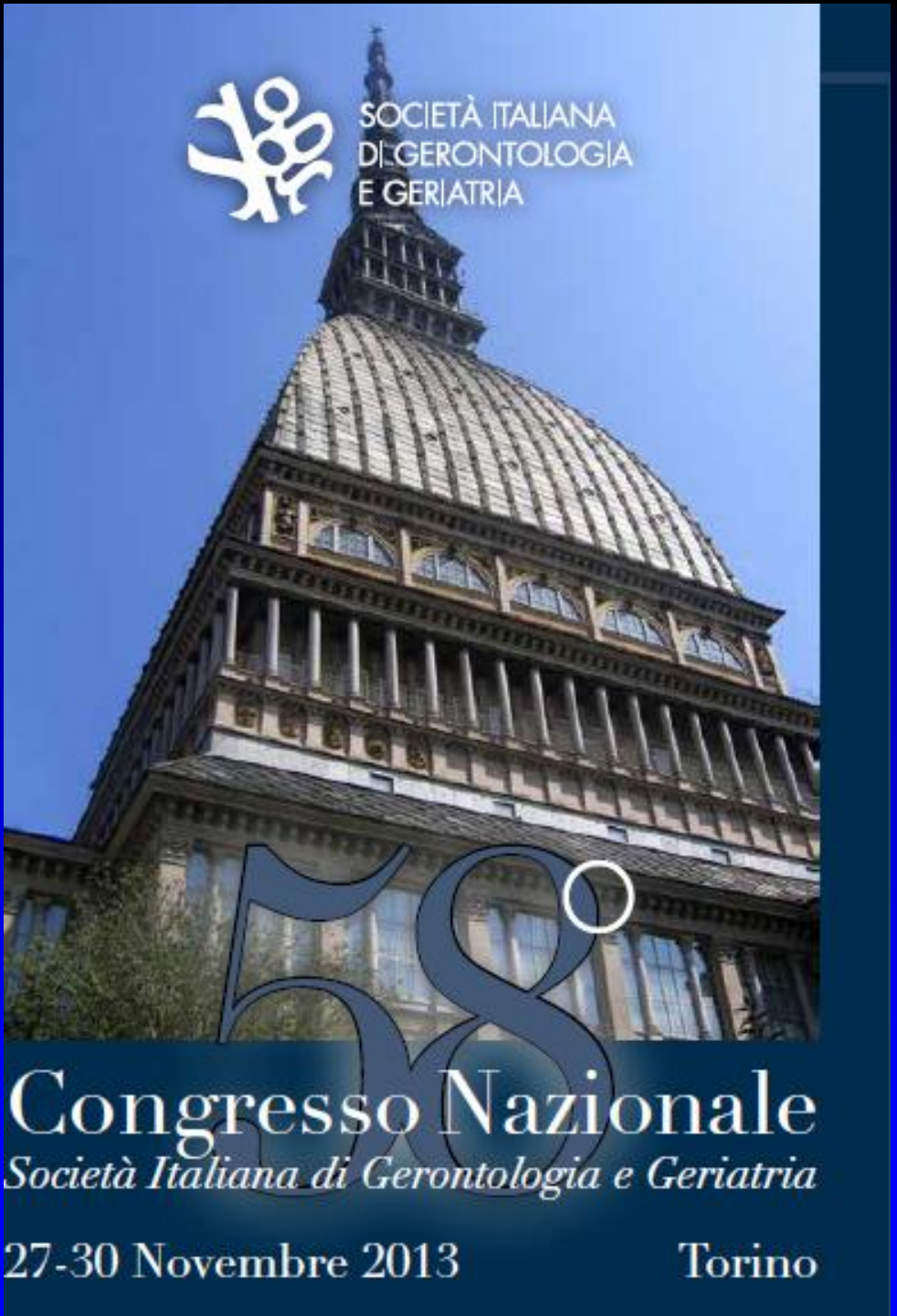

Simposio

TERAPIA E QUALITÀ DI VITA NELLE DIVERSE FASI DELLA MALATTIA DI ALZHEIMER

Prospettive future del trattamento dell'AD

Angelo Bianchetti

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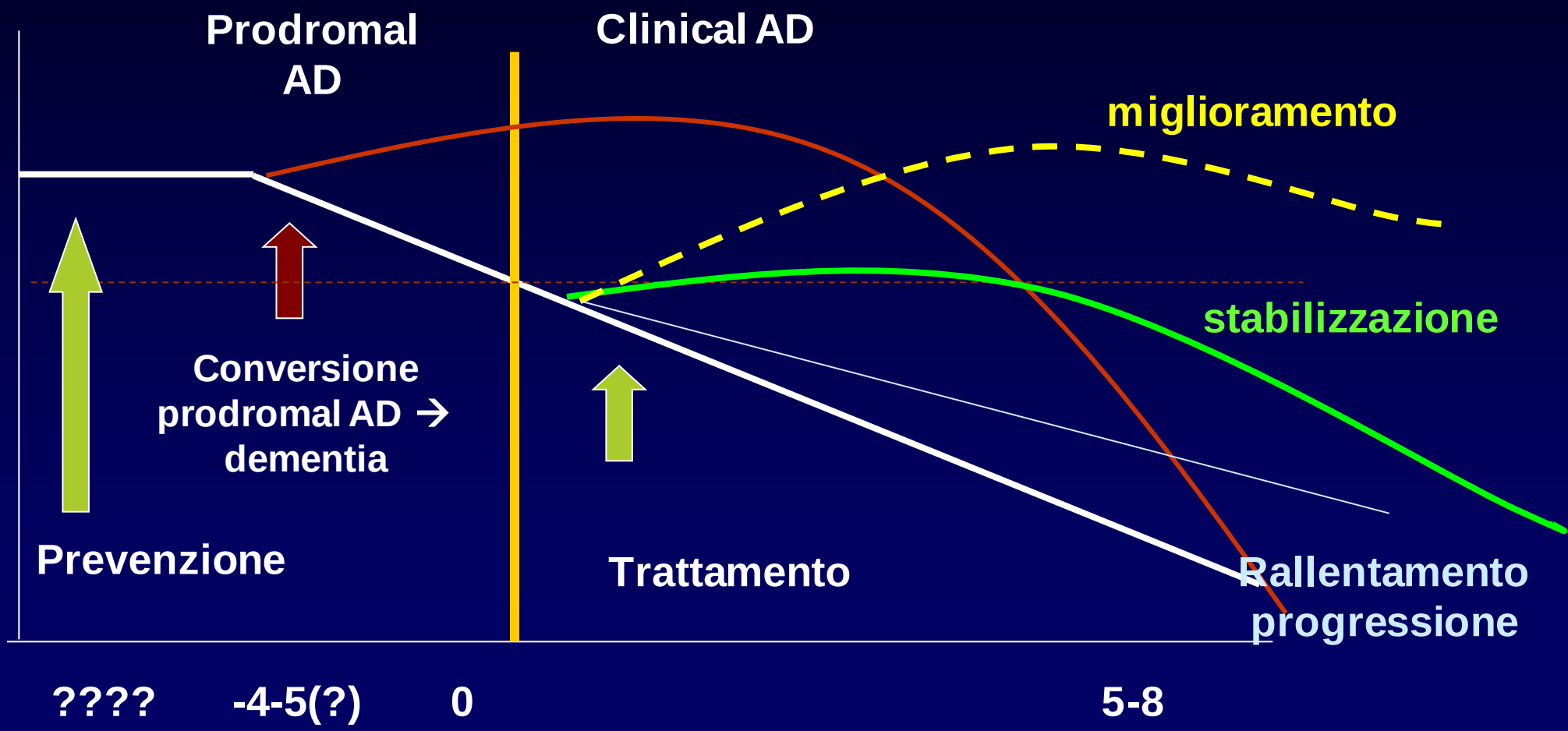
Scuola di Specializzazione in Geriatria, Università degli Studi di Brescia

Quali outcome per la Malattia di Alzheimer



Perspective

New Insights into the Dementia Epidemic

Eric B. Larson, M.D., M.P.H., Kristine Yaffe, M.D., and Kenneth M. Langa, M.D., Ph.D.

November 27, 2013 | DOI: 10.1056/NEJMp1311405

Selected Recent Studies of the Dementia Epidemic.

Study	Outcome	Data Source	Key Findings	Factors
Manton et al. (United States)[1]	Prevalence of severe cognitive impairment	National long-term care survey interviews, 1982–1999	Decline in dementia prevalence among people ≥65 yr of age (5.7% to 2.9%)	Higher educational level, decline in stroke incidence
Langa et al. (United States)[2]	Prevalence of cognitive impairment	Ongoing population-based survey of people ≥51 yr of age	Prevalence of cognitive impairment among people ≥70 yr of age (12.2% in 1993 vs. 8.7% in 2002)	Higher educational level; combination of medical, lifestyle, demographic, and social factors
Schrijvers et al. (Rotterdam)[3]	Incidence of dementia	Population-based cohort ≥55 yr of age in 1990, extended in 2000	Incidence rate ratios (6.56 per 1000 person-yr in 1990 vs. 4.92 per 1000 person-yr in 2000)	Higher educational level, reduction in vascular risk, decline in stroke incidence
Qiu et al. (Stockholm)[4]	Prevalence of DSM-III-R dementia*	Cross-sectional survey of people ≥75 yr of age, 1987–1989 and 2001–2004	Age- and sex-standardized dementia prevalence (17.5% in 1987–1989 vs. 17.9% in 2001–2004); lower hazard ratio for death in later cohort suggests decreased dementia incidence	Favorable changes in risk factors, especially vascular risk; healthier lifestyles
Matthews et al. (England)[5]†	Prevalence of dementia in 3 regions	Survey interviews of people ≥65 yr of age, 1989–1994 (in CFAS I) and 2008–2011 (in CFAS II)	Dementia prevalence (8.3% in CFAS I vs. 6.5% in CFAS II)	Higher educational level, better prevention of vascular disease

* In the study by Qiu et al., dementia was diagnosed according to the criteria provided in the *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised (DSM-III-R).

† CFAS denotes Cognitive Function and Ageing Study.

Physical and cognitive functioning of people older than 90 years: a comparison of two Danish cohorts born 10 years apart

www.thelancet.com **Published online July 11, 2013**

Kaare Christensen, Mikael Thinggaard, Anna Oksuzyan, Troels Steenstrup, Karen Andersen-Ranberg, Bernard Jeune, Matt McGue, James W Vaupel

	Both sexes			Men			Women		
	1905 cohort (n=1814)	1915 cohort (n=1247)	p value	1905 cohort (n=494)	1915 cohort (n=336)	p value	1905 cohort (n=1320)	1915 cohort (n=911)	p value
Cognitive composite score									
Mean (SD)	0·01 (3·6)	0·49 (3·6)	0·0003*	0·12 (3·6)	0·76 (3·6)	0·012*	−0·03 (3·6)	0·38 (3·6)	0·008*
Median (IQR)	0·05 (−2·25 to 2·26)	0·30 (−1·93 to 2·69)		0·09 (−2·23 to 2·30)	0·55 (−1·69 to 3·06)		0·05 (−2·25 to 2·24)	0·15 (−1·98 to 2·62)	..
Mini-mental state examination results									
Mean (SD)	21·4 (6·0)	22·8 (5·6)	<0·0001‡						
Median (IQR)	23·0 (18·0–26·0)	24·0 (19·0–27·0)							
Missing data, n (%)	16 (1%)	24 (2%)	0·015†						
Grouped results, n (%)§			<0·0001†						
0–17 (severe impairment)	400 (22%)	209 (17%)							
18–22 (mild impairment)	458 (25%)	281 (23%)							
23–27 (normal)	705 (39%)	456 (37%)							
28–30 (maximum)	235 (13%)	277 (23%)							

variance (test of equal variance is rejected). §Missing data are excluded from the totals for percentage calculations. ¶Grouped by dividing the total distribution into quartiles.

