Expo Milano 2015 Word Pasta Day
October 26 2015

The Mediterranean Diet and Brain Health

Can we Delay the Onset of Neurodegenerative Diseases? Investigations across Populations and Continents

Giancarlo Logroscino MD PhD
Neurodegenerative Diseases Unit
Department of Basic Medicine Neuroscience and Sense Organs
Department of Clinical Research in Neurology of the University of Bari at
"Pia Fondazione Card G. Panico" Hospital Tricase (Le)
University Aldo Moro . Bari.

Flagelli come fame e patologie legate alla miseria colpiscono meno di un tempo, ma obesità e ipertensione sono diffuse ormai anche nei Paesi in via di sviluppo

WEB

Per saperne di più L'intero documento Global Burden of diseases (in inglese) http://press.thelancet.com / GBDpaper1.pdf

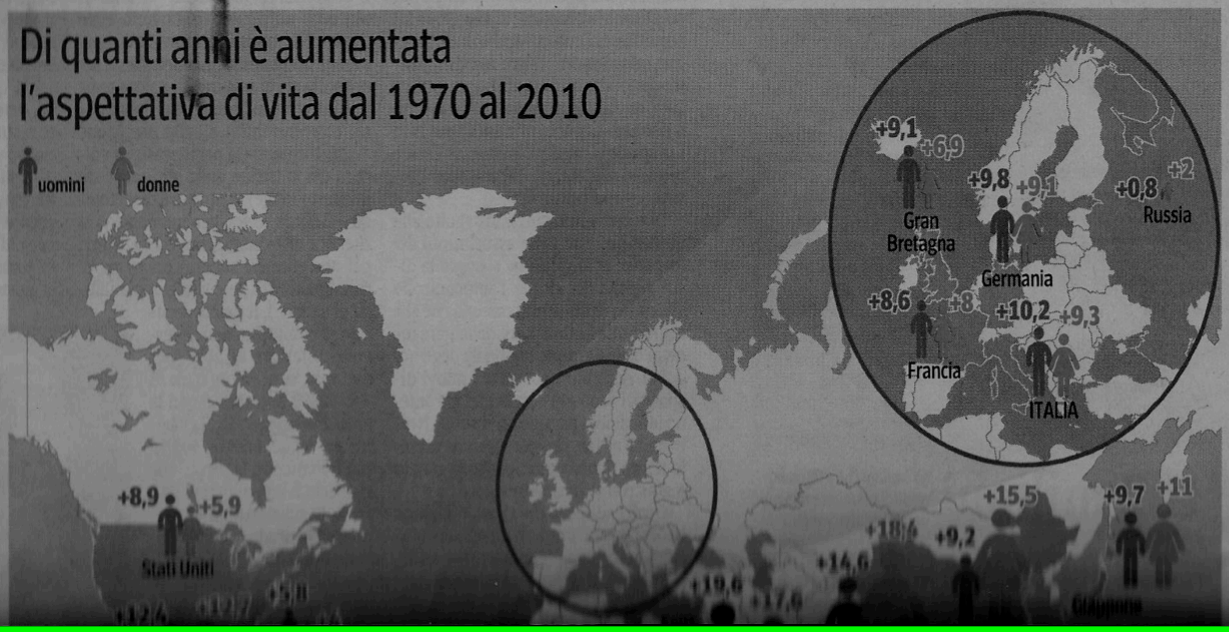
Corriere della Sera

Dom 6 gennaio 2013

Epidemiologia Un gigantesco studio disegna la mappa della situazione sanitaria della popolazione del pianeta

Nel mondo si vive più a lungo Ora l'obiettivo è invecchiare meglio

Guadagnati 10 anni in quattro decadi. Pesa il dazio da pagare alle malattie neurodegenerative



I più longevi

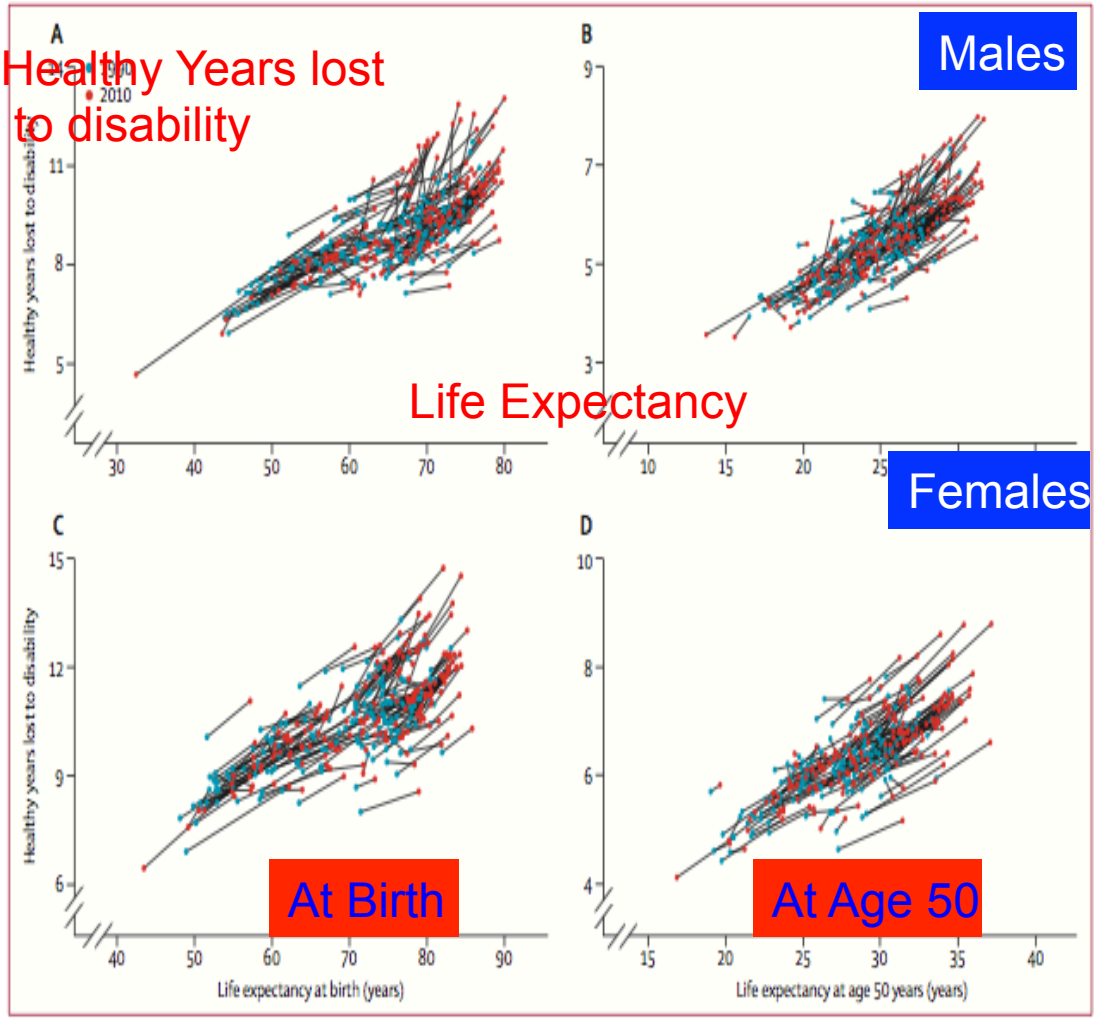
I giapponesi battono sempre tutti

Il dato che, più degli altri, rende conto delle migliori condizioni di salute della popolazione mondiale è l'aspettativa di vita: dal 1970 al 2010, quella delle donne è passata da 61,2 anni a 73,3; quella degli uomini da 56,4 a 67,5. Meglio di tutti hanno fatto le Maldive, i cui abitanti hanno guadagnato oltre 27 anni. Ma avanzamenti solo di poco inferiori si sono registrati anche in Bangladesh, Bhutan, Iran e Perù. Un po' ovunque, il miglioramento

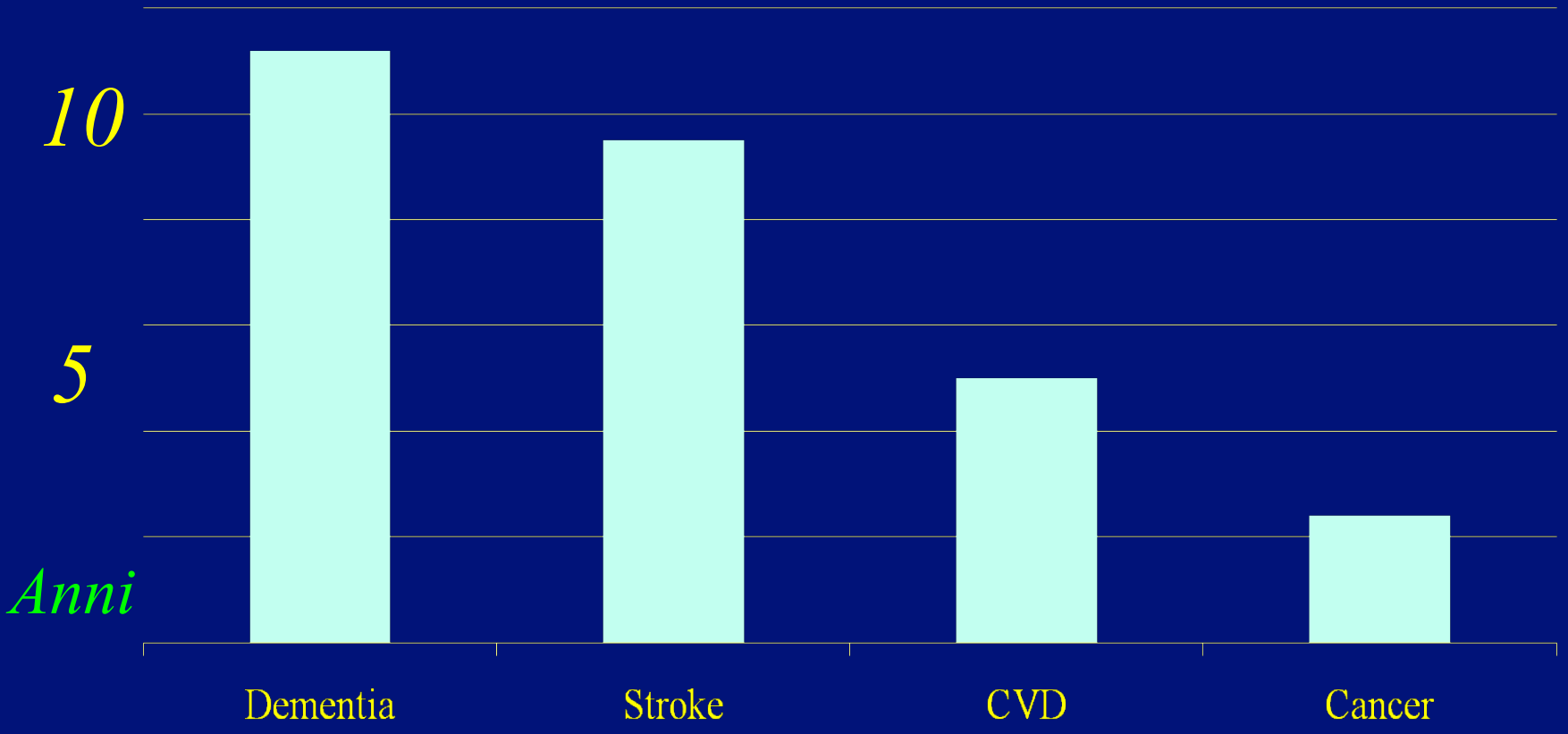
The Global Burden of Disease Study:

Differential Increase in Healthy Years Lost to Disability vs Life Expectancy 1970-2010

