The Mediterranean diet (MeDi) and Alzheimer's disease (AD): feeding your brain

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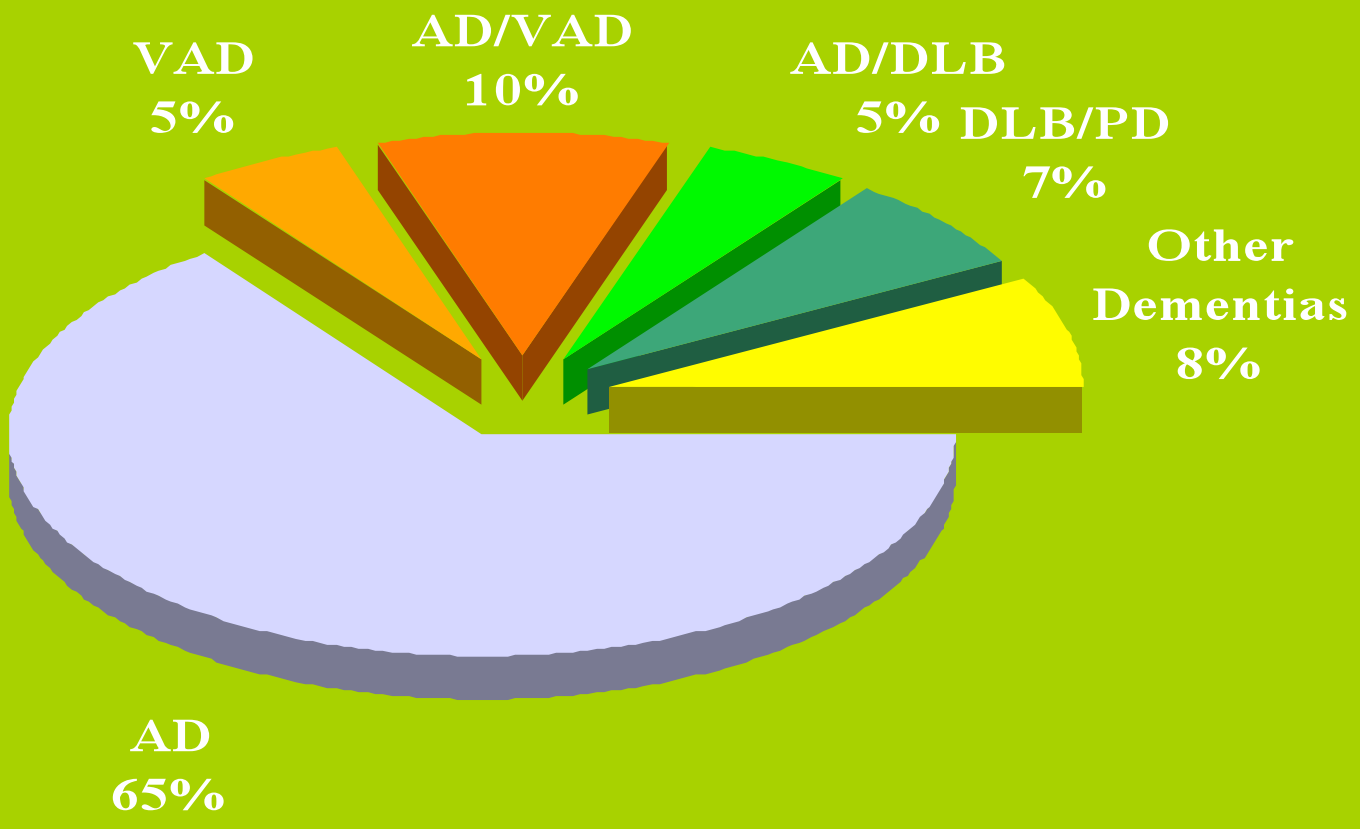
Dementia (DSM-IV criteria)

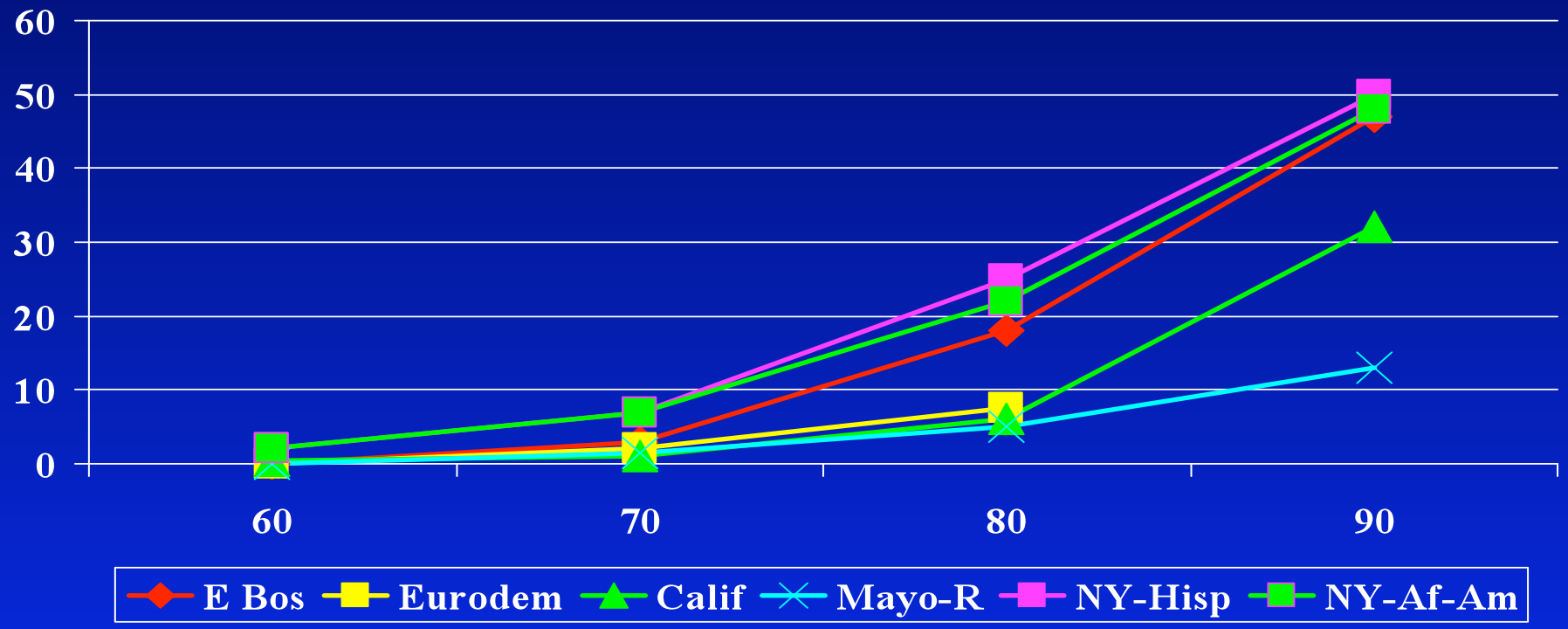
- Loss of cognitive abilities including
  - memory
  - PLUS at least one of the following:
    - impaired language
    - impaired abstract thinking
    - impaired perception
    - impaired judgment
    - personality change
- Impairment in social or occupational functioning (decline from a previous level)
- No delirium

Dementia



Small GW, et al JAMA 1997
Morris JC. Clin Geriatri Med 1994

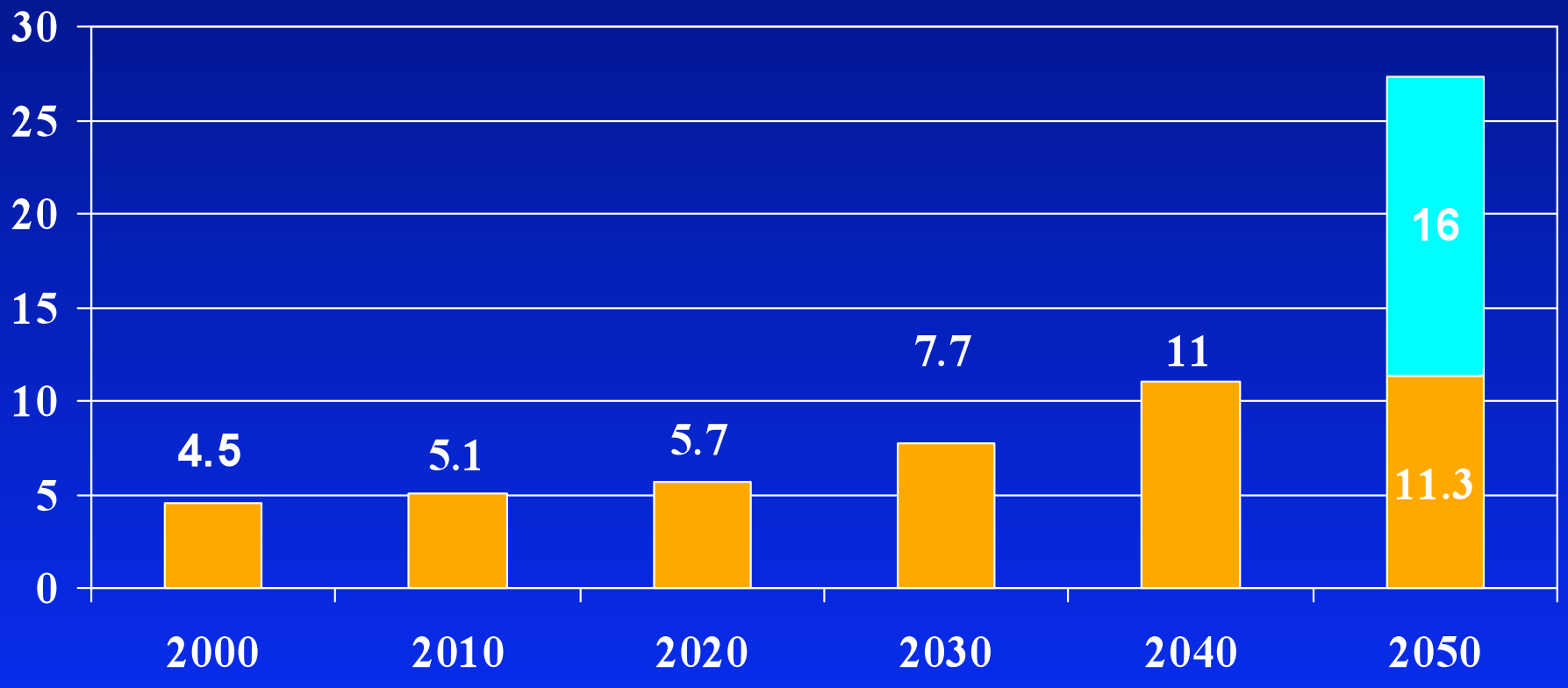
Prevalence of Alzheimer's Disease (AD)



AD prevalence doubles every 5 years

Age	60	65	70	75	80	85	90
Prevalence (%)	1	2	4	8	16	32	64

Rapid Growth of Alzheimer's Disease
(in millions)



By 2050, the number of people with Alzheimer's will range from 11.3 - 16 million.

Symptoms in AD

- *MEMORY*
  - *Learning and retaining **new** material:*
    - Repeating same question multiple times
    - Forgets recent events / conversations
    - Forgets appointments / take medications
    - Inceasing need for lists and notes for things to do
    - Forgetting faces – not recognizing people
  - *Long term memory (**old** material) well preserved*

Symptoms in AD

- *VISUAL SPATIAL SKILLS*
  - Disorientation in unfamiliar places / own neighborhood / even own appartment
  - Problems with driving (missing exits, north vs south, east vs west)
  - Problems changing subway or bus lines
- *ARITHMETIC SKILLS*
  - Keeping track of finances, bank account balances
  - Count correct change when shopping
  - Calculate tips
- *ORIENTATION*
  - Confusing dates, months, years, days of the week

Symptoms in AD

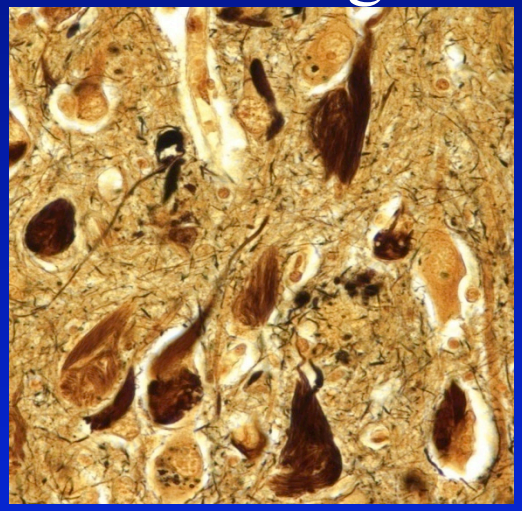
- *MOOD*
  - Symptoms of depression (30-50%, often intermittent)
    - Usually apathy, lack of interest or motivation to do things
    - Anhedonia
    - Sleep problems
- *BEHAVIORAL*
  - Agitation – Irritability - Aggressiveness (50%, often persistant)
- *PERCEPTUAL DISORDERS*
  - Usually paranoia – suspiciousness
  - More rarely illusions, hallucinations

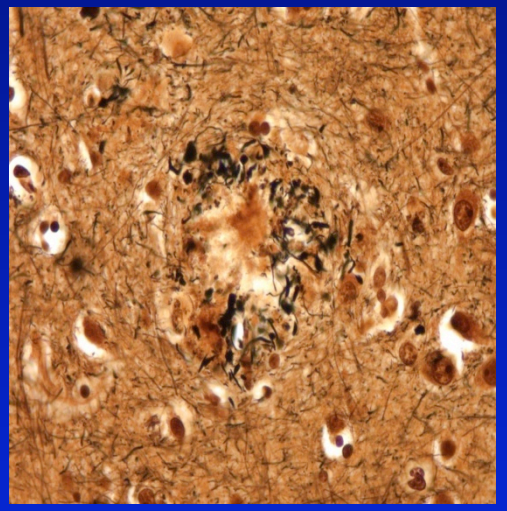
NINCDS/ADRDA Criteria for AD

- Definite AD
  - Histologic confirmation of the disorder
- Probable AD
  - Characteristic clinical course and findings
  - Insidious onset
  - Continuous progression
  - Deficits in 2 or more areas of cognition
  - Absence of other disorders that could account for dementia
- Possible AD
  - Patients with an atypical course
  - Patients with concurrent illnesses that may partially account for the cognitive problems

Criteria for AD (NINCDS/ADRDA)

- Definite AD
  –Histologic confirmation





•Nevertheless, clinical diagnosis quite accurate:

80% sensitivity

90% specificity

Disease Progression

- Not direct cause of death.
  -dehydration, injuries, malnutrition, infection

- Average course is about 7 to 12 yrs.
  - Early stage: 1- 2 years
  - Middle stage: 2-12 yrs
  - Late stage: 1 yr
  - Terminal stage: mos.

- Predicting progression
  - EPS (rigidity, bradykinesia) at baseline assoc. w/:
    - increased mortality
    - more rapid functional decline
    - increased risk of SNF placement/equivalent
  - psychosis (hallucinations or delusions) assoc. w/ more rapid decline

Stern et al

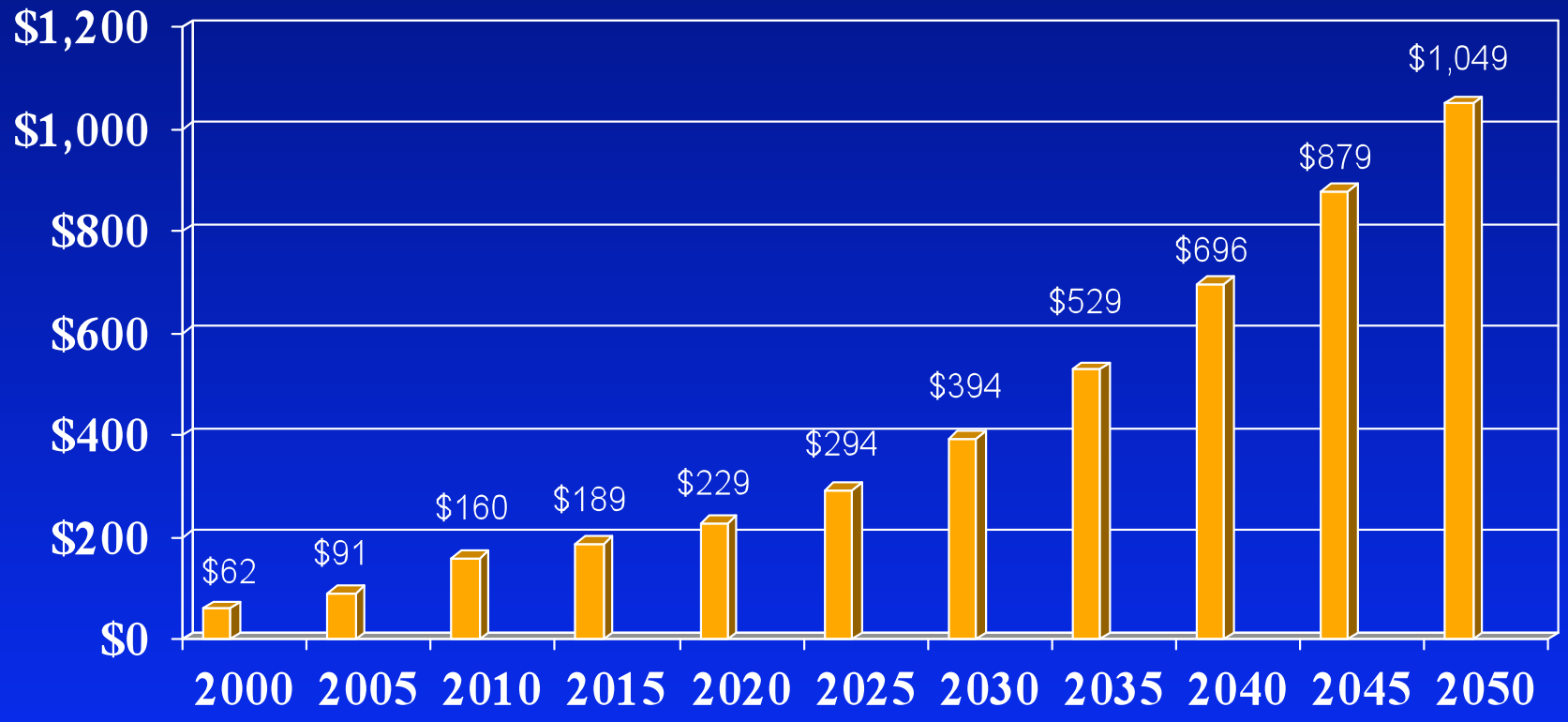
Strategies to Treat AD
Symptomatic Treatment

- Anticholinesterases
  - Tacrine 1993
  - Donepezil 1996
  - Rivastigmine 2000
  - Galantamine 2001
- NMDA inhibitor
  - Memantine 2003

Treatment of Behavioral-Mood symptoms

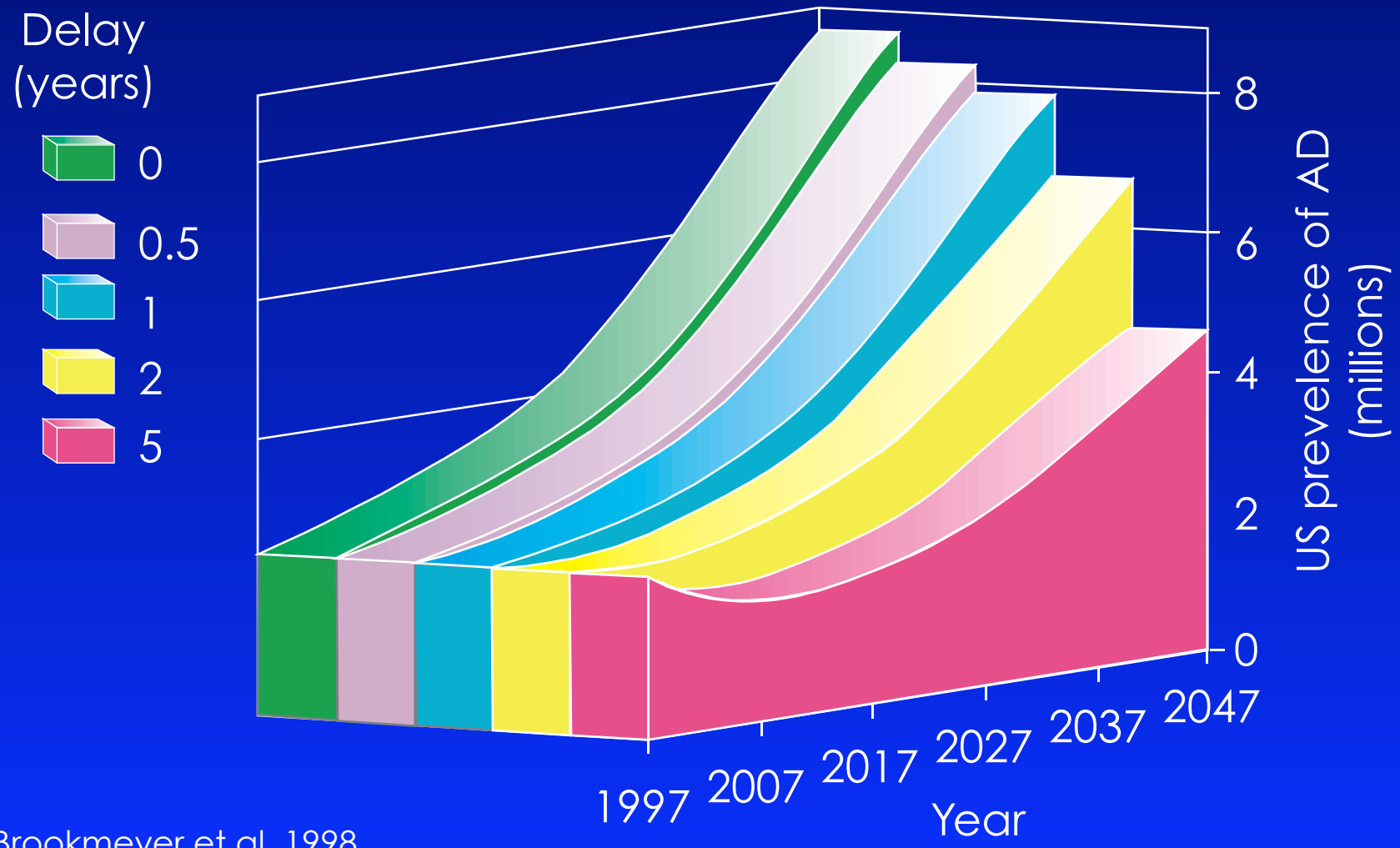
- Agitation – Aggression – Irritability
- Perceptual disorders (paranoid delusions, more rarely hallucinations
  - 30-50% develop them
  - Problematic for caregivers, reason for hospitalization or institutionalization
  - New atypical neuroleptics
    - Quetiapine (Seroquel)
    - Olanzapine (Zyprexa)
    - Risperidone (Risperdal)
    - ***Very sensitive to typical neuroleptics (Haldol): become very parkinsonian
- Depression
  - 30% develop it – usually intermittent
  - SSRIs

Medicare Spending on Alzheimer's Disease
(in billions)



Source: "Saving Lives, Saving Money: Dividends for Americans Investing in Alzheimer's Research", The Lewin Group & the Alzheimer's Association, June 2004.