Table 2: **Cognitive measures and depression symptomatology for the 1905 and 1915 cohorts (in-person participants only)**

Alzheimer disease in the United States (2010–2050) estimated using the 2010 census

Figure 1 Estimated number of people with Alzheimer disease (AD) in the United States in 2010 and projections through 2050

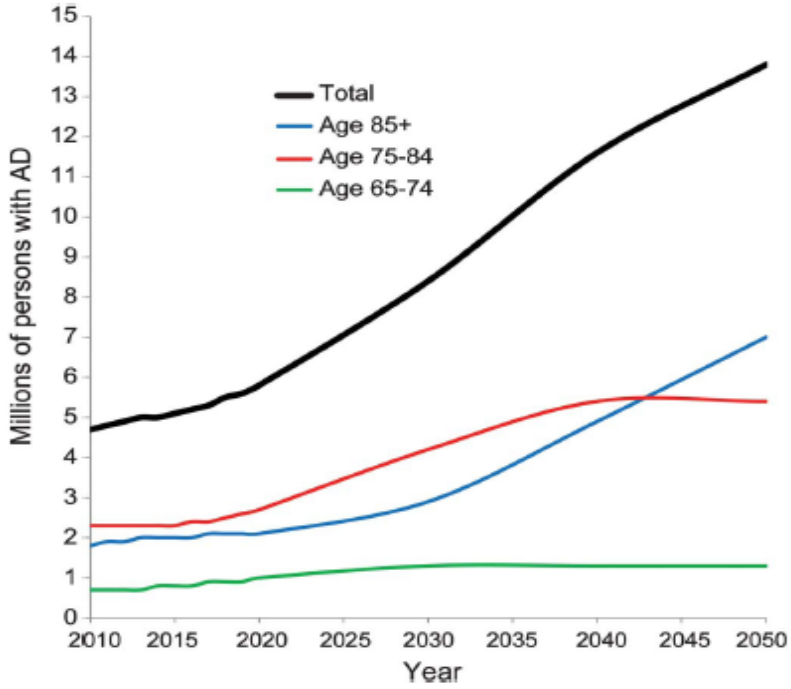
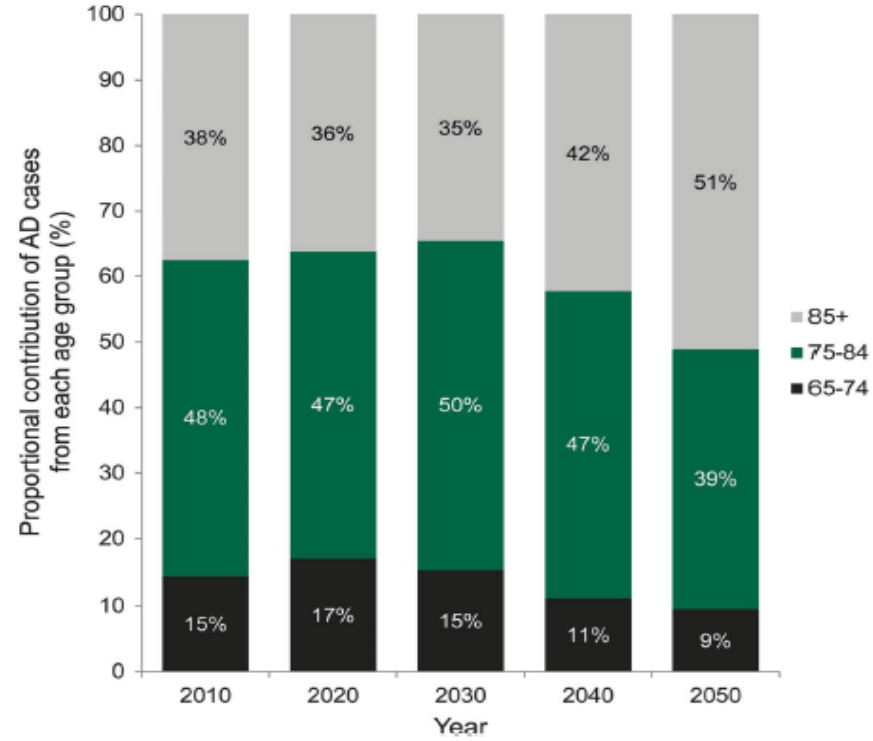


Figure 2 Age distribution of number of persons with Alzheimer disease (AD) in the United States, 2010 through 2050



Hebert LE, Weuve J, Scherr PA, Evans DA. Neurology. 2013 May 7;80(19):1778-83

Perspective

New Insights into the Dementia Epidemic

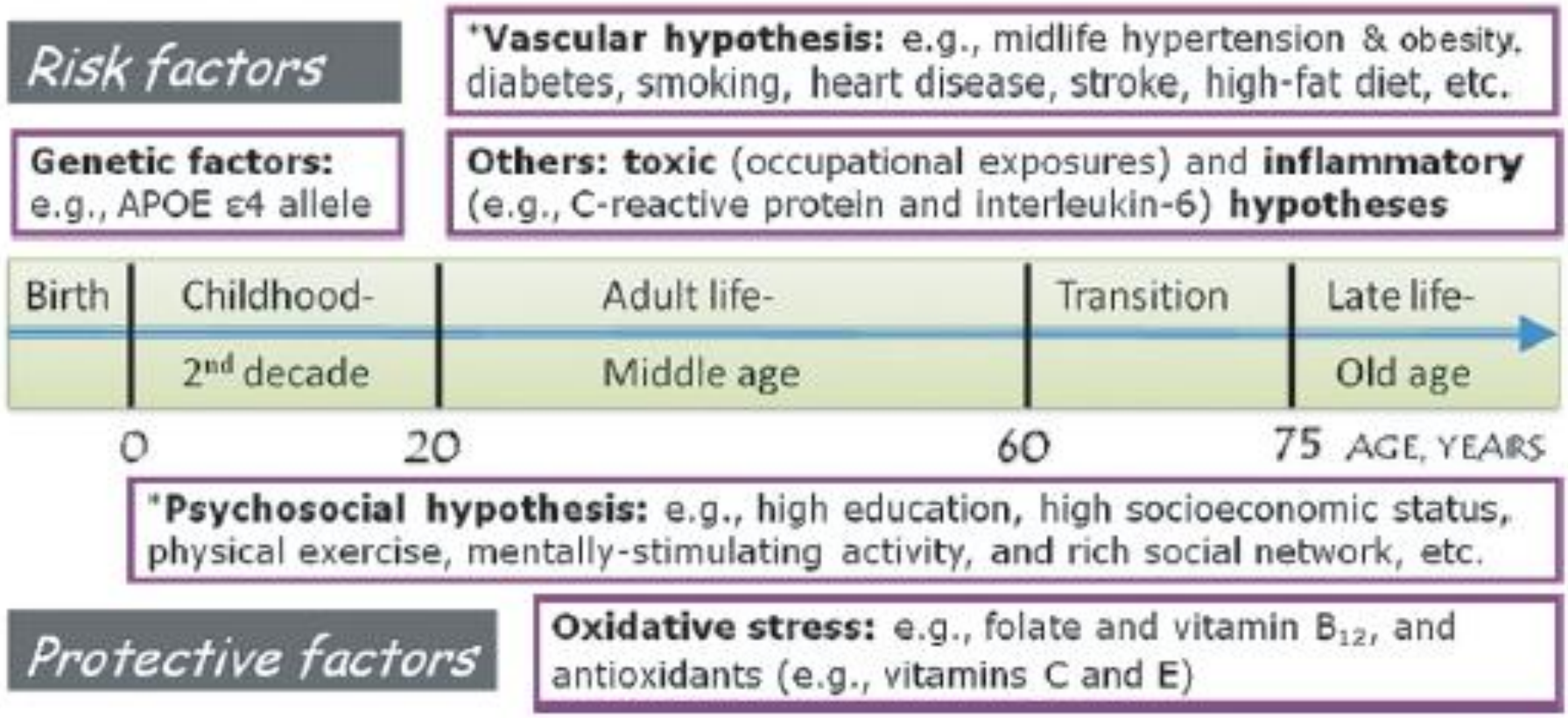
Eric B. Larson, M.D., M.P.H., Kristine Yaffe, M.D., and Kenneth M. Langa, M.D., Ph.D.

November 27, 2013 | DOI: 10.1056/NEJMp1311405

Although demographics will drive an increase in the number of dementia cases, recent reports — generally based on population-based community studies or survey data — point to declining age-specific prevalence or incidence rates among people born later in the first half of the 20th century.

We believe these reports are intriguing and inform our understanding of potentially modifiable factors that contribute to the epidemic of this common and often tragic condition.

Knowing about contributing factors is especially important for the study and development of prevention strategies, and prevention is often the key to better control of epidemics, including epidemics of chronic diseases.



Qiu, Xu and Fratiglioni, JAD, 2010

ONLINE FIRST

Blood Pressure and Progression of Brain Atrophy

The SMART-MR Study

Hadassa M. Jochemsen, MD; Majon Muller, MD, PhD; Frank L. Visseren, MD, PhD; Philip Scheltens, MD, PhD; Koen L. Vincken, PhD; Willem P. Mali, MD, PhD; Yolanda van der Graaf, MD, PhD; Mirjam I. Geerlings, PhD; for the SMART Study Group

Importance: Studies have shown that both high and low blood pressure (BP) may play a role in the etiology of brain atrophy. High BP in midlife has been associated with more brain atrophy later in life, whereas studies in older populations have shown a relation between low BP and more brain atrophy. Yet, prospective evidence is limited, and the relation remains unclear in patients with manifest arterial disease.

Objective: To examine the associations of baseline BP and change in BP over time with progression of brain atrophy.

Design: The Secondary Manifestations of ARTerial disease–Magnetic Resonance (SMART-MR) Study is a prospective cohort study with baseline measurements in 2001-2005 and follow-up measurements in 2006-2009. The mean follow-up time was 3.9 years.

Setting: University Medical Center Utrecht, the Netherlands.

Participants: A total of 663 patients (mean [SD] age, 57 [9] years; 81% male) with coronary artery disease, cerebrovascular disease, peripheral artery disease, or abdominal aortic aneurysm were included.

Main Outcomes and Measures: Using automated segmentation at baseline and follow-up, change in brain parenchymal fraction, cortical gray matter fraction, and ventricular fraction (%ICV) were quantified as indicators of progression of global, cortical, and subcortical brain atrophy.

Results: Multivariable adjusted regression analysis showed that patients with lower baseline diastolic BP (DBP) or mean arterial pressure had more progression of subcortical atrophy. The mean differences in the change in ventricular fraction between low and high DBP was 0.07% (95% CI, 0.01-0.14) and between low and high mean arterial pressure was 0.05% (95% CI, 0.00-0.10). Furthermore, in patients with higher baseline BP (DBP, mean arterial pressure, or systolic BP), those with declining BP levels over time had less progression of subcortical atrophy compared with those with rising BP levels.

Conclusions and Relevance: In patients with manifest arterial disease, low baseline DBP was associated with more progression of subcortical atrophy, irrespective of the BP course during follow-up. Furthermore, in patients with higher baseline BP, declining BP levels over time were associated with less progression of subcortical atrophy. This could imply that BP lowering is beneficial in patients with higher BP levels, but caution should be taken with further BP lowering in patients who already have a low DBP.

JAMA Neurol. Published online June 10, 2013.
doi:10.1001/jamaneurol.2013.217

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Glucose Levels and Risk of Dementia

Paul K. Crane, M.D., M.P.H., Rod Walker, M.S., Rebecca A. Hubbard, Ph.D., Ge Li, M.D., Ph.D., David M. Nathan, M.D., Hui Zheng, Ph.D., Sebastien Haneuse, Ph.D., Suzanne Craft, Ph.D., Thomas J. Montine, M.D., Ph.D., Steven E. Kahn, M.B., Ch.B., Wayne McCormick, M.D., M.P.H., Susan M. McCurry, Ph.D., James D. Bowen, M.D., and Eric B. Larson, M.D., M.P.H.

