Vascular and Degenerative Causes of Cognitive Impairment: How are they linked?

MCI Symposium, Public Education Forum



Presented by: Rebecca Gottesman, MD PhD January 20, 2019



• I am an Associate Editor for the journal Neurology.



Alzheimer's disease is on the rise



From www.alzheimersweekly.com



Year

What we knew "then"

- Alzheimar'a Diagona in caused plaques
- Vascula by sequ stroke-l
- These t



ofibrillary tangles au aggregates)

MINIM

et al., Front Phys 2015



Source: Plassman, BL; Langa, KM; Fisher, GG; Heeringa, SG; Weir, DR; Ofstedal, MB, et al. "Prevalence of Dementia in the United States: The Aging Demographics, and Memory Study. *Neuroepidemiology* 2007; 29:125-132.³¹







DEMENTIA

9 WAYS TO REDUCE YOUR RISK

cases of dementia could be prevented by addressing these lifestyle factors

IN

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



DECREASE Hearing Loss Hypertension Obesity Smoking Depression Diabetes

HNS HOPKINS

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, Neuron 2015



HIGH BLOOD PRESSURE

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 Mind Your Risks.nih.gov







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High Blood Pressure

- At the end of 2017, the definitions and guidelines for management of hypertension were changed:
 - Normal is <120/80 mm Hg

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- "Elevated BP": 120-120 systolic (the upper number)
- Stage 1 hypertension: systolic BP 130-139 mm Hg; diastolic (lower number) 80-89 mm Hg
- Stage 2 hypertension: SBP above 140 mm Hg and DBP above 90 mm Hg
- These changes mean that more people meet criteria: A THIRD of Americans had hypertension by prior definitions, and now it is nearly *HALF*, many of whom don't know it



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

Figure 2. Adjusted Association of Visit 2 (1990-1992) Systolic Blood Pressure Change Among Whites



Adapted from Gottesman et al., JAMA Neurology 2014

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Table 2. Cox Proportional Hazards Regression Model of Time to Incident Dementia Overall and Stratified by Race

