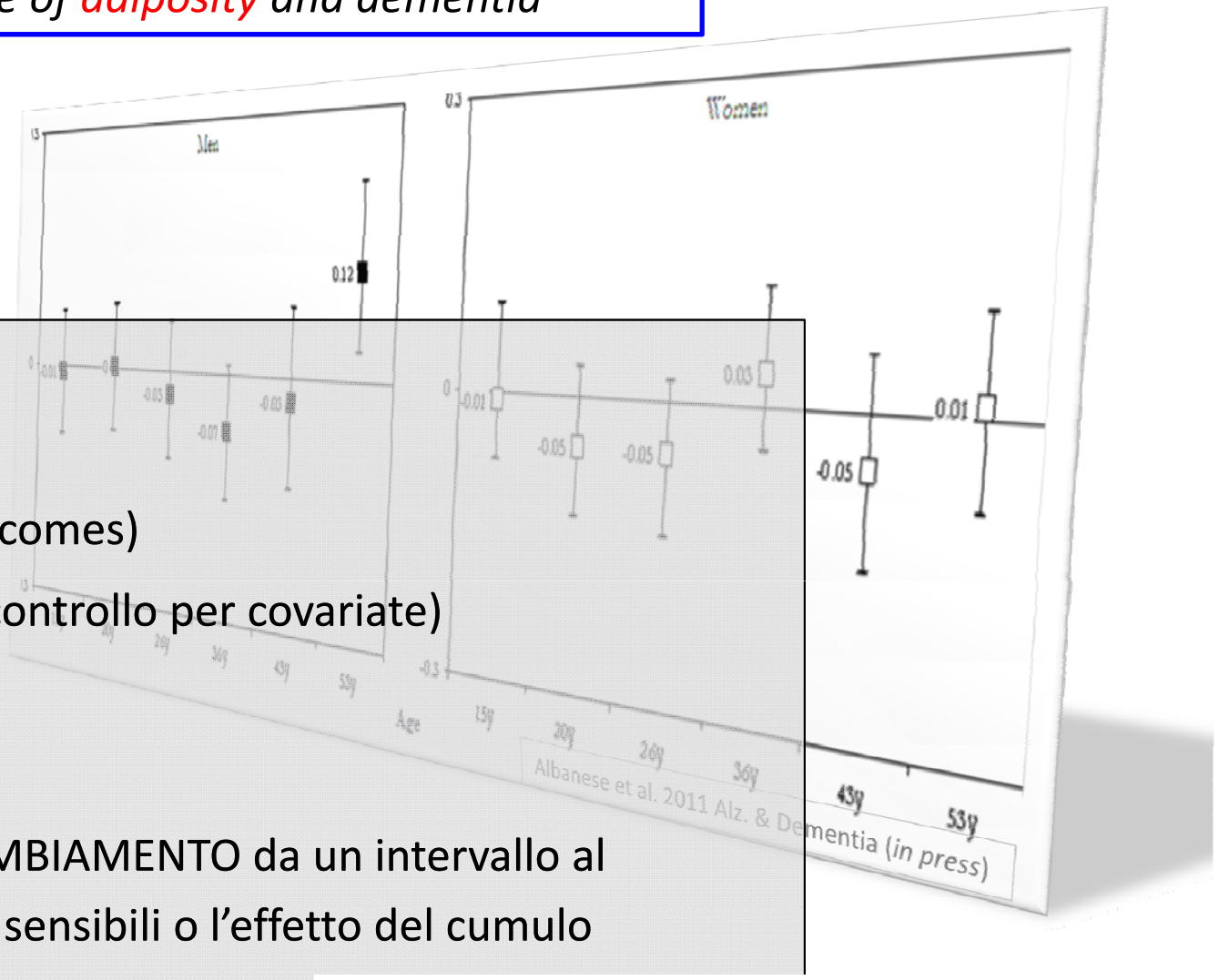
No association between gain in body mass index across the life cou
and midlife cognitive function and cognitive reserve—The 1946 British birth cohort study