Potential Impact of Interventions to Delay Onset of AD



Source: Brookmeyer et al, 1998.

Lower risk of AD or slower cognitive decline

- Vitamin C
  - Masaki, Losonczy et al. 2000; Engelhart, Geerlings et al. 2002; Zandi, Anthony et al. 2004; Morris, Beckett et al. 1998
- Vitamin E
  - Masaki, Losonczy et al. 2000; Engelhart, Geerlings et al. 2002; Morris, Beckett et al. 1998; Morris, Evans et al. 2002; Morris, Evans et al. 2002; Zandi, Anthony et al. 2004; Corrada, Kawas et al. 2005
- Vitamin B12
  - La Rue, Koehler et al. 1997; Clarke, Smith et al. 1998; Wang, Wahlin et al. 2001; Haan et al. 2007; Tangney 2009
- Vitamin B6
  - Corrada, Kawas et al. 2005
- Folate
  - Clarke, Smith et al. 1998; Wang, Wahlin et al. 2001; Ravaglia 2005; Corrada, Kawas et al. 2005; Balk 2007 (metaanal-interv).
- Modest to Moderate ETOH
  - Orgogozo, Dartigues et al. 1997; Ruitenberg, van Swieten et al. 2002; Truelsen, Thudium et al. 2002; Mukamal, Kuller et al. 2003; Luchsinger, Tang et al. 2004; Ganguli , Vander Bilt et al. 2005; Espeland, Gu et al. 2004; Stampfer Kang et al 2005
- Flavonoids
  - Commenges, Scotet et al. 2000
- Caroten
  - Barberger-Gateau et al 2007;
- Fish
  - Barberger-Gateau, Letenneur et al. 2002; Morris, Evans et al. 2003; Morris, Evans et al. 2005; Huang, Zandi et al; 2005; Barberger-Gateau et al 2007;
- Unsaturated fatty acids
  - Kalmijn, Feskens et al. 1997; Morris, Evans et al. 2003; Morris, Evans et al. 2003; Schaefer, Bongard et al. 2006; Laitinen et al. 2006; Barberger-Gateau et al 2007;
- Lower total fats, cholesterol, saturated fats
  - Kalmijn, Launer et al. 1997; Kalmijn, vanBoxtel et al. 2004; Morris, Evans et al. 2003; Luchsinger, Tang et al. 2002; Laitinen et al. 2006
- Coffee
  - Maia, de Mendonca 2002
- Fruits
  - Dai, Borenstein et al 2006; Barberger-Gateau et al 2007;
- Vegetables (polyphenol antioxidants?)
  - Dai, Borenstein et al 2006, Kang, Grodstein; Research-Practice AD 2007, Barberger-Gateau et al 2007;
- Curry (curcumin - antiinflammatory? antioxidant?)
  - Tze-Pin Ng et al 2006

Risk for AD or cognitive decline not associated with

- Vitamin C
  - Luchsinger, Tang et al. 2003, Masaki, Losonczy et al. 2000, Heart Protection Study 2002; Laurin, Masaki et al. 2004; Dai, Borenstein et al 2006; Yaffe 2004
- Vitamin E
  - Sano 1997; Luchsinger, Tang et al. 2003, Masaki, Losonczy et al. 2000; Heart Protection Study 2002; Laurin, Masaki et al. 2004; Yaffe 2004; Dai, Borenstein et al 2006; Kang 2006
- Vitamin B12
  - Crystal, Ortof et al. 1994, Seshadri, Baser et al. 2002; Morris 2006; Ravaglia 2005; Balk 2007 (metaanal-interv); Aisen 2008
- Vitamin B6
  - Seshadri, Baser et al. 2002; Morris 2006; Balk 2007 (metaanal-interv); Aisen 2008
- Folate
  - Seshadri, Baser et al. 2002; Balk 2007 (metaanal-interv); Haan 2007; Middleton 2007; Morris 2006; Aisen 2008
- Fish
  - Schaefer, Bongard et al. 2006;
- Fats
  - Engelhart, Geerlings et al. 2002
- Omega-3
  - O.van de Rest et al. 2008
- Carotenes
  - Heart Protection Study 2002; Luchsinger, Tang et al. 2003; Laurin, Masaki et al. 2004; Yaffe 2004.
- Calcium (high worse)
  - Van Vliet 2004.
- Wine
  - Dai, Borenstein et al 2006; Barberger-Gateau et al 2007;
- Flavonoids
  - Laurin, Masaki et al. 2004.
- Tea
  - Forster, Newens et al. 1995; Rogers, Simon et al. 1999
- Fruits
  - Kang, Grodstein; Research-Practice AD 2007

Diet and AD

- **One of the reasons for discrepancies** between studies: we look at isolated-individual food or nutrients and not composite dietary patterns. Individuals do not consume foods or nutrients in isolation but rather as components of their overall daily diet.

- Growing attention in dietary pattern analysis (Jacobson, Stanton 1986) in relation to
  - Cirrhosis
    - Corrao, Zambon et al. 2004
  - Various cancers
    - McCann, Weiner et al. 2001; Rouillier, Senesse et al. 2004; Cottet, Bonithon-Kopp et al. 2005

- Dietary patterns not explored in the neurological literature

Dietary Pattern approach - Advantages

- Capture the multidimensionality of the diet since they can reduce confounding and integrate complex or subtle interactive effects of many dietary exposures (Jacques and Tucker 2001)
  - Fish consumption had a greater effect in reducing platelet aggregation when part of a low-fat rather than a high-fat diet (Mori, Beilin et al. 1997).
  - Effect of fish consumption in lowering blood pressure (Vandongen, Mori et al. 1993) and blood lipids (Mori, Vandongen et al. 1994) seems to be much more pronounced in subjects following a low fat diet.
  - Higher copper consumption associated with faster cognitive decline only among subjects with high intake of saturated and trans fats (Morris, Evans et al. 2006).
- Reduce problems generated by multiple testing
- Reduce problems related to high correlations - colinearity that may exist among nutritional elements
- Useful when well-developed hypotheses for association with particular dietary elements do not exist
- Useful for public health policy

Dietary Pattern – MeDi approach - Disadvantages

•It assumes underlying monotonic effects and does not address possible thresholds or the shape of the underlying curve.

•It weighs equally the underlying individual food categories, which in turn are composed of different number of food constituents.

•

•Because they cannot isolate food or nutrient-specific effects, they do not elucidate our understanding of the biological mechanisms that mediate their association with disease.

Dietary Pattern approach

- Can be developed **a posteriori** on the basis of already existing data (empirical aggregation of individuals with similar diets based on their reported intake of food)
  - Use of various multivariate methods such as discriminant analyses, principal components analyses or cluster analyses
    - McCann, Weiner et al. 2001; Costacou, Bamia et al. 2003; Villegas, Salim et al. 2004; Corrao, Zambon et al. 2004; McCann, Weiner et al. 2001; Rouillier, Senesse et al. 2004; Cottet, Bonithon-Kopp et al. 2005
- Can be developed **a priori** on the basis of previous knowledge concerning a favorable or adverse health effect of various dietary constituents
  - Such an example is the **Mediterranean Diet (MeDi)**

Mediterranean Diet

- High intake of
  - Vegetables
  - Legumes
  - Fruits
  - Cereals
  - Fish
  - Unsaturated fatty acids (mostly in the form of olive oil), but low intake of saturated fatty acids
- Low-to-moderate intake of
  - Dairy products (mostly cheese or yogurt)
  - Meat and Poultry
- Regular but moderate amount of
  - Ethanol, primarily in the form of wine and generally during meals

- Seems to include many of the components reported as potentially beneficial for AD and cognitive performance


Inwood
BRONX
Washington Heights
145th St
Harlem
125th St
Morningside Heights
110th St
96th St
Upper West Side
Central Park
Upper East Side
72nd St
59th St
Midtown West
Midtown East
Queens
42nd St
Lincoln Tunnel
34th St
Chelsea
Gramercy
14th St
Greenwich Village
East Village
Houston St
Soho
Little Italy
Lower East Side
Canal St
Tribeca
Chinatown
Lower Manhattan
BROOKLYN


MANHATTAN
NEW YORK


Broadway Bridge
Isham Park
Inwood Hill Park
Inwood
University Heights Bridge
Dyckman Farmhouse Museum
The Bronx
The Cloisters
Fort Tryon Park
High Bridge Park
Henry Hudson Pkwy
Riverside Dr
Washington Bridge
Trans-Manhattan Expwy
Alexander Hamilton Bridge
George Washington Bridge
The Little Red Lighthouse
BRONX
Washington Heights
High Bridge Park
Harlem River Dr
Jumel Terrace
Morris-Jumel Mansion Museum
American Academy of Arts and Letters
The Hispanic Society of America
Trinity Cemetery
Audubon Terrace
Harlem
Jackie Robinson Park
Macombs Dam Bridge
FDR Dr
Riverbank State Park

Washington's Heights and Inwood Columbia Aging Project (WHICAP)

- Survey population (1992 and 1999 cohorts)
  - Probability sample of Medicare beneficiaries aged 65 or older
  - Washington's Heights and Inwood communities in Manhattan, New York
- Baseline Visit
  - Medical – Neurological / Demographic information
  - Neuropsychological evaluation
    - Memory (short and long-term verbal (Buschke and Fuld 1974) and nonverbal (Benton 1955));
    - Orientation;
    - Abstract reasoning (verbal (Wechsler 1981) and non-verbal (Mattis 1976));
    - Language (naming (Goodglass and Kaplan 1983), verbal fluency(Benton and Hamsher 1976; Goodglass and Kaplan 1983) comprehension (Goodglass and Kaplan 1983) and repetition(Goodglass and Kaplan 1983));
    - Construction (copying (Rosen 1981) and matching (Benton 1955)).

WHICAP

- Baseline visit
  - Diet: 61-item semi-quantitative food frequency questionnaire (Willett, Sampson et al. 1985)
    - Validity (two 7-day food records) and reliability (two 3-month frequency assessments) of various components of the questionnaire in WHICAP (Luchsinger, Tang et al. 2002; Luchsinger, Tang et al. 2003; Luchsinger, Tang et al. 2004)
- Consensus diagnosis Neurologists- Neuropsychologists
  - All ancillary information (medical charts, CTs or MRIs) considered, if available.
  - Evidence of cognitive deficits using a fixed paradigm (Stern, Andrews et al. 1992): criterion scores applied to each neuropsychological test, and subjects performing below these scores on 2/3 aspects of memory testing as well as 2 other areas (orientation, language, abstract reasoning, or construction) meet dementia criteria.
  - Evidence of impairment in social or occupational function (Blessed Dementia Rating Scale, the Schwab and England Activities of Daily Living Scale and the physician's assessment),
  - Evidence of cognitive and social-occupational function decline from the past
  - Diagnosis of dementia (DSM-III-R)(American Psychiatric Association 1987).
  - Diagnosis of AD NINCDS-ADRDA (McKhann, Drachman et al. 1984)
- Neuropsychological testing, Physician's Evaluations, Diagnosis repeated every ~ 1.5 years

Mediterranean Diet

- High intake of
  - Vegetables
    - (tomato, brocolli, cabbage, carrot, corn, peas, yams, spinach, yellow squash)
  - Legumes
    - (beans-lentils)
  - Fruits
    - (apple, orange, orange or grapefruit juice, peaches-appricots-plums, bananas, other fruit, nuts)
  - Cereals
    - (white bread, dark bread, rice or pasta)
  - Fish
  - Unsaturated fatty acids (mostly in the form of olive oil), but low intake of saturated fatty acids
- Low-to-moderate intake of
  - Dairy products
    - (cottage cheese, other cheese, skim milk, milk, yogurt, ice cream, margarin, butter)
  - Meat and Poultry
    - (chicken or turkey with skin, without skin, bacon, hot dog, processed meat, liver, hamburger, beef or other meat, sandwitch beef or other meat)
- Regular but moderate amount of
  - Ethanol, primarily in the form of wine and generally during meals

MeDi Calculation (Trichopoulou, Costacou et al. 2003)

1. Average frequency of food consumption over the course of last year
   - <1 serving/month,
   - 1-3 servings/month,
   - 1 serving/week,
   - 2-4 servings/week,
   - 5-6 servings/week,
   - 1 serving/day,
   - 2-3 servings/day,
   - 4-5 servings/day,
   - >6 servings/day.
2. Using (i) frequencies and (ii) standard serving sizes, calculate daily gram intake for
   - Dairy
   - Meat
   - Fruits
   - Vegetables
   - Legumes
   - Cereals
   - Fish
   - MUFA
   - SFA

MeDi Calculation

3. Regress caloric intake (kcal) and derive residuals of daily gram intake (Willett and Stampfer 1998) for each of the above categories (Trichopoulou, Costacou et al. 2003)

4. Calculate sex-specific medians of residuals and assign a value of 0 or 1 for each of the above categories for each subject.
   - For beneficial components (fruits, vegetables, legumes, cereals, fish, MUFA / SFA)
     - ≥ sex-specific median 1
     - < sex-specific median 0
   - For detrimental components (meat and dairy products)
     - ≥ sex-specific median 0
     - < sex-specific median 1
   - For alcohol
     - no (0 g/day; 68%) 0
     - ≥ moderate (≥30 g/day; 1%) 0
     - mild-moderate (>0 to <30 g/day; 31%) 1

5. MeDi score: SUM of the above (theoretically ranging 0-9) with higher score indicating higher adherence to the MeDi.

ORIGINAL CONTRIBUTION

Mediterranean Diet, Alzheimer Disease, and Vascular Mediation

Nikolaos Scarmeas, MD; Yaakov Stern, PhD; Richard Mayeux, MD; Jose A. Luchsinger, MD

Objectives: To examine the association between the Mediterranean diet (MeDi) and Alzheimer disease (AD) in a different AD population and to investigate possible mediation by vascular pathways.

Design, Setting, Patients, and Main Outcome Measures: A case-control study nested within a community-based cohort in New York, NY. Adherence to the MeDi (0- to 9-point scale with higher scores indicating higher adherence) was the main predictor of AD status (194 patients with AD vs 1790 nondemented subjects) in logistic regression models that were adjusted for cohort, age, sex, ethnicity, education, apolipoprotein E genotype, caloric intake, smoking, medical comorbidity index, and body mass index (calculated as weight in kilograms divided by height in meters squared). We investigated whether there was attenuation of the association between MeDi and AD when vascular variables (stroke, diabetes mellitus, hypertension, heart disease, lipid levels) were simultaneously introduced in the models (which would constitute evidence of mediation).

Results: Higher adherence to the MeDi was associated with lower risk for AD (odds ratio, 0.76; 95% confidence interval, 0.67-0.87; $P<.001$). Compared with subjects in the lowest MeDi tertile, subjects in the middle MeDi tertile had an odds ratio of 0.47 (95% confidence interval, 0.29-0.76) and those at the highest tertile an odds ratio of 0.32 (95% confidence interval, 0.17-0.59) for AD (P for trend <.001). Introduction of the vascular variables in the model did not change the magnitude of the association.

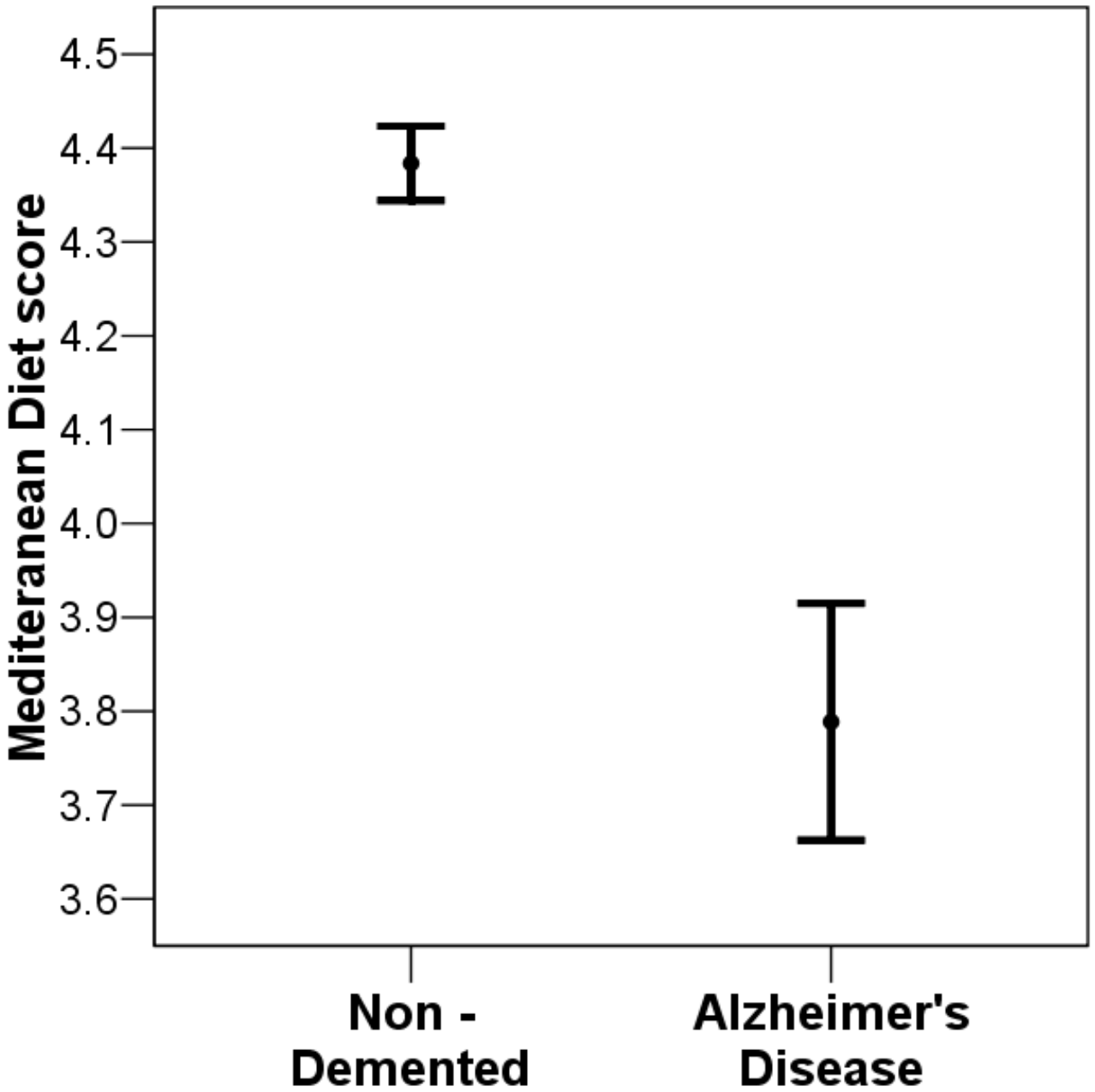
Conclusions: We note once more that higher adherence to the MeDi is associated with a reduced risk for AD. The association does not seem to be mediated by vascular comorbidity. This could be the result of either other biological mechanisms (oxidative or inflammatory) being implicated or measurement error of the vascular variables.