| | | Hazard Ratio (95% CI) | | | | | | |
|----------|---|---------------------------------------|---------------------|-----------------------|--|--|--|--|
| Variable | | Full Eligible Cohort (n = 15 407)ª | Black (n = 4004) | White (n = 11 403) | | | | |
| | Female | 0.89 (0.79-0.99) | 0.87 (0.72-1.06) | 0.92 (0.80-1.05) | | | | |
| | Black | 1.36 (1.21-1.54) | NA | NA | | | | |
| | Visit 1 age, y ^b | | | | | | | |
| | 44-49 | 1 [Reference] | 1 [Reference] | 1 [Reference] | | | | |
| | 50-54 | 2.04 (1.66-2.49) | 2.22 (1.66-2.98) | 1.98 (1.49-2.62) | | | | |
| | 55-59 | 3.97 (3.28-4.81) | 3.53 (2.63-4.73) | 4.37 (3.37-5.65) | | | | |
| | 60-66 | 8.06 (6.69-9.72) | 6.20 (4.64-8.28) | 9.54 (7.41-12.27) | | | | |
| | Educational attainment | | | | | | | |
| | <high school<="" td=""><td>1.37 (1.20-1.57)</td><td>1.61 (1.28-2.03)</td><td>1.29 (1.09-1.53)</td></high> | 1.37 (1.20-1.57) | 1.61 (1.28-2.03) | 1.29 (1.09-1.53) | | | | |
| | High school graduate or GED | 1.05 (0.93-1.20) | 1.17 (0.90-1.53) | 1.02 (0.88-1.18) | | | | |
| | >High school | 1 [Reference] | 1 [Reference] | 1 [Reference] | | | | |
| | Visit 1 BMI | | | | | | | |
| | Underweight | 0.99 (0.53-1.87) | 1.15 (0.36-3.66) | 0.92 (0.43-1.97) | | | | |
| | Normal | 1 [Reference] | 1 [Reference] | 1 [Reference] | | | | |
| | Overweight | 1.05 (0.92-1.19) | 0.95 (0.73-1.22) | 1.08 (0.93-1.26) | | | | |
| | Obese | 1.14 (0.99-1.31) | 0.92 (0.71-1.20) | 1.22 (1.03-1.45) | | | | |
| | Visit 1 smoking ^b | | | | | | | |
| | Current | 1.41 (1.23-1.61) | 1.07 (0.85-1.35) | 1.62 (1.37-1.92) | | | | |
| | Former | 1.00 (0.89-1.13) | 0.77 (0.61-0.98) | 1.13 (0.97-1.31) | | | | |
| | Never | 1 [Reference] | 1 [Reference] | 1 [Reference] | | | | |
| | APOE ε4 genotype ^b | | | | | | | |
| | 0 Alleles | 1 [Reference] | 1 [Reference] | 1 [Reference] | | | | |
| | ≥1 Alleles | 1.98 (1.78-2.21) | 1.61 (1.34-1.92) | 2.23 (1.96-2.54) | | | | |
| | Unknown APOE | 1.18 (0.89-1.56) | 1.84 (0.97-3.47) | 1.11 (0.81-1.52) | | | | |
| | Visit 1 diabetes | 1.77 (1.53-2.04) | 1.85 (1.50-2.29) | 1.69 (1.39-2.07) | | | | |
| | Visit 1 hypertension | | | | | | | |
| | Normal | 1 [Reference] | 1 [Reference] | 1 [Reference] | | | | |
| | Prehypertension | 1.31 (1.14-1.51) | 1.17 (0.86-1.59) | 1.35 (1.14-1.59) | | | | |
| | Hypertension | 1.39 (1.22-1.59) | 1.36 (1.04-1.77) | 1.37 (1.17-1.60) | | | | |
| | Visit 1 total cholesterol, mg/dL | | | | | | | |
| | <200 | 1 [Reference] | 1 [Reference] | 1 [Reference] | | | | |
| y i | 20,260 to <240 | 0.87 (0.77-0.98) | 0.91 (0.74-1.13) | 0.86 (0.74-1.00) | | | | |
| | ≥240 | 0.91 (0.80-1.04) | 0.78 (0.62-0.98) | 0.99 (0.84-1.16) | | | | |

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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





From Selvin et al., Diabetes Care 2006



Table 2. Cox Proportional Hazards Regression Model of Time to Incident Dementia Overall and Stratified by Race