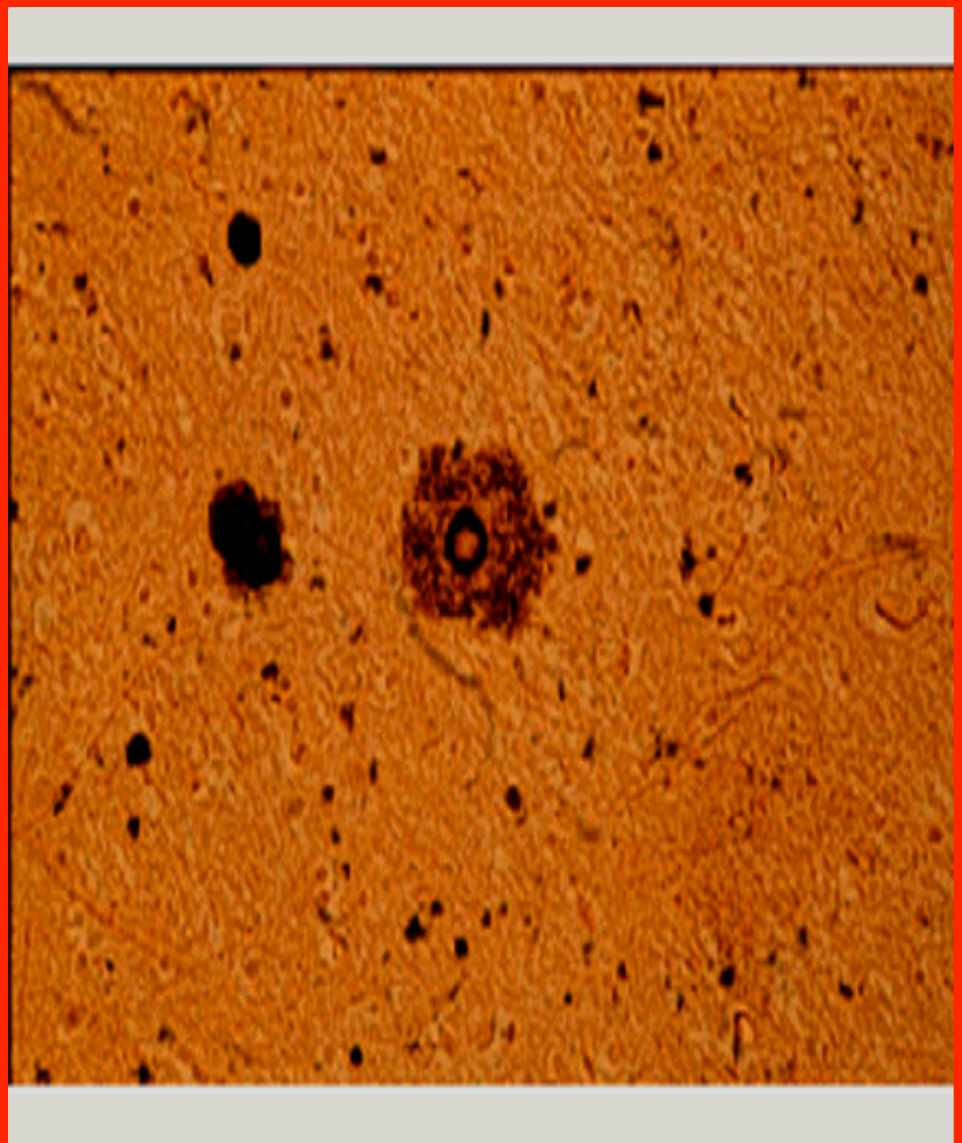
Wang H et al Lancet 2012;380: 2071-94



Demenze e Numero di Anni con Disabilità



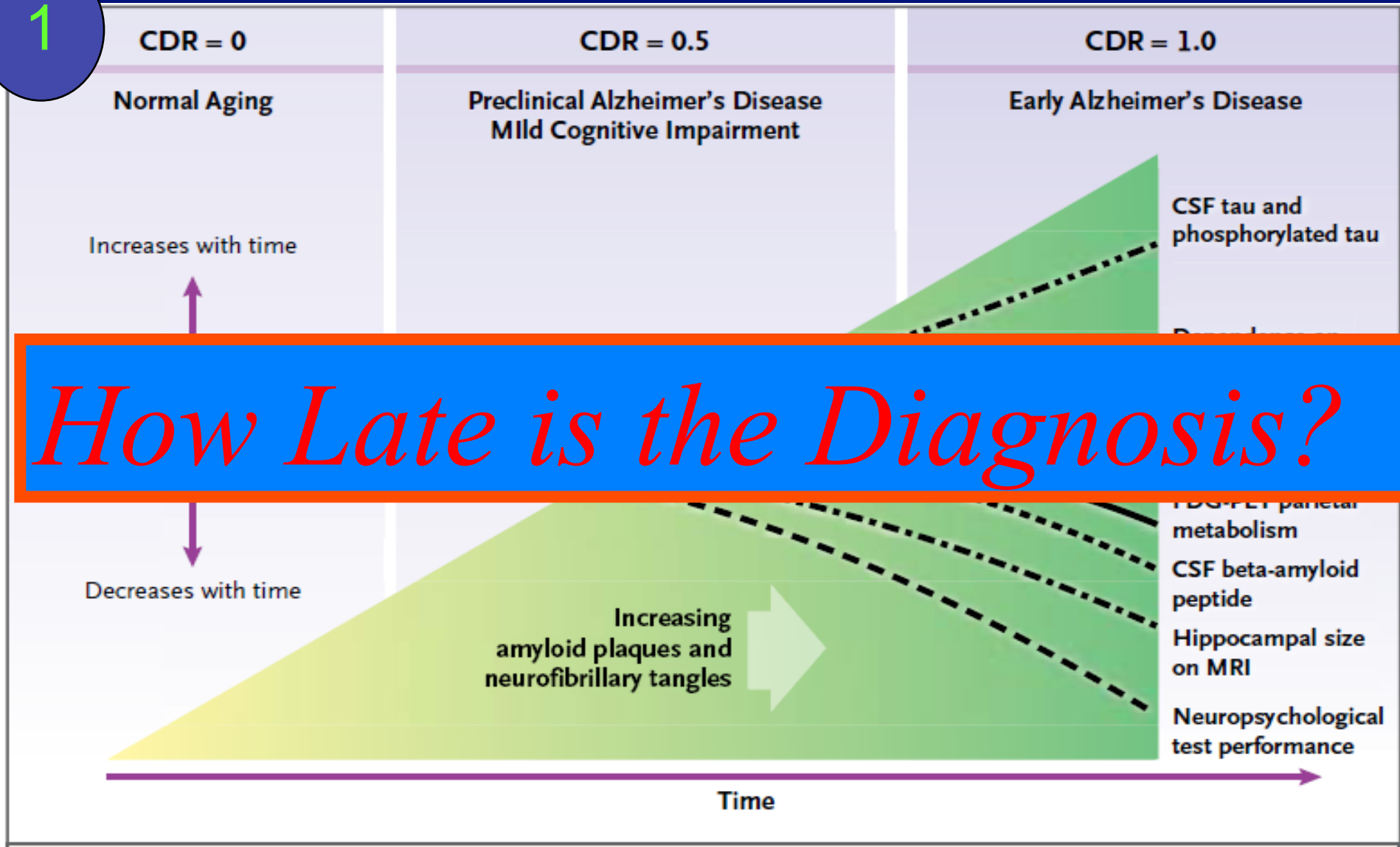
Beta-amyloid Plaque Deposition: The Desert in the Brain



Sequence of Pathological, Clinical, and Radiologic Changes from Normal Aging to Early AD

Mayeux R. NEJM 2010; 362:2194-201

1



How Late is the Diagnosis?

Disappointing Results from AD Trials: Hope is Still The

2

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Two Phase 3 Trials of Bapineuzumab in Mild-to-Moderate Alzheimer's Disease

Stephen Salloway, M.D., Reis[illegible], Nick C. Fox, M.D., Kaj Blennow, M.D., William Klunk, M.D., [illegible], Marwan Sabbagh, M.D., Lawrence S. Honig, M.D., Ph[illegible], Steven Ferris, Ph.D., Marcel Reichert, M.D., Nzeera Ketter, [illegible], Volkmar Guenzler, M.D., Maja Miloslavsky, Ph.D., Daniel [illegible], Julia Lull, M.A., Julia Cristina Tudor, Ph.D., Enchi Liu, Ph[illegible], M.D., M.P.H., Eric Yuen, M.D., Ronald Black, M.D., and [illegible], M.D., for the Bapineuzumab 301 and 302 Clinical [illegible]*

ABSTRACT

BACKGROUND

Bapineuzumab, a humanized anti–amyloid-beta monoclonal antibody, is in [illegible] development for the treatment of Alzheimer's disease.

METHODS

We conducted two double-blind, randomized, placebo-controlled, phase 3 trials involving patients with mild-to-moderate Alzheimer's disease — one involving 1121 carriers of the apolipoprotein E (*APOE*) ε4 allele and the other involving 1331 noncarriers. Bapineuzumab or placebo, with doses varying by study, was administered by intravenous infusion every 13 weeks for 78 weeks. The primary outcome measures were scores on the 11-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog11, with scores ranging from 0 to 70 and higher scores indicating greater impairment) and the Disability Assessment for Dementia (DAD, with scores ranging from 0 to 100 and higher scores indicating less impairment). A total of 1090 carriers and 1114 noncarriers were included in the efficacy analysis. Secondary outcome measures included findings on positron-emission tomographic amyloid imaging with the use of Pittsburgh compound B (PIB-PET) and cerebrospinal fluid phosphorylated tau (phospho-tau) concentrations.

RESULTS

There were no significant between-group differences in the primary outcomes. At week 78, the between-group differences in the change from baseline in the ADAS-cog11 and DAD scores (bapineuzumab group minus placebo group) were −0.2 (P=0.80) and −1.2 (P=0.34), respectively, in the carrier study; the corresponding differences in the noncarrier study were −0.3 (P=0.64) and 2.8 (P=0.07) with the 0.5-mg-per-kilogram dose of bapineuzumab and 0.4 (P=0.62) and 0.9 (P=0.55) with the 1.0-mg-per-kilogram dose. The major safety finding was amyloid-related imaging abnormalities with edema among patients receiving bapineuzumab, which increased with bapineuzumab dose and *APOE* ε4 allele number and which led to discontinuation of the 2.0-mg-per-kilogram dose. Between-group differences were observed with respect to PIB-PET and cerebrospinal fluid phospho-tau concentrations in *APOE* ε4 allele carriers but not in noncarriers.

CONCLUSIONS

Bapineuzumab did not improve clinical outcomes in patients with Alzheimer's disease, despite treatment differences in biomarkers observed in *APOE* ε4 carriers. (Funded by Janssen Alzheimer Immunotherapy and Pfizer; Bapineuzumab 301 and 302 ClinicalTrials.gov numbers, NCT00575055 and NCT00574132, and EudraCT number, 2009-012748-17.)

From Butler Hospital, Providence, RI (S.S.); Brigham and Women's Hospital, Boston (R.S.); University College London, Institute of Neurology, London (N.C.F.); University of Göteborg, Sahlgrenska University Hospital, Mölndal, Sweden (K.B.); University of Pittsburgh, Pittsburgh (W.K.); Veterans Affairs Medical Center, Seattle (M.R.); Cleo Roberts Center for Clinical Research/Sun Health Research Institute, Sun City, AZ (M.S.); Columbia University (L.S.H.) and New York University Langone Medical Center (S.F.), New York; University of Rochester School of Medicine and Dentistry, Rochester, NY (A.P.F.); Janssen Alzheimer Immunotherapy Research and Development, South San Francisco, CA (M.R., N.K., B.N., V.G., M.M., D.W., Y.L., E.C.T., E.L., E.Y., H.R.B.); Janssen Research and Development, Titusville, NJ (J.L.); Global R&D Partners and the University of California, San Diego — both in San Diego (M.G.); and Pfizer, Collegeville, PA (R.B.). Address reprint requests to Dr. Salloway at Butler Hospital, Warren Alpert Medical School of Brown University, 345 Blackstone Blvd., Providence, RI 02906, or at ssalloway@butler.org.

Drs. Salloway and Sperling contributed equally to this article.

*A complete list of the Bapineuzumab Study 301 and 302 investigators is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2014;370:322-33.
DOI: 10.1056/NEJMoa1304839

ORIGINAL ARTICLE

Phase 3 Trials of Solanezumab for Mild-to-Moderate Alzheimer's Disease

Rachelle S. Doody, M.D., Ph.D., Ronald G. Thomas, Ph.D., Martin Farlow, M.D., Takeshi Iwatsubo, M.D., Ph.D., Bruno Vellas, M.D., Steven Joffe, M.D., M.P.H., Karl Kieburtz, M.D., M.P.H., Rema Raman, Ph.D., Xiaoying Sun, M.S., and Paul S. Aisen, M.D., for the Alzheimer's Disease Cooperative Study Steering Committee; and Eric Siemers, M.D., Hong Liu-Seifert, Ph.D., and Richard Mohs, Ph.D., for the Solanezumab Study Group

ABSTRACT

BACKGROUND

Alzheimer's disease is characterized by amyloid-beta plaques, neurofibrillary tangles, gliosis, and neuronal loss. Solanezumab, a humanized monoclonal antibody, preferentially binds soluble forms of amyloid and in preclinical studies promoted its clearance from the brain.

METHODS

In two phase 3, double-blind trials (EXPEDITION 1 and EXPEDITION 2), we randomly [illegible]ed 1012 and 1040 patients, respectively, with mild-to-moderate Alzheimer's dis[illegible] placebo or solanezumab (administered intravenously at a dose of 400 mg) [illegible] 18 months. The primary outcomes were the changes from baseline to [illegible] the 11-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-[illegible].1; range, 0 to 70, with higher scores indicating greater cognitive impairment) [illegible] the Alzheimer's Disease Cooperative Study–Activities of Daily Living scale (ADCS-ADL; range, [illegible] with lower scores indicating worse functioning). After analysis of data from [illegible], the primary outcome for EXPEDITION 2 was revised to the change in [illegible] cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-[illegible] to 90, with higher scores indicating greater impairment), in patients with [illegible] disease.

RESULTS

Neither study showed significant improvement in the primary outcomes. The modeled difference between groups (solanezumab group minus placebo group) in the change from baseline was −0.8 points for the ADAS-cog11 score (95% confidence interval [CI], −2.1 to 0.5; P=0.24) and −0.4 points for the ADCS-ADL score (95% CI, −2.3 to 1.4; P=0.64) in EXPEDITION 1 and −1.3 points (95% CI, −2.5 to 0.3; P=0.06) and 1.6 points (95% CI, −0.2 to 3.3; P=0.08), respectively, in EXPEDITION 2. Between-group differences in the changes in the ADAS-cog14 score were −1.7 points in patients with mild Alzheimer's disease (95% CI, −3.5 to 0.1; P=0.06) and −1.5 in patients with moderate Alzheimer's disease (95% CI, −4.1 to 1.1; P=0.26). In the combined safety data set, the incidence of amyloid-related imaging abnormalities with edema or hemorrhage was 0.9% with solanezumab and 0.4% with placebo for edema (P=0.27) and 4.9% and 5.6%, respectively, for hemorrhage (P=0.49).

CONCLUSIONS

Solanezumab, a humanized monoclonal antibody that binds amyloid, failed to improve cognition or functional ability. (Funded by Eli Lilly; EXPEDITION 1 and 2 ClinicalTrials.gov numbers, NCT00905372 and NCT00904683.)

From the Alzheimer's Disease and Memory Disorders Center, Department of Neurology, Baylor College of Medicine, Houston (R.S.D.); Alzheimer's Disease Cooperative Study, Department of Family and Preventive Medicine (R.G.T., R.R., X.S.), and the Department of Neurosciences (R.G.T., R.R., P.S.A., R.M.), University of California at San Diego, San Diego; Indiana Alzheimer Disease Center, Indiana University (M.F.), and Eli Lilly (E.S., H.L.-S., R.M.) — both in Indianapolis; the Department of Neuropathology, School of Medicine, and the Department of Neuropathology and Neuroscience, School of Pharmacological Science, University of Tokyo, Tokyo (T.I.); Gerontopole, Unité Mixte de Recherche 1027, Centre Hospitalier Universitaire Toulouse, Toulouse, France (B.V.); the Department of Medical Ethics and Health Policy, University of Pennsylvania, Philadelphia (S.J.); and the Center for Human Experimental Therapeutics, University of Rochester Medical Center, Rochester, NY (K.K.). Address reprint requests to Dr. Doody at the Department of Neurology, Alzheimer's Disease and Memory Disorders Center, Baylor College of Medicine, 1977 Butler Blvd., Suite E 5.101, Houston, TX 77030, or at rdoody@bcm.edu.

