Università degli Studi di Palermo. Scuola di Medicina e Chirurgia
U.O.C. di Geriatria e Lungodegenza
Direttore prof. M. Barbagallo

SOCIETÀ ITALIANA DI GERONTOLOGIA E GERIATRIA

INTERNATIONAL ASSOCIATION OF GERONTOLOGY AND GERIATRICS

Il ruolo dell'anemia nel determinismo della fragilità

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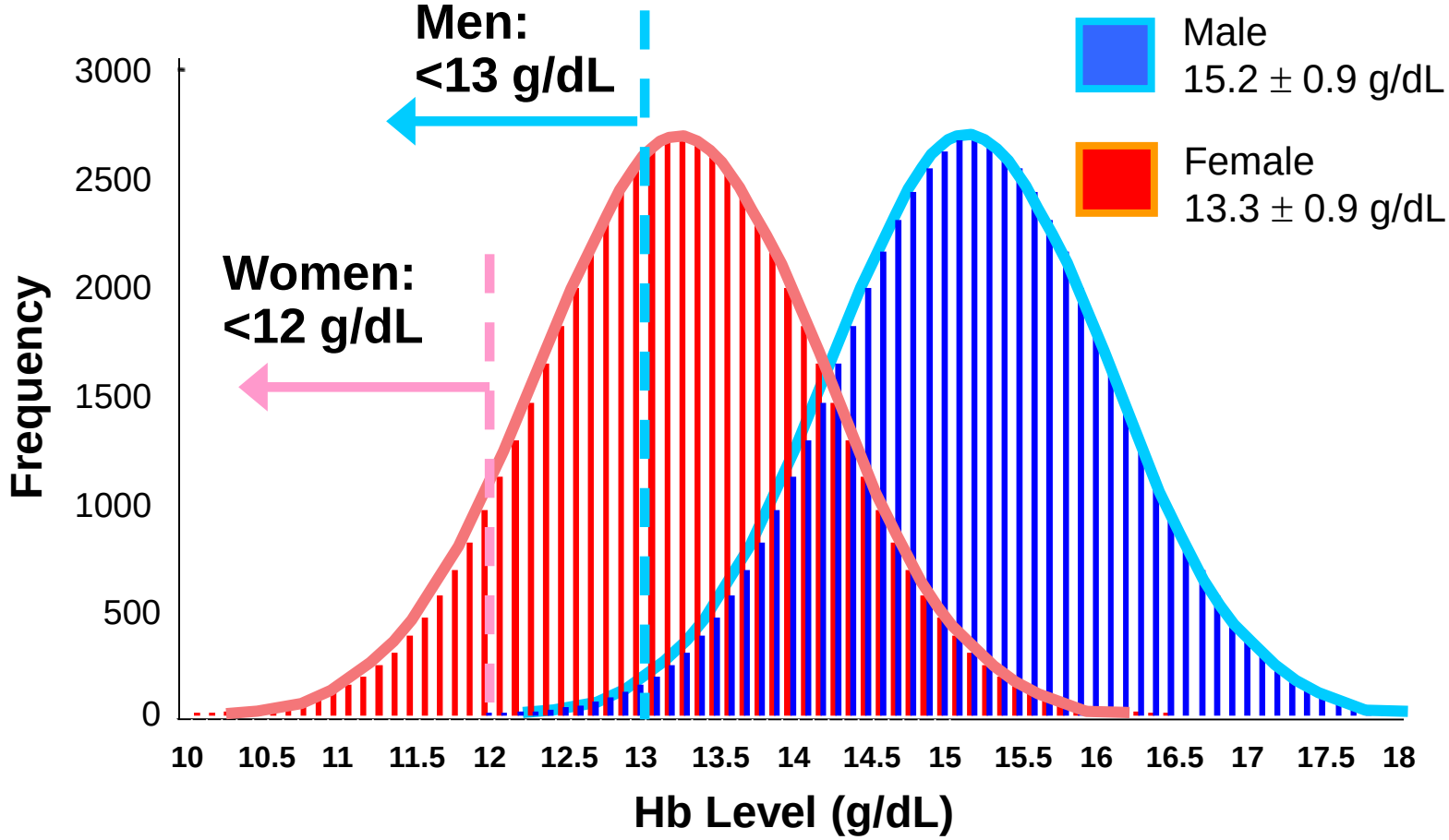
Outline

- Considerazioni Epidemiologiche
- Cause e Meccanismi
- Anemia, Infiammazione e malattie croniche
- Anemia nell’anziano come meccanismo di fragilità, dipendenza funzionale ed aumentato rischio di mortalità

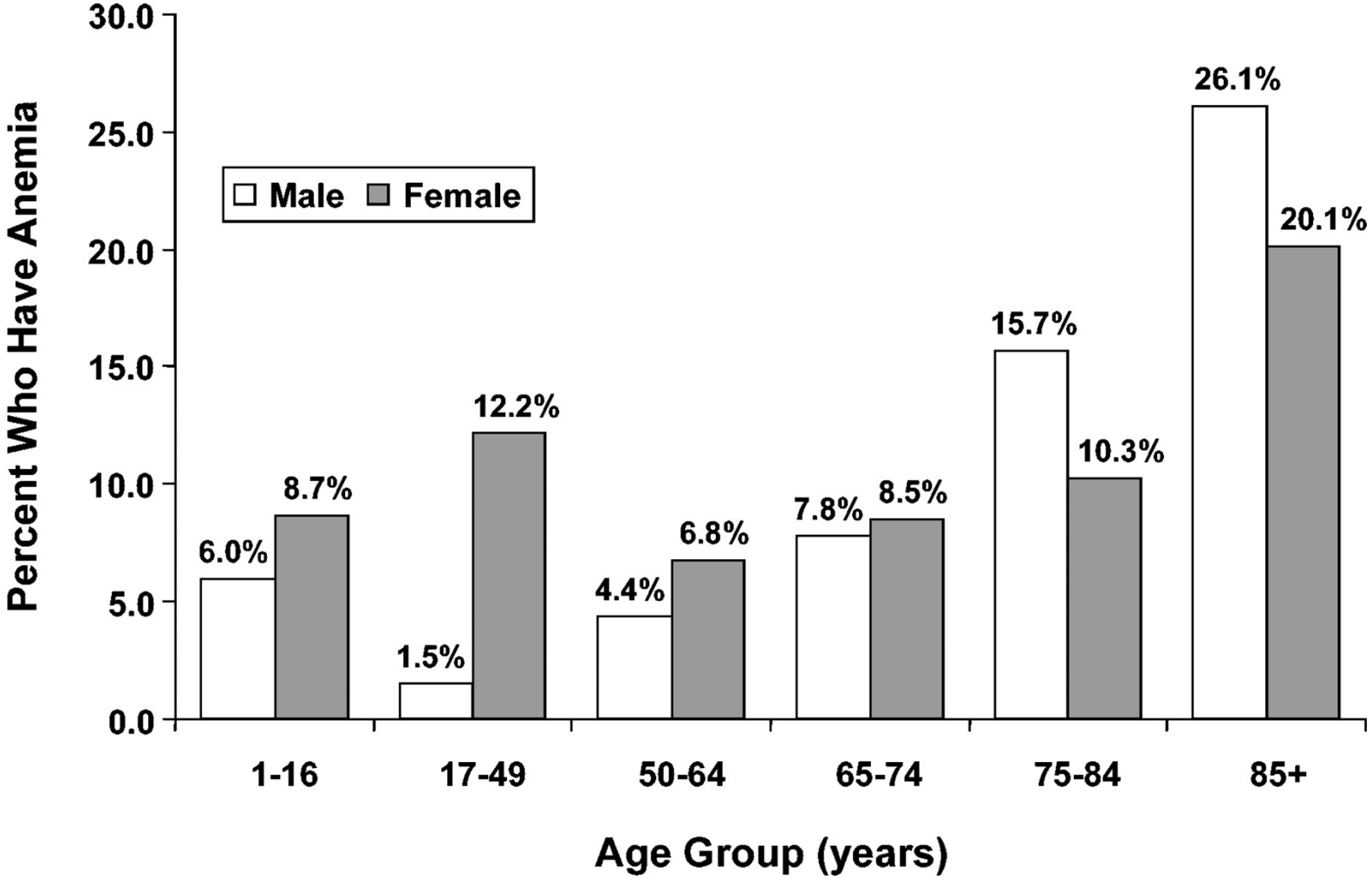
WHO Anemia Definition[1] vs Normal Hb Distribution[2]



Although a hemoglobin level lower than Hb < 13 g/dL in men and < di 12 g/dL in women (1) is commonly used, it has become clear that hemoglobin is actually a <u>continuous variable.</u>

1. World Health Organization. Geneva, Switzerland; 2001. 2. Dallman et al. In: *Iron Nutrition in Health and Disease*. London, UK: John Libbey & Co; 1996:65-74.

Epidemiology of Anemia and Aging according to age and sex



Guralnik JM et al. NHANES III, Blood 2004;104:2263-2268

Anemia in Geriatric Populations

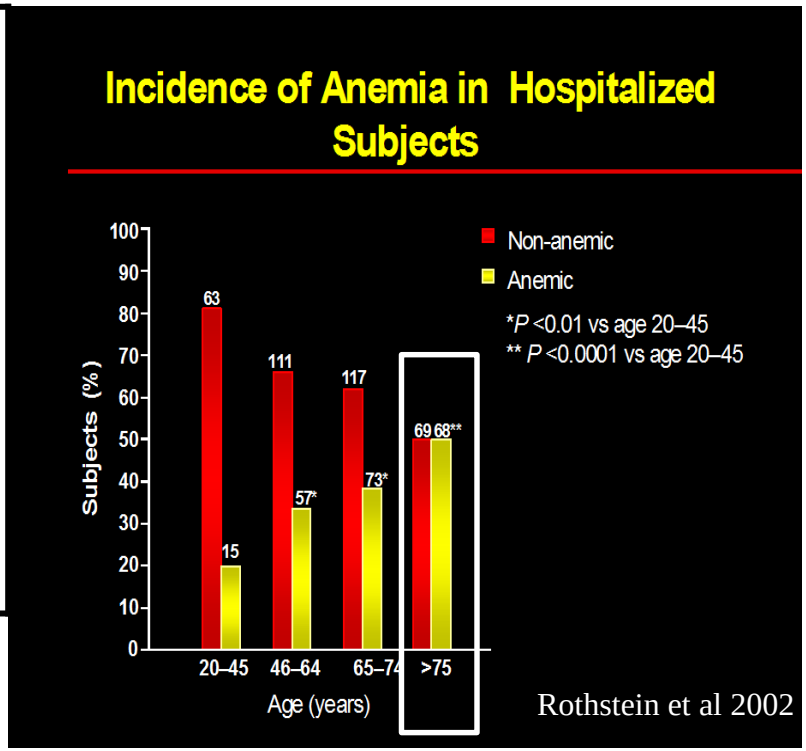
	Population	% Anemic
Guralnik et al. *Blood*. 2004;104:2263-2268.	Community (NHANESIII)	11%
Ble et al. *Arch Intern Med*. 2005;165:2222-2227.	Community (InCHIANTI)	10%
Tecson et al. ASIA.	Community, internal medicine practices	21%
Artz et al. *Arch Gerontol Geriatr*. 2004;39:201-206.	Nursing Home (NGRC)	48%

Only one fourth of examined medical records from older adults identified anemia as a concern, despite documented Hgb levels below 11.0 g/dL

Schrier. *Blood*. 2004;104:2214.

Prevalence of anemia in institutions

Chen et al, 1989	23.8%
Chernetsky et al, 2002	31%
Kalchthaler & Tan, 1980	39%
Joosten et al, 1992	42%
Bird et al, 1977	37%
Celestin-Roux, 1987	34.5%
Robinson et al, 2007	59.6%
Pandya et al, 2008	56%
Artz et al, 2008	48%



Rothstein et al 2002

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ANEMIA AND AGING: CAUSES

	ANIA	JOOSTEN	GURALNIK (NHANES III)
INFECTION	23%	13%	-
Anemia Chronic Disease (ACD)	17%	33%	20%
Iron deficiency	8%	17%	20%
Nutritional	8%	11%	14%
Chronic Kidney Disease	8%	8%	12%
Unexplained Anemia (UA)	36%	18%	34%

1) Anía BJ, et al. Prevalence of anemia in medical practice: community versus referral patients. *Mayo Clin Proc*. 1994;**69**: 730-735.
2) Joosten E, et al. Prevalence and causes of anemia in a geriatric hospitalized population. *Gerontology*. 1992;**38**:111-117.
3) Guralnik JM et al. Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia Blood 2004;104:2263-2268

ANEMIA AND AGING:CAUSES

	Anemic elderly			Mildly anemic elderly		
	n	%	%	n	%	%
Thalassemia trait	71	14.4		67	15.4	
Thalassemia			11.2			12.0
Thalassemia + low B_{12} or folate			3.2			3.4
Vitamin B_{12} or folate deficiency	50	10.1		44	10.1	
Low vitamin B_{12} and MCV higher than 95 fL			3.9			4.2
Low folate and MCV higher than 95 fL			4.2			4.1
Low vitamin B_{12} + low folate and MCV higher than 95 fL			2.0			1.8
Iron deficiency anemia (IDA)	79	16.0		54	12.4	
IDA			9.5			7.1
IDA + low vitamin B_{12} and/or folate			6.5			5.3
Anemia of chronic disease (ACD)	86	17.4		80	18.4	
ACD			8.1			9.0
ACD + low vitamin B_{12} or folate			3.7			4.1
ACD + IDA			2.4			2.8
ACD + IDA and/or low vitamin B_{12} or folate			1.4			1.1
Hematologic malignancy			1.8			1.4
Renal insufficiency	74	15.0		63	14.5	
Renal insufficiency			9.7			10.0
Renal insufficiency + thalassemia			0.6			0.4
Renal insufficiency + IDA and/or low vitamin B_{12} and/or low folate			4.7			4.1
Unexplained anemia	130	26.4		124	28.5	
Unexplained			18.3			20.0
Possible myelodysplastic syndromes[a]			8.1			8.5
Other types of anemia	3	0.6		3	0.7	
Total anemia types	493	100		435	100	
Insufficient laboratory data	33	6.3		30	6.4	
Total anemic subjects	526			465		

