Invecchiamento fisiologico e patologico

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Epidemiologia

- La Demenza non è una condizione ineludibile associata all'invecchiamento cronologico
- L'età è un ''proxy'' di condizioni neuropatologiche con eterogenea espressività clinica nel paziente anziano, più che un vero e proprio fattore causativo
- Dopo I 90 anni esiste una ampia variabilità nella prevalenza di demenza con un trend di diminuzione osservato

Skoog I, Börjesson-Hanson A, Kern S, Johansson L, Falk H, Sigström R, Östling S (2017) Decreasing prevalence of dementia in 85-year olds examined 22 years apart: the influence of education and stroke. *Sci Rep* **7**, 6136.

[6] Qiu C, Fratiglioni L (2018) Aging without Dementia is Achievable: Current Evidence from Epidemiological Research. *J Alzheimers Dis* **62**, 933-942.

Epidemiologia

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SCIENTIFIC REPORTS

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Decreasing prevalence of dementia in 85-year olds examined 22 years apart: the influence of education and stroke

Ingmar Skoog, Anne Börjesson-Hanson, Silke Kern, Lena Johansson, Hanna Falk, Robert Sigström & Svante Östling

Individuals aged 80 years and older constitute the fastest growing segment of the population worldwide, leading to an expected increase in dementia cases. Education level and treatment of vascular risk factors has increased during the last decades. We examined whether this has influenced the prevalence of dementia according to DSM-III-R using population-based samples of 85-year-olds (N = 1065) examined with identical methods 1986–87 and 2008–10. The prevalence of dementia was 29.8% in 1986–87 and 21.7% in 2008–10 (OR 0.66; 95%-CI: 0.50–0.86). The decline was mainly observed for vascular dementia. The proportion with more than basic education (25.2% and 57.7%), and the prevalence of stroke (20% and 30%) increased, but the odds ratio for dementia with stroke decreased from 4.3 to 1.8 (interaction stroke*birth cohort; p = 0.008). In a logistic regression, education (OR 0.70; 95%-CI 0.51–0.96), stroke (OR 3.78; 95%-CI 2.28–6.29), interaction stroke*birth cohort (OR 0.50; 95%-CI 0.26–0.97), but not birth cohort (OR 0.98; 95%-CI 0.68–1.41), were related to prevalence of dementia. Thus, the decline in dementia prevalence was mainly explained by higher education and lower odds for dementia with stroke in later born birth cohorts. The findings may be related to an increased cognitive reserve and better treatment of stroke in later-born cohorts.

RIDUZIONE INCIDENZA DEMENZA

Età media 79 anni
Demenza di grado lieve
Tipo prevalente: demenza vascolare/ demenza mista
Associazione: educazione/riserva cognitiva
Aumento stroke ma migliore trattamento in acuto

Framingham study
MRC cognitive and ageing study CFAS

Satizabal, C. L. et al. Incidence of Dementia over Three Decades in the Framingham Heart Study. The New England journa medicine374, 523–532, doi:10.1056/NEJMoa1504327 (2016). 6. Matthews, F. E. et al. A two decade dementia incidence comparison from the Cognitive Function and Ageing Studies I and II. Nat Commun7, 11398, 2012

American studies
Rotterdam study

Hebert, L. E. et al. Change in risk of Alzheimer disease over time. Neurology75, 786–791, doi:10.1212/WNL.0b013e3181f0754f 37. Schrijvers, E. M. et al. Is dementia incidence declining?: Trends in dementia incidence since 1990 in the Rotterdam Study. Neurology78, 1456–1463, (2012).

THE SPECTRUM OF BRAIN AGING AND THE TRESHOLD TO THE CLINICAL EXPRESSION OF DEMENTIA IN THE OLDEST OLD: A PATHOPHYSIOLOGICAL INSIGHT
BRAIN AGING

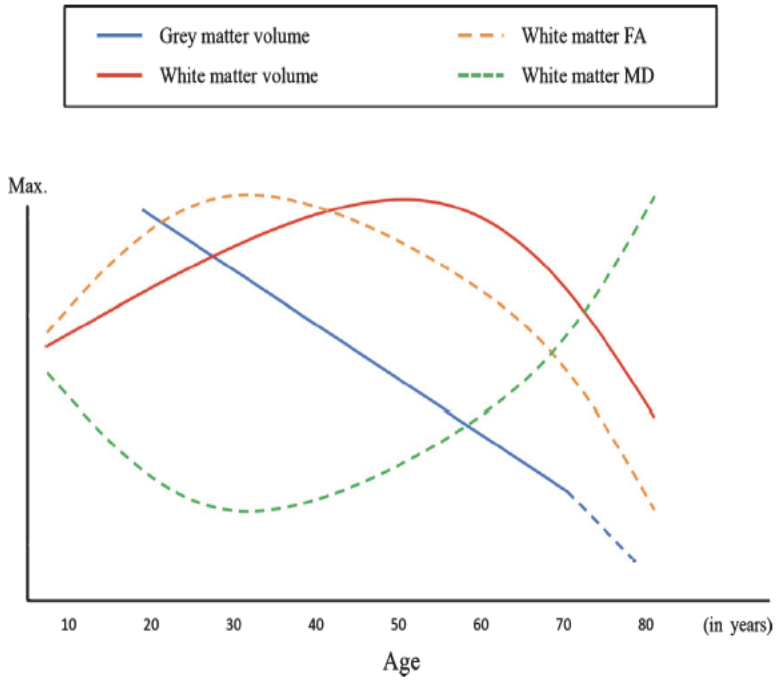

Fig. 1. Hypothetical model of global structural cerebral changes across the lifespan (particularly based upon the results of Good et al. [23] and Westlye et al. [41]). The diagram illustrates the different patterns of changes in grey matter volume, white matter volume, and white matter integrity (FA, fractional anisotropy; MD, mean diffusivity). Relations between the different measures are not considered. Whereas global grey matter volume alterations describe a relatively linear decline until an age of 70 (analog courses for cortical thinning and brain tissue surface), white matter volume and integrity show inverted U-shaped patterns with peaks in different decades of life. The blue dashed line indicates that there may be accelerated grey matter atrophy at older ages (with region-specific differences) [24, 25].