N Engl J Med 2014;370:311-21.
DOI: 10.1056/NEJMoa1312889

NEJM January 2014

The most pressing problem of our

AGE

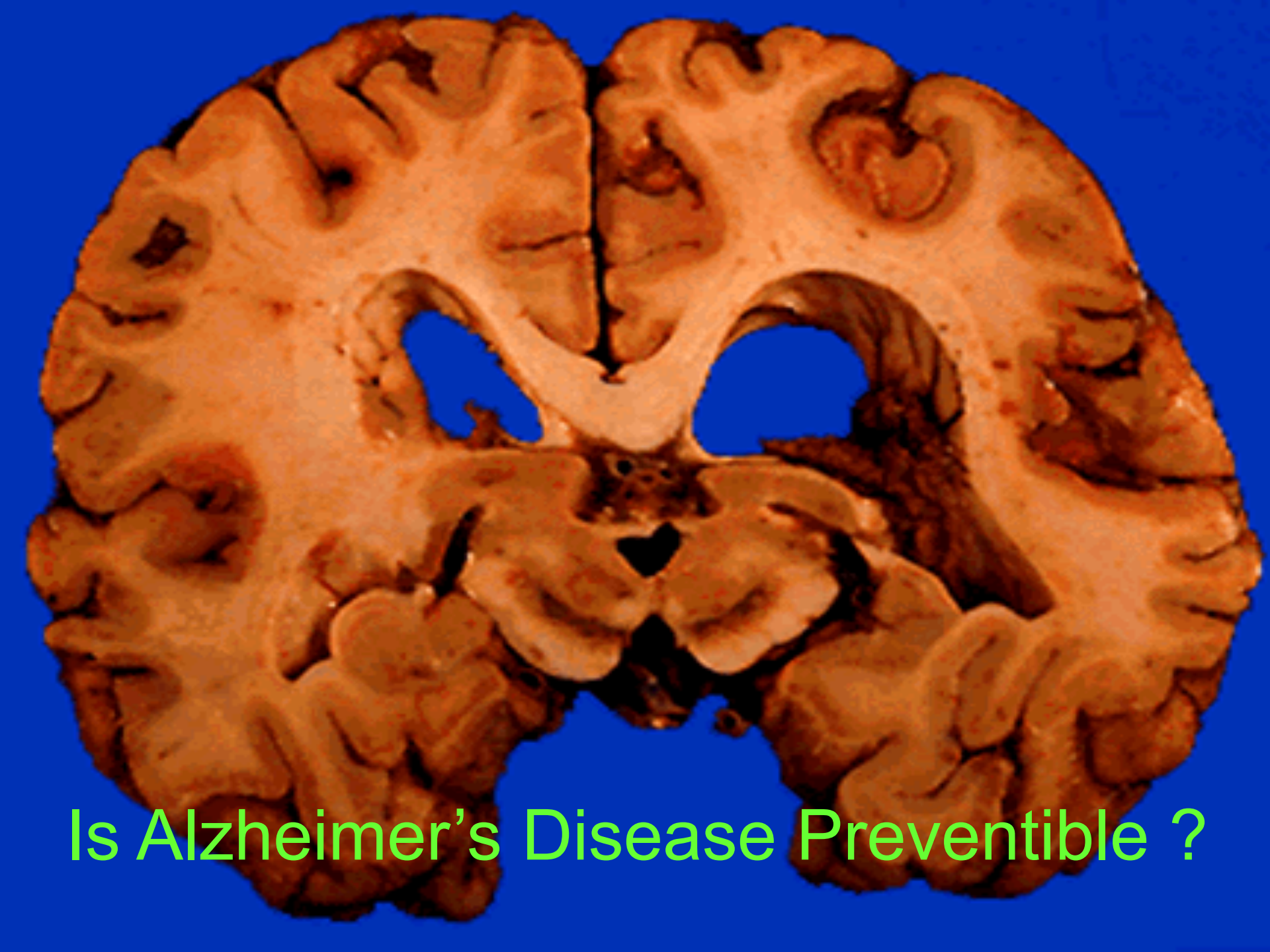
3

Frailty

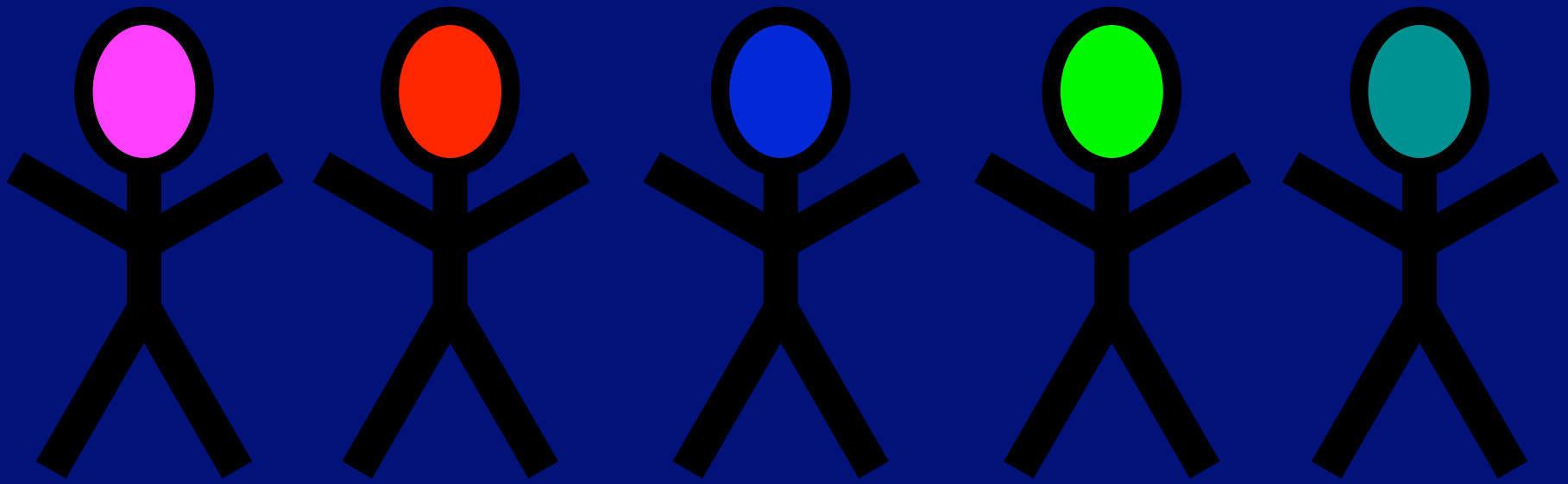
BMJ 2003

Thomas Kirkwood

BMJ VOLUME 320 14 JUNE bmj.com

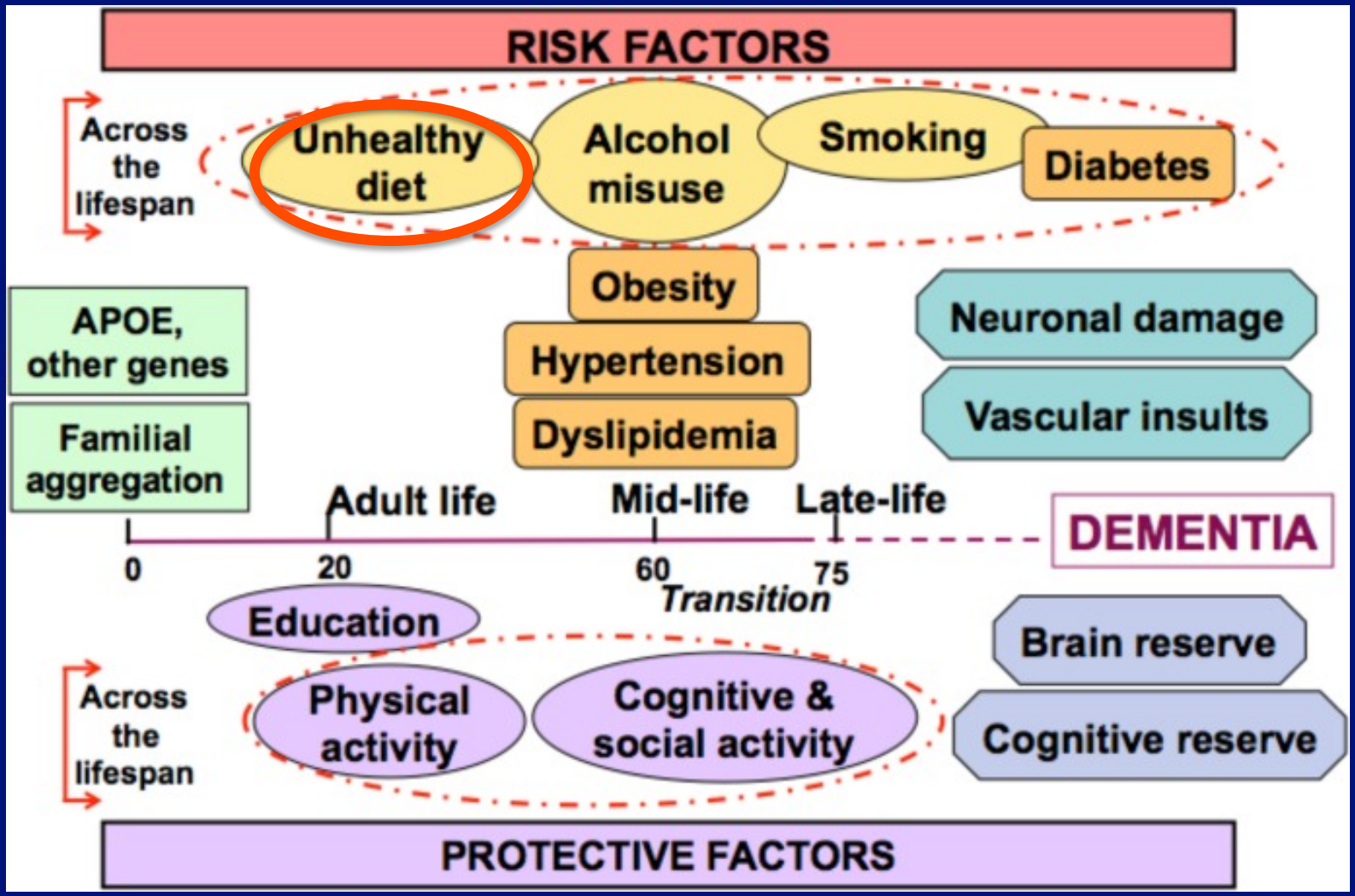

Is Alzheimer's Disease Preventible ?