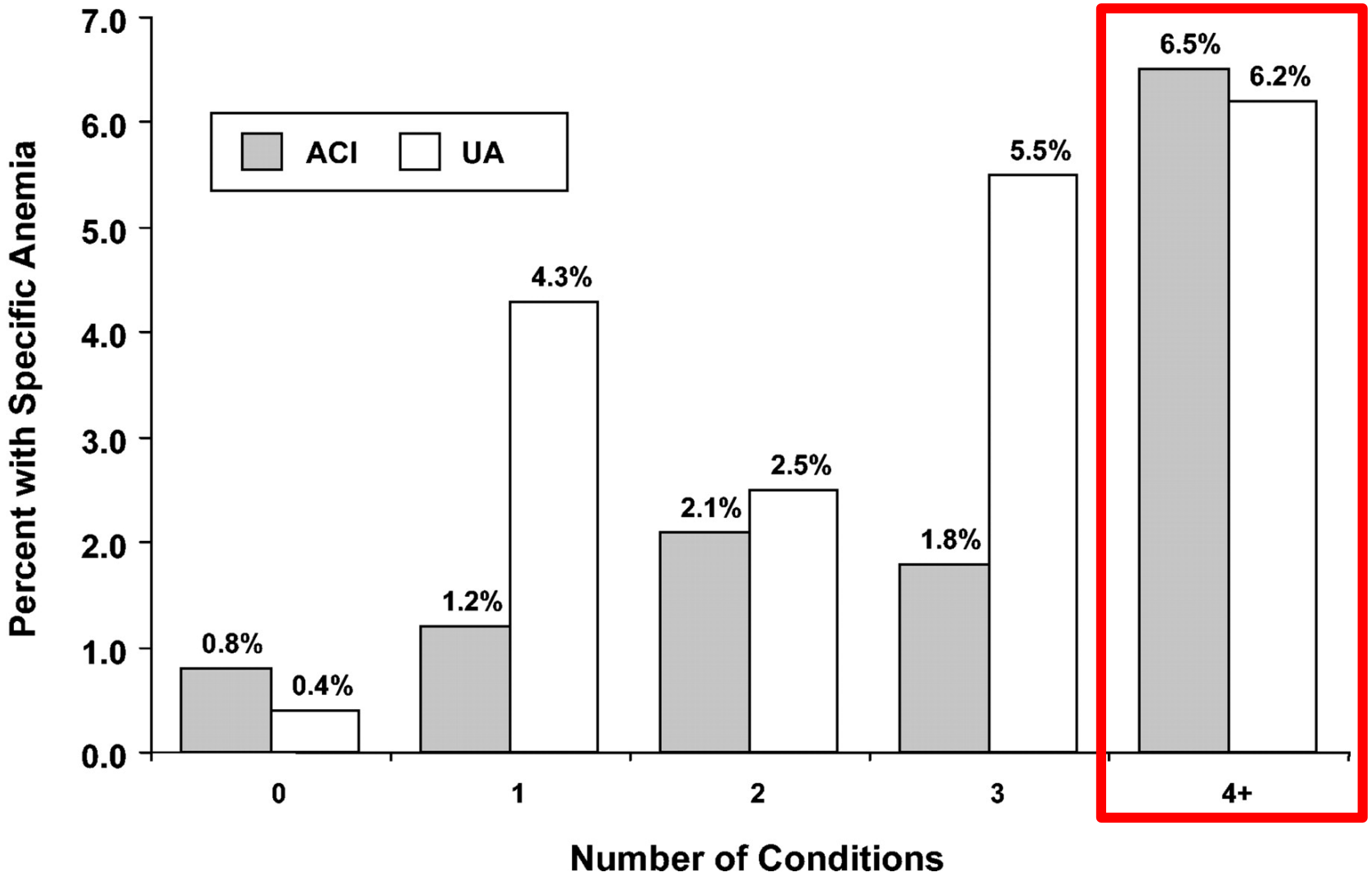
[a]*Possible myelodysplastic syndromes: macrocytosis, leukopenia, or thrombocytopenia.*

Tettamanti, M. et al. Haematologica 2010;95:1849-1856

Defining "Unexplained Anemia (UA)"

- Normocytic, usually mild (Hgb 11 g/dL)
- Normal iron and vitamin levels
- Creatinine clearance ≥30 mL/min
- No inflammatory disease (by history) and no serological evidence for active inflammation (ESR, CRP)
- No evidence (peripheral blood) of myelodysplasia

Anemia of Chronic Disease (ACI), Unexplained Anemia (UA) and Comorbidity



Conditions include asthma, arthritis, hypertension, stroke, cancer, congestive heart failure, diabetes.

Guralnik JM et al. Blood 2004;104:2263-2268

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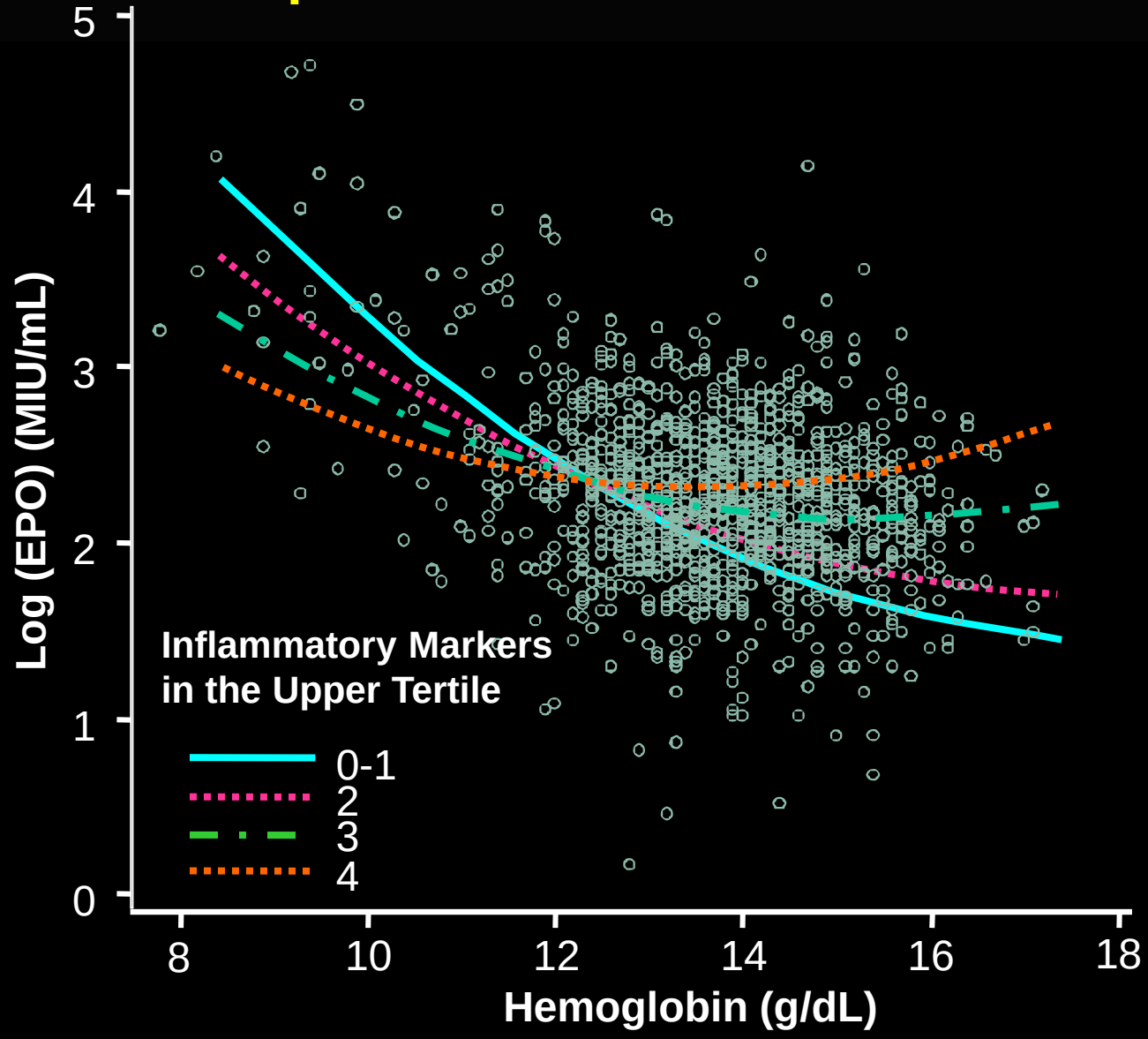
Anemia e Inflammation

Reduced EPO response with elevated inflammation markers



Ferrucci et al. *Am J Med*. 2005;118.1288.

Erythropoietin Deficiency

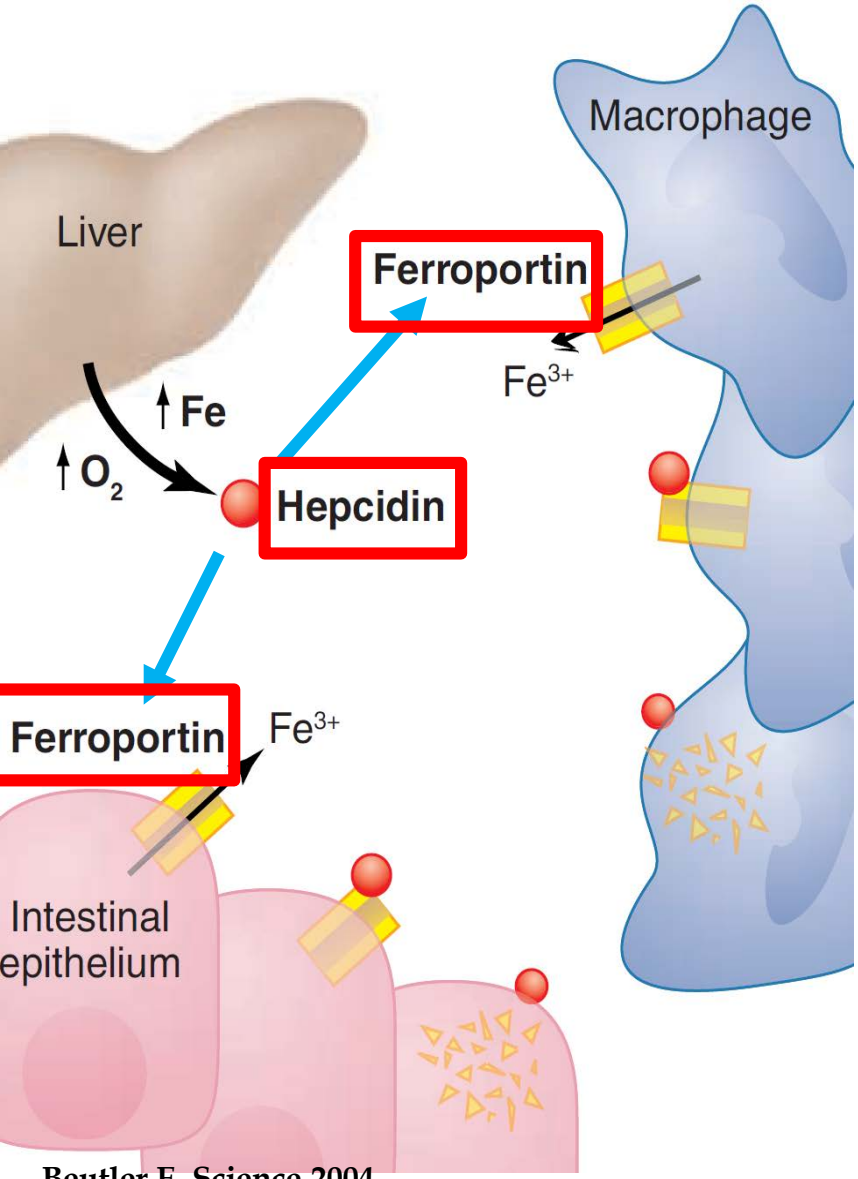
Relative epo insufficiency: a new concept?