Declino lineare età correlato della sostanza grigia
(accelerazione >70 anni specie in ippocampo)

Inverted U shape patterns per sostanza bianca specialmente nelle decadi più avanzate

Esiste un gradiente anteroposteriore di vulnerabilità prefrontale per disconnessione fibre frontali

Alterazioni della attivazione funzionale network frontale con specifica vulnerabilità funzionale

AMPIA ETEROGENEITA'
Grado di compensazione deficit morfologici e funzionali nel tempo attraverso meccanismi di resilienza

THE SPECTRUM OF BRAIN AGING AND THE TRESHOLD TO THE CLINICAL EXPRESSION OF DEMENTIA IN THE OLDEST OLD: A PATHOPHYSIOLOGICAL INSIGHT BRAIN AGING

Negli anziani (oldest old) esiste un accumulo di hallmarks neuropatologici (amyloid-β and tau [σ] protein deposits) non correlate alle manifestazioni cliniche di AD
Differenti gradienti strutturali e funzionali qualitativi (volume, integrità, attivazione, connettività funzionale, neurotrasmissione) e quantitativi (estensione e progressione del danno), possono render conto di differenze sostanziali neuro cognitive

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Brain pathologies in extreme old age

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Abstract

With an emphasis on evolving concepts in the field, we evaluated neuropathologic data from very old research volunteers whose brain autopsies were performed at University of Kentucky (UK-ADC), incorporating data from the Georgia Centenarian Study (N=49 cases included), the Nun Study (N=17), and UK-ADC (N=11) cohorts. Average age of death was 102.0 years (range: 98–107) overall. Alzheimer's disease (AD) pathology was not universal (62% with "moderate" or "frequent" neuritic amyloid plaque densities) whereas frontotemporal lobar degeneration (FTLD) was absent. By contrast, some hippocampal neurofibrillary tangles (including primary age-related tauopathy [PART]) were observed in every case. Lewy body pathology was seen in 16.9% of subjects, hippocampal sclerosis of aging (HS-Aging) in 20.8%. We describe anatomical distributions of pigment-laden macrophages, expanded Virchow-Robin spaces, and arteriolosclerosis among Georgia Centenarians. Moderate or severe arteriolosclerosis pathology, throughout the brain, was associated with both HS-Aging pathology and an *ABCC9* gene variant. These results provide fresh insights into the complex cerebral multimorbidity, and a novel genetic risk factor, at the far end of the human aging spectrum.

….

supporting the hypothesis that AD pathology is not a mandatory phenomenon of increasing chronologic age or, perhaps, that the very old individuals display a striking resistance to the neurodegenerative process.

THE SPECTRUM OF BRAIN AGING AND THE TRESHOLD TO THE CLINICAL EXPRESSION OF DEMENTIA IN THE OLDEST OLD: A PATHOPHYSIOLOGICAL INSIGHT
SCLEROSI IPPOCAMPALE (HS)

- Substrato anatomico funzionale (gliosi e atrofia ippocampale)
- Substrato di sindrome amnestica negli oldest old con andamento età correlato indipendente da patologia AD
- Sopravvivenza ogni anno oltre I 90 anni conferisce un rischio di sviluppo di HS
- CARTS (cerebral age related TDP-43 with sclerosis (synergistic model for HS aging (ABCC gene variant) and protein misfolding
- Profilo neuropsicologico (indolente: deficit episodico, di fluenza semantica , ridotto recall wordlist)
- BORDER LINE ZONE TRA brain aging, lo spettro di disordini cognitivi correlati a HS e neurodegenerazione cerebrale non AD

Brenowitz Wd et al. J Alzheimer Dis. 2014
Cykowski Md et al. ARchPathol Lab Med 2017

THE SPECTRUM OF BRAIN AGING AND THE TRESHOLD TO THE CLINICAL EXPRESSION OF DEMENTIA IN THE OLDEST OLD: A PATHOPHYSIOLOGICAL INSIGHT
RESILIENZA COGNITIVA

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IOS Press

Cognitive Resilience to Alzheimer's Disease Pathology in the Human Brain

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Handling Associate Editor: Ozioma Okonkwo

Accepted 24 January 2019

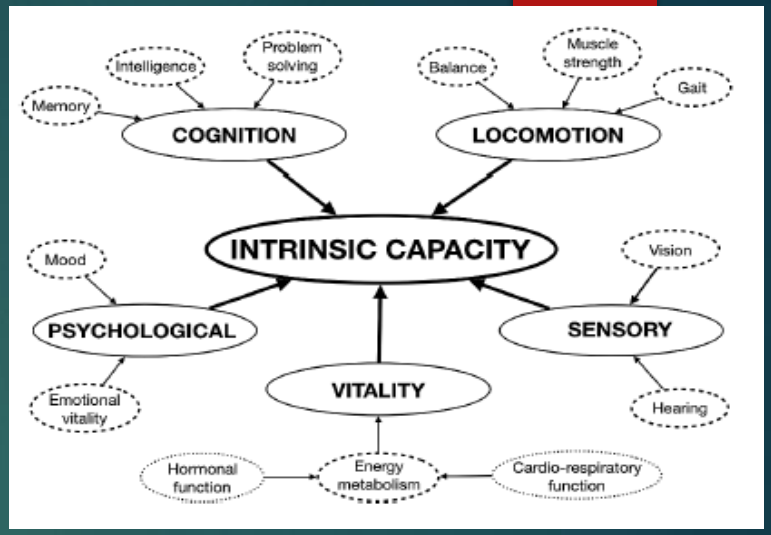
Abstract.
Background: Past research has focused on risk factors for developing dementia, with increasing recognition of "resilient" people who live to old age with intact cognitive function despite pathological features of Alzheimer's disease (AD).
Objective: To evaluate demographic factors, mid-life characteristics, and non-AD neuropathology findings that may be associated with cognitive resilience to AD pathology.
Methods: We analyzed data from 276 autopsy cases with intermediate or high levels of AD pathology from the Adult Changes in Thought study. We defined cognitive resilience as having Cognitive Abilities Screening Instrument scores ≥86 within two years of death and no clinical dementia diagnosis; non-resilient people had dementia diagnoses from AD or other causes before death. We compared mid-life characteristics, demographics, and additional neuropathology findings between resilient and non-resilient people. We used multivariable logistic regression to estimate odds ratios (ORs) with 95% confidence intervals (CIs) for being resilient compared to not being resilient adjusting for demographic and neuropathology factors.
Results: We classified 68 (25%) people as resilient and 208 (75%) as not resilient. A greater proportion of resilient people had a college degree (50%) compared with non-resilient (32%, $p = 0.01$). The odds of being resilient were significantly increased among people with a college education (OR = 2.01, 95% CI = 1.01–3.99) and significantly reduced among people with additional non-AD neuropathology findings such as hippocampal sclerosis (OR = 0.28, 95% CI = 0.09–0.89) and microinfarcts (OR = 0.34, 95% CI = 0.15–0.78).
Conclusion: Increased education and absence of non-AD pathology may be independently associated with cognitive resilience, highlighting the importance of evaluating co-morbid factors in future research on mechanisms of cognitive resilience.

