

Prevalenza dell'anemia e di quella non spiegata nel soggetto anziano: le dimensioni del problema



Graziano Onder
Centro Medicina Invecchiamento
Università Cattolica Sacro Cuore
Policlinico A. Gemelli



Definizione

The World Health Organization (WHO) defines anemia in the adult or elderly population, as hemoglobin (Hb) concentration <12 g/dL for non-pregnant women and <13 g/dL for men.

It is recommended that a reference centre be established for the determination of serum iron and iron binding capacity. Such a centre should establish procedures for checking the collaborating laboratories, and should keep in touch with the Expert Panel on Iron of the International Committee for Standardization in Haematology, which is concerned with the standardization of methods for determining serum iron and iron binding capacity.

Haemoglobin

It is essential that haemoglobin determinations be standardized. The procedure¹ recommended by the International Committee for Standardization in Haematology should be followed, under the supervision of the designated iron reference centre.

3. CRITERIA FOR THE DIAGNOSIS OF ANAEMIA

In detecting and evaluating an anaemia problem in a community, reference standards are necessary, even though they may be somewhat arbitrary. The report² of the 1958 WHO Study Group recommended haemoglobin values below which anaemia could be considered to exist. These figures were chosen arbitrarily and it is still not possible to define normality precisely.³ However, more recent data⁴ indicate that the values given previously should be modified. It is recommended that, in future studies, anaemia should be considered to exist in those whose haemoglobin levels are lower than the figures given below (the values given are in g/100 ml of venous blood of persons residing at sea level):

children aged 6 months to 6 years:	11
children aged 6-14 years:	12
adult males:	13
adult females, nonpregnant:	12
adult females, pregnant:	11

At all ages the normal mean corpuscular haemoglobin concentration should be 34. Consequently, the haematocrit values corresponding to the haemoglobin concentrations given above may be obtained by multiplying

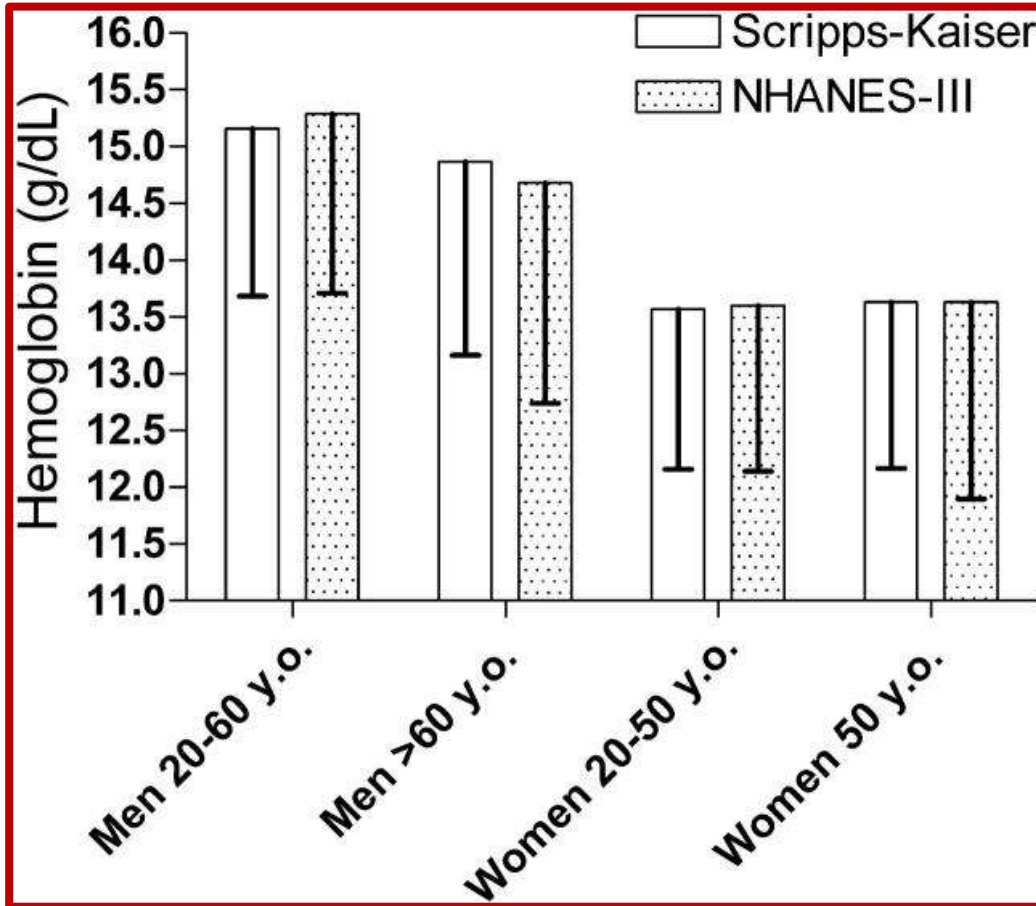
¹ International Committee for Standardization in Haematology (1967) *Brit. J. Haemat.*, 13 (Suppl.), 71.

