



Hosted by BC Transplant and the BC Renal Agency

2015

Mara McAdams-DeMarco, PhD

Assistant Professor

Departments of Epidemiology and Surgery

# Frailty: A novel concept in ESRD risk prediction

# Disclosure

- The research on frailty at JHU was supported by:
  - Clinical Scientist Development Award from the Doris Duke Charitable Foundation
  - NIA: R01AG042504 (PI: Dorry Segev) and K01AG043501 (PI: Mara McAdams-DeMarco)
  - K24DK101828 (PI: Dorry Segev)
  - The American Society of Nephrology (Carl W. Gottschalk Research Scholar Grant)
  - Johns Hopkins University Claude D. Pepper Older Americans Independence Center (P30-AG021334)
- I have no conflict of interest to report.

# Why study frailty?

Who will have better outcomes after KT?	42 Year Old	68 Year Old
---	-------------	-------------

# Why study frailty?

Who will have better outcomes after KT?	42 Year Old Frail	68 Year Old Nonfrail
--	----------------------	-------------------------

# Why study frailty?

Who will have better outcomes after KT?	42 Year Old Frail	68 Year Old Nonfrail
Delayed Graft Function		
2 Week KT Length of Stay		
Early Hospital Readmission		
Mortality		

# Why study frailty?

Who will have better outcomes after KT?	42 Year Old Frail	68 Year Old Nonfrail
Delayed Graft Function	16%	16%
2 Week KT Length of Stay		
Early Hospital Readmission		
Mortality		

# Why study frailty?

Who will have better outcomes after KT?	42 Year Old Frail	68 Year Old Nonfrail
Delayed Graft Function	16%	16%
2 Week KT Length of Stay	32%	21%
Early Hospital Readmission		
Mortality		

# Why study frailty?

Who will have better outcomes after KT?	42 Year Old Frail	68 Year Old Nonfrail
Delayed Graft Function	16%	16%
2 Week KT Length of Stay	32%	21%
Early Hospital Readmission	64%	27%
Mortality		



# Why study frailty?

Who will have better outcomes after KT?	42 Year Old Frail	68 Year Old Nonfrail
Delayed Graft Function	16%	16%
2 Week KT Length of Stay	32%	21%
Early Hospital Readmission	64%	27%
Mortality	9%	4%

# Demystifying frailty

- A measure of physiologic reserve
- Validated, well studied way to quantify the “Foot of The Bed Test”
- Borrow from our geriatrics colleagues
  - Identified frailty in community-dwelling older adults
- “Elderly” is a very different construct for
  - Community-dwelling older adults
  - Adults of all ages with ESRD
- **What is an older adult with ESRD?**
  - 43 year old elderly adult with ESRD

# Frailty at Johns Hopkins

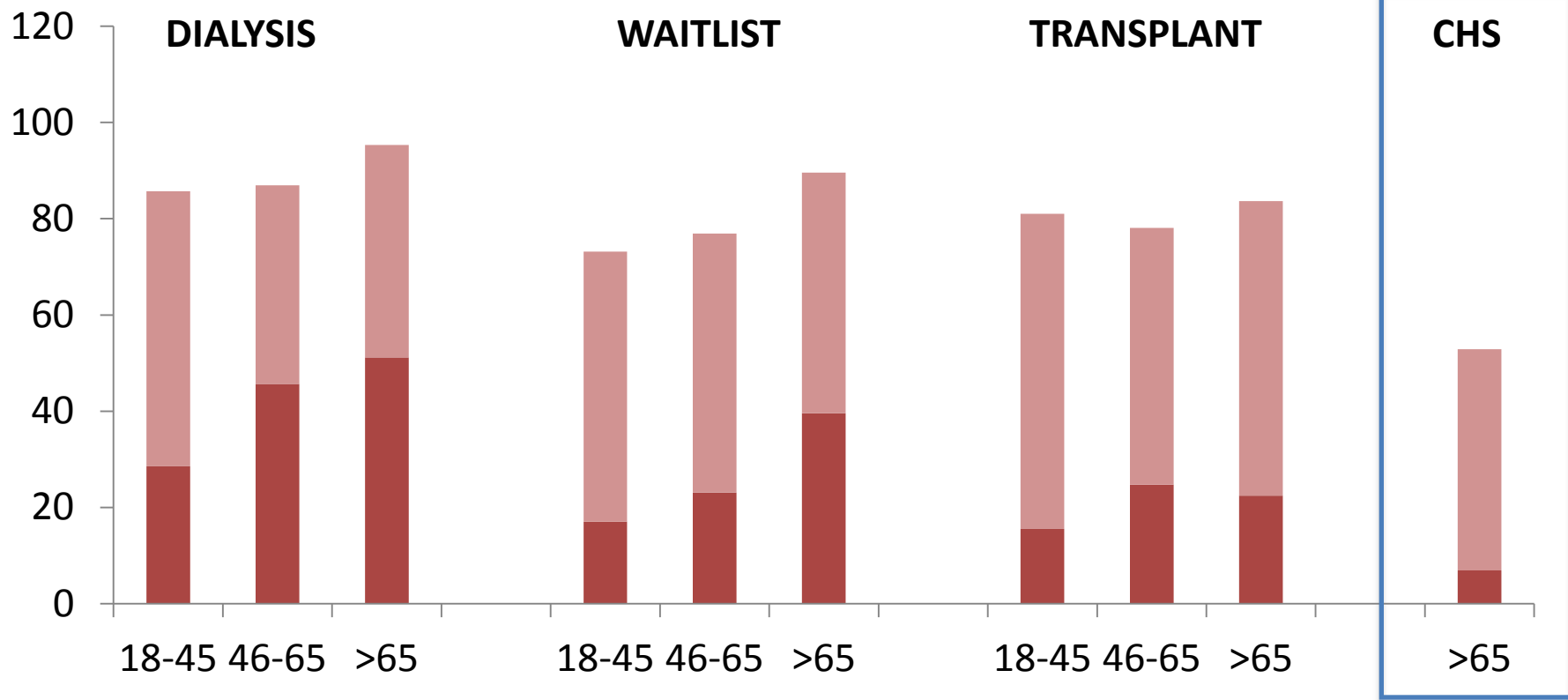
- Frailty was identified and validated at Johns Hopkins by Linda Fried in 2001
- 8 years ago we began studying frailty in patients with ESRD
  - Observational studies of patients undergoing
    - Hemodialysis
    - Waitlist Patients
    - Kidney Transplantation
- Look at longer and longer term outcomes

# Frailty prevalence: By cohort, all ages

	DIALYSIS	WAITLIST	TRANSPLANT	CHS
Non-Frail	9.6%	19.7%	20.1%	46.0%
Intermediately Frail	44.2%	53.5%	58.4%	46.0%
Frail	46.2%	26.8%	21.5%	6.9%

**DOES FRAILTY INCREASE WITH AGE?**

# Frailty prevalence: By cohort, by age

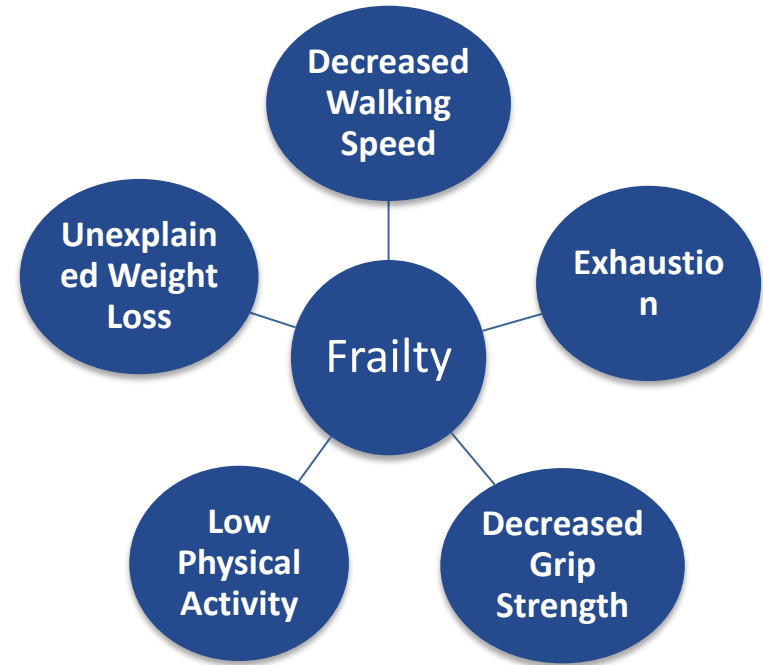


# Outline

- What is frailty?
- Studies of frailty and ESRD
- Studies of frailty in kidney transplant (KT) recipients
- How can frailty improve clinical care for transplant recipients?