Arch Neurol. 2006;63:1709-1717

MeDi and Prevalent AD

- 1790 non-demented at baseline [CDR = 0].
- 194 with a diagnosis of AD at baseline [CDR = 1].

- Logistic Regression analyses
  - Outcome
    - Prevalent AD vs. Non-demented
  - Main predictor
    - MeDi (continuous)
    - MeDi (tertiles)
  - Covariates adjusted for
    - cohort, age, gender, education, ethnicity, caloric intake, APOE, BMI, smoking, modified comorbidity index (Charlson)


Mediteranean Diet score
4.5
4.4
4.3
4.2
4.1
4.0
3.9
3.8
3.7
3.6
Non - Demented
Alzheimer's Disease

Mediterranean Diet and Risk for Alzheimer's Disease

Nikolaos Scarmeas, MD,[1–3] Yaakov Stern, PhD,[1–3] Ming-Xin Tang, PhD,[1,4] Richard Mayeux, MD,[1–3] and Jose A. Luchsinger, MD[1,5]

Objective: Previous research in Alzheimer's disease (AD) has focused on individual dietary components. There is converging evidence that composite dietary patterns such as the Mediterranean diet (MeDi) is related to lower risk for cardiovascular disease, several forms of cancer, and overall mortality. We sought to investigate the association between MeDi and risk for AD.

Methods: A total of 2,258 community-based nondemented individuals in New York were prospectively evaluated every 1.5 years. Adherence to the MeDi (zero- to nine-point scale with higher scores indicating higher adherence) was the main predictor in models that were adjusted for cohort, age, sex, ethnicity, education, apolipoprotein E genotype, caloric intake, smoking, medical comorbidity index, and body mass index.

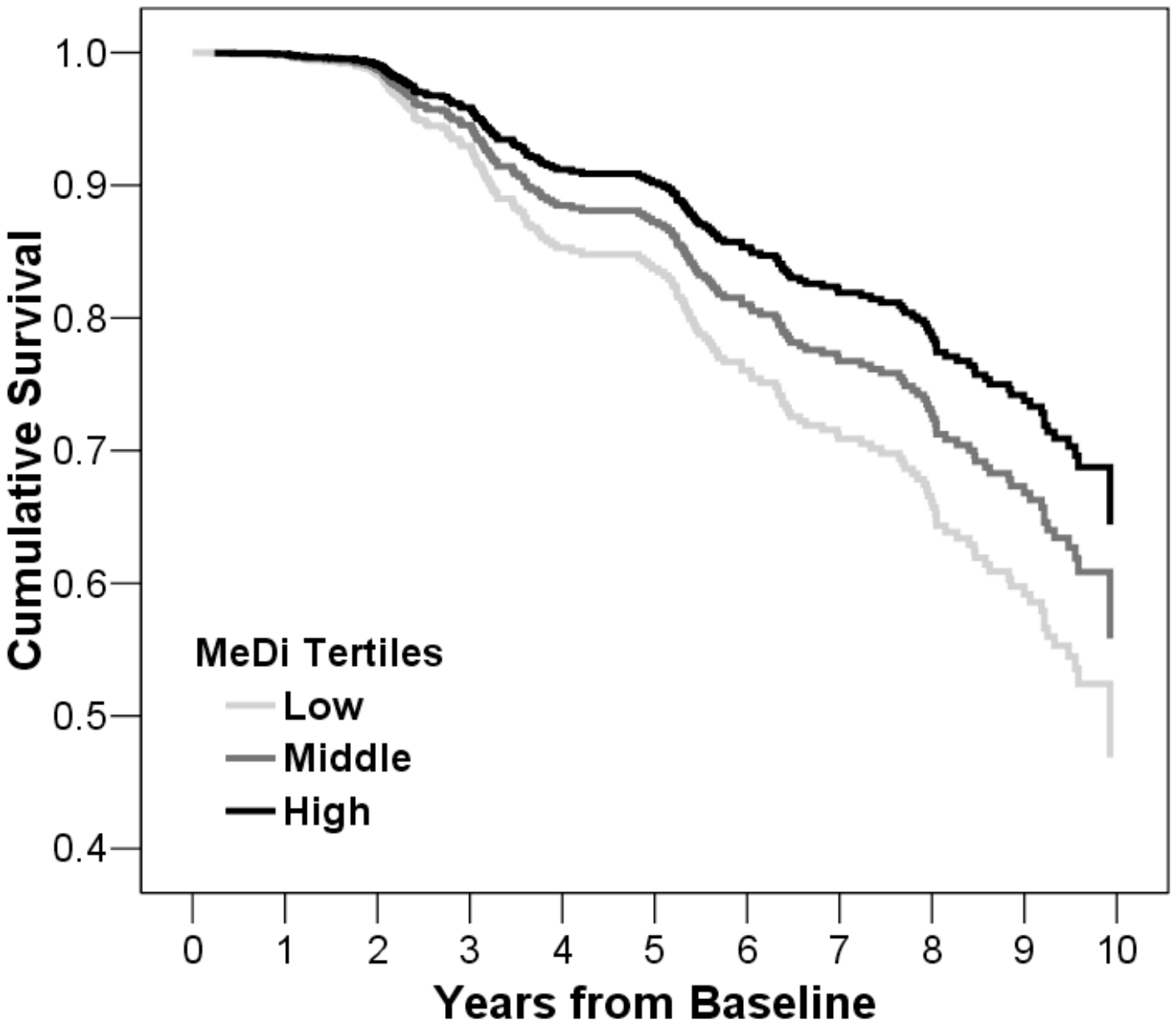
Results: There were 262 incident AD cases during the course of 4 (±3.0; range, 0.2–13.9) years of follow-up. Higher adherence to the MeDi was associated with lower risk for AD (hazard ratio, 0.91; 95% confidence interval, 0.83–0.98; $p = 0.015$). Compared with subjects in the lowest MeDi tertile, subjects in the middle MeDi tertile had a hazard ratio of 0.85 (95% confidence interval, 0.63–1.16) and those at the highest tertile had a hazard ratio of 0.60 (95% confidence interval, 0.42–0.87) for AD (p for trend = 0.007).

Interpretation: We conclude that higher adherence to the MeDi is associated with a reduction in risk for AD.

Ann Neurol 2006;59:912–921

MeDi and Incident AD

- 2226 non-demented at baseline
- Follow-up
  - 4.0 (± 3.0, 0.2– 13.9) years
- 262 subjects developed AD during follow-up
  - 184 AD without stroke
  - 78 AD with stroke
- Survival analyses - Cox models
  - Outcome
    - Incident AD vs. Non-demented
    - Time to AD incidence or to last follow-up
  - Main predictor
    - MeDi (continuous)
    - MeDi (tertiles)
  - Covariates adjusted for
    - cohort, age, gender, education, ethnicity, caloric intake, APOE, BMI, smoking, modified comorbidity index (Charlson)


1.0
0.9
0.8
0.7
0.6
0.5
0.4
Cumulative Survival
MeDi Tertiles
Low
Middle
High
0
1
2
3
4
5
6
7
8
9
10
Years from Baseline

Model	At risk	AD (%)	MeDi continuous HR (95%CI)	P		MeDi tertiles HR (95%CI)	P for trend
1	2226	262 (12)	0.90 (0.83 – 0.96)	0.003	Low	1 (reference)	0.003
					Middle	0.79 (0.60 – 1.04)	
					High	0.61 (0.44 – 0.85)	
2	1759	219 (12)	0.91 (0.83 – 0.98)	0.015	Low	1 (reference)	0.007
					Middle	0.85 (0.63 – 1.16)	
					High	0.60 (0.42 – 0.87)	

Model 1 is unadjusted.

Model 2 is adjusted for cohort, age, gender, ethnicity, education, APOE genotype, caloric intake, smoking, comorbidity index and BMI.

MeDi and incident AD – Supplementary analyses

- Individual dietary components as predictors in forward selection Cox models

- Unadjusted
  - Mild-Moderate alcohol consumption
    - 0.61 [0.45-0.82]; p = 0.001
  - Higher vegetable consumption
    - 0.76 [0.60-0.97]; p = 0.030

- Adjusted for cohort, age, gender, ethnicity, education, APOE genotype, caloric intake, smoking, comorbidity index and body mass index.
  - None of the individual components was a significant AD predictor.

Conclusions

- Higher adherence to MeDi associated with lower risk for AD
  - ~10% risk reduction for each additional unit of MeDi
- Gradual reduction in AD risk for higher tertiles of MeDi adherence, suggesting a possible dose-response effect
  - 20% - 45% reduction for middle MeDi adherence tertile
  - 40% - 65% reduction for highest MeDi adherence tertile
- Association over and above other potential confounders
  - cohort, age, gender, ethnicity, education, APOE genotype, caloric intake, smoking, comorbidity index and BMI
- Association not driven by any individual dietary component but by whole pattern of MeDi

ORIGINAL CONTRIBUTION

Mediterranean Diet and Mild Cognitive Impairment

Nikolaos Scarmeas, MD; Yaakov Stern, PhD; Richard Mayeux, MD; Jennifer J. Manly, PhD; Nicole Schupf, PhD; Jose A. Luchsinger, MD

Background: Higher adherence to the Mediterranean diet (MeDi) may protect from Alzheimer disease (AD), but its association with mild cognitive impairment (MCI) has not been explored.

Objective: To investigate the association between the MeDi and MCI.

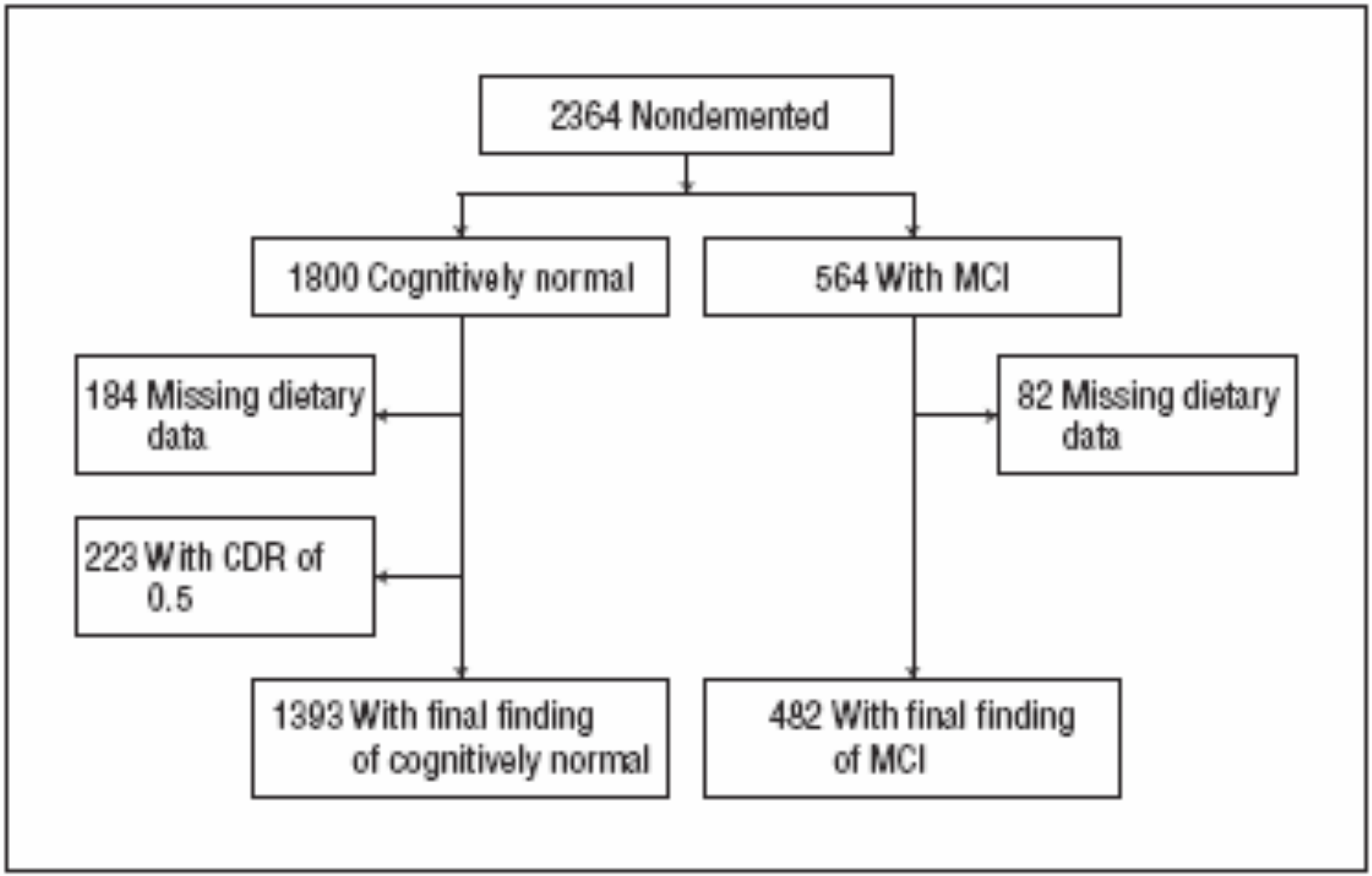
Design, Setting, and Patients: In a multiethnic community study in New York, we used Cox proportional hazards to investigate the association between adherence to the MeDi (0-9 scale; higher scores indicate higher adherence) and (1) the incidence of MCI and (2) the progression from MCI to AD. All of the models were adjusted for cohort, age, sex, ethnicity, education, *APOE* genotype, caloric intake, body mass index, and duration between baseline dietary assessment and baseline diagnosis.

Main Outcome Measures: Incidence of MCI and progression from MCI to AD.

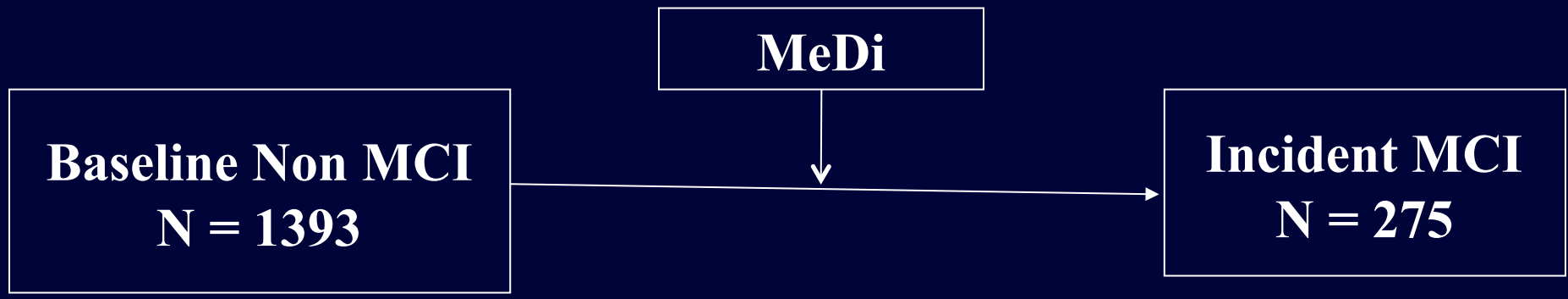
Results: There were 1393 cognitively normal participants, 275 of whom developed MCI during a mean (SD) follow-up of 4.5 (2.7) years (range, 0.9-16.4 years). Compared with subjects in the lowest MeDi adherence tertile, subjects in the middle tertile had 17% less risk (hazard ratio [HR]=0.83; 95% confidence interval [CI], 0.62-1.12; *P*=.24) of developing MCI and those in the highest tertile had 28% less risk (HR=0.72; 95% CI, 0.52-1.00; *P*=.05) of developing MCI (trend HR=0.85; 95% CI, 0.72-1.00; *P* for trend=.05). There were 482 subjects with MCI, 106 of whom developed AD during a mean (SD) follow-up of 4.3 (2.7) years (range, 1.0-13.8 years). Compared with subjects in the lowest MeDi adherence tertile, subjects in the middle tertile had 45% less risk (HR=0.55; 95% CI, 0.34-0.90; *P*=.01) of developing AD and those in the highest tertile had 48% less risk (HR=0.52; 95% CI, 0.30-0.91; *P*=.02) of developing AD (trend HR=0.71; 95% CI, 0.53-0.95; *P* for trend=.02).

Conclusions: Higher adherence to the MeDi is associated with a trend for reduced risk of developing MCI and with reduced risk of MCI conversion to AD.

Arch Neurol. 2009;66(2):216-225


2364 Nondemented
1800 Cognitively normal
564 With MCI
184 Missing dietary data
82 Missing dietary data
223 With CDR of 0.5
1393 With final finding of cognitively normal
482 With final finding of MCI

Baseline non-MCI Incident MCI



Follow-up
4.5 (0.9 – 16.4)years

Annual Incidence: ~ 5%

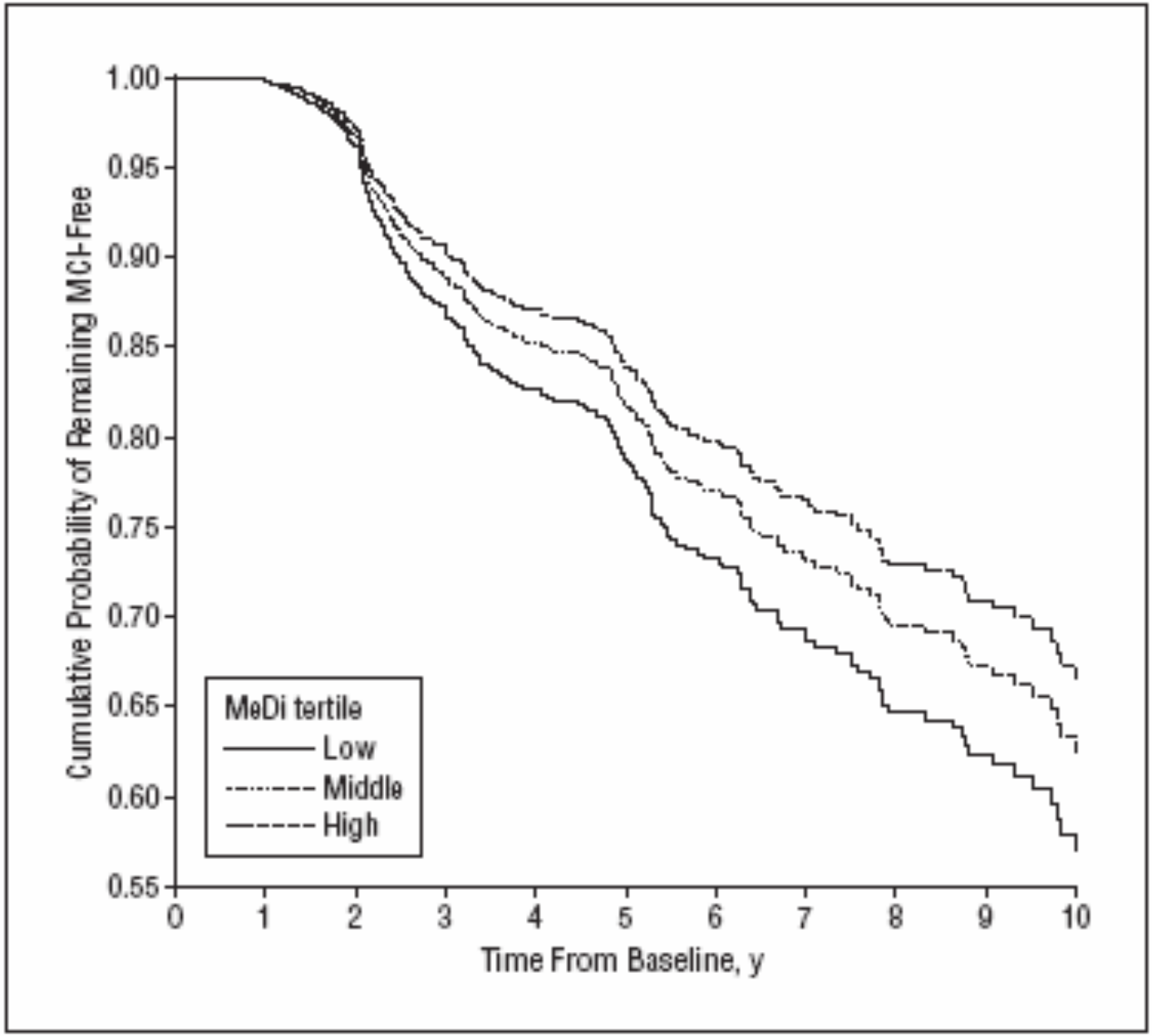

1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
Cumulative Probability of Remaining MCI-Free
0
1
2
3
4
5
6
7
8
9
10
Time From Baseline, y
MeDi tertile
Low
Middle
High

Table 3. Cox Proportional Hazard Ratios for Incidence of Mild Cognitive Impairment for Subjects Who Were Cognitively Normal at the First Evaluation by Mediterranean Diet Score

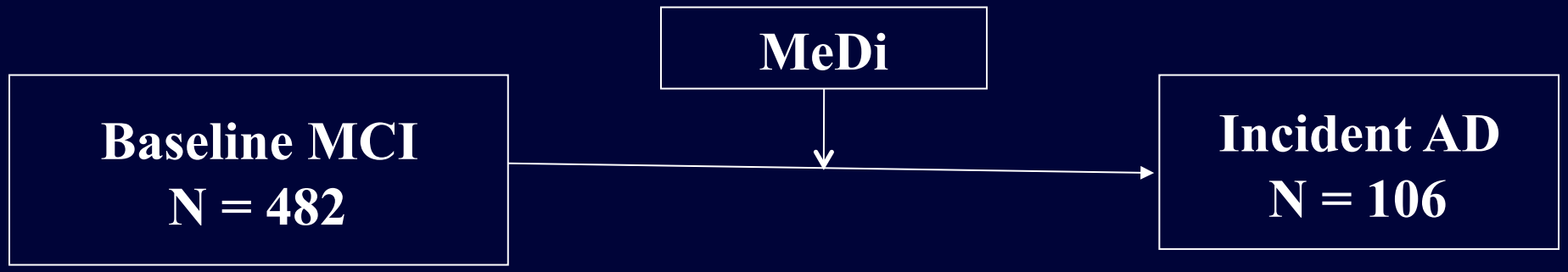
Predictor	HR (95% CI)	*P* Value
Unadjusted[a]		
MeDi continuous	0.93 (0.87-1.00)	.06
MeDi tertile		
Low	1 [Reference]	NA
Middle	0.87 (0.66-1.14)	.33
High	0.73 (0.53-1.00)	.05
Trend	0.85 (0.73-1.00)	.05
Adjusted[b]		
MeDi continuous	0.92 (0.85-0.99)	.04
MeDi tertile		
Low	1 [Reference]	NA
Middle	0.83 (0.62-1.12)	.24
High	0.72 (0.52-1.00)	.05
Trend	0.85 (0.72-1.00)	.05

Abbreviations: CI, confidence interval; HR, hazard ratio; MeDi, Mediterranean diet; NA, not applicable.