² *Wld Hlth Org. techn. Rep. Ser.*, 1959, No. 182, p. 4.

³ Wintrobe, M. M. (1967) *Clinical hematology*, 6th ed., Philadelphia, Pa., Lea & Febiger.

⁴ Natvig, K. (1966) *Acta med. scand.*, 180, 613; Tibblin, G., unpublished observations; Kilpatrick, G. S. & Hardisty, R. M. (1961) *Brit. med. J.*, 1, 778; De Leeuw, N. K. M., Lowenstein, L. & Hsieh, Y. S. (1966) *Medicine (Baltimore)*, 45, 291; Sturgeon, P. (1959) *Brit. J. Haemat.*, 5, 31.

Definizione

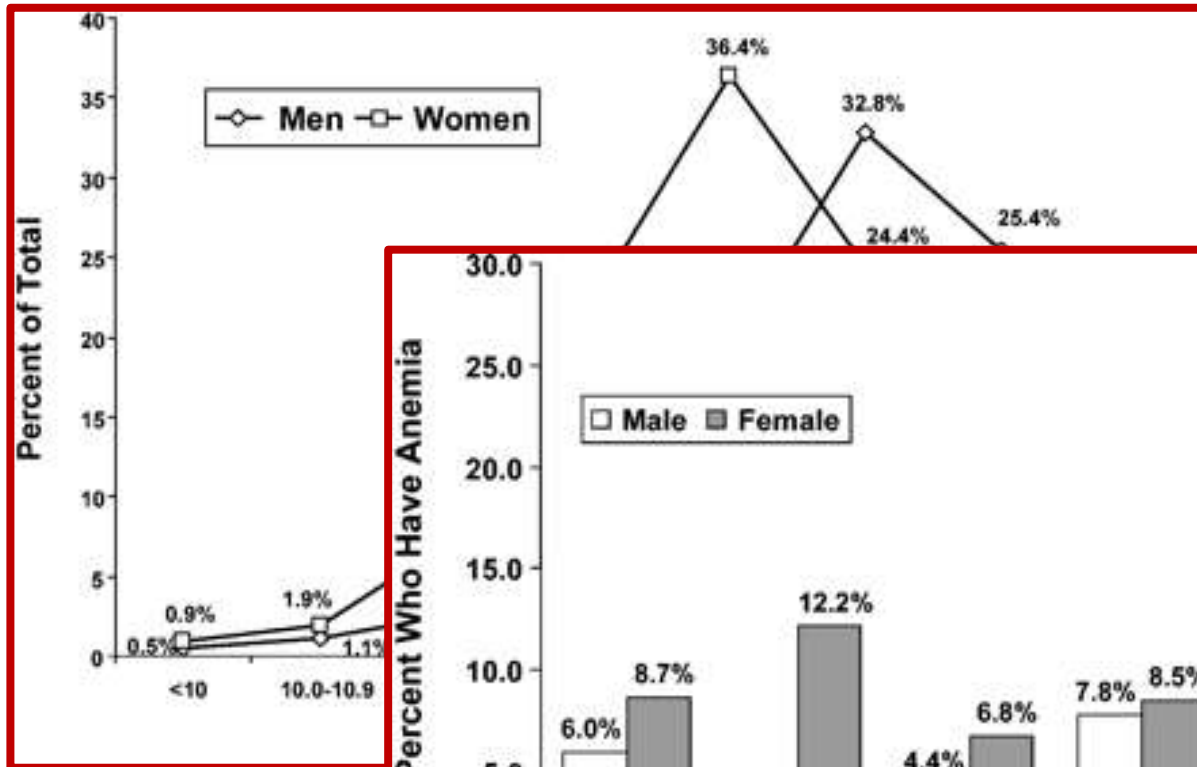


Group	Hemoglobin, g/dL
White men, y	
20-59	13.7
60+	13.2
White women, y	
20-49	12.2
50+	12.2
Black men, y	
20-59	12.9
60+	12.7
Black women, y	
20-49	11.5
50+	11.5