- **Absolute**
  - **Renal Insufficiency (clinical or subclinical)**
  - **Primary Erythropoietin Deficiency (Reduced Epo secretion)**
- **Relative**
  - **Anemia of inflammation**

Anemia of Chronic Disease

- **Anemia of chronic disease reflects current concepts in the pathophysiology of the disease, with elevated inflammatory cytokines stimulating the production of hepcidin, which causes reduced intestinal iron absorption and decreased release of iron by the macrophages.**
- **One feature of this condition that has remained consistent from its earliest description is reduced levels of circulating serum iron despite adequate or increased total iron stores, and this was used for the definition we used for ACI.**
- **Distinguishing ACI from iron deficiency can be difficult.**

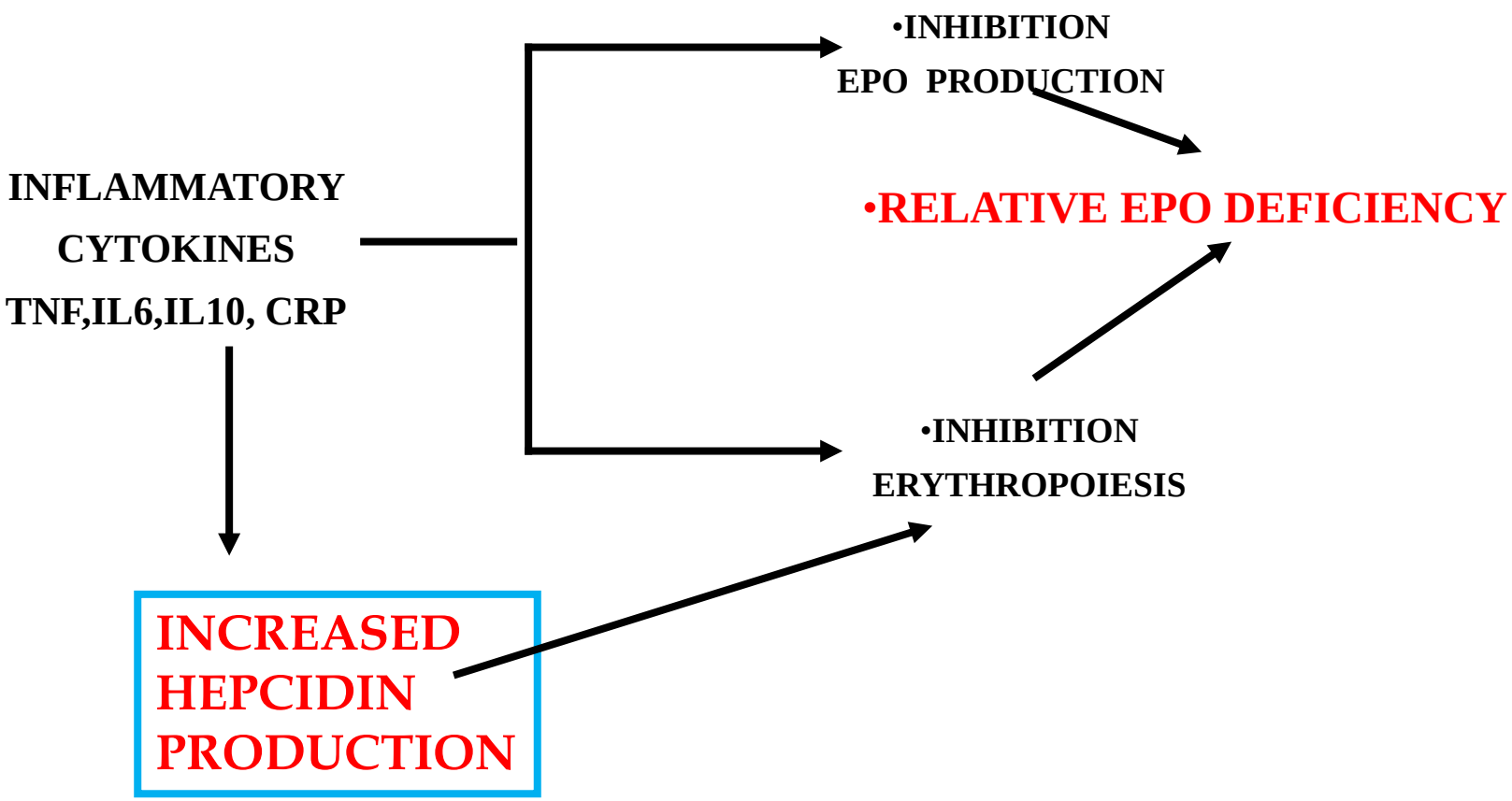
Anemia and Inflammation: Role of Hepcidin



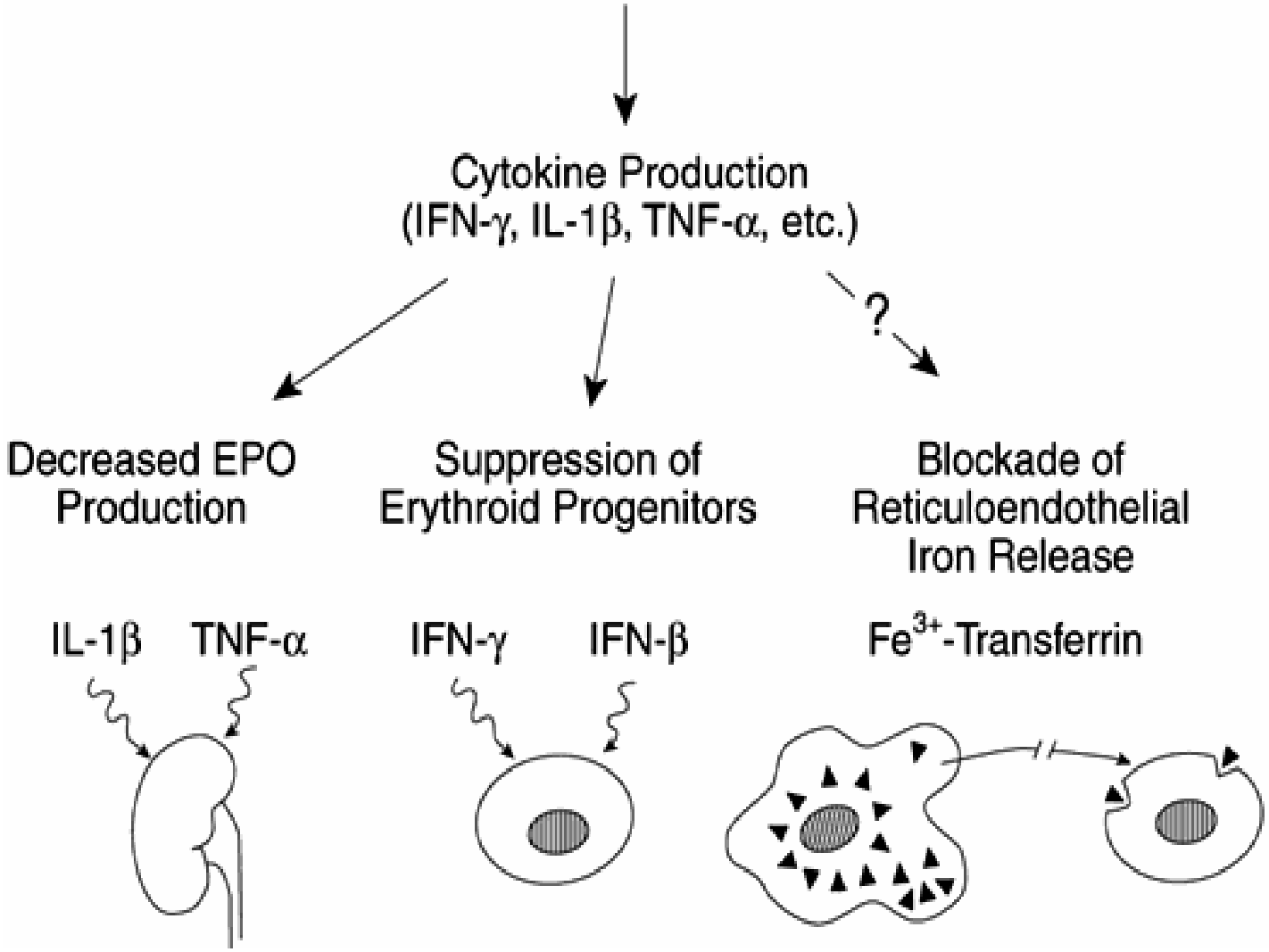
Beutler E, Science 2004

- **Hepcidin is an acute phase protein and an essential mediator of the complex anemia of inflammation (ACI), a form of anemia present in numerous disorders in which the blockage of iron absorption and recycling plays a major role.**
- **Hepcidin is produced by the liver in response to iron overload or inflammation, regulates the transport of iron out of cells. It is up-regulated by cytokines**
- **Hepcidin binds to the iron exporter ferroportin expressed on the surface of gut enterocytes and catabolizes it. Ferroportin is the protein that transports iron from the GI to the stores and from the stores to the erythropoietic precursors,**
- **Hepcidin may also prevent iron absorption on patients with ACI.**

Anemia of Chronic Disease
Role of Inflammation

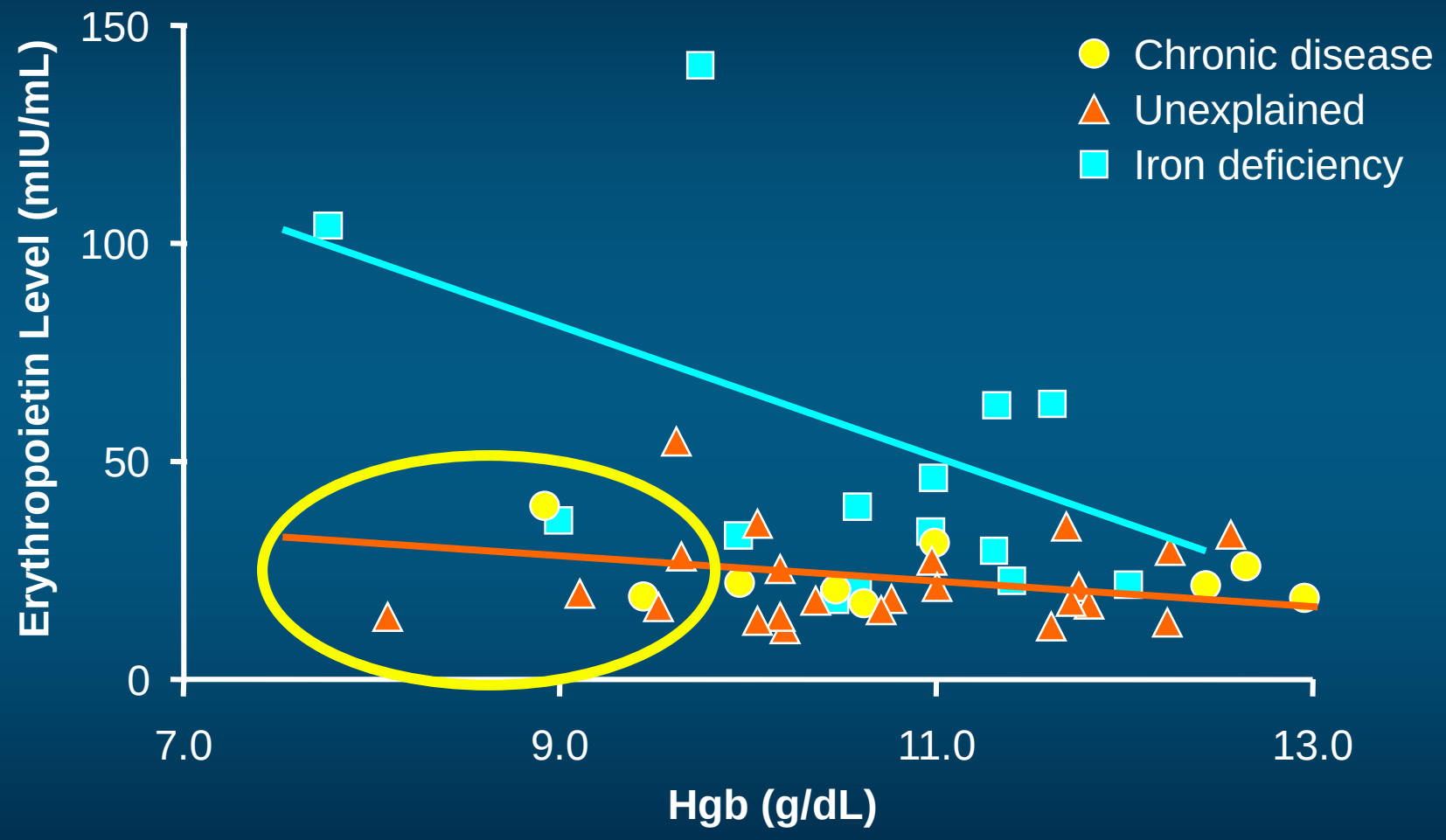


Pathogenesis of the Anemia of Chronic Disease



Balducci LM, 2003

"Anemia Unexplained"
Blunted EPO Production

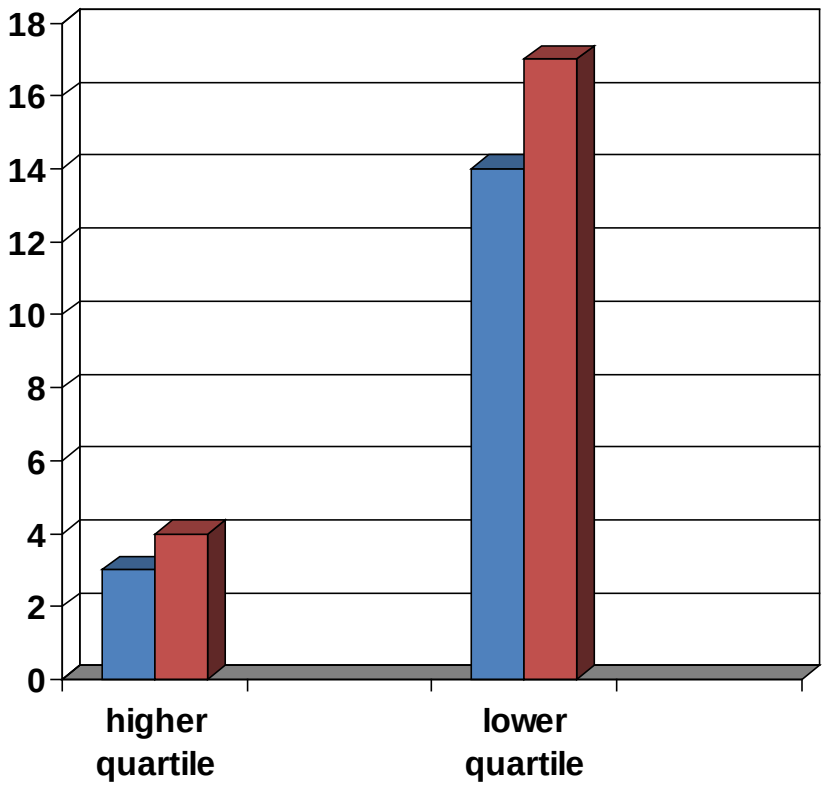


Artz et al. *J Am Geriar Soc*. 2004;52:423-427.

