Analyzing patient-reported outcomes data: Symptoms and their Outcomes

Heather Allore, PhD
Professor Yale School of Medicine
School of Public Health
Department of Biostatistics

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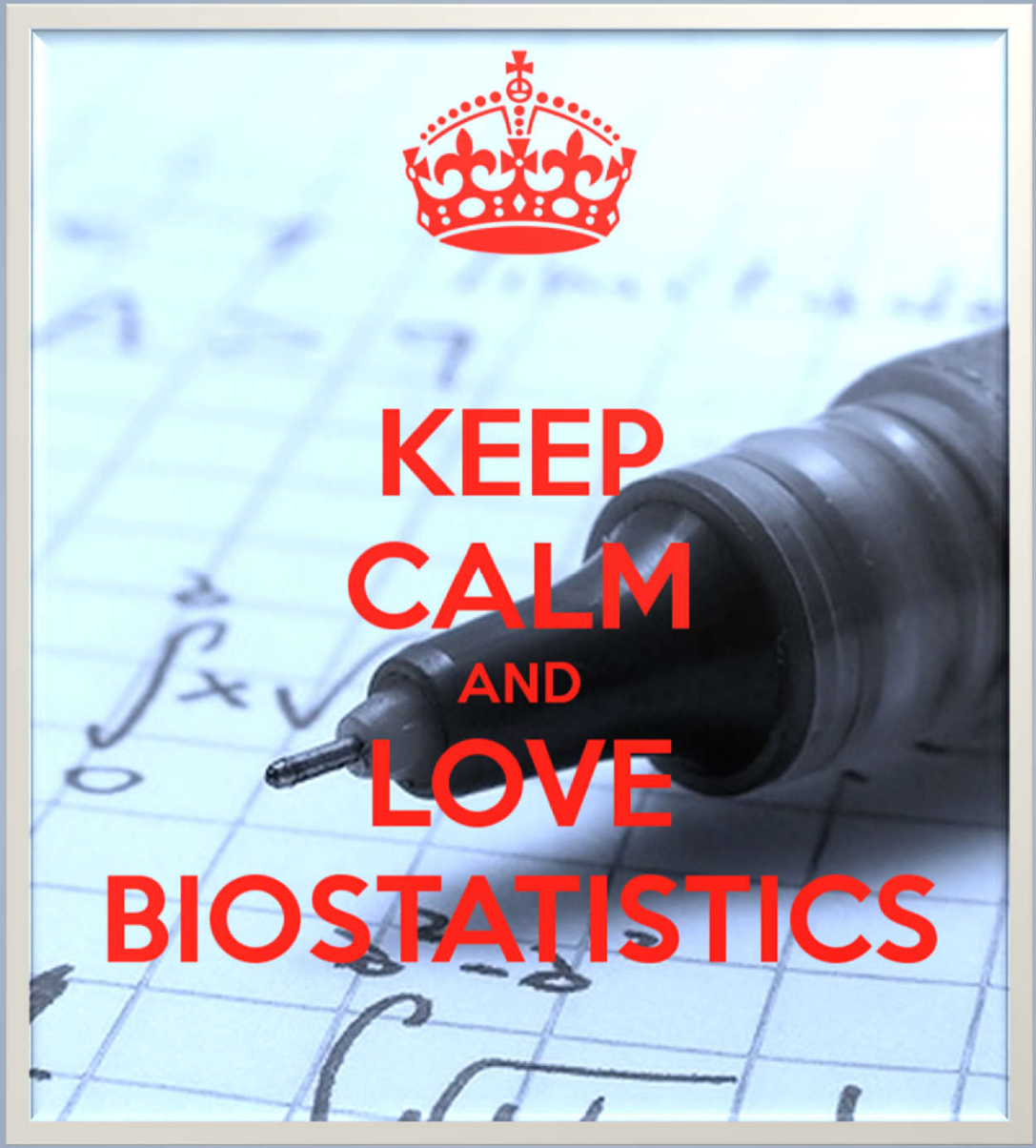
Disclosure

Dr. Allore has no conflicts of interest, lodging to present was received from PROM conference.


KEEP
CALM
AND
LOVE
BIOSTATISTICS

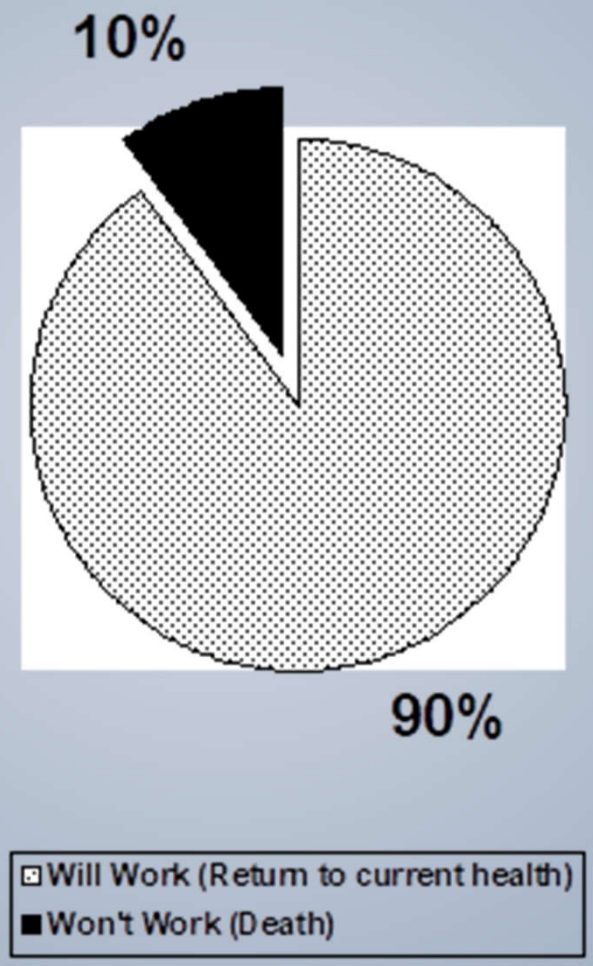
Understanding the Treatment Preferences of Seriously Ill Patients

- A preference measure combining different treatment burdens, potential treatment outcomes, and likelihoods of these outcomes was administered to 226 persons age ≥60 years with a limited life-expectancy secondary to cancer, congestive heart failure, or chronic obstructive pulmonary disease.
- Asked if they would want to receive a given treatment when the outcome was known with certainty
- then with different likelihoods of the outcome.
- The outcome without treatment was specified as dying of the underlying disease.

Fried TR, et al. 2002; 346:1061-1066

The NEW ENGLAND JOURNAL of MEDICINE

Pie chart used to illustrate the likelihood of a desirable versus an undesirable outcome.