Keywords: Aging, Alzheimer's disease, cognition, dementia, education, neuropathology

THE SPECTRUM OF BRAIN AGING AND THE TRESHOLD TO THE CLINICAL EXPRESSION OF DEMENTIA IN THE OLDEST OLD: A PATHOPHYSIOLOGICAL INSIGHT
RESILIENZA COGNITIVA

- La resilienza cognitiva individuale rappresenta un mediatore del carico neuropatologico cerebrale , modulando la espressività clinica delle demenze nelle età più avanzate
- Intelligenza , coinvolgimento educativo/occupazionale, attività cognitivamente e mentalmente stimolanti, attività ricreative
- La componente del continuous learning over time può conferire il vantaggio protettivo ed aumentando la soglia
- Definizione limitativa che non comprende i multipli livelli attraverso il processo di invecchiamento (resilienza psicologica, variabile socio economica)
- Resilienza cognitiva mostra similarità concettuale con la capacità intrinseca geriatrica

THE SPECTRUM OF BRAIN AGING AND THE TRESHOLD TO THE CLINICAL EXPRESSION OF DEMENTIA IN THE OLDEST OLD: A PATHOPHYSIOLOGICAL INSIGHT RESILIENZA COGNITIVA



RESILIENZA COGNITIVA

- Plasticità neuronale (Volume cerebrale/numero di sinapsi)
- Abilità di reclutare networks cerebrali con capacità di compensazione cerebrale (corteccia prefrontale dorsolaterale destra DFLC: correlazioni metaboliche con corteccia frontotemporale, giro hippocampale, precuneo) in pazienti con AD prodromico ed elevate educazione) Riserva neurale
- EMIF –AD 90+ study sta discriminando i confini tra resilienza cognitiva e demenza nel grande vecchio (marcatori di aging e di neurodegenerazione, social networks, attività fisica, fattori protettivi vascolari)

Il processo di mantenere l'abilità funzionale che permette Il well being attraverso la capacità intrinseca, che include e le abilità fisiche e mentali e l'interazione con l'ambiente

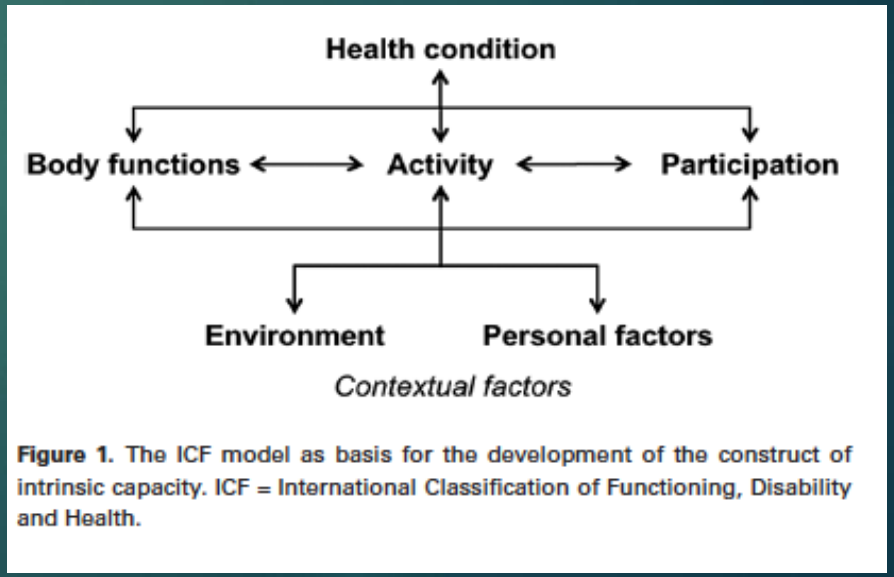


Figure 1. The ICF model as basis for the development of the construct of intrinsic capacity. ICF = International Classification of Functioning, Disability and Health.

Aiello Bowles EJ et al. J Alzheimer Dis 2019
Morbelli S et al. J Nucl Med 2013
Legdeur N et al. BMC geriatr 2018

Cesari M et al. J Gerontol a Biol sci Med Sci 2018

Brain aging, sclerosi ippocampale e resilienza cognitiva

Table 1: The spectrum of brain aging, its clinical entities with related neuroanatomic and neurophysiological main finings

	Definition	**Neuroanatomic and neuropathological features/ alterations**	**Neuropsychological correlates**
Brain aging	Physiological changes in the human brain that generally accompany ageing and occur at molecular, cellular, and tissue levels	- Decreased grey matter volume - Changes in prefrontal and posterior network - Accumulation of cellular waste	- Attentional and executive dysfunction - Affected cognitive flexibility - Age-related memory dysfunction
Hippocampal sclerosis (HS or HS-aging)	Common neuropathological finding that causes a cognitive impairment and may rival AD cognitive deficits.	- Cellular changes in the hippocampus - Brain arteriosclerosis - Chronic vascular dysfunction	- Lowe cognitive impairment - Higher verbal fluency - Low wordlist recall
Cognitive resilience	Mediator of neuropathological burden influenced by educational/occupational attainment, premorbid intelligence quotient, leisure, cognitive and mental stimulating activities that modulates the progression rate to late life dementia	- Brain microinfarcts - Any hippocampal sclerosis - Increased brain weight at death - Metabolic correlations between DLFC and cortical regions in higher educated prodromal AD - Neural reserve to cope better with neurodegeneration	- Loss of cognitive reserve - No aging well - Reduction or loss of all the physical and mental capacities.

