The intersection between comorbidity, multimorbidity and frailty

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U13 Gemsstar Conference  March, 2015
Definitions

- Comorbidity: additional diseases beyond the index disease
- Multimorbidity: co-occurrence of multiple diseases
- Frailty: increased vulnerability to stressors and adverse outcomes
Goals of this Presentation

• Overview: Multiple Chronic Conditions
  • Disease specific
  • Geriatric conditions
• Multiple chronic conditions and frailty
• Links to theory in aging research
• Research gaps
Frailty: A Conceptual Model

- **Primary Cause**
  - Genetic
- **Secondary Causes**
  - Diabetes
  - Heart Failure
  - Lung Disease
  - Inflammatory Diseases

**Physiology**
- Metabolism
- Endocrine
- Inflammation
- Oxidative stress

**Signs and Symptoms**
- Loss of muscle mass
- Altered energy metabolism
- Decreased endurance
- Cognitive impairment

**Frailty: Clinical syndrome**
- Disability
- Death

- **NYU Langone Medical Center**
“The most common chronic condition experienced by adults is multimorbidity, the coexistence of multiple chronic diseases or conditions.”

Tinetti et al. JAMA 2012.
**It’s Not Easy Living with Multimorbidity**

<table>
<thead>
<tr>
<th>Time</th>
<th>Medications</th>
<th>Non-pharmacologic Therapy</th>
<th>All Day</th>
<th>Periodic</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 AM</td>
<td>Ipratropium MDI Alendronate 70mg weekly</td>
<td>Check feet</td>
<td>Joint protection</td>
<td>Pneumonia vaccine, Yearly influenza vaccine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sit upright 30 min.</td>
<td>Energy conservation</td>
<td>All provider visits: Evaluate Self-monitoring blood glucose, foot exam and BP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Check blood sugar</td>
<td>Exercise (non-weight bearing if severe foot disease, weight bearing for osteoporosis)</td>
<td>Quarterly HbA1c, biannual LFTs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Muscle strengthening exercises, Aerobic Exercise ROM exercises</td>
<td>Yearly creatinine, electrolytes, microalbuminuraria, cholesterol</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Avoid environmental exposures that might exacerbate COPD</td>
<td>Referrals: Pulmonary rehabilitation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Wear appropriate footwear</td>
<td>Physical Therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Albuterol MDI prn</td>
<td>DEXA scan every 2 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Limit Alcohol</td>
<td>Yearly eye exam</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maintain normal body weight</td>
<td>Medical eye exam</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Medical nutrition therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Patient Education: High-risk foot conditions, foot care, foot wear</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Osteoarthritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>COPD medication and delivery system training</td>
</tr>
<tr>
<td>8 AM</td>
<td>Eat Breakfast HCTZ 12.5 mg Lisinopril 40mg Glyburide 10 mg ECASA 81 mg Metformin 850mg Naproxen 250mg Omeprazole 20mg Calcium + Vit D 500mg</td>
<td>2.4gm Na, 90mm K, Adequate Mg, ↓ cholesterol &amp; saturated fat, medical nutrition therapy for diabetes, DASH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 PM</td>
<td>Eat Lunch Ipratropium MDI Calcium+ Vit D 500 mg</td>
<td>Diet as above</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 PM</td>
<td>Eat Dinner</td>
<td>Diet as above</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 PM</td>
<td>Ipratropium MDI Metformin 850mg Naproxen 250mg Calcium 500mg Lovastatin 40mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 PM</td>
<td>Ipratropium MDI</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Boyd et al. JAMA 2005;294:716-724*
Figure 4.1  Co-morbidity among Chronic Conditions for Medicare FFS Beneficiaries: 2010

NYU Langone Medical Center

Slide Courtesy of R. Goodman, CDC
Geriatric conditions are associated with ADL dependency

