Risks and Prevention Across the Lifespan

UCI MIND

30th SoCal Alzheimer’s Disease Research Conference

Presented by: Rebecca Gottesman, MD PhD
October 25, 2019
Disclosures

- I am an Associate Editor for the journal *Neurology*. 
Alzheimer’s disease is on the rise

From Hebert et al., Neurology 2013

By 2030 there will be 72.1 million older Americans
DEMENTIA

9 WAYS TO REDUCE YOUR RISK

1 IN 3 cases of dementia could be prevented by addressing these lifestyle factors

INCREASE
- Education
- Physical Activity
- Social Contact

DECREASE
- Hearing Loss
- Hypertension
- Obesity
- Smoking
- Depression
- Diabetes

Source: Lancet Commission on Dementia Prevention and Care
Credit: Keck Medicine of USC
National Academy of Medicine: Preventing Dementia

• Recommendations from this systematic review:
  – Cognitive training
  – Control of high BP (especially during ages 35-65)
  – Increasing physical activity
Vascular contribution to Alzheimer’s Disease

- In autopsy studies of patients who were diagnosed with Alzheimer’s disease, >50% had evidence of strokes ("silent strokes")
  - Fewer Alzheimer’s-type changes are seen in people with higher levels of vascular changes in the brain (for an equivalent level of dementia)

AD=Alzheimer’s Disease
I=Infarcts
LB=Lewy Bodies

Schneider et al., Annals of Neurology 2009
Heart disease risk factors (vascular risk factors) that may also affect brain health

- High blood pressure
- Diabetes
- Smoking
- High cholesterol
- Obesity
- Physically inactive lifestyle
- Poor diet
- Inflammation
How do heart disease risk factors lead to problems with memory and thinking?

- Strokes
- “Silent” strokes or related brain changes
- Not enough flow/oxygen to brain through diseased blood vessels
- Changes in ability to clear brain toxins or block access to the brain

Iadecola & Gottesman, Circulation Research 2019 (124(7): 1025-1044

October 25, 2019
Importance of considering the whole life course

- Vascular factors have strongest relationships with cognitive decline and dementia when considered in middle age
- Changes in vascular risk factor status over the life course may change the way a risk factor affects an individual person

From Livingston et al., Lancet 2017
HIGH BLOOD PRESSURE IS EVEN RISKIER

Dementia and stroke are more likely to affect people with high blood pressure. Don’t take unnecessary risks. Keep your blood pressure under control.

LEARN MORE AT

MindYourRisks.nih.gov

MillionHearts™

JOHNS HOPKINS MEDICINE
# High Blood Pressure: New AHA/ACC definitions in 2017

## Blood Pressure Categories

<table>
<thead>
<tr>
<th>Blood Pressure Category</th>
<th>Systolic mm Hg (Upper Number)</th>
<th>Diastolic mm Hg (Lower Number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Less Than 120</td>
<td>Less Than 80</td>
</tr>
<tr>
<td>Elevated</td>
<td>120 – 129</td>
<td>Less Than 80</td>
</tr>
<tr>
<td>High Blood Pressure (Hypertension) Stage 1</td>
<td>130 – 139</td>
<td>80 – 89</td>
</tr>
<tr>
<td>High Blood Pressure (Hypertension) Stage 2</td>
<td>140 or Higher</td>
<td>90 or Higher</td>
</tr>
<tr>
<td>Hypertensive Crisis (Consult your doctor immediately)</td>
<td>Higher Than 180</td>
<td>Higher Than 120</td>
</tr>
</tbody>
</table>

©American Heart Association

heart.org/bplevels

Muntner et al., Circulation 2017

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Higher BP, especially in middle age, is associated with worse cognition

Adapted from Gottesman et al., JAMA Neurology 2014
Hypertension in middle age is associated with a **39% higher chance** of dementia. Prehypertension in middle age is associated with a **31% higher chance** of dementia... compared to people with normal BP’s.

From Gottesman et al., JAMA Neurology 2017.
Life course and hypertension

• In our studies, similar associations are not found for high blood pressure in later life
  – Risk of cognitive decline and dementia is most pronounced for people with midlife (aged 45-64 in our study) high blood pressure
Low blood pressure in late life may not be as well tolerated for people with midlife hypertension
Life course blood pressure trajectories may need to consider earlier exposures than midlife

Associations between blood pressure across adulthood and late-life brain structure and pathology in the neuroscience substudy of the 1946 British birth cohort (Insight 46): an epidemiological study

**Interpretation** High and increasing blood pressure from early adulthood into midlife seems to be associated with increased WMHV and smaller brain volumes at 69–71 years of age. We found no evidence that blood pressure affected cognition or cerebral amyloid-β load at this age. Blood pressure monitoring and interventions might need to start around 40 years of age to maximise late-life brain health.
Diabetes

From Selvin et al., Diabetes Care 2006
Diabetes as a risk factor for cognitive decline

Figure 2: Difference in global cognitive Z score decline by clinical category of HbA1c level compared with decline in persons without diabetes and HbA1c level <5.7%.
Diabetes in middle age is associated with a \textit{77\% higher chance} of dementia. This near-doubling is almost as high as the risk from the APOE \textit{e4} genotype, the strongest genetic risk factor for Alzheimer’s disease.

From Gottesman et al., JAMA Neurology 2017
Smoking, Heart Disease, and Dementia

Smoking in middle age is associated with a **41% higher chance** of dementia.