# What is the Fried frailty phenotype?

- Phenotype of physiologic reserve and resistance to stressors
- Multi-component syndrome
  - Physical and self-reported components
- Identified in the Cardiovascular Health Study (CHS)
  - Cohort of 5,317 community-dwelling older adults
- 7% of the older population was frail and 7% developed incident frailty over the first 3 years
- Frail older adults were 2.24-fold more likely to die than their nonfrail counterparts





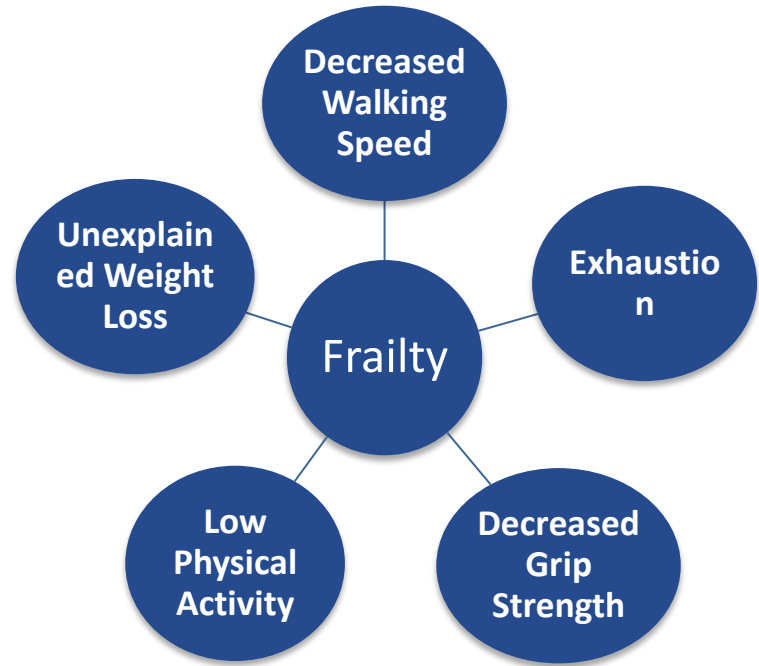
# Frailty

	Component	Definition/Measurement
1	Shrinking	Unintentional weight loss > 10 lbs in the past year
2	Weakness	Determined by grip strength test, adjusted for gender and BMI
3	Exhaustion	Measured using 2 questions from the modified 10-item Center for Epidemiological Studies- Depression scale
4	Low Physical Activity	Version of the Minnesota Leisure Time Activities Questionnaire will assess physical activity in 2 weeks prior to study
5	Slowed Walking Speed	Averaging the results of 3 trials of walking 15 feet at a normal pace

Fried et al, J Gerontol, 2001

# What is the Fried frailty phenotype?

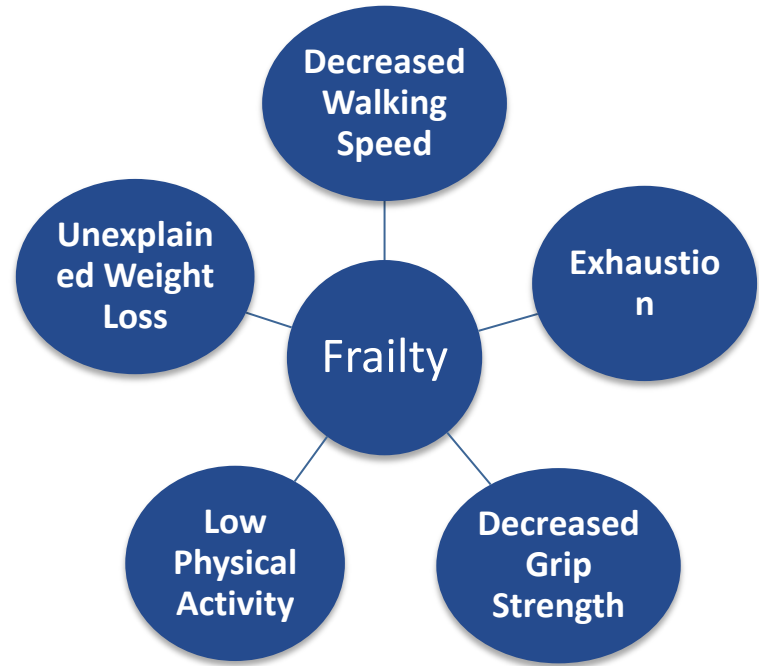
- Definition in older adults:
  - Frail  $\geq 3$  components
  - Intermediately frail = 1 or 2 components
  - Non-frail = 0 components



