Inflammation & Nutrition:
Where We Are and Where We Need To Be

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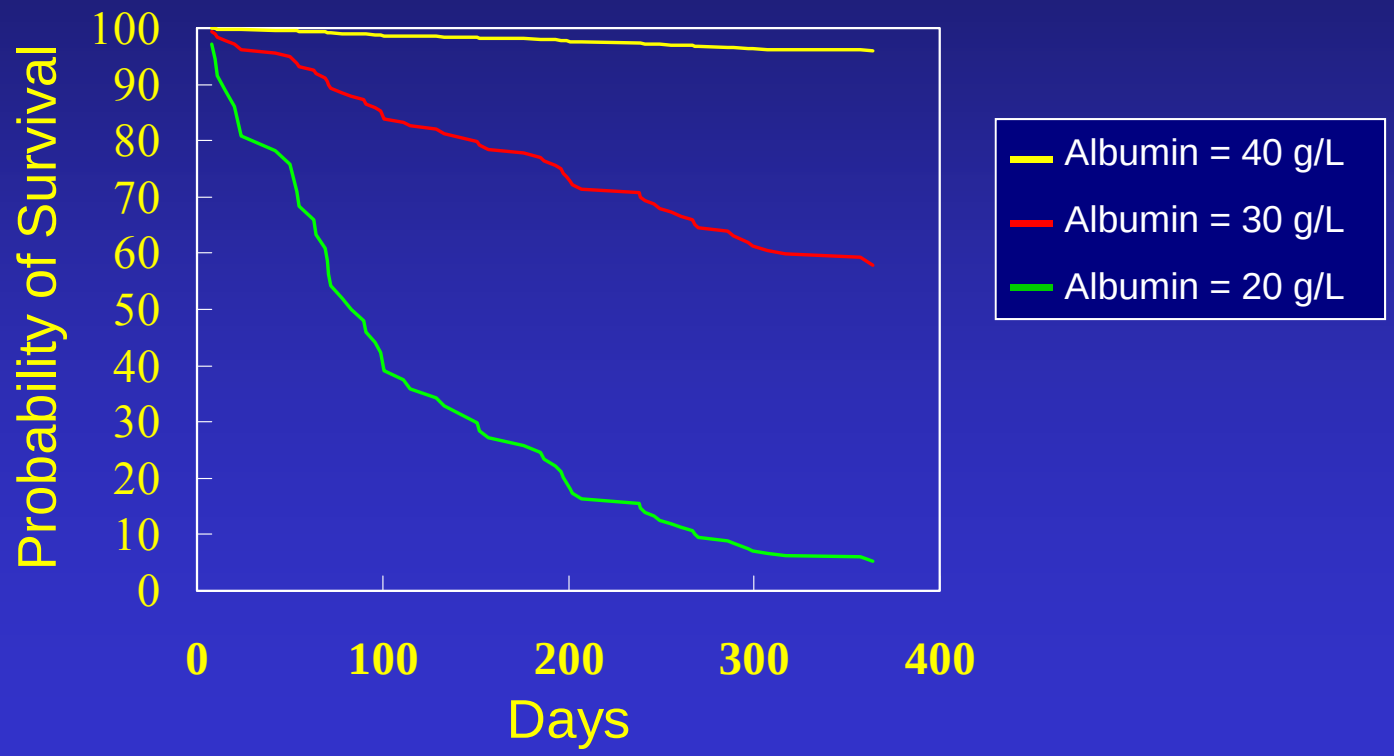
Protein-Energy Undernutrition among the Elderly

- Common, potentially serious, yet inadequate studied problem
- Prevalence
  - Community: 5 to 12%
  - Hospital: 30 to 61%
  - Nursing homes: 40 to 85%
- Variance in figures related to differences in population evaluated and diagnostic criteria utilized

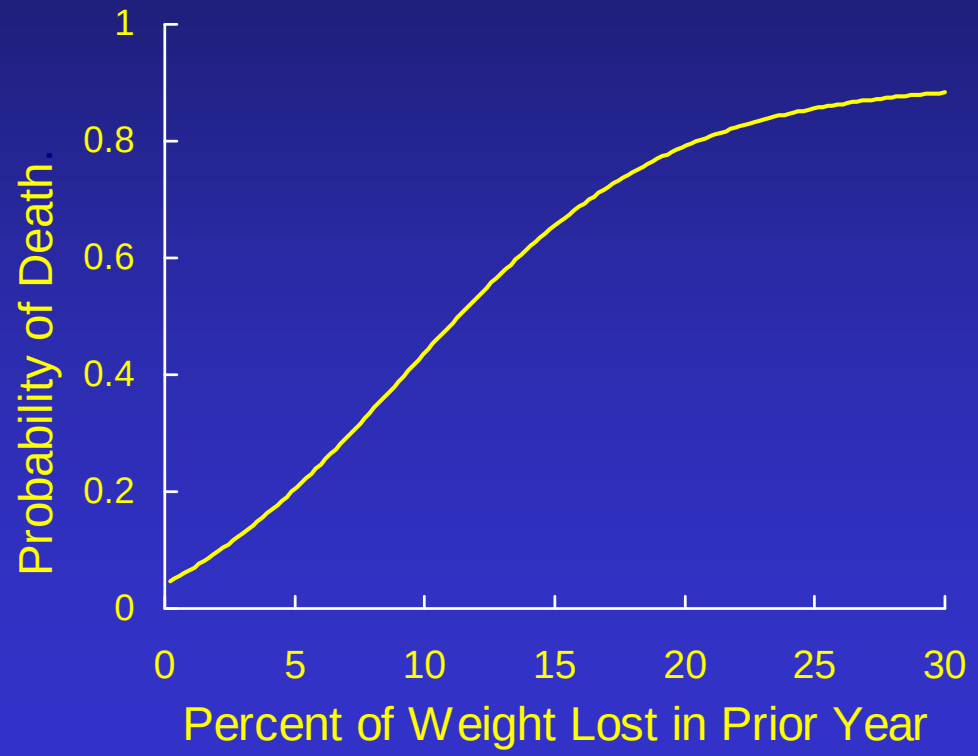
Protein-Energy Undernutrition Need for Definition