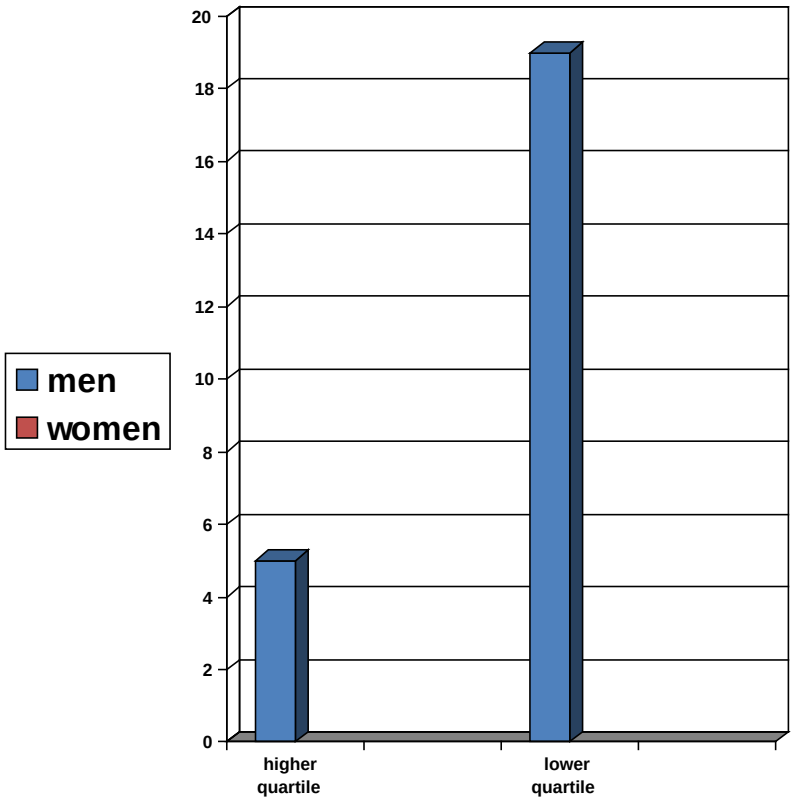
Anemia and aging: possible causes of unexplained anemia

- Relative erythropoietin insufficiency
- Subclinical chronic renal disease
- Myelodysplasia or Aplastic Anemia
- Hypogonadism

Anemia and testosterone



PREVALENCE



RISK OVER 3 YEARS

FERRUCCI ET AL, ARCH INTERN MED, 2006

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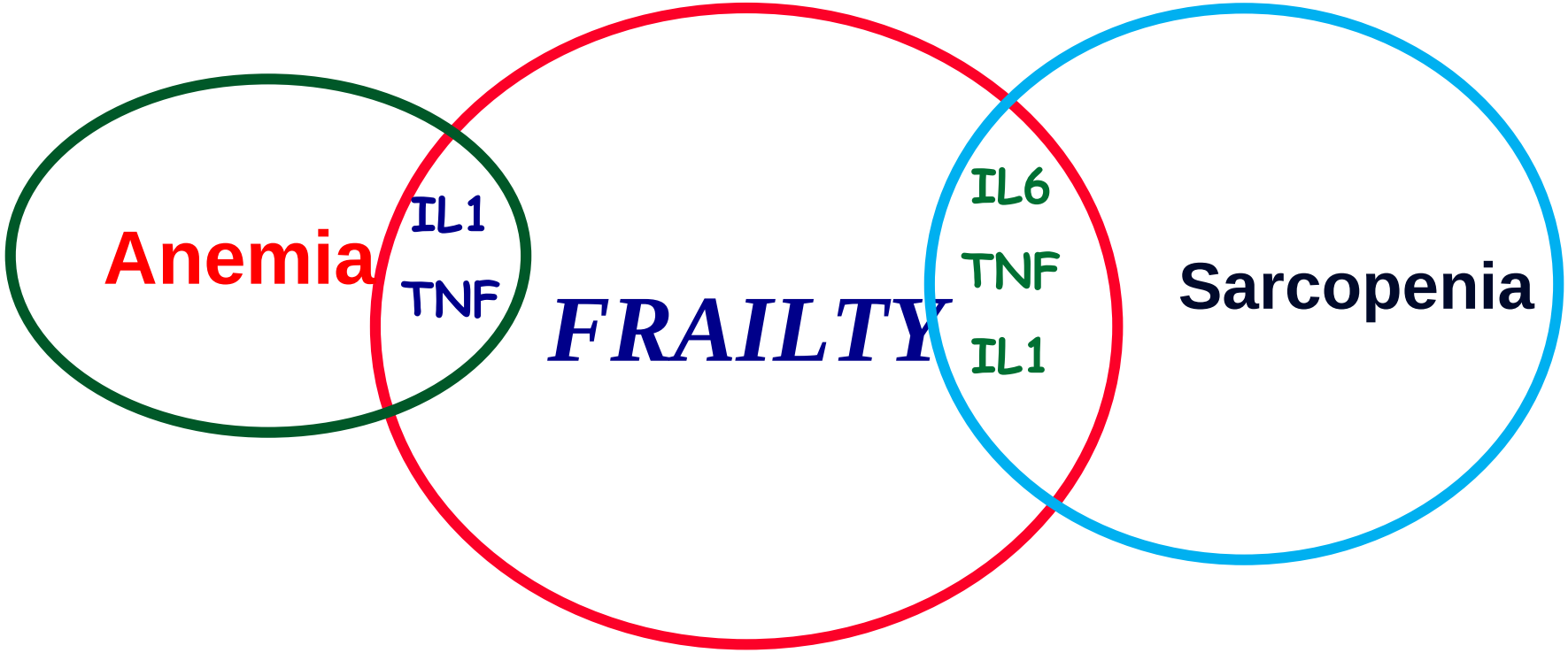
Consequences of Anemia in the Aged

- Functional Decline
- Cognitive Decline
- Cardiovascular complications
- Falls
- Mortality
- Iatrogenic complications
  - delirium
  - chemotherapy-related toxicity
  - Post-operative complications

Anemia and Frailty: a cytokine connection?



Understanding the impact of anemia

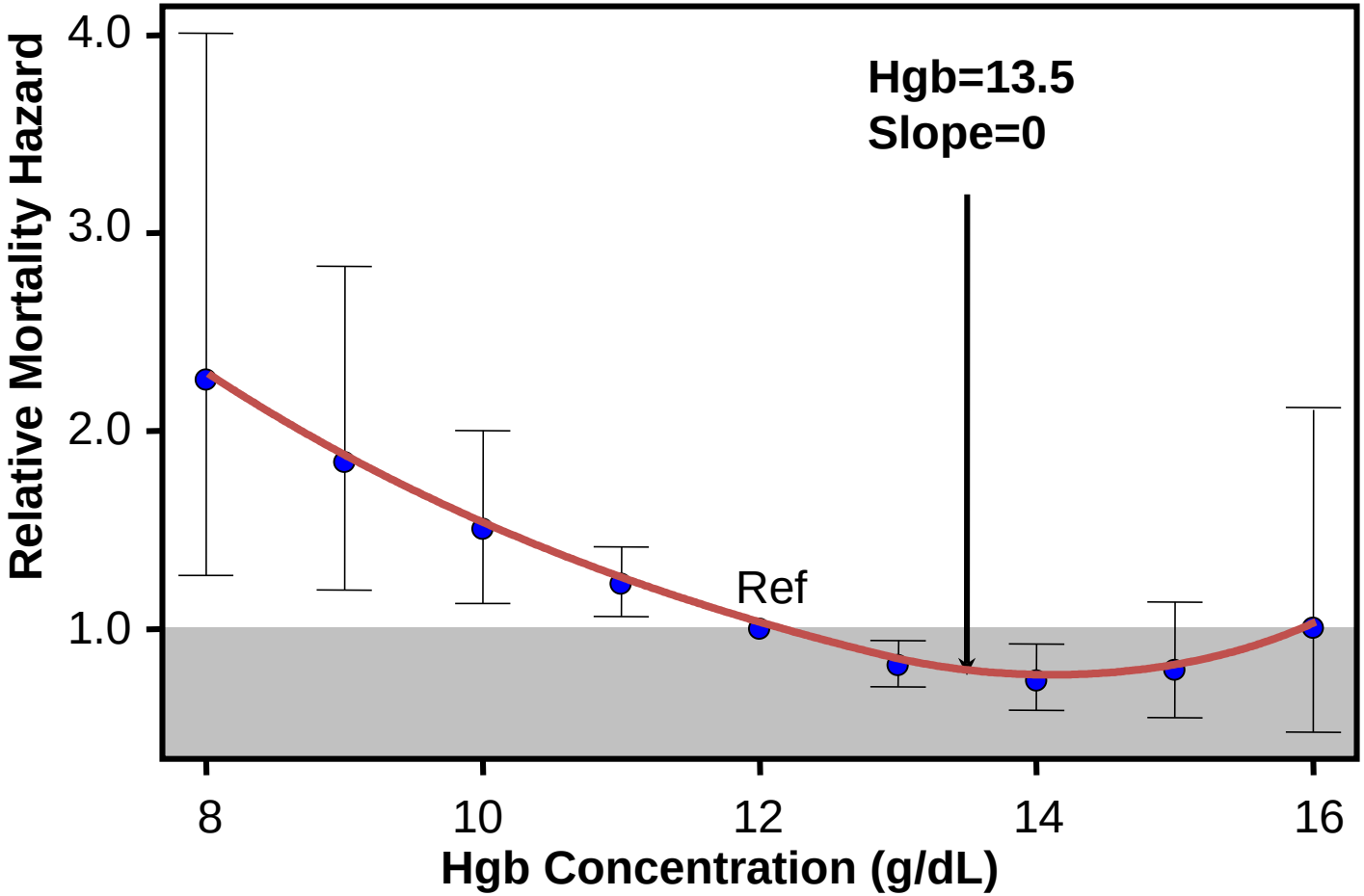
- Several studies have demonstrated poorer outcomes in older persons with anemia, than in nonanemic persons of the same age.
- These studies have shown this effect for mortality, for difficulty in mobility and for decline over time in objective measures of physical performance.
- In these studies, persons with anemia have more comorbidity, but statistical analysis suggests anemia as an independent predictor.
- Amelioration of anemia may have a beneficial impact on morbidity and mortality.

Anemia and Aging: Mortality

Mortality risk is significantly increased in elderly individuals with anemia
This increased risk is independent of diseases at baseline, or functional impairment

Chaves et al	>65, 2004	<13.4
Kikuchi et al	> 70, 2000	< 12
Den Elzen et al	> 85, 2010	<12
Ania et al	>70, 1999	<12
Zakai et al	> 65, 2005	< 13.7 men < 12.6 women
Penninx et al	>65, 2006	WHO criteria
Landi et al	>65, 2006	WHO
Riva et al	>65, 2009	12.2 & 13.2
Endres et al,	>65, 2009	WHO (men only)
Longo et al	> 65, 2005	WHO criteria