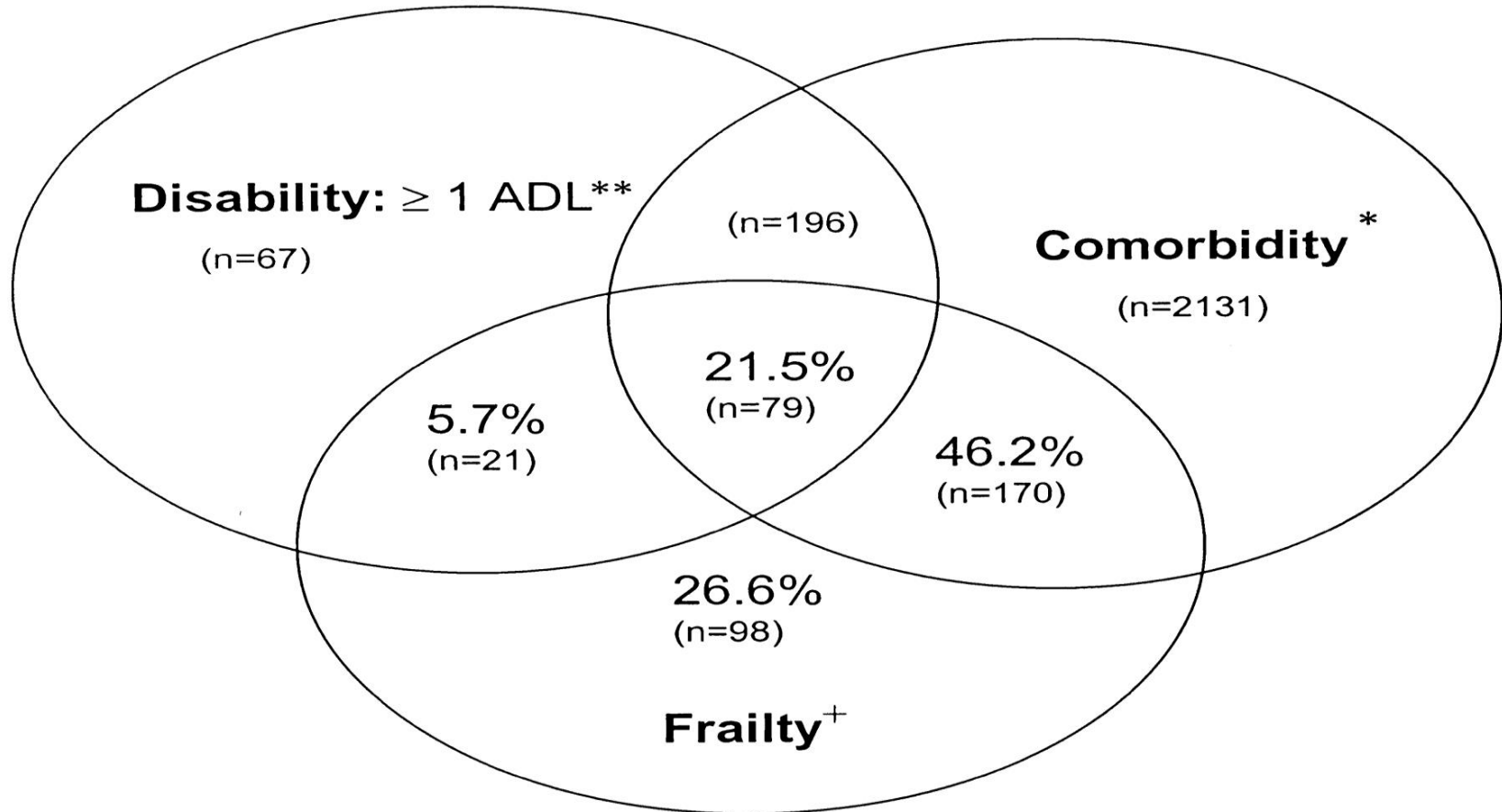
**WHAT ARE THE POTENTIAL LIMITATIONS  
TO STUDYING FRAILITY IN ESRD?**

# What is the Fried frailty phenotype?

- Definition in older adults:
  - Frail  $\geq 3$  components
  - Intermediately frail = 1 or 2 components
  - Non-frail = 0 components
- Definition has been refined for other populations, namely KT recipients
  - Too few KT recipients with 0 components



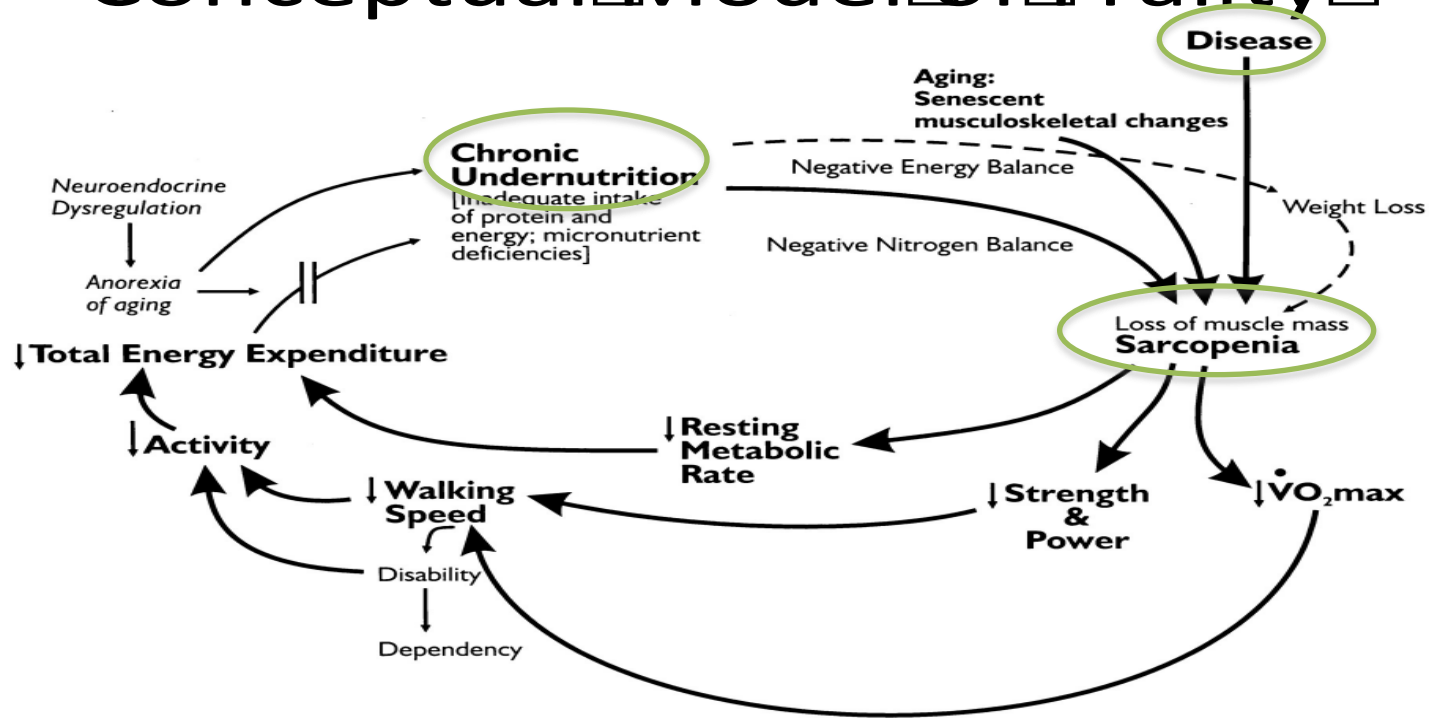
# Frailty is not disability or comorbidity



**DOES THE BIOLOGICAL BASIS OF FRAILTY  
PERTAIN TO ESRD?**

# Biological basis for Fried frailty phenotype

## Conceptual Model of Frailty



# Frailty is associated with poor outcomes in surgery patients

- In older patients undergoing general surgery, frailty is independently associated with:
  - Postoperative complications <sup>1,2</sup>
  - Length of stay <sup>1</sup>
  - Discharge to a skilled or assisted-living facility <sup>2,3</sup>
  - Mortality <sup>1</sup>
- In general surgery patients of all ages, intermediately frail and frail patients have twice the odds of 30-day complications <sup>4</sup>

<sup>1</sup> Robinson *Am J Surg*, 2013; <sup>2</sup> Makary *Am Col Surg*, 2010; <sup>3</sup> Robinson *Am Col Surg*, 2011; <sup>4</sup> Revenig *Am Col Surg*, 2013.



