Dementia Caregiving, Focus on Psychobiology and Stress Resilience

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UNIVERSITY OF CALIFORNIA SAN DIEGO
Lecture Objectives

Following the lecture, attendees will be able to:

- Identify the association between caregiver strain and risk for:
  - Mortality
  - Onset of cardiovascular diseases (CVDs)

- Understand possible biological mechanisms by which caregiver strain may promote risk for mortality/CVDs, including:
  - Biomarkers of coagulation and inflammation
  - Markers of vascular pathology

- Understand preliminary treatment data suggesting that reductions in psychological distress may result in reductions to biomarkers of disease risk.
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Caregiving and CVD

- National REACH Study
  - > 800 caregivers from 6 U.S. cities
  - Followed for 18-months and inquired as to new diagnosis of CVD
    - Heart disease
    - Heart attack
    - Congestive heart failure
    - Angina
    - Myocardial infarction
  - Primary interest was to determine if clinically significant symptoms of depression and/or distress associated with CR problem behaviors are prospectively related to diagnosis of CVD over 18-month period.
# Distress and CVD: Group Comparisons

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<tr>
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**Source:** Mausbach et al. (2007). Depression and distress predict time to cardiovascular disease in dementia caregivers. *Health Psychology, 26*, 539-544.
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Why are caregivers at risk for CVD? Translation of distress to CVD
Stress or injury activates the body’s “clotting system” via release of clotting molecules.

- Thrombin is produced, which contributes to the formation of fibrin.
- Fibrin molecules link together to form a “net” of protein strands that form the basis of a blood clot.

- Fibrin also activates the “clot dissolving” system (fibrinolytic system)
  - As the body’s “clot dissolving system” dissolves clots, fibrin fragments called “d-dimers” are released.

Thus, presence of d-dimer is an indicator that the body’s “clot formation and dissolving systems” have been activated.
Are d-dimer levels an indication of risk? Risk for Future Venous Thrombosis

D-dimer in Caregivers vs Non-Caregivers

D-dimer in Caregivers vs Non-Caregivers by Age

Why are caregivers at risk for CVD? Translation of distress to CVD
Caregiving and Inflammation

**Interleukin-6**
- Inflammatory molecule tailored to function as an SOS signal during the stress response.
- Its presence represents a “coordinated response of the body to aggression.”
  - Injury or infection, as well as acute psychological stress, is promptly followed by a massive induction of IL-6 by white blood cells
  - Helps initiate the activation of T Cells and the formation of blood and blood cells of the innate immune response
  - Stimulates antibody production
Interleukin-6

- However, high concentrations indicate ongoing inflammation in the body, which has been found to predict Cardiovascular Diseases and events.

- In summary, short-term presence of IL-6 is helpful for responding to “aggressors”, but long-term presence of IL-6 is harmful.
Are IL-6 levels an indicator of Risk? Risk for Coronary Heart Disease

IL-6 in Caregivers vs Non-Caregivers

IL-6 in Caregivers vs Non-Caregivers by Age

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Translation of stress/distress to CVD
The endothelium

- Thin lining covering the internal surface of blood vessels
- Senses changes in hemodynamic forces (blood flow)
- Responds by releasing vasoactive substances
- Helps keep balance between constricting and relaxing of arteries via release of Nitrous Oxide (NO)
- Implicated in the pathogenesis and clinical course of all known cardiovascular diseases

**Source:** Verma & Anderson (2002). Fundamentals of endothelial function for the clinical cardiologist. Circulation, 105, 546-549

**Image:** http://www.examiner.com/article/prevent-a-heart-attack-tomorrow-mind-your-endothelium-today
Flow Mediated Dilation
Flow Mediated Dilation

FMD and Risk for Cardiovascular Event

Endothelial dysfunction in Caregivers

Translation of stress/distress to CVD
Baroreflex Sensitivity

• The arterial baroreflex normally acts to oppose increases in blood pressure by inhibiting sympathetic activity, causing vasodilation and slowing heart rate.

• Important to both short and long-term regulation of blood pressure

• Sustained increases in pressure trigger a resetting of the operating point of the reflex to a higher level of pressure

• Impaired arterial baroreflex sensitivity has been associated with cardiac mortality and nonfatal cardiac arrests after a myocardial infarction.

• Baroreflex impairment may be of prognostic significance in hypertensive patients without overt cardiovascular disease.

