Mediterranean Diet and Cognition: Epidemiology and Mechanisms

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Disclosures: None

Risk for AD or cognitive decline not associated with

- Folate
  - Borenstein et al 2006; Morris, Beckett et al. 1998; Morris, Evans et al. 2002; Morris, Evans et al. 2003; Morris, Evans et al. 2005
  - Corrada, Kawas et al. 2005
  - Corrada, Kawas et al. 2005

- Vitamins
  - A, B1, B6, B12, C, E

- Fruits
  - Masaki, Losonczy et al. 2000

- Vegetables
  - Masaki, Losonczy et al. 2000

- Coffee
  - A, B1, B6, B12, C, E

- Fish
  - A, B1, B6, B12, C, E

- Vegetables
  - A, B1, B6, B12, C, E

- Fruits
  - A, B1, B6, B12, C, E

- Coffee
  - A, B1, B6, B12, C, E

- Fish
  - A, B1, B6, B12, C, E

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  - A, B1, B6, B12, C, E

- Fruits
  - A, B1, B6, B12, C, E

Diet and AD

- One of the reasons for discrepancies between studies: we look at isolated-individual foods 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.

- Dietary patterns not explored enough in the neurological literature.
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

- 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 and Alzheimer's?
Mediterranean Diet and Alzheimer Disease, and Vascular Mediation

Mediterranean Diet and Risk for Alzheimer’s Disease

Mediterranean Diet and Mild Cognitive Impairment
Baseline non-MCI Incident MCI

Follow-up
4.5 (0.9 – 16.4) years
Annual Incidence: ~ 5%

Baseline MCI Incident AD:

Follow-up
4.3 (1 – 13.8) years
Annual incidence 5%

Biological mediating mechanisms?

Scarmeas, Anastasia, Yannakoulia; Lancet Neurology; 2018; under review
Mediterranean Diet and White Matter Hyperintensity Volume

Table 3. Association Between Mediterranean Diet and White Matter Hyperintensity Volume

<table>
<thead>
<tr>
<th>Mediterranean Diet Score</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-365 mg/d</td>
<td>1.00 (1)</td>
<td>1.00 (1)</td>
<td>1.00 (1)</td>
<td>1.00 (1)</td>
</tr>
<tr>
<td>366-730 mg/d</td>
<td>1.00 (1)</td>
<td>1.00 (1)</td>
<td>1.00 (1)</td>
<td>1.00 (1)</td>
</tr>
<tr>
<td>731-1095 mg/d</td>
<td>1.00 (1)</td>
<td>1.00 (1)</td>
<td>1.00 (1)</td>
<td>1.00 (1)</td>
</tr>
<tr>
<td>1096-1460 mg/d</td>
<td>1.00 (1)</td>
<td>1.00 (1)</td>
<td>1.00 (1)</td>
<td>1.00 (1)</td>
</tr>
<tr>
<td>&gt;1460 mg/d</td>
<td>1.00 (1)</td>
<td>1.00 (1)</td>
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<td>1.00 (1)</td>
</tr>
</tbody>
</table>

*Controlling for age of magnetic resonance imaging.

**Controlling for age of magnetic resonance imaging, sex, race, and education.

***Controlling for age, sex, race, education, total caloric intake, total saturated fat energy intake, total carbohydrate energy intake, total alcohol intake, smoking status, and history of hypertension.

****Controlling for age, sex, race, education, total caloric intake, total saturated fat energy intake, total carbohydrate energy intake, total alcohol intake, smoking status, history of hypertension, and BMI.

**Table 3: Odds for Stroke by MRS Scans Either in Cerebrospinal Fissure or in Temporal Fissure**

<table>
<thead>
<tr>
<th>Model</th>
<th>MRS Scans</th>
<th>MRS Presence</th>
<th>OR (95% CI)</th>
<th>p for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Low</td>
<td>0.31 (0.16-0.60)</td>
<td>0.49</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Middle</td>
<td>0.78 (0.32-1.96)</td>
<td>0.64</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>0.42 (0.21-0.85)</td>
<td>0.02</td>
<td>Low</td>
</tr>
<tr>
<td>2</td>
<td>Low</td>
<td>0.31 (0.16-0.60)</td>
<td>0.49</td>
<td>High</td>
</tr>
<tr>
<td>3</td>
<td>Low</td>
<td>0.31 (0.16-0.60)</td>
<td>0.49</td>
<td>Low</td>
</tr>
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<td></td>
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</tr>
<tr>
<td>4</td>
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<td>0.49</td>
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Notes: **p** = 0.05. **OR** = odds ratio. **CI** = confidence interval. **p** for Trend = trend in the odds ratio across ordered MRS categories (Low, Middle, High). **Model** = adjusted for age, sex, race, smoking status, hypertension, and diabetes.
Figure 2
Spatial patterns of CMRglc as a function of physical activity and diet on FDG-PET. Top row: Partial Least Square regression maps (PLS maps; spatial biomarker patterns) that represent the optimal association between FDG-PET images and (A) leisure time physical activity (LTA), (B) Mediterranean Diet (MeDi), and (C) the combination of LTA and MeDi. P values are shown on a color-coded scale to the right.