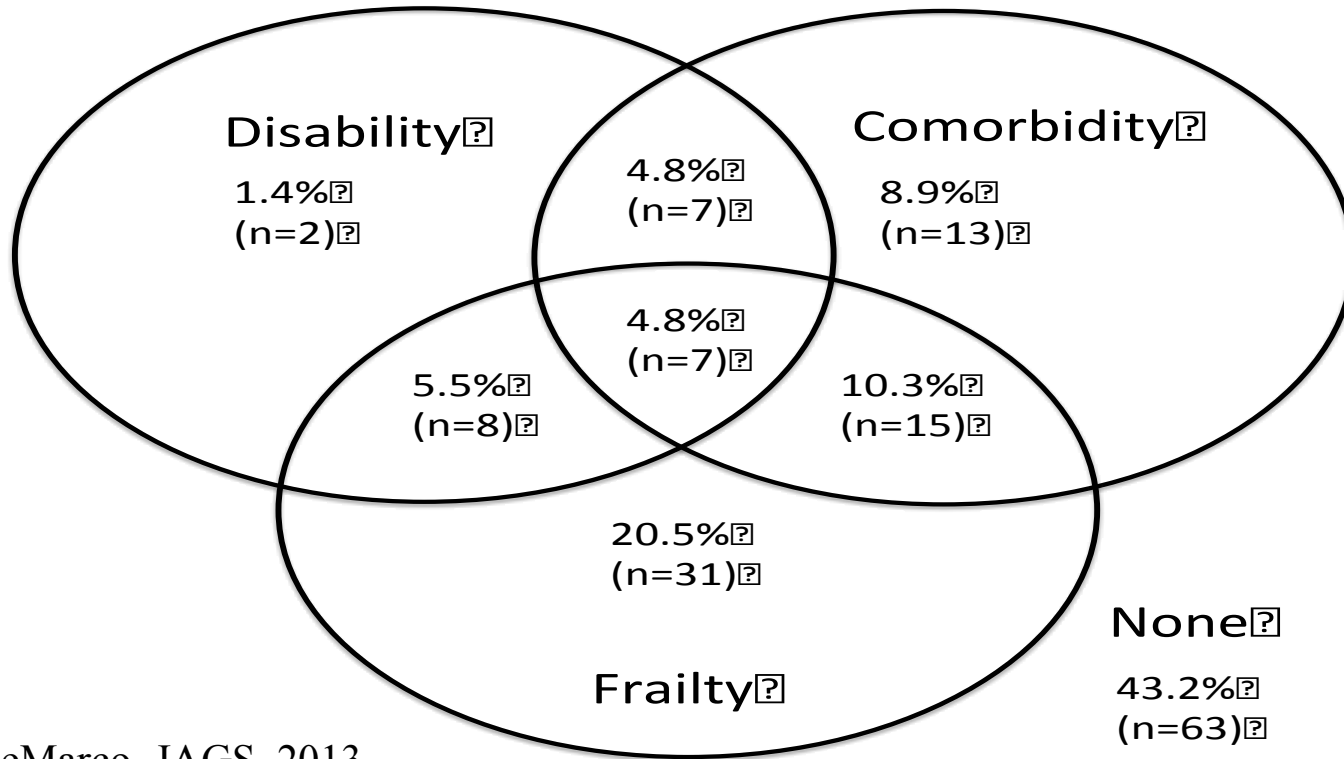
# Outline

- What is frailty?
- Studies of frailty and ESRD
- Studies of frailty in kidney transplant (KT) recipients
- How can frailty improve clinical care for transplant recipients?

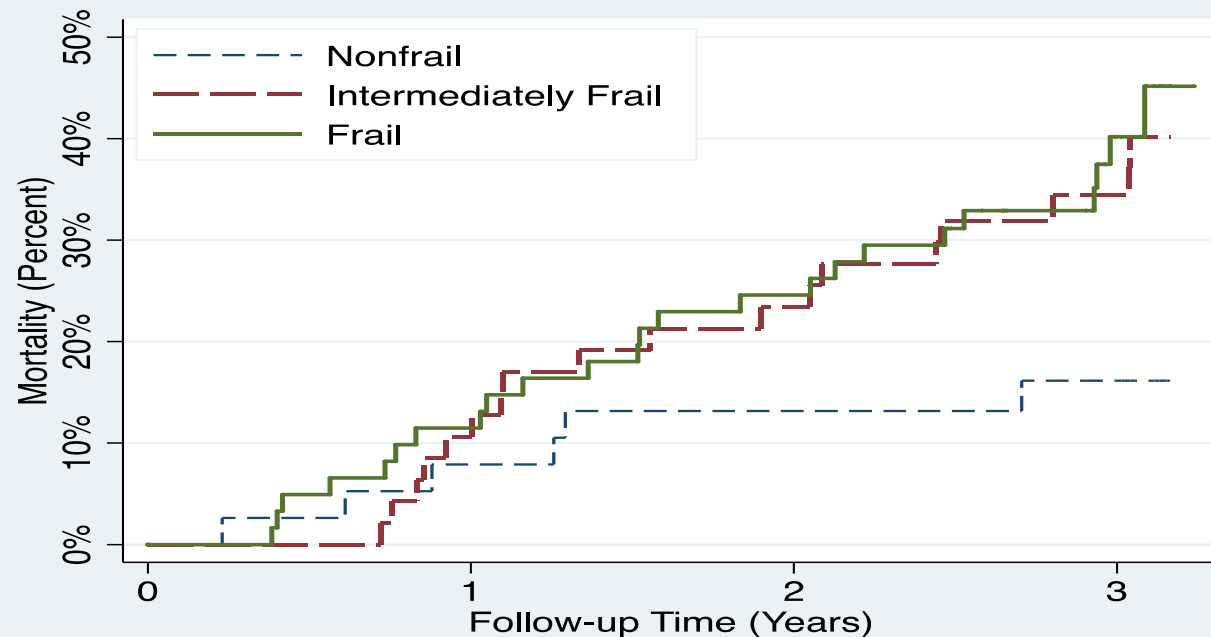
# Frailty prevalence is high in ESRD

- There is a high prevalence of frailty regardless of the ESRD treatment modality:
  - 42% of Prevalent Hemodialysis Patients
    - McAdams-DeMarco, JAGS, 2013
  - 34% of Incident Hemodialysis Patients
    - McAdams-DeMarco, CJASN, under revision
  - 19% of Kidney Transplant (KT) recipients
    - McAdams-DeMarco, AJT, 2013 and 2014
- Frailty is emerging as an important risk factor in adults of all ages with ESRD

# Frailty is not comorbidity, and disability in adults undergoing HD



# Frail adults undergoing HD are at increased risk of mortality



HR: 2.60 (95% CI: 1.04, 6.49)

# Frail adults undergoing HD are at increased risk of poor outcomes

- Frailty was independently associated with a
  - 2.6-fold higher risk of mortality<sup>1</sup>
  - 1.4-fold higher number of hospitalizations<sup>1</sup>
  - 1.3-fold higher risk of first hospitalization<sup>2</sup>
  - 3.1-fold higher number of falls<sup>2</sup>