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td># geriatric conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3.0 (2.6-3.4)</td>
<td>2.6 (2.3-3.0)</td>
<td>2.2 (2.0-2.5)</td>
</tr>
<tr>
<td>2</td>
<td>7.3 (6.3-8.3)</td>
<td>5.4 (4.7-6.2)</td>
<td>3.9 (3.6-4.4)</td>
</tr>
<tr>
<td>≥3</td>
<td>16.9 (14.8-18.9)</td>
<td>11.5 (9.9-13.0)</td>
<td>7.5 (6.4-8.5)</td>
</tr>
<tr>
<td># chronic diseases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1.9 (1.8-2.1)</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>-</td>
<td>2.8 (2.6-3.1)</td>
</tr>
<tr>
<td>≥3</td>
<td>-</td>
<td>-</td>
<td>4.0 (3.5-4.5)</td>
</tr>
</tbody>
</table>

Cohorts:

- **Assets and Health Dynamics Among the Oldest Old (AHEAD)**
  - Birth Years: 1890-1924
  - Baseline: 1993

- **Children of the Depression (CODA)**
  - Birth Years: 1924-1930
  - Baseline: 1998

- **Original Health and Retirement Study (HRS)**
  - Birth Years: 1931-1941
  - Baseline: 1992

- **War Babies (WB)**
  - Birth Years: 1942-1947
  - Baseline: 1998

- **Early Boomers (EB)**
  - Birth Years: 1948-1953
  - Baseline: 2004

- **Middle Boomers (MB)**
  - Birth Years: 1953-1959
  - Baseline: 2012
## Common Comorbidities Among Older Adults: Diseases and Geriatric Conditions

HRS, representative of 35 million people 65 and older, 2004 (Lee et al, JAGS 2009:57;840)

<table>
<thead>
<tr>
<th>Index Condition (%)</th>
<th>Weighted Prevalence (%) of Other Conditions Among Respondents Having Index Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CAD</td>
</tr>
<tr>
<td>CAD (8.7)</td>
<td></td>
</tr>
<tr>
<td>CHF (4.8)</td>
<td>58%</td>
</tr>
<tr>
<td>Diabetes (19.4)</td>
<td>24%</td>
</tr>
<tr>
<td>UI (25.0)</td>
<td>19%</td>
</tr>
<tr>
<td>Falls (23.2)</td>
<td>23%</td>
</tr>
</tbody>
</table>
Incidence of Geriatric Conditions Among Adults With Diabetes Aged 51 and Older: HRS 2004 to 2006

(Cigolle, et al, JGIM, 2010)
Framework for Considering Comorbid Conditions

**Clinically dominant comorbid conditions:**
so complex or serious that they eclipse the management of other health problems
– end-stage, severely symptomatic, recently diagnosed
  e.g. heart failure

**Concordant conditions:**
represent parts of the same overall pathophysiologic risk profile
and are more likely to be the focus of the same disease management plan (may include ‘complicating’)
- e.g. coronary atherosclerosis and hyperlipidemia

**Discordant conditions:**
not directly related in either their pathogenesis or management
and do not share an underlying predisposing factor
- arthritis or urinary incontinence

Piette JD and Kerr EA Diabetes Care 29:725-731, 2006
Diabetes and Vascular Complications

Modifiers: Blood pressure, lipids, physical activity, treatment

Complications:
- Atherosclerotic
- Microvascular
Diabetes and Distal Complications

Modifiers: Blood pressure, lipids, physical activity, treatment

Outcomes:
- Geriatric conditions
- Disability
- Mortality

Complications:
- Atherosclerotic
- Microvascular

IR, obesity

Impairments:
- Cognitive
- Affective
- Neurologic
- Muscle/fat
Most frequently co-occurring chronic conditions, women 65+ in community (WHAS screenees)

- Arthritis, visual impairment 44%
- Visual Impairment, HBP 40%
- Arthritis, HBP 34%
- Heart disease, visual imp. 17%
- Visual imp, hearing imp 15%
- Heart disease, arthritis 14%
- Heart disease, HBP 13%
- Arthritis, hearing imp 12%
- Diabetes, visual imp 12%
# Heart Failure and Cognition