| | Hazard Ratio (95% CI) | | | |
|---|---|---------------------|-----------------------|--|
| Variable | Full Eligible Cohort (n = 15 407) ^a | Black (n = 4004) | White (n = 11 403) | |
| Female | 0.89 (0.79-0.99) | 0.87 (0.72-1.06) | 0.92 (0.80-1.05) | |
| Black | 1.36 (1.21-1.54) | NA | NA | |
| Visit 1 age, y ^b | | | | |
| 44-49 | 1 [Reference] | 1 [Reference] | 1 [Reference] | |
| 50-54 | 2.04 (1.66-2.49) | 2.22 (1.66-2.98) | 1.98 (1.49-2.62) | |
| 55-59 | 3.97 (3.28-4.81) | 3.53 (2.63-4.73) | 4.37 (3.37-5.65) | |
| 60-66 | 8.06 (6.69-9.72) | 6.20 (4.64-8.28) | 9.54 (7.41-12.27) | |
| Educational attainment | | | | |
| <high school<="" td=""><td>1.37 (1.20-1.57)</td><td>1.61 (1.28-2.03)</td><td>1.29 (1.09-1.53)</td></high> | 1.37 (1.20-1.57) | 1.61 (1.28-2.03) | 1.29 (1.09-1.53) | |
| High school graduate or GED | 1.05 (0.93-1.20) | 1.17 (0.90-1.53) | 1.02 (0.88-1.18) | |
| >High school | 1 [Reference] | 1 [Reference] | 1 [Reference] | |
| VISIT 1 BMI | | | | |
| Underweight | 0.99 (0.53-1.87) | 1.15 (0.36-3.66) | 0.92 (0.43-1.97) | |
| Normal | 1 [Reference] | 1 [Reference] | 1 [Reference] | |
| Overweight | 1.05 (0.92-1.19) | 0.95 (0.73-1.22) | 1.08 (0.93-1.26) | |
| Obese | 1.14 (0.99-1.31) | 0.92 (0.71-1.20) | 1.22 (1.03-1.45) | |
| Visit 1 smoking ^b | | | | |
| Current | 1.41 (1.23-1.61) | 1.07 (0.85-1.35) | 1.62 (1.37-1.92) | |
| Former | 1.00 (0.89-1.13) | 0.77 (0.61-0.98) | 1.13 (0.97-1.31) | |
| Never | 1 [Reference] | 1 [Reference] | 1 [Reference] | |
| APOE ε4 genotype ^b | | | | |
| 0 Alleles | 1 [Reference] | 1 [Reference] | 1 [Reference] | |
| ≥1 Alleles | 1.98 (1.78-2.21) | 1.61 (1.34-1.92) | 2.23 (1.96-2.54) | |
| Unknown APOE | 1.18 (0.89-1.56) | 1.84 (0.97-3.47) | 1.11 (0.81-1.52) | |
| Visit 1 diabetes | 1.77 (1.53-2.04) | 1.85 (1.50-2.29) | 1.69 (1.39-2.07) | |
| Visit 1 hypertension | | | | |
| Normal | 1 [Reference] | 1 [Reference] | 1 [Reference] | |
| Prehypertension | 1.31 (1.14-1.51) | 1.17 (0.86-1.59) | 1.35 (1.14-1.59) | |
| Hypertension | 1.39 (1.22-1.59) | 1.36 (1.04-1.77) | 1.37 (1.17-1.60) | |
| Visit 1 total cholesterol, mg/dL | | | | |
| <200 | 1 [Reference] | 1 [Reference] | 1 [Reference] | |
| 200 to <240 | 0.87 (0.77-0.98) | 0.91 (0.74-1.13) | 0.86 (0.74-1.00) | |
| ≥240 | 0.91 (0.80-1.04) | 0.78 (0.62-0.98) | 0.99 (0.84-1.16) | |

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JOHNS HOPKINS

Smoking, Heart Disease, and **Dementia** Table 2. Cox Proportional Hazards Regression Model of Time to Incident Dementia Overall and Stratified by Race