1 McAdams-DeMarco, JAGS, 2013

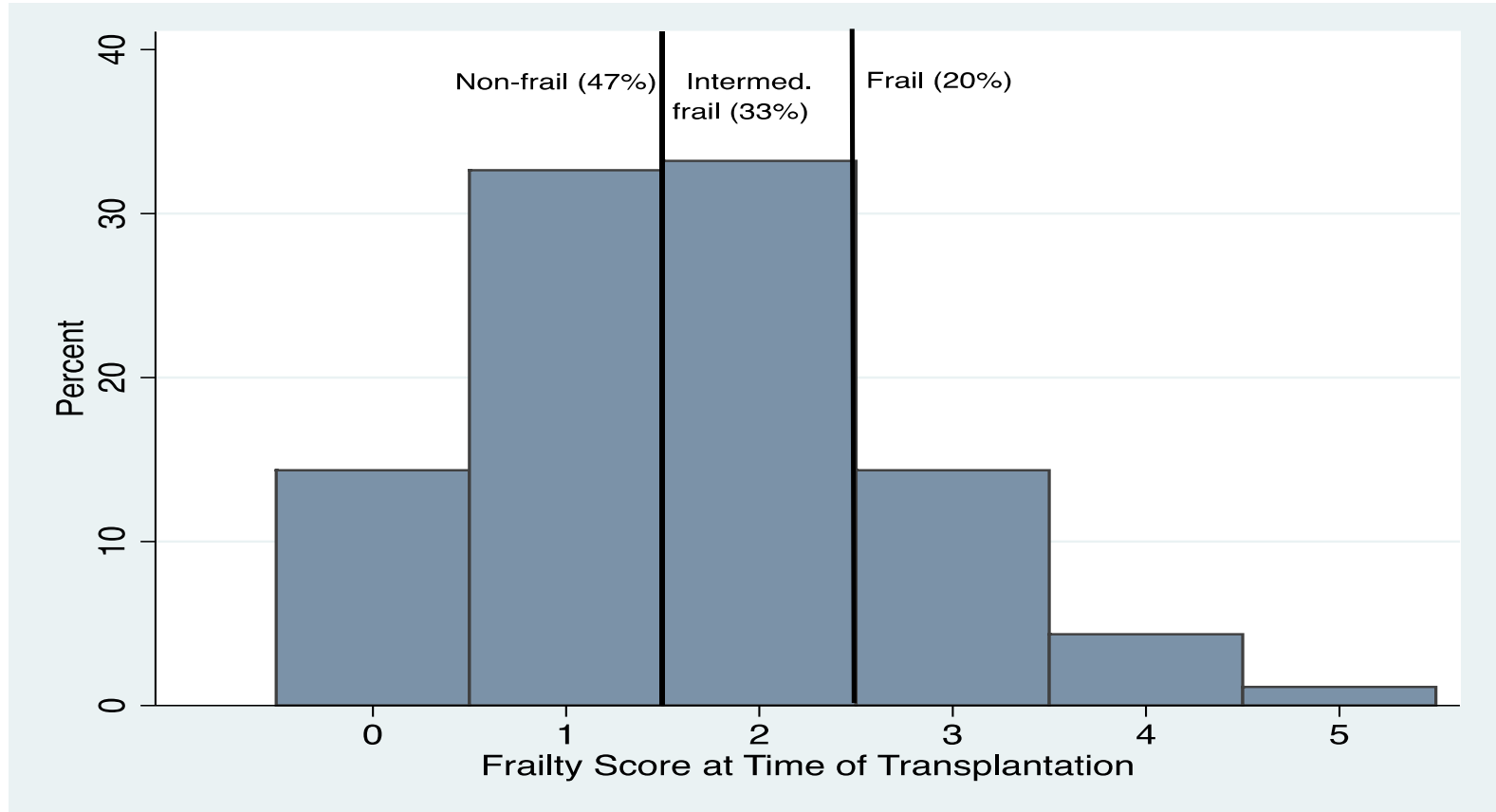
2 Bao, Arch of Internal Med, 2012

3 McAdams-DeMarco, BMC Nephrology, 2013

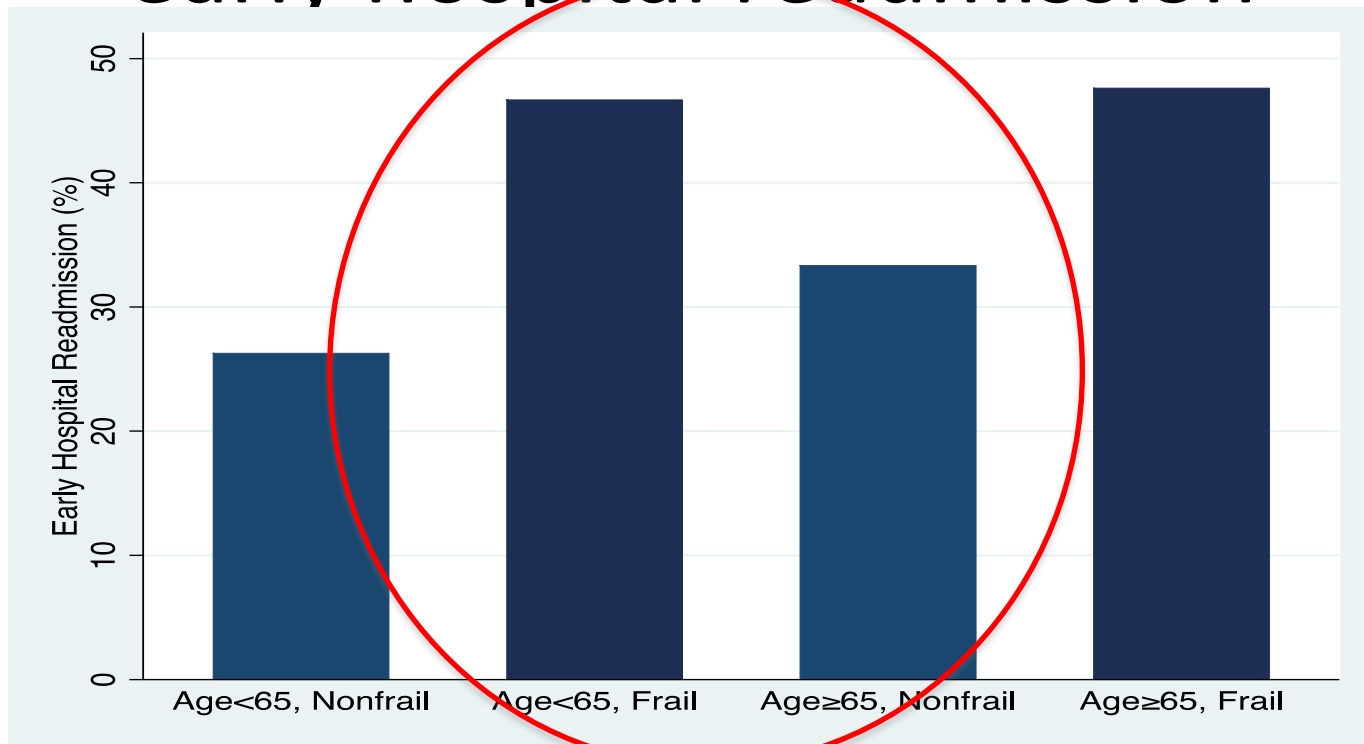
# Outline

- What is frailty?
- Studies of frailty and ESRD
- Studies of frailty in kidney transplant (KT) recipients
- How can frailty improve clinical care for transplant recipients?

# Frailty prevalence is high at KT



# Frail KT recipients are at increased risk of early hospital readmission



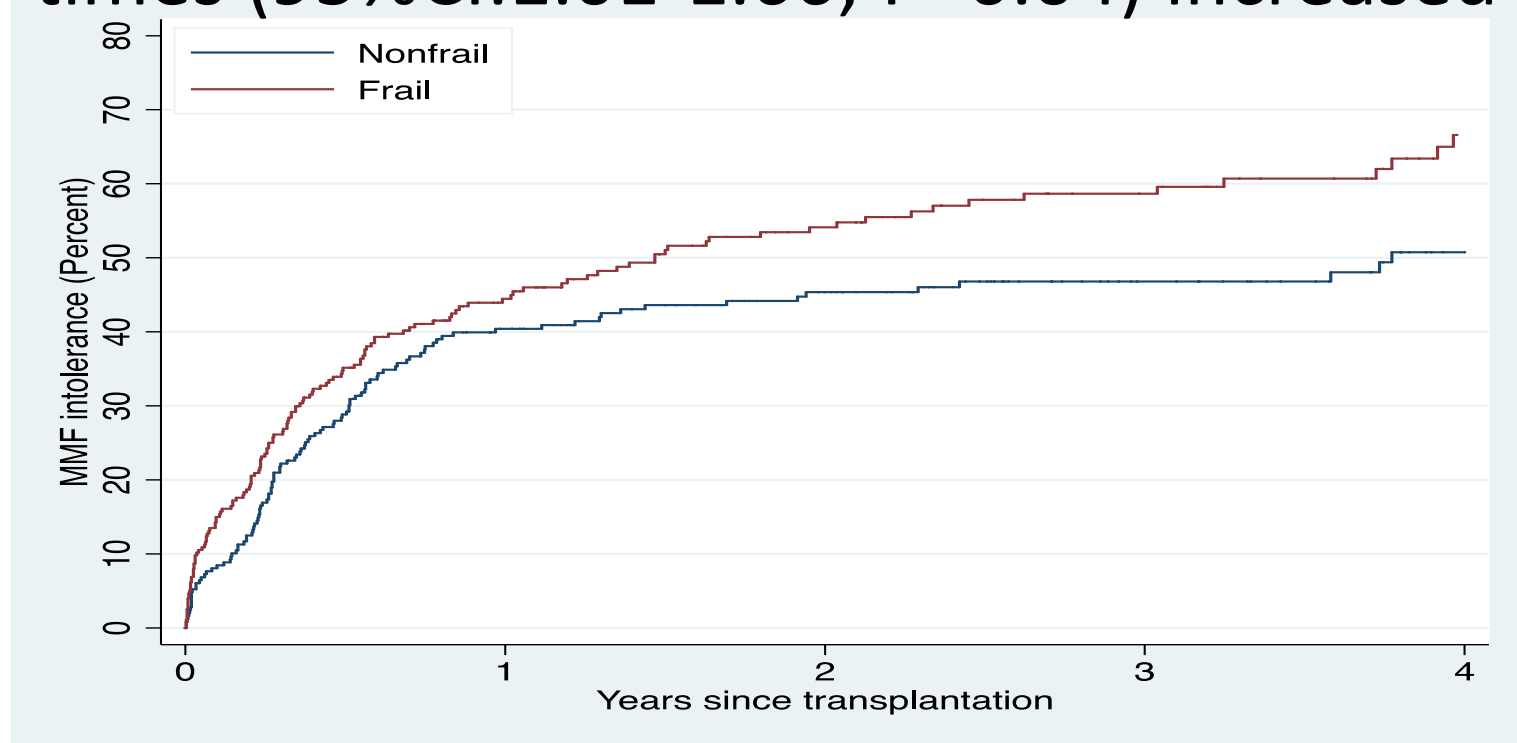


# Frail KT recipients are at increased risk of poor outcomes

- KT recipients who are frail at admission for KT are at:
  - 1.9-times (95% CI: 1.13-3.36) increased risk of DGF
    - Garonzik-Wang/Segev, JAMA Surgery, 2012
  - 2.2-fold (95% CI: 1.00-4.80) increased risk of mortality
    - McAdams-DeMarco/Segev, AJT, 2014
  - 1.6-fold (95% CI: 1.15-2.43) increased risk of >2 week KT length of stay
    - McAdams-DeMarco/Segev. In Preperation