*(Gure, TR et al, JAGS 60, 2012)*

<table>
<thead>
<tr>
<th></th>
<th>No heart failure</th>
<th>Heart disease but low probability heart failure</th>
<th>High probability heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIC’s score: mean ± sd, (range 0-27)</td>
<td>14.5 ± 4.3</td>
<td>13.7 ±4.6</td>
<td>12.7 ±4.3</td>
</tr>
<tr>
<td>Normal cognition</td>
<td>71 (70-71)</td>
<td>68 (65-70)</td>
<td>61 (57-65)</td>
</tr>
<tr>
<td>MCI % (confidence interval)</td>
<td>21 (19-22)</td>
<td>22 (22-24)</td>
<td>24 (21-28)</td>
</tr>
<tr>
<td>Mod-severe cognitive impairment</td>
<td>8 (7-9)</td>
<td>10 (9-11)</td>
<td>15 (12-18)</td>
</tr>
</tbody>
</table>
Changes in ADL/IADL with time in respondents with and without diabetes in HRS (51 and over)
ADL/IADL with time by diabetes and hypertension (HRS, ages 51 and up)
Competing risks in older adults with diabetes: falls and strokes (Min, L, preliminary data)

Cumulative Incidence of Injurious Fall vs Stroke
N=365 Diabetics Aged 65+ With Competing Risk of Death

Years after 1998 interview

Probability
Grouping Chronic Diseases and Geriatric Conditions: The HRS

(Cigolle, Ha, et. al, 2012, JGIM paper presentation)
# RESULTS: Disability and Mortality Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Healthy BP, MS</th>
<th>BP, CV, MS, falls</th>
<th>Ger cond, dementia</th>
<th>Healthy DM, MS, BP</th>
<th>DM, CV</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>New ADL dependency at 2 years (%)</td>
<td>3.0</td>
<td>7.7</td>
<td>42.0</td>
<td>7.8</td>
<td>10.0</td>
<td>26.3</td>
</tr>
<tr>
<td>New IADL dependency at 2 years (%)</td>
<td>5.1</td>
<td>13.9</td>
<td>60.2</td>
<td>11.5</td>
<td>15.3</td>
<td>53.2</td>
</tr>
<tr>
<td>Mortality at 2 years (%)</td>
<td>4.8</td>
<td>13.7</td>
<td>44.4</td>
<td>6.4</td>
<td>13.0</td>
<td>35.5</td>
</tr>
<tr>
<td>Mortality at 4 years (%)</td>
<td>10.3</td>
<td>25.7</td>
<td>73.3</td>
<td>13.8</td>
<td>24.2</td>
<td>59.8</td>
</tr>
</tbody>
</table>
Goal-Oriented Patient Care

<table>
<thead>
<tr>
<th>Measurement Domain</th>
<th>Examples of Diseases</th>
<th>Traditional Outcomes</th>
<th>Goal-Oriented Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>Cancer, heart failure</td>
<td>Overall, disease-specific, and disease-free survival</td>
<td>None if survival not a high-priority goal; survival until personal milestones are met (e.g., grandchild’s wedding)</td>
</tr>
<tr>
<td>Biomarkers</td>
<td>Diabetes, COPD</td>
<td>Change in indicators of disease activity (e.g., glycated hemoglobin level, CRP level, and pulmonary-function tests)</td>
<td>None (not a meaningful outcome observed or felt by patient)</td>
</tr>
<tr>
<td>Signs and symptoms</td>
<td>Heart failure, COPD, arthritis</td>
<td>Inventory of disease-specific signs and symptoms (e.g., dyspnea, edema, and back pain)</td>
<td>Symptoms that have been identified as important by the patient (e.g., control of dyspnea or pain sufficient to perform an activity such as bowling or walking grandchild to school)</td>
</tr>
<tr>
<td>Functional status, including mobility</td>
<td>Cancer, heart failure, COPD</td>
<td>Usually none or disease-specific (e.g., Karnofsky score, NYHA functional classification, and 6-minute walk test)</td>
<td>Ability to complete or compensate for inability to complete specific tasks identified as important by the patient (e.g., ability to get dressed without help)</td>
</tr>
</tbody>
</table>

* COPD denotes chronic obstructive pulmonary disease, CRP C-reactive protein, and NYHA New York Heart Association.

Tinetti and Reuben NEJM 2012
Multiple Chronic Conditions in Context

Moving from “What is the matter?” to “What Matters to You?”