[a]A total of 1393 subjects were cognitively normal at the first evaluation; 275 subjects developed incident mild cognitive impairment.

[b]A total of 1199 subjects were cognitively normal at the first evaluation; 241 subjects developed incident mild cognitive impairment. Adjusted models include a slightly lower number of subjects because of missing data in some of the covariates; they simultaneously control for cohort, age, sex, ethnicity, education, *APOE* genotype, caloric intake, body mass index, and time between the first dietary assessment and the first cognitive assessment.

Baseline MCI Incident AD:



Follow-up
4.3 (1 – 13.8) years

Annual incidence 5%

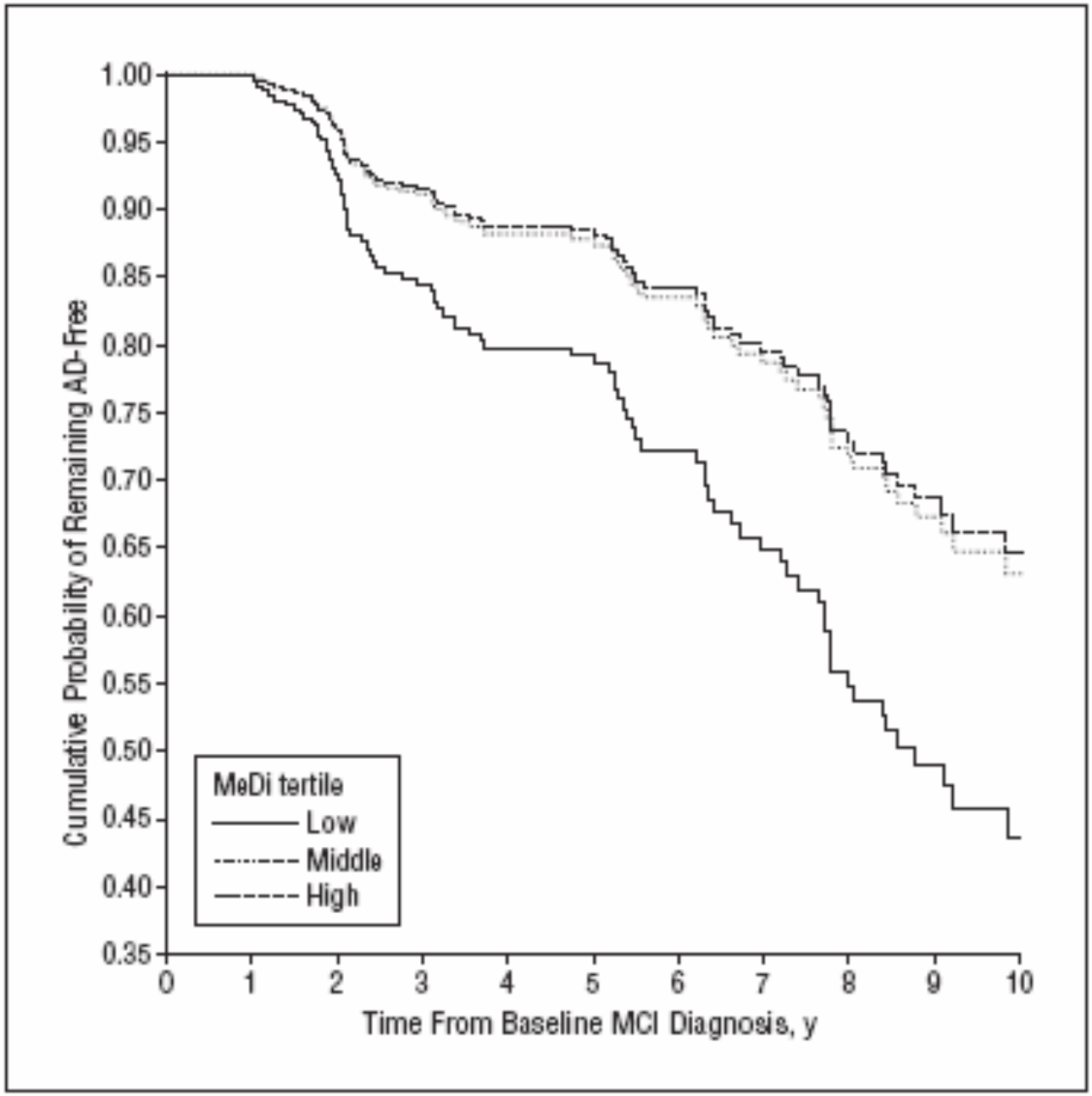

1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
Cumulative Probability of Remaining AD-Free
0
1
2
3
4
5
6
7
8
9
10
Time From Baseline MCI Diagnosis, y
MeDi tertile
Low
Middle
High

Table 4. Cox Proportional Hazard Ratios for Incidence of Alzheimer Disease for Subjects With Mild Cognitive Impairment at the First Evaluation by Mediterranean Diet Score

Predictor	HR (95% CI)	*P* Value
Unadjusted[a]		
MeDi continuous	0.95 (0.85-1.07)	.48
MeDi tertile		
Low	1 [Reference]	NA
Middle	0.62 (0.39-0.98)	.04
High	0.69 (0.41-1.14)	.15
Trend	0.82 (0.63-1.07)	.15
Adjusted[b]		
MeDi continuous	0.89 (0.78-1.02)	.09
MeDi tertile		
Low	1 [Reference]	NA
Middle	0.55 (0.34-0.90)	.01
High	0.52 (0.30-0.91)	.02
Trend	0.71 (0.53-0.95)	.02

Abbreviations: CI, confidence interval; HR, hazard ratio; MeDi, Mediterranean diet; NA, not applicable.

[a]A total of 482 subjects had mild cognitive impairment at the first evaluation; 106 subjects developed incident Alzheimer disease.

[b]A total of 409 subjects had mild cognitive impairment at the first evaluation; 96 subjects developed incident Alzheimer disease. Adjusted models include a slightly lower number of subjects because of missing data in some of the covariates; they simultaneously control for cohort, age, sex, ethnicity, education, *APOE* genotype, caloric intake, body mass index, and time between the first dietary assessment and the first cognitive assessment.

Conclusions
MeDi and MCI

- Higher adherence to MeDi is associated with reduced risk for incident MCI
- Higher adherence to MeDi is associated with reduced risk for conversion of MCI to incident AD (in particular for non-memory MCI)


WEBSHOTS

- MeDi seems to be protective for development of AD.

- What about after AD onset? Does MeDi affect AD course and prognosis???

Mediterranean diet and Alzheimer disease mortality

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ABSTRACT

Background: We previously reported that the Mediterranean diet (MeDi) is related to lower risk for Alzheimer disease (AD). Whether MeDi is associated with subsequent AD course and outcomes has not been investigated.

Objectives: To examine the association between MeDi and mortality in patients with AD.

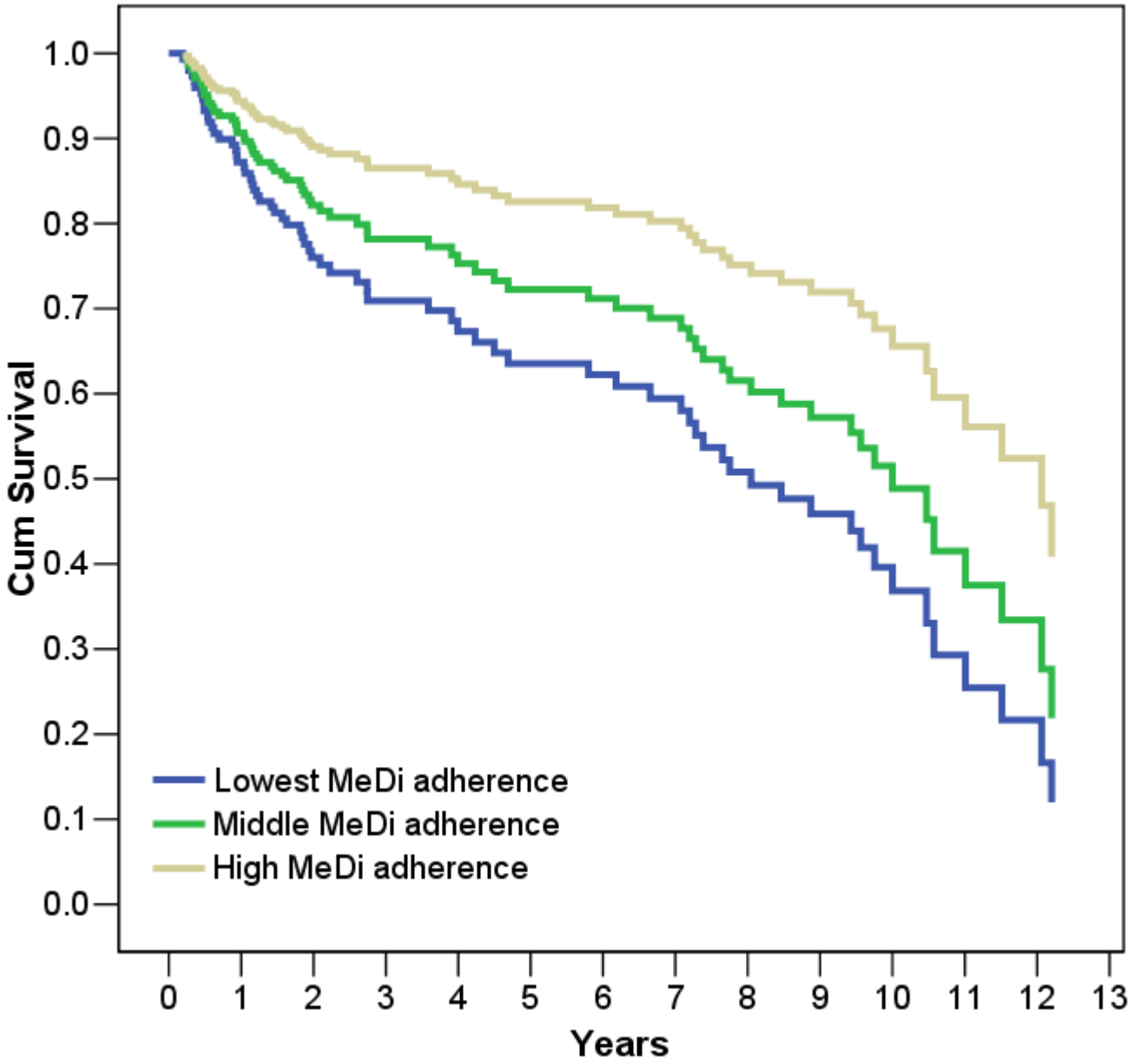
Methods: A total of 192 community-based individuals in New York who were diagnosed with AD were prospectively followed every 1.5 years. Adherence to the MeDi (0- to 9-point scale with higher scores indicating higher adherence) was the main predictor of mortality in Cox models that were adjusted for period of recruitment, age, gender, ethnicity, education, *APOE* genotype, caloric intake, smoking, and body mass index.

Results: Eighty-five patients with AD (44%) died during the course of 4.4 (±3.6, 0.2 to 13.6) years of follow-up. In unadjusted models, higher adherence to MeDi was associated with lower mortality risk (for each additional MeDi point hazard ratio 0.79; 95% CI 0.69 to 0.91; $p = 0.001$). This result remained significant after controlling for all covariates (0.76; 0.65 to 0.89; $p = 0.001$). In adjusted models, as compared with AD patients at the lowest MeDi adherence tertile, those at the middle tertile had lower mortality risk (0.65; 0.38 to 1.09; 1.33 years' longer survival), whereas subjects at the highest tertile had an even lower risk (0.27; 0.10 to 0.69; 3.91 years' longer survival; p for trend = 0.003).

Conclusion: Adherence to the Mediterranean diet (MeDi) may affect not only risk for Alzheimer disease (AD) but also subsequent disease course: Higher adherence to the MeDi is associated with lower mortality in AD. The gradual reduction in mortality risk for higher MeDi adherence tertiles suggests a possible dose–response effect. ***Neurology*® 2007;69:1084–1093**

MeDi and mortality
Prevalent AD
[Overall n = 184; Deaths = 68; Follow-up = 4.4 years]

- Survival analyses - Cox models
  - Outcome
    - Dead vs. Alive
    - Time to either death or to last follow-up
  - Main predictor
    - MeDi (continuous)
    - MeDi (tertiles)
  - Covariates adjusted for
    - cohort, age, gender, education, ethnicity, caloric intake, APOE, BMI, smoking



Scarmeas N., Luchsinger J., Mayeux R., Stern Y. Mediterranean diet and Alzheimer's disease mortality. Neurology, Neurology 2007; 69: 1084 - 1093.

MeDi and mortality

	HR	95% CI		p value
• Unadjusted continuous				
	.79	.68	.93	.003
• Adjusted continuous				
	.77	.64	.92	.004
• Adjusted tertiles (lowest tertile of adherence reference)				p for trend
middle tertile	.67	.37	1.22	.02
highest tertile	.32	.11	.95	

Mean survival:

- Lower adherence tertile: 6.6 years
- Middle adherence tertile: 7.9 years
- Higher adherence tertile: 10.5 years

Conclusions
MeDi and Mortality

- Higher adherence to MeDi is associated with reduced mortality in AD
- Effect present even when adjusting for multiple covariates
- Possible dose-response

Concerns - Limitations

- Replication
- “Healthy Person Bias” -
  “Residual Confounding”

Concerns - Limitations

- Replication
- "Healthy Person Bias" -
  "Residual Confounding"

Adherence to a Mediterranean Diet, Cognitive Decline, and Risk of Dementia

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Hélène Amieva, PhD
Florence Portet, MD, PhD
Jean-François Dartigues, MD, PhD
Nikolaos Scarmeas, MD
Pascale Barberger-Gateau, MD, PhD

Context Higher adherence to a Mediterranean-type diet is linked to lower risk for mortality and chronic diseases, but its association with cognitive decline is unclear.

Objective To investigate the association of a Mediterranean diet with change in cognitive performance and risk for dementia in elderly French persons.

Design, Setting, and Participants Prospective cohort study of 1410 adults (≥65 years) from Bordeaux, France, included in the Three-City cohort in 2001-2002 and reexamined at least once over 5 years. Adherence to a Mediterranean diet (scored as 0 to 9) was computed from a food frequency questionnaire and 24-hour recall.

Main Outcome Measures Cognitive performance was assessed on 4 neuropsychological tests: the Mini-Mental State Examination (MMSE), Isaacs Set Test (IST), Benton Visual Retention Test (BVRT), and Free and Cued Selective Reminding Test (FCSRT). Incident cases of dementia (n=99) were validated by an independent expert committee of neurologists.

Results Adjusting for age, sex, education, marital status, energy intake, physical activity, depressive symptomatology, taking 5 medications/d or more, apolipoprotein E genotype, cardiovascular risk factors, and stroke, higher Mediterranean diet score was associated with fewer MMSE errors (β=–0.006; 95% confidence interval [CI], –0.01 to –0.0003; *P*=.04 for 1 point of the Mediterranean diet score). Performance on the IST, BVRT, or FCSRT over time was not significantly associated with Mediterranean diet adherence. Greater adherence as a categorical variable (score 6-9) was not significantly associated with fewer MMSE errors and better FCSRT scores in the entire cohort, but among individuals who remained free from dementia over 5 years, the association for the highest compared with the lowest group was significant (adjusted for all factors, for MMSE: β=–0.03; 95% CI, –0.05 to –0.001; *P*=.04; for FCSRT: β=0.21; 95% CI, 0.008 to 0.41; *P*=.04). Mediterranean diet adherence was not associated with the risk for incident dementia (fully adjusted model: hazard ratio, 1.12; 95% CI, 0.60 to 2.10; *P*=.72), although power to detect a difference was limited.

Conclusions Higher adherence to a Mediterranean diet was associated with slower MMSE cognitive decline but not consistently with other cognitive tests. Higher adherence was not associated with risk for incident dementia.

JAMA. 2009;302(6):638-648 www.jama.com

THE TRADITIONAL MEDITERRANEAN diet is characterized by high consumption of plant foods (vegetables, fruits, legumes, and cereals), high intake of olive oil as the principal source of monounsaturated fat but low intake of saturated fat, moderate intake of fish, low to moderate intake of dairy products, low consumption of meat and poultry, and wine consumed in low to moderate amounts, normally with meals.[1] Adherence to a Mediterranean-type diet has been associated with longer survival, reduced risk of cardiovascular or cancer mortality, and reduced risk of neurodegenerative disease.[2,3]

A Mediterranean diet might also have protective effects against cognitive decline in older individuals, because it combines several foods and nutrients potentially protective against cognitive dysfunction or dementia, such as fish, monounsaturated fatty acids, vitamins B_{12} and folate, antioxidants (vitamin E, carotenoids, flavonoids), and moderate amounts of alcohol.[4-10] A single study showed a reduced risk for Alzheimer disease and mild cognitive impairment in participants with greater Mediterranean diet adherence.[11,12] These results were obtained in a non-Mediterranean older population, mainly US Hispanics and blacks (<30% whites), which limits its generalizability.

See also pp 627 and 686 and Patient Page.

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Concerns - Limitations

- Replication

- "Healthy Person Bias" -
  "Residual Confounding"

Physical Activity, Diet, and Risk of Alzheimer Disease

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Nicole Schupf, PhD
Adam M. Brickman, PhD
Stephanie Cosentino, PhD
Ming X. Tang, PhD
Yaakov Stern, PhD

Context Both higher adherence to a Mediterranean-type diet and more physical activity have been independently associated with lower Alzheimer disease (AD) risk but their combined association has not been investigated.

Objective To investigate the combined association of diet and physical activity with AD risk.

Design, Setting, and Patients Prospective cohort study of 2 cohorts comprising 1880 community-dwelling elders without dementia living in New York, New York, with both diet and physical activity information available. Standardized neurological and neuropsychological measures were administered approximately every 1.5 years from 1992 through 2006. Adherence to a Mediterranean-type diet (scale of 0-9; trichotomized into low, middle, or high; and dichotomized into low or high) and physical activity (sum of weekly participation in various physical activities, weighted by the type of physical activity [light, moderate, vigorous]; trichotomized into no physical activity, some, or much; and dichotomized into low or high), separately and combined, were the main predictors in Cox models. Models were adjusted for cohort, age, sex, ethnicity, education, apolipoprotein E genotype, caloric intake, body mass index, smoking status, depression, leisure activities, a comorbidity index, and baseline Clinical Dementia Rating score.

Main Outcome Measure Time to incident AD.