| | Hazard Ratio (95% CI) | | | |
|--|---------------------------------------|---------------------|-----------------------|--------------|
| arlable | Full Eligible Cohort (n = 15 407)ª | Black (n = 4004) | White (n = 11 403) | |
| emale | 0.89 (0.79-0.99) | 0.87 (0.72-1.06) | 0.92 (0.80-1.05) | |
| lack | 1.36 (1.21-1.54) | NA | NA | |
| isit 1 age, y ^b | | | | |
| 44-49 | 1 [Reference] | 1 [Reference] | 1 [Reference] | |
| 50-54 | 2.04 (1.66-2.49) | 2.22 (1.66-2.98) | 1.98 (1.49-2.62) | |
| 55-59 | 3.97 (3.28-4.81) | 3.53 (2.63-4.73) | 4.37 (3.37-5.65) | |
| 60-66 | 8.06 (6.69-9.72) | 6.20 (4.64-8.28) | 9.54 (7.41-12.27) | |
| ducational attainment | | | | |
| <high school<="" td=""><td>1.37 (1.20-1.57)</td><td>1.61 (1.28-2.03)</td><td>1.29 (1.09-1.53)</td><td></td></high> | 1.37 (1.20-1.57) | 1.61 (1.28-2.03) | 1.29 (1.09-1.53) | |
| High school graduate or GED | 1.05 (0.93-1.20) | 1.17 (0.90-1.53) | 1.02 (0.88-1.18) | |
| >High school | 1 [Reference] | 1 [Reference] | 1 [Reference] | |
| Isit 1 BMI | | | | |
| Underweight | 0.99 (0.53-1.87) | 1.15 (0.36-3.66) | 0.92 (0.43-1.97) | |
| Normal | 1 [Reference] | 1 [Reference] | 1 [Reference] | |
| Overweight | 1.05 (0.92-1.19) | 0.95 (0.73-1.22) | 1.08 (0.93-1.26) | |
| Obese | 1.14 (0.99-1.31) | 0.92 (0.71-1.20) | 1.22 (1.03-1.45) | |
| isit 1 smoking ^b | | | | |
| Current | 1.41 (1.23-1.61) | 1.07 (0.85-1.35) | 1.62 (1.37-1.92) | |
| Former | 1.00 (0.89-1.13) | 0.77 (0.61-0.98) | 1.13 (0.97-1.31) | |
| Never | 1 [Reference] | 1 [Reference] | 1 [Reference] | |
| POE ε4 genotype ^b | | | | |
| 0 Alleles | 1 [Reference] | 1 [Reference] | 1 [Reference] | - |
| ≥1 Alleles | 1.98 (1.78-2.21) | 1.61 (1.34-1.92) | 2.23 (1.96-2.54) | |
| Unknown APOE | 1.18 (0.89-1.56) | 1.84 (0.97-3.47) | 1.11 (0.81-1.52) | |
| isit 1 diabetes | 1.77 (1.53-2.04) | 1.85 (1.50-2.29) | 1.69 (1.39-2.07) | |
| isit 1 hypertension | | | | |
| Normal | 1 [Reference] | 1 [Reference] | 1 [Reference] | |
| Prehypertension | 1.31 (1.14-1.51) | 1.17 (0.86-1.59) | 1.35 (1.14-1.59) | |
| Hypertension | 1.39 (1.22-1.59) | 1.36 (1.04-1.77) | 1.37 (1.17-1.60) | |
| isit 1 total cholesterol, ng/dL | | | | |
| <200 | 1 [Reference] | 1 [Reference] | 1 [Reference] | LINE HODEINE |
| 200 to <240 | 0.87 (0.77-0.98) | 0.91 (0.74-1.13) 5 | 0.86 (0.74-1.00) | HIN2 HOLVIN2 |
| ≥240 | 0.91 (0.80-1.04) | 0.78 (0.62-0.98) | 0.99 (0.84-1.16) | MEDICINE |

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High cholesterol: Risk factor for heart disease and dementia



Obesity and Dementia



| | Number of observations in the analysis | | | | | | |
|-------------------|--|------|------|------|------|------|------|
| | -28 | -24 | -20 | -16 | -12 | -8 | -4 |
| Years | to | to | to | to | to | to | to |
| | -24 | -20 | -16 | -12 | -8 | -4 | 0 |
| Dementia free | 9135 | 7161 | 5513 | 2944 | 4086 | 6353 | 6040 |
| Dementia cases | 219 | 196 | 141 | 126 | 147 | 133 | 112 |

| | Number of observations in the analysis | | | | | | |
|----------|--|------|------|------|------|------|------|
| | -28 | -24 | -20 | -16 | -12 | -8 | -4 |
| Years | to | to | to | to | to | to | to |
| | -24 | -20 | -16 | -12 | -8 | -4 | 0 |
| Controls | 1460 | 1381 | 1044 | 1003 | 1245 | 1135 | 1512 |
| Cases | 219 | 196 | 141 | 126 | 147 | 133 | 112 |

Singh-Manoux et al., Alzheimer's and Dementia 2017







Physical activity in midlife and risk of dementia



Wang et al., Am J Geriatr Psychiatry, 2014





Reference: High physical activity

Adjusted for age, sex, education, race-center, ApoE4, smoking, household income, neighborhood SES



But how are vascular and degenerative changes linked?