Monacelli F et al. J Alzheimer Disease submitted

Traiettoria neurodegenerativa nel grande anziano: espressione di crescente complessità clinica

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BRAIN
A JOURNAL OF NEUROLOGY

REVIEW

Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report

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We describe a recently recognized disease entity, limbic-predominant age-related TDP-43 encephalopathy (LATE). LATE neuropathological change (LATE-NC) is defined by a stereotypical TDP-43 proteinopathy in older adults, with or without coexisting hippocampal sclerosis pathology. LATE-NC is a common TDP-43 proteinopathy, associated with an amnestic dementia syndrome that mimicked Alzheimer's-type dementia in retrospective autopsy studies. LATE is distinguished from frontotemporal lobar degeneration with TDP-43 pathology based on its epidemiology (LATE generally affects older subjects), and relatively restricted neuroanatomical distribution of TDP-43 proteinopathy. In community-based autopsy cohorts, ~25% of brains had sufficient burden of LATE-NC to be associated with discernible cognitive impairment. Many subjects with LATE-NC have comorbid brain pathologies, often including amyloid-β plaques and tauopathy. Given that the 'oldest-old' are at greatest risk for LATE-NC, and subjects of advanced age constitute a rapidly growing demographic group in many countries, LATE has an expanding but under-recognized impact on public health. For these reasons, a working group was convened to develop diagnostic criteria for LATE, aiming both to stimulate research and to promote awareness of this pathway to dementia. We report consensus-based recommendations including guidelines for diagnosis and staging of LATE-NC. For routine autopsy workup of LATE-NC, an anatomically-based preliminary staging scheme is proposed with TDP-43 immunohistochemistry on tissue from three brain areas, reflecting a hierarchical pattern of brain involvement: amygdala, hippocampus, and middle frontal gyrus. LATE-NC appears to affect the medial temporal lobe structures preferentially, but other areas also are impacted. Neuroimaging studies demonstrated that subjects with LATE-NC also had atrophy in the medial temporal lobes, frontal cortex, and other brain regions. Genetic studies have thus far indicated five genes with risk alleles for LATE-NC: *GRN*, *TMEM106B*, *ABCC9*, *KCNMB2*, and *APOE*. The discovery of these genetic risk variants indicate that LATE shares pathogenetic mechanisms with both frontotemporal lobar degeneration and Alzheimer's disease, but also suggests disease-specific underlying mechanisms. Large gaps remain in our understanding of LATE. For advances in prevention, diagnosis, and treatment, there is an urgent need for research focused on LATE, including *in vitro* and animal models. An obstacle to clinical progress is lack of diagnostic tools, such as biofluid or neuroimaging biomarkers, for ante-mortem detection of LATE. Development of a disease biomarker would augment observational studies seeking to further define the risk factors, natural history, and clinical features of LATE, as well as eventual subject recruitment for targeted therapies in clinical trials.

Proteinopatia TDP 43 con o senza compresenza di sclerosi Ippocampale

Comorbilità neuroanatomica per beta amiloide, tauopatia

5 alleli predominanti: GNR, TMEM 106B, ABCC9, KCNMB2. APO E

Registri autoptici : 25% di oldest old presenta un carico cerebrale compatibile con LATE

Box 1 LATE and LATE-NC summary points

LATE-NC features

- A sampling and staging system for routine autopsy diagnosis is proposed to characterize the anatomical distribution of TDP-43 proteinopathy
  - Stage 1: amygdala only
  - Stage 2: + hippocampus
  - Stage 3: + middle frontal gyrus
- Hippocampal sclerosis pathology may be observed (and should be reported), but is neither necessary nor sufficient for diagnosis of LATE-NC

LATE-NC is present in 20% (up to 50%) of individuals past age 80 years according to large community-based autopsy series

LATE is associated with substantial disease-specific cognitive impairment, usually an amnestic dementia syndrome ('dementia of the Alzheimer's type')

The overall public health impact of LATE is on the same order of magnitude as Alzheimer's disease neuropathological changes; the diseases are often comorbid, but which pathology is more severe varies greatly between individuals

Genetic risk factors for LATE have some overlap with FTLD-TDP and with Alzheimer's disease

There is no molecule-specific biomarker for LATE. This is an important area of need for use in clinical trials (including as a potential exclusion criterion for Alzheimer's disease clinical trials) and longitudinal studies of the clinical and pathological progression of LATE

Traiettoria neurodegenerativa nel grande anziano: espressione di crescente complessità clinica

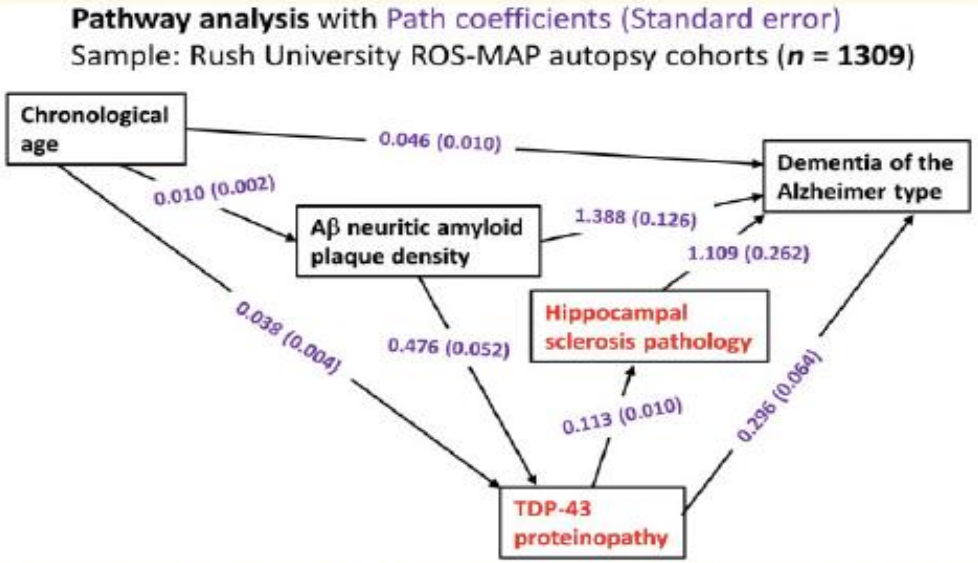

Figure 2 Statistical analyses on data related to LATE from the Rush University community-based autopsy cohort depicting the results of pathway analyses. Data were analysed from research volunteers (total *n* = 1309) in two clinical-pathological studies of ageing from Rush University as described previously (Power *et al.*, 2018). In this sample, the mean age of death was 89.7 years [standard deviation (SD) 6.5 years, range 65–108 years]. These analyses incorporated age, density of amyloid-β neuritic amyloid plaques (to factor in ADNC), TDP-43 proteinopathy, hippocampal sclerosis pathology, and the endpoint of Alzheimer's-type clinical dementia. The components of the pathway analyses most strongly associated with LATE-NC are shown in red. The numbers are path coefficients with standard error in parentheses (shown in purple). These numbers help to quantify the effects of individual pathways. For instance, the data are compatible with there being two pathways from TDP-43 proteinopathy to dementia, one direct pathway (TDP-43 proteinopathy→dementia) and the other indirect pathway that includes hippocampal sclerosis pathology (TDP-43 proteinopathy→hippocampal sclerosis→dementia): in the statistical model, the TDP-43 proteinopathy is independently associated with both hippocampal sclerosis pathology and clinical dementia status. Further, the data indicate that a subset of TDP-43 proteinopathy is 'downstream' of ADNC-type neuritic amyloid plaque pathology. In a practical sense, this means that brains with more neuritic amyloid plaques are more likely to have TDP-43 proteinopathy, with all other known factors being the same. Aβ = amyloid-β.