Results A total of 282 incident AD cases occurred during a mean (SD) of 5.4 (3.3) years of follow-up. When considered simultaneously, both Mediterranean-type diet adherence (compared with low diet score, hazard ratio [HR] for middle diet score was 0.98 [95% confidence interval {CI}, 0.72-1.33]; the HR for high diet score was 0.60 [95% CI, 0.42-0.87]; $P=.008$ for trend) and physical activity (compared with no physical activity, the HR for some physical activity was 0.75 [95% CI, 0.54-1.04]; the HR for much physical activity was 0.67 [95% CI, 0.47-0.95]; $P=.03$ for trend) were associated with lower AD risk. Compared with individuals neither adhering to the diet nor participating in physical activity (low diet score and no physical activity; absolute AD risk of 19%), those both adhering to the diet and participating in physical activity (high diet score and high physical activity) had a lower risk of AD (absolute risk, 12%; HR, 0.65 [95% CI, 0.44-0.96]; $P=.03$ for trend).

Conclusion In this study, both higher Mediterranean-type diet adherence and higher physical activity were independently associated with reduced risk for AD.

JAMA. 2009;302(6):627-637 www.jama.com

PREVIOUS RESEARCH HAS SHOWN that physical activity can slow down or prevent functional decline associated with aging and improve health in older individuals.[1,2] However, regarding Alzheimer disease (AD) or dementia, the relationship is less clear, with many studies reporting exercise being associated with lower rates of cognitive decline[1,3] or dementia[4-7] and others reporting no significant association.[8-10] Dietary habits also may play an important role but epidemiological data on diet and AD have been conflicting.[11] In this cohort, we previously found that higher adherence to a Mediterranean-type diet is associated with lower risk for AD[12,13] and mild cognitive impairment.[14]

Nevertheless, it is important to know whether physical activity and diet confer independent associations because individuals who exercise often belong to higher educational-socioeconomic strata, are more health conscious, and in general tend to follow healthier eating habits. The magnitude of such potential associations with AD in individuals engaging in such activities is also of great interest from a public health point of view. To our knowledge, there is scarce literature examining diet and exercise combined.

For editorial comment see p 686.

In the current study, we first sought to examine the association between physical activity and risk of AD. We then investigated the extent to which physical activity and adherence to a Mediterranean-type diet had independent associations with AD risk. We hypothesized that both adherence to a Mediterranean-type diet and physical activity would be

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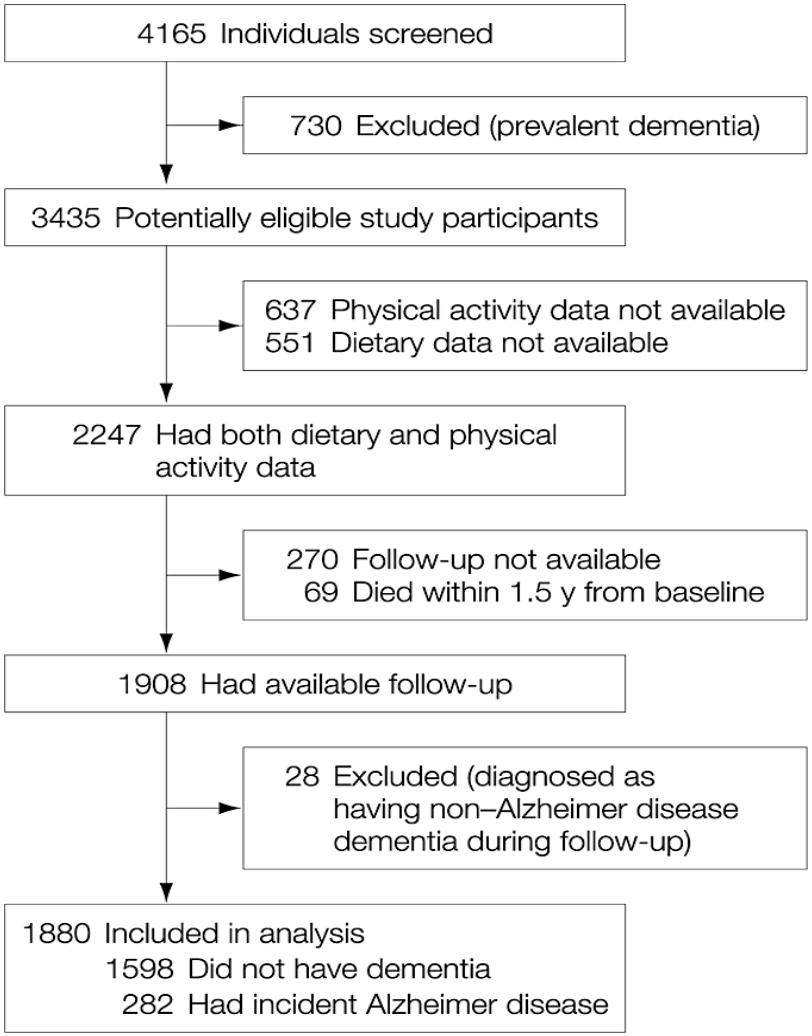
Selection of Individuals for Study Inclusion Who Were From the Washington Heights-Inwood Columbia Aging Project



Scarmeas, N. et al. JAMA 2009;302:627-637.

Cox Proportional Hazard Ratios (HRs) for Alzheimer Disease (AD) Incidence by Physical Activity and Mediterranean-Type Diet Scores

Table 3. Cox Proportional Hazard Ratios (HRs) for Alzheimer Disease (AD) Incidence by Physical Activity and Mediterranean-Type Diet Scores

Model	Unadjusted Model				Adjusted Model			
	No. of Individuals				No. of Individuals			
	No Dementia	Incident AD	HR (95% CI)	*P* Value	No Dementia	Incident AD	HR (95% CI)[a]	*P* Value
Physical activity[b]								
No	418	102	1 [Reference]		308	71	1 [Reference]	
Some	551	99	0.59 (0.45-0.78)	.001	445	84	0.71 (0.51-0.98)	.04
Much	629	81	0.50 (0.39-0.67)	<.001	499	69	0.63 (0.45-0.90)	.01
Trend (range, 1-3)	1598	282	0.70 (0.61-0.82)	<.001	1252	224	0.78 (0.67-0.95)	.01
Physical activity + Mediterranean-type diet								
Diet score								
Low (range, 0-3)	498	100	1 [Reference]		397	81	1 [Reference]	
Middle (range, 4-5)	661	118	0.86 (0.66-1.13)	.28	508	93	0.98 (0.72-1.33)	.88
High (range, 6-9)	439	64	0.68 (0.50-0.94)	.02	347	50	0.60 (0.42-0.87)	.007
Trend (range, 1-3)	1598	282	0.82 (0.71-0.96)	.01	1252	224	0.79 (0.66-0.94)	.008
Physical activity[b]								
No	418	102	1 [Reference]		308	71	1 [Reference]	
Some	551	99	0.62 (0.47-0.82)	.001	445	84	0.75 (0.54-1.04)	.08
Much	629	81	0.52 (0.39-0.70)	<.001	499	69	0.67 (0.47-0.95)	.02
Trend (range, 1-3)	1598	282	0.72 (0.62-0.83)	<.001	1252	224	0.82 (0.68-0.97)	.03

Abbreviation: CI, confidence interval.

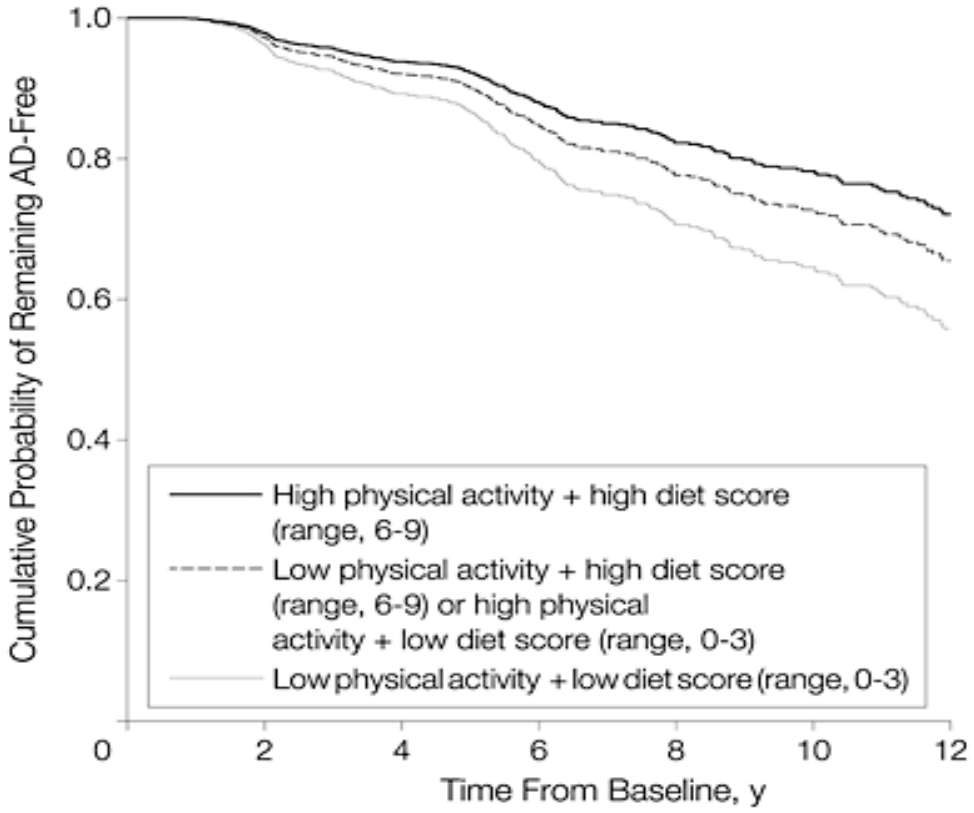
[a] Adjusted models include slightly lower number of individuals because of missing data in some of the covariates. Adjusted models simultaneously control for cohort, age, sex, ethnicity, education, apolipoprotein E *ε4* allele, caloric intake, body mass index (calculated as weight in kilograms divided by height in meters squared), smoking, depression, leisure activities, comorbidity index, baseline Clinical Dementia Rating score, and time between first dietary and first physical activity assessment.

[b] No physical activity was defined as a median of 0 hours per week. Some physical activity was defined as a median of 0.1 hours per week of vigorous, 0.8 hours per week of moderate, or 1.3 hours per week of light physical activity, or a combination thereof. Much physical activity was defined as a median of 1.3 hours per week of vigorous, 2.4 hours per week of moderate, or 3.8 hours per week of light physical activity, or a combination thereof.

Scarmeas, N. et al. JAMA 2009;302:627-637.

JAMA

Alzheimer Disease (AD) Incidence by High or Low Physical Activity Levels and Mediterranean-Type Diet Adherence Scores



No. at risk							
High + high	490	462	330	129	95	71	40
Low + high or high + low	903	834	578	243	178	124	56
Low + low	487	434	283	129	95	61	31

Scarmeas, N. et al. JAMA 2009;302:627-637.

JAMA

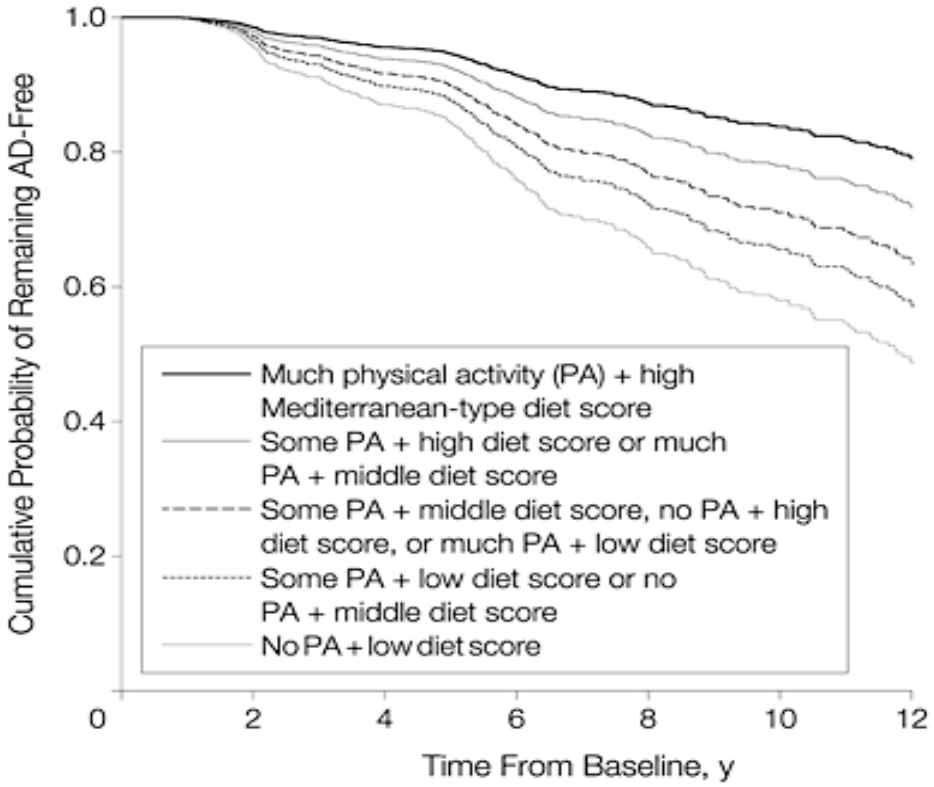
Alzheimer Disease (AD) Incidence in Individuals by No, Some, or Much Physical Activity and Low, Middle, and High Mediterranean-Type Diet Adherence Scores

Unadjusted HR:

0.78 (0.53-1.14)
0.63 (0.43-0.92)
0.46 (0.31-0.69)
0.33 (0.19-0.57)
Trend: 0.77 (0.69-0.85) p<0.001

Adjusted HR:

0.96 (0.60-1.55)
0.92 (0.59-1.43)
0.58 (0.36-0.95)
0.39 (0.20-0.76)
Trend: 0.80 (0.71-0.90) p<0.001



No. at risk							
Much PA + high diet	200	192	141	60	45	35	19
Some PA + high diet or much PA + middle diet	496	470	332	135	106	73	37
Some PA + middle diet, no PA + high diet, or much PA + low diet	573	526	374	168	121	82	35
Some PA + low diet or no PA + middle diet	421	377	241	99	72	48	27
No PA + low diet	190	165	103	39	27	18	9

Scarmeas, N. et al. JAMA 2009;302:627-637.

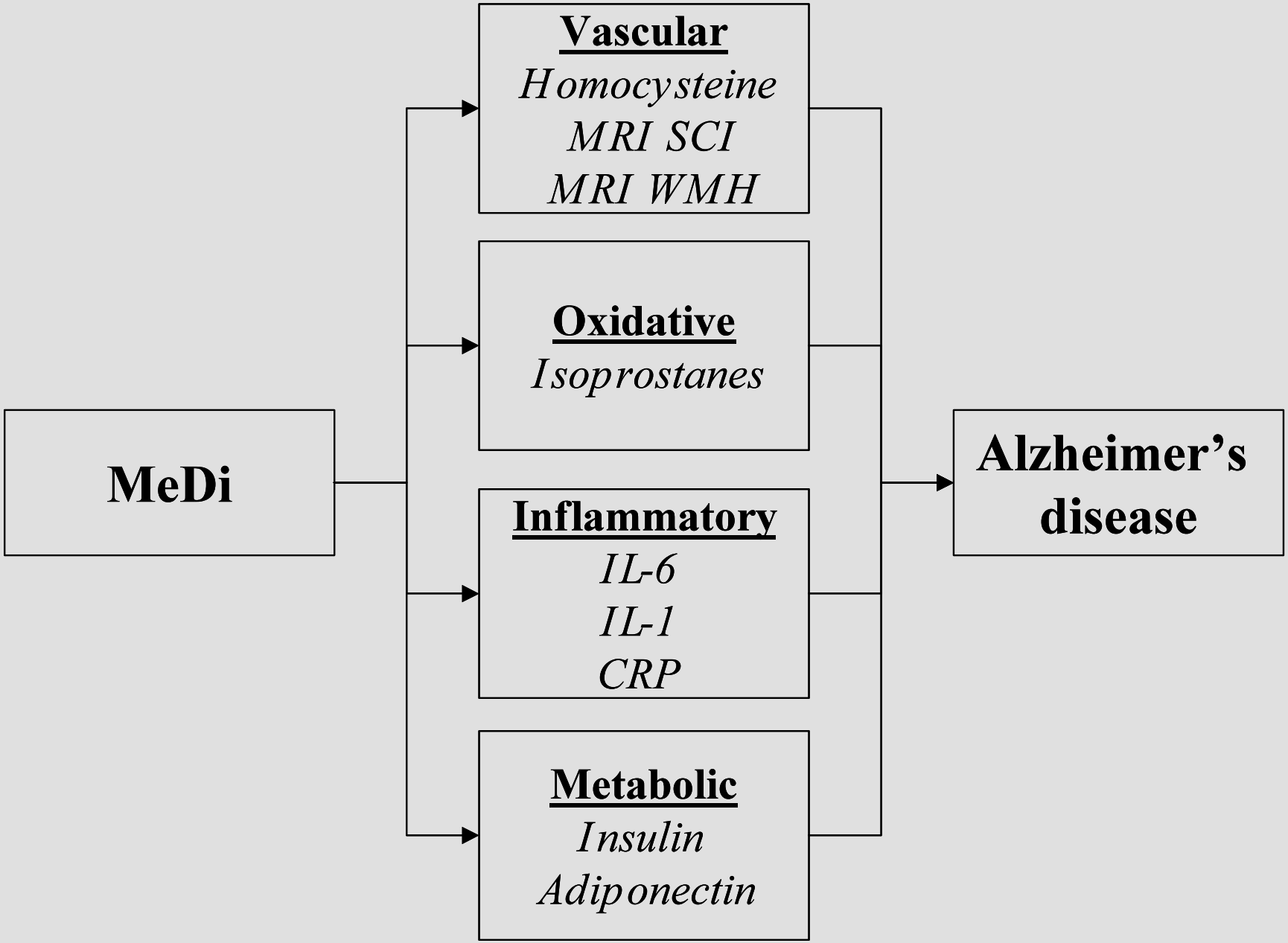
JAMA

MeDi - Physical activity and AD Conclusions

- More physical activity is associated with lower risk for AD development
- There is an independent effect of physical activity and Mediterranean diet adherence in protecting from AD onset
- The above are present over and above adjustment for various potential confounders
- Subjects in the highest tertiles of both physical activity and Mediterranean diet adherence have 61-67% reduction in risk for developing AD.

Mediterranean Diet, and Cognition:

- Possible Mechanism(s)??


MeDi
Vascular
Homocysteine
MRI SCI
MRI WMH
Oxidative
Isoprostanes
Inflammatory
IL-6
IL-1
CRP
Metabolic
Insulin
Adiponectin
Alzheimer's disease

Overall Conclusions

- MeDi (and composite dietary patterns in general) not adequately explored in neurological literature
- MeDi adherence is associated with
  - reduced AD risk
  - lower risk for MCI and lower conversion of MCI to AD
- Possible mechanisms could be vascular, inflammatory, oxidative, metabolic; not adequately investigated yet.
- MeDi adherence can affect further AD course: associated with prolonged survival.
- Both a healthy diet such as the MeDi and physical activity seem to be associated with reduced AD risk in an independent way.

Future plans

- Investigation of possible mechanisms
  - vascular
  - inflammatory
  - oxidative
  - Metabolic
- Other possible dietary patterns
  - Reduced Rank Regression analyses (RRR)
  - Canonical Variance Analyses (CVA)
- Intervention?