Etiologic Heterogeneity of Neurodegeneration



Toxin 1 Toxin 2 High Risk Behavior Gene 1 Gene 2

Genetic, Lifestyle, and “Vascular” Risk Factors

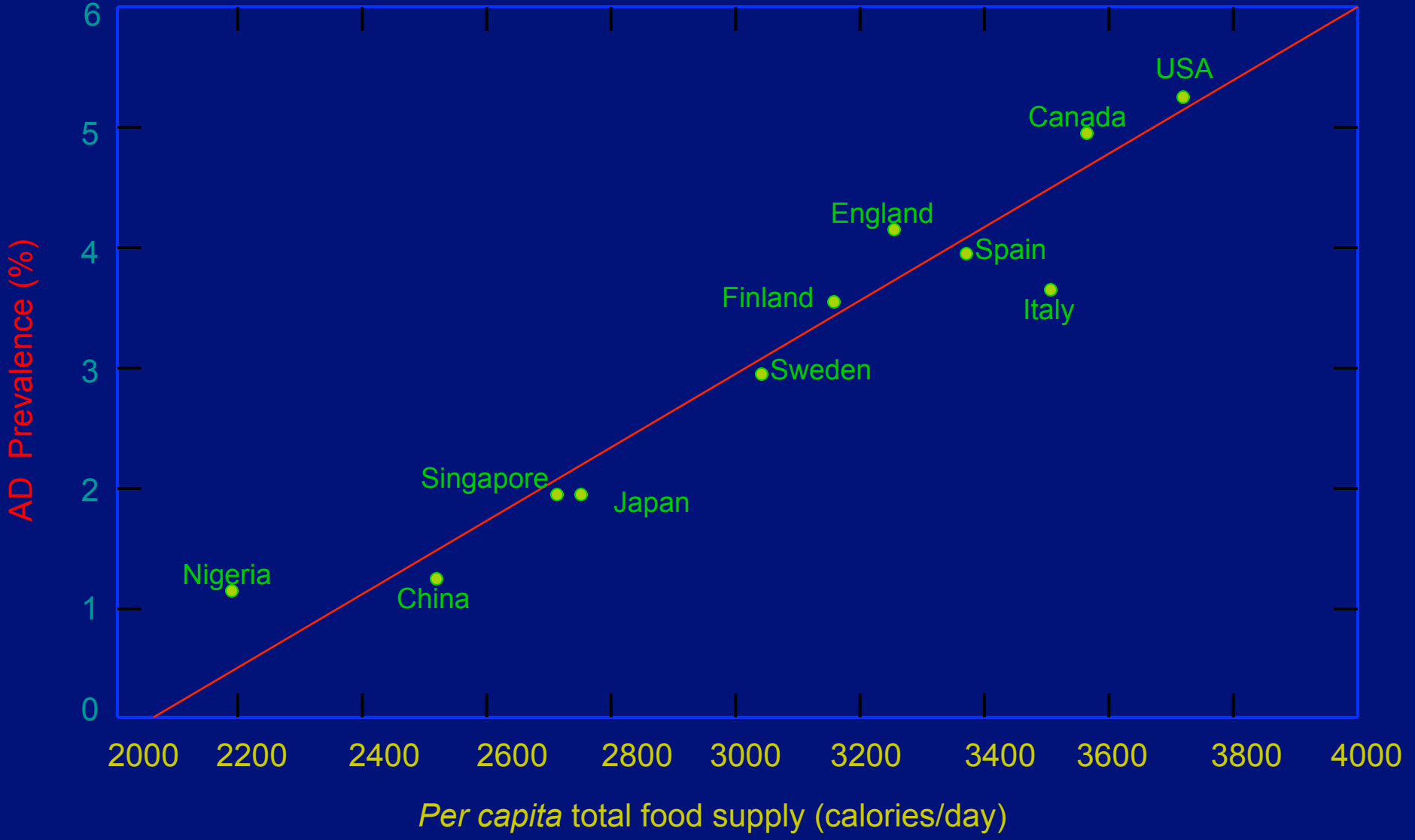


F1000 Prime Reports 2015;7:50

Individuals and Populations

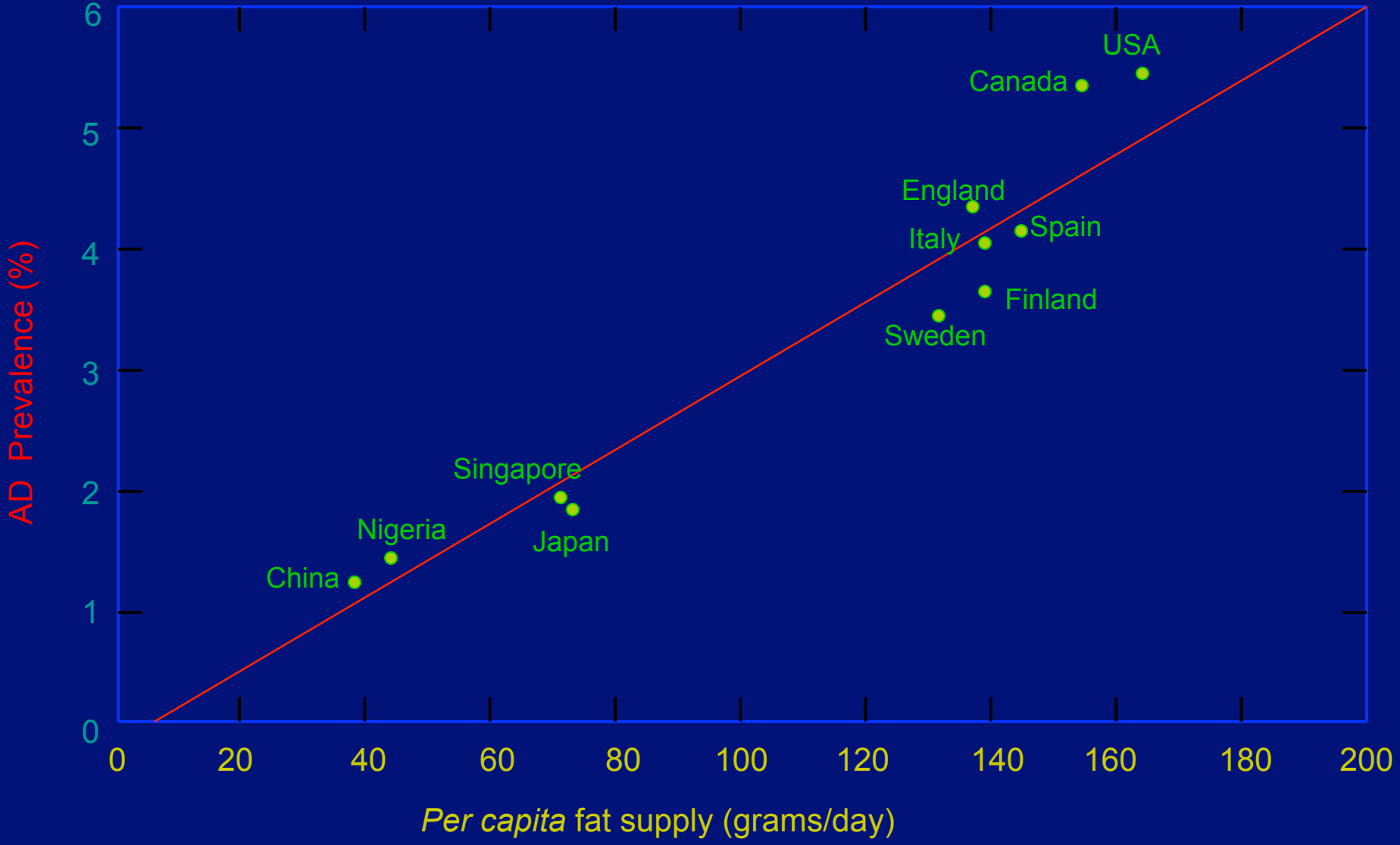
AD Prevalence (65+) Vs Food Supply

Grant W B Alzheimer's Disease review, 1997; 2:42-55



AD Prevalence (65+) vs. Fat Supply

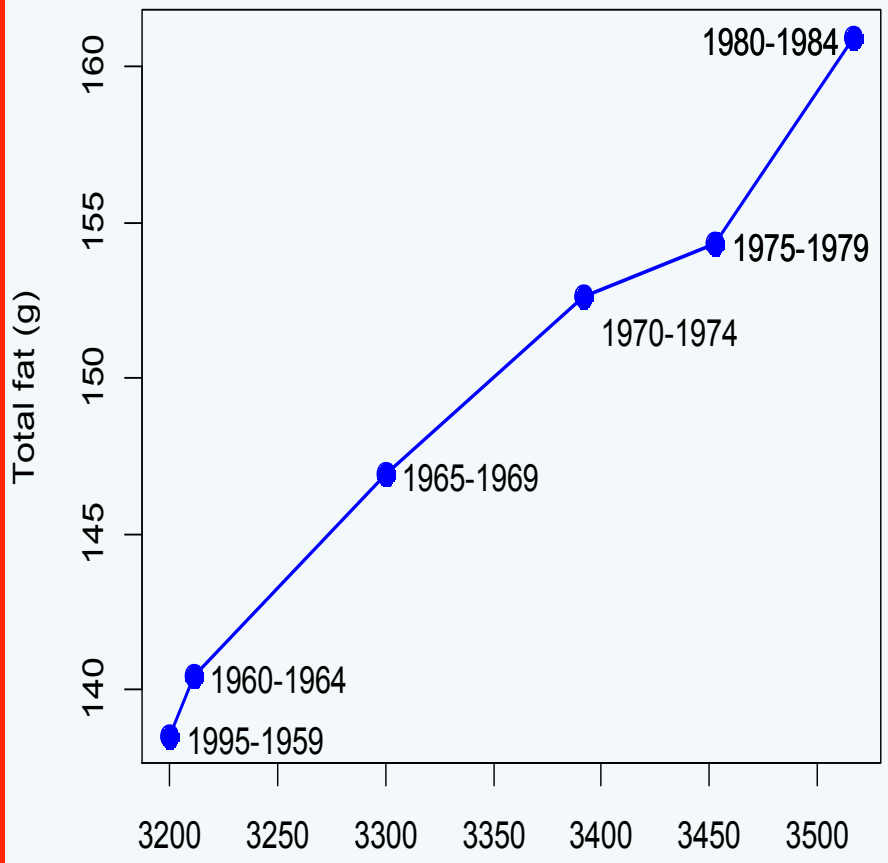
Grant W B Alzheimer's Disease review, 1997; 2:42-55

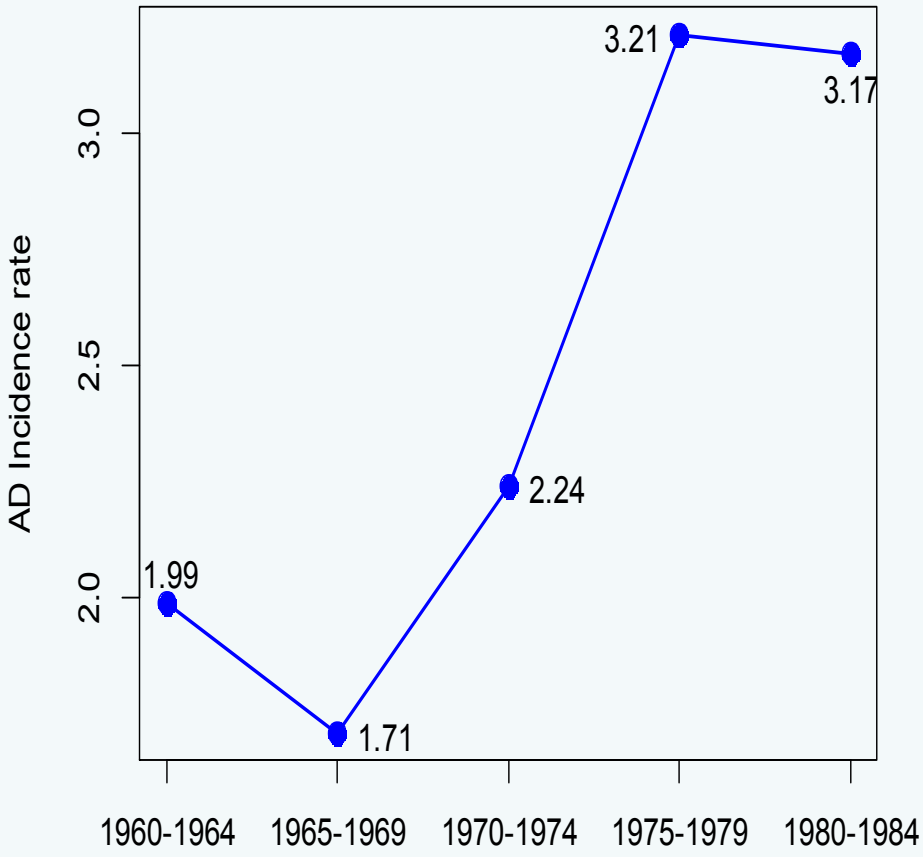



MANITOBA
CANADA
ONTARIO
Thunder Bay
Grand Forks
RED LAKE I.R.
Eagle Mountain 701 m
Lake Superior
406 m
NORTH DAKOTA
Red River
WHITE EARTH I.R.
Fargo
James
Duluth
Mount Arvon 603 m
MICHIGAN
MINNESOTA
S U P E R I O R
STATI UNITI
SISSETON I.R.
Aberdeen
Saint Cloud
WISCONSIN
U P L A N D
Coon Rapids
Saint Paul
Wausau
Eau Claire
Green Bay
SOUTH DAKOTA
Bloomington
Appleton
Winona
Mankato
Oshkosh
Rochester
Sheboygan
La Crosse
Sioux Falls
IOWA
West Bend
Lake Michigan

AD Incidence Rates for the 65+ population from Rochester, MN, along with Average US Total Food Supply Levels

Grant W B Alzheimer's Disease review, 1997; 2:42-55





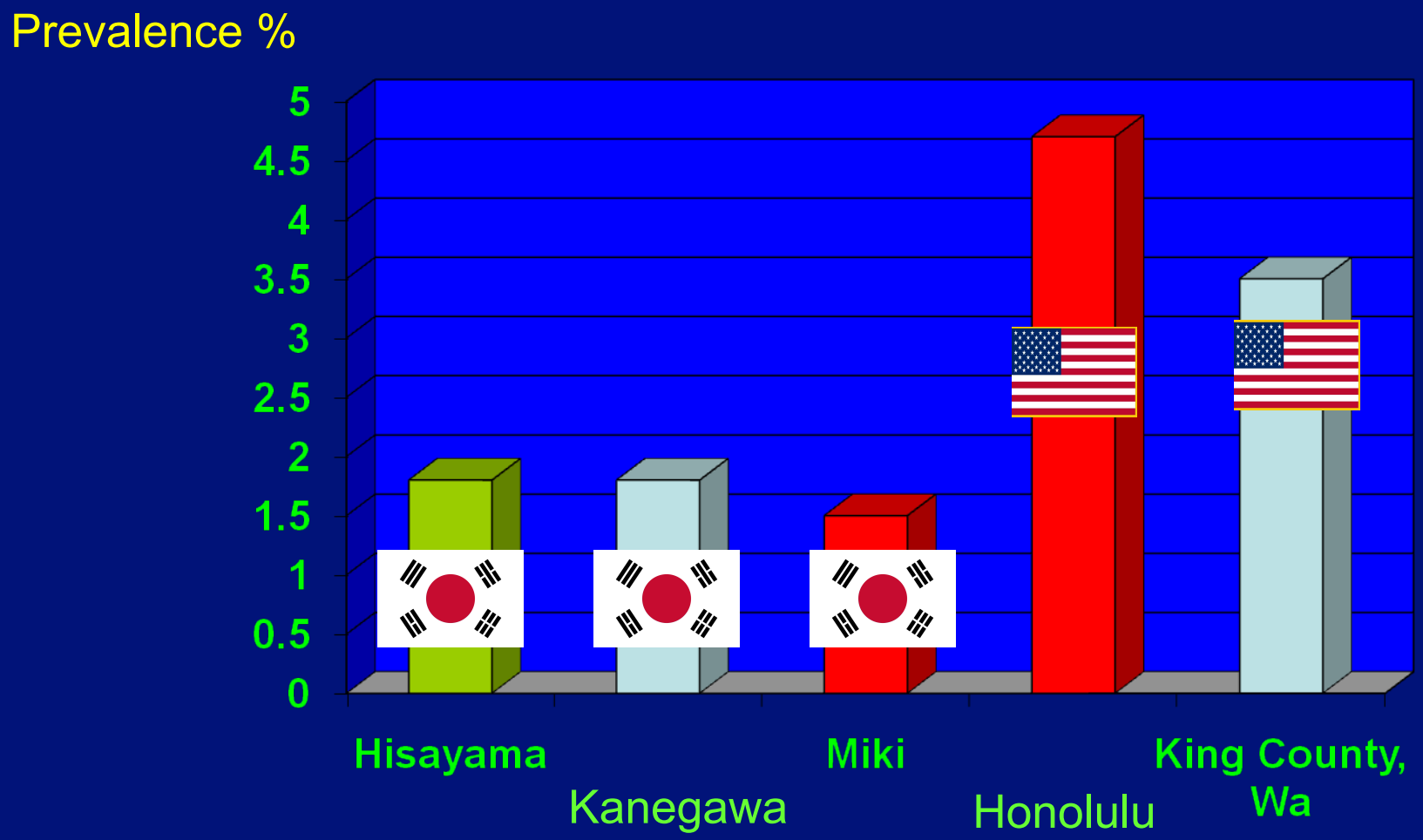
Hawaii, the diet, the heart and the brain: what is the link?