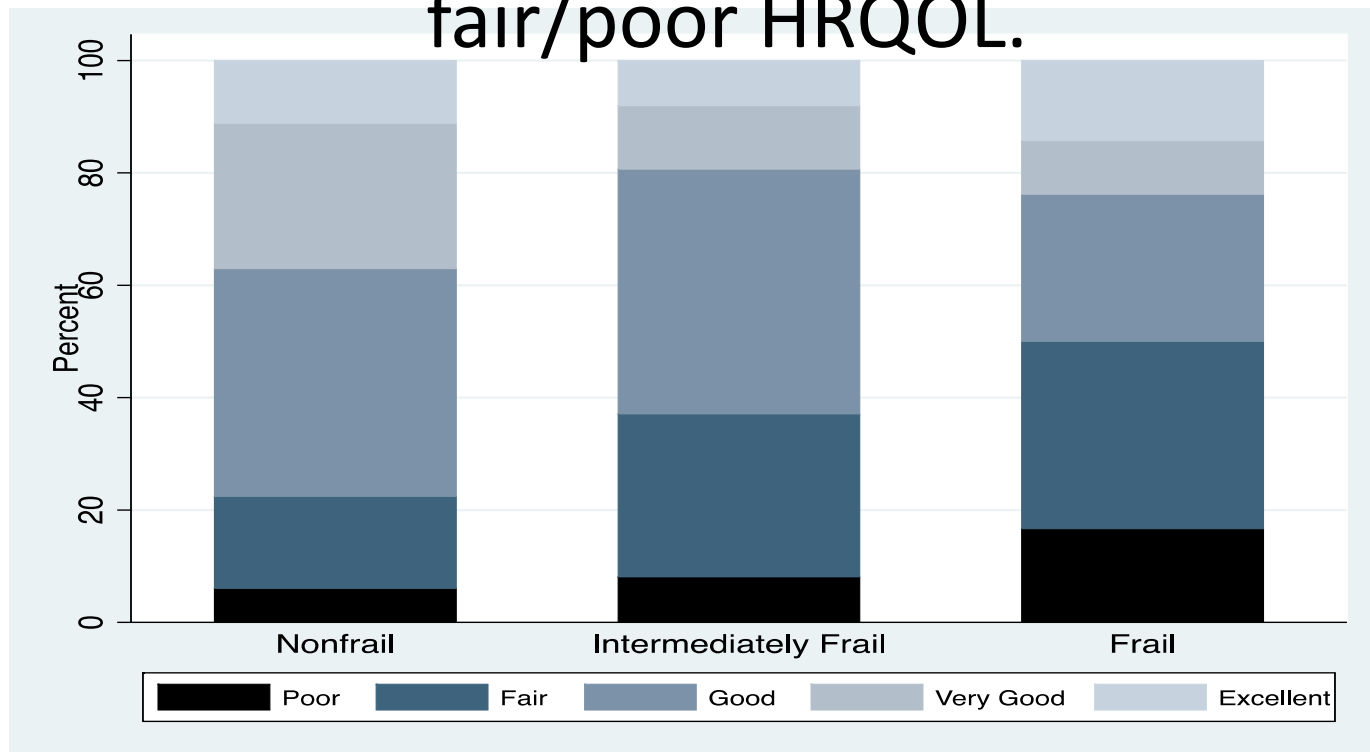
# Frail KT recipients are more likely to require an MMF dose reduction

1.29-times (95%CI:1.01-1.66; P=0.04) increased risk.

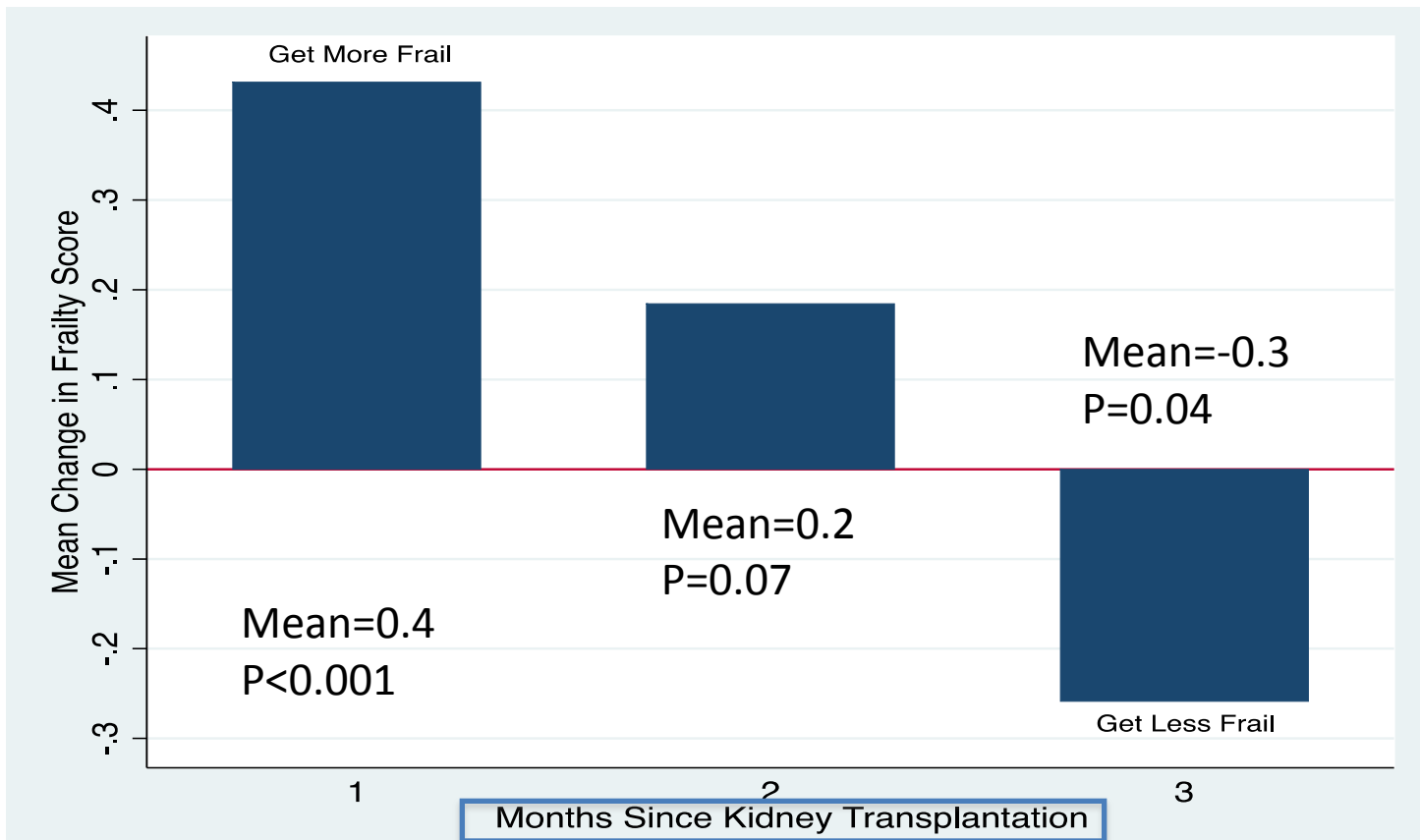


# Frail KT recipients report worse HRQOL

2.97-fold (95% CI: 1.48-5.98) higher odds of fair/poor HRQOL.