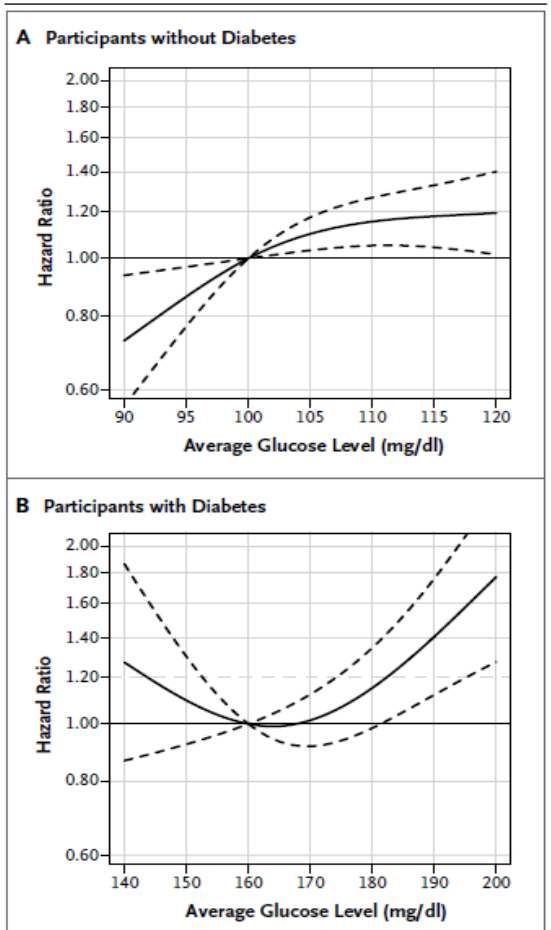


Figure 1. Risk of Incident Dementia Associated with the Average Glucose Level during the Preceding 5 Years, According to the Presence or Absence of Diabetes.

ABSTRACT

BACKGROUND

Diabetes is a risk factor for dementia. It is unknown whether higher glucose levels increase the risk of dementia in people without diabetes.

METHODS

We used 35,264 clinical measurements of glucose levels and 10,208 measurements of glycated hemoglobin levels from 2067 participants without dementia to examine the relationship between glucose levels and the risk of dementia. Participants were from the Adult Changes in Thought study and included 839 men and 1228 women whose mean age at baseline was 76 years; 232 participants had diabetes, and 1835 did not. We fit Cox regression models, stratified according to diabetes status and adjusted for age, sex, study cohort, educational level, level of exercise, blood pressure, and status with respect to coronary and cerebrovascular diseases, atrial fibrillation, smoking, and treatment for hypertension.

RESULTS

During a median follow-up of 6.8 years, dementia developed in 524 participants (74 with diabetes and 450 without). Among participants without diabetes, higher average glucose levels within the preceding 5 years were related to an increased risk of dementia (P=0.01); with a glucose level of 115 mg per deciliter (6.4 mmol per liter) as compared with 100 mg per deciliter (5.5 mmol per liter), the adjusted hazard ratio for dementia was 1.18 (95% confidence interval [CI], 1.04 to 1.33). Among participants with diabetes, higher average glucose levels were also related to an increased risk of dementia (P=0.002); with a glucose level of 190 mg per deciliter (10.5 mmol per liter) as compared with 160 mg per deciliter (8.9 mmol per liter), the adjusted hazard ratio was 1.40 (95% CI, 1.12 to 1.76).

CONCLUSIONS

Our results suggest that higher glucose levels may be a risk factor for dementia, even among persons without diabetes. (Funded by the National Institutes of Health.)

I fattori nutrizionali influenzano il rischio di AD/demenza, la progressione dell'AD/demenza e le prestazioni cognitive anche in soggetti non dementi

- **Dati epidemiologici**:
  - un elevato consumo di frutta e vegetali riduce del 38% il rischio di sviluppare demenza in uno studio osservazionale di 7 anni *(Ritchie et al, BMJ 2010)*
  - una elevata assunzione di vitamina C e vitamina E è associata ad un rischio più basso di sviluppare malattia di Alzheimer (82%) *(Engelhart et al, JAMA 2002)*
  - una dieta ricca di insalata, noci, pesce, pomodori, pollame, verdura, frutta e ortaggi a foglia verde si associa a una riduzione del rischio di sviluppare malattia di Alzheimer del 48% *(Gu et al, Arch Neurol. 2010)*
  - Una dieta "mediterranea" riduce il rischio di sviluppare AD e MCI *(Scarmeas et al, Ann Neurol 2006; Scarmeas et al, Arch Neurol 2009)*

I fattori nutrizionali influenzano il rischio di AD/demenza, la progressione dell'AD/demenza e le prestazioni cognitive anche in soggetti non dementi

- **Dati clinici**
  - In soggetti anziani sani, elevati livelli plasmatici di vitamine del gruppo B (B1, B2, B6, folati, B12), C, D, e E, e di acidi grassi ω-3 si associano a migliori prestazioni cognitive e minore atrofia cerebrale alla RMN *(Bowman GL et al Neurology 2012)*
  - In soggetti sedentari, ipertesi e in sovrappeso, una dieta ipocalorica, povera di sodio, ricca di potassio, calcio e magnesio, di frutta e vegetali, a basso contenuto di grassi animali, ricca di fibre, si associa a miglioramento delle prestazioni cognitive. *(Smith PJ et al, Hypertension 2010)*
  - Una dieta ricca di cibi ad elevata capacità antiossidante (olio di oliva, noci) si associa a migliori prestazioni cognitive mnesiche;. associazione indipendente fra escrezione urinaria di polifenoli e prestazioni mnesiche. *(Valls-Pedret et al, JAD 2012)*

ORIGINAL CONTRIBUTION

ONLINE FIRST

Effect of Apolipoprotein E Genotype and Diet on Apolipoprotein E Lipidation and Amyloid Peptides

Randomized Clinical Trial

Angela J. Hanson, MD; Jennifer L. Bayer-Carter, PhD; Pattie S. Green, PhD; Thomas J. Montine, MD, PhD; Charles W. Wilkinson, PhD; Laura D. Baker, PhD; G. Stennis Watson, PhD; Laura M. Bonner, PhD; Maureen Callaghan, MD; James B. Leverenz, MD; Elaine Tsai, MD; Nadia Postupna, PhD; Jing Zhang, PhD; Johanna Lampe, PhD; Suzanne Craft, PhD

Importance: Sporadic Alzheimer disease (AD) is caused in part by decreased clearance of the β-amyloid (Aβ) peptide breakdown products. Lipid-depleted (LD) apolipoproteins are less effective at binding and clearing Aβ, and LD Aβ peptides are more toxic to neurons. However, not much is known about the lipid states of these proteins in human cerebrospinal fluid.

Objective: To characterize the lipidation states of Aβ peptides and apolipoprotein E in the cerebrospinal fluid in adults with respect to cognitive diagnosis and *APOE* ε4 allele carrier status and after a dietary intervention.

Design: Randomized clinical trial.

Setting: Veterans Affairs Medical Center clinical research unit.

Participants: Twenty older adults with normal cognition (mean [SD] age, 69 [7] years) and 27 with amnestic mild cognitive impairment (67 [6] years).

Interventions: Randomization to a diet high in saturated fat content and with a high glycemic index (High diet; 45% of energy from fat [>25% saturated fat], 35%-40% from carbohydrates with a mean glycemic index >70, and 15%-20% from protein) or a diet low in saturated fat content and with a low glycemic index (Low diet; 25% of energy from fat [<7% saturated fat], 55%-60% from carbohydrates with a mean glycemic index <55, and 15%-20% from protein).

Main Outcomes and Measures: Lipid-depleted Aβ42 and Aβ40 and apolipoprotein E in cerebrospinal fluid.

Results: Baseline levels of LD Aβ were greater for adults with mild cognitive impairment compared with adults with normal cognition (LD Aβ42, $P=.05$; LD Aβ40, $P=.01$). These findings were magnified in adults with mild cognitive impairment and the ε4 allele, who had higher LD apolipoprotein E levels irrespective of cognitive diagnosis ($P<.001$). The Low diet tended to decrease LD Aβ levels, whereas the High diet increased these fractions (LD Aβ42, $P=.01$; LD Aβ40, $P=.15$). Changes in LD Aβ levels with the Low diet negatively correlated with changes in cerebrospinal fluid levels of insulin (LD Aβ42 and insulin, $r=-0.68$ [$P=.01$]; LD Aβ40 and insulin, $r=-0.78$ [$P=.002$]).

Conclusions and Relevance: The lipidation states of apolipoproteins and Aβ peptides in the brain differ depending on *APOE* genotype and cognitive diagnosis. Concentrations can be modulated by diet. These findings may provide insight into the mechanisms through which apolipoprotein E4 and unhealthy diets impart risk for developing AD.

JAMA Neurol. Published online June 17, 2013. doi:10.1001/jamaneurol.2013.396

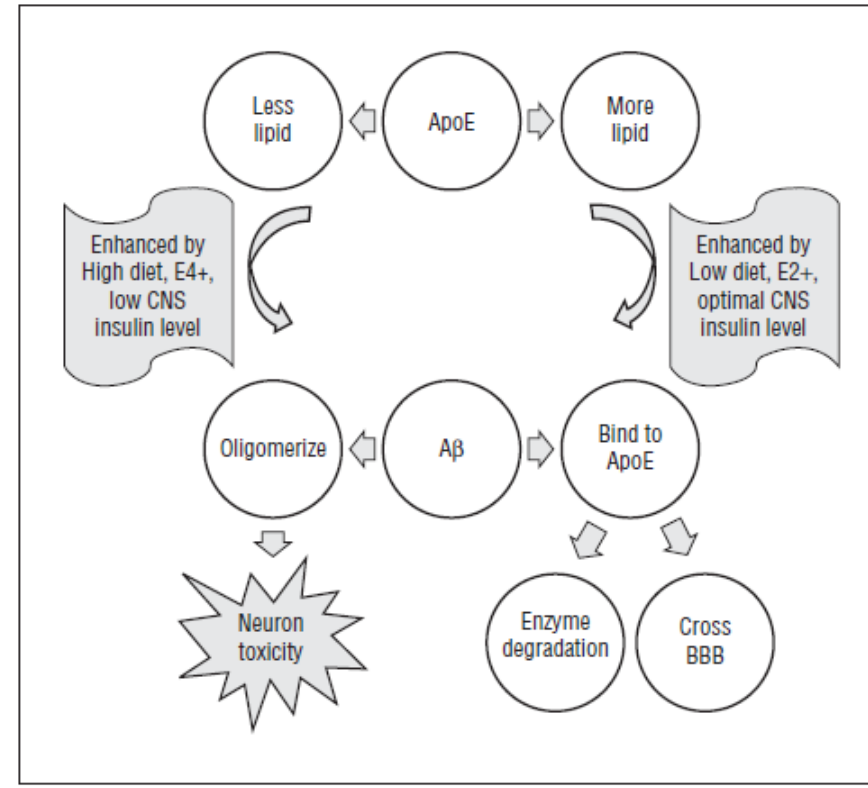


Figure 6. Theoretical model of β-amyloid (Aβ) peptide and apolipoprotein E (ApoE) interaction in the central nervous system (CNS). In the top panel, when ApoE is more lipidated, such as with an ε2 allele (E2+) or a healthy diet, it may be more able to bind Aβ and facilitate its clearance and degradation. When ApoE is less lipidated, such as with the E4+ state or a diet with a high level of saturated fat and a high glycemic index (High diet), it may be less able to bind Aβ. In the bottom panel, when Aβ binds to carrier proteins, such as ApoE, it is more likely to be cleared by enzymatic degradation or by crossing the blood-brain barrier (BBB). However, when Aβ is not bound to proteins, it can form oligomers that are toxic to synapses and neurons. High diets may decrease Aβ-lipoprotein binding, which will increase the toxic forms of Aβ. Conversely, diets with low levels of saturated fat and glycemic index (Low diet) may enhance Aβ-lipoprotein binding, in part by raising CNS insulin levels to optimal.