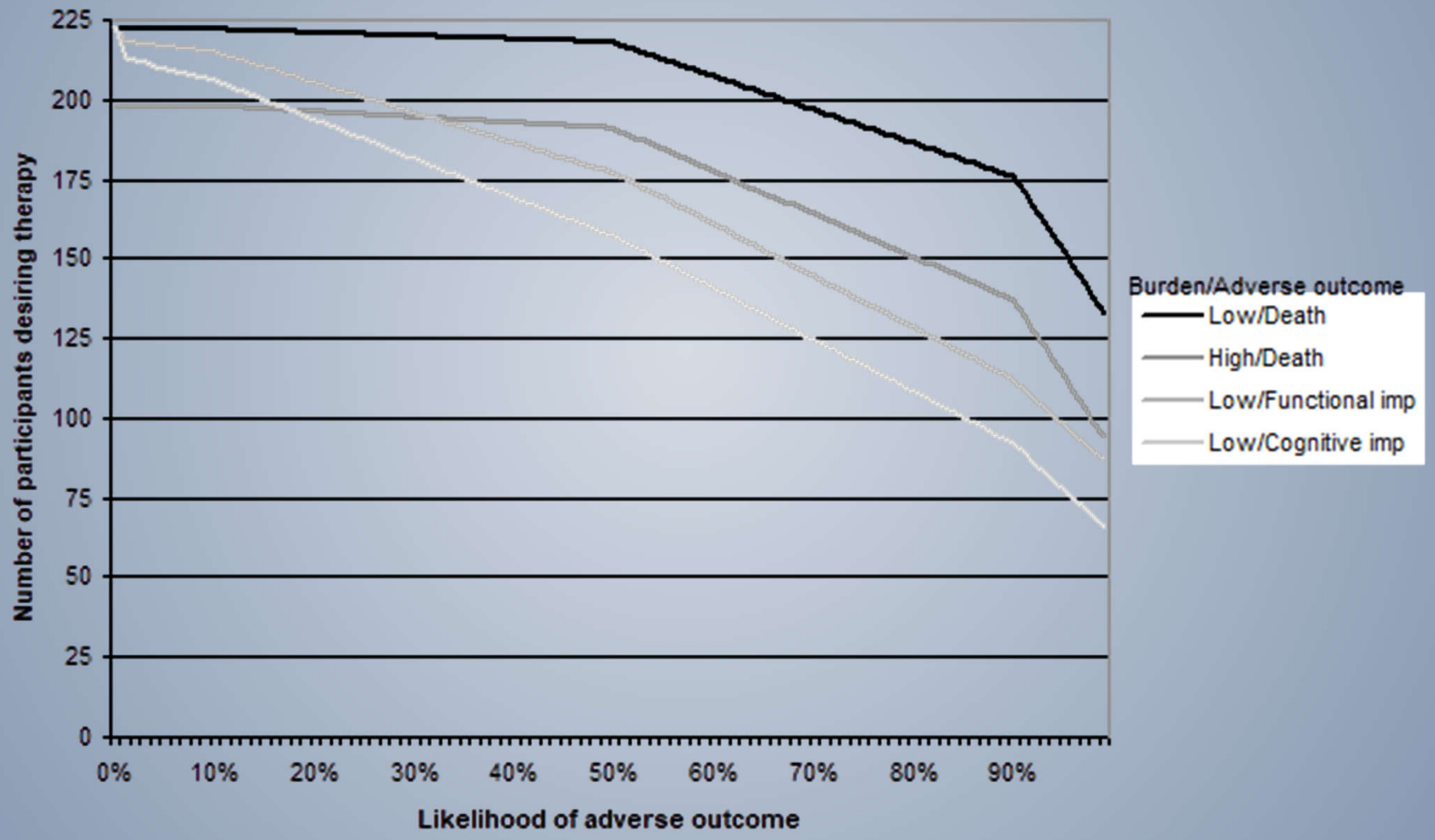
Fried TR, et al. N Engl J Med 2002; 346:1061-1066

Treatment Preferences of Seriously Ill Patients

Treatment Burden Outcome	Low Current Health	High Current Health	Low Functional Impairment	Low Cognitive Impairment
Diagnosis	Wants Tx (%) P=0.39	Wants Tx (%) P=0.15	Wants Tx (%) P=0.6	Wants Tx (%) P=0.51
Cancer (n=79)	100.0	83.5	27.9	11.4
CHF (n=66)	98.5	93.9	21.2	7.6
COPD (n=81)	97.5	86.4	25.9	13.6

Fried TR, et al. N Engl J Med 2002; 346:1061-1066

Figure 3: Preferences according to treatment burden and likelihood of adverse treatment outcome



Prospective Study of Health Status Preferences and Changes in Preferences Over Time in Older Adults

- In-home interviews of 226 older community-dwelling persons with advanced cancer, congestive heart failure, or chronic obstructive pulmonary disease at least every 4 months for up to 2 years.
- Patients were asked to rate whether treatment for their illness would be acceptable if it resulted in 1 of 4 health states.
- To determine factors associated with ratings, we used generalized linear mixed-effects models by implementing repeated measures logistic regression with inclusion of a patient-level random effect.

Fried at al, Arch Intern Med. 2006;166(8):890-895.

Statistical Methods

- We chose the mixed-effects model over a competing approach, for example, a marginal model approach using generalized estimating equations, because we wanted to account for irregular interview times and to draw inferences at the subject-specific level.
- We developed 4 multivariable models, using a forward selection approach, with no correction for multiple comparisons.
- For each model, the dependent variable was the rating of a given health state as acceptable or unacceptable as a result of treatment at each time point.
- Independent variables were eligible for inclusion in each of the multivariable models if they were associated with the health state rating in a bivariate model with $P<.20$. To be included in the final model, the variable needed to maintain $P<.10$.

Table 1. Characteristics of 226 Participants at Baseline*

Characteristic	Value
Diagnosis	
Cancer	35
Chronic obstructive pulmonary disease	36
Congestive heart failure	29
Age, mean ± SD, y	73 ± 7
Education, mean ± SD, y	12 ± 3
White race	91
Female sex	43
Married	58
Has a living will	53
Self-rated health: excellent, very good or good	36
Self-rated quality of life: best possible or good	64
Depressed	47
Moderate or severe pain	27
≥2 Hospitalizations in past year	47
Intensive care unit admission in past year	34
Self-rated life expectancy	
<2 y	14
≥2 y	42
Uncertain	44

*Data are given as percentages unless otherwise stated.

Arch Intern Med. 2006;166(8):890-895.
doi:10.1001/archinte.166.8.890

Table 2. Trajectories of Health State Ratings*

Health State	Trajectory of Ratings, No. (%)				
	Acceptable Throughout	Unacceptable Throughout	Acceptable to Unacceptable	Unacceptable to Acceptable	Variable
Unable to leave house	106 (56)	16 (8)	11 (6)	36 (19)	20 (11)
Only able to get from bed to chair; requires assistance with bathing and dressing	61 (32)	36 (19)	12 (6)	38 (20)	42 (22)
Severe memory problems; unable to recognize family	4 (2)	142 (75)	16 (8)	5 (3)	22 (12)
Daily pain (eg, like having a broken bone or appendicitis)	22 (12)	69 (37)	33 (17)	12 (6)	53 (28)

*Based on 189 participants who participated in at least 1 follow-up interview.

Arch Intern Med. 2006;166(8):890-895. doi:10.1001/archinte.166.8.890

Table 3. Trajectories of Health State Rating for State of Being Confined to Going From Bed to Chair According to Trajectories of Functional Status*

	Trajectory of Ratings for Severe Functional Impairment, No. (%)				
Patient's Functional Status	Acceptable Throughout	Unacceptable Throughout	Acceptable to Unacceptable	Unacceptable to Acceptable	Variable
Unchanged (n = 22)	8 (36)	8 (36)	0	5 (23)	1 (5)
Improved (n = 17)	3 (18)	7 (41)	3 (18)	2 (12)	2 (12)
Declined (n = 70)	21 (30)	10 (14)	6 (9)	19 (27)	14 (20)
Other (n = 80)	29 (36)	11 (14)	3 (4)	12 (15)	25 (31)

*Based on 189 participants who participated in at least 1 follow-up interview.

Arch Intern Med. 2006;166(8):890-895. doi:10.1001/archinte.166.8.890

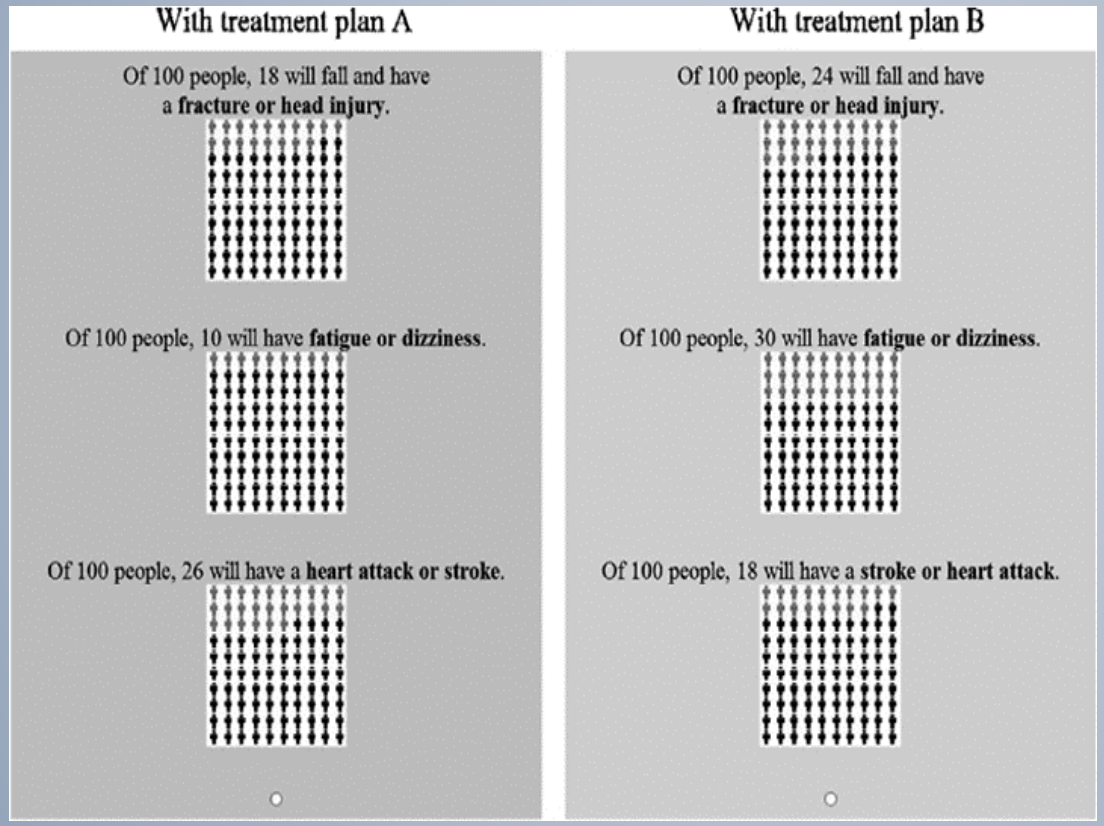
Table 4. Factors Associated With a Health State Rating of Acceptable Among All 226 Participants*