Middle row: LV scores extracted from each significant pattern show reduced FDG uptake, reflecting reduced CMRglc, in NL showing lower vs. higher engagement in leisure time physical activity (LTA− < LTA+); in NL showing lower vs. higher adherence to the MeDi (MeDi− < MeDi+) and as a function of LTA × MeDi (LTA−/MeDi− < LTA−/MeDi+ < LTA+/MeDi− < LTA+/MeDi+). $R^2$ values are reported for each figure (all p's < 0.001).

Bottom row: LV scores are adjusted by age.
Figure 3 Predicted origin of divergence and differentiation in (A) FDG-PET uptake within Alzheimer disease–related regions between MeDi groups.
Figure 2 Baseline and longitudinal changes in 11C-PiB PET Aβ deposition as a function of MeDi adherence

Figure 3 Predicted origin of divergence and differentiation in (B) PiB-PET uptake within Alzheimer disease-related regions between MeDi groups

ANOVA: comparing change of abeta among tertiles of MeDi.

Higher MeDi adherence at baseline had less (%) increase of RIB abeta in the brain over 3 years.

Concerns - Limitations

• Replication
Concerns - Limitations

- Replication

- “Healthy Person Bias” - “Residual Confounding” - Physical Activity
Cox Proportional Hazard Ratios (HRs) for Alzheimer Disease (AD) Incidence by Physical Activity and Mediterranean-Type Diet Scores

<table>
<thead>
<tr>
<th>Physical Activity</th>
<th>No Physical Activity</th>
<th>Some Physical Activity</th>
<th>Much Physical Activity</th>
<th>Trend</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted Model</td>
<td>0.96</td>
<td>0.92</td>
<td>0.58</td>
<td>0.80</td>
<td>&lt;0.001</td>
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<td>Unadjusted Model</td>
<td>0.78</td>
<td>0.63</td>
<td>0.46</td>
<td>0.77</td>
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Concerns - Limitations

- Replication
- “Healthy Person Bias” - “Residual Confounding” – Physical Activity
- Observation vs. Randomization

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

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Mediterranean food for thought!

Observational Studies Clinical Trials

- Specific Food Patterns
  - MHO
  - DASH diet
  - Mediterranean diet (components of DASH = MHO)
  - Alternative Healthy Eating Index
  - CARDED Dietary Quality Score
  - Healthy Diet Indicator (WHOD)
  - Healthy Eating Index
  - Healthy Diet Score
  - Low carbohydrate, high protein diet
  - Population-specific prudent diet patterns
  - Multidomain interventions

Unadjusted HR: 0.78 (0.53-1.14) 0.63 (0.43-0.92) 0.46 (0.31-0.68) 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

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Changes in Cognitive Function Measured With Composites by Intervention Group

Error bars indicate 95% CIs. P values by analysis of covariance were adjusted for sex, baseline age, years of education, marital status, APOE ε4 genotype, ever smoking, baseline body mass index, energy intake, physical activity, type 2 diabetes mellitus, hyperlipidemia, ratio of total cholesterol to high-density lipoprotein cholesterol, statin treatment, hypertension, use of anticholinergic drugs, and time of follow-up, with the Bonferroni post hoc test. For each cognitive composite, the changes between the 2 Mediterranean arms were not statistically different (P > .99 for all). The changes for memory between the Mediterranean diet plus olive oil and control groups and for frontal and global cognition between the Mediterranean diet plus nuts and control groups had values of P < .25. aP < .05. bP < .01.

Problems – Issues – Challenges

- Small numbers [150-200 per arm]
- Not a pre-registered clinical trial by itself, but just a subset of a registered clinical trial
- Lack of predefined primary and secondary outcomes.
  - If for example MMSE was the pre-specified primary outcome then it is a negative trial.
  - If Trails was, then it is a positive trial.
- Incomplete cognitive assessment battery [crystallized IQ, non-verbal memory etc]
- Lack of multiple cognitive assessments
- Significant loss to follow-up,
- Differential by intervention group follow-up,
- Extremely unequal duration of follow-up with cognitive assessments ranging from 1-8 years.

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- Observation vs. Randomization

Thank you for your attention