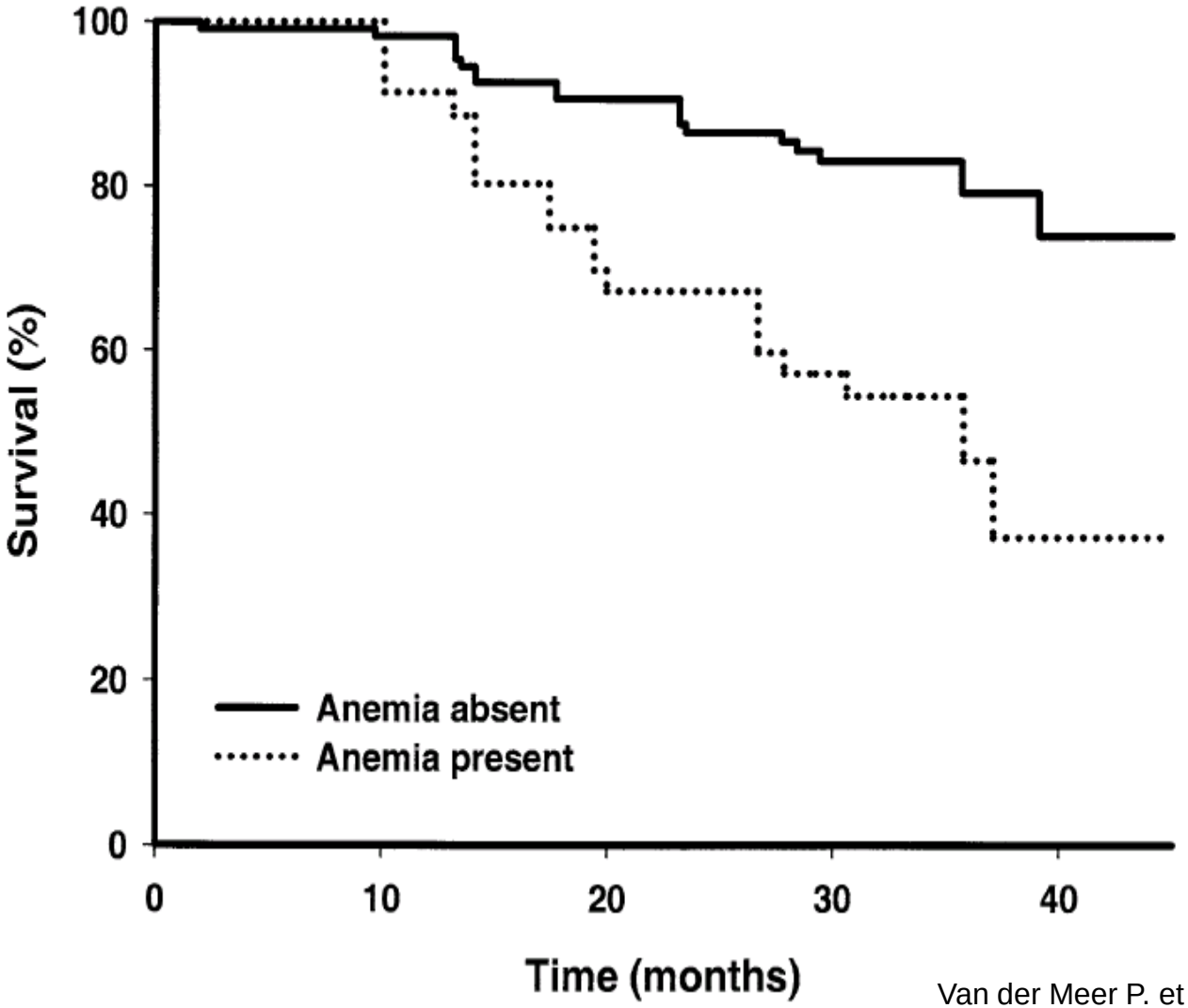
Hemoglobin and Mortality in Community-Dwelling Older Women (WHAS)



The Women's Health and Aging Studies (WHAS)

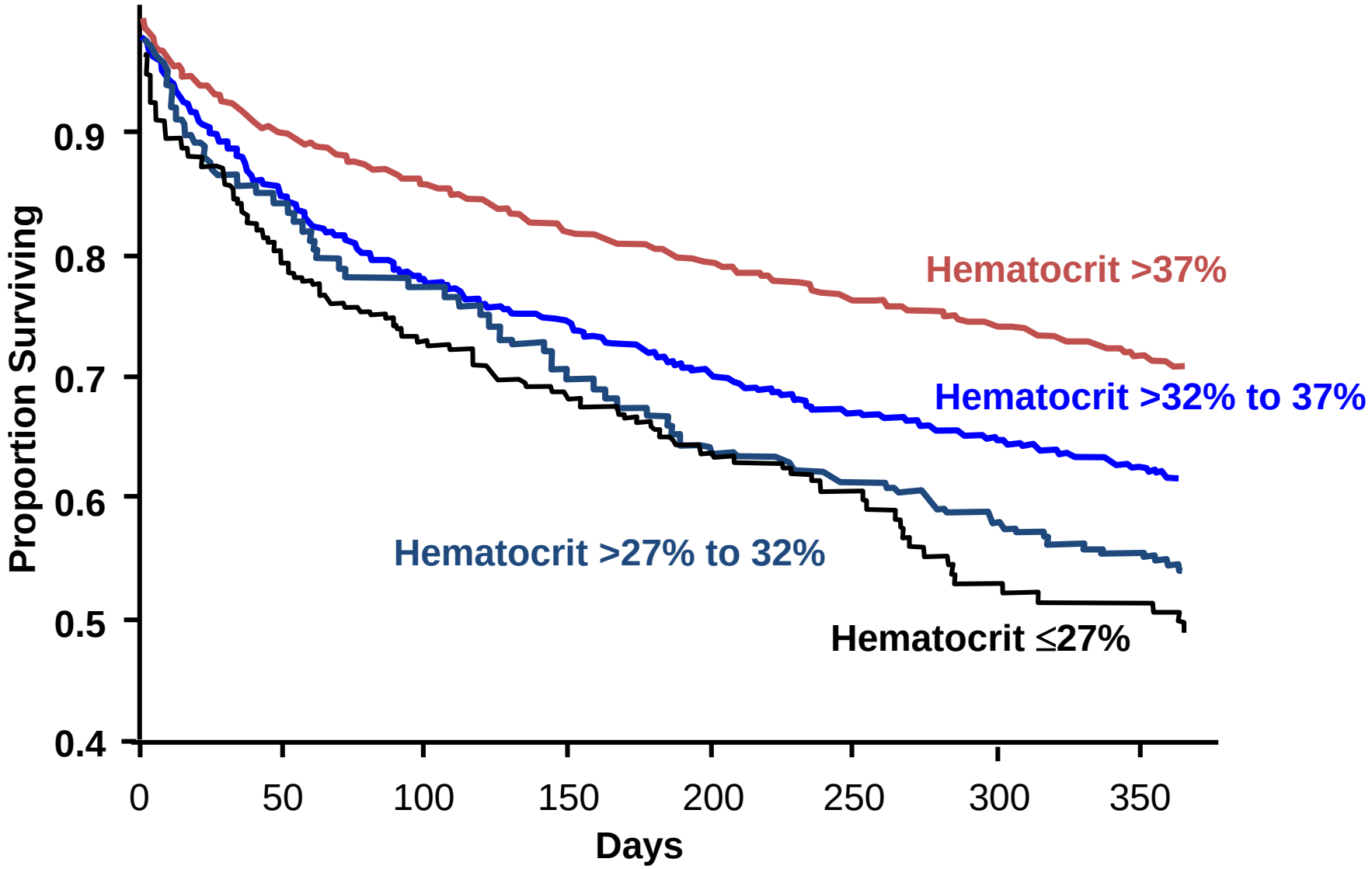
Chaves et al. *J Am Geriatri Soc.* 2002;52:1811-1816.

Prognostic Importance of Anemia in Heart Failure



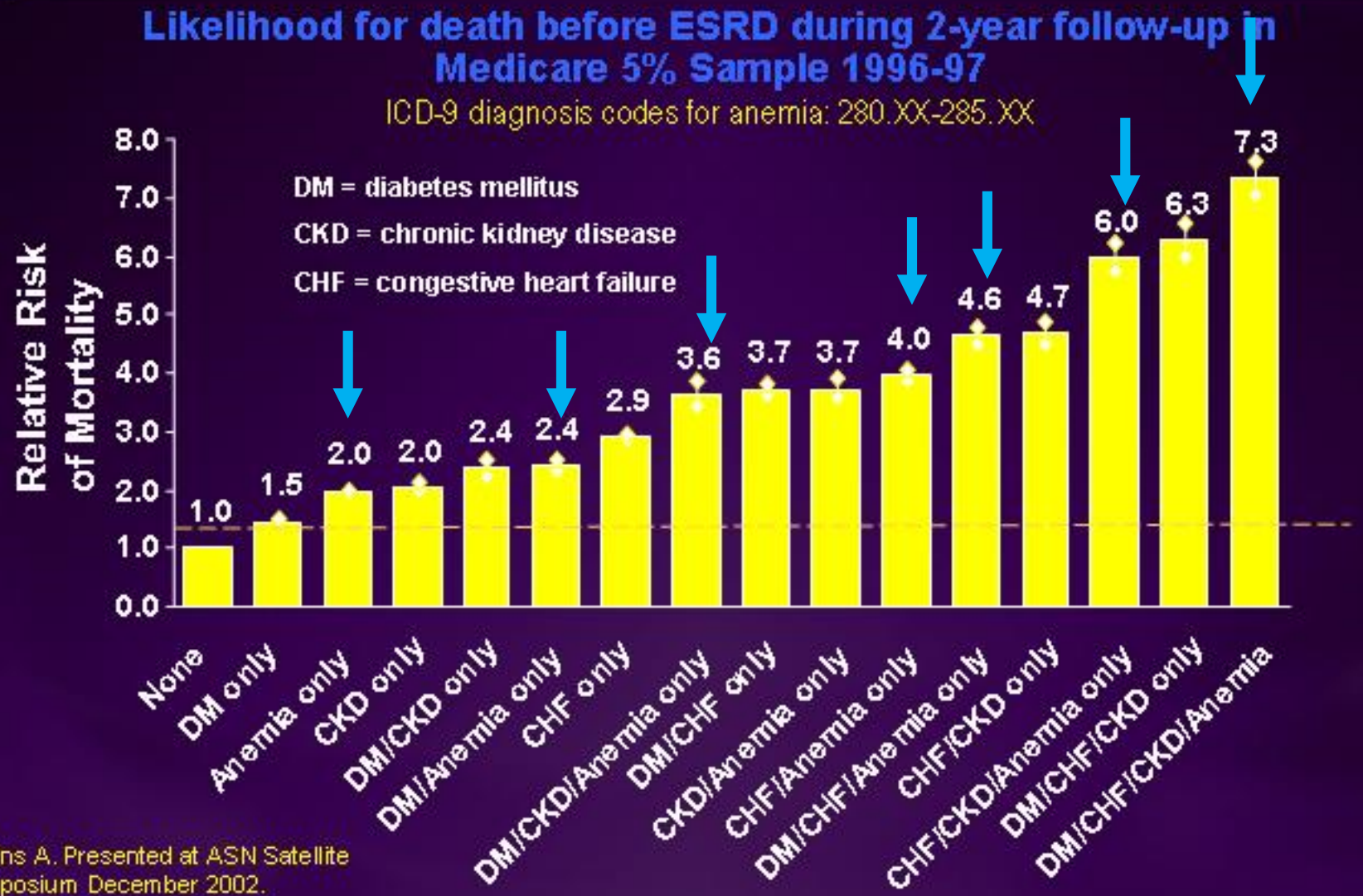
Van der Meer P. et al JACC, 2004

Survival in Older Patients With Heart Failure



Kosiborod et al. *Am J Med*. 2003;114:112-119.

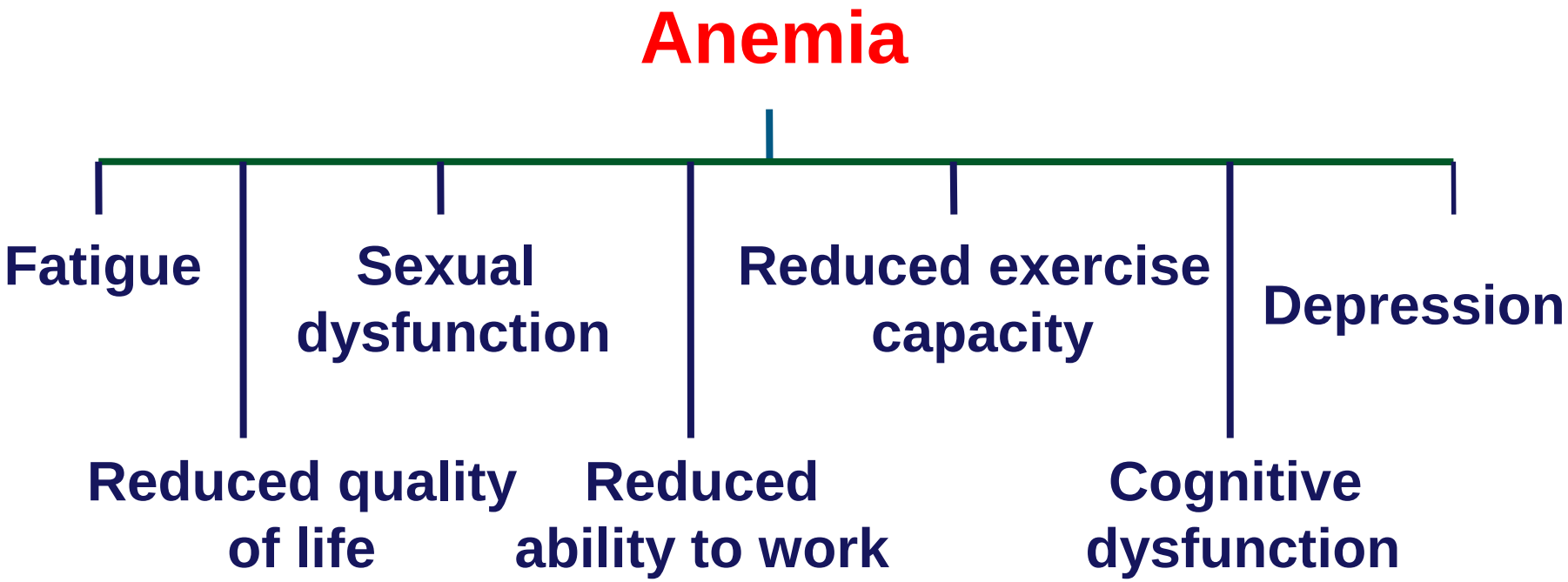
Anemia Is a Mortality Risk Multiplier



Collins A. Presented at ASN Satellite Symposium December 2002.