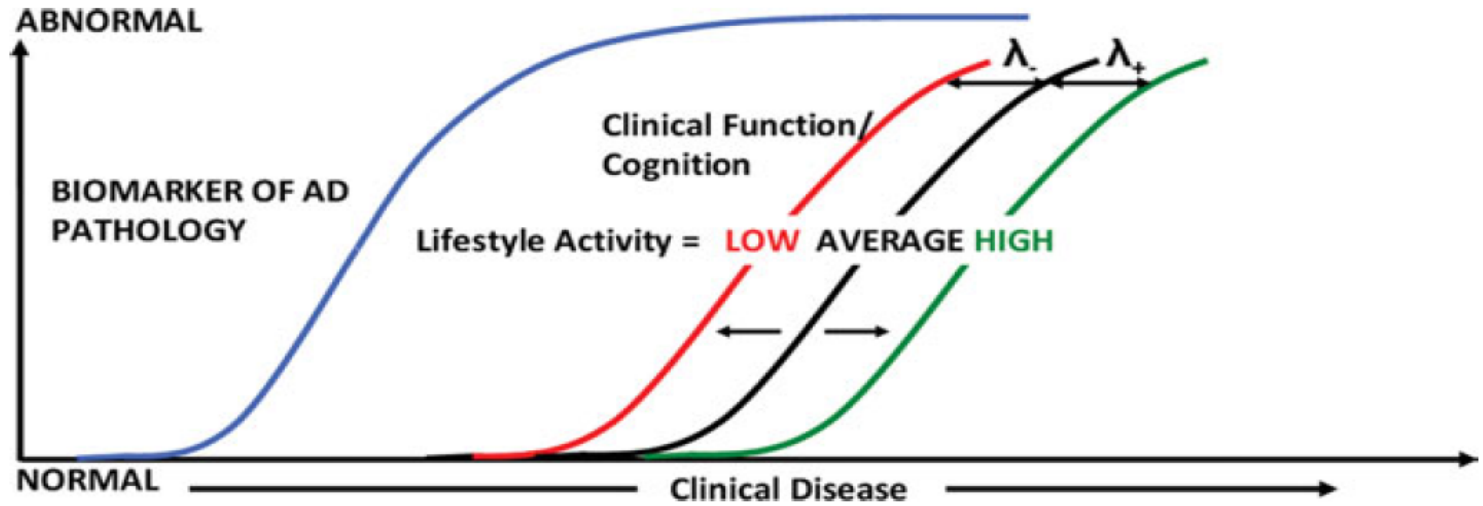
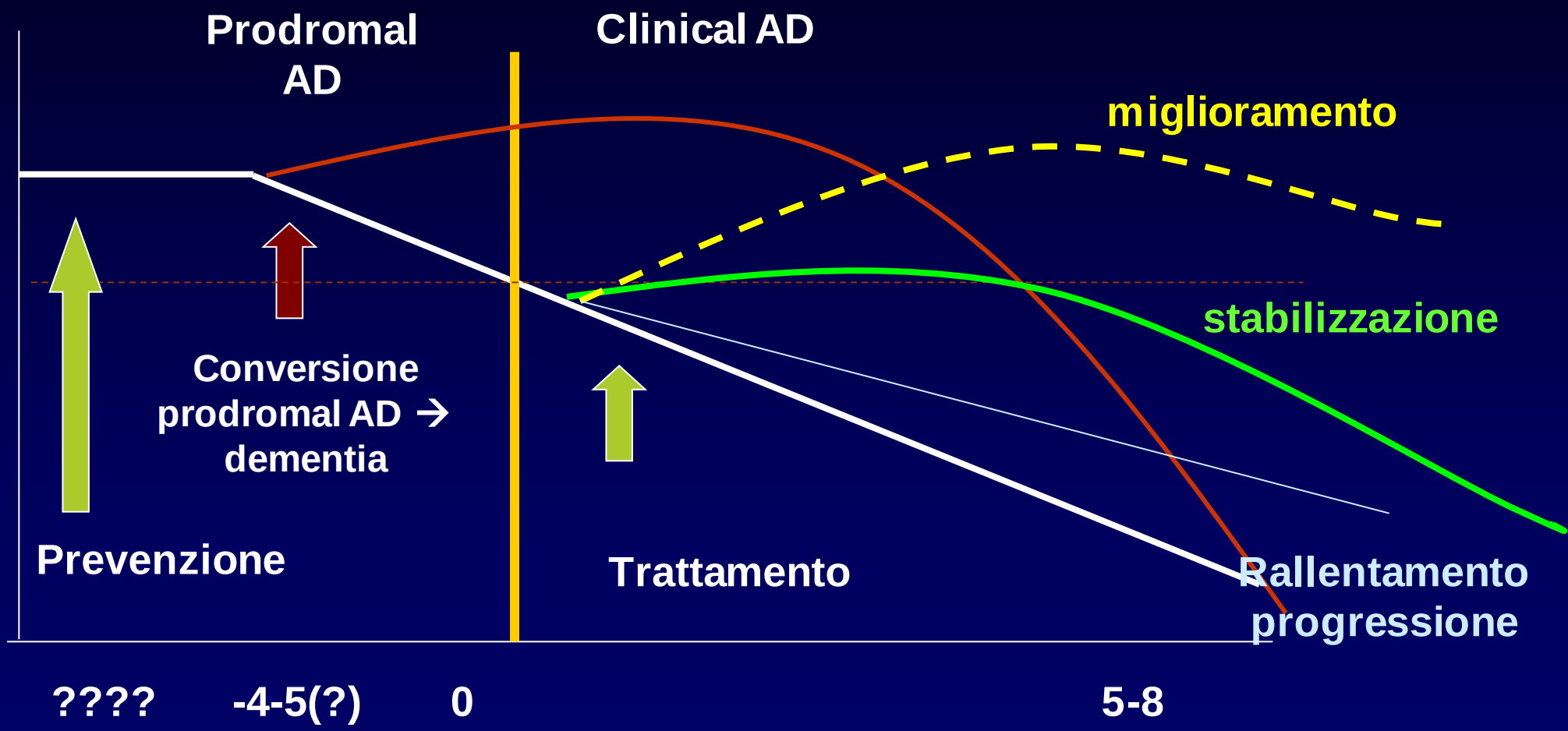


FIGURE 2: Model illustrating the effect of lifestyle activities on Alzheimer disease (AD) biomarkers and cognition or clinical function in subjects. Clinical disease stage is indicated on the horizontal axis and the magnitude of biomarker abnormalities and cognition (from normal to maximally abnormal) on the vertical axis. The cognition or clinical function curve is moved left or right based on the individual's lifestyle activity. The variable λ for lifetime intellectual activity is greater than that for current intellectual activity, and the variable λ for physical activity is close to zero.

ANN NEUROL 2012;72:730–738

Quali outcome per la Malattia di Alzheimer



Good news on dementia prevalence—we can make a difference

Dementia remains very common, very expensive, and profoundly negative in its effects on people with the disorder and their families.

Sube Banerjee

Alzheimer's Disease International

World Alzheimer Report 2011

The treatment gap

Research shows that most people currently living with dementia have not received a formal diagnosis. In high income countries, only 20-50% of dementia cases are recognised and documented in primary care. This 'treatment gap' is certainly much greater in low and middle income countries, with one study in India suggesting 90% remain unidentified. If these statistics are extrapolated to other countries worldwide, it suggests that approximately 28 million of the 36 million people with dementia have not received a diagnosis, and therefore do not have access to treatment, care and organised support that getting a formal diagnosis can provide.

This is clearly a major concern, given that the world's population is growing older, new cases of dementia and Alzheimer's disease are increasing relentlessly, and – as this Report shows – earlier diagnosis and early intervention are important mechanisms by which the treatment gap can be closed.

Le ragioni per la mancanza di una diagnosi precoce dell'AD

- Una scarsa conoscenza dei sintomi dell'AD da parte dei medici
- Il mancato riconoscimento della malattia da parte del medico
- L'accettazione da parte dei familiari del deficit cognitivo come correlato "normale" dell'età
- L'idea che le terapie disponibili per l'AD non siano utili nell'incidere sul decorso della malattia

1. Bond J, et al. Int J Clin Pract. 2005;59(suppl 146):8-14;
2. Cummings JL. N Engl J Med. 2004;351:56-67;
3. De Lepeleire J, et al. Age Ageing. 2004; 33:321.

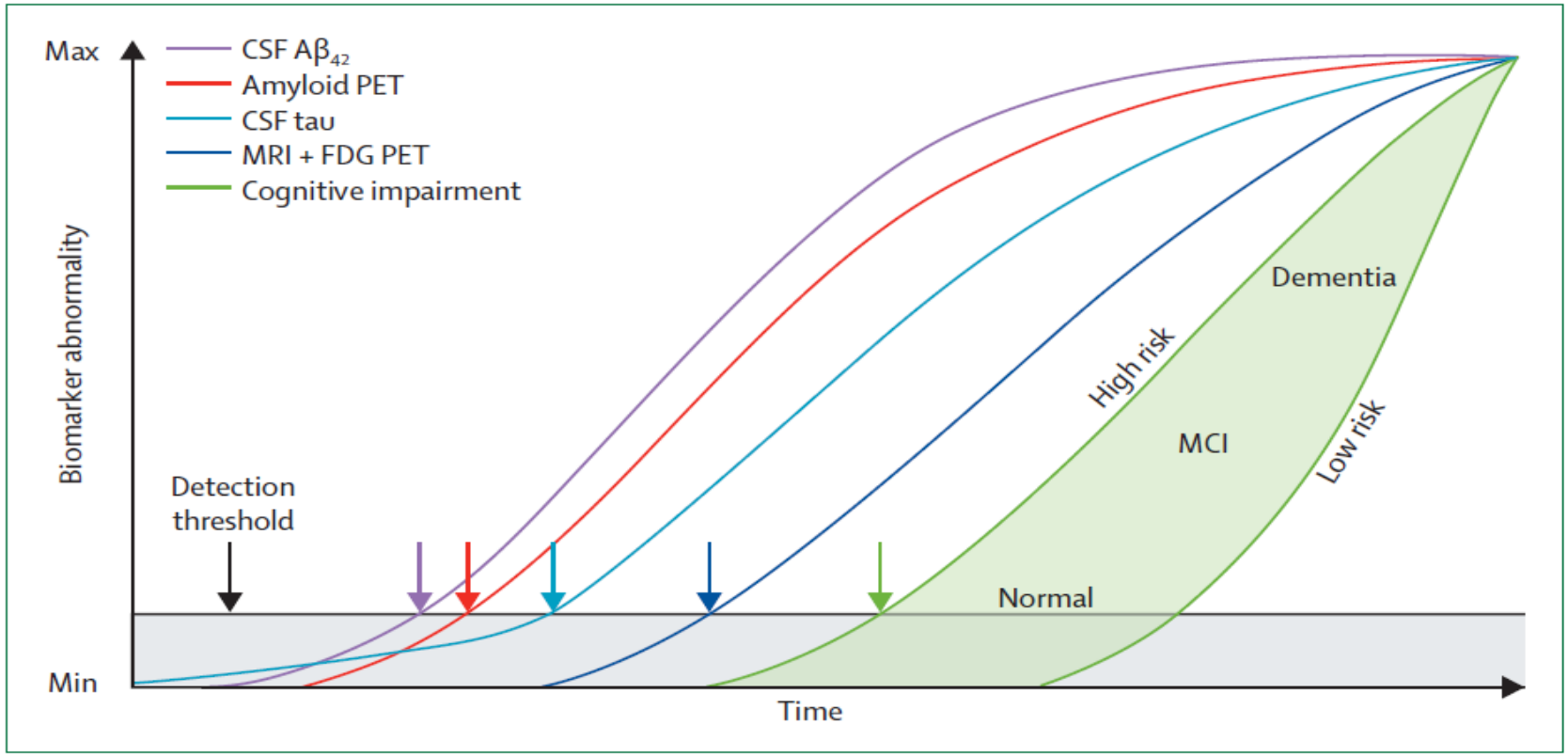


Figure 6: **Model integrating Alzheimer's disease immunohistology and biomarkers**
The threshold for biomarker detection of pathophysiological changes is denoted by the black horizontal line. The grey area denotes the zone in which abnormal pathophysiological changes lie below the biomarker detection threshold. In this figure, tau pathology precedes Aβ deposition in time, but only early on at a subthreshold biomarker detection level. Aβ deposition then occurs independently and rises above the biomarker detection threshold (purple and red arrows). This induces acceleration of tauopathy and CSF tau then rises above the detection threshold (light blue arrow). Later still, FDG PET and MRI (dark blue arrow) rise above the detection threshold. Finally, cognitive impairment becomes evident (green arrow), with a range of cognitive responses that depend on the individual's risk profile (light green-filled area). Aβ=amyloid β. FDG=fluorodeoxyglucose. MCI=mild cognitive impairment.

EDITORIAL

A Peek Behind the Curtain

Amyloid Imaging, Referrals, and Specialist Memory Evaluations

Norman L. Foster, MD, William J. Jagust, MD,† and Nick C. Fox, MD‡*

Alzheimer Dis Assoc Disord • Volume 27, Number 1, January–March 2013

- In part because of low diagnostic confidence and pervasive therapeutic nihilism, the evaluation and management of dementing disease is a low medical priority.
- **The widespread availability of amyloid PET imaging would revolutionize how evaluations for dementia are conducted, but if it is for better or worse will depend upon whether it is used wisely and judiciously. There is considerable concern that misapplication of this new technology could lead to severe adverse consequences for patients and families.**
- The uncritical embrace of a positive scan as indicative of AD by dementia experts in this study is worrisome.