# Frailty improves after KT



# Outline

- What is frailty?
- Studies of frailty and ESRD
- Studies of frailty in kidney transplant (KT) recipients
- How can frailty improve clinical care for transplant recipients?

# Frailty in the clinical care of transplant recipients

- In patients with ESRD frailty:
  - measures the ability of a patient to respond to a stressor
  - captures a unique domain of risk
- Frailty can be used for clinical decision-making
  - Better patient selection
  - Interventions prior to KT

**WHERE DO YOU SEE FRAILTY  
FITTING IN PATIENT SELECTION?**

# Frailty and recipient selection

- Incorporating frailty into the transplant evaluation would improve recipient selection
- May help transplant surgeons:
  - Accept marginal candidates who are not frail
  - Decide against transplanting frail candidates
  - Identify older adults who would do well with transplant despite their age



**HOW CAN FRAILITY BE USED TO  
IMPROVE PATIENT OUTCOMES?**

# Pre-habilitation of frail candidates

- Pre-habilitation can improve a patients surgical outcomes
- Transplantation is beneficial in many patients
  - We're trying to work out which frail patients will benefit vs not benefit from KT
- KT is one of the only situations in this entire field of frailty research where an intervention has been shown to reverse this physiologic reserve
- We are launching a study on pre-habilitation in patients undergoing hemodialysis now

# Epidemiology Research Group in Organ Transplantation

Dorry Segev, MD PhD, Director

## Medicine/Surgery

**Morgan Grams, MD PhD**  
Nephrology Faculty  
**Christine Durand, MD**  
Infectious Diseases Faculty  
**Bonnie Lonze, MD PhD**  
Surgery Faculty  
**Rizwan Ahmed, MD**  
Surgery Resident  
**Rebecca Craig-Schapiro, MD**  
Surgery Resident  
**Sandra DiBrito, MD**  
Surgery Resident  
**Jackie Garonzik-Wang, MD PhD**  
Surgery Resident  
**Elizabeth King, MD**  
Surgery Resident  
**Babak Orandi, MD PhD MSc**  
Surgery Resident  
**Kyle Van Arendonk, MD PhD**  
Surgery Resident  
**Israel Olorundare, MBBS MPH**  
PostDoc  
**Jennifer Alejo**  
Medical Student  
**Natasha Gupta**  
Medical Student  
**Jessica Moore**  
Medical Student  
**Ashton Shaffer**  
Medical Student  
**Megan Salter, PhD**  
Medical Student  
**Lauren Kucirka, ScM**  
MD/PhD Student  
**Maria Lourdes Perez, DVM**  
Laboratory Science

## Core Research Group

### Epidemiology

**Allan Massie, PhD**  
Epidemiology  
**Mara McAdams-DeMarco, PhD**  
Epidemiology  
**Tanjala Purnell, PhD**  
Epidemiology  
**Abi Muzaale, MD MHS**  
Epidemiology Postdoc  
**Xun Luo, MD MPH**  
Epidemiology Staff  
**Sunjae Bae, KMD MPH**  
Epidemiology Staff  
**Anna Poon, MHS**  
Epidemiology Staff  
**Hao Ying, ScM**  
Epidemiology Staff

### Economics

**Lauren Nicholas, PhD**

### Graduate Students

**Mohammed Alfawzan**  
Epidemiology MPH Student  
**Mary Grace Bowring**  
Epidemiology MPH Student  
**Ayla Cash**  
Epidemiology MPH Student  
**Lara Fahmy**  
Epidemiology MSc Student

## Computational Science

**Sommer Gentry, PhD**  
Computer Science  
**Eric Chow, MHS**  
Decision Process Models  
**Corey Wickliffe**  
Geographic Information Systems

## Research Assistants

Full-Time:  
**Saad Anjum**  
**Ryan Brown**  
**Richmond Castillo**  
**Cassandra Delp**  
**Kyle Fisk**  
**Erika Jones**  
**Jonathan Konel**  
**Komal Kumar**  
**Claudia Landazabal**  
**Kathryn Marks**  
**James Tonascia**  
**Nicole Zonnenberg**

Part-Time:  
**Nathalia Aldana**  
**Maurice Dunn**  
**Nathaniel Green**  
**Billy Kim**  
**Arnaldo Mercado-Perez**  
**Maisa Nimer**  
**Ana Quintanal**  
**Katrina Rios**  
**Sumukh Shetty**  
**Joanna Wexler**

