Cardiovascular Risk and Cognition

Ralph L. Sacco, MS MD FAAN FAHA
Olemberg Family Chair in Neurological Disorders
Miller Professor of Neurology, Public Health Sciences, Human Genetics, & Neurosurgery
Executive Director, Evelyn McKnight Brain Institute
Miller School of Medicine, University of Miami
Jackson Memorial Hospital

Supported by grants R37 NS 29993, U54 NS 081763, R01 NS 240807, R01 42912, 047655, DE 13094, Evelyn McKnight Brain Institute
Consultant: Boehringer Ingelheim (RESPECT), UCSF (SOCRATES DSMB), DCRI (EUCLID DSMB)
Cardiovascular Risk and Cognition

• Vascular Disease and Cognition
• Findings from NOMAS
  – GVRS and Successful Cognitive Aging
  – Metabolic Syndrome and Cognition
  – AHA Ideal CV Health and Cognitive Decline
• Heart function and Brain Aging
  – Cardiac Index
  – LV Ejection Fraction
  – Global longitudinal Strain and LV Systolic Dysfunction
Relationships between Vascular and Neurodegenerative Processes in Cognitive Impairment and Dementia

• It is accepted that many traditional risk factors for stroke are also risk markers for AD and VCI

• There may be a convergence of pathogenic mechanisms in vascular and neurodegenerative processes which cause cognitive impairment

• Epidemiologic studies also point to linkages between traditional CV risk factors and AD risk

Model for the Pathophysiology of VCI

- **Risk factors**: HTN, Diabetes, smoking, cholesterol, inflammatory
- **Primary pathology**: Atherosclerosis, arterial stiffness, endothelial dysfunction
- **Vascular changes**: Microvascular disease, Lg vessel stenosis, Cardiac failure
- **End organ effects**: Chronic hypoperfusion
- **Mediating factors**: Loss of autoregulation, White matter hyperintensities
- **Genetic (ApoE, Notch3)**
- **AD pathology**

**Behavioral outcome**: Cognitive impairment

Marshall & Lazar Stroke 2011;42:221-226
Cognitive Aging: Progress in Understanding and Opportunities for Action

www/iom.edu/cognitiveaging
1. Increase Research and Tools for Assessing Cognitive Aging and Cognitive Trajectories

2. Collect and Disseminate Population-based data on Cognitive Aging
   - high-risk populations, longitudinal assessments, diverse populations

3. Take Actions to Reduce Risks of Cognitive Decline with Age
   - Physically active
   - Reduce and manage CV disease risk factors

4. Increase Research on Risk and Protective Factors and Interventions
NORTHERN MANHATTAN STUDY
Prospective Cohort

1993
1998
2003
2008
2015

BASELINE ASSESSMENT
Sociodemographics
Vascular Risk Profile
BP Measures
Anthropometrics
Fasting bloods
Neurological Exam
N = 3,298

Annual Follow-up
Phone Screen, In-person Validation, Hospital Surveillance
Stroke MI Death

CIMT sub-study
Candidate gene sub-study
Brain-MRI sub-study
Cognitive decline sub-study
GWAS

Funding: NINDS R37 NS 29993 (Sacco), R01 NS 40807 (Sacco),
R01 HL 108623 (Wright), K24 (Rundek), R01 NS 047655 (Rundek),
R01 NS 36286 (Di Tullio), R01 DE 013094 (Desvarieux),
Evelyn McKnight Brain Institute
Modifiable Vascular Risk Factors
- Global Vascular Risk Score
- AHA Ideal CV Health
- Heart Function

Subclinical Brain Disease
- White Matter Hyperintensities
- Cortical Volumes
- Silent Infarcts

Cognitive Function
- MMSE, TICS
- Neuropsych Tests
- Cognitive Aging

Presumed causal pathways
Association Between Northern Manhattan Study Global Vascular Risk Score and Successful Aging

Jessica R. L. Warsch, MD, PhD,* Tatjana Rundek, MD, PhD,* Myunghee C. Paik, PhD,† Mitchell S. V. Elkind, MD, MS,‡§ Ralph L. Sacco, MD, MS,*∥ and Clinton B. Wright, MD, MS*∥