Emiliano Albanese[a,b,*], Rebecca Hardy[a], Andrew Wills[a], Diana Kuh[a], Jack Guralnik[b], Marcus Richards[a]

Esempio

'A life course of adiposity and dementia'

NSHD



VANTAGGI:

- Differenze statistiche
- Variabili continue (outcomes)
- Analisi multi-variate (controllo per covariate)

SVANTAGGI:

- BMI Tracking?
- Stiamo testando il CAMBIAMENTO da un intervallo al seguente, non periodi sensibili o l'effetto del cumulo

No association between gain in body mass index across the life course and midlife cognitive function and cognitive reserve—The 1946 British birth cohort study

Emiliano Albanese[a,b,*], Rebecca Hardy[a], Andrew Wills[a], Diana Kuh[a], Jack Guralnik[b], Marcus Richards[a]

Esempio

'A life course of adiposity and dementia'

- **Il BMI e' associato alla demenza? = *forse***
- **Come esattamente?:**
  1. Esistono **periodi sensibili**?
  2. Essere sovrappeso/obesi per lunghi periodi e' peggio (**accumulation**)?

Per rispondere a queste domande esistono diversi approacci statistici possibili, che superano le analisi *multi-level.*

…ma che sono ad oggi ancora dibatutti.

Commentary: Methods for analysing life course influences on health—untangling complex exposures†

Kate Tilling,[1]* Laura D Howe[2] and Yoav Ben-Shlomo[1]

Association of Maternal Weight Gain in Pregnancy With Offspring Obesity and Metabolic [illegible] in Childhood

Abigail Fraser, PhD; Kate Tilling, PhD; Corrie Macdonald-Wal
Marie-Jo Brion, PhD; Li Benfield, PhD; Andy Ness, PhD, FF
Aroon Hingorani, PhD, FRCP; Scott M. Ne
George Davey Smith, MD, DSc; Debbie A.

Background—We sought to examine the association of gestational weight gain (GWG) an
offspring adiposity and cardiovascular risk factors.
Methods and Results—Data from 5154 (for adiposity and blood pressure) and 3457 (for blood assays) mother-offspring pairs from a UK prospective pregnancy cohort were used. Random-effects multilevel models were used to assess incremental GWG (median and range of repeat weight measures per woman: 10 [1, 17]). Women who exceeded the

Immediate Postnatal Growth Is Associated With Blood Pressure in Young Adulthood

The Barry Caerphilly Growth Study

Yoav Ben-Shlomo, Anne McCarthy, Rachael Hughes, Kate Tilling,

analysis of all 14 childhood measurements in developing a linear spline random-effects model with 2 knots (thus dividing follow-up

Socioeconomic differences in childhood growth trajectories: at what age do height inequalities emerge?

Laura D Howe,[1,2] Kate Tilling,[1] Bruna Galobardes,[1] George Davey Smith,[1,2]

height trajectories from birth to 10 years (N=12366) were modelled. Individual trajectories were estimated using mixed-effects models. Differences in trajectories
by socioeconomic position (SEP) were investigated

Un approccio *life-course* alla demenza e' una Chimera?

Demenza

- Sappiamo molto, ma cause e l'eziopatogenesi sono ignote e non c'e' una terapia.
- QUINDI: l'epidemiologia e la prevenzione sono importanti.

Epidemiologia delle Demenze

- La demenza e' in aumento e ha un grande impatto (e costi)
- Lo studio dei fattori di rischio (e protettivi) e' importante per la prevenzione ma anche..
- Per comprendere la malattia

Un approccio A *Life-course* alla demenza

1. Abbiamo un **modello concettuale**
2. Abbiamo i **dati** (e gli studi) adeguati
3. Ci stiamo attrezzando per i **metodi statistici**

Emiliano Albanese
Supported by the National Institute on Aging