- Surrogate measures: anthropometrics, SSPs, wt/wt loss, inadequate nutrient intake, many others
- Severity of PEU defined based on relationship between putative surrogates and clinical outcomes such as mortality, hospital LOS, complication risk (esp infections), poor wound healing, etc.
- Inflammation may effect the surrogates and outcomes independent of nutritional status as well as nutrient metabolism

Adjusted One-Year Survival as a Function of Discharge Serum Albumin



Relationship Between Weight Loss and One-Year Mortality



Inflammation as a Risk Factor for Nutritional Deterioration

- Weight loss is often rapid and profound during serious illness or after a major injury
- There is usually a pathologic triad
  - Prolonged bed rest
  - Profound anorexia
  - metabolic shift to catabolic state
- Inflammation-associated cytokines my be the mediators of each of these effects

Effects of 10 Days of Bed Rest in Older Adults*

	No. of Participants	Change	P Value
Muscle fractional synthetic rate, % per h	10	-0.027	.02
% change		-30%	
DEXA lean mass, kg			
Whole body	10	-1.5O	.004
% Change		-3%	
Lower Extremity	10	-0.95	.003
% Change		-6%	
Isokinetic muscle strength Nm per s	11	-19	.001
% Change		-16%	

* Kortebein et al., JAMA 297: 1772-4, 2007

Impact of Low Nutrient Intake on Physical Function and Survival*

- Prospective cohort study of 500 cancer-free hosp older patients (74 ± 8 yrs) with LOS 4 days or more
- After comprehensive admission assessments, all subjects monitored daily
- 102 subjects (21%) average daily nutrient intake <50% of maintenance requirements (low group)

* Sullivan et al. JAMA 281:2013-19, 1999

Low Nutrient Intake Group Compared to Remaining Patients

- In better health at hospital admission:
  - greater BMI, MAMC, TSF ($p<.05$)
  - More admitted to surgery (61 vs 43%), adm electively (42 vs 31%), have GI disorder (49 vs. 34%)
  - Less likely to state own health poor (50 vs. 63%)
- No difference in any other admission measure of illness severity or LOS (median 8 days)
- Major difference in outcomes

Outcomes after Adjusting for Admission Illness Severity

Clinical Outcome	Adjusted RR (95% CI)
In-hospital mortality	7.6 (2.6-22)
Functionally dependent	2.2 (1.1-4.6)

Contributors to Low Nutrient Intake

- Inadequate food consumptions is often underdiagnosed
  - Staff usually over estimate amount patients eating
  - Little correlation between nutrient intake and weight loss
  - Edema often present
- Observation confirmed in multiple studies
- There is no reliable method of assessing change in fluid status in the clinical setting

Correlates of Weight Loss
Key Findings to Date

- Study of 300 recuperative care patients
- All assessed to have good prognosis for full recovery yet most frail
  - Average age 79 (64-93)
  - BMI 26 $\pm$ 6 (17 – 55)
- Median LOS 21 days