The Honolulu Heart Study

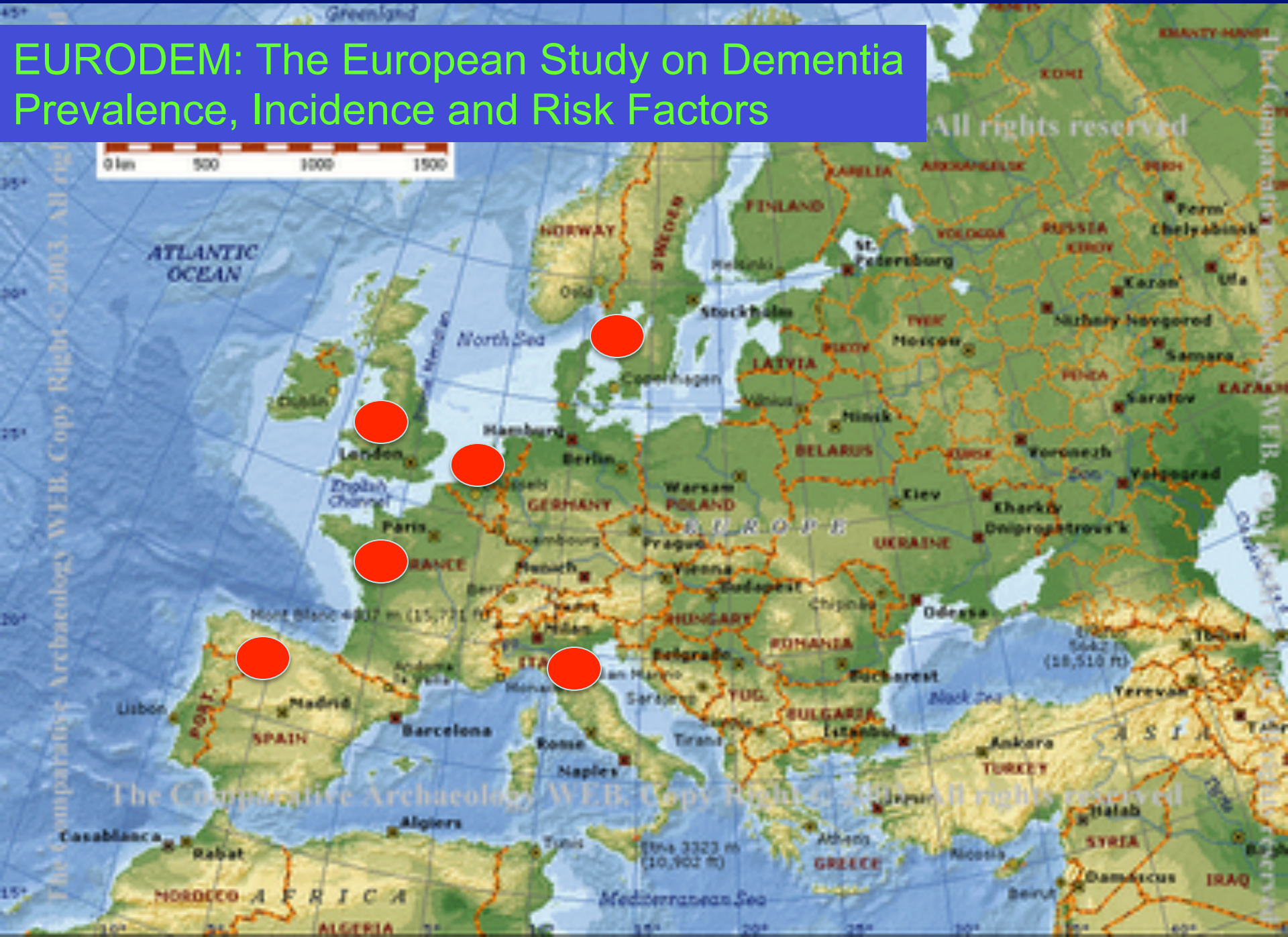
The Japanese Men in Hawaii

Alzheimer' Disease Prevalence among Elderly Japanese in Japan and US

Grant W B Alzheimer's Disease review, 1997; 2:42-55



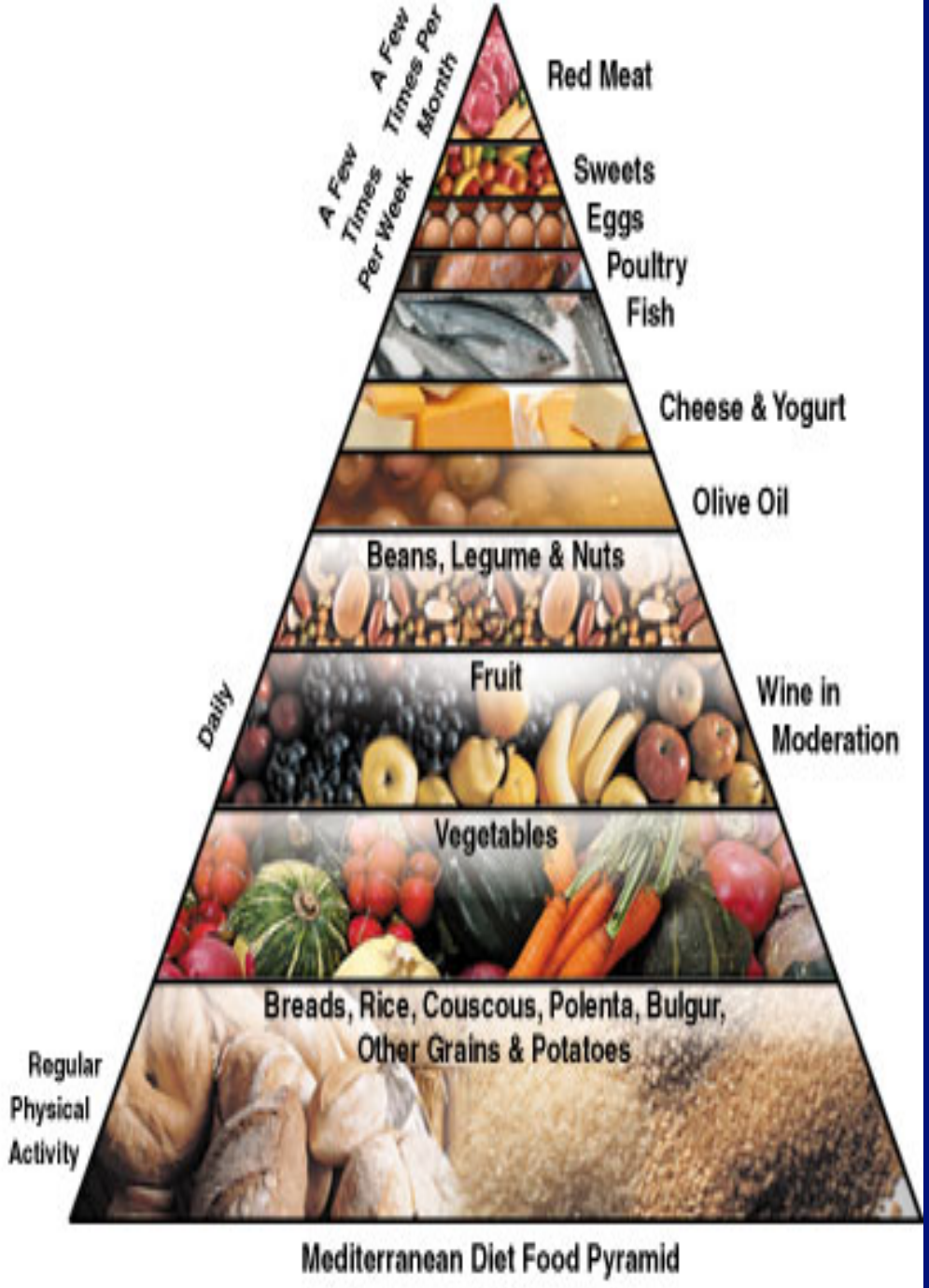
EURODEM: The European Study on Dementia Prevalence, Incidence and Risk Factors



Incidence of Dementias by Geographic Area in Europe

Fratiglioni et al. Neurology 2000: 54 Suppl 5: S10-15

Mediterranean Diet



Mediterranean Diet Food Pyramid

1. Using "good" fats, such as olive ,rather than butter or lard, and limiting dairy products like high-fat cheese and milk

2. An abundance of plant foods, such as fruits, vegetables, cereals, nuts, and beans;

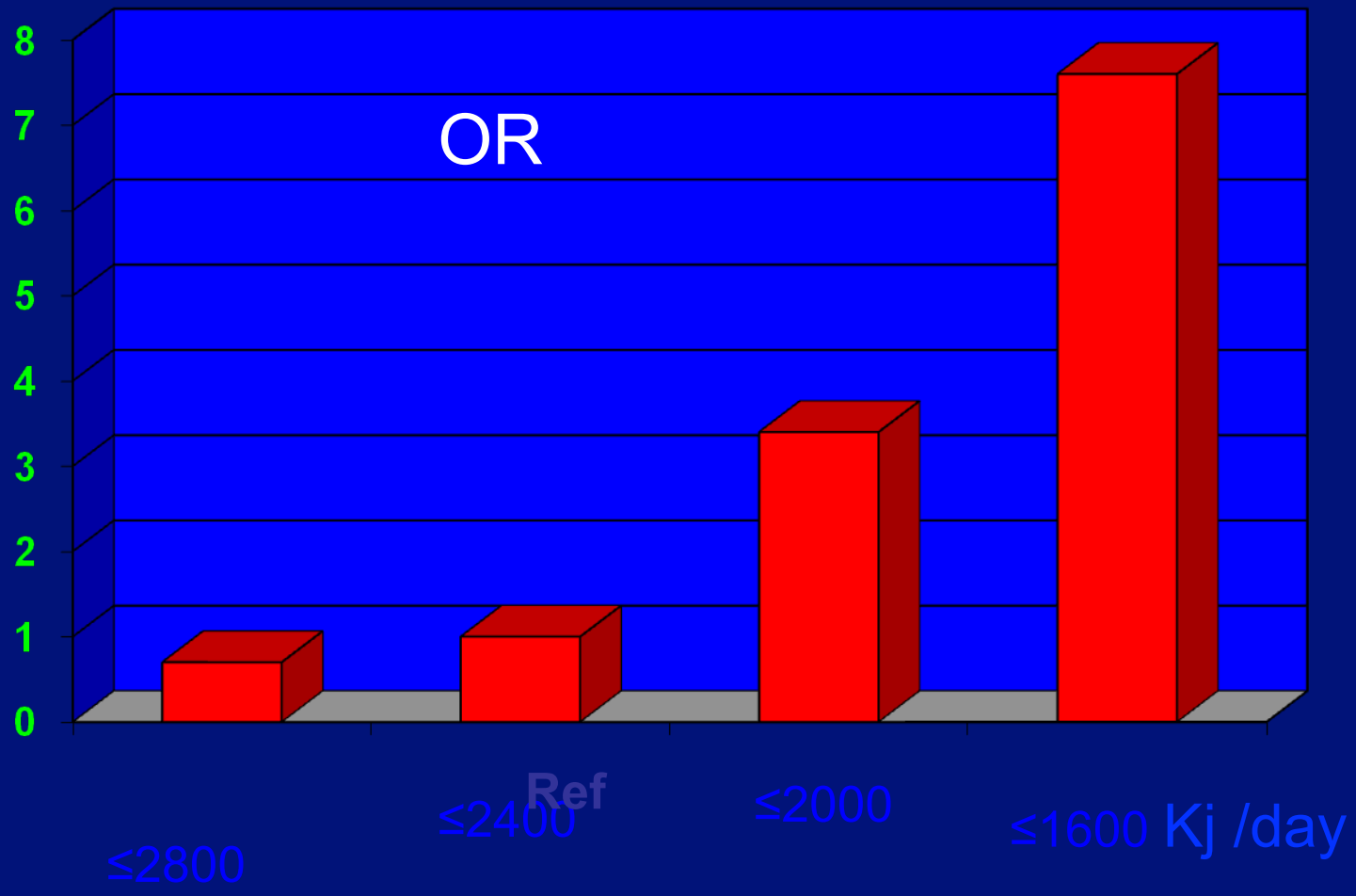
3. Eating moderate amounts of fish and poultry, rather than red meat;

4. Drinking a glass or two of red wine a day (Men 10-50 g/day, Women 5-25 mg day).

1st Component
Using “good” fats, such as olive ,rather than butter or lard, and limiting dairy products like high-fat cheese and milk