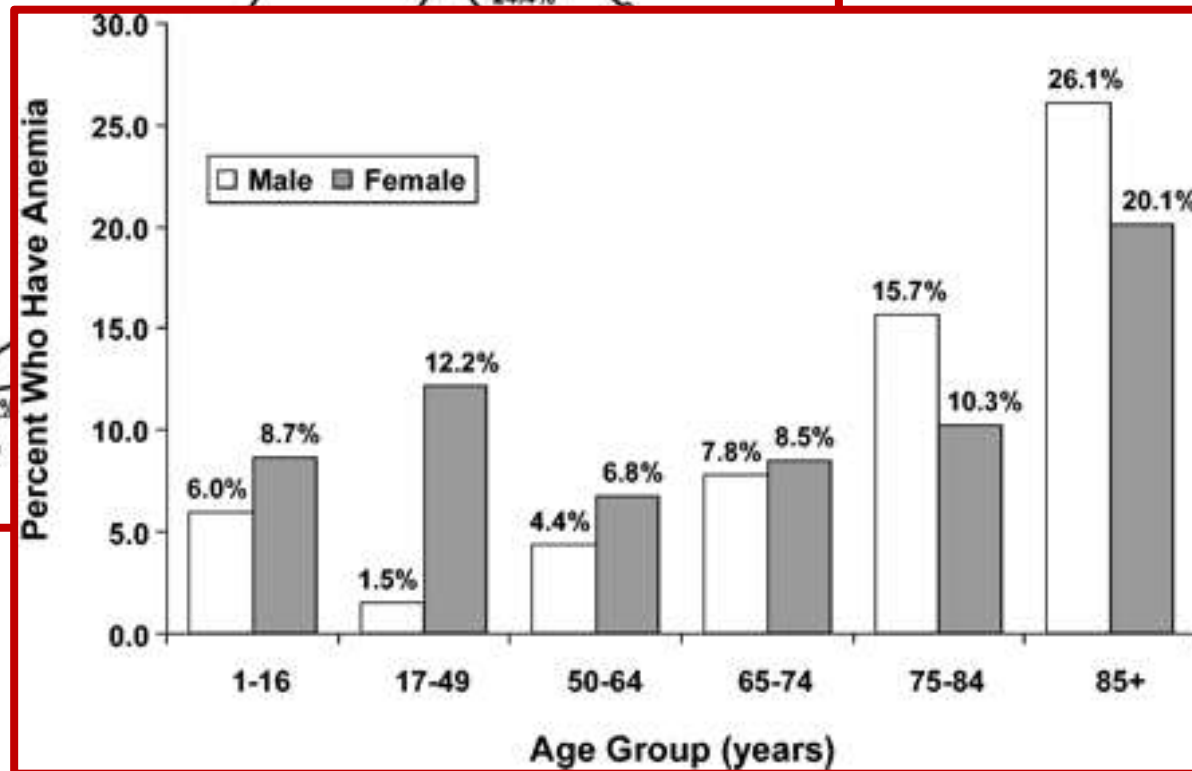
Beutler et al. Blood 2006



Prevalenza di anemia: NHANES III



n=26372



Cause of anemia: NHANES III

Anemia	No. in the United States	Type, %	All anemia, %
With nutrient deficiency			
Iron only	467 000	48.3	16.6
Folate only	181 000	18.8	6.4
B ₁₂ only	166 000	17.2	5.9
Folate and B ₁₂	56 000	5.8	2.0
Iron with folate or B ₁₂ or both	95 000	9.9	3.4
Total	965 000	100.0	34.3
Without nutrient deficiencies			
Renal insufficiency only	230 000	12.4	8.2
ACI, no renal insufficiency	554 000	30.0	19.7
Renal insufficiency and ACI	120 000	6.5	4.3
UA	945 000	51.1	33.6
Total	1 849 000	100.0	65.7
Total, all anemia	2 814 000	NA	100.0