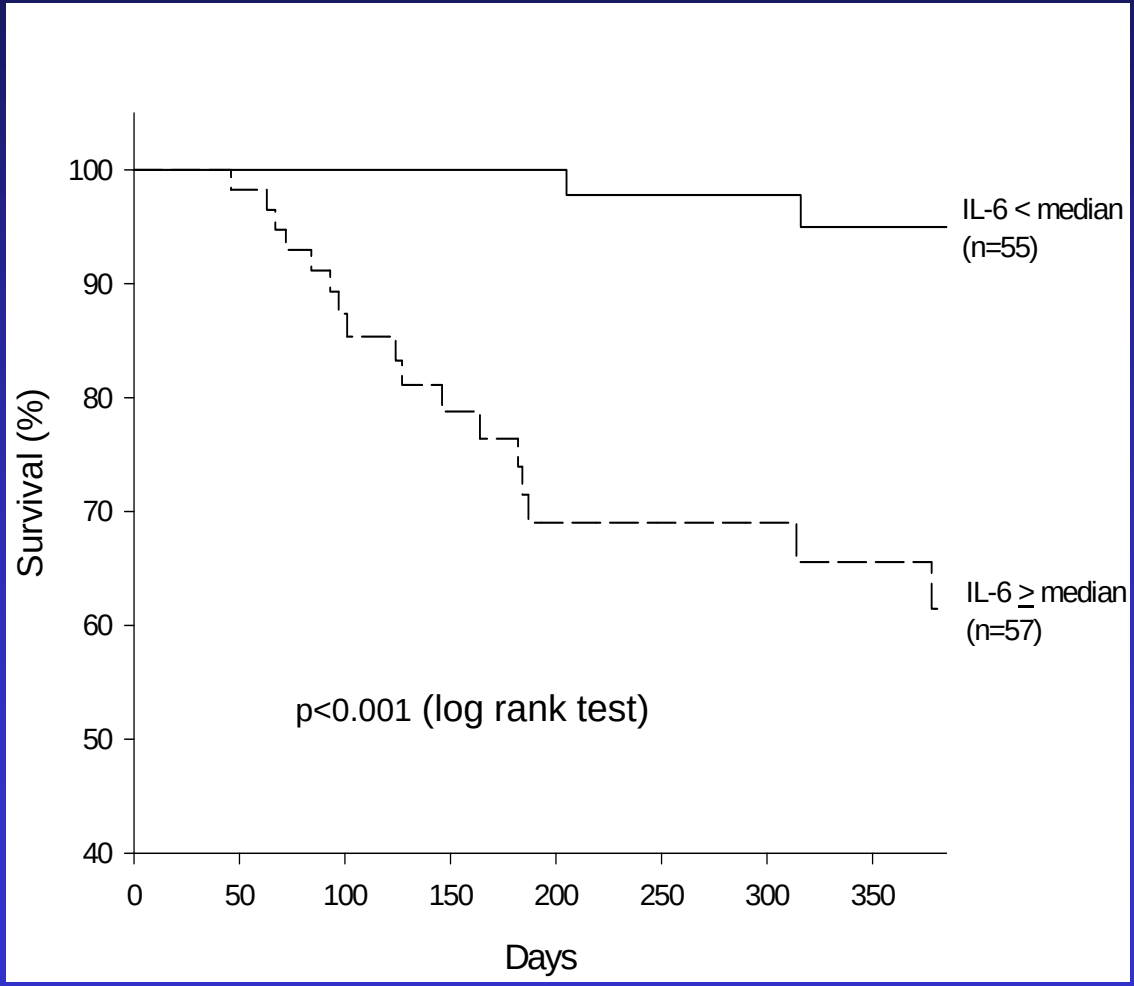
Current Study
Key findings to date

- Weight change common:
  - 14% experienced weight loss of $\geq$ 5%
  - 15% had weight gain of $\geq$ 5%
- Nearly half (48%) had edema
- Average daily energy intake was:
  - < 75% of calculated needs in 36%
  - < 50% of needs in 10%

Current Study
Key findings to date

- Strongest correlate of weight change was 'mid-calf circumference change' ($R^2 = 0.30$) followed by:
  - Average energy intake (as percentage of needs)
  - Interaction of protein intake by time
- Model $R^2 = 0.49$
- Strong inverse correlation between markers of inflammation and both nutrient intake and mortality but not wt change

Post-TCU Unit Survival as a Function of IL-6



Current Study
Key findings to date

- Study underscores importance of monitoring nutrient intake – a challenge in any setting
- Even during recuperation from illness, weight indices not adequate to assess change in body cell mass or physiologic function
- Inflammation is an important risk factor for nutritional deterioration & mortality; little known about regulating factors