ILSA: Association between Cognitive Decline and MUFA Intake

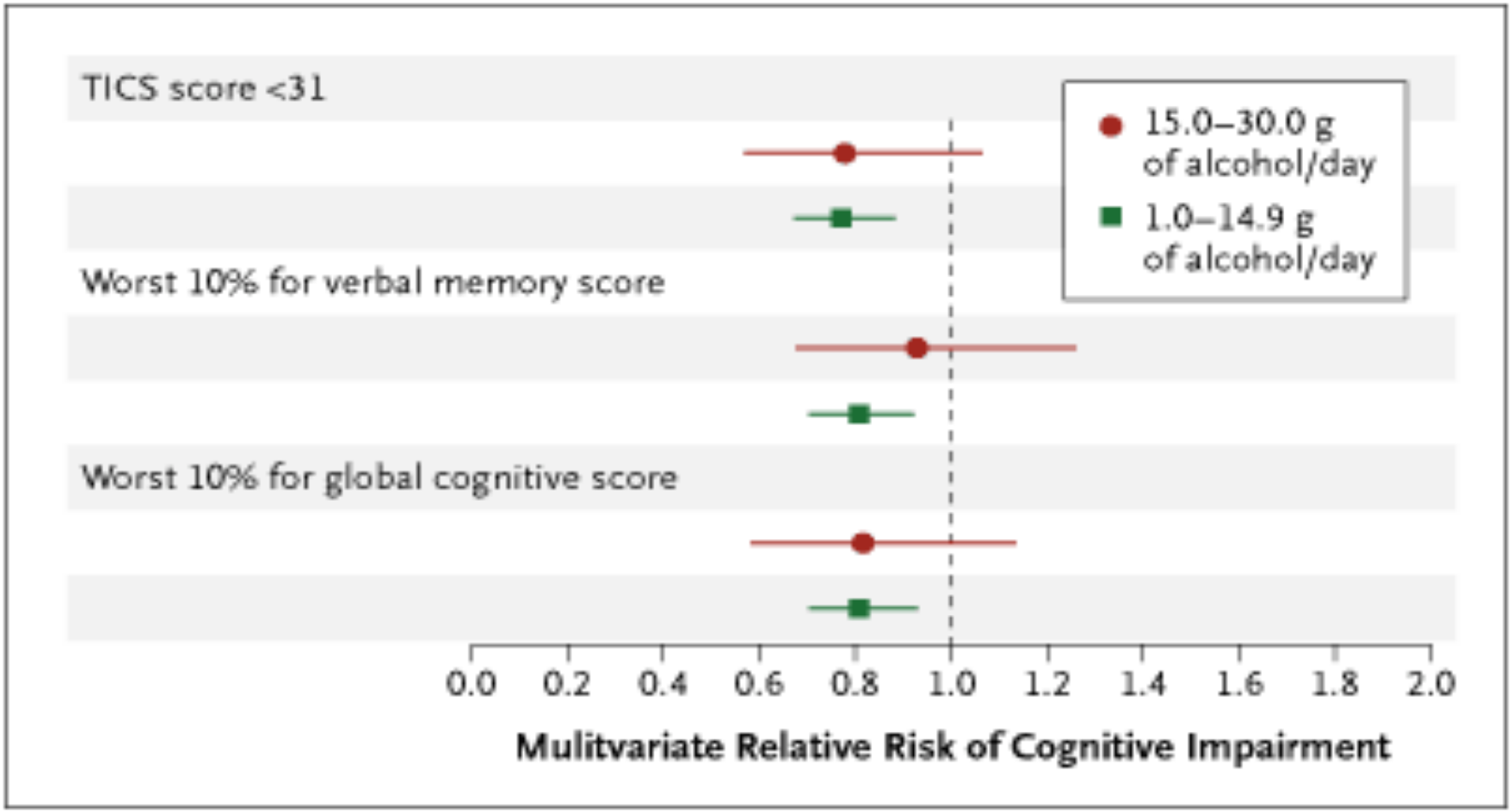
Solfrizzi et al Neurology 1999; 52:1563-74



2nd component
Drinking a glass or two of red wine a day
(Men 10-50 g/d;Women 5-25 mg day)

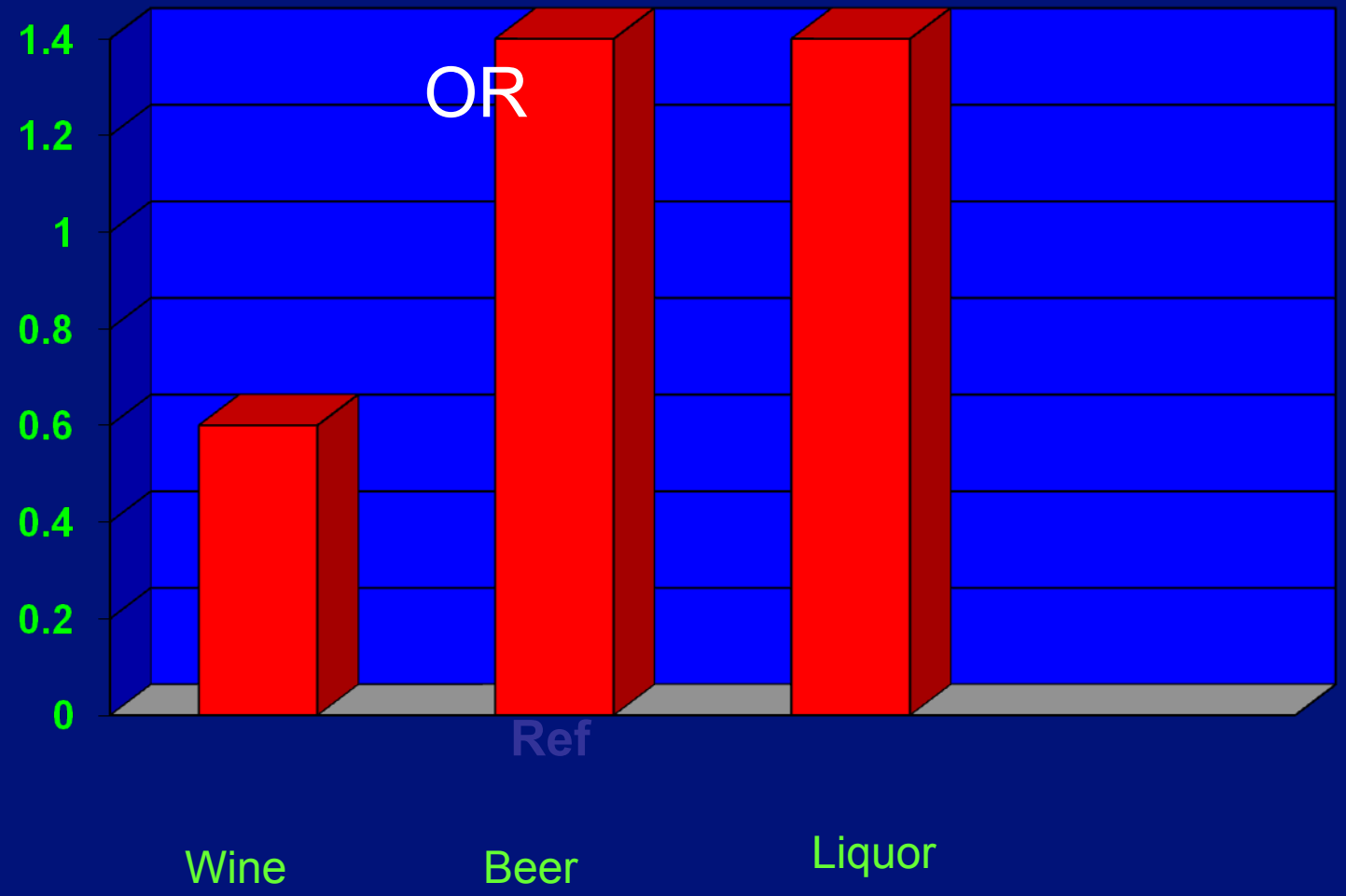
Effects of Moderate Alcohol Consumption on Cognitive Function in Women

Stampfer MJ et al. NEJM 2005 Volume 352:245-253



Relationship between Alcoholic Beverage Intake and Incident AD

Luchsinger J A et al JAGS 2004; 52:540-46



3rd component

Abundance of plant foods, such as fruits, vegetables, cereals, nuts, and beans:

Differences in Cognitive Decline over 2 years between Women in Quintile 5 versus Quintile 1 of Fruit and Vegetable Intake

Kang J H at al Ann Neurol 2005; 57:713-720

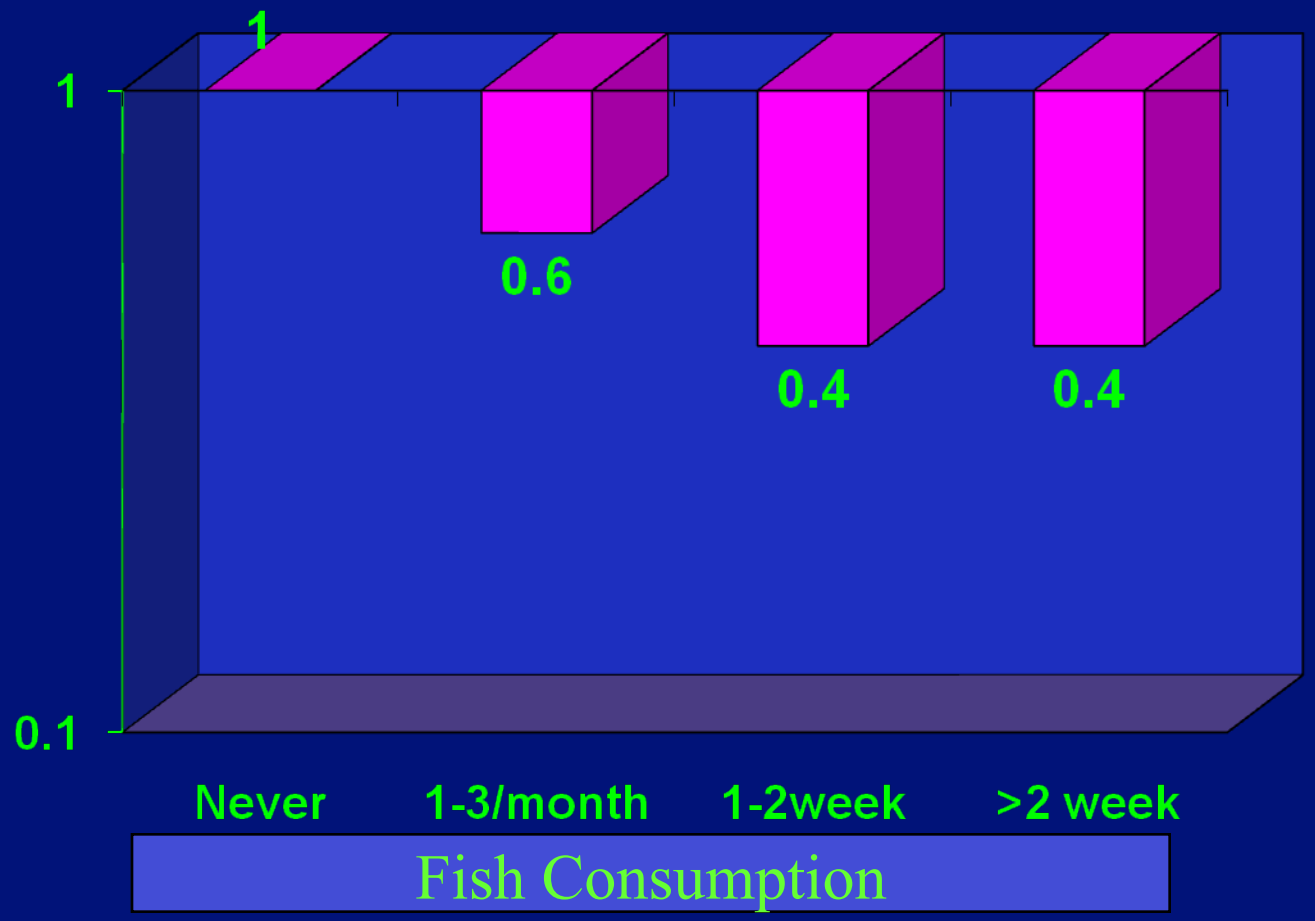
Intake type	TICS (n=133888)	Episodic Memory (n=11585)
All vegetable	0.13(-0.02 to 0.28) p trend=0.1	0.06(0.02 to 0.11) p trend=0.002
All fruits	0.02(-0.13 to 0.17) p trend=0.9	-0.02 (-0.06 to 0.02) p trend=0.6
Green leafy veg	0.23 (0.009 to 0.38) p trend=0.003	0.06(0.02 to 0.10) p trend=<0.001
Cruciferus veg	0.12(-0.02 to 0.26) p trend=0.2	0.05 (0.01 to 0.09) p trend=0.02
Yellow veg	0.01(-0.14 to 0.16) p trend=0.7	0.02(-0.02 to 0.07) p trend=0.5
Legumes	0.08 (-0.07 to 0.22) p trend=0.3	0.05(0.01 to 0.09) p trend=0.01

4th Component :
Eating moderate amounts of fish and poultry, rather than red meat

RR of Incident AD by Frequency of Fish Consumption

Chicago Health and Aging Project, 1993-2000

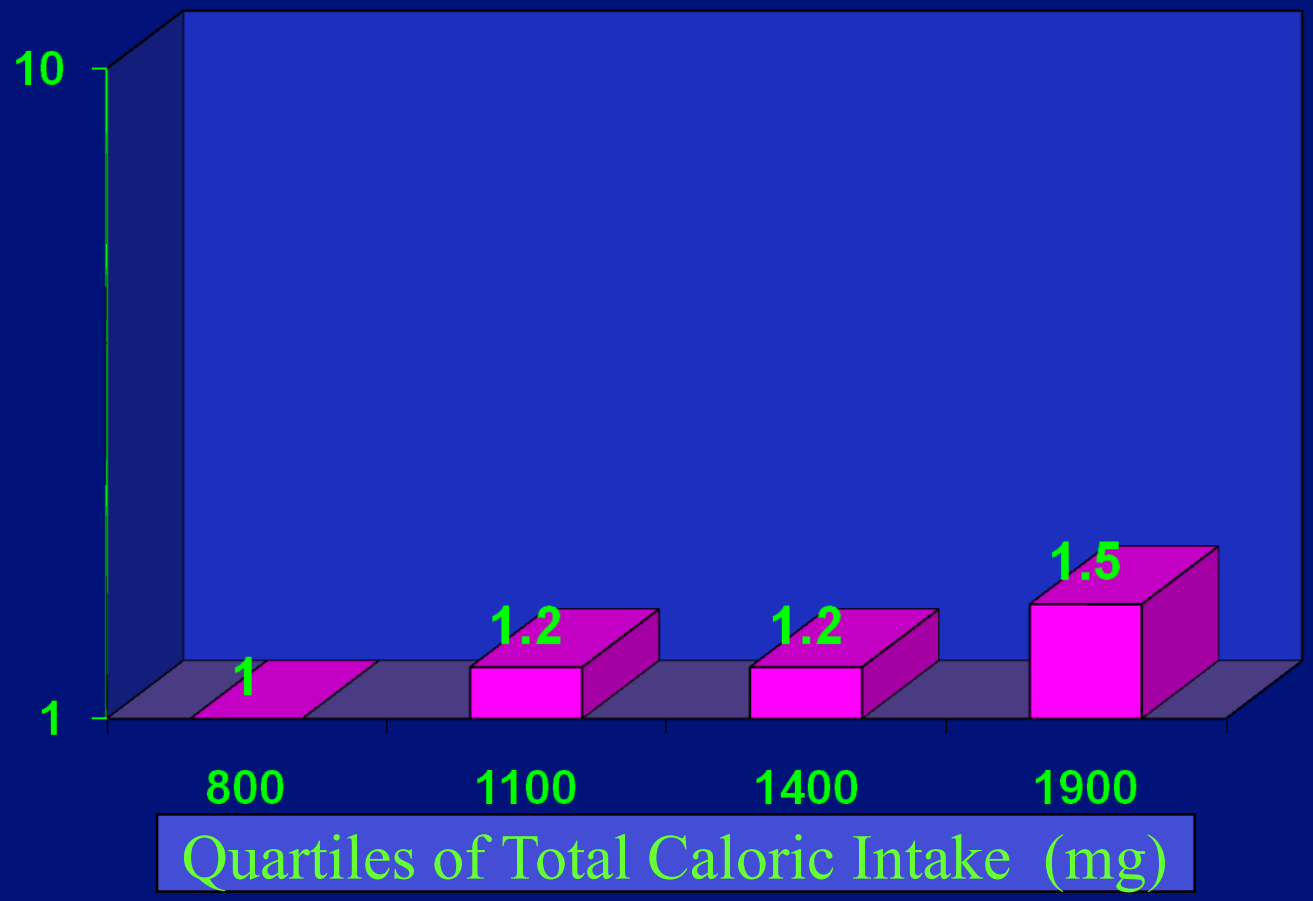
Morris MC et al. Arch Neurol. 2003; 60: 940-946