Variable	Health State			
	Unable to Leave House	Able to Go From Bed to Chair	Unable to Recognize Family	Severe Pain
Time, mo	1.11 (1.06-1.16)	1.06 (1.03-1.09)	0.95 (0.91-0.99)	0.98 (0.96-1.01)
Nonwhite race	1.16 (0.24-5.50)	1.70 (0.46-6.27)	3.63 (0.98-13.5)	0.96 (0.27-3.48)
Better than high school education	0.38 (0.15-0.98)	0.48 (0.22-10.4)		
Disease diagnosis				
Congestive heart failure	0.29 (0.10-0.90)	0.39 (0.16-0.92)		
Cancer	0.42 (0.14-1.27)	0.67 (0.28-1.61)		
Self-rated health: excellent, very good, or good	2.14 (1.14-4.02)			
Self-rated quality of life: best possible or good		2.41 (1.47-3.94)	2.23 (1.15-4.35)	2.53 (1.58-4.03)
Depressed	1.81 (0.96-3.43)	2.46 (1.48-4.09)		
Has living will			0.43 (0.20-0.91)	0.41 (0.22-0.74)
Self-rated life expectancy				
<2 y	0.68 (0.27-1.70)	0.86 (0.40-1.82)		
Uncertain	1.90 (0.94-3.85)	2.15 (1.24-3.70)		
Increased IADLs disability	1.23 (1.08-1.40)	1.23 (1.11-1.37)		
Moderate or severe pain				2.55 (1.56-4.19)

Abbreviation: IADL, instrumental activity of daily living.
*Data are given as odds ratio (95% confidence interval).

Arch Intern Med. 2006;166(8):890-895. doi:10.1001/archinte.166.8.890

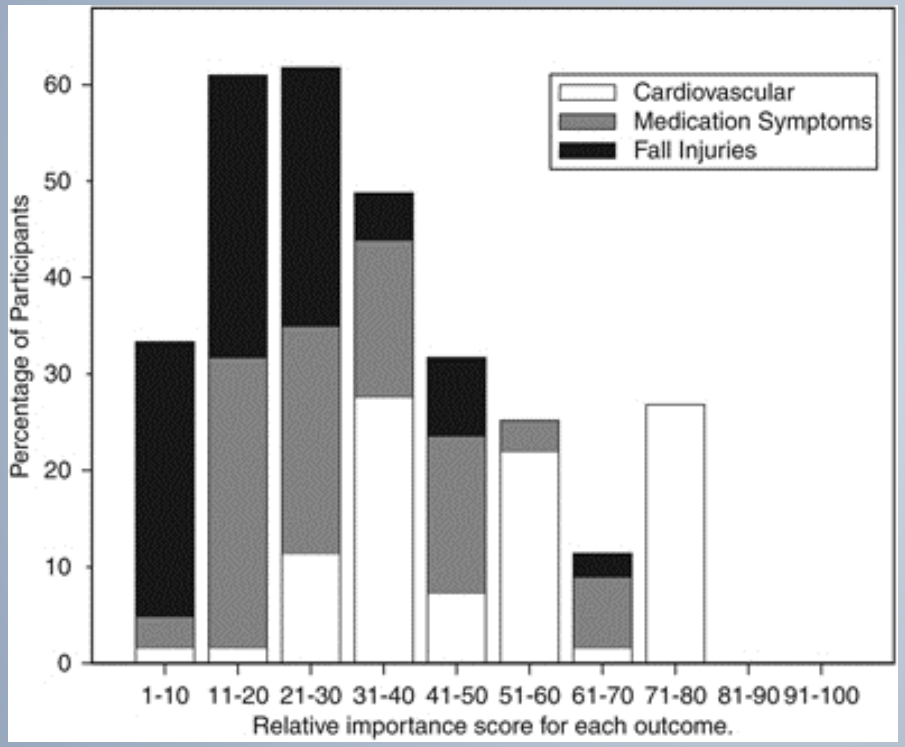
Health Outcome Priorities Among Competing Cardiovascular, Fall Injury, and Medication -Related Symptom Outcomes



- Primary outcome was the relative importance score for the three outcome domains, ascertained from a discrete choice task.
- 11 sets of choices, each composed of a pair of options that display risk for each health outcome with or without antihypertensive medications.
- Relative importance scores, which sum to 100, reflect the priority participants place on the difference between the risk estimates of each outcome

Tinetti et al, JAGS, 2008; 56:8 (1409-1416)

Health Outcome Priorities Among Competing Cardiovascular, Fall Injury, and Medication-Related Symptom Outcomes



- 123 participants, the mean age was 81.5 years (range 70-96), 71% female, 21% MMSE <19
- Median importance score was 51 for cardiovascular outcomes, 19 for fall injuries, and 27 for medication symptoms.
- % of participants prioritizing cardiovascular outcomes (importance score for CVD outcomes >50) was higher for participants without COPD (P=.02), a balance problem or unsteadiness walking (P=.02), dependency in any basic or instrumental ADL(P=.06), lower cognitive score (P=.02) and depressive symptoms (P=.03)

Tinetti et al, JAGS, 2008; 56:8 (1409-1416)

Precipitating Events Project

Thomas M. Gill, MD

- Prospective cohort study of 754 nondisabled, community-living persons aged 70 years or older assembled in 1998-99
- Overall research objectives
  - to rigorously evaluate the natural history of disability among community-living older persons
  - to elucidate the mechanisms underlying the development of, and recovery from, functional decline and disability among community-living older persons

PEP Eligibility Criteria

- Inclusion
  - aged 70 years or older
  - community-living
  - nondisabled in 4 key ADLs:
    - bathing,
    - dressing,
    - walking inside the house,
    - transferring from a chair
- Exclusion
  - life expectancy < 1 yr
  - plan to move out of area during next yr
  - significant cognitive impairment (n=28 or 3.6%) or profound hearing loss with no available proxy (n=0)
- Oversampled persons who were physically **frail** denoted by a timed score of greater than 10 seconds on the rapid gait test (i.e. walk back and forth over a 3-m course)

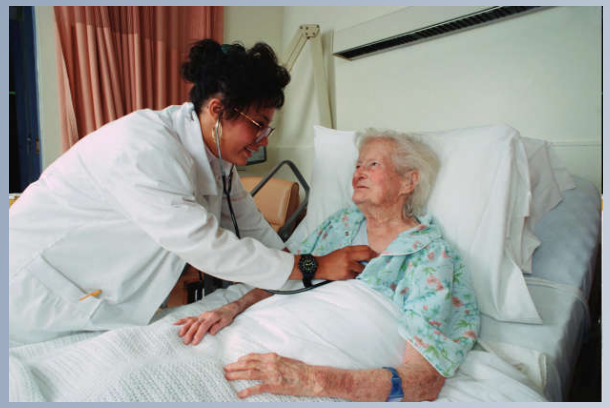
DATA COLLECTION

- Deaths were ascertained by review of the local obituaries and/or from an informant during a subsequent telephone interview.
- In person assessments every 18 mn
- Monthly telephone interviews ~ 220 mn
  - functional status (ADL, IADL, Mobility)
  - precipitating events
    - » acute hospital admissions (Kappa = 0.94)
    - » **restricted activity (Kappa = .90)**
      - » **have you cut down on your usual activities due to an illness, injury or other problem?**
      - » **have you stayed in bed for at least half a day due to an illness, injury or other problem?**