EDITORIAL

A Peek Behind the Curtain

Amyloid Imaging, Referrals, and Specialist Memory Evaluations

Norman L. Foster, MD, William J. Jagust, MD,† and Nick C. Fox, MD‡*

Alzheimer Dis Assoc Disord • Volume 27, Number 1, January–March 2013

- Demonstrating that amyloid PET imaging alters patient management is important.
- Unfortunately, the study limited management outcomes to planned prescribing of medication and referral to clinical trials.
- **More important are personalized, comprehensive management including patient and family self-management education, family support and referral to community services and support groups, and preventative planning.**
- Increased physician diagnostic confidence is likely to encourage these aspects of management and provide more consistent recommendations.

ASL Brescia

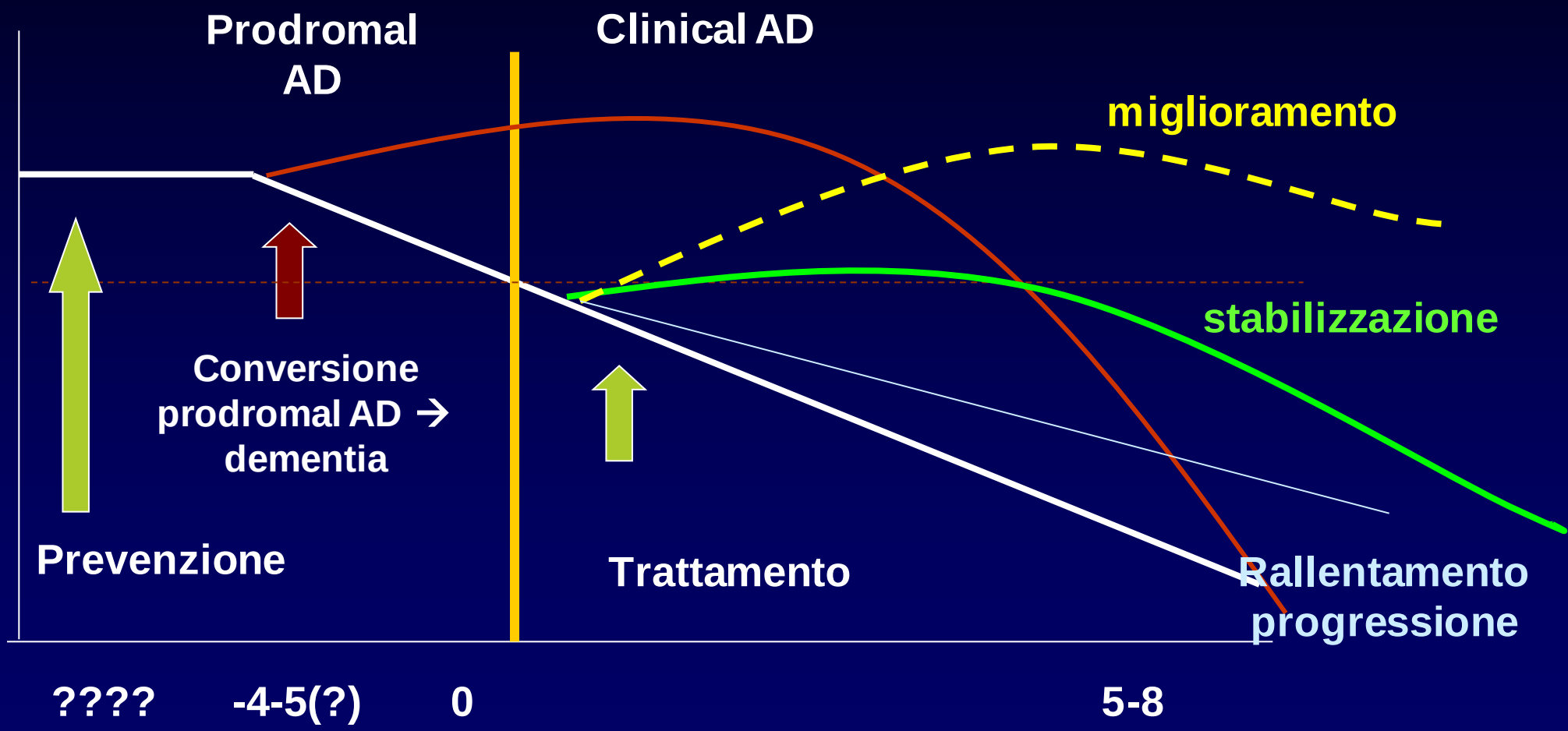
- 1.130.000 abitanti
- circa 19.000 pazienti con demenza potenziali (11.500 circa con malattia di Alzheimer)
- pazienti affetti da demenza censiti attraverso la banca dati ASL: 12.643 (64% circa dei pazienti potenziali)
  - 3.947 pazienti con malattia di Alzheimer
  - 8.696 pazienti affetti da demenza senile o demenze non Alzheimer
- 83% età superiore a 75 anni
- 2/3 vivono a domicilio
- Il 20% dei pazienti è in cure domiciliari e il 5,6% in centri diurni.
- 4.693 sono ospiti presso le RSA (38% dei pazienti con diagnosi nota; 57% della popolazione residente in RSA).

ASL Brescia
prevalenza della demenza
attesa ed osservata

età	attesi	osservati	%	attesi	osservati	%	attesi	osservati	%
60-64	448	210	46,9%	622	157	25,2%	1070	367	34,3%
65-74	1520	589	38,7%	2336	682	29,2%	3856	1271	33,0%
75-84	2144	1589	74,1%	5121	3048	59,5%	7265	4637	63,8%
85 e più	1267	1129	89,1%	5914	5079	85,9%	7181	6208	86,5%

I trattati con achei corrispondono all'8.6% dei pazienti con AD attesi e al 13.4% di coloro la cui diagnosi è nota.

Quali outcome per la Malattia di Alzheimer



ELSEVIER

Alzheimer's & Dementia 8 (2012) 131–168

Alzheimer's & Dementia

Alzheimer's Association Report

2012 Alzheimer's disease facts and figures

Alzheimer's Association*

Treatment of AD

- **No treatment is available to slow or stop AD.**
- The U.S. Food and Drug Administration has approved five drugs that temporarily improve symptoms.
- The effectiveness of these drugs varies across the population. None of the treatments available today alters the underlying course of this terminal disease.
- Despite the lack of disease-modifying therapies, studies have consistently shown that **active medical management of AD and other dementias can significantly improve quality of life** through all stages of the disease **for individuals with dementia and their caregivers**.
- Active management includes
  - ***(1) appropriate use of available treatment options;***
  - ***(2) effective management of coexisting conditions;***
  - ***(3) coordination of care among physicians, other health care professionals, and lay caregivers;***
  - ***(4) participation in activities and adult day care programs; and***
  - ***(5) taking part in support groups and supportive services such as counseling.***

SPECIAL ARTICLE

AMERICAN ACADEMY OF NEUROLOGY

Quality improvement in neurology

Dementia management quality measures

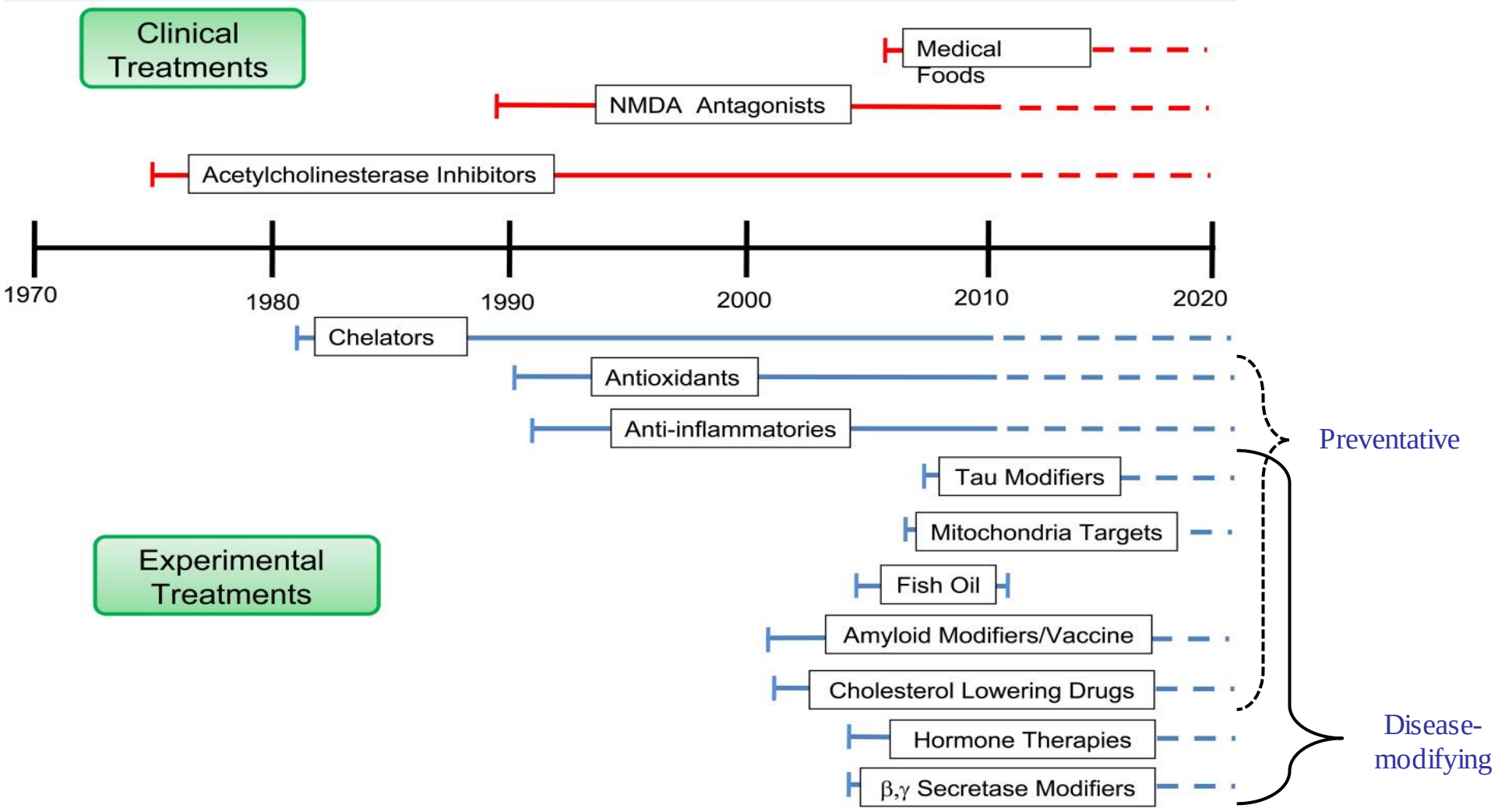
Neurology 81 October 22, 2013

Table Measure title and description of the final 10 dementia measures (measures copyrighted by the American Medical Association, 2012)

Measure title	Description
No. 1: Staging of dementia	Percentage of patients, regardless of age, with a diagnosis of dementia whose severity of dementia was classified as mild, moderate, or severe at least once within a 12-month period
No. 2: Cognitive assessment	Percentage of patients, regardless of age, with a diagnosis of dementia for whom an assessment of cognition is performed and the results are reviewed at least once within a 12-month period
No. 3: Functional status assessment	Percentage of patients, regardless of age, with a diagnosis of dementia for whom an assessment of functional status is performed and the results are reviewed at least once within a 12-month period
No. 4: Neuropsychiatric symptom assessment	Percentage of patients, regardless of age, with a diagnosis of dementia and for whom an assessment of neuropsychiatric symptoms is performed and the results are reviewed at least once in a 12-month period
No. 5: Management of neuropsychiatric symptoms	Percentage of patients, regardless of age, with a diagnosis of dementia who have one or more neuropsychiatric symptoms who received or were recommended to receive an intervention for neuropsychiatric symptoms within a 12-month period
No. 6: Screening for depressive symptoms	Percentage of patients, regardless of age, with a diagnosis of dementia who were screened for depressive symptoms within a 12-month period
No. 7: Counseling regarding safety concerns	Percentage of patients, regardless of age, with a diagnosis of dementia, or their caregiver(s), who were counseled or referred for counseling regarding safety concerns within a 12-month period
No. 8: Counseling regarding risks of driving	Percentage of patients, regardless of age, with a diagnosis of dementia, or their caregiver(s), who were counseled regarding the risks of driving and the alternatives to driving at least once within a 12-month period
No. 9: Palliative care counseling and advance care planning	Percentage of patients, regardless of age, with a diagnosis of dementia, or their caregiver(s), who 1) received comprehensive counseling regarding ongoing palliation and symptom management and end-of-life decisions and 2) have an advance care plan or surrogate decision-maker in the medical record or documentation in the medical record that the patient did not wish or was not able to name a surrogate decision-maker or provide an advance care plan within 2 years of initial diagnosis or assumption of care
No. 10: Caregiver education and support	Percentage of patients, regardless of age, with a diagnosis of dementia whose caregiver(s) were provided with education on dementia disease management and health behavior changes and were referred to additional resources for support within a 12-month period

Full specifications are available on the Physician Consortium for Performance Improvement Web site at www.physicianconsortium.org. Readers interested in examples of how to meet the measurement requirements are referred to this document. Readers are also referred to the full manuscript for this article in appendix e-1.