SUPER SIZE ME
A FILM OF EPIC PORTIONS

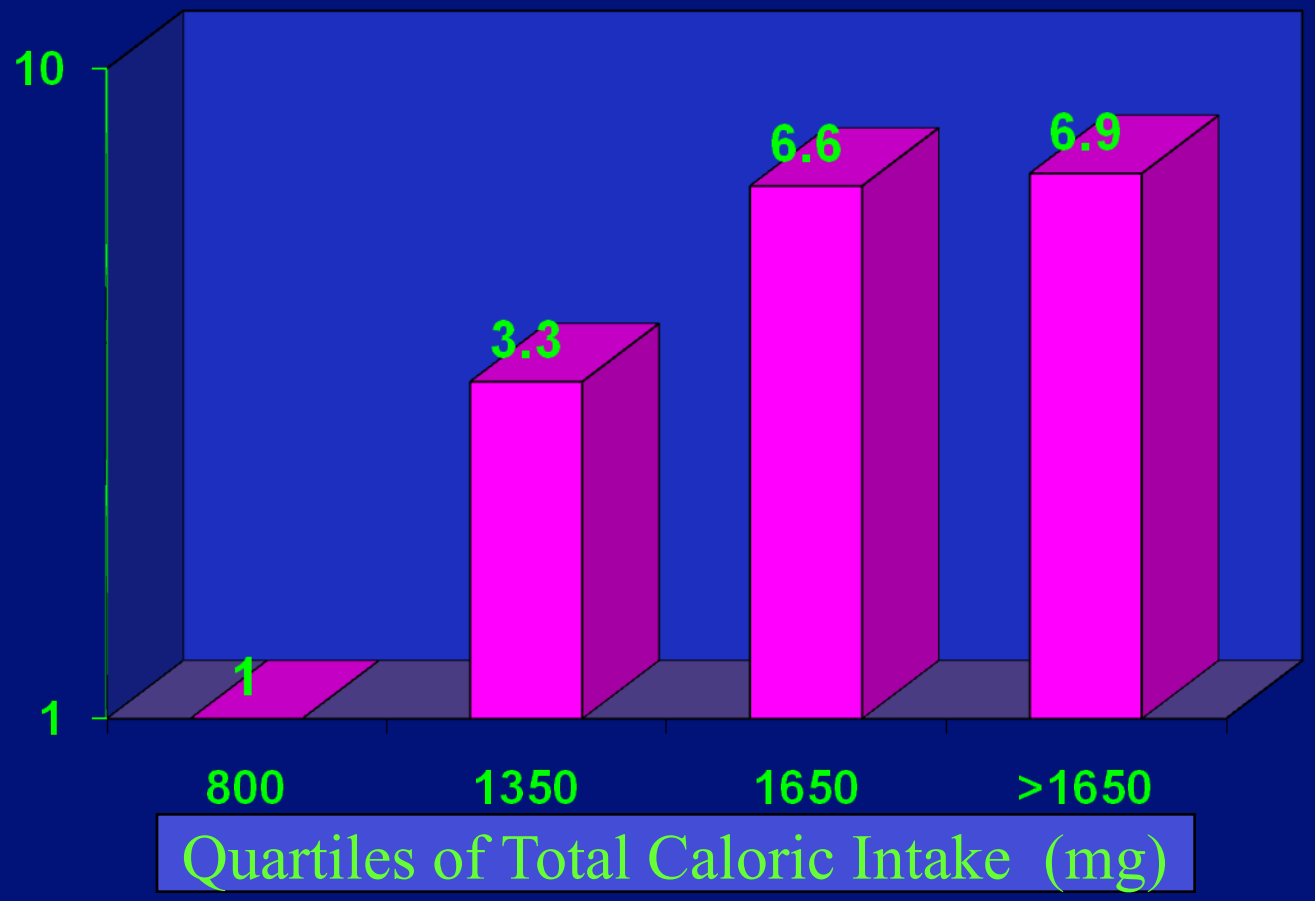
Adjusted Odds Ratios (OR) and 95% (CI) for the Associations of AD with Caloric Intake

Luchsinger et al. Arch Neurol. 2002;59:1258-1263



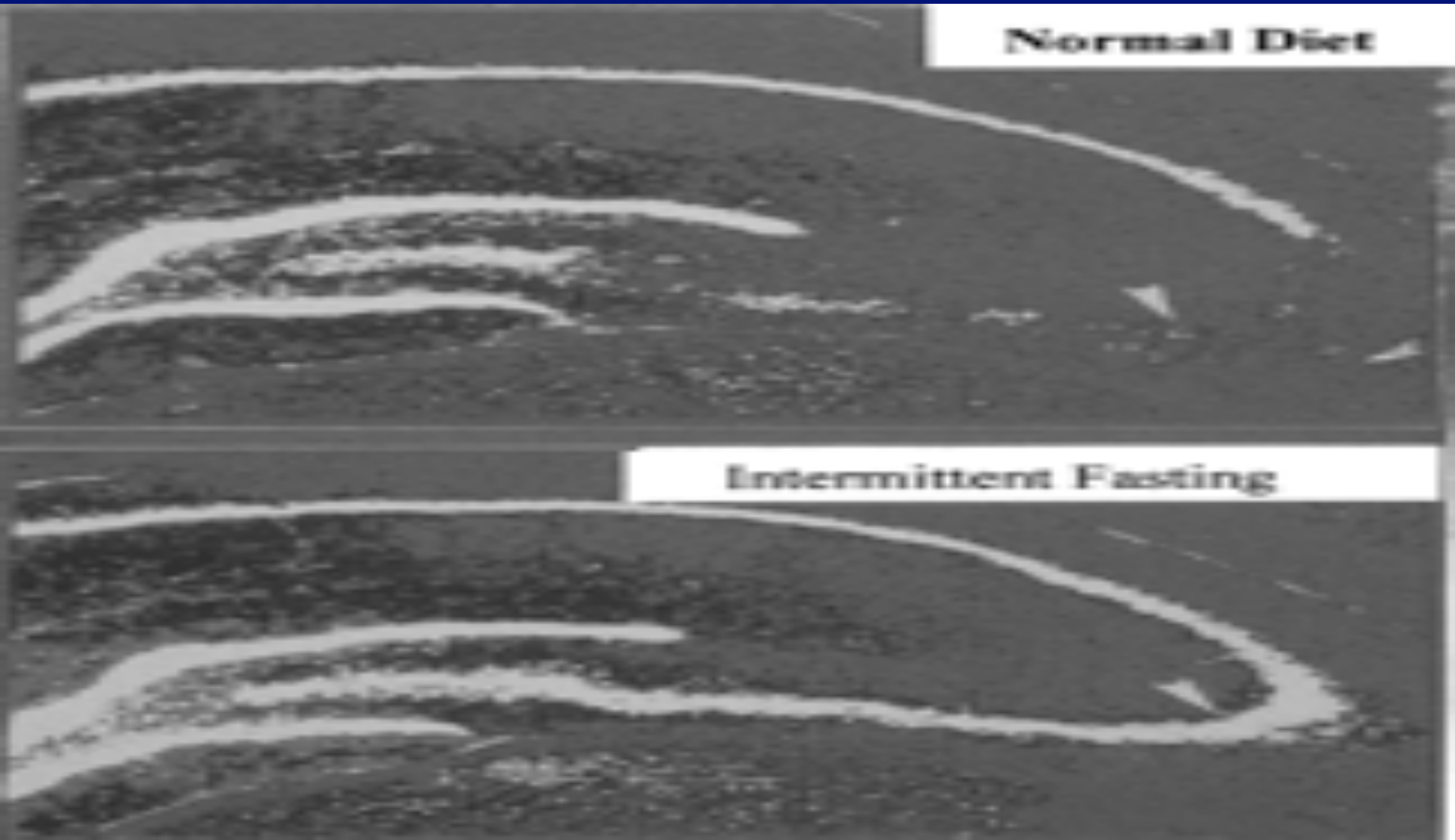
Adjusted Odds Ratios (OR) and 95% (CI) for the Associations of PD with Caloric Intake

Logroscino et al. An Neurol 1996; 39: 89-94



Dietary Restriction protects Hippocampal Neurons against Degeneration induced by Excitotoxin

Mattson MP et al. Neurology 2003;60:690-695



Mediterranean Diet in New York


The Northern Manhattan
Aging Project


Metropolitan Transportation Authority
MTA New York City Subway
THE BRONX
MANHATTAN
QUEENS
CENTRAL PARK
VAN CORTLANDT PARK
BRONX ZOO
ORCHARD BEACH
PELHAM BAY PARK
FLUSHING MEADOWS PARK
LAGUARDIA AIRPORT
Hudson River
Harlem River
Long Island Sound
Wakefield 241 St
Nereid Av (238 St)
233 St
225 St
219 St
Gun Hill Rd
Burke Av
Allerton Av
Pelham Pkwy
Morris Park
Bronx Park East
E 180 St
Eastchester Dyre Av
Baychester Av
Pelham Bay Park
Buhre Av
Middletown Rd
Westchester Sq East Tremont Av
Zerega Av
Castle Hill Av
Parkchester–E 177 St
St Lawrence Av
Morrison–Sound View Avs
Elder Av
Whitlock Av
Hunts Point Av
Longwood Av
E 149 St
E 143 St St Mary's St
Cypress Av
Brook Av
3 Av 138 St
3 Av–149 St
Jackson Av
Prospect Av
Intervale Av
Simpson St
Freeman St
174 St
174–175 Sts
170 St
167 St
161 St Yankee Stadium
Tremont Av
182–183 Sts
183 St
Fordham Rd
Kingsbridge Rd
Mt Eden Av
176 St
Burnside Av
Norwood 205 St
Bedford Pk Blvd
Bedford Pk Blvd Lehman College
Mosholu Pkwy
Woodlawn
Van Cortlandt Park 242 St
238 St
231 St
Marble Hill
215 St
207 St
Inwood–207 St
Dyckman St
191 St
190 St
181 St
175 St
168 St–Broadway
163 St Amsterdam Av
155 St
157 St
145 St
137 St City College
135 St
125 St
116 St
110 St
Cathedral Pkwy (110 St)
103 St
96 St
86 St
81 St–Museum of Natural History
79 St
72 St
66 St Lincoln Center
59 St Columbus Circle
57 St
57 St
Lexington Av–59 St
Lexington Avenue
5 Av
68 St Hunter College
77 St
Roosevelt Island
21 St–Queensbridge
Queensboro Plaza
Astoria–Ditmars Blvd
Astoria Blvd
30 Av
Broadway
36 Av
39 Av
Steinway St
46 St
Northern Blvd
65 St
74 St–Broadway
82 St–Jackson Hts
69 St
61 St–Woodside
52 St
46 St
40 St
33 St
Jackson Hts Roosevelt Av
Flushing–Main St
Willets Pt–Shea Stadium
111 St
103 St–Corona Plaza
Junction Blvd
90 St–Elmhurst Av
Elmhurst Av
Grand Av Newtown
Woodhaven Blvd Queens Mall
63 Dr Rego Park
67 Av
71 Av Forest Hills
75 Av
Kew Gardens Union Turnpike
Briarwood/Van Wyck Blvd
Jamaica–Van Wyck
Jamaica–179 St
169 St
Parsons Blvd
Sutphin Blvd
Jamaica Center Parsons/Archer
Sutphin Blvd Archer Av
121 St