Cretan Villages

- Kastelli
- Thrapsano
- Xidas (Lytos)
- Voni
- Apostoli
- Agies Paraskies

Corfu Villages

- Korakiana
- Skriperon
- San Marcos

Mediterranean Diet - History

- 7 countries study (Ancel Keys 1978; Keys 1970)
  - In Greece (preliminary 1957; official 1961) in villages in Crete (n=686) and in Corfu (n=529)
  - 7 day assessments of food and chemical analyses in random samples of groups of 30-40 men in Greece
    - Repeated 3 times in Crete (1960; 1962; 1965)
    - Repeated Twice in Corfu (1961; 1963)


ΛΟΥΠΑΣΗΣ Α.Ε.
Ηράκλειο
Κόλπος Ηρακ
Δία
Κόλπος Μ
Ίδη
Άγιος Μύρων
Καστέλι
Άγιες Παρασκιές
Θραψανό
Βόροι
Μοίρες
Πύργος
Άνω Βιάννος
Κάτω Βιάννος
Μπαλί
Σίσες
Βλιχάδα
Αγία Πελαγία
Αχλάδα
Φόδελε
Μονή Σαβαθιανών
Ροδιά
Μελιδόνι
Αλοίδες
Απλαδιανά
Μουρτζανά
Χελιανά
Γαράζο
Αγρίδια
Μικρή Επισκοπή
Τσαχιανά
Αϊμονας
Αδάμαστα
Καστρί
Βενί
Μονή Χαλέπα
Αξός
Καμαριώτης
Λιβάδια
Σκλαβόκαμπος
Γωνιές
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Αρολίθος
Γάζι
Φορτέτσα
Κνωσός
Γούρνες
Κερομούτοι
Βούτες
Βασιλείες
Κορφές
Σίλαμος
Άγιος Σύλλας
Κρουσώνας
Πυργού
Δάφνες
Προφήτης Ηλίας
Βαθύπετρο
Γιούχτας
Πεζά
Κάτω Αρχάνες
Κουνάβοι
Επάνω Αρχάνες
Μυρτιά
Μονή Αγκαράθου
Απόστολοι
Σκλαβεροχώρι
Λύττος
Μονή Βιάννης
Αβδού
Κερά
Σφενδύλι
Μονή Καρδιώτ
Μάλια
Σταλίδα
Χερσόνησος
Λιμήν Χερσονήσου
Καλό Χωριό
Βόρος
Γάλιπε
Σκαλάνι
Σκοτεινό
Ελιά
Αϊτάνια
Γαλίφα
Επισκοπή
Λαγός
Καρτερός
Σπήλαιο Ειλειθυίας
Αμμούδα Χάνι
Κοκκίνη
Αλικαρνασσός
Νέα
Κάτω Ασίτες
Άνω Ασίτες
Βενεράτο
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Μαθιά
Ροussοχώρια
Σπήλαιο Δικταίου Άντρο
Γεράκι
Νιπιδίτος
Αγία Σεμνή
Αρκαλοχώρι
Καλό Χωριό
Αυλή
Παναγία
Πάνω Πούλια
Πάρτιρα
Χαράκι
Μελιδοχώρι
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Απομαρμά
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Γρηγορία
Ιωάννης
Κόκκινος Πύργος
Τυμπάκι
Γαλιά
Ρουκάς
Μονόχωρο
Γεωργική Σχολή
Αγία Τριάδα
Φαιστός
Μητρόπολη
Άγιοι Δέκα
Γόρτυνα
Γκαγκάλες
Βαλής
Ίνια
Ατσιπάδες
Στόλοι
Λούρας
Ασήμι
Νεοχώρι
Προτόρια
Λιγόρτυνος
Τεφέλι
Δραπέτι
Γαρίπα
Ίνιο
Έμπαρος
Κάσανοι
Ξενιακός
Κατσφύγι
Μιλλιαράδες
Λουτράκι
Μάρβα
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Σκινιάς
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Άνω Καστελλιάνα
Φίλλιποι
Κάτω Δεμάτι Καστελλιάνα
Χόντρος
Κάτω Βιάννος
Άγιος Βασίλειος
Κερατόκαμπος
Άρβη
Νέα Άρβη
Τσούτσουρας
Αχεντριάς
Άγιος Παντελεήμονας
Αγία Παρασκευή
Ροτάσι
Μεσοχώρι
Δοράκι
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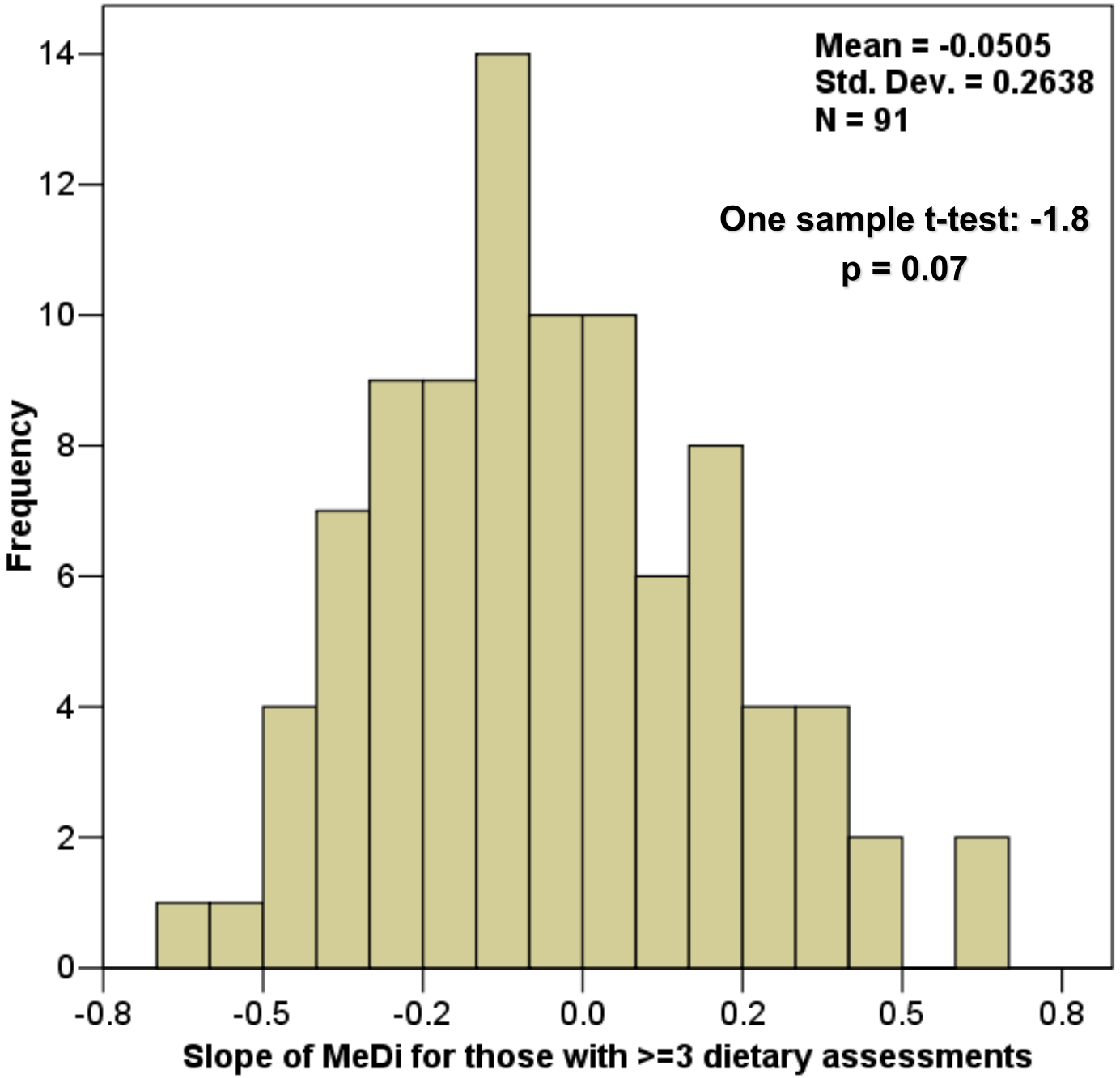
Χάρακας
Βαγιονιά
Πλάτανος
Απεσωκάρι
Πλώρα
Πόμπια
Σίβας
Πιτσίδια
Κομμός
Μάταλα
Άγιος Ιωάννης
Καμηλάρι
Πηγαϊδάκια
Μονή Απεζανών
Άγιος Κύριλλος
Βασιλική
Λούκια
Μιαμού
Κρότος
Μονή Οδηγήτριας
Καλοί Λιμένες

MeDi stability

- 1015 subjects with multiple dietary assessments (no dementia during follow-up).
  - 2 dietary assessments for 831 subjects
  - 3 dietary assessments for 137 subjects
  - 4 dietary assessments for 43 subjects.
  - 5 dietary assessments for 4 subjects
  - Mean time interval between dietary assessments 6.1 years (sd 3.1, range 1 – 12.8).
- Generalized estimating equations (GEE) in subjects with >1 dietary assessments
  - MeDi score as the dependent variable
  - Time (years) as predictor
- MeDi score stable ($\beta = -0.01$, $p = 0.44$).


Mean = -0.0505
Std. Dev. = 0.2638
N = 91
One sample t-test: -1.8
p = 0.07
Frequency
14
12
10
8
6
4
2
0
-0.8
-0.5
-0.2
0.0
0.2
0.5
0.8
Slope of MeDi for those with >=3 dietary assessments

MCI definition

- Retrospectively applied after consensus for each visit
  - Memory complaint, in 1 or more from 11 items
    - Disability and Functional Limitations Scale (IADL)
      - (any memory difficulties, any memory problem past month, memory for things read or heard, memory for names, remembering right word).
    - Blessed functional activities scale
  - Cognitive impairment (<1.5 sd for age, gender, education, ethnicity corrected norms) in at least 1 cognitive domain (summary z-scores for each domain).
    - Memory (total recall SRT, free recall SRT, recognition BVRT)
    - Executive (letter fluency, category fluency, WAIS-R similarities)
    - Language (Boston naming, BDAE repetition, BDAE comprehension)
    - Visuospatial (Rosen, BVRT matching)
  - Preserved IADL
    - Disability and Functional Limitations Scale (IADL) summary measure on 6 domains (phone, cooking, shopping, finances, change, medications): complaints in not more than 2 domains.
  - No dementia diagnosis in consensus conference

Clinical – demographics by diagnosis

Table 1. Demographic and Clinical Characteristics During the First Evaluation for All Subjects

Characteristic	Cognitively Normal (n=1393)	MCI (n=482)	All Subjects (n=1875)	*P* Value
Men, No. (%)	447 (32)	156 (32)	603 (32)	.91
Age, mean (SD), y	76.7 (6.5)	77.5 (6.6)	76.9 (6.5)	.02
Ethnicity, No. (%)				
White	434 (31)	124 (26)	558 (30)	<.001
Black	479 (34)	144 (30)	623 (33)	
Hispanic	473 (34)	214 (44)	687 (36)	
Other	7 (1)	0	7 (1)	
Education, mean (SD), y	10.8 (4.6)	9.1 (4.9)	10.4 (4.7)	<.001
≥1 ε4 allele, No. (%)	327 (27)	127 (30)	454 (28)	.18
BMI, mean (SD)	27.5 (5.5)	27.2 (5.3)	27.4 (5.4)	.34
Energy, mean (SD), kcal	1426.1 (498.0)	1421.8 (591.9)	1425.0 (523.6)	.88
MeDi score, mean (SD)	4.37 (1.69)	4.31 (1.62)	4.36 (1.67)	.47

Clinical – demographics by MeDi

Table 2. Demographic and Clinical Characteristics During the First Evaluation for All Subjects by Mediterranean Diet Adherence Tertiles

Characteristic	MeDi Adherence Tertile: Low (n=609)	Middle (n=775)	High (n=491)	*P* Value
Men, No. (%)	442 (69)	532 (69)	318 (65)	.23
Age, mean (SD), y	76.9 (6.6)	76.8 (6.5)	77.2 (6.2)	.48
Ethnicity, No. (%)				
White	182 (30)	223 (29)	153 (31)	.001
Black	234 (38)	260 (33)	139 (26)	
Hispanic	190 (31)	289 (37)	208 (42)	
Other	3 (1)	3 (1)	1 (1)	
Education, mean (SD), y	10.5 (4.5)	10.3 (4.7)	10.4 (4.9)	.77
≥1 ε4 allele, No. (%)	146 (27)	179 (27)	129 (29)	.70
BMI, mean (SD)	27.7 (5.8)	27.4 (5.2)	27.1 (5.3)	.19
Energy, mean (SD), kcal	1494.9 (608.2)[a]	1395.4 (472.5)[a]	1385.1 (477.4)[a]	<.001

Baseline non-MCI Incident MCI: Relation of MeDi and MCI to covariates

- Incident MCI more common in
  - Hispanics (less in Whites)
  - Older
  - Lower Education
- MeDi higher (more adherent)
  - Hispanics (Blacks less)
  - Lower Caloric intake

MCI subtypes definition

- MCI amnestic
  - Impairment in Memory domain
  - Normal all other domains (Executive, Language, Visuospatial)
- MCI Executive
  - Impairment in Executive domain
  - Normal all other domains (Memory, Language, Visuospatial)
- MCI Language
  - Impairment in Language domain
  - Normal all other domains (Memory, Executive, Visuospatial)
- MCI Visuospatial
  - Impairment in Visuospatial domain
  - Normal all other domains (Memory, Executive, Language)

- MCI Multiple Cognitive Domains with Memory
  - Impairment in Memory domain
  - Impairment in at least one other domain (Executive, Language, Visuospatial)
- MCI Multiple Cognitive Domains without Memory
  - Normal Memory domain
  - Impairment in at least two other domains (Executive, Language, Visuospatial)

Incident AD *adjusted

(i)Baseline Multiple domain Memory and

(ii)Baseline Multiple domain Non-Memory

Predictor	HR	95 % CI		P
Baseline Mult. domain Memory MCI (N = 175) – Incident AD (N = 49)				
MeDi continuous (0-9)	0.99	0.82	1.20	0.96
Low MeDi tertile	1 (ref)	-	-	-
Middle MeDi tertile	0.48	0.22	1.04	0.06
High MeDi tertile	0.71	0.32	1.59	0.41
MeDi tertile trend	0.84	0.55	1.29	0.45
Baseline Mult. domain Non-Memory MCI (N = 234) – Incident AD (N = 47)				
MeDi continuous (0-9)	0.74	0.60	0.91	**0.005**
Low MeDi tertile	1 (ref)	-	-	**-**
Middle MeDi tertile	0.49	0.24	1.01	**0.05**
High MeDi tertile	0.25	0.10	0.63	**0.003**
MeDi tertile trend	0.50	0.32	0.79	**0.003**

Mediterranean Diet and other diseases

- Lower risk for **Total Mortality**
  - ~22000 participants in Greece
    - Trichopoulou, Kouris-Blazos et al.1995; Trichopoulou, Costacou et al. 2003
  - ~2500 participants in 11 European countries
    - Knoops, deGroot et al. 2004
  - ~75000 adults in 11 European countries
    - Trichopoulou, Orfanos et al. 2005
  - ~380000 NIH AmAsRetPersons Diet and Health study in the U S
    - Mitrou, Kipnis et al. 2007

Characteristics of All Individuals at First Evaluation, Stratified by Alzheimer Disease (AD) Incidence

Table 1. Characteristics of All Individuals at First Evaluation, Stratified by Alzheimer Disease (AD) Incidence

	No. (%) of Individuals[a]			
	No Dementia (n = 1598)	Incident AD (n = 282)	All (N = 1880)	*P* Value
Male sex	497 (31)	90 (32)	587 (31)	.79
Age, mean (SD), y	76.4 (6.3)	82 (6.8)	77.2 (6.6)	<.001
Ethnicity				
White	498 (31)	33 (12)	531 (28)	<.001
Black	513 (32)	92 (33)	605 (32)	
Hispanic	561 (35)	154 (55)	715 (38)	
Other[b]	26 (2)	3 (1)	29 (2)	
Education, mean (SD), y	10.6 (4.6)	7.4 (4.4)	10.1 (4.8)	<.001
≥1 Apolipoprotein E ε*4* allele	364 (23)	79 (28)	443 (24)	.07
Energy, mean (SD), kcal/d	1424.7 (526.6)	1465.7 (550.9)	1430.8 (530.4)	.23
Body mass index, mean (SD)[c]	27.6 (5.4)	26.6 (5.9)	27.4 (5.5)	.007
Comorbidity index, mean (SD)	1.1 (1.4)	1.9 (1.5)	1.9 (1.4)	.24
Smoker	199 (13)	40 (14)	239 (13)	.42
Depression	117 (7)	27 (10)	144 (8)	.20
Leisure activities, mean (SD)	5.2 (2.2)	5.6 (2.1)	5.3 (2.2)	.005
Mediterranean-type diet score				
Low (range, 0-3)	498 (31)	100 (36)	598 (32)	.18
Middle (range, 4-5)	661 (41)	118 (42)	779 (41)	
High (range, 6-9)	439 (28)	64 (23)	503 (27)	
Physical activity				
No	418 (26)	102 (36)	520 (28)	<.001
Some[d]	551 (35)	99 (35)	650 (35)	
Much[e]	629 (39)	81 (29)	710 (38)	

[a] Unless otherwise indicated. Percentages may not equal 100% due to rounding.
[b] Defined as non-white, non-black, American Indian or Pacific Islander, or Asian.
[c] Calculated as weight in kilograms divided by height in meters squared.
[d] Defined as a median of 0.1 hours per week of vigorous, 0.8 hours per week of moderate, or 1.3 hours per week of light physical activity, or a combination thereof.
[e] Defined as a median of 1.3 hours per week of vigorous, 2.4 hours per week of moderate, or 3.8 hours per week of light physical activity, or a combination thereof.

Scarmeas, N. et al. JAMA 2009;302:627-637.

JAMA

Characteristics of All Individuals at First Evaluation, Stratified by Physical Activity

Table 2. Characteristics of All Individuals at First Evaluation, Stratified by Physical Activity

	Physical Activity[a]			
	No (n = 520)	Some (n = 650)	Much (n = 710)	*P* Value
Male sex	137 (26)	188 (29)	262 (37)	.001
Age, mean (SD), y	77.9 (6.9)[b]	77.6 (6.6)[b]	76.3 (6.3)[b]	<.001
Ethnicity				
White	136 (26)	171 (26)	224 (32)	.06
Black	173 (33)	209 (32)	223 (31)	
Hispanic	207 (40)	261 (40)	247 (35)	
Other	4 (1)	9 (1)	16 (2)	
≥1 Apolipoprotein E ε*4* allele	114 (22)	155 (24)	174 (25)	.77
Education, mean (SD), y	9.7 (4.9)[b]	9.9 (4.7)[b]	10.6 (4.7)[b]	.001
Energy, mean (SD), kcal/d	1392.7 (571.1)[b]	1389.6 (518.5)[b]	1496.5 (503.7)[b]	<.001
Body mass index, mean (SD)[c]	28.3 (6.0)[b]	27.5 (5.4)[b]	26.7 (5.1)[b]	<.001
Comorbidity index, mean (SD)	2.2 (1.5)[b]	2.0 (1.4)[b]	1.8 (1.4)[b]	<.001
Smoker	72 (14)	71 (11)	96 (14)	.24
Depression	58 (11)	49 (8)	37 (5)	.001
Leisure activities, mean (SD)	5.3 (2.1)	5.4 (2.1)	5.1 (2.2)	.06
Mediterranean-type diet score				
Low (range, 0-3)	190 (37)	191 (29)	217 (31)	<.001
Middle (range, 4-5)	230 (44)	256 (39)	293 (41)	
High (range, 6-9)	100 (19)	203 (31)	200 (28)	

[a] Values are expressed as number (percentage) unless otherwise indicated. No physical activity was defined as a median of 0 hours per week. Some physical activity was defined as a median of 0.1 hours per week of vigorous, 0.8 hours per week of moderate, or 1.3 hours per week of light physical activity, or a combination thereof. Much physical activity was defined as a median of 1.3 hours per week of vigorous, 2.4 hours per week of moderate, or 3.8 hours per week of light physical activity, or a combination thereof.

[b] $P<.05$ for subgroup comparisons indicated with a "b" footnote. These comparisons were calculated by post hoc Bonferroni and Tukey tests. The no and some physical activity groups were compared with the much physical activity group.

[c] Calculated as weight in kilograms divided by height in meters squared.

Scarmeas, N. et al. JAMA 2009;302:627-637.

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Table 5. Mediterranean Diet Adherence and Age-Adjusted Risk for Dementia and Alzheimer Disease Among Older Persons Living in Bordeaux—the Three-City Study, Wave 1 (2001-2002)[a]

	Model 1[b]			Model 2[c]			Model 3[d]			Model 4[e]		
Category	HR (95% CI)	*P* Value	*P* Value Overall	HR (95% CI)	*P* Value	*P* Value Overall	HR (95% CI)	*P* Value	*P* Value Overall	HR (95% CI)	*P* Value	*P* Value Overall
Risk for Dementia With An Increase of 1 Point of Mediteranean Diet Score or Compared With the Low Score Category												
Diet score (0-9)	0.99 (0.87-1.13)	.90		1.04 (0.91-1.20)	.53		0.99 (0.87-1.14)	.97		1.06 (0.92-1.21)	.43	
Middle category	0.92 (0.56-1.52)	.75	.70	1.02 (0.59-1.76)	.94	.86	0.97 (0.58-1.63)	.92	.80	1.11 (0.63-1.94)	.71	.72
High category	0.89 (0.50-1.59)	.70		1.06 (0.57-1.96)	.86		0.92 (0.51-1.66)	.78		1.12 (0.60-2.10)	.72	
Risk for Alzheimer Disease With An Increase of 1 Point of Mediterranean Diet Score or Compared With the Low Score Category												
Diet score (0-9)	0.92 (0.78-1.08)	.92		0.99 (0.83-1.17)	.88		0.93 (0.79-1.09)	.37		1.00 (0.85-1.19)	.96	
Middle category	0.76 (0.42-1.39)	.38	.26	0.93 (0.48-1.79)	.82	.59	0.80 (0.43-1.46)	.46	.31	0.99 (0.51-1.94)	.98	.72
High category	0.67 (0.33-1.37)	.28		0.81 (0.37-1.75)	.59		0.70 (0.34-1.43)	.33		0.86 (0.39-1.88)	.71	

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] *P* values from Cox proportional hazard models with delayed entry and age as a time scale. There were 99 incident cases of dementia and 66 incident cases of Alzheimer disease. Middle category indicates scores of 4 through 5; high category, scores of 6 through 9.