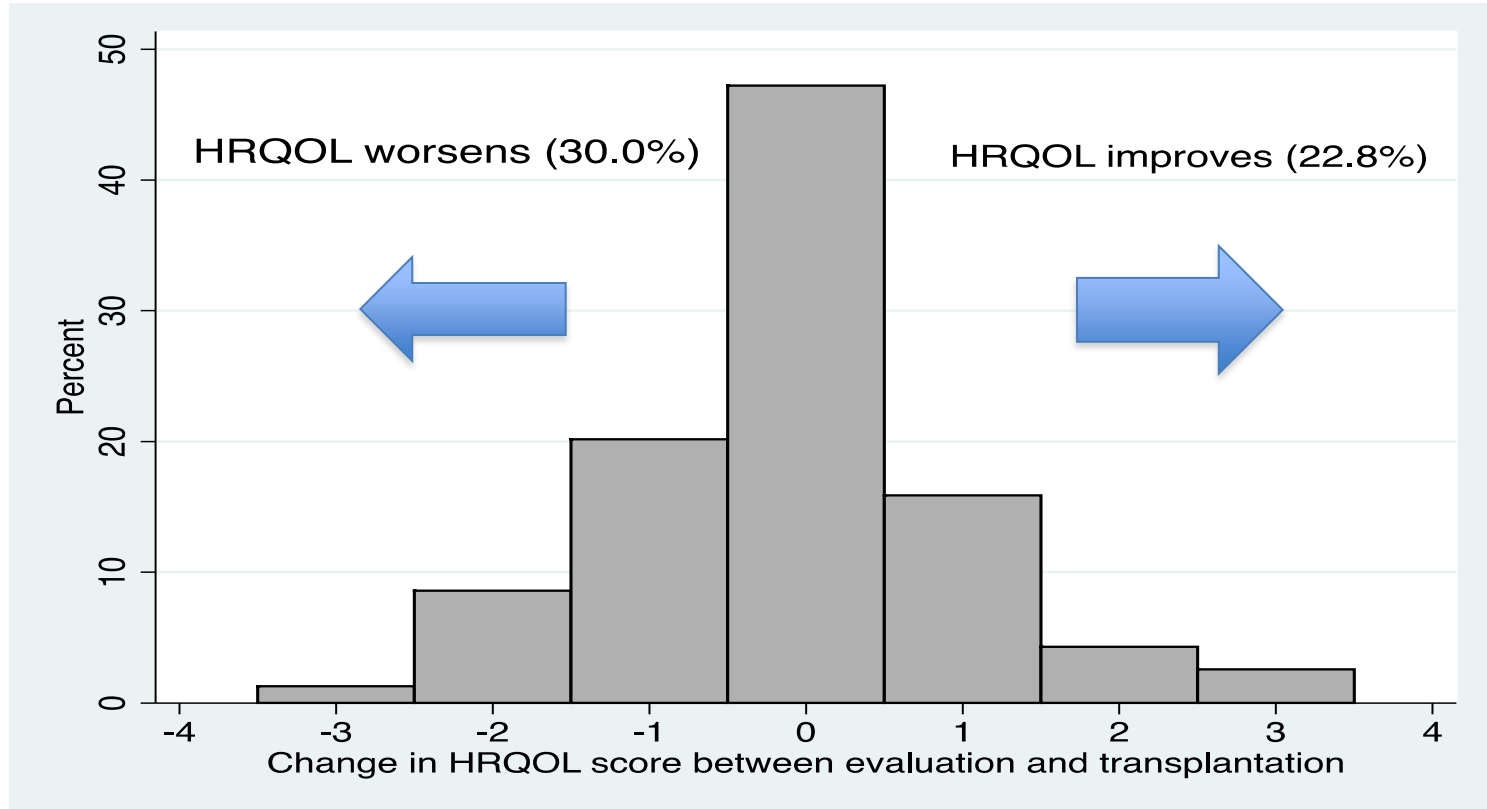
## Affiliated

**Daniel Scharfstein, ScD**  
Biostatistics  
**Ravi Vardhan, PhD**  
Biostatistics  
**Lucy Meoni, ScM**  
Biostatistics  
**Josef Coresh, MD PhD**  
Epidemiology  
**Andrew Cameron, MD PhD**  
Surgery  
**Niraj Desai MD**  
Surgery  
**Robert Montgomery, MD DPhil**  
Surgery  
**Nabil Dagher, MD**  
Surgery  
**Elliott Haut, MD PhD**  
Surgery  
**Kim Steele, MD PhD**  
Surgery  
**Diane Schwartz, MD**  
Surgery  
**Aliaksei Pustavoitau, MD**  
Anesthesiology

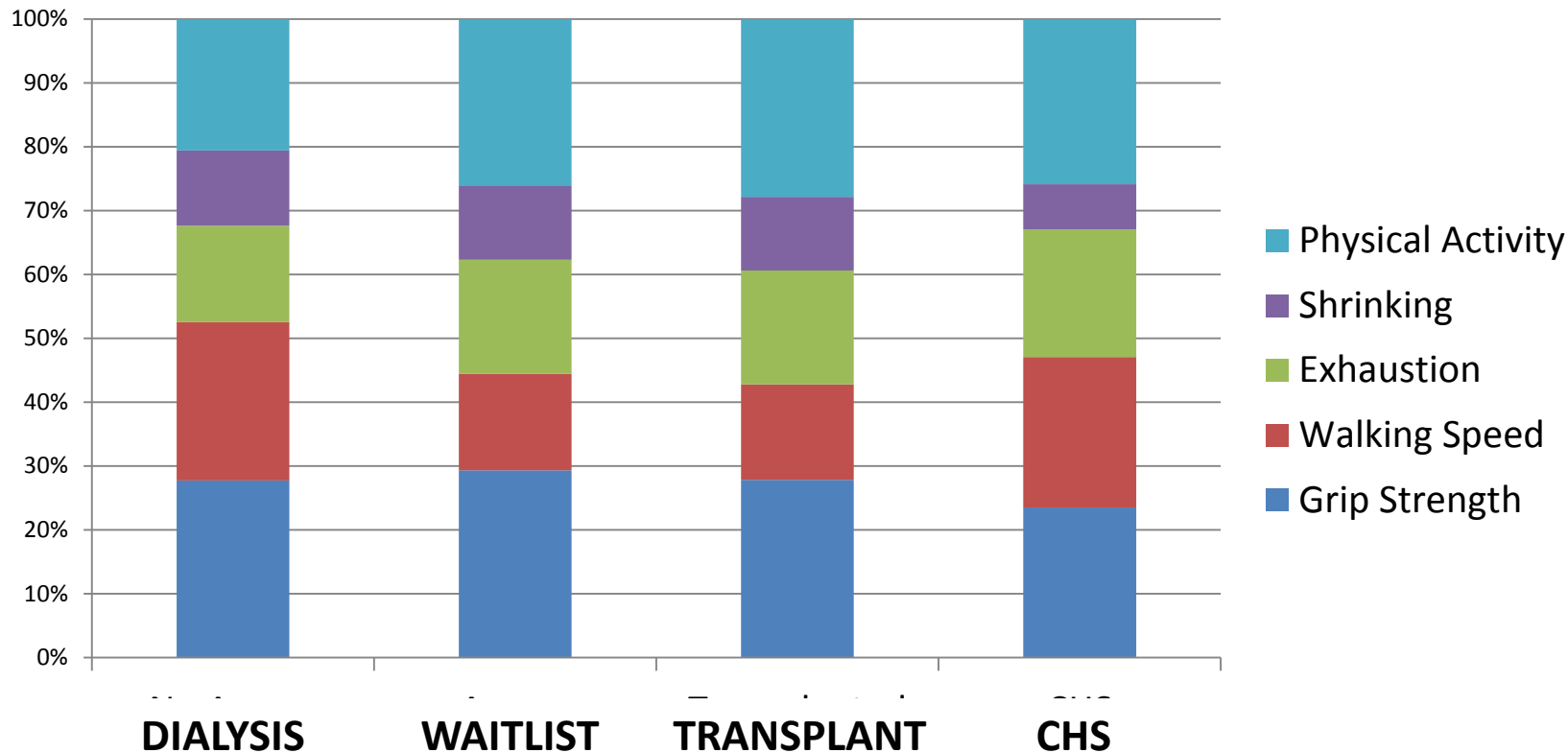
<b>Shrinking</b>	<p>Determined by asking patients their current weight and their weight one year ago. Alternatively, current weight and their weight one year ago could be obtained from a patients' medical records. Patients who report unintentionally losing 10 pounds or more in the last year are considered frail by the shrinking component.</p>
<b>Exhaustion</b>	<p>Determined by asking 2 questions from the CES-D (26): "How often in the last week did you feel this way?"</p> <p>(a) I felt that everything I did was an effort</p> <p>(b) I could not get going</p> <p>Patients who reported (a) or (b) for 3 or more days in the past week are considered frail by the exhaustion component.</p>
<b>Physical Activity</b>	<p>The short version of the Minnesota Leisure Time Activity (27) questionnaire is used to assess frequency of physical activities. Physical activity is converted to Kcals/week expended using a standardized algorithm (number of days physical activity took place in the past 2 weeks x duration of activity in minutes x kcals burned per minute). Men who expended &lt;383 Kcals/week and women who expended &lt;270 Kcals/ week are considered frail for the low physical activity component.</p>
<b>Walking speed</b>	<p>Patients are timed while walking 15 ft. Stratified by gender and height, men who are <math>\leq 173</math> cm and required <math>\geq 7</math> seconds, or were <math>&gt;173</math> cm and required <math>\geq 6</math> seconds are considered frail. Women who are <math>\leq 159</math> cm and required <math>\geq 7</math> seconds, or who are <math>&gt;159</math> cm and required <math>\geq 6</math> seconds are considered frail for the decreased walking speed component. Patients who are unable to complete this assessment due to physical limitations are considered frail for the decreased walking speed component.</p>

<b>Grip Strength</b>	Grip strength is measured using a Jamar hand-held dynamometer. The cutoffs are gender and BMI specific:	
	<b>Men</b>	<b>Cutoff for Grip Strength (kg) criterion for frailty</b>
	BMI $\leq 24$	$\leq 29$
	BMI 24.1 - 28	$\leq 30$
	BMI $> 28$	$\leq 32$
	<b>Women</b>	
	BMI $\leq 23$	$\leq 17$
	BMI 23.1 - 26	$\leq 17.3$
	BMI 26.1-29	$\leq 18$
	BMI $> 29$	$\leq 21$
	Patients below these cutoffs for grip strength are considered frail for the low grip strength component. Patients who are unable to complete this assessment due to physical limitations are considered frail for the low grip strength component.	

# Change in HRQOL



# Frailty Components, Normalized



# Fried frailty phenotype represents inflammatory state

- In older adults, frailty is an inflammatory state of increased vulnerability to stressors.
- Immune system dysregulation may play a leading role, resulting in heightened inflammation and alteration in innate and adaptive immune systems (Yao, 2011).
- Frailty is associated with dysregulation of multiple physiologic systems, including a generalized inflammatory state (Walston, 1999).