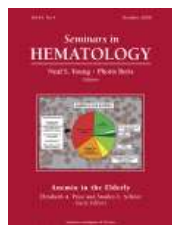
UA= Unexplained Anemia

ACI= Anemia chronic inflammation

Guralnik et al. Blood 2004



... “unexplained anemia” (UA) is an **unfortunate term**, perhaps reflecting negatively on our capacity to understand erythropoiesis. However, UA is not so much unexplained as it is **multi-factorial ...** Several **age-related physiological changes** may contribute to either a decline in red blood cell production or shortened red blood cell survival...

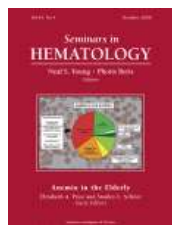


Anemia non spiegata negli anziani

	Population	% Anemic	% UA
Joosten et al	Geriatrics inpatient unit	24%	17%
Ania et al	Community	7-9%	16%
Guralnik et al	Community (NHANES III)	11%	33%
Ble et al	Community (InCHIANTI)	10%	37%
Tecson J	Community	21%	N/A
Artz et al	Nursing home	49%	43%

Caratteristiche anemia non spiegata

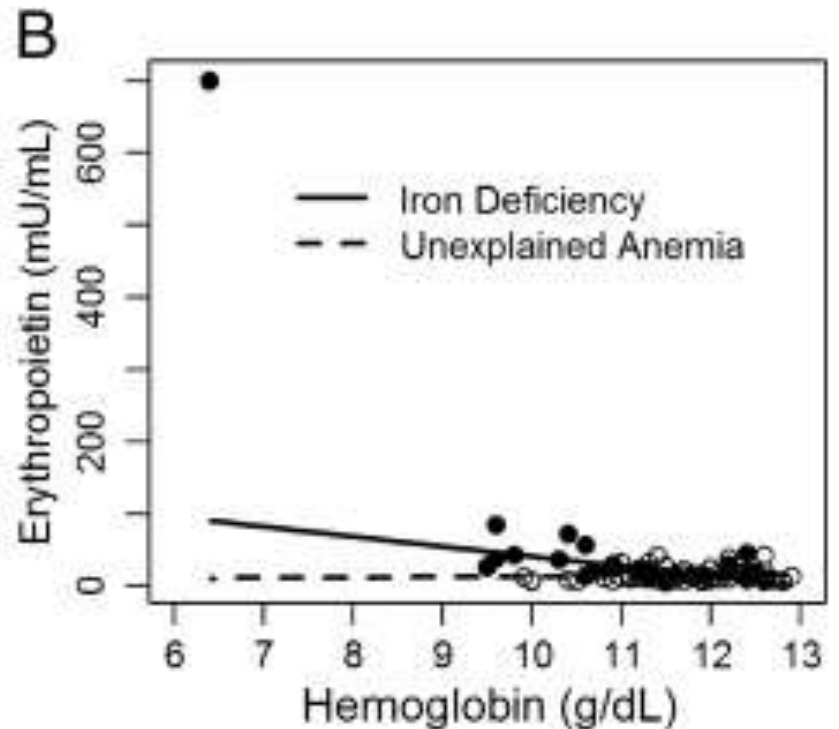
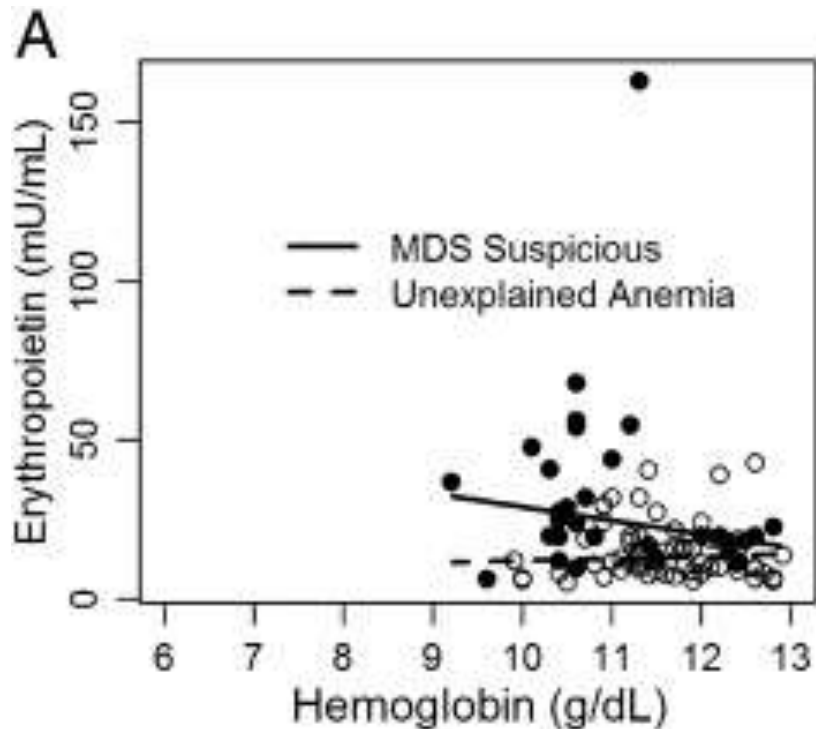
Emoglobina	10.5-12 gr/dL
Reticolociti	↓
PLT e GB	Nella norma
Striscio periferico	Non elementi displastici
Vit B12 e folati	Nella norma
Sideremia	Nella norma o leggermente ↓
VES	Nella norma
EPO	Non elevata
Cr Clearance	> 30 - < 90 ml/min
TSH	Nella norma