DATA COLLECTED - ONGOING

- Median follow-up 111 months; attrition rate < 5%
- Completed over 85,000 monthly telephone interviews with a success rate of 99.2%
- Completion of follow-up assessments
  - 18-months: 96.2% of 708
  - 36-months: 95.4% of 656
  - 54-months: 94.9% of 588
  - 72 months: 94.3% of 523
  - 90 months: 94.2% of 467
  - 108 months: 94.3% of 401
  - 144 months: 92.5% of 265
  - 162 months: 92% of 212
  - 180 months: 89.9% of 159
  - 198 months: 89.6% of 125
  - 216 months: 89.5% of 86
- 680 (90.2%) deaths as of 12/31/2017

Vulnerability Model of Disability



Precipitating Event

↓

Non-disabled → Disability

↑

Risk Factor

Association Between New Intervening Events and Disability According to Physical Frailty at Baseline

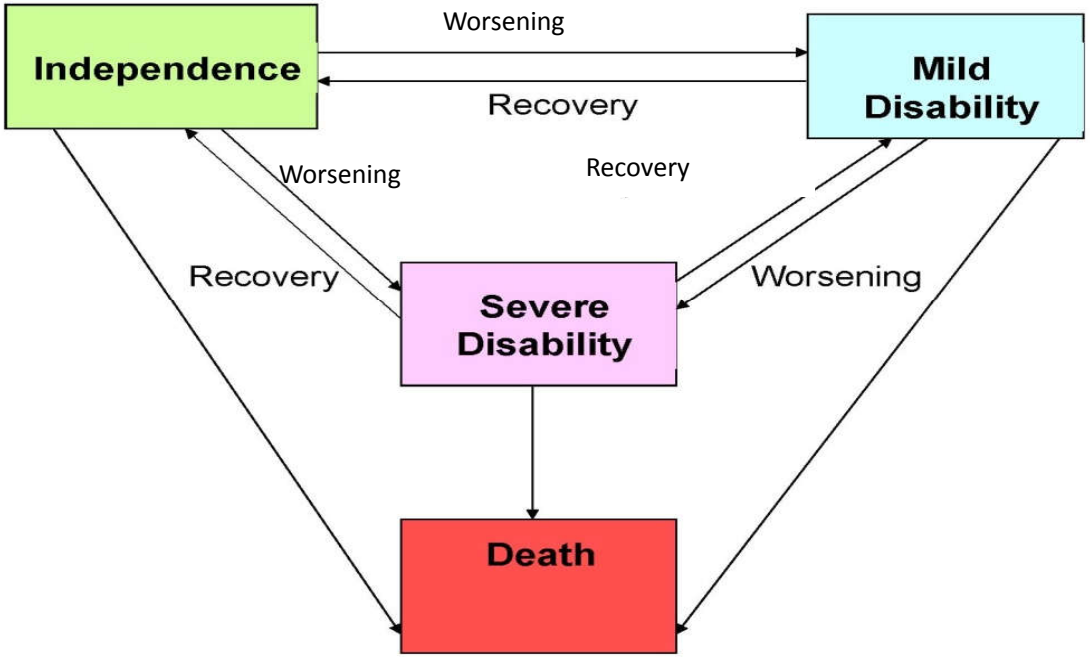
Table 4. Association Between New Intervening Events and Disability According to Physical Frailty at Baseline

Intervening Event†	Hazard Ratio (95% Confidence Interval)*		
	Any Disability	Persistent Disability	Disability With Nursing Home Admission
Hospitalization‡			
Physically frail at baseline	31.8 (22.5-45.0)	29.5 (20.2-43.1)	191 (102-357)
Not physically frail at baseline	122 (82.4-180)	76.5 (47.3-124)	312 (141-691)
Restricted activity only§			
Physically frail at baseline	4.13 (2.87-5.95)	2.76 (1.39-5.46)	4.52 (1.95-10.5)
Not physically frail at baseline	6.45 (4.06-10.3)	3.30 (2.15-5.07)	1.71 (0.35-8.29)

JAMA Gill et al 2004;292:2115-2124.

Dynamic Process of Disability

Modeling the transitions among the different states of disability and death.



Statistical Methods

- Extended Cox models for multiple states
- Exact method was used to handle tied event times.
- The hazard ratios refer to the risk of developing disability at month *t*+1 based on exposure to hospitalization or **restricted activity** only during the preceding month (*t*).
- The reference group was participants who had no hospitalization or **restricted activity** during the preceding month.
- Exposure for the prior events was defined as the number of months with hospitalization and the **number of months with restricted activity** only

Table 2. Associations of Physical Frailty, Hospitalization, and Restricted Activity With Functional Transitions[a]

Transition	Physical Frailty		Hospitalization[b]		Restricted Activity[b,c]	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
From no disability to						
Mild disability	4.34 (3.58-5.27)	<.001	8.90 (7.05-11.22)	<.001	2.59 (2.23-3.02)	<.001
Severe disability	3.53 (2.68-4.63)	<.001	168 (118-239)	<.001	8.03 (5.28-12.21)	<.001
Death	1.79 (1.20-2.68)	.005	23.8 (15.9-35.7)	<.001		
From mild disability to						
No disability	0.30 (0.21-0.41)	<.001	0.41 (0.30-0.54)	<.001	0.95 (0.77-1.17)	.62
Severe disability	2.15 (1.51-3.04)	<.001	7.73 (5.47-10.9)	<.001	1.45 (1.14-1.84)	.002
Death	1.26 (0.59-2.67)	.55	10.9 (6.70-17.7)	<.001		
From severe disability to						
No disability	0.13 (0.08-0.21)	<.001	1.04 (0.65-1.66)	.87	0.78 (0.46-1.32)	.35
Mild disability	0.57 (0.39-0.83)	.003	0.70 (0.51-0.95)	.02	0.93 (0.69-1.27)	.66
Death	0.87 (0.51-1.49)	.61	6.40 (4.49-9.12)	<.001		

JAMA Gill, T. M. et al. 2010;304:1919-1928

Health Outcome Prioritization as a Tool for Decision Making Among Older Persons With Multiple Chronic Conditions

Table. Proportion of Participants With Different Health Outcome Rankings, Organized by Health Outcome Ranked as Most Important

Health Outcome Ranking				
First (Most Important)	Second	Third	Fourth	No. (%)[a]
Independence				270 (76)[b]
	Pain relief	Symptom relief	Staying alive	104 (39)[c]
	Symptom relief	Pain relief	Staying alive	76 (28)[c]
	Staying alive	Pain relief	Symptom relief	38 (14)[c]
	Staying alive	Symptom relief	Pain relief	22 (8)[c]
	Pain relief	Staying alive	Symptom relief	19 (7)[c]
	Symptom relief	Staying alive	Pain relief	11 (4)[c]
Staying alive				40 (11)[b]
	Independence	Pain relief	Symptom relief	13 (33)[c]
	Independence	Symptom relief	Pain relief	13 (33)[c]
	Pain relief	Independence	Symptom relief	7 (18)[c]
	Pain relief	Symptom relief	Independence	5 (13)[c]
	Symptom relief	Independence	Pain relief	2 (5)[c]
Pain relief				26 (7)[b]
	Independence	Symptom relief	Staying alive	11 (42)[c]
	Symptom relief	Independence	Staying alive	7 (27)[c]
	Independence	Staying alive	Symptom relief	4 (15)[c]
	Symptom relief	Staying alive	Independence	3 (12)[c]
	Staying alive	Symptom relief	Independence	1 (4)[c]
Symptom relief				21 (6)[b]
	Independence	Pain relief	Staying alive	11 (52)[c]
	Staying alive	Independence	Pain relief	4 (19)[c]
	Independence	Staying alive	Pain relief	3 (14)[c]
	Pain relief	Independence	Staying alive	2 (10)[c]
	Pain relief	Staying alive	Independence	1 (5)[c]

[a] Percentages do not add up to 100% because of rounding.
[b] Percentage of total participants (N=357).
[c] Percentage of health outcome ranked first.

