Modifiable risk factors for cognitive decline, MCI and AD in Northern Manhattan

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Alzheimer’s disease

Genes:
- APP
- PS1
- PS2
- APOE-ε4

Modifiable risk factors
- Diet
- Education
- Ethnicity

Cerebrovascular disease

Amyloid beta deposits

- AD
- aMCI
Vascular cognitive syndromes

**Modifiable risk factors:**
- Hypertension
- Diabetes
- Dyslipidemia
- Smoking

**Stroke**
**White matter disease**

**Vascular cognitive impairment**
**Vascular dementia**
**Non-amnestic MCI**
**Dysexecutive syndrome**

???
Alzheimer

Vascular
Normal cognition  Mild cognitive impairment  Dementia
WHICAP (PI: R. Mayeux)

• Longitudinal study of aging in Northern Manhattan
• > 64 years
• Multiethnic
  – 44% Hispanic
  – 32% African American
  – 24% White
• Without dementia at baseline
• Mean follow-up > 6 years
Outcome measures

- Dementia
  - DSM IV
  - NINDS-AIREN
- MCI
  - Similar to Petersen’s definition
  - Amnestic
  - Non Amnestic

- 4 cognitive scores from factor analysis
  - Memory
  - Executive
  - Visuospatial
  - Language
Questions pursued

• Is a risk factor associated with dementia or MCI?
  – Survival analyses

• Is a relation with dementia mediated by vascular mechanisms?
  – Attenuation of coefficients

• Does a risk factor modify cognitive decline?
  – Mixed models or GEE

• Could a risk factor modify the progression from MCI to dementia?
  – Logistic regression
Modifiable risk factors

• Diabetes:
  – Prevalence approximately 20%
  – Ascertained by history

• Hypertension:
  – Prevalence approximately 70%
  – Ascertained by history or BP
## Diabetes: relation to dementia

<table>
<thead>
<tr>
<th>Category</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer disease</td>
<td>1.7</td>
</tr>
<tr>
<td>DAS</td>
<td>2.8</td>
</tr>
<tr>
<td>All dementia</td>
<td>1.9</td>
</tr>
</tbody>
</table>
# Diabetes: relation to MCI

## Table 3. HRs and 95% CIs Relating Diabetes to MCI, Amnestic MCI, and Nonamnestic MCI*

<table>
<thead>
<tr>
<th></th>
<th>MCI Cases (Rate)</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>All-cause MCI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diabetes</td>
<td>241 (7.2)</td>
<td>1.0</td>
<td>.007</td>
<td>1.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>93 (9.4)</td>
<td>1.4 (1.1-1.8)</td>
<td>.007</td>
<td>1.3 (1.0-1.7)</td>
</tr>
<tr>
<td>Amnestic MCI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diabetes</td>
<td>117 (3.5)</td>
<td>1.0</td>
<td>.05</td>
<td>1.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>43 (4.4)</td>
<td>1.4 (1.0-1.9)</td>
<td>.05</td>
<td>1.5 (1.0-2.1)</td>
</tr>
<tr>
<td>Nonamnestic MCI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diabetes</td>
<td>124 (3.7)</td>
<td>1.0</td>
<td>.04</td>
<td>1.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>50 (5.1)</td>
<td>1.4 (1.0-1.9)</td>
<td>.04</td>
<td>1.3 (0.9-1.8)</td>
</tr>
</tbody>
</table>

*Abbreviations: CI, confidence interval; HR, hazard ratio; MCI, mild cognitive impairment.

*Model 1 is adjusted for age and sex; model 2 is also adjusted for ethnic group, years of education, and APOE ε4; and model 3 is also adjusted for hypertension, low-density lipoprotein cholesterol level, current smoking, heart disease, and stroke. Rates are per 100 person-years.

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### Hypertension: relation to dementia

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>Total at risk</th>
<th>Developed AD, n (%)</th>
<th>AD, RR (95% CI)</th>
<th>Developed VaD, n (%)</th>
<th>VaD, RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>731</td>
<td>84 (11.5)</td>
<td>0.9 (0.7–1.3)</td>
<td>39 (5.3)</td>
<td>1.8 (1.0–3.2)*</td>
</tr>
<tr>
<td>Absent</td>
<td>528</td>
<td>73 (13.8)</td>
<td>1.0 (reference)</td>
<td>17 (3.2)</td>
<td>1.0 (reference)</td>
</tr>
</tbody>
</table>

Unadjusted risk ratio (RR) and 95% CI are shown. When AD model was repeated adjusting for age, education, ethnic group, and history of heart disease, the RR decreased to 0.8 (95% CI, 0.6–1.1). Similarly, the RR decreased to 1.6 (0.9–2.9) for the VaD model when it was adjusted for these factors. The RR did not change when stratified by treatment.