Association of BRS to Risk of Cardiovascular Death

Baroreflex Sensitivity (BRS) in Caregivers and Non-Caregivers

Source: UC San Diego Caregiver Project (under review)
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Treating Depression, Treating CVD Risk?

Primary Aims

To determine if a brief, evidence-based caregiver intervention is more effective than a time-equivalent support and education intervention for reducing depressive symptoms in dementia caregivers.

To determine if our intervention can successfully modify IL-6, relative to a support and information condition.

A “proof-of-concept” study
  - If we can show change on this biomarker, we might have evidence we can change other markers of CVD risk.
Methods

Sample
- 100 caregivers of family member with dementia
- ≥ 55 years of age
- Living with the CR in the same home

Assessments
- Pre- and post-treatment

Data analysis
- Statistical and clinical significance - What % in each treatment group showed 50% reduction from baseline?
## Methods – Intervention Conditions

<table>
<thead>
<tr>
<th>Behavioral Activation</th>
<th>Education and Support</th>
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<tbody>
<tr>
<td><strong># sessions</strong></td>
<td>6</td>
</tr>
<tr>
<td><strong>Length of Sessions</strong></td>
<td>60 minutes</td>
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<tr>
<td><strong>Meeting milieu</strong></td>
<td>Caregivers’ homes</td>
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<tr>
<td><strong>Emphasis</strong></td>
<td>Often, stresses are beyond our control, but personal behaviors are not</td>
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<td>Distress is a function of reduced exposure to pleasant situations</td>
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<td>Help caregivers systematically increase exposure to positive events and reduce avoidant behaviors</td>
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<td>Provide education on communication with CR, managing emotions, and planning for the future.</td>
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Response in Depressive Symptoms

Reduction in Symptoms From Baseline Levels

- 10%: 53.5% Education and Support, 67.4% Behavioral Activation
- 20%: 46.5% Education and Support, 55.8% Behavioral Activation
- 30%: 25.6% Education and Support, 51.2% Behavioral Activation
- 40%: 16.3% Education and Support, 44.2% Behavioral Activation
- 50%: 14.0% Education and Support, 37.2% Behavioral Activation

Percent of Group Showing Reduction

Education and Support
Behavioral Activation
Response in IL-6

Reduction in Symptoms From Baseline Levels

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<td>50%</td>
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- **Education and Support**
  - 10%: 36.8%
  - 20%: 31.4%
  - 30%: 13.2%
  - 40%: 10.5%
  - 50%: 7.9%

- **Behavioral Activation**
  - 10%: 34.3%
  - 20%: 31.4%
  - 30%: 31.4%
  - 40%: 25.7%
  - 50%: 25.7%
Conclusions

- Providing caregivers with a systematic means of raising their engagement in pleasurable activities effectively reduced depressive symptoms and IL-6, a marker of inflammation.

- Significant reduction in both depression and IL-6 is theoretically linked to reduced CVD risk.

- Behavioral activation therapy improves overall quality of life and MAY reduce long-term risk for developing CVD.
Conclusions

- However, IL-6 is only ONE marker of CVD risk among many.

- Therefore, more work is needed to determine if other CVD risk markers also change as a function of therapeutic interventions.

- Currently conducting a randomized clinical trial to determine if our Behavioral Activation intervention can successfully modify other risk markers:
  - Coagulation (e.g., D-dimer)
  - Inflammation (e.g., IL-6, CRP)
  - Vascular pathology (e.g., Flow-mediated Dilation, Intima Media Thickness)
# UC San Diego Alzheimer's Caregiver Project

## Current Team
- Igor Grant, MD
- Jean-Loup Bitterlin
- Ian Abramson, PhD
- Michael Daniels
- Matthew Allison, MD
- Christine Gonzaga, RN
- Sonia Ancoli-Israel, PhD
- Lianqi Liu, PhD
- Joel Dimsdale, MD
- Milos Milic, MD
- Paul J Mills, PhD
- Jessica Reit, MA
- Thomas L Patterson, PhD
- Roland von Känel, MD
- Michael G Ziegler, MD

## Prior Members
- Kirstin Aschbacher, PhD
- Susan Calleran, MA
- Jennifer Ceglowski, MA
- Elizabeth Chattillion, PhD
- Alexandria Harmell
- Raeanne Moore, PhD
- Susan Roepke, PhD