[b] Adjusted for sex, education, marital status, total energy intake, practice of physical exercise, taking 5 medications/d or more, Center for Epidemiological Studies-Depression Scale score, and apolipoprotein E genotype. N=86 for dementia and 58 for Alzheimer disease.

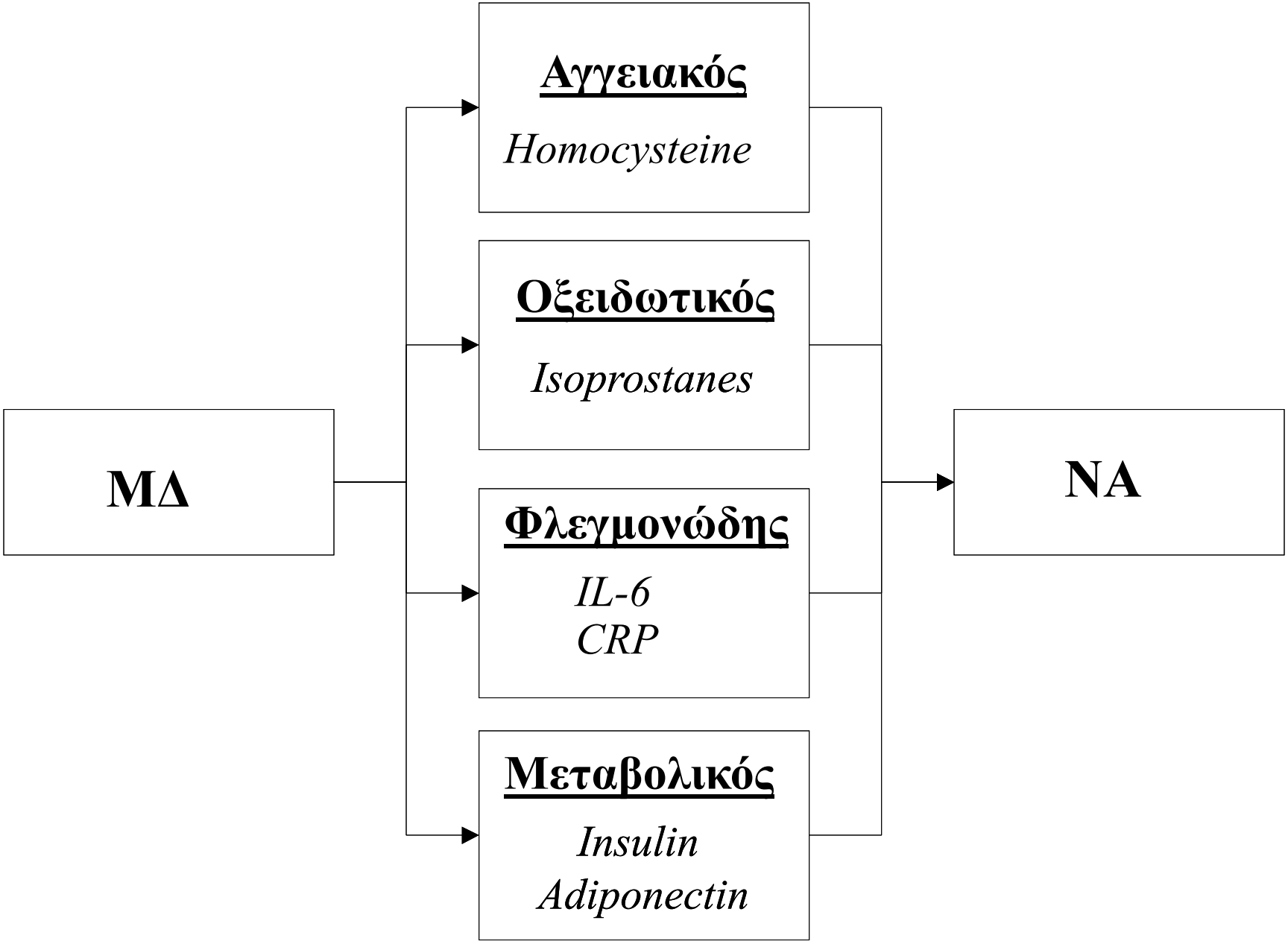
[c] Adjusted for covariates in model 1 plus additional adjustment for body mass index, hypertension, hypercholesterolemia, diabetes, and tobacco use. N=76 for dementia and 51 for Alzheimer disease.

[d] Adjusted for covariates in model 1 plus additional adjustment for stroke. N=84 for dementia and 57 for Alzheimer disease.

[e] Adjusted for covariates in model 2 plus additional adjustment for stroke. N=74 for dementia and 50 for Alzheimer disease.

Initial N:1410 (vs. 2258)

Incident AD: 66 (vs. 262)


ΜΔ
Αγγειακός
Homocysteine
Οξειδωτικός
Isoprostanes
Φλεγμονώδης
IL-6
CRP
Μεταβολικός
Insulin
Adiponectin
ΝΑ

Incident AD

		Low Tertile (MeDi score 0-3)	Middle Tertile (MeDi score 4-5)	High Tertile (MeDi score 6-9)	P
Cohort WHICAP99 N (%)		395 (55)	508 (55)	312 (54)	0.99
Age yrs, mean (SD)		77.3 (6.8)	77.0 (6.6)	77.3 (6.3)	0.50
Gender-Men N (%)		218 (30)	303 (33)	199 (35)	0.23
Education yrs, mean (SD)		10.2 (4.5)	9.9 (4.8)	10.1 (4.9)	0.45
Ethnicity, N (%)	**White**	204 (28)	251 (27)	165 (29)	<0.001
	Black	280 (39)	292 (31)	150 (26)	
	Hispanic	225 (31)	374 (40)	249 (43)	
	Other	13 (2)	13 (1)	10 (2)	
Presence of ε4 allele (%)		164 (27)	214 (27)	148 (29)	0.68
Smoking (%)		111 (15)	119 (13)	45 (8)	<0.001
Comorbidity, mean (SD)		1.9 (1.4)	1.9 (1.4)	2.0 (1.5)	0.95
Energy (kcal), mean (SD)		1498 (605)	1399 (467)	1387 (473)	<0.001
Body Mass Index (SD)		27.5 (5.8)	27.5 (5.5)	27.2 (5.3)	0.55

Prevalent AD		Low Tertile (MeDi score 0-3)	Middle Tertile (MeDi score 4-5)	High Tertile (MeDi score 6-9)	P
Cohort -WHICAP 1999 N (%)		402 (60)	500 (62)	321 (63)	0.66
Age yrs, mean (SD)		76.5 (6.8)	76.4 (6.6)	75.8 (6.2)	0.15
Gender-Men N (%)		210 (32)	241 (30)	179 (35)	0.10
Education yrs, mean (SD)		10.5 (4.5)	10.7 (4.8)	10.9 (4.6)	0.45
Ethnicity, N (%)	**White**	220 (33)	265 (33)	158 (31)	**0.006**
	Black	250 (38)	261 (32)	145 (29)	
	Hispanic	190 (29)	271 (34)	193 (38)	
	Other	7 (1)	13 (2)	11 (2)	
Presence of ε4 allele (%)		131 (25)	180 (27)	121 (28)	0.46
Smoking (%)		96 (14)	88 (11)	39 (8)	**0.001**
Comorbidity Index, mean (SD)		1.9 (1.4)	2.0 (1.5)	1.9 (1.3)	0.46
Energy (kcal), mean (SD)		1512 (590)	1400 (473)	1425 (545)	**<0.001**
Body Mass Index (SD)		27.8 (6.0)	27.6 (5.3)	27.6 (6.0)	0.68
Stroke, N (%)		58 (9)	64 (8)	31 (6)	0.21
Diabetes, N (%)		112 (18)	151 (20)	89 (19)	0.72
Hypertension, N (%)		381 (61)	500 (65)	311 (64)	0.33
Heart Disease, N (%)		161 (26)	189 (25)	122 (25)	0.86
TC, mg/dl, mean (SD)		201.0 (38.2)	201.8 (39.8)	204.0 (39.7)	0.48
HDL, mg/dl, mean (SD)		48.0 (15.2)	48.4 (15.8)	48.2 (15.1)	0.89
TG, mg/dl, mean (SD)		153.9 (84.3)	158.3 (86.4)	153.2 (81.6)	0.55
LDL, mg/dl, mean (SD)		122.3 (33.5)	121.7 (34.5)	125.2 (34.6)	0.25

MeDi and incident AD – Supplementary analyses

- Individual dietary components as predictors in forward selection Cox models

- Unadjusted
  - Mild-Moderate alcohol consumption
    - 0.61 [0.45-0.82]; p = 0.001
  - Higher vegetable consumption
    - 0.76 [0.60-0.97]; p = 0.030

- Adjusted for cohort, age, gender, ethnicity, education, APOE genotype, caloric intake, smoking, comorbidity index and body mass index.
  - None of the individual components was a significant AD predictor.

Model	Non-Demented	AD	MeDi continuous OR (95%CI)	P		MeDi tertiles OR (95%CI)	P for trend
1	1790	194	0.81 (0.74 – 0.88)	<0.001	Low	1 (reference)	<0.001
					Middle	0.58 (0.42 – 0.81)	
					High	0.40 (0.26 – 0.61)	
2	1300	137	0.76 (0.67 – 0.87)	<0.001	Low	1 (reference)	<0.001
					Middle	0.47 (0.29 – 0.76)	
					High	0.32 (0.17 – 0.59)	
3	1259	135	0.76 (0.66 – 0.86)	<0.001	Low	1 (reference)	<0.001
					Middle	0.48 (0.29 – 0.79)	
					High	0.31 (0.16 – 0.58)	

Model 1 is unadjusted.

Model 2 is adjusted for cohort, age, gender, ethnicity, education, APOE genotype, caloric intake, smoking, comorbidity index and BMI.

Model 3 is adjusted for all variables of model 2, plus the following additional vascular variables: history of stroke, diabetes, hypertension, heart disease, and plasma TC, HDL, TG, LDL..

MeDi and incident AD – Missing data analyses

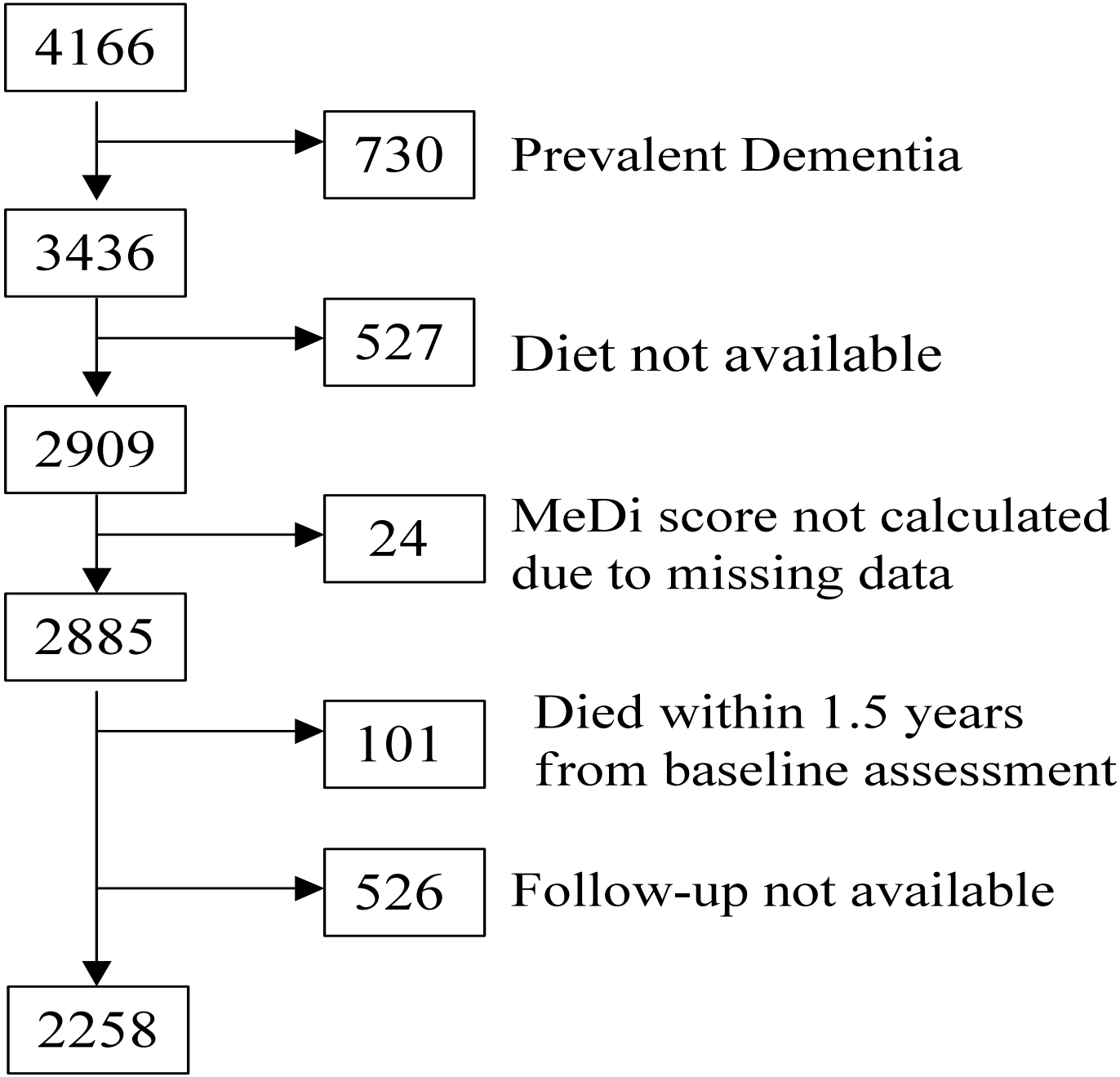
- Dietary data - MeDi available for 2885 subjects at their baseline evaluation
- Missing cognitive follow-up (n = 627) vs. available cognitive follow-up (n = 2258)
  - Slightly younger (76.4 vs. 77.2, p = 0.01)
  - Lower education (9.4 vs. 10.0, p = 0.005)
  - More medical comorbidities (2.2 vs. 1.9, p = 0.002)
  - Higher mortality (30% vs. 15%, p <0.001)

  - No significant differences in
    - caloric intake (1466 vs. 1428, p = 0.12)
    - gender (35% male vs. 33% male, p = 0.42)
    - ethnicity (White 26%, Black 36%, Hispanic 38% Other 1% vs. White 28%, Black 33%, Hispanic 38% Other 2%, p = 0.39)
    - APOE genotype (ε4 carriers 29% vs. 28%, p = 0.67)
    - MeDi score (4.3 vs. 4.4, p = 0.21)

MeDi and incident AD – Missing data analyses

- Missing dietary information (n = 527) vs. available dietary information
  - Slightly lower education (9.1 vs. 9.9, p = 0.001).
  - Higher proportions of dementia (17.5% vs. 11%, p < 0.001)
  - Higher mortality (32% vs. 18%, p < 0.001)
    - dietary assessment was added after initiation of the study and was not available for subjects recruited earlier on.

  - No significant differences in
    - age (76.7 vs. 77, p = 0.30)
    - gender (33% male vs. 33% male, p = 0.68)
    - ethnicity (White 25%, Black 31%, Hispanic 43% Other 1% vs. White 27%, Black 33%, Hispanic 39% Other 1%, p = 0.24)
    - medical comorbidity index (2.1 vs. 2.0, p = 0.27)
    - APOE genotype (ε4 carriers 27% vs. 28%, p = 0.79)


4166
730
Prevalent Dementia
3436
527
Diet not available
2909
24
MeDi score not calculated
due to missing data
2885
101
Died within 1.5 years
from baseline assessment
526
Follow-up not available
2258

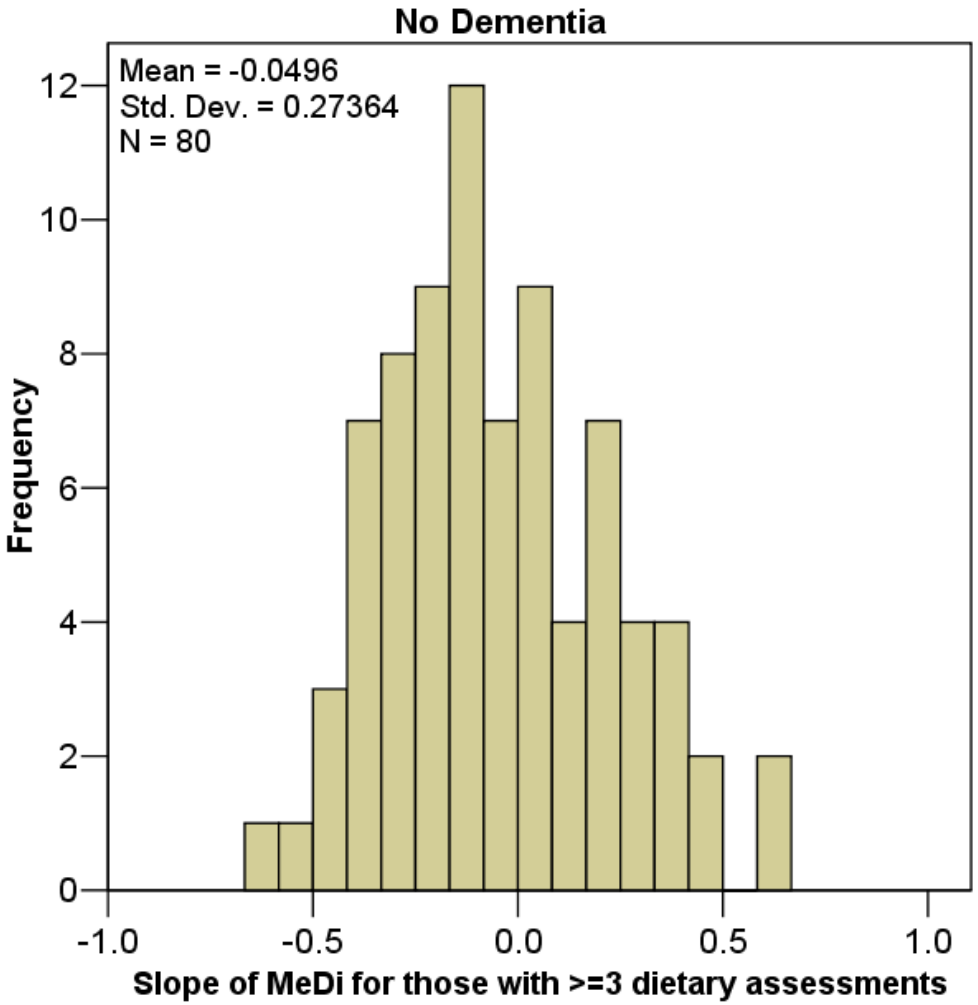
		Non-demented N = 1964	Incident AD N = 262	All N = 2226	P
Age yrs, mean (SD)		76.5 (6.3)	81.8 (6.9)	77.2 (6.6)	<0.001
Gender-Men, N (%)		634 (32)	86 (33)	720 (32)	0.86
Education yrs, mean (SD)		10.5 (4.6)	7.0 (4.5)	10.1 (4.7)	<0.001
Ethnicity, N (%)	**White**	592 (30)	28 (11)	620 (28)	<0.001
	Black	636 (32)	86 (33)	722 (32)	
	Hispanic	705 (36)	143 (55)	848 (38)	
	Other	31 (2)	5 (2)	36 (2)	
Presence of ε4 allele (%)		452 (27)	74 (32)	526 (27)	0.10
Smoking N (%)		242 (12)	33 (13)	275 (12)	0.90
Comorbidity Index, mean		1.9 (1.4)	1.9 (1.5)	1.9 (1.4)	0.87
Energy (kcal), mean (SD)		1422 (513)	1475 (560)	1428	0.15
Body Mass Index, mean (SD)		27.5 (5.5)	26.5 (5.9)	27.4 (5.5)	0.005
MeDi score, mean (SD)		4.4 (1.7)	4.2 (1.7)	4.3 (1.7)	0.05
Low MeDi tertile, N (%)		326 (32)	96 (37)	722 (32)	0.23
Middle MeDi tertile, N (%)		823 (42)	107 (41)	930 (42)	
High MeDi tertile, N (%)		515 (26)	59 (23)	574 (26)	