Traiettoria neurodegenerativa nel grande anziano: espressione di crescente complessità clinica

Acta Neuropathol (2014) 128:755–766
DOI 10.1007/s00401-014-1349-0

CONSENSUS PAPER

Primary age-related tauopathy (PART): a common pathology associated with human aging

John F. Crary · John Q. Trojanowski · Julie A. Schneider · Jose F. Abisambra · Erin L. Abner · Irina Alafuzoff · Steven E. Arnold · Johannes Attems · Thomas G. Beach · Eileen H. Bigio · Nigel J. Cairns · Dennis W. Dickson · Marla Gearing · Lea T. Grinberg · Patrick R. Hof · Bradley T. Hyman · Kurt Jellinger · Gregory A. Jicha · Gabor G. Kovacs · David S. Knopman · Julia Kofler · Walter A. Kukull · Ian R. Mackenzie · Eliezer Masliah · Ann McKee · Thomas J. Montine · Melissa E. Murray · Janna H. Neltner · Ismael Santa-Maria · William W. Seeley · Alberto Serrano-Pozo · Michael L. Shelanski · Thor Stein · Masaki Takao · Dietmar R. Thal · Jonathan B. Toledo · Juan C. Troncoso · Jean Paul Vonsattel · Charles L. White 3rd · Thomas Wisniewski · Randall L. Woltjer · Masahito Yamada · Peter T. Nelson

Received: 24 July 2014 / Revised: 26 September 2014 / Accepted: 28 September 2014 / Published online: 28 October 2014

Abstract We recommend a new term, "primary age-related tauopathy" (PART), to describe a pathology that is commonly observed in the brains of aged individuals. Many autopsy studies have reported brains with neurofibrillary tangles (NFTs) that are indistinguishable from those of Alzheimer's disease (AD), in the absence of amyloid (Aβ) plaques. For these "NFT+/Aβ−" brains, for which formal criteria for AD neuropathologic changes are not met, the NFTs are mostly restricted to structures in the medial temporal lobe, basal forebrain, brainstem, and olfactory areas (bulb and cortex). Symptoms in persons with PART usually range from normal to amnestic cognitive changes, with only a minority exhibiting profound impairment. Because cognitive impairment is often mild, existing clinicopathologic designations, such as "tangle-only dementia" and "tangle-predominant senile dementia", are imprecise and not appropriate for most subjects. PART is almost universally detectable at autopsy among elderly individuals, yet this pathological process cannot be specifically identified pre-mortem at the present time. Improved biomarkers and tau imaging may enable diagnosis of PART in clinical settings in the future. Indeed, recent studies have identified a common biomarker profile consisting of temporal lobe atrophy and tauopathy without evidence of Aβ accumulation. For both researchers and clinicians, a revised nomenclature will raise awareness of this extremely common pathologic change while providing a conceptual foundation for future studies. Prior reports that have elucidated features of the pathologic entity we refer to as PART are discussed, and working neuropathological diagnostic criteria are proposed.

Taupatia senza evidenza di accumulo di beta amiloide (lobo temporale mediale)
Sindrome amnestica indolente

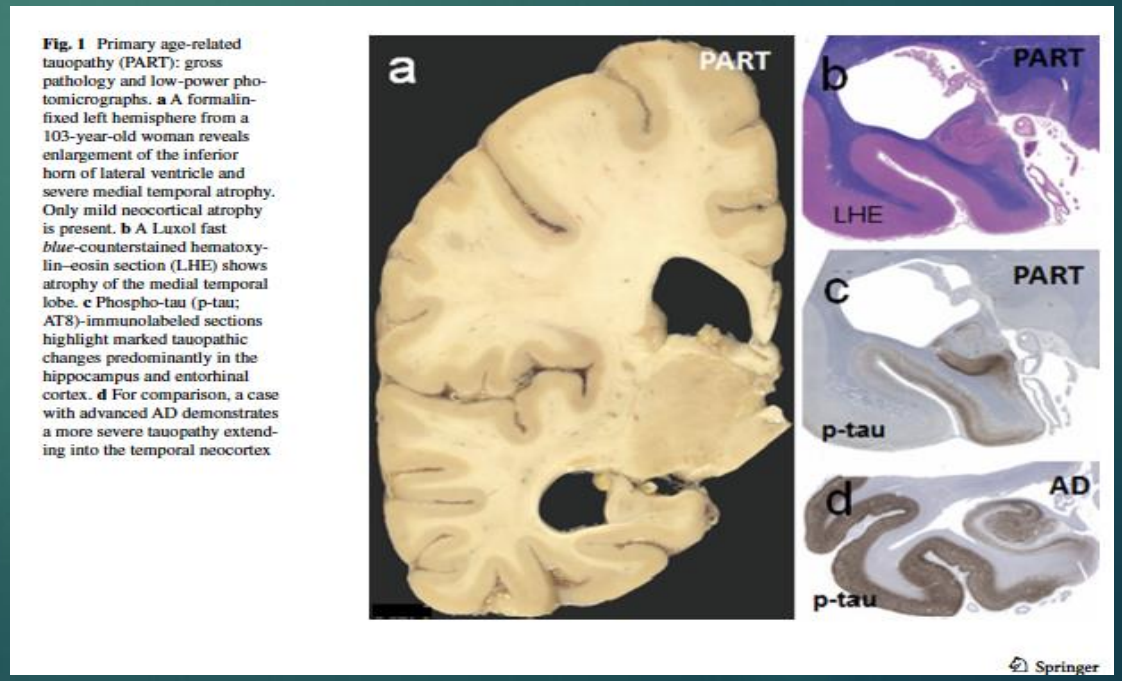

Fig. 1 Primary age-related tauopathy (PART): gross pathology and low-power photomicrographs. **a** A formalin-fixed left hemisphere from a 103-year-old woman reveals enlargement of the inferior horn of lateral ventricle and severe medial temporal atrophy. Only mild neocortical atrophy is present. **b** A Luxol fast *blue*-counterstained hematoxylin–eosin section (LHE) shows atrophy of the medial temporal lobe. **c** Phospho-tau (p-tau; AT8)-immunolabeled sections highlight marked tauopathic changes predominantly in the hippocampus and entorhinal cortex. **d** For comparison, a case with advanced AD demonstrates a more severe tauopathy extending into the temporal neocortex

Fragilità clinica: moderatore della traiettoria neurodegenerativa nel paziente grande anziano

Investigation of frailty as a moderator of the relationship between neuropathology and dementia in Alzheimer's disease: a cross-sectional analysis of data from the Rush Memory and Aging Project

Lindsay M K Wallace, Olga Theou, Judith Godin, Melissa K Andrew, David A Bennett, Kenneth Rockwood

Summary

Background Some people with substantial Alzheimer's disease pathology at autopsy had shown few characteristic clinical symptoms or signs of the disease, whereas others with little Alzheimer's disease pathology have been diagnosed with Alzheimer's dementia. We aimed to examine whether frailty, which is associated with both age and dementia, moderates the relationship between Alzheimer's disease pathology and Alzheimer's dementia.