Possibili cause anemia non spiegata

- **Ridotta produzione eritropoietina**

Eritropoietina e unexplained anemia

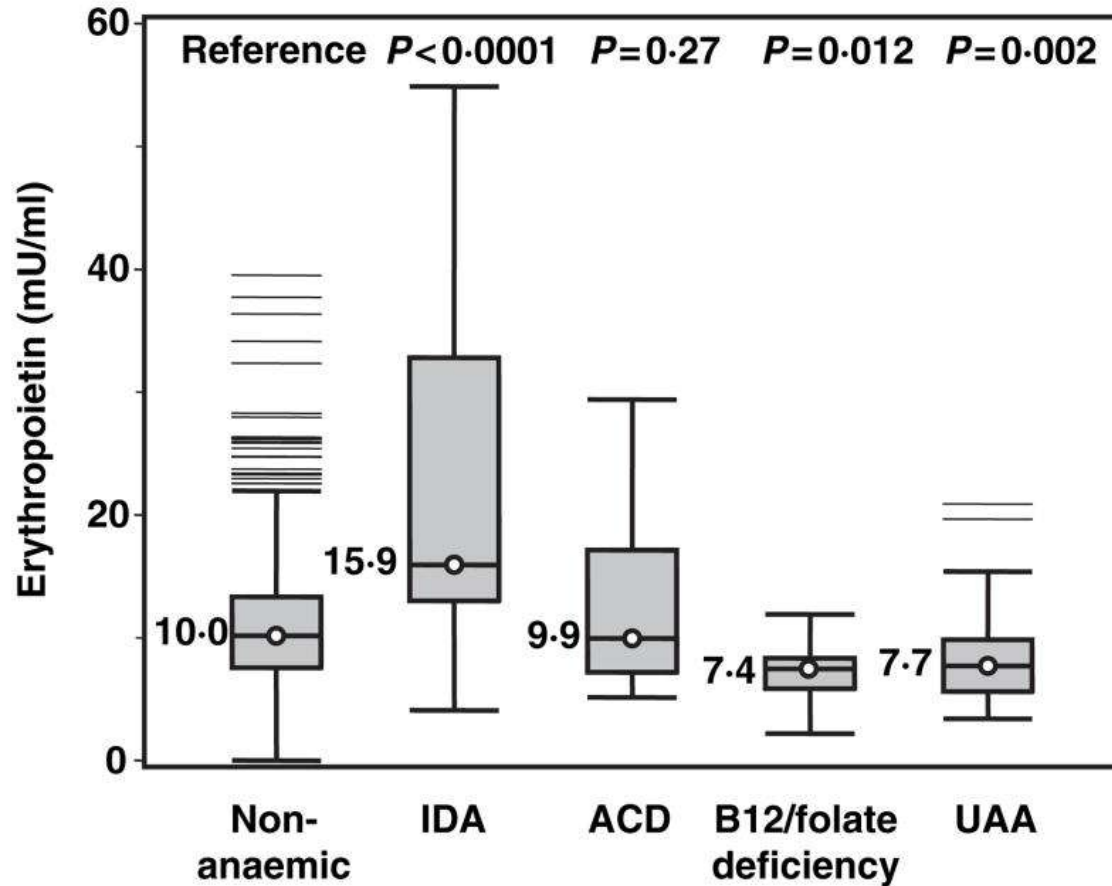


Anemia ed eritropoietina

Type	Hemoglobin, g/dL*	Erythropoietin, mIU/mL†	Mean				Albumin, g/dL¶	C-Reactive Protein, mg/dL#
			Corpuscular Volume, fL‡	Ferritin, ng/mL§	Interleukin-6, pg/mL	Standard Deviation		
Iron deficiency anemia (n = 14)	10.6 ± 1.1	29.0 ± 16.2	85.4 ± 7.0	22.5 ± 14.5	6.6 ± 2.7	3.7 ± 0.5	10.1 ± 15.4	
Anemia of chronic disease (n = 8)	11.0 ± 1.5	20.3 ± 7.6	93.1 ± 3.4	167.4 ± 79.1	44.3 ± 72.4	3.6 ± 0.4	36.9 ± 35.5	
Idiopathic anemia (n = 27)	10.8 ± 1.0	14.6 ± 7.3	92.3 ± 5.9	201.6 ± 195.6	8.5 ± 7.8	3.6 ± 0.3	6.0 ± 5.0	
Other** (n = 5)	10.0 ± 1.2	13.4 ± 1.6	87.0 ± 9.3	356.0 ± 577.1	98.0 ± 106.8	3.6 ± 0.3	41.1 ± 68.7	
Chronic renal insufficiency** (n = 6)	11.5 ± 0.8	12.5 ± 4.2	89.5 ± 6.5	177.8 ± 215.9	7.5 ± 1.4	3.9 ± 0.3	8.3 ± 5.6	
All (n = 60)	10.7 ± 1.1	18.6 ± 11.6	90.1 ± 6.7	166.9 ± 233.6	19.0 ± 41.0	3.7 ± 0.4	13.6 ± 25.7	