Pharmacological treatment of AD



Stone JG, et al. Frontiers in Alzheimer's disease therapeutics. Ther Adv Chronic Dis 2011; 2: 9-23

New Research on Alzheimer Treatments Ventures Beyond Plaques and Tangles

M. J. Friedrich

JAMA, December 26, 2012—Vol 308, No. 24

A number of factors may contribute to the failure of AD therapeutics in clinical trials. One possibility is that the drugs are initiated when the disease has progressed too far to be reversed, said Ottavio Arancio, MD, PhD, of Columbia University, New York City. Alzheimer disease may begin decades before it can be detected, so moving toward early detection and initiation of treatment may be an important goal, he said.

Another possibility is that the drugs that have been developed for AD do not zero in on the pathways that are crucial to the development of the disease.

INSULIN RESISTANCE IN THE BRAIN

Growing evidence about insulin's important role in normal brain function and cognition points to a new avenue for treating AD.

Another novel strategy for treating AD involves targeting neuroinflammation.

MIMICKING APOE3

Another approach for tamping down inflammation in the brain is to develop drugs that mimic apolipoprotein E (ApoE), the lipid-carrier molecule that in one of its forms is the risk factor most commonly associated with sporadic AD.

SECTION EDITOR: IRA SHOULSON, MD

Intranasal Insulin Therapy for Alzheimer Disease and Amnestic Mild Cognitive Impairment

A Pilot Clinical Trial

Suzanne Craft, PhD; Laura D. Baker, PhD; Thomas J. Montine, MD, PhD; Satoshi Minoshima, MD, PhD; G. Stennis Watson, PhD; Amy Claxton, PhD; Matthew Arbuckle, BA; Maureen Callaghan, MD; Elaine Tsai, MD; Stephen R. Plymate, MD; Pattie S. Green, PhD; James Leverenz, MD; Donna Cross, PhD; Brooke Gerton, MD

Objective: To examine the effects of intranasal insulin administration on cognition, function, cerebral glucose metabolism, and cerebrospinal fluid biomarkers in adults with amnestic mild cognitive impairment or Alzheimer disease (AD).

Design: Randomized, double-blind, placebo-controlled trial.

Setting: Clinical research unit of a Veterans Affairs medical center.

Participants: The intent-to-treat sample consisted of 104 adults with amnestic mild cognitive impairment (n=64) or mild to moderate AD (n=40).

Intervention: Participants received placebo (n=30), 20 IU of insulin (n=36), or 40 IU of insulin (n=38) for 4 months, administered with a nasal drug delivery device (Kurve Technology, Bothell, Washington).

Main Outcome Measures: Primary measures consisted of delayed story recall score and the Dementia Severity Rating Scale score, and secondary measures included the Alzheimer Disease's Assessment Scale–cognitive subscale (ADAS-cog) score and the Alzheimer's Disease Cooperative Study–activities of daily living (ADCS-ADL) scale. A subset of participants underwent lumbar puncture (n=23) and positron emission tomography with fludeoxyglucose F 18 (n=40) before and after treatment.

Results: Outcome measures were analyzed using repeated-measures analysis of covariance. Treatment with 20 IU of insulin improved delayed memory ($P<.05$), and both doses of insulin (20 and 40 IU) preserved caregiver-rated functional ability ($P<.01$). Both insulin doses also preserved general cognition as assessed by the ADAS-cog score for younger participants and functional abilities as assessed by the ADCS-ADL scale for adults with AD ($P<.05$). Cerebrospinal fluid biomarkers did not change for insulin-treated participants as a group, but, in exploratory analyses, changes in memory and function were associated with changes in the Aβ42 level and in the tau protein–to–Aβ42 ratio in cerebrospinal fluid. Placebo-assigned participants showed decreased fludeoxyglucose F 18 uptake in the parietotemporal, frontal, precuneus, and cuneus regions and insulin-minimized progression. No treatment-related severe adverse events occurred.

Conclusions: These results support longer trials of intranasal insulin therapy for patients with amnestic mild cognitive impairment and patients with AD.

Trial Registration: clinicaltrials.gov Identifier: NCT00438568

Arch Neurol. 2012;69(1):29-38. Published online September 12, 2011. doi:10.1001/archneurol.2011.233

BMJ open

Effects of centrally acting ACE inhibitors on the rate of cognitive decline in dementia

Yang Gao,[1,2] Rónán O'Caoimh,[1] Liam Healy,[1] David M Kerins,[3,4] Joseph Eustace,[5] Gordon Guyatt,[6] David Sammon,[2] D William Molloy[1,7]

ABSTRACT

Objectives: There is growing evidence that antihypertensive agents, particularly centrally acting ACE inhibitors (CACE-Is), which cross the blood–brain barrier, are associated with a reduced rate of cognitive decline. Given this, we compared the rates of cognitive decline in clinic patients with dementia receiving CACE-Is (CACE-I) with those not currently treated with CACE-Is (NoCACE-I), and with those who started CACE-Is, during their first 6 months of treatment (NewCACE-I).

Design: Observational case–control study.

Setting: 2 university hospital memory clinics.

Participants: 817 patients diagnosed with Alzheimer's disease, vascular or mixed dementia. Of these, 361 with valid cognitive scores were included for analysis, 85 CACE-I and 276 NoCACE-I.

Measurements: Patients were included if the baseline and end-point (standardised at 6 months apart) Standardised Mini-Mental State Examination (SMMSE) or Quick Mild Cognitive Impairment (Qmci) scores were available. Patients with comorbid depression or other dementia subtypes were excluded. The average 6-month rates of change in scores were compared between CACE-I, NoCACE-I and NewCACE-I patients.

Results: When the rate of decline was compared between groups, there was a significant difference in the median, 6-month rate of decline in Qmci scores between CACE-I (1.8 points) and NoCACE-I (2.1 points) patients ($p=0.049$), with similar, non-significant changes in SMMSE. Median SMMSE scores improved by 1.2 points in the first 6 months of CACE treatment (NewCACE-I), compared to a 0.8 point decline for the CACE-I ($p=0.003$) group and a 1 point decline for the NoCACE-I ($p=0.001$) group over the same period. Multivariate analysis, controlling for baseline characteristics, showed significant differences in the rates of decline, in SMMSE, between the three groups, $p=0.002$.

Conclusions: Cognitive scores may improve in the first 6 months after CACE-I treatment and use of CACE-Is is associated with a reduced rate of cognitive decline in patients with dementia.

WFN-RGD members now have access to
Journal of Alzheimer's Disease

Journal of Alzheimer's Disease 33 (2013) 177–190
DOI 10.3233/JAD-2012-112039
IOS Press

A Specific Multi-Nutrient Diet Reduces Alzheimer-Like Pathology in Young Adult $A\beta PP_{swe}/PS1_{dE9}$ Mice

Laus M. Broersen[a,*], Almar A.M. Kuipers[a], Martin Balvers[a], Nick van Wijk[a], Paul J.M. Savelkoul[a], Martijn C. de Wilde[a], Eline M. van der Beek[a], John W.C. Sijben[a], Robert J.J. Hageman[a], Patrick J.G.H. Kamphuis[a,b] and Amanda J. Kiliaan[c]

Abstract. Diet is an important lifestyle factor implicated in the etiology of Alzheimer's disease (AD), but so far it is not fully elucidated to which nutrients the suggested protective effect of diet can be attributed. Recent evidence obtained in the amyloid-β 1-42 ($A\beta_{42}$) infusion model in rats has shown that a multi-nutrient intervention known as Fortasyn™ Connect (FC) may protect the central cholinergic system against $A\beta_{42}$-induced toxicity. FC comprises the nutritional precursors and cofactors for membrane synthesis, viz. docosahexaenoic acid (DHA), eicosapentaenoic acid, uridine-mono-phosphate (UMP), choline, phospholipids, folic acid, vitamins B6, B12, C, E, and selenium. In order to investigate whether the combined administration of these nutrients may also affect AD-like pathology, we now evaluated the effects of the FC diet intervention in the transgenic $A\beta PP_{swe}/PS1_{dE9}$ mouse model with endogenous Aβ production. In addition we evaluated the effects of diets containing the individual nutrients DHA and UMP and their combination in this model. Between the age of 3 and 6 months, FC diet decreased brain Aβ levels and amyloid plaque burden in the hippocampus of AβPP/PS1 mice. The FC diet also reduced ongoing disintegrative degeneration in the neocortex, as indicated by Amino Cupric Silver staining. Although all three DHA-containing diets were equally effective in changing brain fatty acid profiles, diets differentially affected amyloid-related measures, indicating that effects of DHA may depend on its dietary context. The current data, showing that dietary enrichment with FC reduces AD-like pathology in AβPP/PS1 mice, confirm and extend our previous findings in the $A\beta_{42}$ infusion model and favor the combined administration of relevant nutrients.

Possibility of a New Anti-Alzheimer's Disease Pharmaceutical Composition Combining Memantine and Vitamin D *

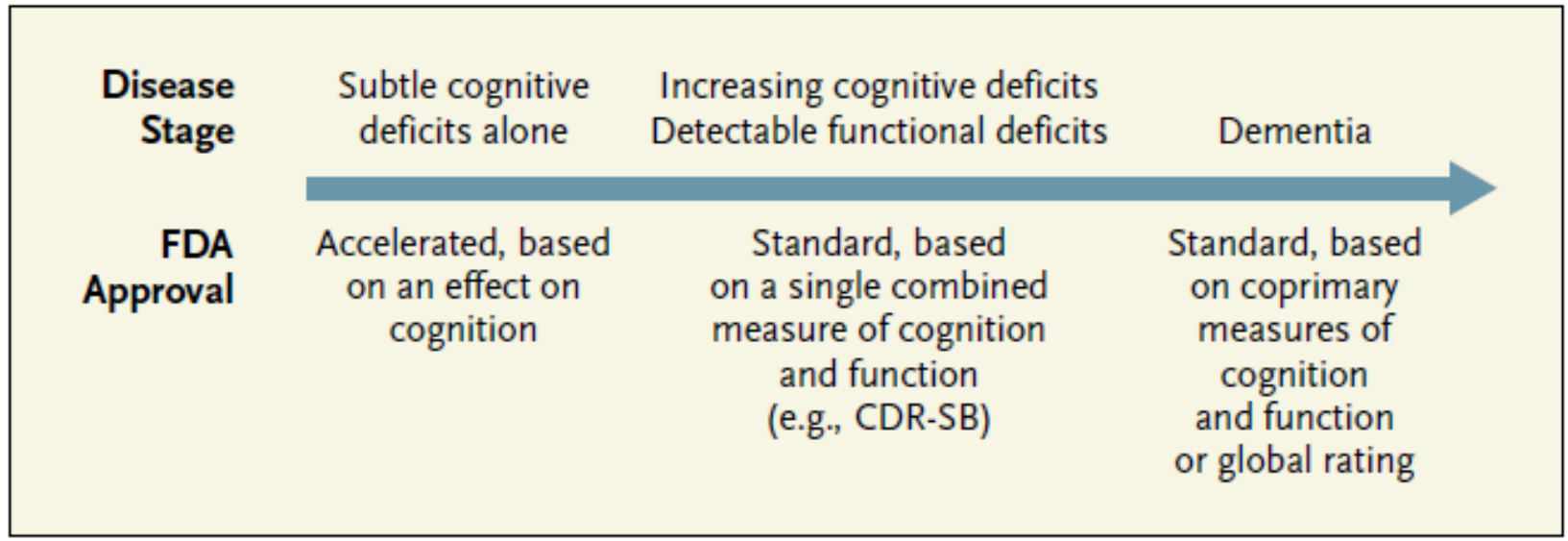
……Patients with AD who took memantine plus vitaminD for 6 months had a statistically and clinically relevant gain in cognition, underlining possible synergistic and potentiating benefits of the combination.