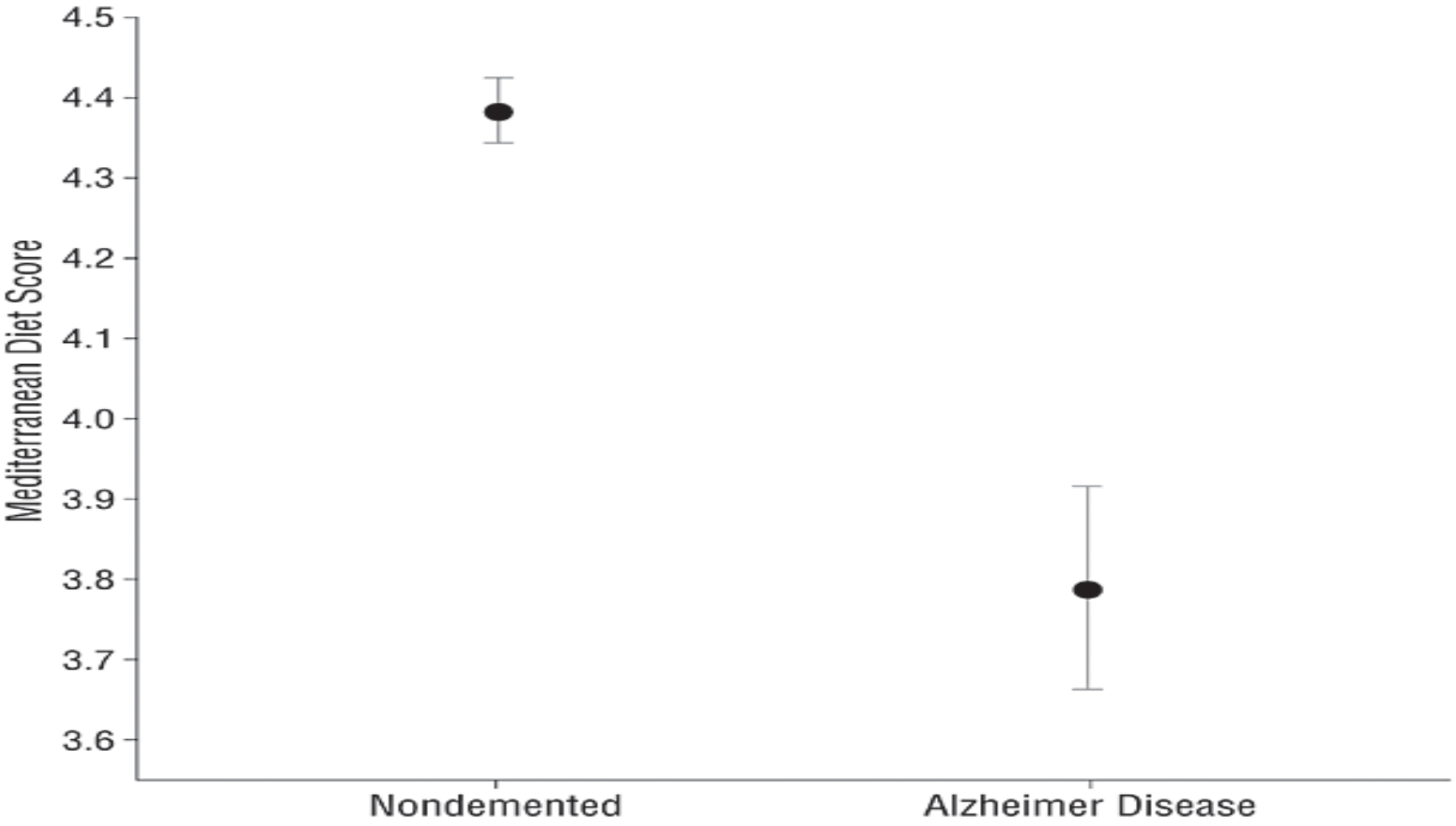
Median Daily Intake for Individual Food Categories by Mediterranean Diet Score Tertiles and Overall

Scarmeas N et al. Ann Neurol 2006: 59:912-921

Food categories	Low Tertile (MeDi score 0-3)	High Tertile (MeDi score 6-9)
Dairy, gm/day	246	152
Meat, gm/day	101	65
Vegetable, gm/day	165	243
Fruit, gm/day	406	556
Legumes, gm/day	44	78
Cereal, gm/day	155	215
Fish, gm/day	15	47
MUFA/SFA ratio	0.57	0.97
Mild-to-moderate ethanol, %	21	45

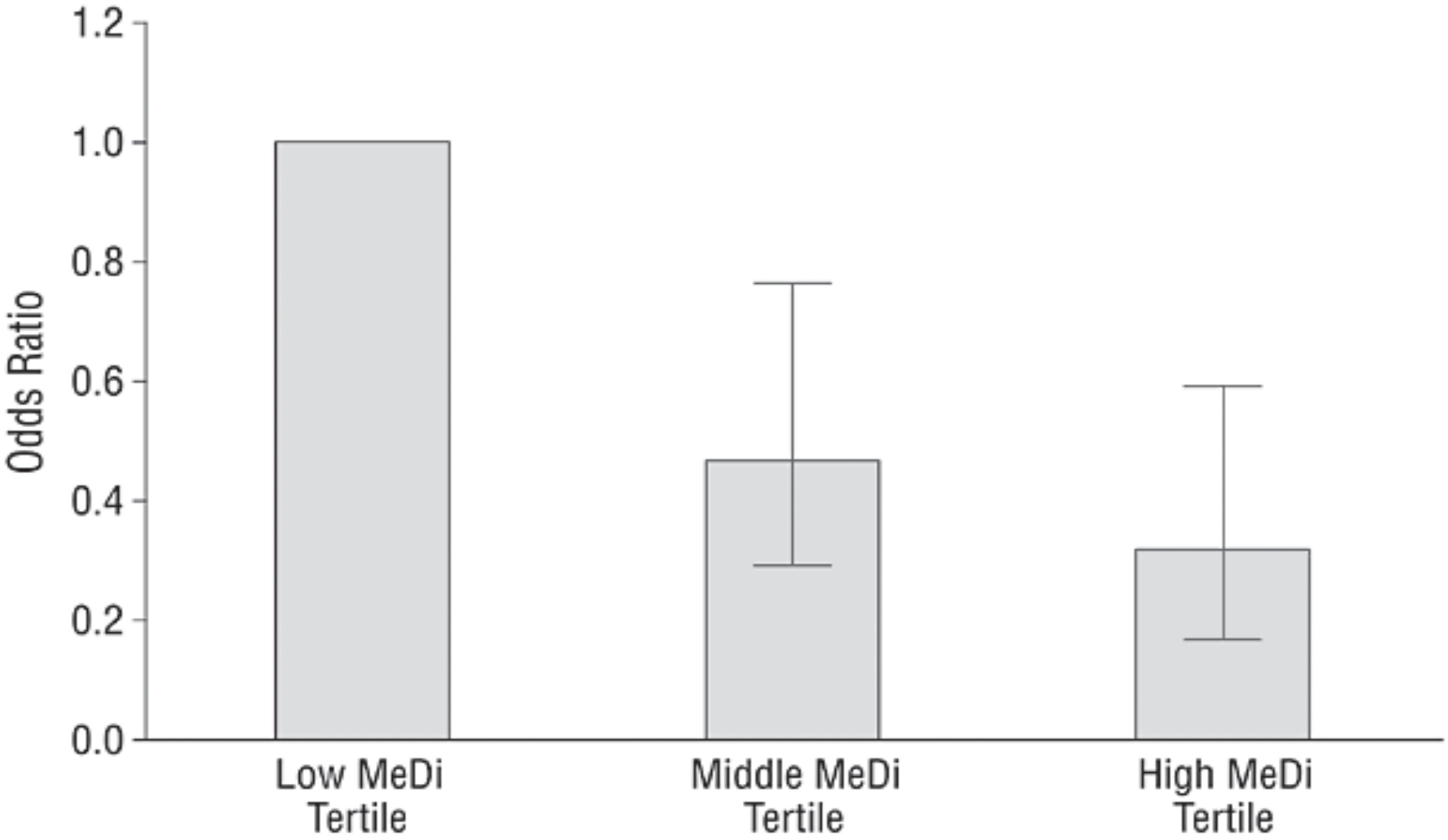
Mediterranean Diet Score for AD and nondemented Subjects

Scarmeas et al Archives of Nerology Arch Neurol. 2006;63:(doi:10.1001



Adherence to MeDI and AD risk (OR and 95% CI)

Scarmeas et al Archives of Nerology Arch Neurol. 2006;63:(doi:10.1001



Associations Between Imaging Markers and Med Nutrients

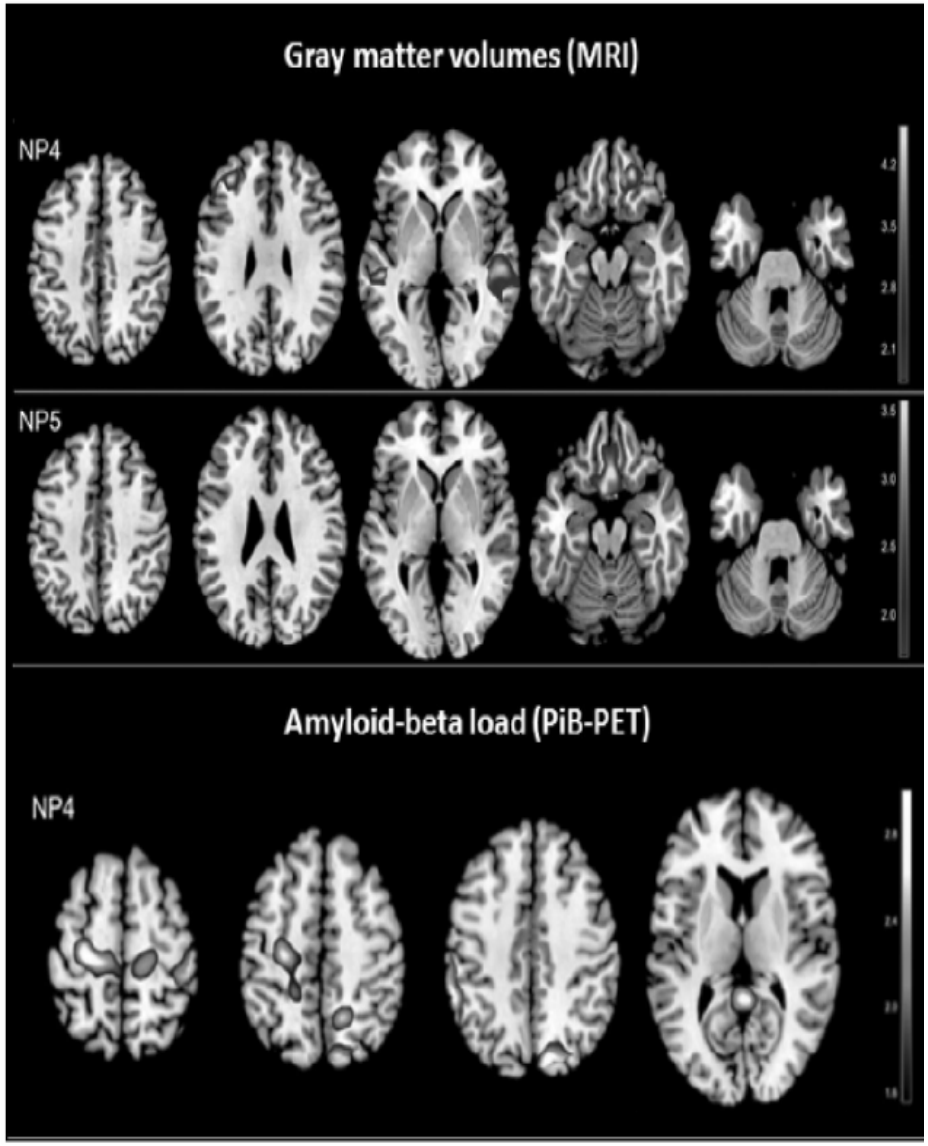


Table 5

Brain regions showing significant relationships between NPs and brain Aβ load on PiB-PET

Cluster extent	x*	y	z	Z†	Anatomical region	Brodmann area
Negative associations between PiB retention and NP4						
307	−14	−12	−42	2.90	Left Cerebrum, Limbic Lobe, Cingulate Gyrus	24
768	−29	25	50	2.79	Left Cerebrum, Frontal Lobe, Superior Frontal Gyrus	8
279	0	−43	8	2.78	Left Cerebrum, Limbic Lobe, Posterior Cingulate Gyrus	29
	−23	−10	50	2.72	Left Cerebrum, Frontal Lobe, Superior Frontal Gyrus	8
134	7	−76	43	2.72	Right Cerebrum, Parietal Lobe, Precuneus	7
30	−53	−45	40	2.66	Left Cerebrum, Parietal Lobe, Inferior Parietal Lobule	40
77	12	−58	46	2.64	Right Cerebrum, Parietal Lobe, Precuneus	7
85	37	−37	54	2.63	Right Cerebrum, Parietal Lobe, Inferior Parietal Lobule	40

*Coordinates (x, y, z) from Talairach and Tournoux.

†Z values at the peak of maximum significance at p<0.001, correcting for age and total caloric intake. Only contrasts yielding signi

Abbreviations: see legend to Table 3

Beneficial Effects of Mediterranean Diet

- Slow cognitive decline in normal older adults
- Reduce the risk of mild cognitive impairment (MCI)
- Reduce the risk of MCI progressing into Alzheimer's disease
- Slow the progression of Alzheimer's disease and prevent disease-related deaths

Estimated Percent and Number of AD cases Attributable to Potentially Modifiable Risk Factors

Barnes&Jaffe Lancet Neurology 2011;10: 819-28

RISK FACTOR	POPULATION PREVALENCE	RELATIVE RISK (95% CI)	PAR% (Confidence Range)	NO. CASES ATTRIBUTABLE, Millions (Confidence Range)
Low education	40.0%	1.59 (1.35, 1.86)	19.1% (12.3%, 25.6%)	6.5 (4.2, 8.7)
Smoking	27.4%	1.59 (1.15, 2.20)	13.9% (3.9%, 24.7%)	4.7 (1.3, 8.4)
Physical inactivity	17.7%	1.82 (1.19, 2.78)	12.7% (3.3%, 24.0%)	4.3 (1.1, 8.1)
Depression	13.2%	1.90 (1.55, 2.33)	10.6% (6.8%, 14.9%)	3.6 (2.3, 5.1)
Mid-life hypertension	8.9%	1.61 (1.16, 2.24)	5.1% (1.4%, 9.9%)	1.7 (0.5, 3.4)
Diabetes	6.4%	1.39 (1.17, 1.66)	2.4% (1.1%, 4.1%)	0.8 (0.4, 1.4)
Mid-life obesity	3.4%	1.60 (1.34, 1.92)	2.0% (1.1%, 3.0%)	0.7 (0.4, 1.0)
Combined (maximum)			50.7%	17,187,028

The Great Age Study in Castellana Grotte
Mediterranean Diet in population:Health, Aging and Diseases

great age