Anemia e EPO

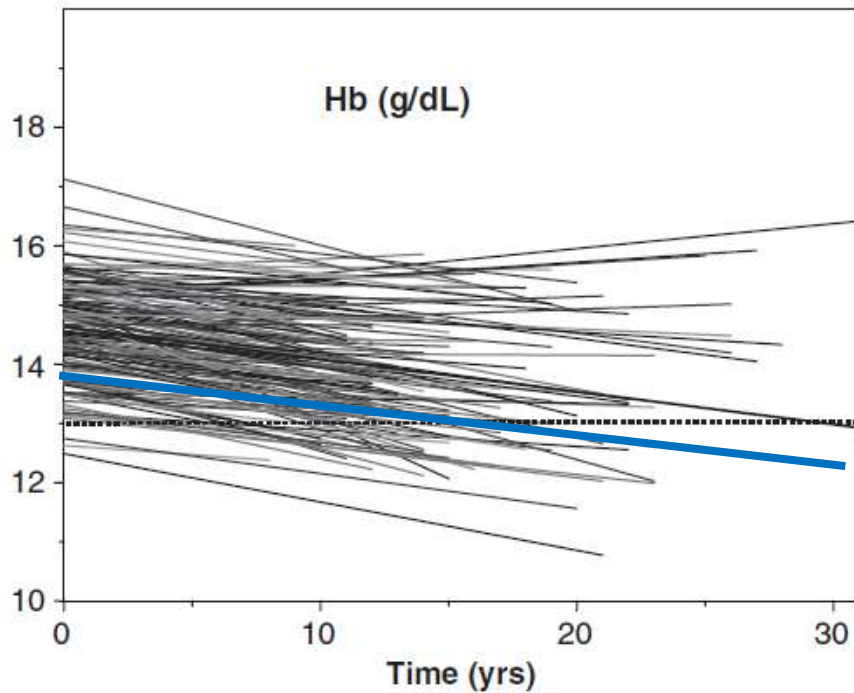


IDA, iron deficiency anaemia
ACD, anaemia of chronic disease
UAA, unexplained anaemia

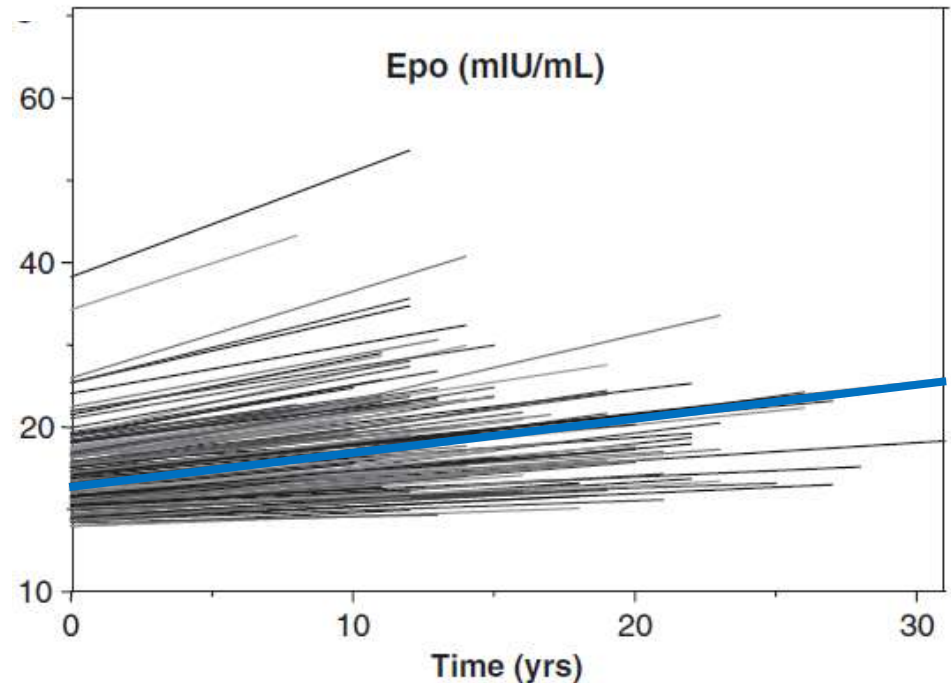
Possibili cause anemia non spiegata

- Ridotta produzione eritropoietina
- **Ridotta sensibilità eritropoietina**

Eritropoietina ed età



The increase in serum EPO with aging may be compensation for subclinical blood loss, increased red blood cell turnover, or **increased EPO resistance...**



Ershler et al JAGS 2005



Età e anemia

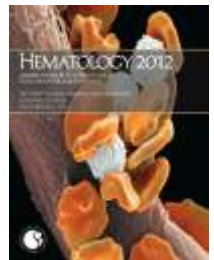
- ↓ cellularità midollare
- ↓ colony forming units erythroid (precursori eritroidi)
- ↑ parametri infiammatori = ↓ sensibilità EPO
- Shift maturativo verso serie mieloide (↑ rischio patologie serie mieloide)