* $p = 0.05$.

Posner, Neurology 2002
# Hypertension: relation to MCI

## Table 2. Data Relating Hypertension and the Risk of Incident MCI

<table>
<thead>
<tr>
<th>MCI Subtype</th>
<th>Incident MCI, No. (%)</th>
<th>Model&lt;sup&gt;b&lt;/sup&gt;</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>All-cause MCI</td>
<td></td>
<td>(Model 1)</td>
<td>(Model 2)</td>
<td>(Model 3)</td>
<td></td>
</tr>
<tr>
<td>Group without hypertension</td>
<td>76 (26.0)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Group with hypertension</td>
<td>258 (41.2)</td>
<td>1.40 (1.06-1.77)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.30 (1.02-1.73)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.20 (0.81-1.69)</td>
<td></td>
</tr>
<tr>
<td>Amnestic MCI</td>
<td></td>
<td>(Model 1)</td>
<td>(Model 2)</td>
<td>(Model 3)</td>
<td></td>
</tr>
<tr>
<td>Group without hypertension</td>
<td>42 (14.4)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Group with hypertension</td>
<td>118 (18.8)</td>
<td>1.10 (0.79-1.63)</td>
<td>1.10 (0.80-1.67)</td>
<td>0.90 (0.54-1.47)</td>
<td></td>
</tr>
<tr>
<td>Nonamnestic MCI</td>
<td></td>
<td>(Model 1)</td>
<td>(Model 2)</td>
<td>(Model 3)</td>
<td></td>
</tr>
<tr>
<td>Group without hypertension</td>
<td>34 (11.6)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Group with hypertension</td>
<td>140 (22.4)</td>
<td>1.70 (1.13-2.42)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.60 (1.06-2.29)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.60 (0.93-2.85)</td>
<td></td>
</tr>
</tbody>
</table>

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**Abbreviation:** MCI, mild cognitive impairment.

<sup>a</sup>A Cox proportional hazards model was used, with age at onset as the time variable, as described in the “Statistical Analyses” subsection of the “Methods” section.

<sup>b</sup>Data are given as hazard ratio (95% confidence interval). Model 1 was adjusted for sex and age; model 2, adjusted for age, sex, years of education, ethnic group, and APOE genotype; and model 3, adjusted for sex, age, ethnic group, years of education, APOE genotype, stroke, diabetes mellitus, heart disease, current smoking, and low-density lipoprotein cholesterol level. In all models, the group without hypertension was the reference group.

<sup>c</sup>Significant difference vs the group without hypertension.

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Progression from MCI to dementia

- Diabetes and Hypertension not related to progression from MCI to dementia

- Caveats:
  - Prevalent vs incident MCI
  - Short follow-up time
  - Temporal relationship between risk factor and MCI
Risk factors and cognitive decline

- Persons with diabetes had lower memory and executive scores at baseline and follow-up, but the slopes of decline were parallel (evidenced by a non-significant interaction term for time and diabetes from mixed models).
- Persons with hypertension had a similar pattern for decline in executive scores.
Limitations

• Misclassification of dementia subtype
• Stability of MCI diagnosis
• Old age vs middle age
  – Lines of cognitive decline may have “split” before onset of follow-up
• Measurement of risk factors
  – Lack of proper measures of severity and duration
  – Bias towards the null
Conclusions

- Diabetes is related to both amnestic and non-amnestic forms of cognitive impairment
- Hypertension seems to be related mostly to non-amnestic forms of cognitive impairment
- These associations are consistent with different but related outcomes in the natural history of cognitive decline
Conclusions

• These associations appear to depend on insults that began before the time of observation
• Thus, studies in younger age groups are needed
• Specific NS domains could be used as early proxies for future cognitive impairment diagnoses
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- American Diabetes Association
Take a deep breath!
Cognitive scores

• Memory: Selective Reminding Test and BVRT recognition;
• Language: (15-item Boston Naming Test, BDAE repetition, and BDAE comprehension);
• Executive function: (Mattis Identities and Oddities, raw score on Wechsler Adult Intelligence Scale–Revised Similarities subtest, and category and letter fluency);
• Visuospatial skill: (Rosen Drawing Test and BVRT matching)
Risk factor in relation to cognitive decline

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<th>Coefficient</th>
<th>P value</th>
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