The Prognostic Significance of Weight Change in the Frail Elderly*

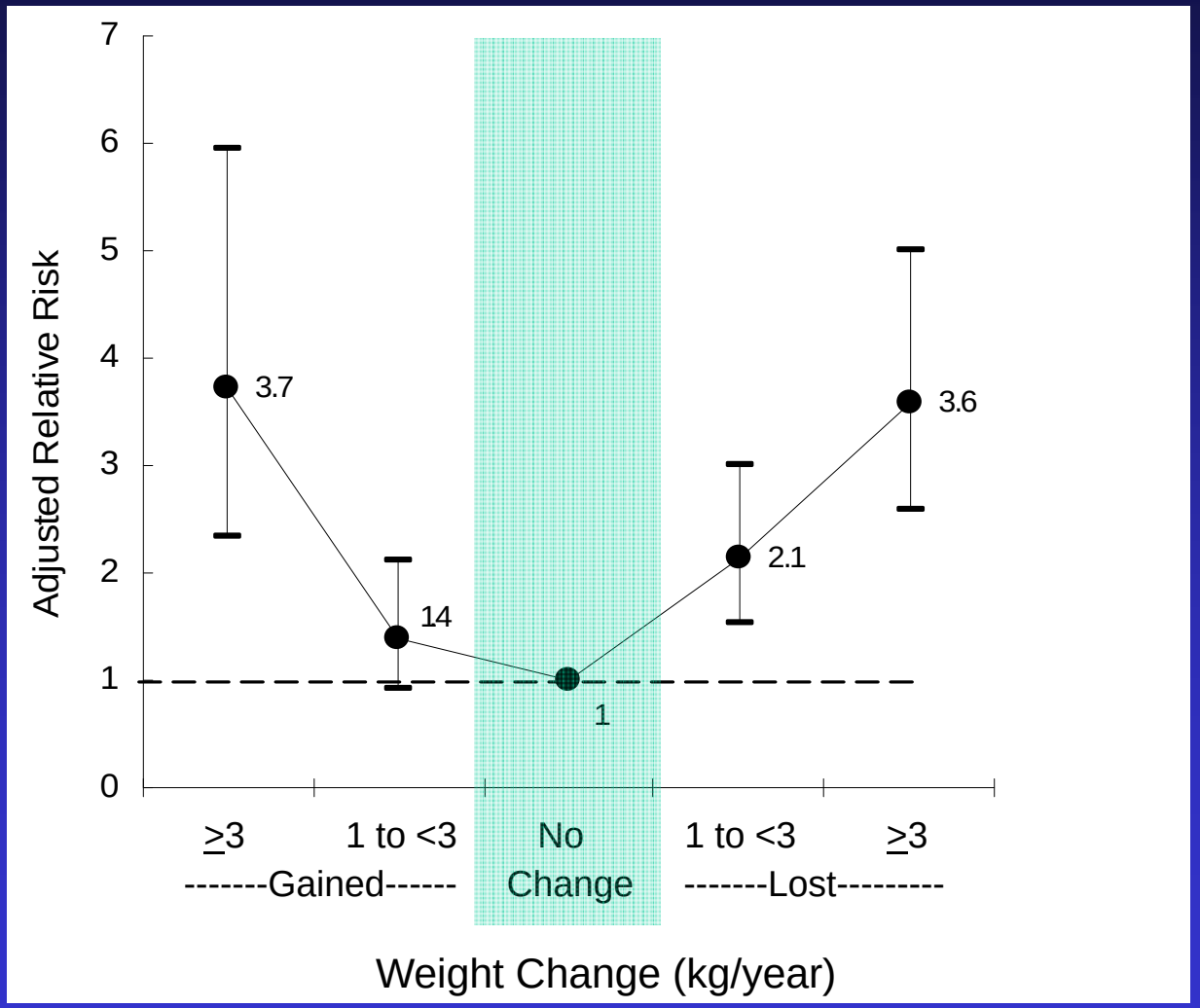
- To determine significance of weight gain, 660 hospitalized patients (age 74 $\pm$ 6) were prospectively followed for 7 years
- Weights were recorded at each hospital and clinic visit
- Association between weight change and mortality determined using Cox PH Regression Analysis

* Sullivan et al. J Am Ger Soc 52:1696-1701, 2004

The Prognostic Significance of Weight Change in the Frail Elderly

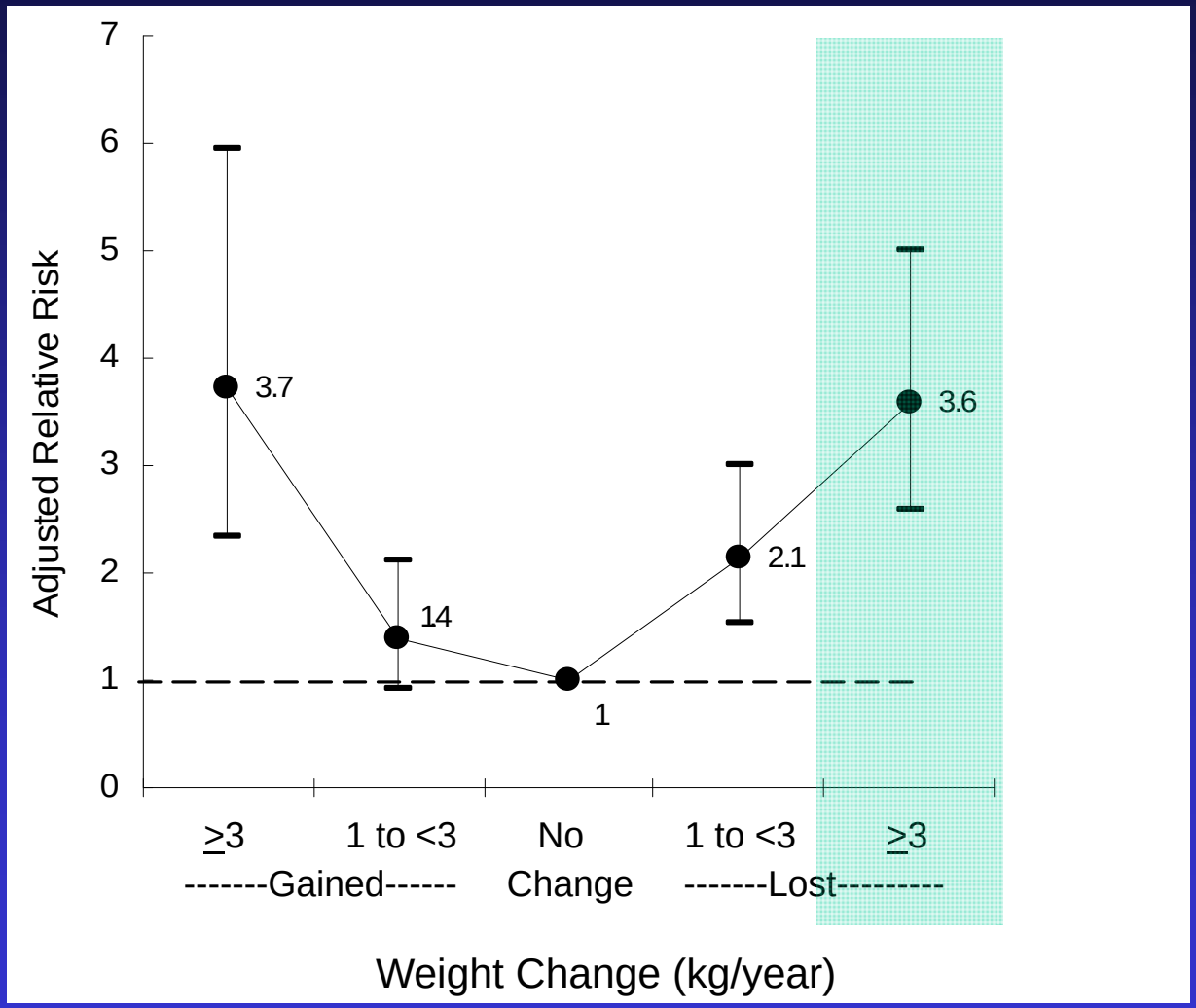
- During the study, 44% experienced an average weight loss of $\geq$ 1 kg/yr; 34% were stable, and 22% gained $\geq$ 1 kg/year.
- The median weight variability was 4%/year
- Weight variability was not associated with mortality