Fried TR et al. Arch Intern Med. 2011;171(20):1856-1858. doi:10.1001/archinternmed.2011.424

Restricting Symptoms in the Last Year of Life

Table 1. Characteristics of Decedents

Characteristic[a]	Overall (n = 491)	Restricting Symptoms (n = 281)	No Restricting Symptoms (n = 210)	*P* Value[b]
Age, mean (SD), y	85.8 (5.9)	85.6 (5.8)	86.0 (6.1)	
Age <85 y, No. (%)	199 (40.5)	119 (42.3)	80 (38.1)	.34
Female sex, No. (%)	304 (61.9)	175 (62.3)	129 (61.4)	.85
Nonwhite race,[c] No. (%)	44 (9.0)	33 (11.7)	11 (5.2)	.01
Education <12 y, No. (%)	168 (34.2)	96 (34.2)	72 (34.3)	.98
Cognitive impairment,[d] No. (%)	100 (20.4)	54 (19.2)	46 (21.9)	.46
Individual comorbid conditions, No. (%)				
Hypertension	310 (63.1)	173 (61.6)	137 (65.2)	.40
Arthritis	220 (44.8)	135 (48.0)	85 (40.5)	.10
Myocardial infarction	119 (24.2)	65 (23.1)	54 (25.7)	.51
Diabetes mellitus	117 (23.8)	65 (23.1)	52 (24.8)	.68
Lung disease	117 (23.8)	74 (26.3)	43 (20.5)	.13
Cancer	111 (22.6)	74 (26.3)	37 (17.6)	.02
Heart failure	76 (15.5)	53 (18.9)	23 (11.0)	.02
Stroke	76 (15.5)	39 (13.9)	37 (17.6)	.26
Hip fracture	51 (10.4)	29 (10.3)	22 (10.5)	.95
Comorbid conditions, No., mean (SD)	2.4 (1.3)	2.5 (1.3)	2.3 (1.4)	.14
Multimorbidity,[e] No. (%)	359 (73.1)	214 (76.2)	145 (69.1)	.08
Conditions leading to death, No. (%)				
Frailty	138 (28.1)	75 (26.7)	63 (30.0)	.42
Organ failure	102 (20.8)	61 (21.7)	41 (19.5)	.56
Cancer	91 (18.5)	55 (19.6)	36 (17.1)	.49
Advanced dementia	79 (16.1)	42 (14.9)	37 (17.6)	.43
Other	67 (13.7)	39 (13.9)	28 (13.3)	.86
Sudden death	14 (2.9)	9 (3.2)	5 (2.4)	.59

[a] Characteristics were determined during the most proximate comprehensive assessment prior to death.

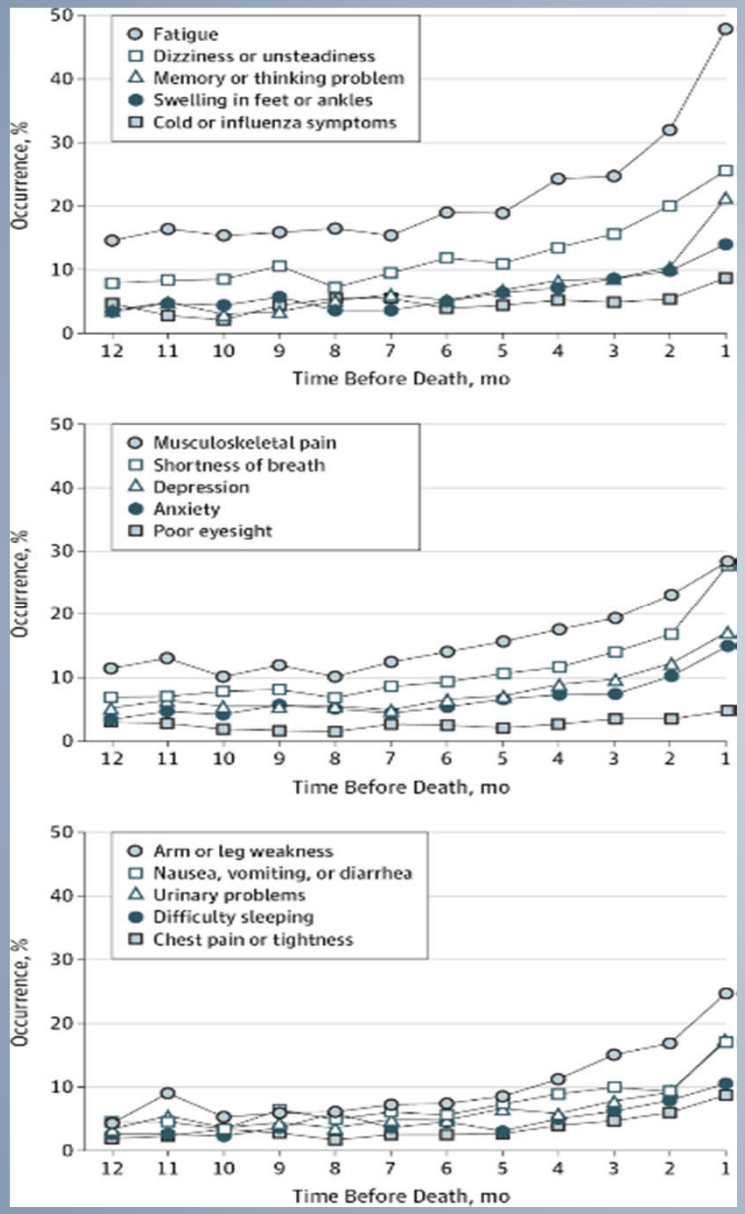
[b] *P* values were calculated from the *t* test for continuous age and χ^2 statistic for all others.

[c] Race was self-reported; nonwhite category included Hispanics.

[d] Cognitive impairment was defined as a Folstein Mini-Mental State examination score of less than 20.

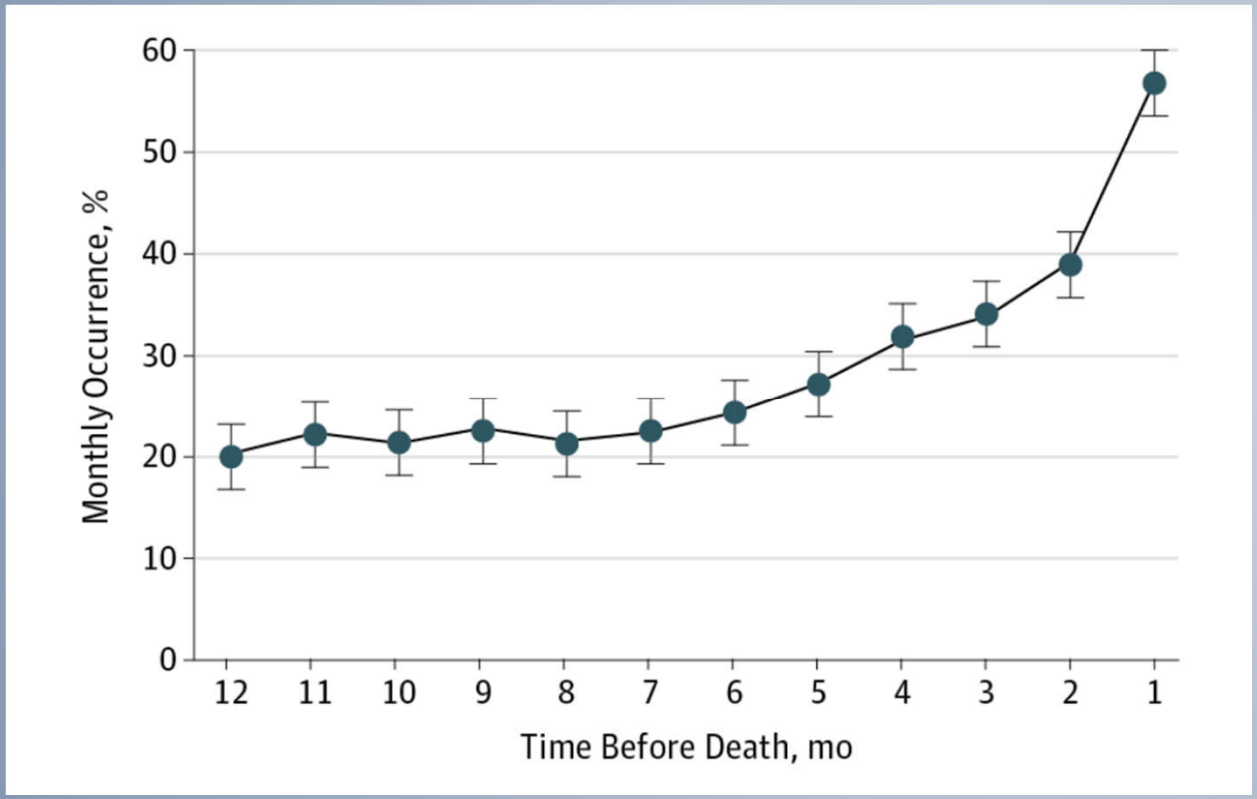
[e] Multimorbidity was defined as the presence of at least 2 comorbid conditions.