Methods We did a cross-sectional analysis of data from participants of the Rush Memory and Aging Project, a clinical–pathological cohort study of older adults (older than 59 years) without known dementia at baseline, living in Illinois, USA. Participants in the cohort study underwent annual neuropsychological and clinical evaluations. In the present cross-sectional analysis, we included those participants who did not have any form of dementia or who had Alzheimer's dementia at the time of their last clinical assessment and who had died and for whom complete autopsy data were available. Alzheimer's disease pathology was quantified by a summary measure of neurofibrillary tangles and neuritic and diffuse plaques. Clinical diagnosis of Alzheimer's dementia was based on clinician consensus. Frailty was operationalised retrospectively using health variable information obtained at each clincial evaluation using the deficit accumulation approach (41-item frailty index). Logistic regression and moderation modelling were used to assess relationships between Alzheimer's disease pathology, frailty, and Alzheimer's dementia. All analyses were adjusted for age, sex, and education.

Findings Up to data cutoff (Jan 20, 2017), we included 456 participants (mean age at death 89·7 years [SD 6·1]; 316 [69%] women). 242 (53%) had a diagnosis of possible or probable Alzheimer's dementia at their last clinical assessment. Frailty (odds ratio 1·76, 95% CI 1·54–2·02; p<0·0001) and Alzheimer's disease pathology (4·81, 3·31–7·01; p<0·0001) were independently associated with Alzheimer's dementia, after adjusting for age, sex, and education. When frailty was added to the model for the relationship between Alzheimer's disease pathology and Alzheimer's dementia, model fit improved (p<0·0001). There was a significant interaction between frailty and Alzheimer's disease pathology (odds ratio 0·73, 95% CI 0·57–0·94; $p_{interaction}$=0·015). People with an increased frailty score had a weakened direct link between Alzheimer's disease pathology and Alzheimer's dementia; that is, people with a low amount of frailty were better able to tolerate Alzheimer's disease pathology, whereas those with higher amounts of frailty were more likely both to have more Alzheimer's disease pathology and for it to be expressed as dementia.

Interpretation The degree of frailty among people of the same age modifies the association between Alzheimer's disease pathology and Alzheimer's dementia. That frailty is related to both odds of Alzheimer's dementia and disease expression has implications for clinical management, since individuals with even a low level of Alzheimer's disease pathology might be at risk for dementia if they have high amounts of frailty. Further research should assess how frailty and cognition change over time to better elucidate this complex relationship.

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Research in context

Evidence before this study

Using the terms "neuropathology", "frailty", "dementia", and "Alzheimer's disease" and their synonyms, which have been published previously, we searched Google Scholar and PubMed for articles published between Jan 29, 2017, and July 3, 2018, in English or French. We found that no pathophysiological mechanism has yet been able to account for: (1) the weak relationship between Alzheimer's disease pathology and dementia (ie, Alzheimer's disease pathology does not seem to be necessary or sufficient to cause dementia symptoms); (2) the high prevalence of mixed dementia; (3) and the many, diverse genetic and environmental risk factors that have been associated with Alzheimer's disease.

Added value of this study

This study shows that the relationship between Alzheimer's disease pathology and dementia changes over levels of frailty, such that as frailty increases, the pathology–dementia relationship weakens. These findings suggest that frailty plays a key role in the natural history of Alzheimer's disease.

Implications of all the available evidence

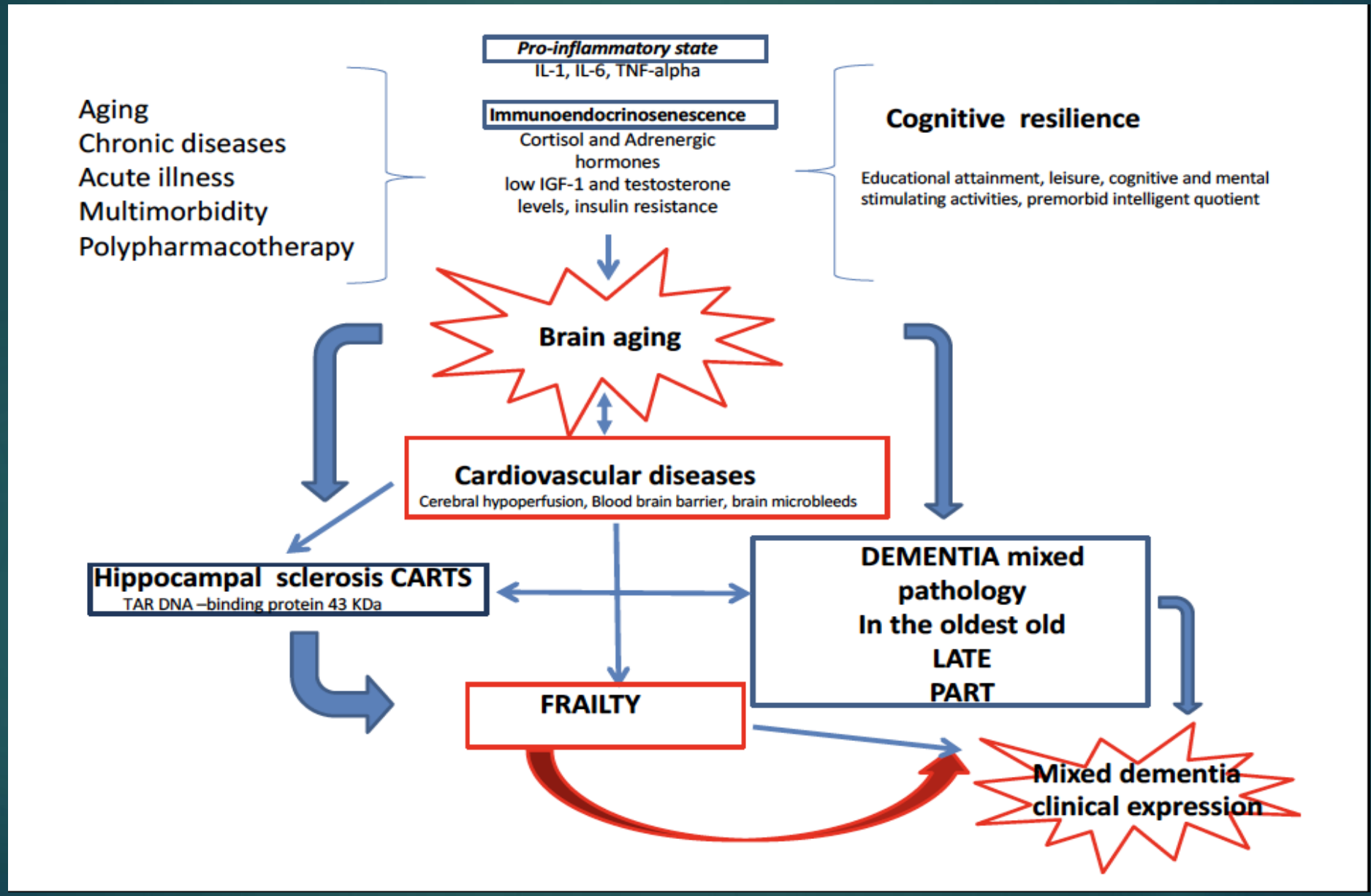
The expression of dementia symptoms results from several causes, particularly in people who are most likely to develop dementia: those who are older and who have several comorbidities. These causes are unlikely to be explained by a single mechanism. Our hypothesis follows an emerging concept of dementia, and particularly Alzheimer's disease dementia, as a complex disease of ageing, rather than a single disease entity marked by genetic risk or a particular protein abnormality. In a specialty with so many competing claims about individual risk factors, understanding how they work together to give rise to clinical dementia is likely to offer a new way to advance the epidemiological study of dementia and the development of targeted treatment options.