Association Between Weight Change and Mortality over 5 Years*



* Relative risk (95%CI) after adjusting for illness severity

Association Between Weight Change and Mortality over 5 Years*



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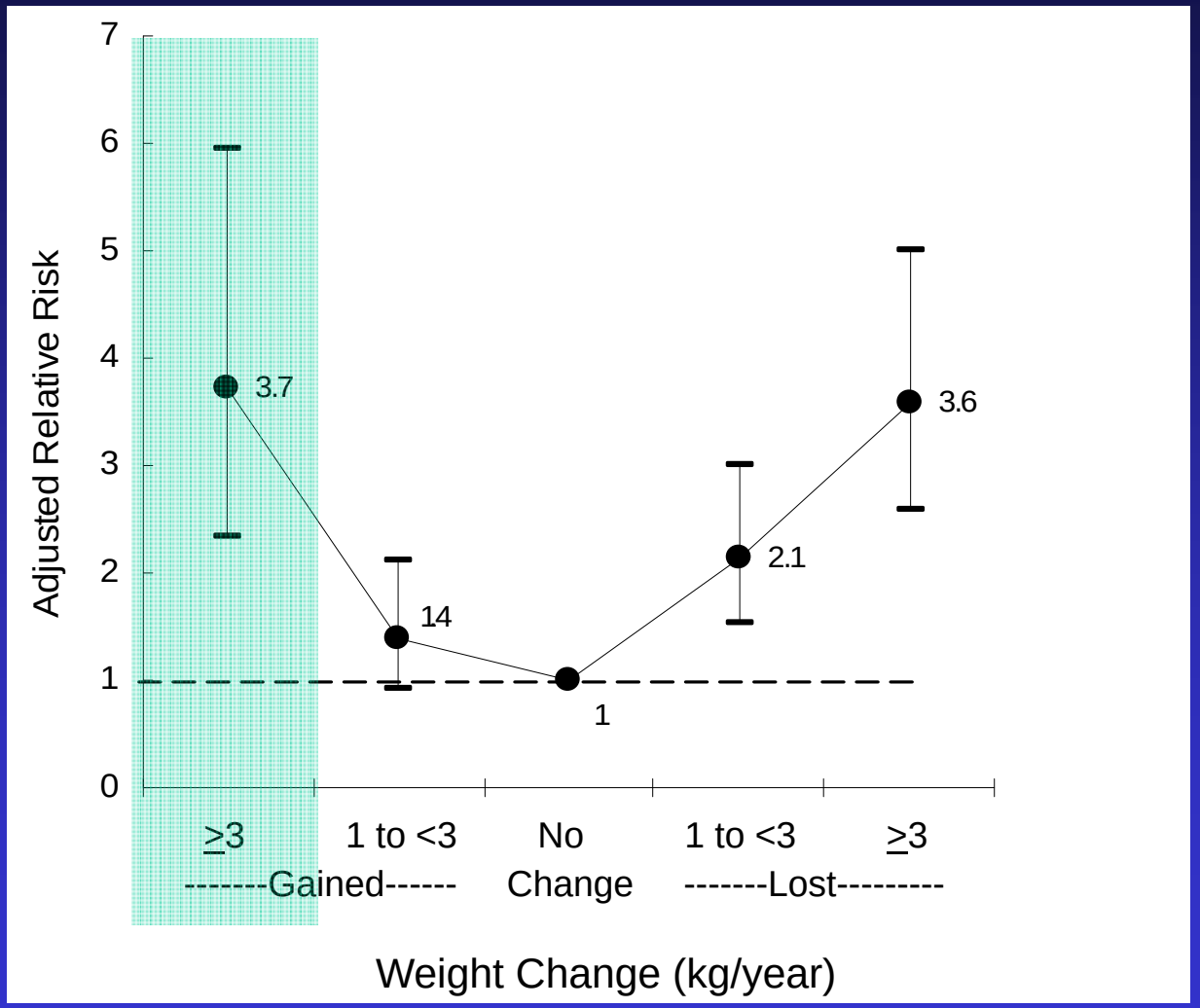