Physical activity and cognition in the Northern Manhattan Study

Joshua Z Willey, MD, MS, Yeseon Park Moon, MS, Rachel Ruder, BA, Yuen K Cheung, PhD, Ralph L. Sacco, MD, MS, Mitchell S.V. Elkind, MD, MS, and Clinton B. Wright, MD, MS

McKnight Brain Institute, University of Miami, Miami, FL

Neuroepidemiology. 2014

CKD Associates with Cognitive Decline

Minesh Khatri,* Thomas Nickolas,† Yeseon P. Moon,‡ Myunghee C. Paik,‡ Tatjana Rundek,§ Mitchell S. V. Elkind,‖ Ralph L. Sacco,§ and Clinton B. Wright§


Modeling Metabolic Syndrome and Its Association with Cognition: The Northern Manhattan Study

Bonnie E. Levin,1,2 Maria M. Llabre,2 Chuanhui Dong,1 Mitchell S.V. Elkind,3 Yaakov Stern,4 Tatjana Rundek,1,5 Ralph L. Sacco,1,5,6 and Clinton B. Wright1,6

1Evelyn F. McKnight Brain Institute, Department of Neurology, University of Miami Leonard M. Miller School of Medicine, Miami, Florida
Odds ratio for Successful Aging without cognitive decline and better GVRS scores
Model 1 adjusted for length of time between baseline and follow-up cognitive testing only
Model 2 adjusted for years of education, health insurance status, and follow-up time.
Modelling Metabolic Syndrome and Cognition

Levin et al, Int J of Neuropsychol, 2014
Links between cardiometabolic risk factors and cognitive factors after controlling for covariates

Levin et al, Int J of Neuropsychol, 2014
# Classification of Cardiovascular Health

**Life’s Simple 7**

<table>
<thead>
<tr>
<th>Smoking</th>
<th>Ideal</th>
<th>Intermediate</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Never or quit &gt; 1 year</td>
<td>Quit &lt; 1 year</td>
<td>Current</td>
</tr>
</tbody>
</table>

| BMI           | < 25 kg/m²                  | 25 - <30 kg/m²          | ≥ 30 kg/m²               |

| Physical activity | ≥ 75 min/wk vigorous or ≥ 150 min/wk moderate or equivalent combination | 1-74 min/wk vigorous or 1-149 min/wk moderate or equivalent combination | No moderate or vigorous activity |

| Diet          | 4-5 healthy components     | 2-3 healthy components  | 0-1 healthy components  |

| Blood pressure | Untreated & SBP < 120 & DBP < 80 mmHg | Treated to <120/<80 or 120-139/80-89 mmHg | SBP ≥ 140 mmHg or DBP ≥ 90 mmHg |

| Fasting glucose | Untreated & < 100 mg/dL | Treated to <100 mg/dL or 100-125 mg/dL | >125 mg/dL |

| Total cholesterol | Untreated & < 200 mg/dL | Treated to < 200 mg/dL or 200-239 mg/dL | ≥ 240 mg/dL |
Ideal Cardiovascular Health

- Strong relationship with stroke, MI, and vascular death in NOMAS
- Ideal CV Health factors may also impact cognitive or brain health.
- We examined the relationship between the number of ideal CV health metrics with
  - Mini-Mental State Exam
  - Domains of cognitive performance (language, memory, executive function, processing speed)
  - Cognitive Decline
Northern Manhattan Study
MRI Subcohort

• 1033 with baseline cognitive data with 722 with follow-up cognitive data
  – Mean age at baseline = 64 ± 8
  – Mean age at first cognitive assessment = 72 ± 8
  – 39% Male; 65% Hispanic, 16% NH-White, 19% NH-Black
Cognitive Assessment

- Cognitive domain Z scores derived from factor analysis of neuropsychological battery
  - Episodic Memory
  - Semantic Memory
  - Executive function
  - Processing speed

- Z scores for change in performance incorporate age, education, time between assessments
What is the risk of brain aging and cognitive impairment in LV dysfunction or heart failure?
Prevalence of heart failure by sex and age