From Gottesman et al., JAMA Neurology 2017
High cholesterol: Risk factor for cognitive decline

From Power et al., Alzheimer’s and Dementia 2017
Obesity Trends* Among U.S. Adults
BRFSS, 1987

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1988

(*BMI \geq 30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1989

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
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Obesity Trends* Among U.S. Adults
BRFSS, 2010

(*BMI $\geq 30$, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity *in midlife* is associated with higher risk of dementia

SAD: sagittal abdominal diameter
Whitmer et al, Neurology 2008
Obesity and Dementia

A. Dementia cases compared to all others
Difference in trajectory, p<0.0001
N dementia= 329, N dementia free=9979, N observations=42306

B. Dementia cases compared to matched controls
Difference in trajectory, p<0.0001
N cases= 329, N controls=1974, N observations=9854

Singh-Manoue et al., Alzheimer’s and Dementia 2017
Physical activity in midlife and risk of dementia

Wang et al., Am J Geriatr Psychiatry, 2014
Leisure-time physical activity sustained since midlife and preservation of cognitive function: The Atherosclerosis Risk in Communities Study

Diet and nutrition

(A) DASH Diet

From Wengreen et al., Amer J Clin Nutrition 2013

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(B) Mediterranean Diet

From www.cnn.com
### Table 3. Adjusted Odds Ratios for the Association of Midlife and Late-Life Number of Vascular Risk Factors With Global Cortex SUVR >1.2 Overall and Stratified by APOE ε4 Genotype (N = 322)

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Overall (n = 322)</th>
<th>0 APOE ε4 Alleles (n = 220)</th>
<th>1 or 2 APOE ε4 Alleles (n = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. With SUVR &gt;1.2/Total No. (%)</td>
<td>Adjusted OR (95% CI)</td>
<td>No. With SUVR &gt;1.2/Total No. (%)</td>
</tr>
<tr>
<td><strong>Midlife (Study Visit 1, 1987-1989)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>20/65 (30.8)</td>
<td>1 [Reference]</td>
<td>14/47 (29.8)</td>
</tr>
<tr>
<td>1</td>
<td>62/123 (50.4)</td>
<td>1.88 (0.95-3.73)</td>
<td>37/85 (43.5)</td>
</tr>
<tr>
<td>≥2</td>
<td>82/134 (61.2)</td>
<td>2.88 (1.46-5.69)</td>
<td>45/90 (50.0)</td>
</tr>
<tr>
<td><strong>Late life (Study Visit 5, 2011-2013)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>13/35 (37.1)</td>
<td>1 [Reference]</td>
<td>6/23 (26.1)</td>
</tr>
<tr>
<td>1</td>
<td>37/82 (45.1)</td>
<td>1.02 (0.43-2.43)</td>
<td>16/50 (32.0)</td>
</tr>
<tr>
<td>≥2</td>
<td>114/205 (55.6)</td>
<td>1.66 (0.75-3.69)</td>
<td>74/149 (49.7)</td>
</tr>
</tbody>
</table>

Abbreviations. OR, odds ratio; SUVR, standardized uptake value ratio.

*Vascular risk factors included body mass index ≥30, current smoking, hypertension, diabetes, and total cholesterol ≥200 mg/dL.*

| ^b^ Models are adjusted for age (at visit 5, 2011-2013), sex, race, education level, and APOE ε4 genotype.
Association between number of risk factors and brain amyloid is reduced when later-life risk factors are considered.
Is there evidence that treatment of vascular risk prevents dementia?

• Previously, few studies had shown a benefit from treatment of risk factors to prevent dementia.

• The recent “SPRINT-MIND” trial showed that tight control of blood pressure (to a goal of Systolic BP<120 mm Hg) was associated with 15% fewer cases of a combined outcome of MCI and dementia (and fewer MCI cases, but no difference in dementia alone).
Effect of Intensive vs Standard Blood Pressure Control on Probable Dementia: A Randomized Clinical Trial

SPRINT-MIND: Williamson et al, JAMA 2019

Figure 2. Probable Dementia by Treatment Group

Table 2. Incidence of Probable Dementia and Mild Cognitive Impairment by Treatment Group

Key Points

**Question**: Does intensive blood pressure control reduce the occurrence of dementia?

**Findings**: In this randomized clinical trial that included 9361 adults with hypertension, randomization to a systolic blood pressure target of less than 120 mm Hg compared with less than 140 mm Hg resulted in a rate of probable dementia of 7.2 vs 8.6 cases per 1000 person-years, a difference that was not statistically significant.

**Meaning**: Among adults with hypertension, intensive blood pressure control did not significantly reduce the risk of probable dementia.

*Intensive treatment group vs standard treatment group based on Cox proportional hazards regression.

Participants adjudicated as having probable dementia at the first follow-up visit (year 2) do not contribute to the analyses of mild cognitive impairment.
Multi-modal approaches to treatment & prevention: Mixed results

- FINGER trial (Ngandu et al., Lancet 2015): randomized Finnish participants to 2-year multidomain intervention (diet, exercise, cognitive training, vascular risk factor monitoring) vs control
  - 2-year followup was better in the intervention group, for cognitive change

- PreDIVA Trial: Evaluated new dementia cases, and found no difference in people randomized to a multidomain vascular intervention over 6 years compared to those with standard care (Moll van Charante et al., Lancet 2016)
Take Home Messages

- Risk factors for heart disease and stroke are also risk factors for cognitive decline and dementia, and **many of these are modifiable**
- These vascular risk factors may directly contribute to changes in the brain that cause Alzheimer’s disease
- Focusing on vascular health in *middle age* is especially important for the maintenance of brain health
- Aggressive treatment of high blood pressure reduces risk of mild cognitive impairment or dementia
- Treatment aimed at overall health: lifestyle, diet/ exercise, and vascular risk, may plan an important role in preserving brain health
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