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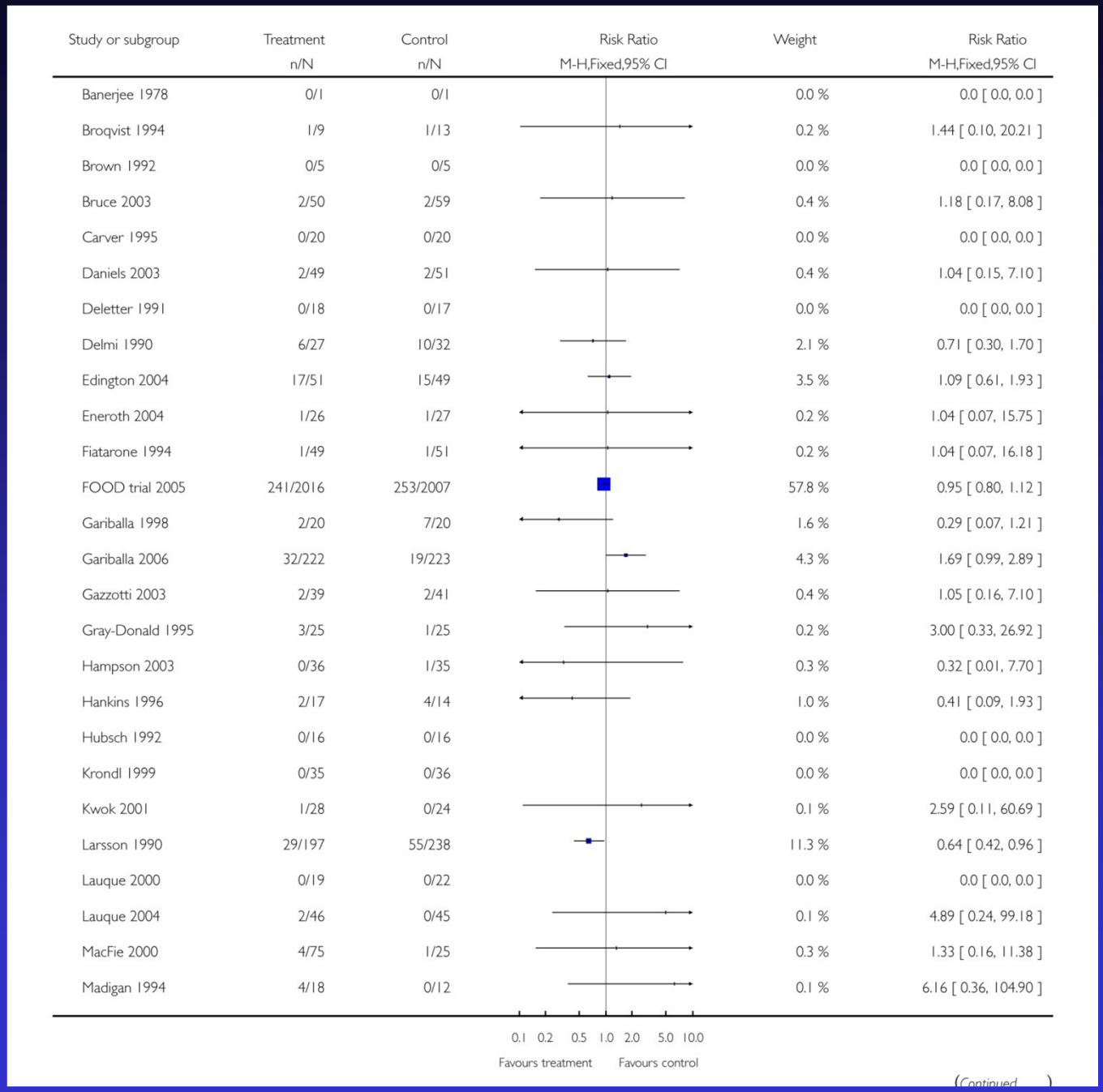
The Relationship between Weight Gain and Mortality

- In long-term studies, weight gain may lead to DM and heart disease, which may be responsible for the higher mortality
- In current study, weight gain may = cardiovascular instability (fluid)
  - Need to know composition of weight gain in frail elderly – fat, fluid, or protein
  - Weight gain ≠ weight recovery

Effectiveness of Nutrition Support

- Parenteral: no data – high complication risk
- Enteral: lack of effectiveness (Cochrane review) high complication risk
- Oral: Not shown to reduce mortality or improve function, QOL
  - May improve outcomes in undernourished long-term hospitalized patients but very poor studies & strong literature bias
  - Effect on overall nutrient intake controversial