	All (n=456)	Frailty index <0·41 (n=233)	Frailty index ≥0·41 (n=223)	p value*
Age at baseline, years	83·1 (5·9)	82·1 (5·8)	84·2 (5·8)	<0·0001
Age at death, years	89·7 (6·1)	88·3 (6·2)	91·2 (5·6)	<0·0001
Sex				
Male	140 (31%)	83 (36%)	57 (26%)	0·020
Female	316 (69%)	150 (64%)	166 (74%)	..
Years of education	14·4 (2·9)	14·5 (3·0)	14·3 (2·9)	0·45
Frailty index at last assessment before death	0·42 (0·18)	0·28 (0·09)	0·58 (0·10)	<0·0001
Alzheimer's disease dementia diagnosed before death	242 (53%)	79 (34%)	163 (73%)	<0·0001
MMSE at last assessment before death	19·8 (9·8)	23·4 (8·2)	16·1 (10·0)	<0·0001
Braak stage	3·7 (1·2)	3·4 (1·2)	3·9 (1·1)	<0·0001
APOE genotype (≥1 ε4 alleles)	106 (23%)	48 (21%)	58 (26%)	0·35
10-item CES-D	2·0 (2·2)	1·4 (1·8)	2·6 (2·5)	<0·0001
Number of medications	1·9 (1·1)	1·7 (1·1)	2·0 (1·2)	0·002

Data are mean (SD) or number (%). CES-D=Center for Epidemiologic Studies Depression Scale. MMSE=Mini-Mental State Examination. *For the difference between frailty groups.

Table 1: **Descriptive characteristics of the study cohort**

DEMENZE NEL GRANDE VECCHIO E COMPLESSITA' CLINICA



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Review

Aging without Dementia is Achievable: Current Evidence from Epidemiological Research

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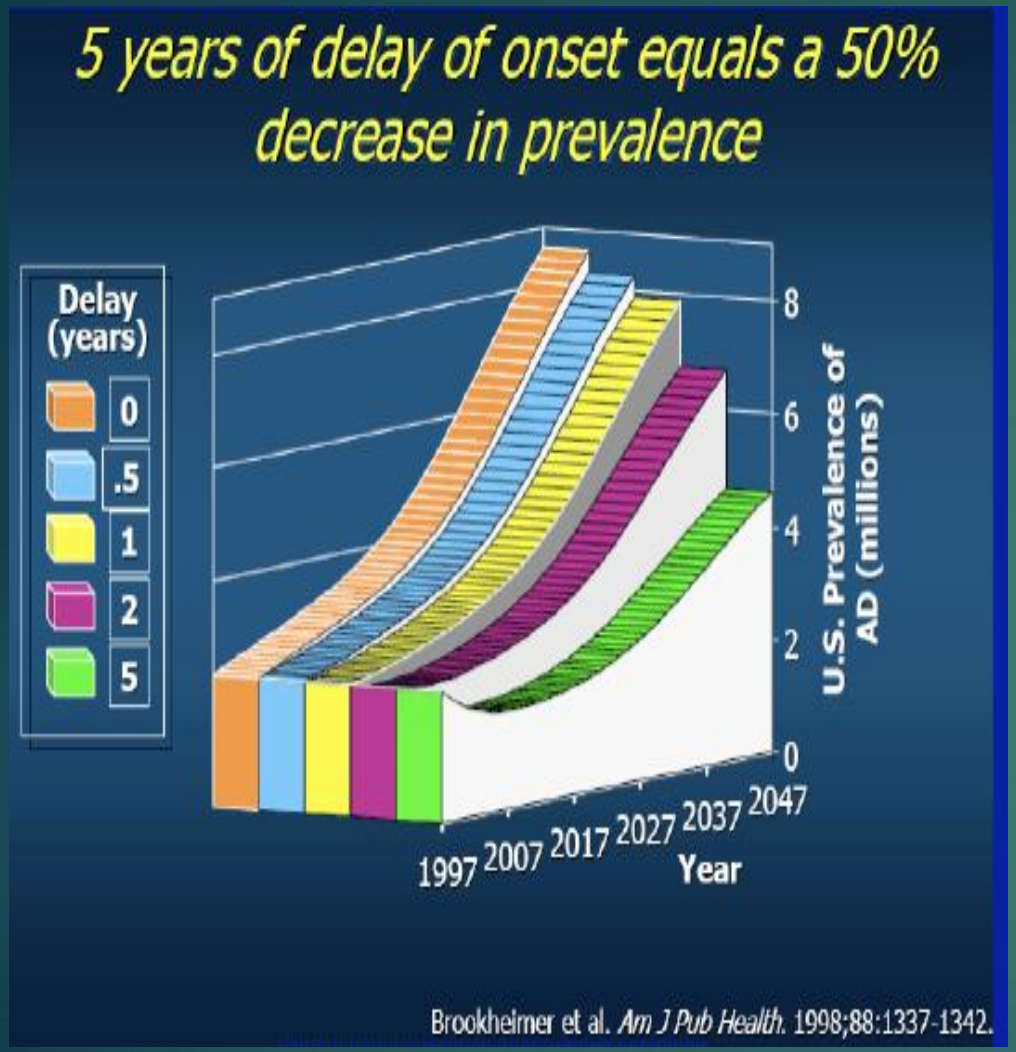
Abstract. Both the incidence and the prevalence of dementia increase exponentially with increasing age. This raises the question of whether dementia is an inevitable consequence of aging or whether aging without dementia is achievable. In this review article, we sought to summarize the current evidence from epidemiological and neuropathological studies that investigated this topic. Epidemiological studies have shown that dementia could be avoided even at extreme old ages (e.g., centenarians or supercentenarians). Furthermore, clinico-neuropathological studies found that nearly half of centenarians with dementia did not have sufficient brain pathology to explain their cognitive symptoms, while intermediate-to-high Alzheimer pathology was present in around one-third of very old people without dementia or cognitive impairment. This suggests that certain compensatory mechanisms (e.g., cognitive reserve or resilience) may play a role in helping people in extreme old ages escape dementia syndrome. Finally, evidence has been accumulating in recent years indicating that the incidence of dementia has declined in Europe and North America, which supports the view that the risk of dementia in late life is modifiable. Evidence has emerged that intervention strategies that promote general health, maintain vascular health, and increase cognitive reserve are likely to help preserve cognitive function till late life, thus achieving the goal of aging without dementia.