- Do people with vascular risk factors develop dementia and Alzheimer's disease because:
 - Having both Alzheimer's-type and vascular-type changes in the brain makes your cognition worse, making you more likely to get a diagnosis of dementia, OR
 - Do vascular risk factors directly lead to any of the changes typical of Alzheimer's disease?

JAMA | Original Investigation

Association Between Midlife Vascular Risk Factors and Estimated Brain Amyloid Deposition

Rebecca F. Gottesman, MD, PhD; Andrea L. C. Schneider, MD, PhD; Yun Zhou, PhD; Josef Coresh, MD, PhD; Edward Green, MD; Naresh Gupta, MD; David S. Knopman, MD; Akiva Mintz, MD; Arman Rahmim, PhD; A. Richey Sharrett, MD, DrPH; Lynne E. Wagenknecht, DrPH; Dean F. Wong, MD, PhD; Thomas H. Mosley, PhD

JAMA. 2017;317(14):1443-1450.

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)

| Overall (n = 322) | | 0 APOE ε4 Alleles (n = 220) | | 1 or 2 APOE ε4 Alleles (n = 100) | | |
|---------------------------|-------------------------------------|--------------------------------------|----------------------------------|--------------------------------------|-------------------------------------|--------------------------------------|
| Risk Factors ^a | No. With SUVR >1.2/Total No. (%) | Adjusted OR (95% CI) ^b | No. With SUVR >1.2/Total No. (%) | Adjusted OR (95% CI) ^b | No. With SUVR >1.2/Total No. (%) | Adjusted OR (95% CI) ^b |
| Midlife (Study V | isit 1, 1987-1989) | | | | | |
| Vascular risk factors | | | | | | |
| 0 | 20/65 (30.8) | 1 [Reference] | 14/47 (29.8) | 1 [Reference] | 6/18 (33.3) | 1 [Reference] |
| 1 | 62/123 (50.4) | 1.88 (0.95-3.73) | 37/85 (43.5) | 1.36 (0.61-3.05) | 25/38 (65.8) | 3.10 (0.84-11.50) |
| ≥2 | 82/134 (61.2) | 2.88 (1.46-5.69) | 45/90 (50.0) | 1.86 (0.83-4.14) | 37/44 (84.1) | 9.15 (2.27-36.89) |
| Late life (Study | Visit 5, 2011-2013) | | | | | |
| Vascular risk factors | | | | | | |
| 0 | 13/35 (37.1) | 1 [Reference] | 6/23 (26.1) | 1 [Reference] | 7/12 (58.3) | 1 [Reference] |
| 1 | 37/82 (45.1) | 1.02 (0.43-2.43) | 16/50 (32.0) | 1.38 (0.43-4.39) | 21/32 (65.6) | 0.56 (0.12-2.67) |
| ≥2 | 114/205 (55.6) | 1.66 (0.75-3.69) | 74/149 (49.7) | 2.21 (0.78-6.26) | 40/56 (71.4) | 1.03 (0.25-4.29) |

Abbreviations: OR, odd ratio; SUVR, stanuaruized uptakesvalue ratio.

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 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. Is there evidence that treatment of vascular risk factors prevents dementia?

- Previously, few studies had shown a benefit from treatment of risk factors to prevent dementia
- The recently presented "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)



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)





What do we know now?

- Risk factors for heart disease and stroke are also risk factors for cognitive decline and dementia
- 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
- Treatment aimed at overall health: lifestyle, diet/ exercise, and vascular risk, may plan an important role in preserving brain health
- You may be able to prevent or delay dementia or cognitive impairment!
- There is tremendous overlap between degenerative and vascular pathologies, and thus treatment and prevention may ultimately be aimed at *both* areas.