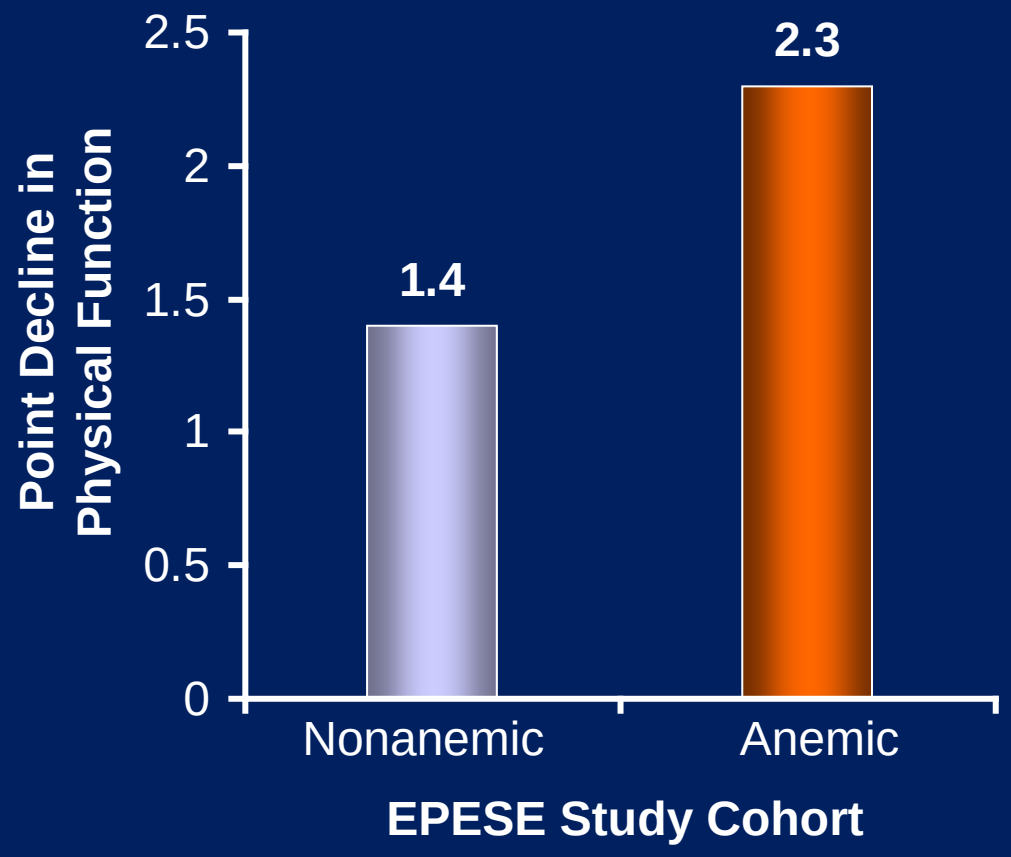
Anemia as a Risk Factor of Frailty and Functional Decline in the older subjects

Anaemia Impacts on Functional Capacity of Virtually all Organs/Tissues



Anemia Independently Leads to a Decline in Physical Performance in Older Adults:

Adjusted 4-years mean decline in physical performance score in the EPESE



- **Physical performance score:**
  - **Standing balance**
  - **Walking speed (8 ft/2.4 m)**
  - **Timed chair rising (1.5 point decline=50% increased risk of developing ADL disability)**

N=1146
Age = ≥71 y

Penninx et al. *Am J Med*. 2003;115:104-110.

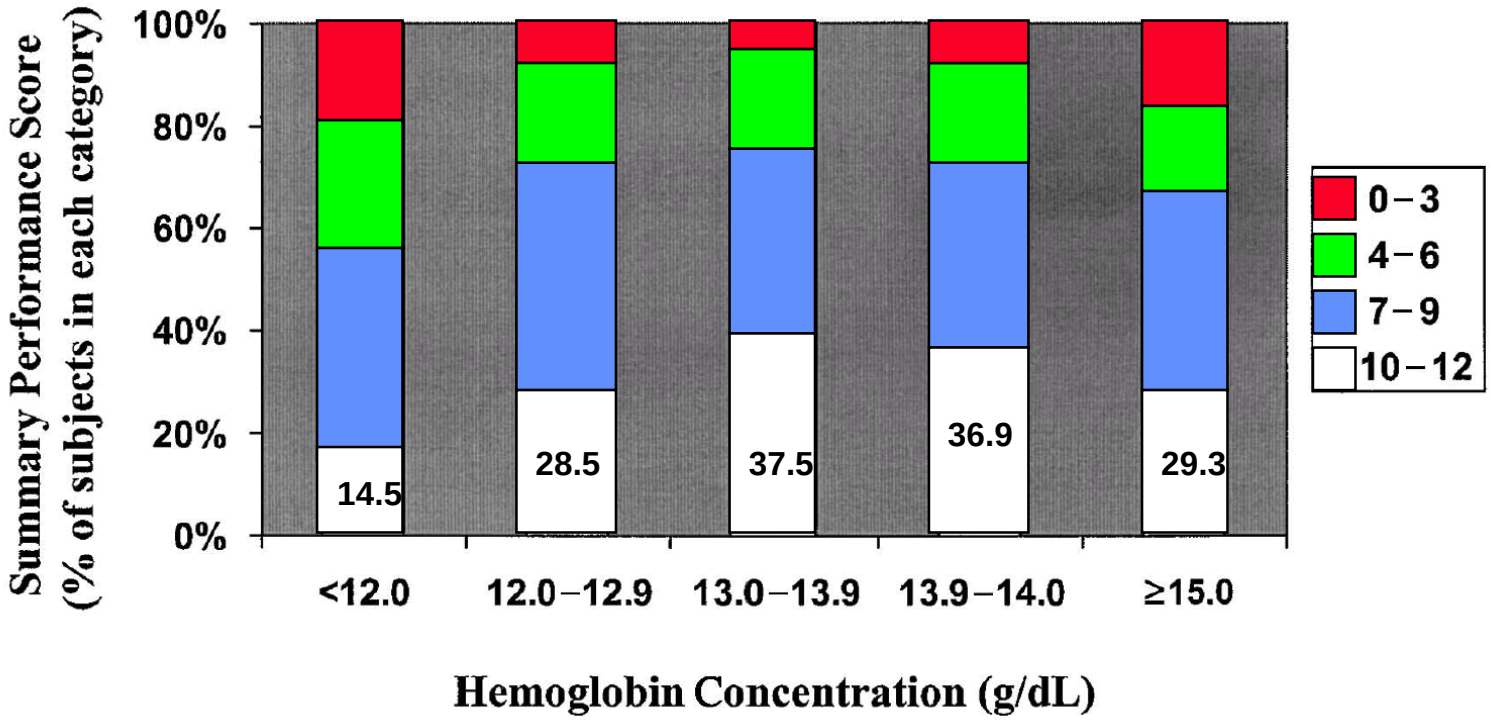
EPESE: Factors associated with a decline in physical performance after 4 years

Group	Number	Mean Adjusted Decline in Performance† (95% Confidence Interval)	*P* Value‡	*P* for Trend
Total sample				
No anemia	906	1.4 (1.2–1.5)	—	0.002
Borderline anemia	172	1.8 (1.5–2.2)	0.02	
Anemia	68	2.3 (1.7–2.8)	0.003	
Sample without cancer, infectious disease, and kidney disease				
No anemia	689	1.4 (1.6–1.2)	—	0.004
Borderline anemia	128	1.8 (2.2–1.4)	0.05	
Anemia	37	2.5 (3.2–1.7)	0.004	
Sample without hospitalizations in year before baseline				
No anemia	792	1.5 (1.3–1.6)	—	0.004
Borderline anemia	147	1.9 (1.6–2.3)	0.02	
Anemia	54	2.3 (1.7–2.9)	0.009	
Sample without hospitalizations in 4 years after baseline				
No anemia	448	1.2 (1.0–1.4)	—	0.09
Borderline anemia	82	1.3 (0.9–1.8)	0.51	
Anemia	25	2.1 (1.3–2.9)	0.03	
Sample with hospitalizations in 4 years after baseline				
No anemia	458	1.6 (1.4–1.8)	—	0.03
Borderline anemia	90	2.3 (1.8–2.8)	0.02	
Anemia	43	2.2 (1.5–3.0)	0.11	

Penninx BW. et al, Am.J.Med., 2003

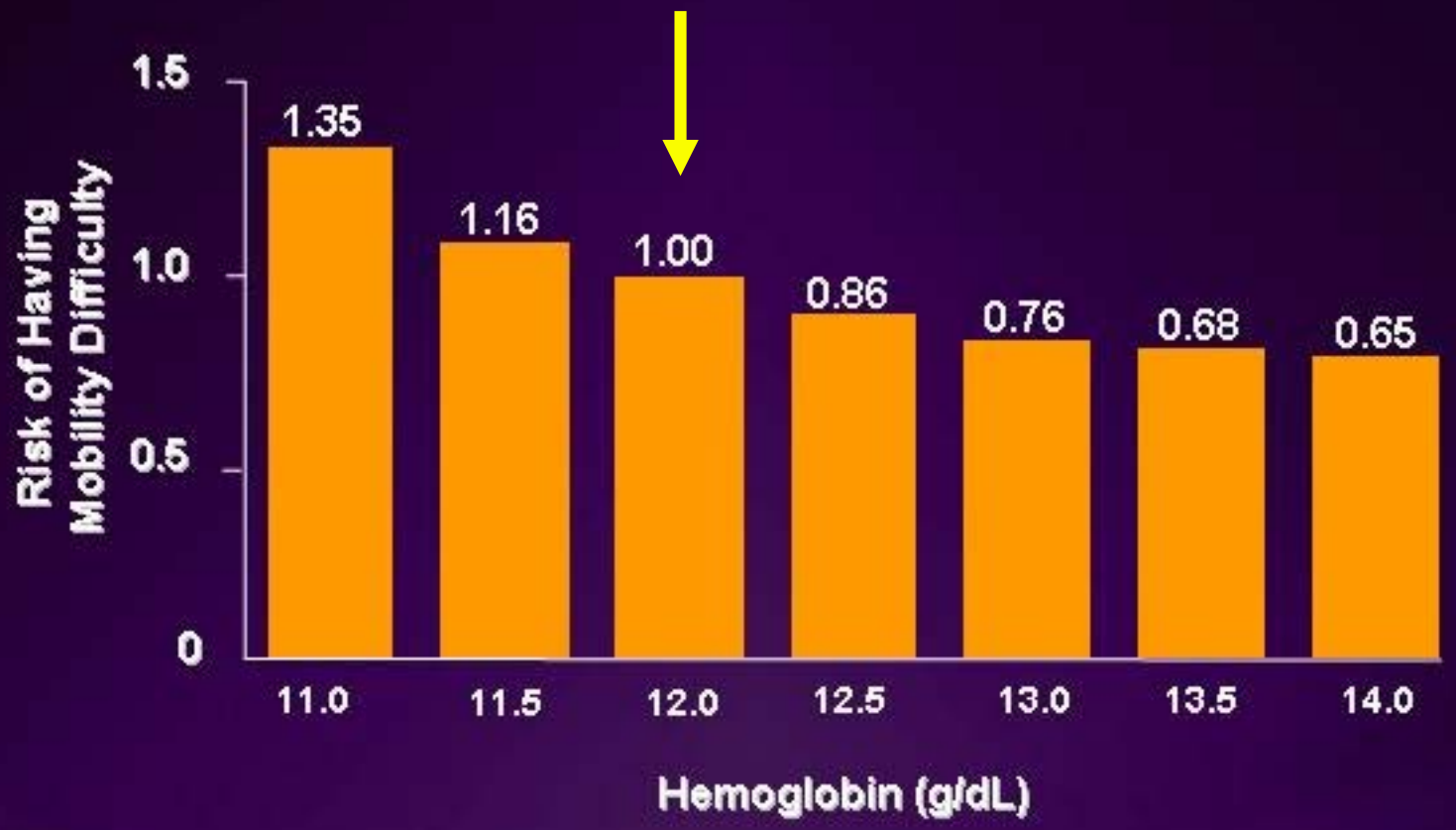
Summary Performance Score according to categories of hemoglobin concentration

Percentage of subjects in the best SPS category: scores 10 to 12 (i.e., best performance)
Women's Health and Aging Study (WHAS)