JAMA Intern Med. 2013;173(16):1534-1540. doi:10.1001/jamainternmed.2013.8732



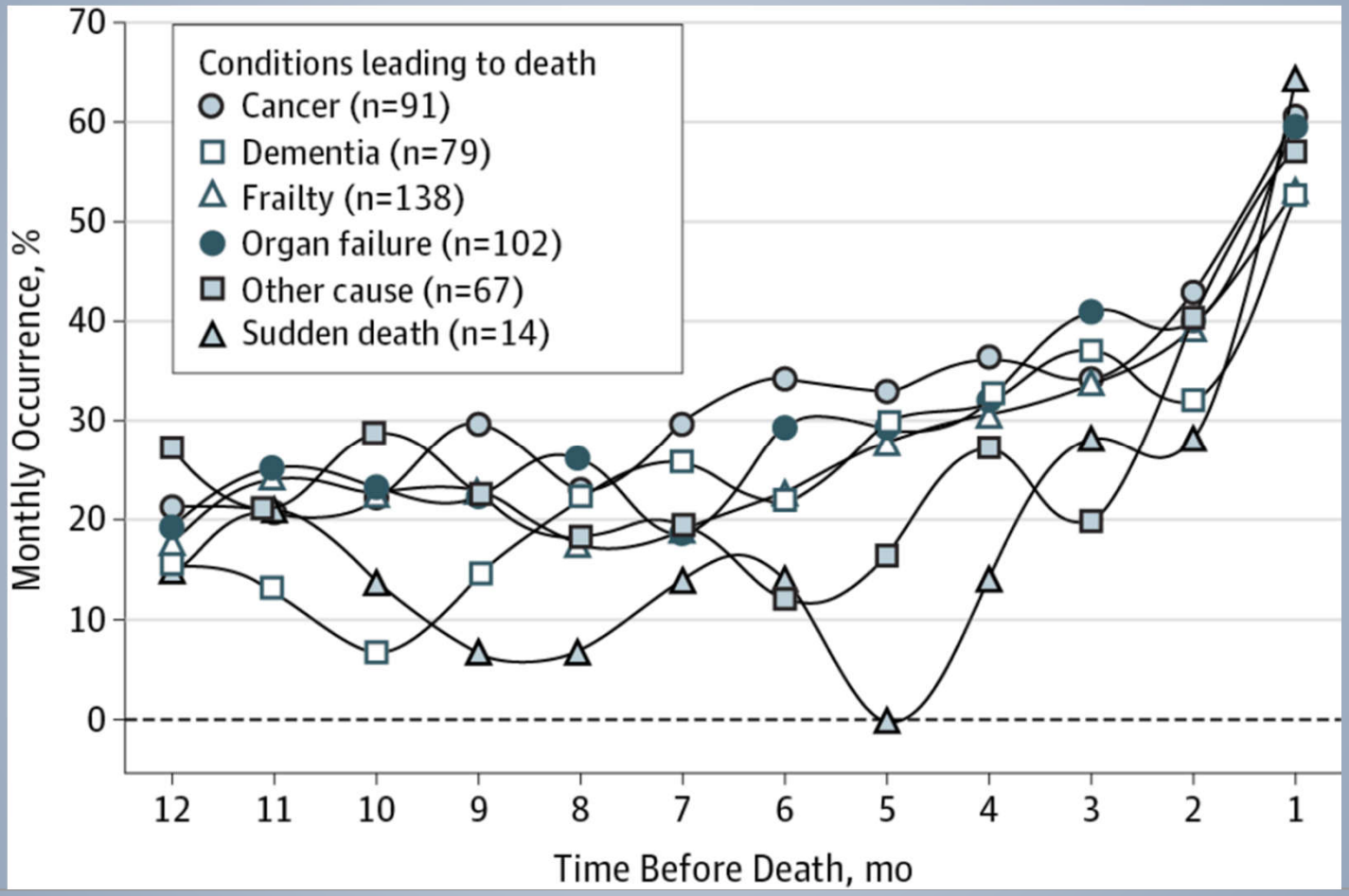
Monthly occurrence of each specific symptom was calculated by dividing the number of participants in each month with that symptom by the total number of participants reporting in that same month.

Monthly Occurrence of 1 or More Restricting Symptoms in the Last Year of Life Monthly



Occurrence was calculated by dividing the number of participants with ≥1 restricting symptoms in that month by the number interviewed in the same month. Bars denote 1 standard error around mean values.

Monthly Occurrence of 1 or More Restricting Symptoms in the Last Year of Life by Condition Leading to Death



Multivariable Associations With Occurrence of Restricting Symptoms

Table 2. Multivariable Associations With Occurrence of Restricting Symptoms[a]

Characteristic[b]	Odds Ratio (95% CI)	*P* Value[c]
Age <85 y	1.30 (1.07-1.57)	.009
Female sex	1.16 (0.96-1.39)	.12
Nonwhite race[d]	1.28 (0.97-1.70)	.08
Education <12 y	1.05 (0.86-1.28)	.64
Multimorbidity	1.38 (1.09-1.75)	.008
Month in last year of life	1.14 (1.11-1.16)	<.001
Cognitive impairment[e]	1.06 (0.76-1.47)	.74
Conditions leading to death[f]		
Cancer	1.80 (1.03-3.14)	.04
Dementia	1.34 (0.74-2.41)	.34
Frailty	1.51 (0.87-2.61)	.14
Organ failure	1.70 (0.98-2.95)	.06
Other	1.37 (0.78-2.41)	.27

[a] All variables shown in this table have been dichotomized, except for month in last year ofl ife, which was considered as a continuous variable, with increasing proximity to time of death associated with increased risk of occurrence of restricting symptoms, which were defined as 1 or more of the following 15 symptoms: fatigue; dizziness or unsteadiness; memory or thinking problem; swelling in feet or ankles; cold or influenza symptoms; musculoskeletal pain; shortness ofb reath; depression; anxiety; poor eyesight; arm or leg weakness; nausea, vomiting, or diarrhea; urinary problems; difficulty sleeping; and chest pain or tightness.

[b] Characteristics were determined during the most proximate comprehensive assessment prior to death.