*Key contextual factors:* public policy, community, health care systems, family, and person, to sub-personal cellular and molecular levels (where most medical knowledge currently is generated)

*New knowledge needed* involves moving from a predominant disease focus toward a person-driven, goal-directed research agenda

NIH/PCORI Meeting on Multiple Chronic Conditions in Context, Feb. 2013
Quality Framework for People with MCC’s

(Giovannetti, ER, et al. Am J Man Care 19, 2013)
Conceptual Framework

Comorbid Disease

Comorbidity

Index Disease

Multimorbidity

Condition

Condition

Condition

Patient

Boyd, CM, Fortin M.  Public Health Reviews, 2011.
Frailty: A Conceptual Model

Primary Cause
- Genetic

Secondary Causes
- Diabetes
- Heart Failure
- Lung Disease
- Inflammatory Diseases

Physiology
- Metabolism
- Endocrine
- Inflammation
- Oxidative stress

Signs and Symptoms
- Loss of muscle mass
- Altered energy metabolism
- Decreased endurance
- Cognitive impairment

Frailty: Clinical syndrome

Disability

Death
Frailty is distinct from comorbidity and disability

Disability: ≥ 1 ADL
(n=67)

Comorbidity
(n=2131)

Frailty
(n=98)

5.7%
(n=21)

21.5%
(n=79)

26.6%
(n=98)

46.2%
(n=170)

Frailty Models
(Cigolle, C et al, JAGS 57, 2008)

• Frailty has been modeled in different ways, reflecting different theoretical understandings of the concept.
  • Biologic Syndrome model (Fried et al.)$^1$: Frailty phenotype - defined in terms of 5 components.
    • Frailty-defining criteria: weight loss, exhaustion, low energy expenditure, slowness, weakness.
    • Not cognition (excluded in original study)

Frailty Models

• **Burden model**\(^2\): frailty index (FI) - a measure of an older adult’s cumulative burden of symptoms, diseases, conditions, disability, etc.

• **Functional Domains model**\(^3\): deficiencies in four domains of functioning (physical, nutritive, cognitive, and sensory).

\(^2\)Rockwood et al., A global clinical measure of fitness and frailty in elderly people, *Cmaj* 2005.

COMPARING MODELS OF FRAILTY:
THE HEALTH AND RETIREMENT STUDY

<table>
<thead>
<tr>
<th>Model</th>
<th>Sample Size</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biologic Syndrome Model</td>
<td>n=220 (of 1,657)</td>
<td>10.9%</td>
</tr>
<tr>
<td>Functional Domains Model</td>
<td>n=353 (of 1,657)</td>
<td>20.3%</td>
</tr>
<tr>
<td>Burden Model</td>
<td>n=245 (of 1,657)</td>
<td>15.4%</td>
</tr>
</tbody>
</table>
Two-Year Functional Decline by Frailty Model

- Functional Domains (n=496)
- Burden (n=566)
- Biologic Syndrome (n=308)
Baseline Association of Diseases and Frailty (CHS)

(Fried, et al. J Gerontology, 2001)
Diseases associated with increased risk of frailty

- Congestive Heart Failure
- ESRD
- Diabetes
- Dementia
- Depression
- Advanced cancers
- COPD
- Chronic inflammatory diseases
- Hip fractures
- Pressure ulcers and chronic wounds
- AIDS, Tuberculosis, other chronic infections
Conditions Related to Frailty

• Sarcopenia: loss of muscle mass
• Weight loss/undernutrition
• Decreased strength, exercise tolerance
• Slowed motor processing, performance
• Slow gait speed, poor mobility
• Decreased balance
• Low physical activity
• Cumulative illness
• Cognitive impairment
• Increased vulnerability to stressors
• Psychosocial stressors
Association of BMI and Frailty
(Blaum, CS, et al, JAGS53, 2005.)

Proportion of Sample

<table>
<thead>
<tr>
<th>BMI kg/m²</th>
<th>Not frail</th>
<th>Pre-frail</th>
<th>Frail</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18.5</td>
<td>80</td>
<td>70</td>
<td>10</td>
</tr>
<tr>
<td>1.85-26</td>
<td>60</td>
<td>50</td>
<td>20</td>
</tr>
<tr>
<td>26-30</td>
<td>50</td>
<td>40</td>
<td>30</td>
</tr>
<tr>
<td>&gt;30</td>
<td>40</td>
<td>30</td>
<td>60</td>
</tr>
</tbody>
</table>
## Prevalence Of Frailty Based On Cognitive Function
(Cigolle C, GSA paper presentation 2012)