Annweiler C Drugs Aging 2012; 29, 81-91

The NEW ENGLAND JOURNAL of MEDICINE

Regulatory Innovation and Drug Development for Early-Stage Alzheimer's Disease

Nicholas Kozauer, M.D., and Russell Katz, M.D.



Potential Regulatory Pathways in Early Alzheimer's Disease.

As the focus of drug development moves to earlier stages of Alzheimer's disease, new guidance from the FDA suggests potential approaches to trial design that allow for regulatory flexibility and innovation. CDR-SB denotes Clinical Dementia Rating Sum of Boxes score.

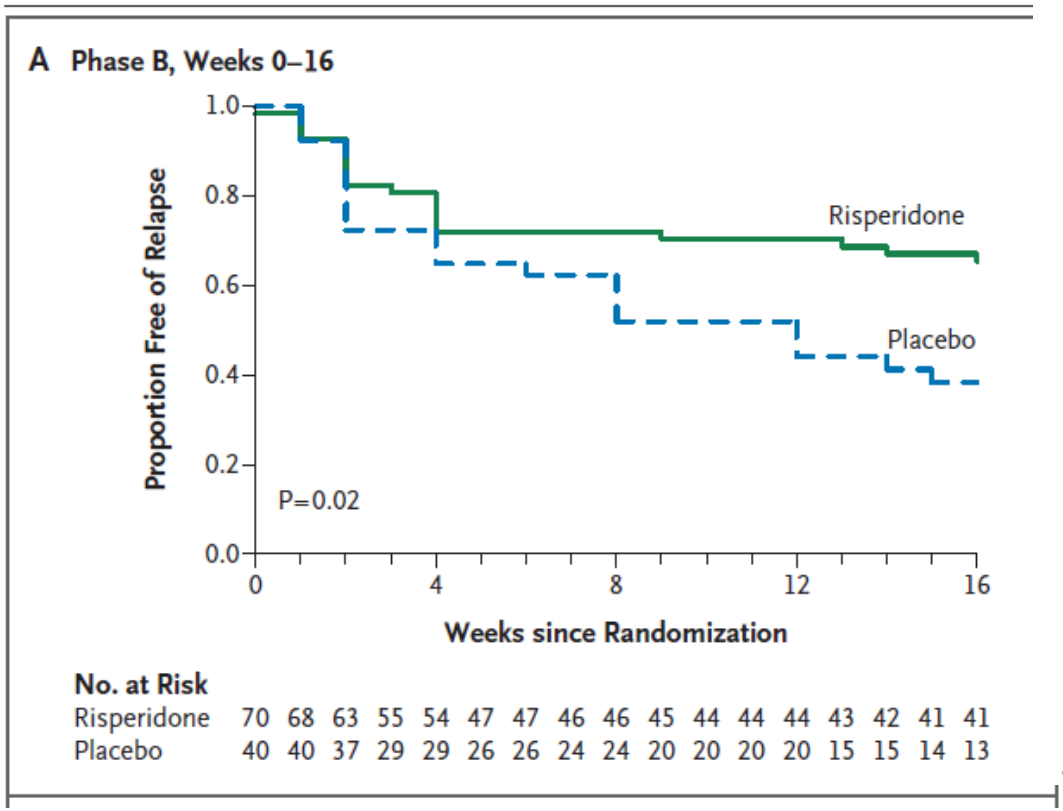
N Engl J Med. 2013 Mar 28;368(13):1169-71.

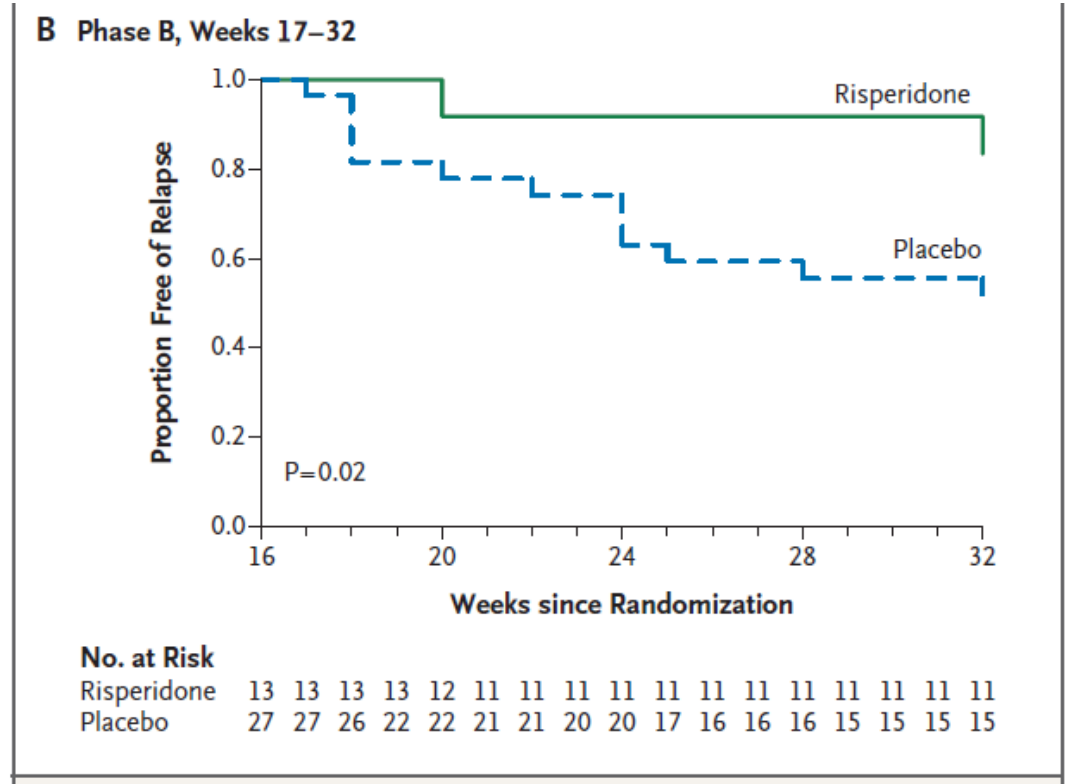
Relapse Risk after Discontinuation of Risperidone in Alzheimer's Disease

D.P. Devanand, M.D., Jacobo Mintzer, M.D., M.B.A., Susan K. Schultz, M.D., Howard F. Andrews, Ph.D., David L. Sultzer, M.D., Danilo de la Pena, M.D., Sanjay Gupta, M.D., Sylvia Colon, M.D., Corbett Schimming, M.D., Gregory H. Pelton, M.D., and Bruce Levin, Ph.D.

Figure 2. Time from Randomization to Relapse among Patients Receiving Risperidone and Those Receiving Placebo.

Panel A shows Kaplan–Meier curves for the risk of relapse during the first 16-week period of phase B (weeks 16 to 32 of the study) among the 70 patients who were randomly assigned to continue to receive risperidone (groups 1 and 2) and the 40 patients who were assigned to be withdrawn from risperidone at the end of phase A and switched to placebo (group 3). Panel B shows Kaplan–Meier curves for the risk of relapse during the second 16-week period of phase B (weeks 33 to 48 of the study) among the 13 patients who continued to receive risperidone (group 1) and the 27 patients who were switched to placebo at the end of the first 16-week period (group 2).



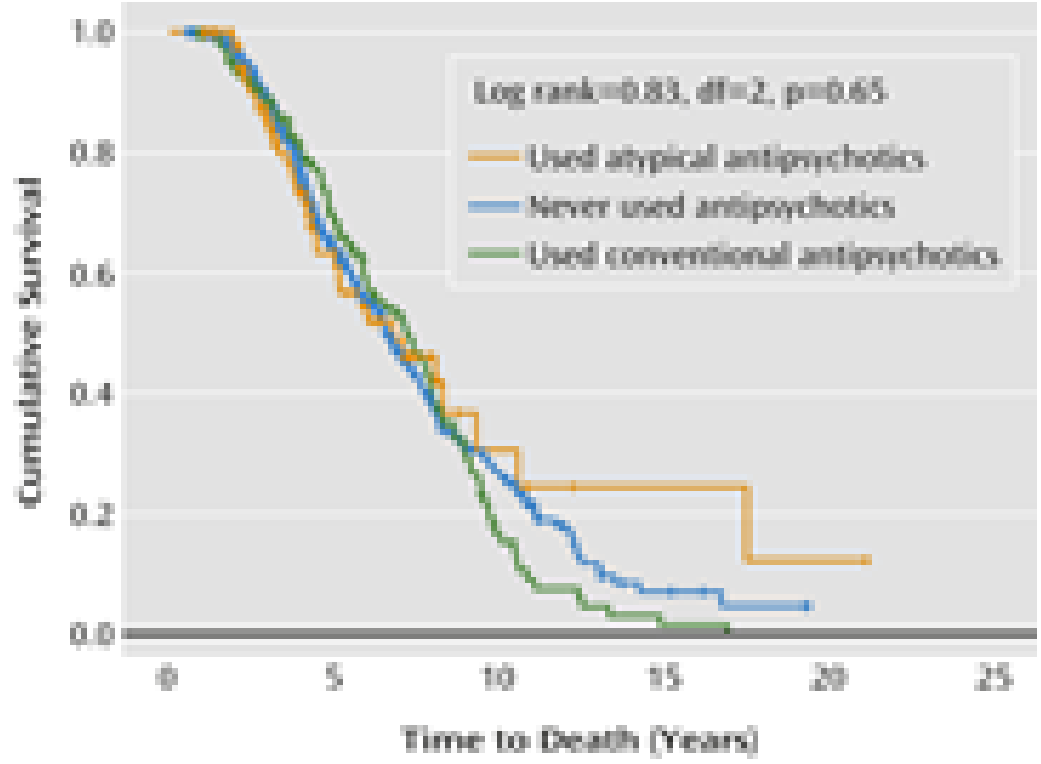


The Long-Term Effects of Conventional and Atypical Antipsychotics in Patients With Probable Alzheimer's Disease

Oscar L. Lopez, M.D.; James T. Becker, Ph.D.; Yue-Fang Chang, Ph.D.; Robert A. Sweet, M.D.; Howard Aizenstein, M.D.; Beth Snitz, Ph.D.; Judith Saxton, Ph.D.; Eric McDade, D.O.; M. Ilyas Kamboh, Ph.D.; Steven T. DeKosky, M.D.; Charles F. Reynolds, III, M.D.; William E. Klunk, M.D., Ph.D.

Am J Psychiatry 2013;170:1051-1058. doi:10.1176/appi.ajp.2013.12081046

The use of antipsychotic medications, both conventional and atypical, was not associated with either time to nursing home admission or time to death after adjustment for relevant covariates. Rather, it was the presence of psychiatric symptoms, including psychosis and agitation, that was linked to increased risk of institutionalization and death after adjustment for exposure to antipsychotics.



BMJ

Sverre Bergh *researcher*[1], Geir Selbæk *head of research department*[1 2], Knut Engedal *professor*[1 2 3]

[1]Centre for Old Age Psychiatric Research, Innlandet Hospital Trust, N-2312 Ottestad, Norway ; [2]Norwegian Centre for Dementia Research, Oslo University Hospital, Oslo, Norway ; [3]University of Oslo, Oslo

BMJ 2012;344:e1566 doi: 10.1136/bmj.e1566 (Published 9 March 2012)

Discontinuation of antidepressants in people with dementia and neuropsychiatric symptoms (DESEP study): double blind, randomised, parallel group, placebo controlled trial

Objective To determine the effect of discontinuing antidepressant treatment in people with dementia and neuropsychiatric symptoms.

Design Double blind, randomised, parallel group, placebo controlled trial.

Setting Norwegian nursing homes; residents recruited by 16 study centres in Norway from August 2008 to June 2010.