Keywords: Aging, Alzheimer's disease, centenarians, dementia, epidemiology, interventions

Table 2
Key findings from major population-based studies on time trends in prevalence of dementia

Authors (country)	Study population and study periods	Diagnostic criteria	Trends in prevalence
North America			
Hall et al. (Indiana, US) [32]	Indianapolis-Ibadan Dementia Project, age ≥65, 1992 to 2001	Dementia: ICD-10	Stable (African-Americans)
Kosteniuk et al. (Saskatchewan, Canada) [33]	Age ≥45, 2005–2006 to 2012–2013, annual prevalence	Dementia: Medical records (ICD-9, 10)	Increased
Langa et al. (US) [34]	US Health and Retirement Study, age ≥65, 2000 to 2012	Dementia: validated self-report	Decreased
Europe			
Lobo et al. (Zaragoza, Spain) [35]	Zaragoza Study, age ≥65, 1988–1989 to 1994–1996	Dementia: DSM-IV	Overall stable; decreased in men
Qiu et al. (Stockholm, Sweden) [36]	Kungsholmen Projects, age ≥75, 1987–1989 to 2001–2004	Dementia: DSM-III-R	Stable
Wiberg et al. (Gothenburg, Sweden) [37]	Gothenburg Study, age 70, 1976–1977 to 2000–2001	Dementia: DSM-III-R	Stable
Matthews et al. (England, UK) [38]	CFAS, age ≥65, 1989–1994 to 2008–2011	Dementia: Geriatric Mental State Scale	Decreased
Wimo et al. (Nordanstig, Sweden) [39]	Nordanstig Projects, age ≥78, 1995–1998 to 2001–2003	Dementia: DSM-III-R	Decreased (north rural areas)
Doblhammer et al. (Germany) [40]	Health insurance claims database, age ≥65, 2007–2009	Dementia, ICD-10	Decreased, mainly in women
Pérès et al. (Bordeaux, France) [41]	PAQUID, age ≥65, 1988–1989 to 2007–2008	Dementia: Clinical: DSM-III-R Algorithm	Clinical diagnosis: increased Algorithm-based diagnosis: decreased
Ahmadi-Abhari et al. (England and Wales, UK) [42]	English Longitudinal Study of Ageing, age ≥50, 2002 to 2013	Dementia: DSM-IV	Decreased
Skoog et al. (Gothenburg, Sweden) [43]	Gothenburg 85-year-old study, age 85, 1986–1987 to 2008–2010	Dementia: DSM-III-R	Decreased
Asia			
Li et al. (Beijing, China) [44]	Urban residents, age ≥60, 1986 to 1997, 2 waves	Dementia: ICD-10, DSM-IV	Increased
Yu et al. (Hong Kong, China) [45]	Systematic review, age ≥70, 1995–2006	Dementia: ICD-9, 10	Increased
Chan et al. (Mainland China) [46]	Systematic review, age ≥55, 1990 to 2010	Dementia and AD: various criteria	Increased
Kim et al. (Korea) [47]	Systematic review, age ≥60, 1990 to 2013	Dementia, AD: various criteria	Increased slightly, especially AD
Ohara et al. (Hisayama, Japan) [48]	Hisayama Study, age ≥65, from 1985, 1992, 1998 and 2005 to 2012	Dementia: DSM-III-R	Increased

AD, Alzheimer's disease; ICD, International Classification of Diseases; DSM, Diagnostic and Statistical Manual of Mental Disorders; CFAS, Cognitive Function and Ageing Studies.



The preventative way:
interventions to delay dementia

Controllo dei fattori di rischio cardiovascolare
Controllo abitudini voluttuarie
Healthy aging
Aumentare la resilienza cognitiva

Epidemiological data show that dementia could be avoided even at extreme old ages (e.g., among centenarians or supercentenarians). This implies that people are able to reach very advanced ages without experiencing severe mental deterioration. Further, clinico-neuropathological studies of centenarians and even older people found that nearly half of those with dementia did not have sufficient brain neuropathology to explain their cognitive symptoms, while intermediate-to-high Alzheimer pathologies were present in around one-third of very old people without dementia or cognitive impairment. This suggests that certain compensatory mechanisms (e.g., cognitive reserve or cognitive resilience) may play a part in helping people escape the dementia syndrome in extreme old age. Finally, recent evidence of a declining incidence of dementia in Europe and

North America suggests that the risk of late-life dementia is modifiable. This supports the potential that intervention strategies that aim to promote general health, maintain vascular health, and increase cognitive reserve may indeed help achieve a life without dementia.

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Thank you for your attention