<table>
<thead>
<tr>
<th>Prevalence of Frailty</th>
<th>Cognitive Function</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal (n=3,328)</td>
</tr>
<tr>
<td>Robust (%)</td>
<td>40.2</td>
</tr>
<tr>
<td>Pre-Frail (%)</td>
<td>47.6</td>
</tr>
<tr>
<td>Frail (%)</td>
<td>12.2</td>
</tr>
</tbody>
</table>
Cognition and Frailty

• Over 50% of older adults with mild cognitive impairment and over 70% of older adults with dementia are classified as frail.

• Over 60% of older adults classified as frail have mild cognitive impairment or dementia.
Results: How Frailty-defining Criteria Sort
AREAS FOR RESEARCH
Research Questions: Clinical

• How can we prevent frailty?
• Does frailty help in prognostication for specialists – oncology, elective surgery?
• How do we manage people with frailty?
• What are the competing risks?
• Should it have a clinical definition?
PREVENTION
PROGNOSTICATION
Diabetes and Distal Complications

Modifiers: Blood pressure, lipids, physical activity, treatment

Outcomes:
- Geriatric conditions
- Disability
- Mortality

Complications:
- Atherosclerotic
- Microvascular

Impairments:
- Cognitive
- Affective
- Neurologic
- Muscle/fat

IR, obesity
Diabetes
Research questions: pathways

• Does frailty result from accumulating comorbidities or is it the underlying pathophysiological disruption that causes comorbidity accumulation, frailty and disability development?

• Is frailty a consequence of comorbidity, or is it causal?
Diabetes, multiple chronic conditions, and health outcomes

Baseline Covariates:
- Sociodemographics:
  - Age
  - Cohort
  - Sex
  - Ethnicity
  - Education
  - Income, assets
  - Insurance
  - Social Support

Risk Factors:
- Smoking
- Physical activity
- Obesity
- HbA1c
- TC/HDL
- Diseases
- Geriatric conditions
- Impairments

Time Varying Covariates:
- CVD Risk Factors
- CVD
- Comorbidities
- Geriatric conditions
- Changes in weight activity level and smoking
- Changes in insurance, social support

Diabetes management

The curved black lines represent possible trajectories of disability. The Y axis is worsening outcome. The trajectories are influenced by baseline and time varying covariates.
ADL/IADL with time by diabetes and hypertension (HRS, ages 51 and up)
Competing risks in older adults with diabetes: falls and strokes  (Min,L, preliminary data)
Research Questions: Aging

• People with multimorbidity at higher risk of getting 2 or more new diseases than those with no disease (van den Akker 1998)

• The Longevity Dividend; slow aging and slow the development of many chronic diseases. (Goldman, D et al. Health Affairs 32, 2013)
Research Collaborators and Support

**University of Michigan**
- Chris Cigolle
- Tanya Gure
- Lillian Min
- Pearl Lee
- Jinkyung Ha
- Jeffrey Halter
- Jersey Liang
- Ken Langa
- Mary Beth Ofstedal
- John Piette
- Michele Heisler
- Eve Kerr
- Mary Rogers
- Kathy Ward
- David Weir

**Johns Hopkins**
- Cynthia Boyd
- Erin Giovinetti
- Jennifer Wolfe
- Jeremy Walston
- Xian Li Xue
- Richard Semba

**NQF**
- Karen Adams
- Aisha Pittman

**NYULMC**
- Ben Han
- Judy Zhong
- Rosie Ferris
- John Dodson
- Corita Grudzen
Research Support

- National Institute on Aging (K08, ROI)
- UM Claude D. Pepper Older American’s Independence Center (NIA) (PESC)
- MICHR (Translational research pilot)
- VA Rehabilitation Research and Development Merit Awards
- Ann Arbor VA GRECC
- AHRQ Complex Patient Grant Program R21 and R24 (ARRA)
- John A. Hartford Foundation
- Diane and Arthur Belfer Research Endowment
- PCORI
Cumulative Incidence Of Mild Impairment And Dementia at Two-years and Four-years

* p < .05, † p < .01
Cumulative Incidence Of Pre-frailty And Frailty At Two-years

* p < .05