Oral Nutrients vs. Routine Care Mortality



Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Banerjee 1978	0/1	0/1		0.0 %	0.0 [0.0, 0.0]
Broqvist 1994	1/9	1/13		0.2 %	1.44 [0.10, 20.21]
Brown 1992	0/5	0/5		0.0 %	0.0 [0.0, 0.0]
Bruce 2003	2/50	2/59		0.4 %	1.18 [0.17, 8.08]
Carver 1995	0/20	0/20		0.0 %	0.0 [0.0, 0.0]
Daniels 2003	2/49	2/51		0.4 %	1.04 [0.15, 7.10]
Deletter 1991	0/18	0/17		0.0 %	0.0 [0.0, 0.0]
Delmi 1990	6/27	10/32		2.1 %	0.71 [0.30, 1.70]
Edington 2004	17/51	15/49		3.5 %	1.09 [0.61, 1.93]
Eneroth 2004	1/26	1/27		0.2 %	1.04 [0.07, 15.75]
Fiatarone 1994	1/49	1/51		0.2 %	1.04 [0.07, 16.18]
FOOD trial 2005	241/2016	253/2007		57.8 %	0.95 [0.80, 1.12]
Gariballa 1998	2/20	7/20		1.6 %	0.29 [0.07, 1.21]
Gariballa 2006	32/222	19/223		4.3 %	1.69 [0.99, 2.89]
Gazzotti 2003	2/39	2/41		0.4 %	1.05 [0.16, 7.10]
Gray-Donald 1995	3/25	1/25		0.2 %	3.00 [0.33, 26.92]
Hampson 2003	0/36	1/35		0.3 %	0.32 [0.01, 7.70]
Hankins 1996	2/17	4/14		1.0 %	0.41 [0.09, 1.93]
Hubsch 1992	0/16	0/16		0.0 %	0.0 [0.0, 0.0]
Krondl 1999	0/35	0/36		0.0 %	0.0 [0.0, 0.0]
Kwok 2001	1/28	0/24		0.1 %	2.59 [0.11, 60.69]
Larsson 1990	29/197	55/238		11.3 %	0.64 [0.42, 0.96]
Lauque 2000	0/19	0/22		0.0 %	0.0 [0.0, 0.0]
Lauque 2004	2/46	0/45		0.1 %	4.89 [0.24, 99.18]
MacFie 2000	4/75	1/25		0.3 %	1.33 [0.16, 11.38]
Madigan 1994	4/18	0/12		0.1 %	6.16 [0.36, 104.90]