Mozaffarian D et al. Circulation. 2015;131:e29-e322
Copyright © American Heart Association, Inc. All rights reserved.
Greater Brain Volumes with better cardiac index

< 2.54    2.54-2.92    >2.92
L/min/m²
Patients with perfusion failure due to low systemic blood pressures, such as occurs in heart failure, can experience tissue injury and cognitive decline.\textsuperscript{12–15} Indeed, cognitive decline due to heart failure has generated great interest because it may be reversible, and it is of great importance to identify markers of cognitive dysfunction at the earliest stages if there is therapeutic potential. However, less is known about the relationship between subclinical reductions in cardiac function in normal populations.
Low Cardiac Index is Associated with Incident Dementia and Alzheimer’s Disease: The Framingham Heart Study


Impaired Cardiac Index < 2.5 L/min/m2

Normal Cardiac Index > 2.5 L/min/m2
Subclinical Left Ventricular Dysfunction and Silent Cerebrovascular Disease
The Cardiovascular Abnormalities and Brain Lesions (CABL) Study

European Journal of Heart Failure (2014) 16, 1301–1309
doi:10.1002/ejhf.154

Prevalence and prognostic value of subclinical left ventricular systolic dysfunction by global longitudinal strain in a community-based cohort

Enhancing Detection of Subclinical End-Organ Damage
Echocardiographic Left Ventricular Strain Holds Up a Mirror to the Brain

LVEF: Long-standing monarch of systolic dysfunction, buckling under the strain?
Myocardial Strain Assessment

Tissue Doppler

- Angle-dependent
- Lower signal/noise ratio
- High temporal resolution

Speckle-tracking

- Angle-independent
- Less noise
- Lower temporal resolution
Modified Definition of LV systolic dysfunction (LVSD) using Global Longitudinal Strain (GLS)

- **Ejection Fraction**
  - Normal
  - Abnormal (<50%)

- **Traditional LVSD definition**
  - Normal
  - Abnormal

- **Global Longitudinal Strain**
  - Normal
  - Abnormal

- **Current study LVSD definition**
  - No LVSD
  - GLS-LVSD
  - EF-LVSD
GLS-LVSD:

- Was present in 16% of study participants (114/708)
- Was 4 times more frequent than EF-LVSD (4%)
Subclinical LVSD and CV risk factors

<table>
<thead>
<tr>
<th>Number of CV risk factors</th>
<th>LVEF-LVSD</th>
<th>GLS-LVSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>1</td>
<td>2.5</td>
<td>12.6</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>15.4</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>16.9</td>
</tr>
<tr>
<td>&gt;3</td>
<td>4</td>
<td>21.3</td>
</tr>
</tbody>
</table>
Subclinical LVSD and Age

Prevalence, %

Age group, years

- ≤ 60
- 61 - 70
- 71 - 80
- > 80

LVEF-LVSD
GLS-LVSD

LVSD and Silent brain infarcts (SBI)

SBI prevalence, %

No LVSD: 9.7%
GLS-LVSD: 23.0%
EF-LVSD: 18.8%

P<0.01
P=0.21

LVSD and White Matter Hyperintensities

Cardiovascular Risk and Cognition

• GVRS, Met Syndrome and ICVH scores are associated with cognitive performance and decline.
• The ICVH components driving the associations are BMI, smoking, diabetes, and SBP.
• A lower cardiac index is associated with brain imaging measures of aging and dementia.
• Subclinical LV dysfunction is frequent and associated with WMHI and SBI.
• Preventing and early treatment of heart failure may be important for reducing age-related cognitive decline.
Mitch Elkind, MD
Bernadette Boden-Albala, DrPH

Tanja Rundek, MD PhD  Clinton Wright, MD MS
Chuanhui Dong, MD PhD; Susan Blanton, PhD

Funding: NINDS R37 NS 29993 (Sacco/Elkind), R01 NS 40807 (Sacco), R01 HL 108623 (Wright), K24 (Rundek), R01 NS 047655 (Rundek/Blanton), R01 NS 36286 (Di Tullio), R01 DE 013094 (Desvarieux), Evelyn McKnight Brain Institute