Chaves PH et al, JAGS 2002, 1257-1264

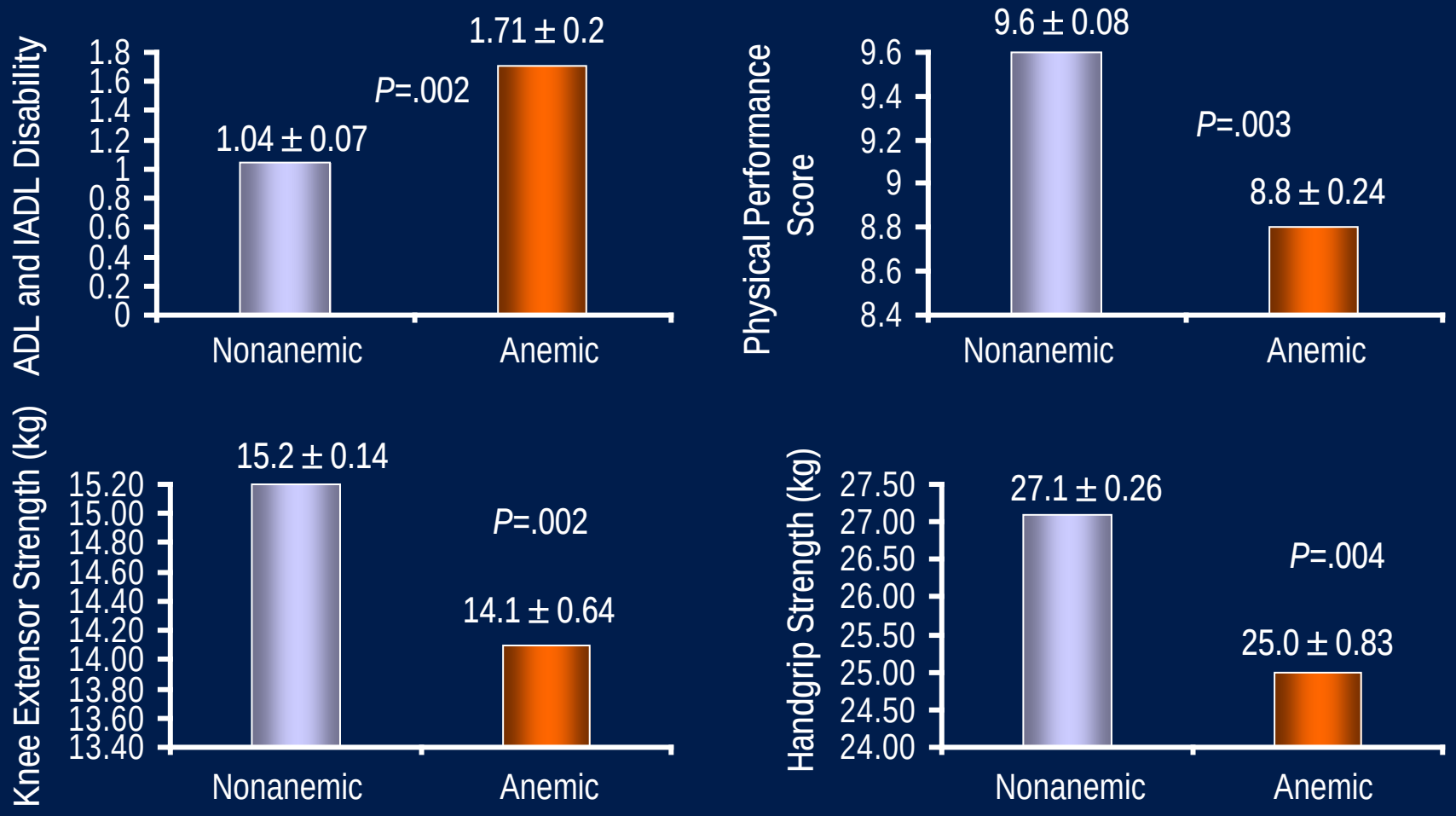
Declining Hemoglobin Linked to Mobility Difficulty



N = 673

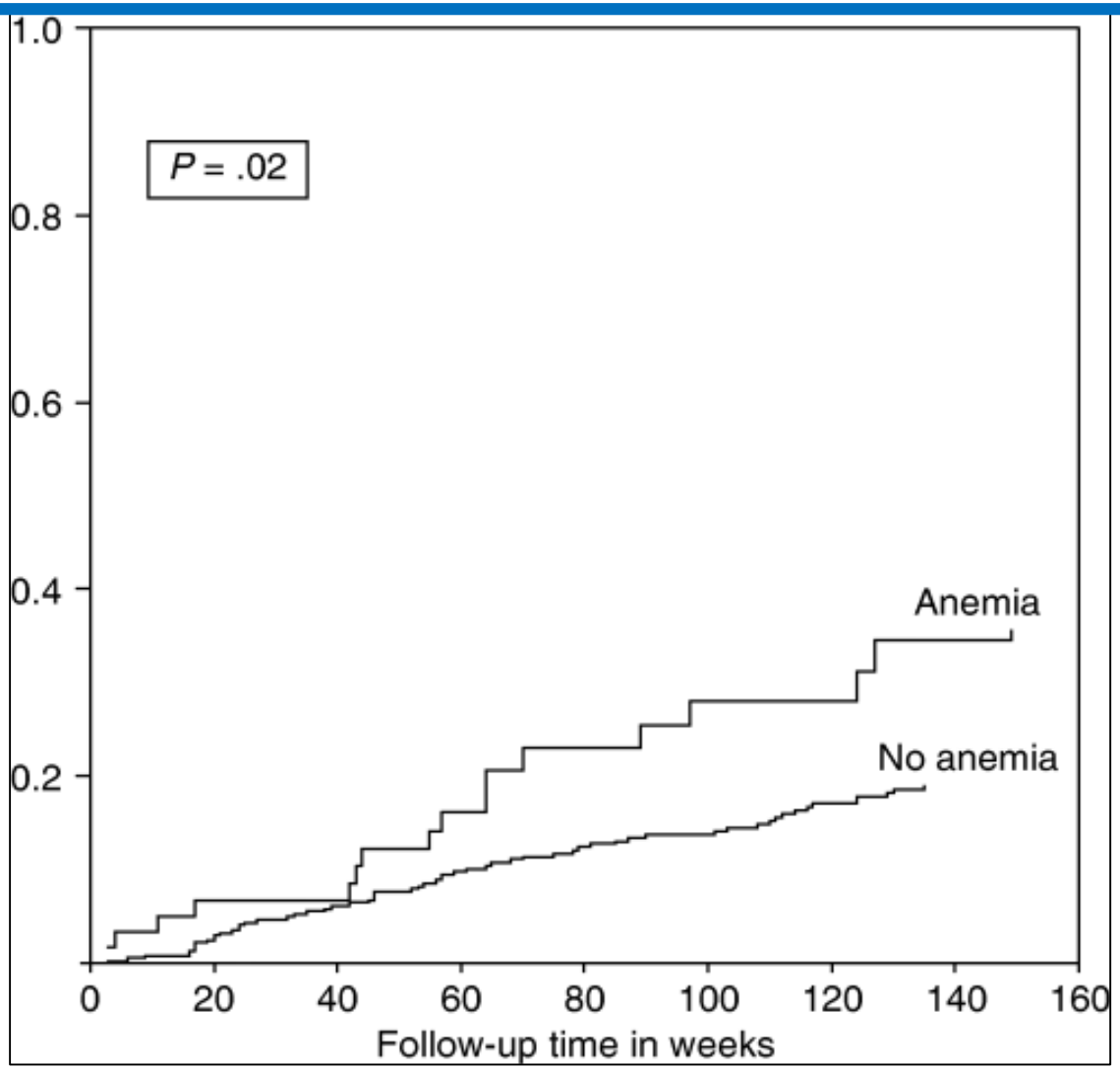
Chaves PHM, et al. *J Am Geriatr Soc*. 2002;50:1257-1264.

Anemia Is Associated With Disability, Poor Physical Performance, and Decreased Muscle Strength (InCHIANTI)



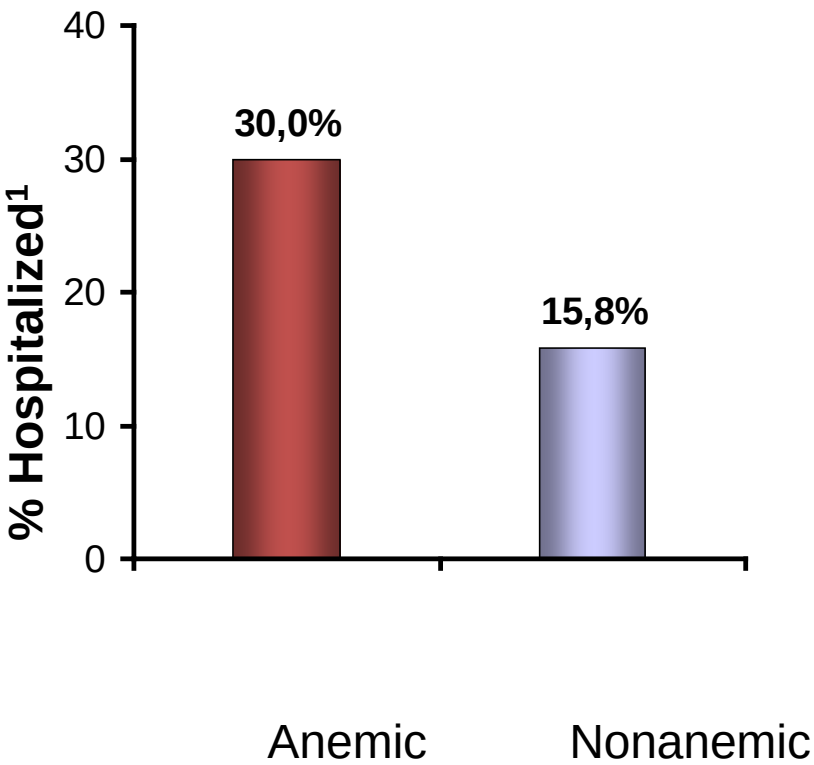
Penninx et al. *J Am Geriatr Soc*. 2004;52:719-724;
Cesari et al. *J Gerontol A Biol Sci Med Sci.* 2004;59:249-254.

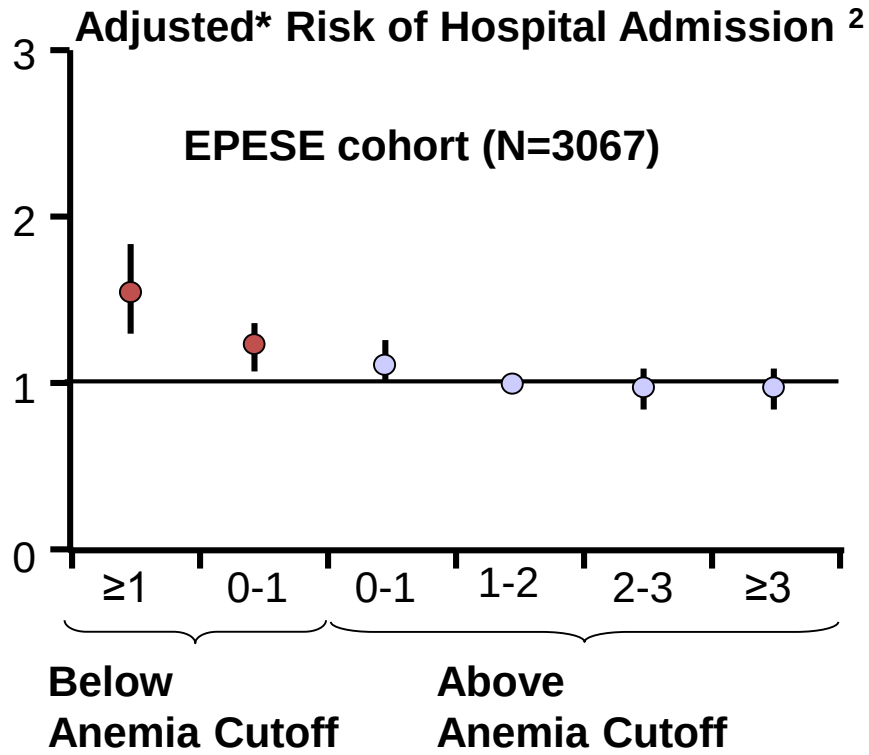
Anemia and Increased Risk of Falls in Older Adults