0.1 0.2 0.5 1.0 2.0 5.0 10.0

Favours treatment Favours control

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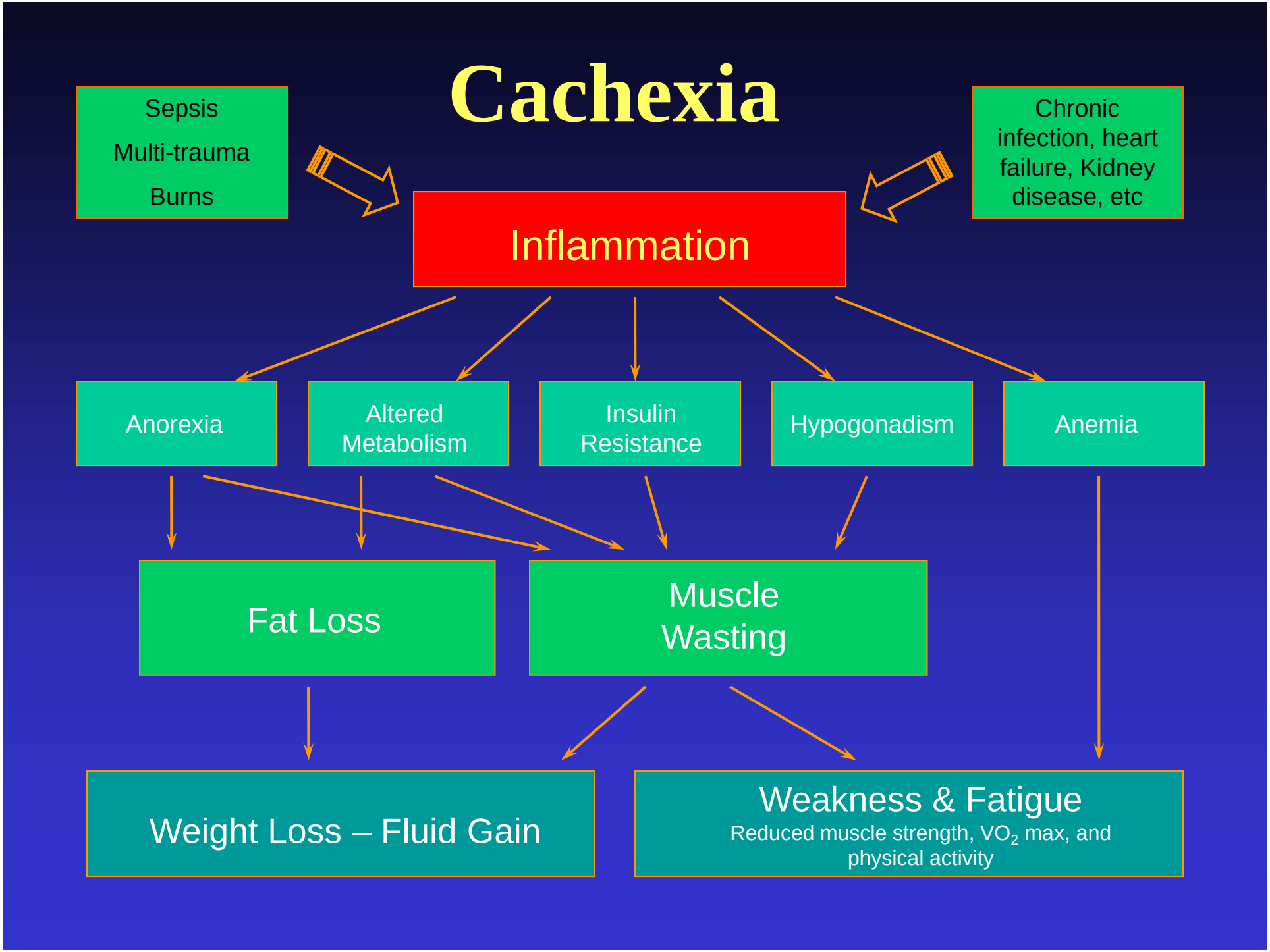
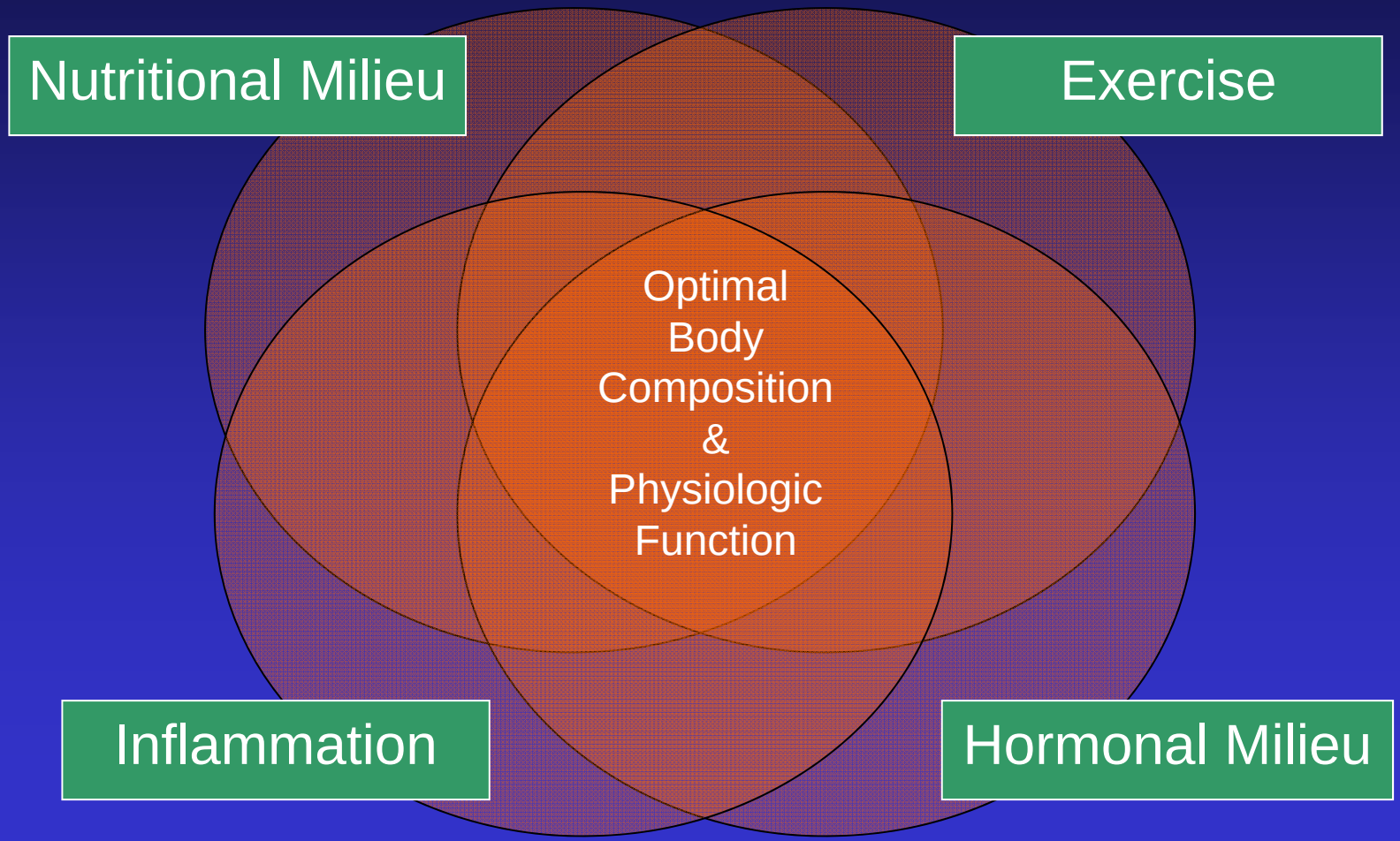

Cachexia
Sepsis
Multi-trauma
Burns
Chronic infection, heart failure, Kidney disease, etc
Inflammation
Anorexia
Altered Metabolism
Insulin Resistance
Hypogonadism
Anemia
Fat Loss
Muscle Wasting
Weight Loss – Fluid Gain
Weakness & Fatigue
Reduced muscle strength, VO_2 max, and physical activity

Major Determinants of Nutritional Status



Many Unresolved Issues

1. Need better methods of assessing change in body composition during illness (triad) and recovery
2. Need to know how to better maintain/ restore lean body mass & physical function during/ after serious illness
3. Need better methods of determining what is an optimal nutrient intake during illness and recovery; What patients are likely to benefit from aggressive nutrition support and which are not? Are we ready for multi-site RCT?
4. Is it necessary to address other factors (such as inflammation, inactivity) along with low nutrient intake? How can this be done:
   a) AA
   b) immunonutrition
   c) anabolic agents
   d) anti-inflammatory agents
   e) exercise