Participants 128 patients with Alzheimer's disease, dementia or vascular dementia, and neuropsychiatric symptoms (but no depressive disorder), who had been prescribed escitalopram, citalopram, sertraline, or paroxetine for three months or more. We excluded patients with severe somatic disease or terminal illness, or who were unable to take tablets or capsules as prescribed.

Interventions Antidepressant treatment was discontinued over one week in 63 patients, and continued in 68 patients. We assessed patients at baseline, four, seven, 13, and 25 weeks.

Conclusions Discontinuation of antidepressant treatment in patients with dementia and neuropsychiatric symptoms leads to an increase in depressive symptoms, compared with those patients who continue with treatment.

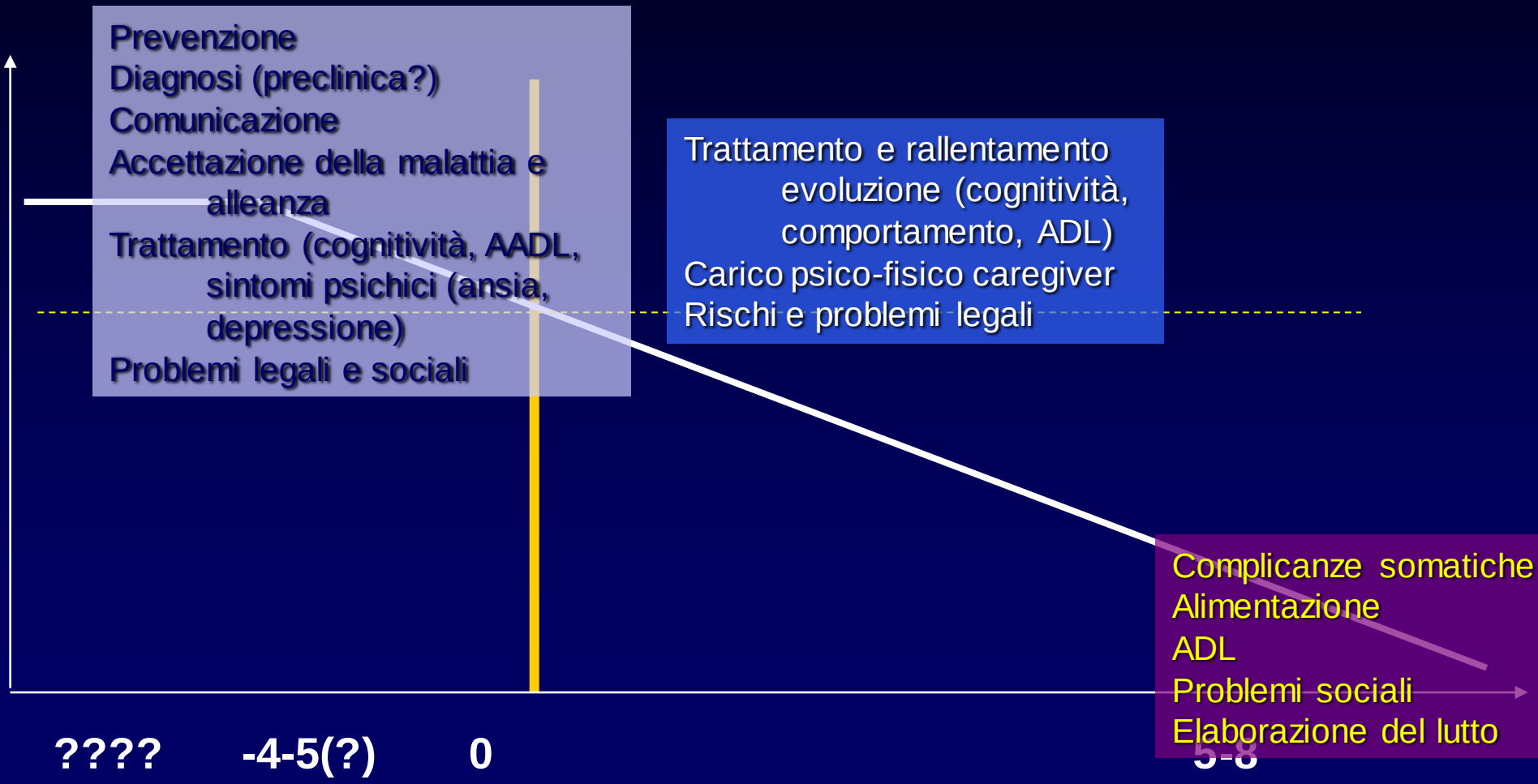
What is already known on this topic

- Psychotropic drugs are frequently prescribed to patients with dementia
- Evidence is weak in relation to the pharmacological treatment of neuropsychiatric symptoms and depressive symptoms in patients with dementia

What this study adds

- Discontinuation of escitalopram, citalopram, sertraline, or paroxetin in patients with dementia led to a significant increase in their depressive symptoms
- Significantly more patients who discontinued treatment than those continuing treatment withdrew from the study prematurely, owing to increased neuropsychiatric symptoms
- Discontinuation of antidepressants was tolerated in most study patients

La Malattia di Alzheimer: l'evoluzione clinica e i bisogni



Slaying Dementia Dragons

- The UVA centers have developed different programs of care: the basic ones, providing diagnosis, prescription of the specific medications for Alzheimer's disease, and periodic – every 6 months – follow-up visits, and an intensive multi-component approach (based on more frequent visits, education of caregivers, cognitive and physical stimulation and treatment of comorbidities).
- Cognitive decline (MMSE pts/y):
  - program of more integrated care show 0.3 ±5.7 points
  - standard approach,: 1.6 ±2.1 points
  - literature : 2.1 points
- An integrated and multidimensional approach may significantly slow the progression of the disease.
- Drugs are the known part of the “map”, while psychosocial and physical approaches belong to the less known areas, still under the control of “dracones”, targets of our fight to really change the approach to dementias.

Bianchetti e Trabucchi, JAGS, 2013

EDITORIAL

"I'm fine; I'm just waiting for my disease"

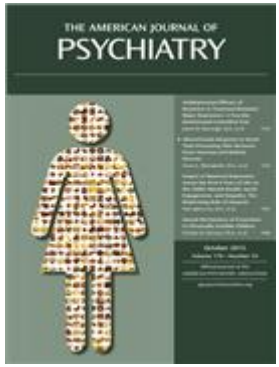
The new and growing class of presymptomatic patients

Jennifer M. Kwon, MD
Robert D. Steiner, MD

Neurology® 2011;77:522–523

"Patient-in-waiting" is an apt description for this particular case. The current practice of medicine is ill-equipped to support and advise individuals who are "affected" yet currently well, diagnosed yet still not diseased. For Pompe disease, a treatment is available, perhaps lessening the blow of presymptomatic diagnosis. However, treatments are not available for some of the conditions being diagnosed presymptomatically. Some patients and families may be able to cope with this state of diagnostic limbo without undue distress. But for others, the healthy good years may be less good because of the dread of what will come.

Effect of Knowledge of APOE Genotype on Subjective and Objective Memory Performance in Healthy Older Adults



AJP in Advance

Tara T. Lineweaver, Ph.D.; Mark W. Bondi, Ph.D.; Douglas Galasko, M.D.; David P. Salmon, Ph.D.

Am J Psychiatry 2013;:. doi:10.1176/appi.ajp.2013.12121590

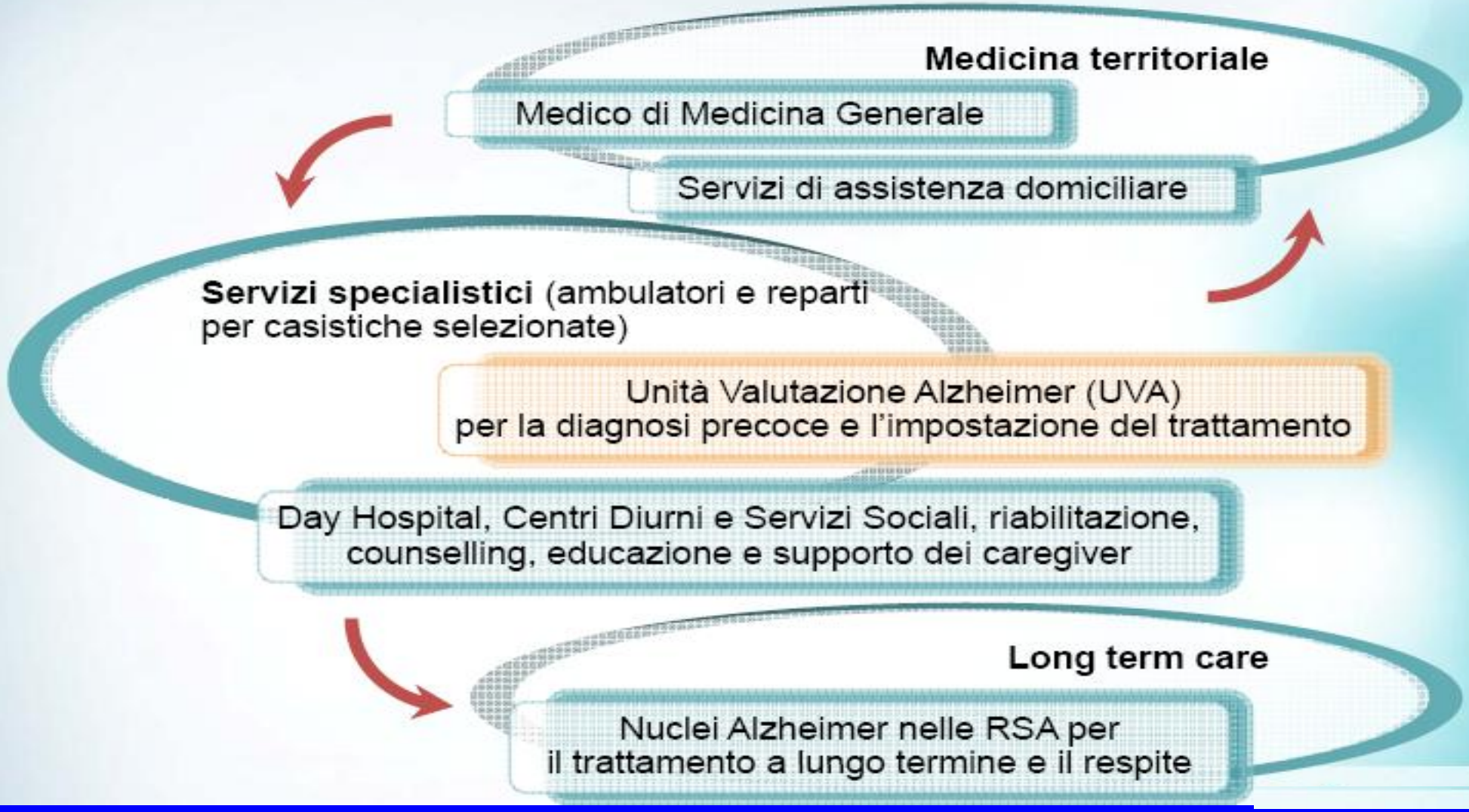
Objective The knowledge that one carries the apolipoprotein E (APOE) ε4 allele risk factor for Alzheimer's disease was recently found to have little short-term psychological risk. The authors investigated the impact of knowledge of carrying the risk allele on subjective ratings of memory and objective memory test performance of older adults.

Method Using a nested case-control design, the authors administered objective verbal and visual memory tests and self-rating scales of memory function to 144 cognitively normal older adults (ages 52–89) with known APOE genotype who knew (ε4+, N=25; ε4−, N=49) or did not know (ε4+, N=25; ε4−, N=45) their genotype and genetic risk for Alzheimer's disease prior to neuropsychological evaluation.

Results Significant genotype-by-disclosure interaction effects were observed on several memory rating scales and tests of immediate and delayed verbal recall. Older adults who knew their ε4+ genotype judged their memory more harshly and performed worse on an objective verbal memory test than did ε4+ adults who did not know. In contrast, older adults who knew their ε4− genotype judged their memory more positively than did ε4− adults who did not know, but these groups did not differ in objective memory test performance.

Conclusions Informing older adults that they have an APOE genotype associated with an increased risk of Alzheimer's disease can have adverse consequences on their perception of their memory abilities and their performance on objective memory tests. The patient's knowledge of his or her genotype and risk of Alzheimer's disease should be considered when evaluating cognition in the elderly.

Modello di “rete” dei servizi per il paziente con demenza



Modificato da Bianchetti and Trabucchi, 2005