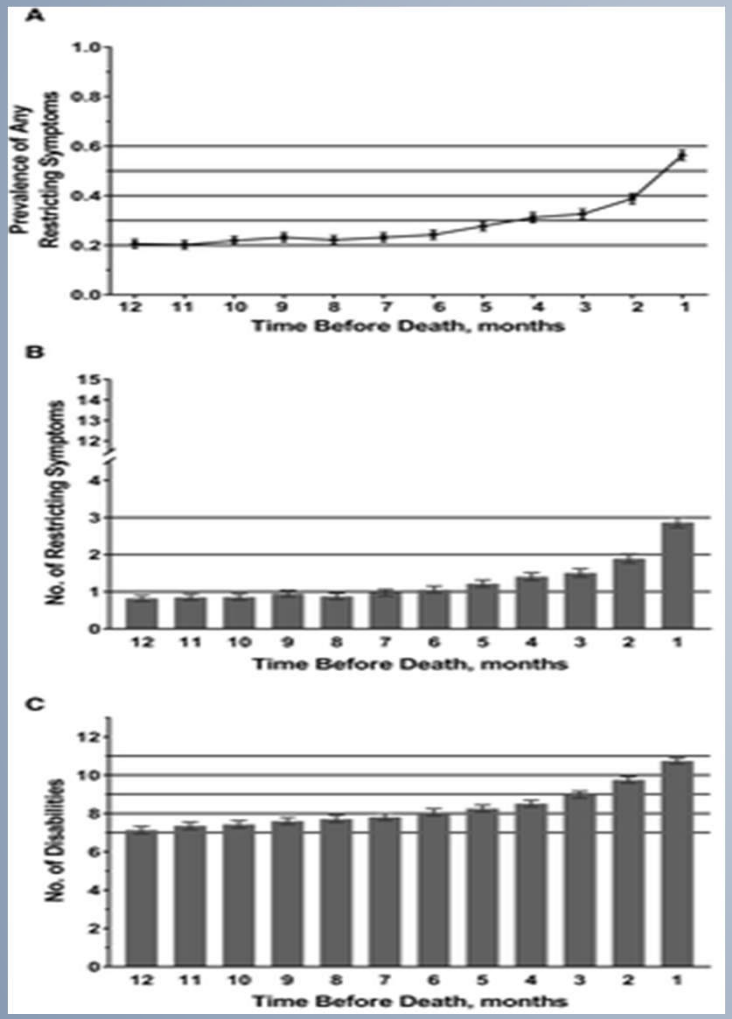
[c] All *P* values are from logistic regression with generalized estimating equations in SAS Proc Genmod.

[d] Race was self-reported; nonwhite category included Hispanics.

[e] Cognitive impairment was defined as a Folstein Mini-Mental State examination score ofl ess than 20.

[f] Participants dying of sudden death were considered the referent category.

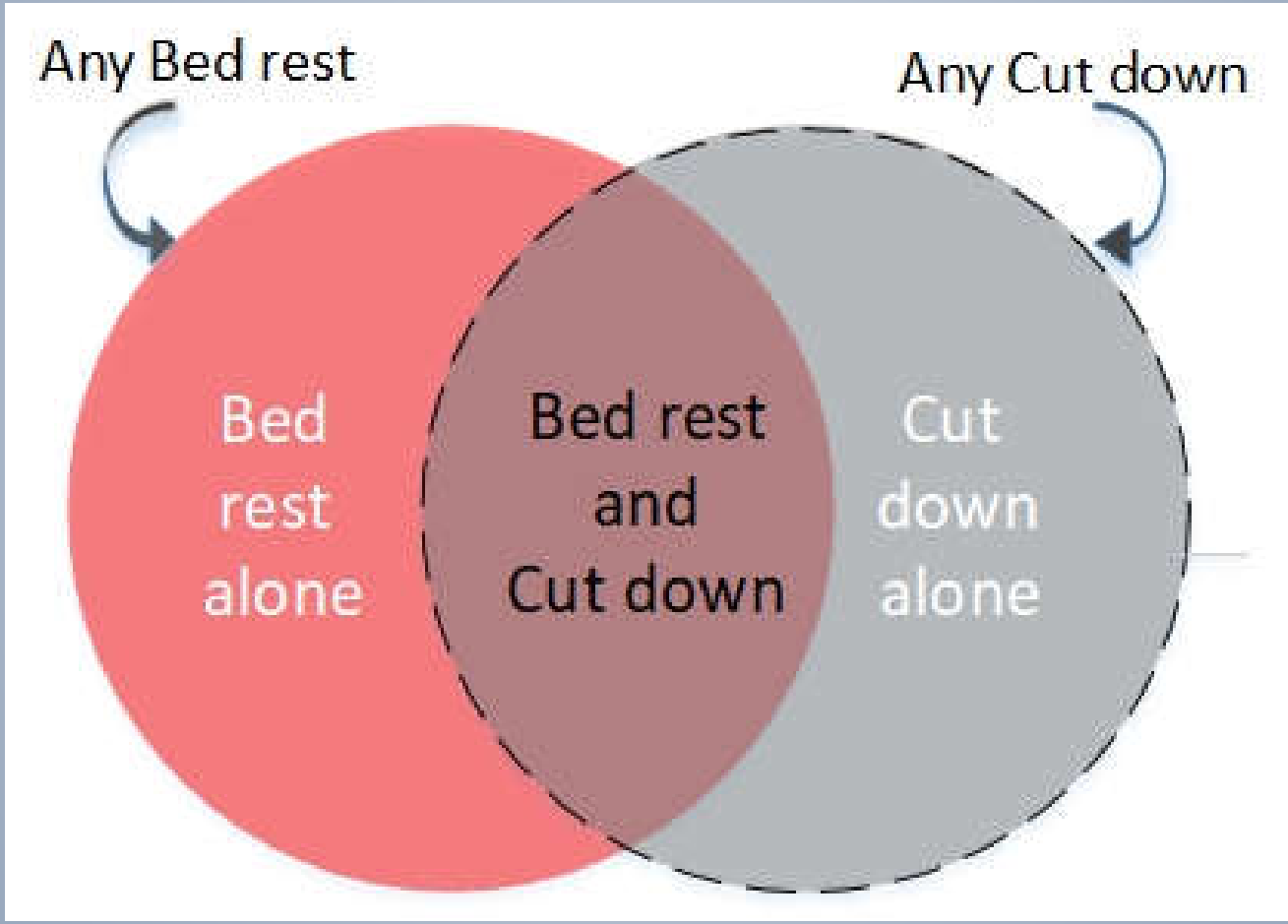
Distressing Symptoms, Disability, and Hospice Services at the End of Life: Prospective Cohort Study