Penninx B. et al. *JAGS 2005: 53: 2106*

Anemia and Increased Risk of Hospitalization in Older Adults

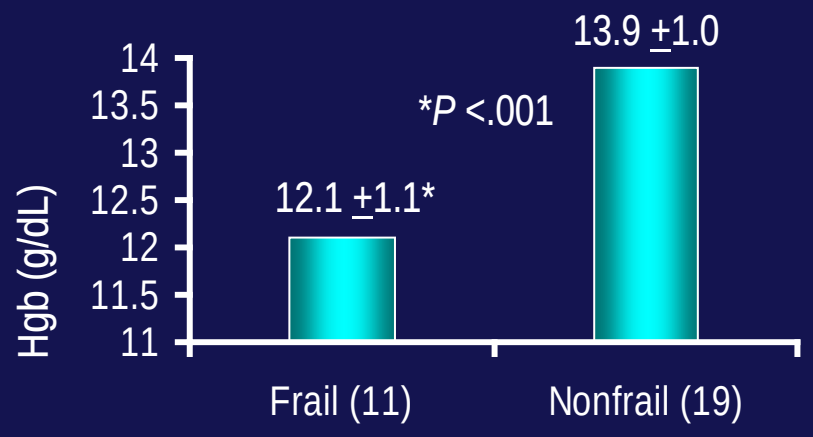


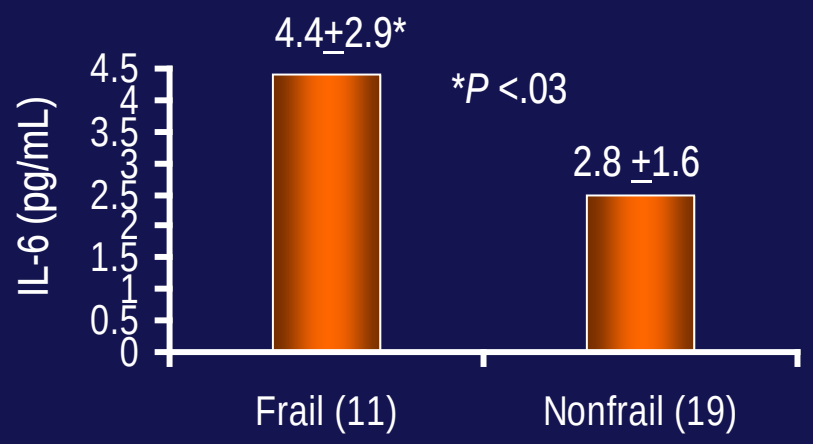


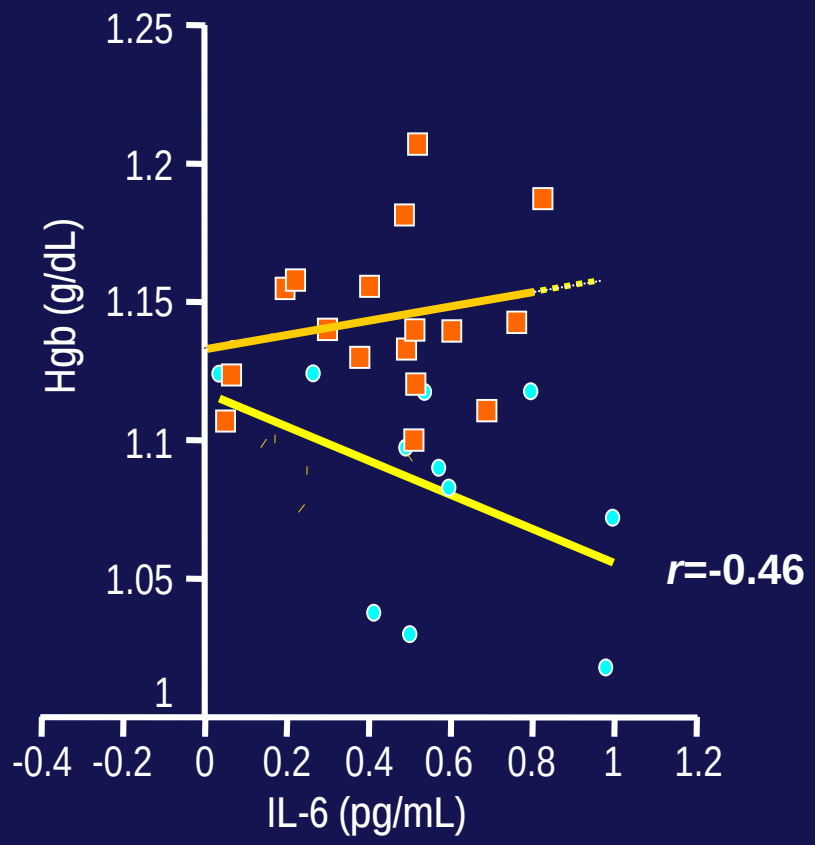
*Adjusted for age, sex, years of education, smoking, body mass index, coronary heart disease, congestive heart failure, diabetes, cancer, infectious disease, kidney disease, and hospital admission in the past year.

[1]Artz et al. *Arch Gerontol Geriatr.* 2004;39:201-206;
[2]Penninx et al. *J Gerontol A Biol Sci Med Sci. 2006; 61:474-479.*

Anemia and Frailty in Community-Dwelling Older Adults







Leng et al. *J Am Geriatr Soc* 2002;50:1268-1271.

Serum Levels of Inflammatory Markers According to Anemia Status

Inflammatory Marker	No Anemia n = 894	Anemia n = 114	*P*-value*
C-reactive protein, mg/L, median (IQR)	2.73 (1.29–5.49)	3.55 (1.52–8.48)	.01
Tertile 1, %	34.1	27.4	
Tertile 2, %	33.8	30.1	.04
Tertile 3, %	32.1	42.5	
Interleukin-6, pg/mL, median (IQR)	1.43 (0.84–2.13)	1.86 (1.10–3.26)	<.001
Tertile 1, %	34.3	21.9	
Tertile 2, %	34.2	28.9	.001
Tertile 3, %	31.4	49.1	
Tumor necrosis factor alpha, pg/mL, median (IQR)	4.81 (2.81–7.66)	5.78 (3.60–7.75)	.03
Tertile 1, %	34.5	22.8	
Tertile 2, %	32.7	39.5	.05
Tertile 3, %	33.0	37.7	

Penninx BW et al, JAGS, 2004

Anemia and Cognive Decline

Risk of Alzheimer's Disease among Elderly Patients with Anemia: a 4 years retrospective study in the Olmsted county

	Controls		Pts with AD		
Group	Total n.	Pts with anemia	Total n.	Pts with anemia	OR (95%CI)
Women Hb<12 g/L	165	27	148	44	1.96 (1.11-3.47)
Men Hb<13 g/L	49	14	43	20	1.81 (0.75-4.39)
Both sexes	214	41	191	64	1.88 (1.17-3.03)

Beard CM et al, Ann. Epidemiol,1997

Anemia and Cognitive Decline

ELSEVIER

Neurobiology of Aging 27 (2006) 278–284

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www.elsevier.com/locate/neuaging

Anaemia increases the risk of dementia in cognitively intact elderly

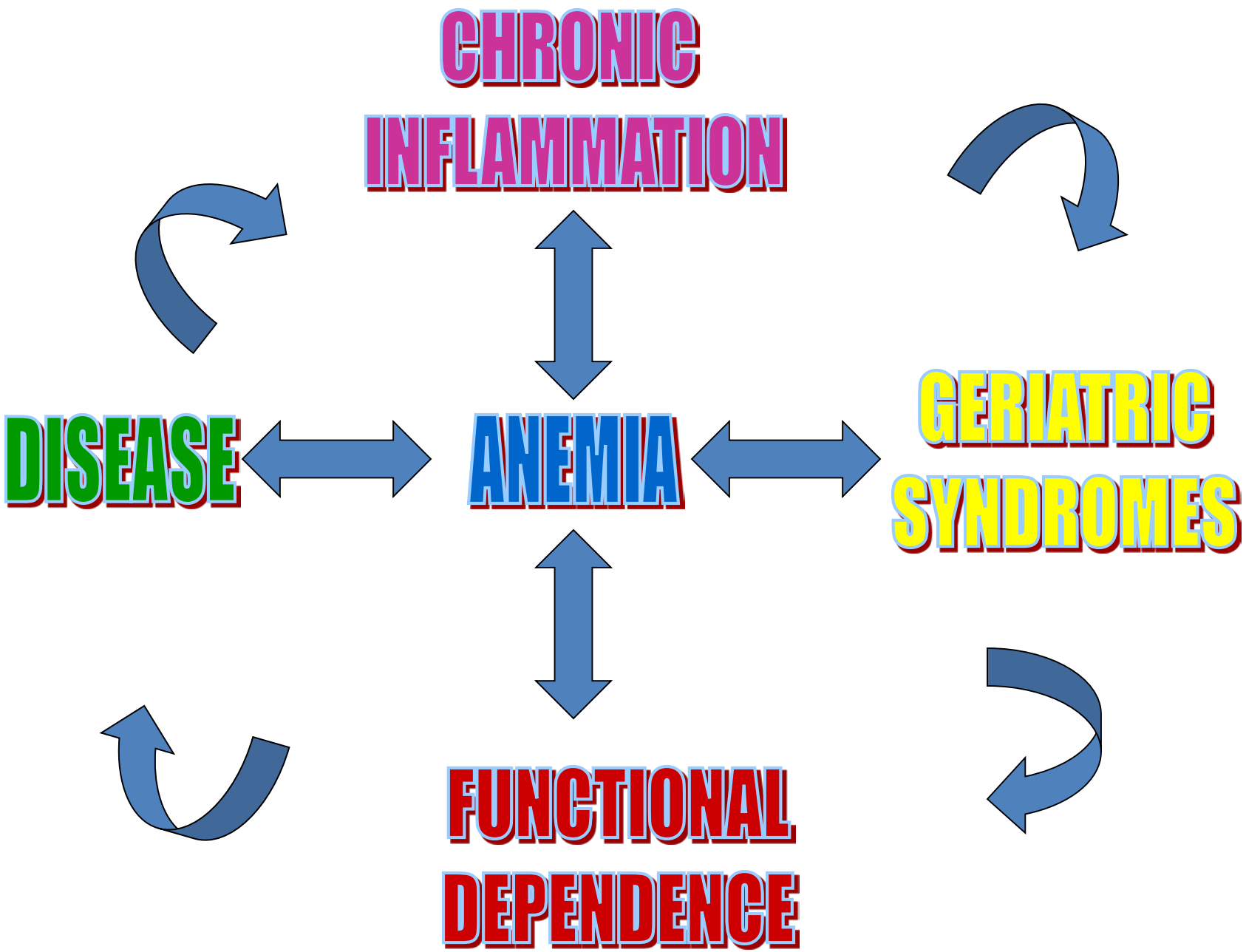
Anna Rita Atti[a,b,*], Katie Palmer[a], Stefano Volpato[b], Giovanni Zuliani[b], Bengt Winblad[a], Laura Fratiglioni[a]

HR for dementia at 3 years in patients with MMS ≥ 26: 1.6 (1.0-2.4)

Increased with drop in hemoglobin

Anemia and Frailty
How does anemia result in greater physical decline?
Possible Hypothesis

- **- Hypoxia resulting from anemia leads to the onset or progression of diseases such as heart failure and renal failure and cognitive decline.**
- **- Anemia could result in a diminished muscle oxygenation.**
- **- Chronic inflammation may have caused greater physical decline.**
- **- Anemia may lead to feelings of weakness and fatigue.**
- **- Anemia as reflection of subclinical disease, or other diseases not measured that could have resulted in physical decline.**


CHRONIC INFLAMMATION
DISEASE
ANEMIA
GERIATRIC SYNDROMES
FUNCTIONAL DEPENDENCE

Conclusions

- **La incidenza e la prevalenza della Anemia aumentano con l'età.**
- **L'anemia nell'anziano è molto spesso multifattoriale. In circa il 30% dei casi la causa non viene identificata.**
- **Una riduzione progressiva della capacità rigenerativa dei progenitori eritropoietici e/o una insufficienza primitiva o secondaria (ACD) sono cause comuni di anemia nell'anziano.**
- **L'anemia nell'anziano si associa a comorbilità ed aumento della mortalità.**
- **Independentemente dalla causa sottostante l'anemia è un fattore di rischio di fragilità, declino della performance fisica e riduzione della capacità funzionale.**

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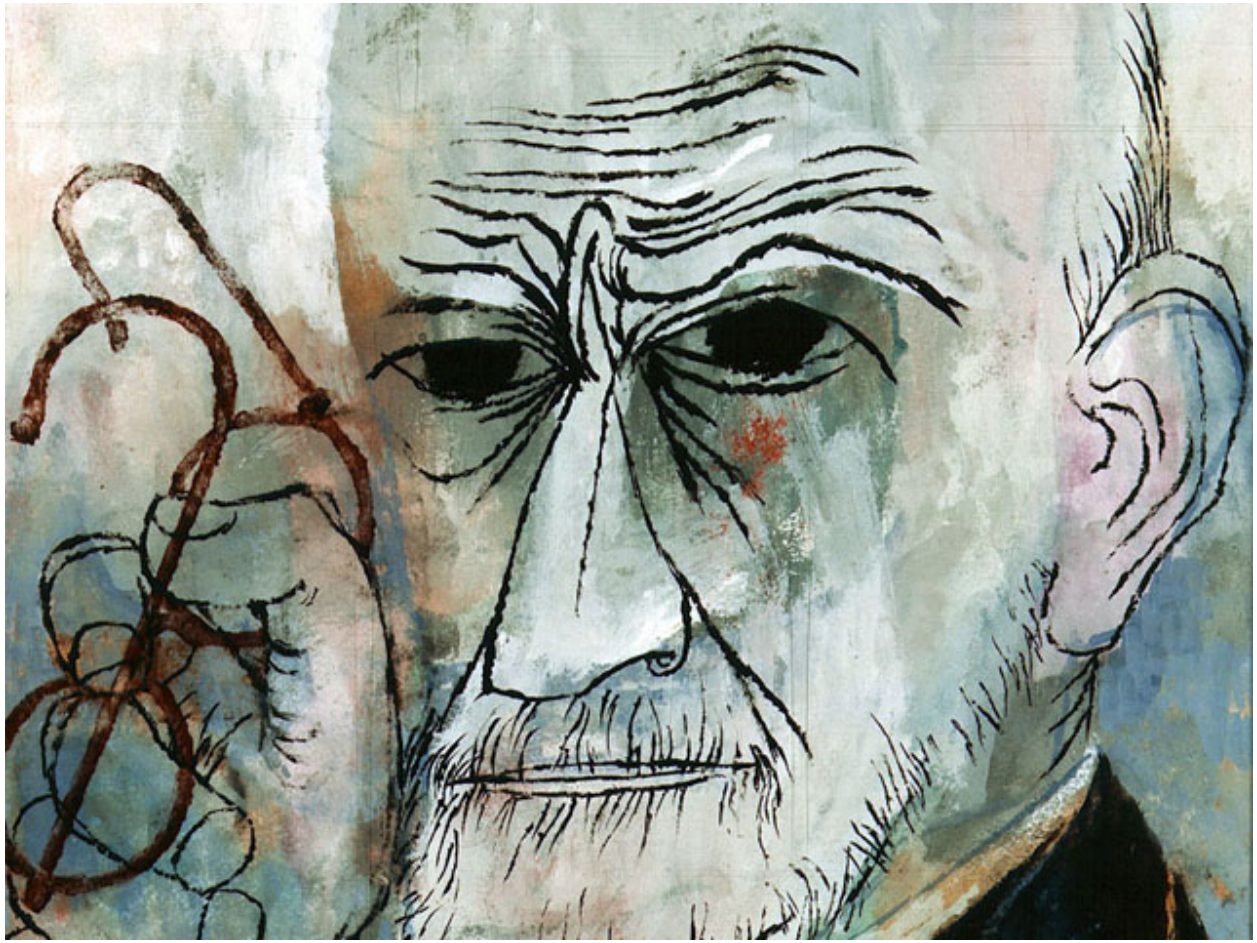
Direttore prof. M. Barbagallo



GRAZIE PER LA CORTESE ATTENZIONE