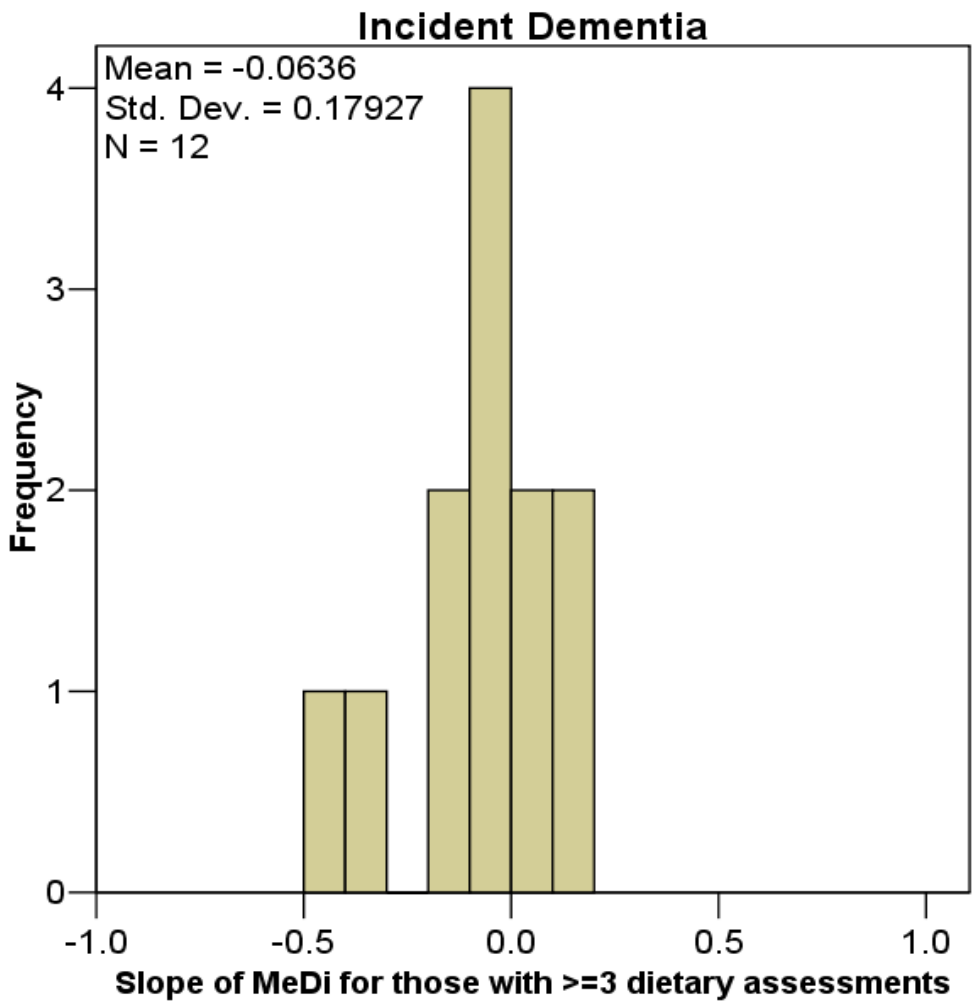
MeDi stability

- Generalized estimating equations (GEE) in subjects with >1 dietary assessments
  - MeDi score as the dependent variable
  - Time (years) as predictor

- 390 subjects who did not develop dementia during follow-up.
  - 2 dietary assessments for 308 subjects
  - 3 dietary assessments for 71 subjects
  - 4 dietary assessments for 11 subjects.
  - Mean time interval between dietary assessments 7.1 years (sd 2.36, range 1 – 12.8).
- MeDi score stable ($\beta = -0.01$, $p = 0.41$).

- 89 subjects who developed AD during follow-up
  - 2 dietary assessments for 78 subjects.
  - 3 dietary assessments for 8 subjects.
  - 4 dietary assessments for 3 subjects.
  - Mean time interval between dietary assessments 8.1 years (sd 1.9, range 1.8 – 11.9).
- MeDi score stable ($\beta = -0.05$, $p = 0.09$).





One sample t-test: -1.6

p = 0.11

One sample t-test: -1.23

p = 0.25

MeDi and incident AD – Supplementary analyses

- Excluding baseline CDR = 0.5
  - 1898 subjects at risk with 156 incident AD cases,
  - Continuous MeDi HR:
    - 0.88 (0.80 – 0.97), p = 0.007
  - Tertile MeDi analyses
    - p for trend 0.018
- Excluding both baseline CDR=0.5 and those followed for less than 2 years
  - 1575 subjects at risk with 134 incident AD cases
  - Continuous MeDi HR:
    - 0.89 (0.80 – 0.98), p = 0.020
  - Tertile MeDi analyses
    - p for trend 0.027

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  - Continuous MeDi HR: 0.88 (0.80 – 0.97), p = 0.007,
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  - Continuous HR: 0.89 (0.80 – 0.98), p = 0.020.
  - Tertile analyses p for trend 0.027.
- Probable AD without stroke as the outcome (excluding AD with coexisting stroke, n = 78):
  - 2144 subjects at risk with 184 incident probable AD without stroke,
  - Continuous HR: 0.90 (0.83 – 0.98), p = 0.015,
  - Tertile analyses p for trend 0.018.

MeDi Calculation

- Using (i) frequencies and (ii) standard portion sizes, calculate daily gram intake for the following categories
  - Dairy
    (whole fat milk, yogurt, ice cream, cottage or ricotta cheese, other cheese)
  - Meat
    (chicken-turkey with skin, bacon, hot dog, processed meats [sausage, salami, etc], liver, hamburger, beef-pork-lamb [sandwitch or mixed dish], beef-pork-lamb [main dish]
  - Fruits
    (apple, orrange, orange-grape fruit juice, peach-apricot-plum, banana, other fruit)
  - Vegetables
    (tomatoes,broccoli, cabbage-cauliflower-Brussels sprouts, carrots raw, carrots cooked, corn, yams-sweet potatoes, spinach-collard green cooked, yellow squash)
  - Legumes
    (peas-lima beans, beans-lentils baked or dried)
  - Cereals
    (cold breakfast cereals, white bread, dark bread, rice-pasta, potatoes baked-broiled-mashed)
  - Fish
  - MUFA
  - SFA

Conclusions

- Higher adherence to MeDi associated with lower risk for AD
  - ~10% risk reduction for each additional unit of MeDi
- Gradual reduction in AD risk for higher tertiles of MeDi adherence, suggesting a possible dose-response effect
  - ~20% reduction for middle MeDi adherence tertile
  - ~40% reduction for highest MeDi adherence tertile
- Association over and above other potential confounders
  - cohort, age, gender, ethnicity, education, APOE genotype, caloric intake, smoking, comorbidity index and BMI
- Association not driven by any individual dietary component but by whole pattern of MeDi

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Mediterranean Diet and other diseases

- Lower risk for
  - Cancer (large bowel, breast, endometrium, prostate)
    - Trichopoulou, Lagiou et al. 2000
  - Obesity
    - Schroder, Marrugat et al. 2004; Esposito, Marfella 2004
  - Hypertension
    - Panagiotakos, Pitsavos et al. 2003; Chrysohoou, Panagiotakos et al. 2004; Psaltopoulou, Naska et al. 2004; Chrysohoou, Panagiotakos et al. 2004; Psaltopoulou, Naska et al. 2004; Singh, Dubnov et al. 2002; Esposito, Marfella et al. 2004
  - Dyslipidemia (decrease in TC, LDL, TG and increase in HDL)
    - Chrysohoou, Panagiotakos et al. 2004; Singh, Dubnov et al. 2002
  - Coronary Heart Disease
    - Knoops, de Groot et al. 2004; Trichopoulou, Costacou et al. 2003); Singh, Dubnov et al. 2002; de Lorgeril, Salen et al. 1999
  - Abnormal Glucose metabolism –Insulin resistance - Diabetes
    - Singh, Dubnov et al. 2002; Esposito, Marfella et al. 2004

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Mediterranean Diet and other diseases

- Lower risk for **Total Mortality**
  - ~22000 participants in Greece
    - Trichopoulou, Kouris-Blazos et al.1995; Trichopoulou, Costacou et al. 2003
  - ~2500 participants in 11 European countries
    - Knoops, deGroot et al. 2004
  - ~75000 adults in 11 European countries
    - Trichopoulou, Orfanos et al. 2005

MeDi and incident AD

- 2258 non-demented at baseline
- Follow-up
  - 4.0 (± 3.0, 0.2– 13.9) years
- 294 subjects developed dementia during follow-up
  - 262 AD
    - 184 AD without stroke
    - 78 AD with stroke
- Survival analyses - Cox models
  - Outcome
    - Incident AD vs. Non-demented
    - Time to AD incidence or to last follow-up
  - Main predictor
    - MeDi (continuous)
    - MeDi (tertiles)
  - Covariates adjusted for
    - cohort, age, gender, education, ethnicity, caloric intake, APOE, BMI, smoking, modified comorbidity index (Charlson)

Mediterranean Diet and Associations with other variables

MeDi characteristics and associations with other variables

Conclusions

- Hispanics adhere more and Blacks less to MeDi
- Higher adherence to MeDi associated with
  - Less smoking
  - Lower total caloric intake
- MeDi not associated with
  - Cohort, Age, Gender,Education, APOE, BMI, Comorbidities
- MeDi stable over time irrespective of future dementia status

Mediterranean Diet and Vascular Comorbidity

MeDi and Vascular Comorbidity Conclusions

- Smokers adhere less to MeDi.
- Higher adherence to MeDi associated with higher LDL in controls
- Higher adherence to MeDi associated with lower HDL in AD
- In general not impressive associations of MeDi with vascular comorbidity in this population

Mediterranean Diet, cognition and AD:

mediation by Vascular Comorbidity?

MeDi cognition and AD: mediation by vascular comorbidity? Conclusions

- Vascular comorbidity does not mediate or mediates very little the association between MeDi and risk for AD or cognitive decline.

Mediterranean Diet and Baseline Cognition

MeDi and Baseline Cognition Overall Conclusions

- Higher adherence to MeDi, higher composite cognitive score
- Association driven by memory and executive-speed domains
- Association more prominent in AD, less so in controls

Mediterranean Diet and Mortality

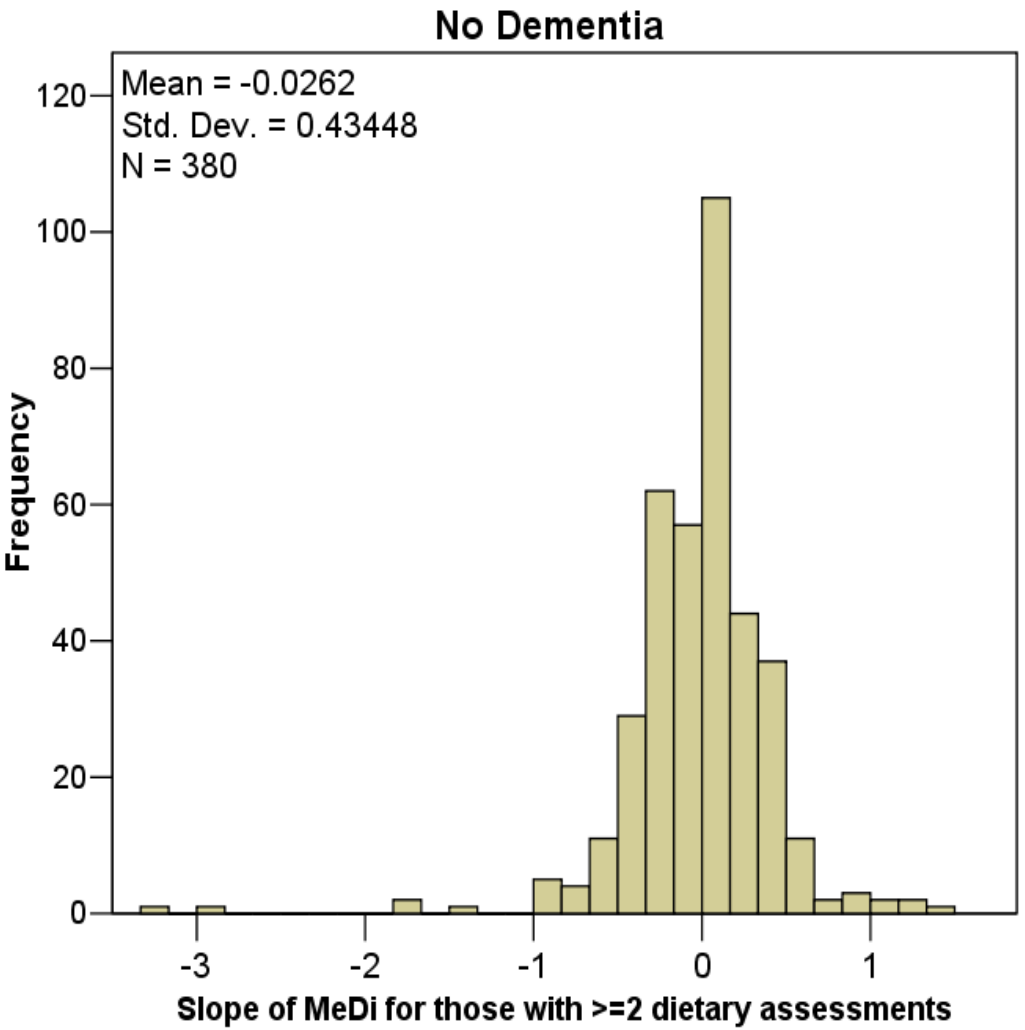
MeDi and Mortality Conclusions

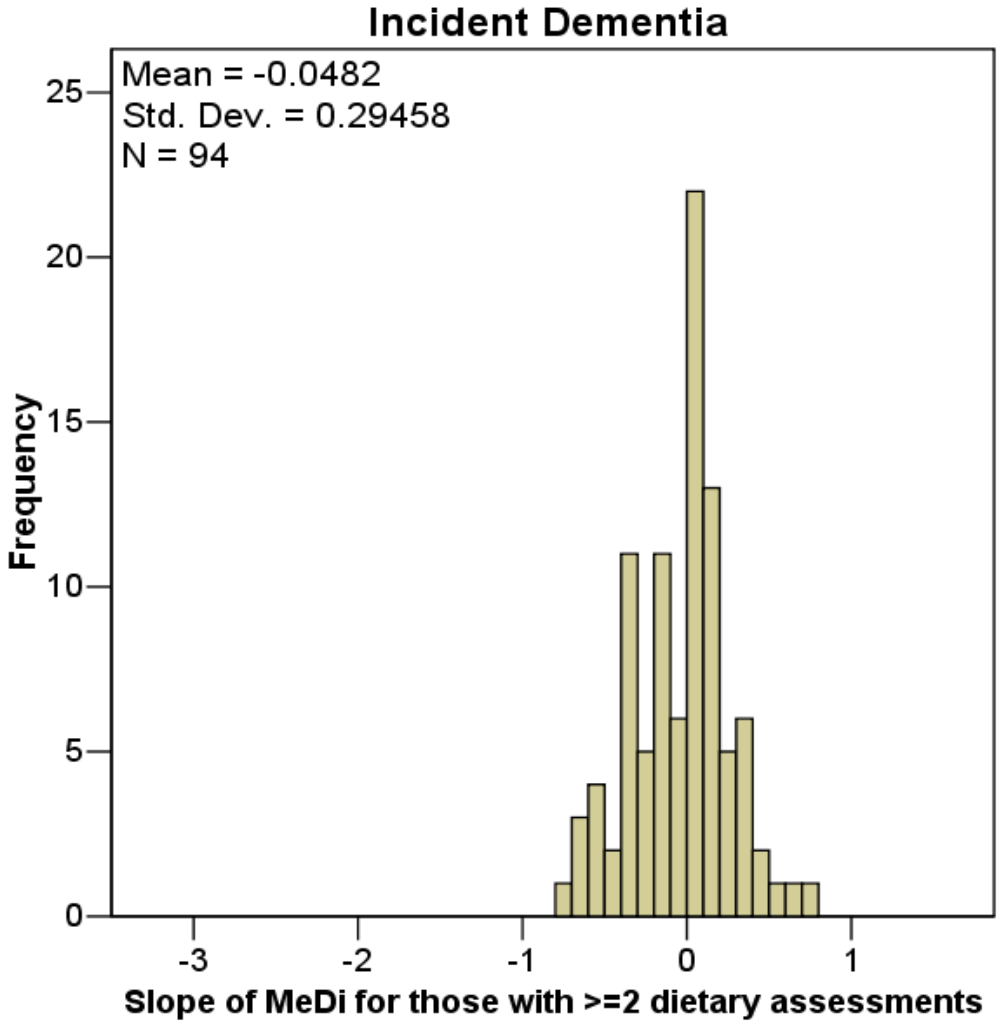
- Higher adherence to MeDi is associated with reduced mortality in both AD and controls
- Effect present even when adjusting for multiple covariates
- Possible dose-response
- Association is stronger in AD

Overall Conclusions

- MeDi associated with lower risk for AD
- Possible dose-response
- MeDi associated with lower rates of cognitive decline (visual spatial, language, executive)
- Associations between MeDi and AD risk of cognitive decline not mediated by vascular factors
- MeDi associated with less mortality, more so in AD, less so in non-demented.

	Low Tertile (MeDi score 0-3)	Middle Tertile (MeDi score 4-5)	High Tertile (MeDi score 6-9)	All (25^{th}, 75^{th} percentiles)
Dairy (g / d)	246	174	151	182 (128 – 292)
Meat (g / d)	101	86	65	85 (60 – 119)
Vegetable (g / d)	165	202	243	197 (153 – 250)
Fruit (g / d)	406	471	556	472 (372 – 582)
Legumes (g / d)	44	58	78	57 (38 – 90)
Cereal (g / d)	155	186	215	184 (140 – 233)
Fish (g / d)	15	21	47	20 (14 – 47)
MUFA / SFA ratio	0.57	0.82	0.97	0.80 (0.18 – 1.37)
Mild-Moderate ETOH (%)	21	33	45	32





One sample t-test: -1.18

p = 0.24

One sample t-test: -1.59

p = 0.12

Diet and AD

Discrepancies between studies could be due to multiple **methodological reasons**:

- Measurement error in nutrients
  - if not related to outcome leads towards null, decreased power
  - if related to outcome either hyper or hypoestimation of associations
- Latency period between diet and cognition-dementia
  - not enough time for diet to manifest its effect
- Preclinical AD

True answer from **clinical trials** – randomization

- Example:Despite observational longitudinal data,
  - Clinical trial of reduced total fat intake, increased vegetables-grains in 48K women over 8 years; no effect on CVD, stroke, Colorectal cancer, Breast CA

Clinical Trials Costly – difficult to implement

Mediterranean Diet

- Lower risk for
  - obesity
  - cardiovascular disease
  - several forms of cancer (large bowel, breast, endometrium, prostate)
  - overall mortality
    - Lagiou, Trichopoulou et al. 1999; Trichopoulou, Kouris-Blazos et al. 1995; Lasheras, Fernandez et al. 2000; Trichopoulou, Lagiou et al. 2000; Panagiotakos, Pitsavos et al. 2003; Trichopoulou, Costacou et al. 2003; de Lorgeril, Salen et al. 1999; Singh, Dubnov et al. 2002; Esposito, Marfella et al. 2004; Trichopoulou, Orfanos et al. 2005; Trichopoulou, Lagiou et al. 2000; Trichopoulos and Lagiou 2004; Schroder, Marrugat et al. 2004

Caloric – Energy issues

- Total Energy Expenditure
  - Resting Metabolic Requirement ~60% invariable
  - Thermogenic Effect of Food (cost of absorbing-processing carbs, protein, fat) ~10% invariable
  - Physical Activity ~30% major determinant
  - Adaptive Thermogenesis (capacity to conserve or expense energy) ~10%

- Physical activity: major determinant of caloric intake-expenditure is
- BMI related to caloric intake-expenditure in the absence of physical activity (chamber); less so related to caloric intake in real life
  - Obese (and women) underreport caloric intake
  - Obese are less physically active
- Metabolic efficiency (unmeasurable)
  - Increased: less thermogenesis, fewer energy losses, more preservation of energy [therefore more weight]; common phenomenon when diet
  - Decreased: more thermogenesis, more energy losses, less preservation of energy [therefore less weight]

Caloric intake issue in dietary analyses

- Residual method: include nutrient residuals and total caloric intake

- Standard multivariate model: include unadjusted nutrients and total caloric intake
  - Interpretation of total caloric intake is different: ie. fat and total caloric intake, then the effect of total caloric intake is the effect of calories unrelated to fat [therefore related to protein and carbohydrates]
  - Presentation of relative risks for disease of nutrient intakes independent of caloric intake would be artificially large (because this degree of variation of nutrients independent of caloric intake would not exist in actuality).
  - Colinearity

- Energy decomposition or Energy partition model: include different terms for calories from different nutrients

- Multivariate nutrient density method: include nutrient density [nutrient / caloric intake] and total caloric intake

Dietary Accuracy Issues

- Variability in dietary questionnaires is higher than dietary records
- Energy expenditure measured by doubly-labeled water is higher as compared to the one measured by dietary records
- Underreporting is larger for obese and women (which are usually accounted for in analyses)
- Underreporting unrelated to dietary composition


WEBSHOTS


IMEDSHOTS