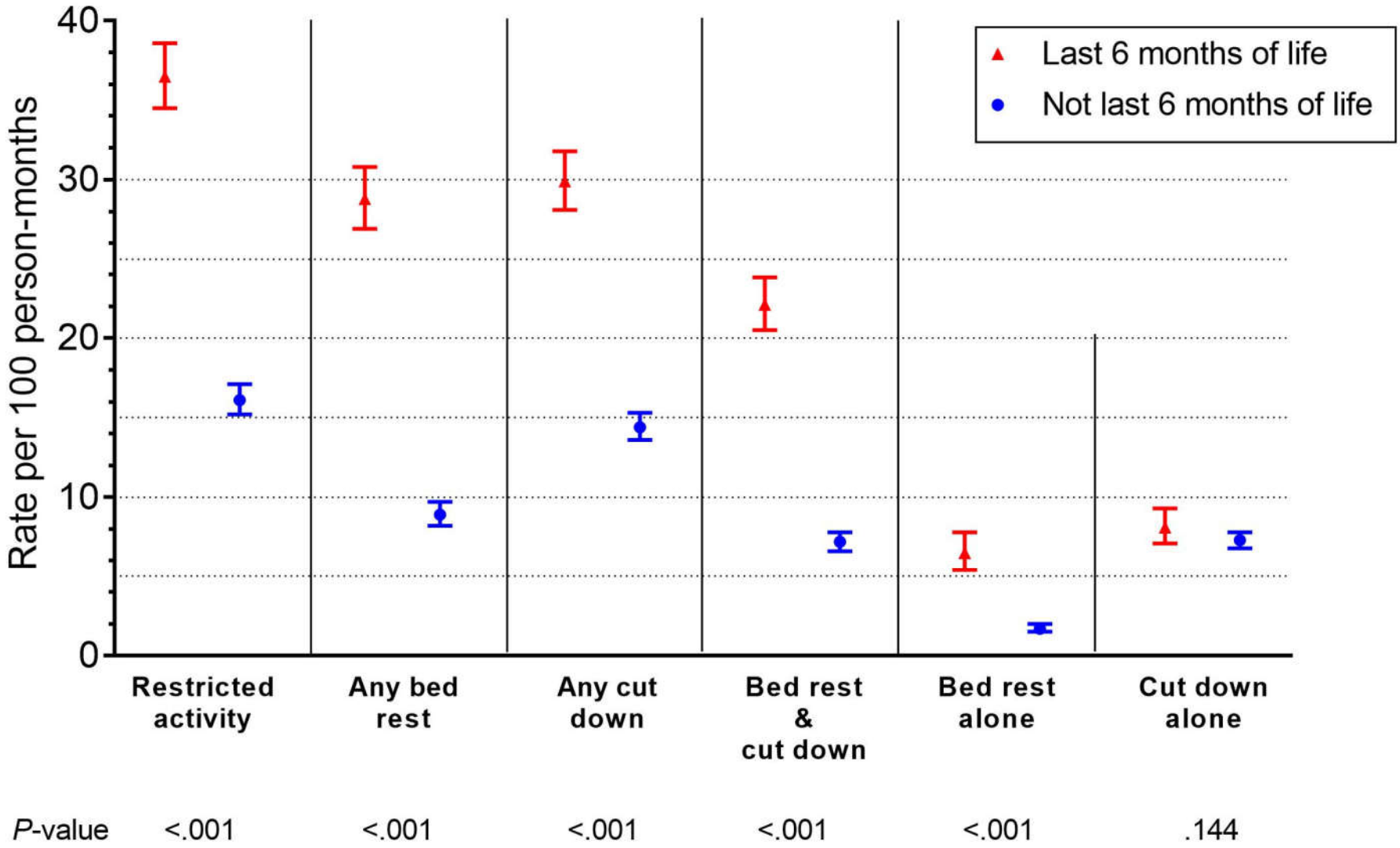


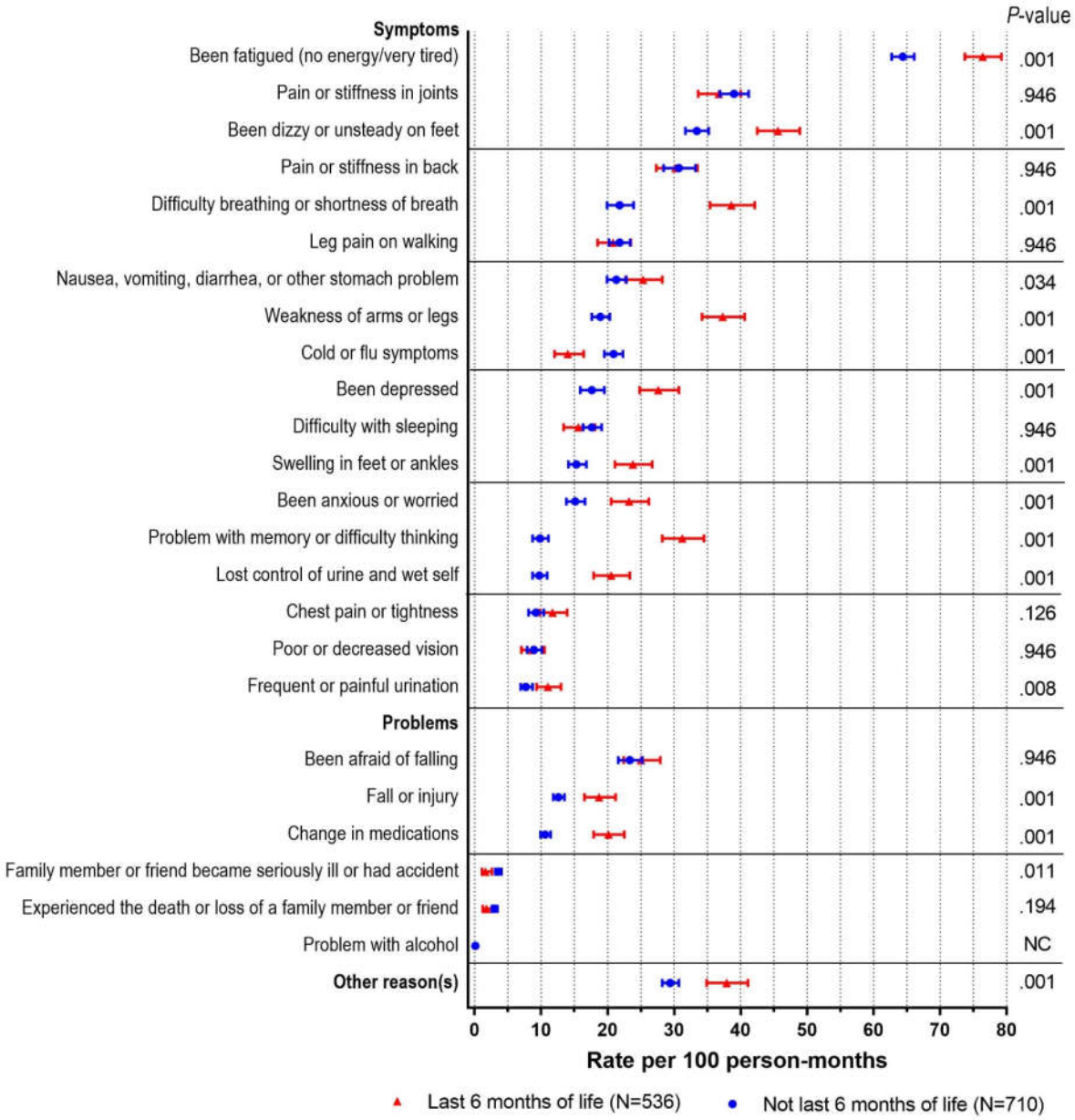
- Exposure to restricting symptoms and disability in the last year of life of all participants.
- For each panel, the error bars represent 1 standard error. The maximum number of restricting symptoms and disabilities were 15 and 13, respectively.

Gill et al JAGS 2017 , 66:1, 41-47, DOI: (10.1111/jgs.15041)

The Burden of Restricted Activity and Associated Symptoms and Problems in Late Life and the End of Life




Rate per 100 person-months
40
30
20
10
0
Last 6 months of life
Not last 6 months of life
Restricted activity
Any bed rest
Any cut down
Bed rest & cut down
Bed rest alone
Cut down alone
P-value
<.001
<.001
<.001
<.001
<.001
.144


P-value
Symptoms
Been fatigued (no energy/very tired) .001
Pain or stiffness in joints .946
Been dizzy or unsteady on feet .001
Pain or stiffness in back .946
Difficulty breathing or shortness of breath .001
Leg pain on walking .946
Nausea, vomiting, diarrhea, or other stomach problem .034
Weakness of arms or legs .001
Cold or flu symptoms .001
Been depressed .001
Difficulty with sleeping .946
Swelling in feet or ankles .001
Been anxious or worried .001
Problem with memory or difficulty thinking .001
Lost control of urine and wet self .001
Chest pain or tightness .126
Poor or decreased vision .946
Frequent or painful urination .008
Problems
Been afraid of falling .946
Fall or injury .001
Change in medications .001
Family member or friend became seriously ill or had accident .011
Experienced the death or loss of a family member or friend .194
Problem with alcohol NC
Other reason(s) .001
0 10 20 30 40 50 60 70 80
Rate per 100 person-months
Last 6 months of life (N=536)
Not last 6 months of life (N=710)

CONCLUSIONS

- Working together to understand patient preferences, priorities, we can research where the evidence is weak to move to patient-centered care.
- Collaboration between clinical and biostatistical experts can improve our understanding of the inter-related symptoms, patient preferences, leading to treatment acceptability, and its effect on patient-reported outcomes.

ACKNOWLEDGMENTS

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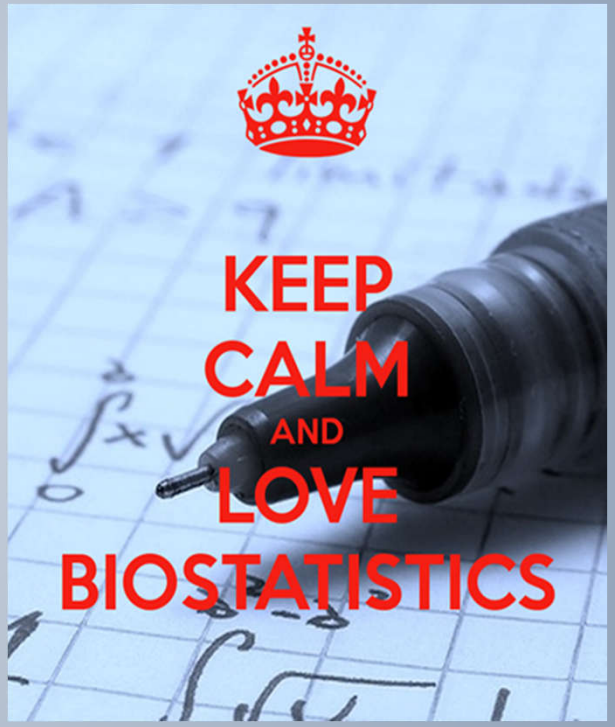


Thank you