Possibili cause anemia non spiegata

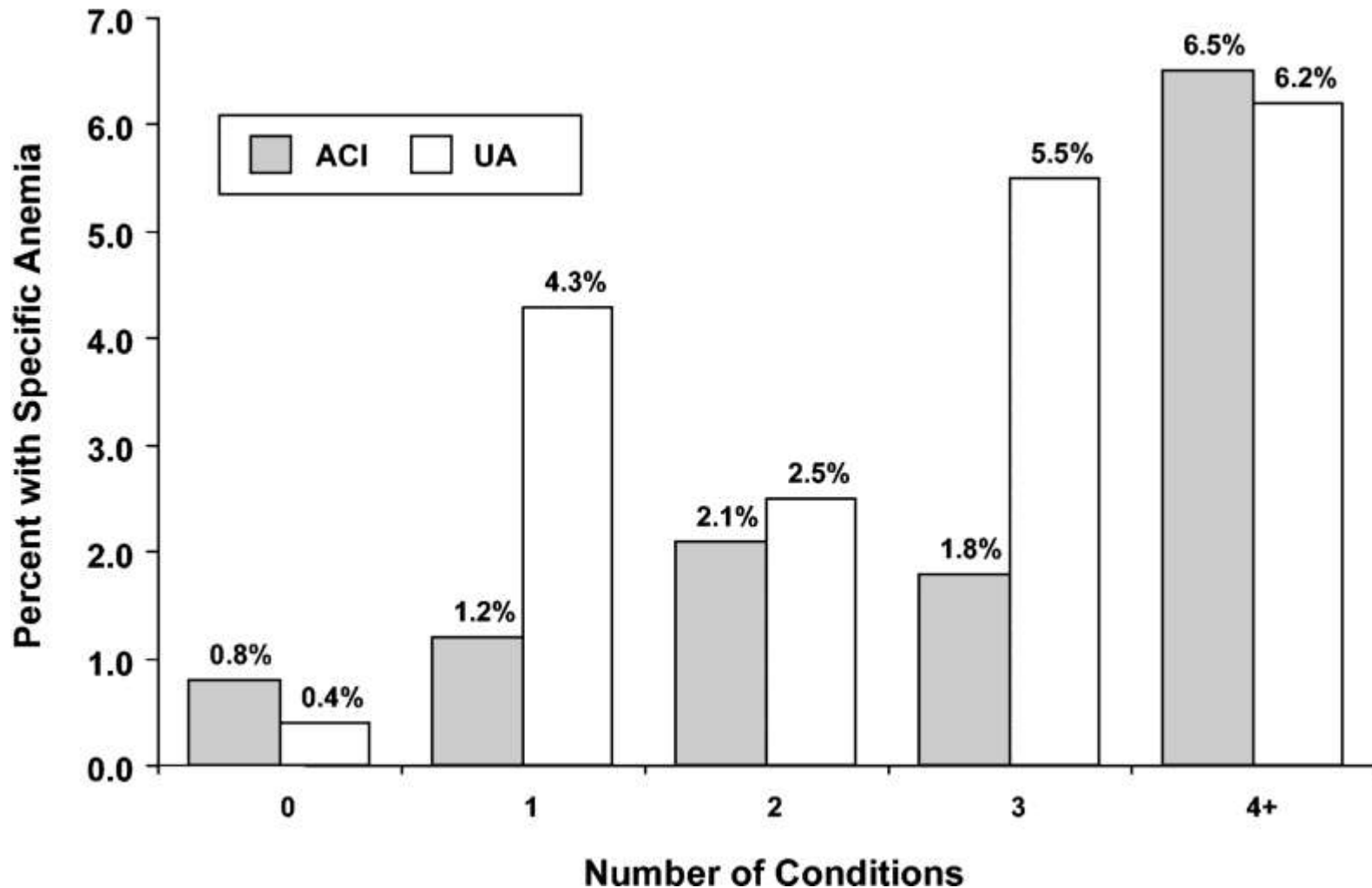
- Ridotta produzione eritropoietina
- Ridotta sensibilità eritropoietina
- **Polipatologia**

Anemia e polipatologia

... careful enumeration of all significant medical conditions in an individual's medical history is important in defining unexplained anemia. **A variety of medical conditions not classically associated with inflammation (e.g., hypothyroidism) may be associated with anemia...**



Cause of anemia: NHANES III



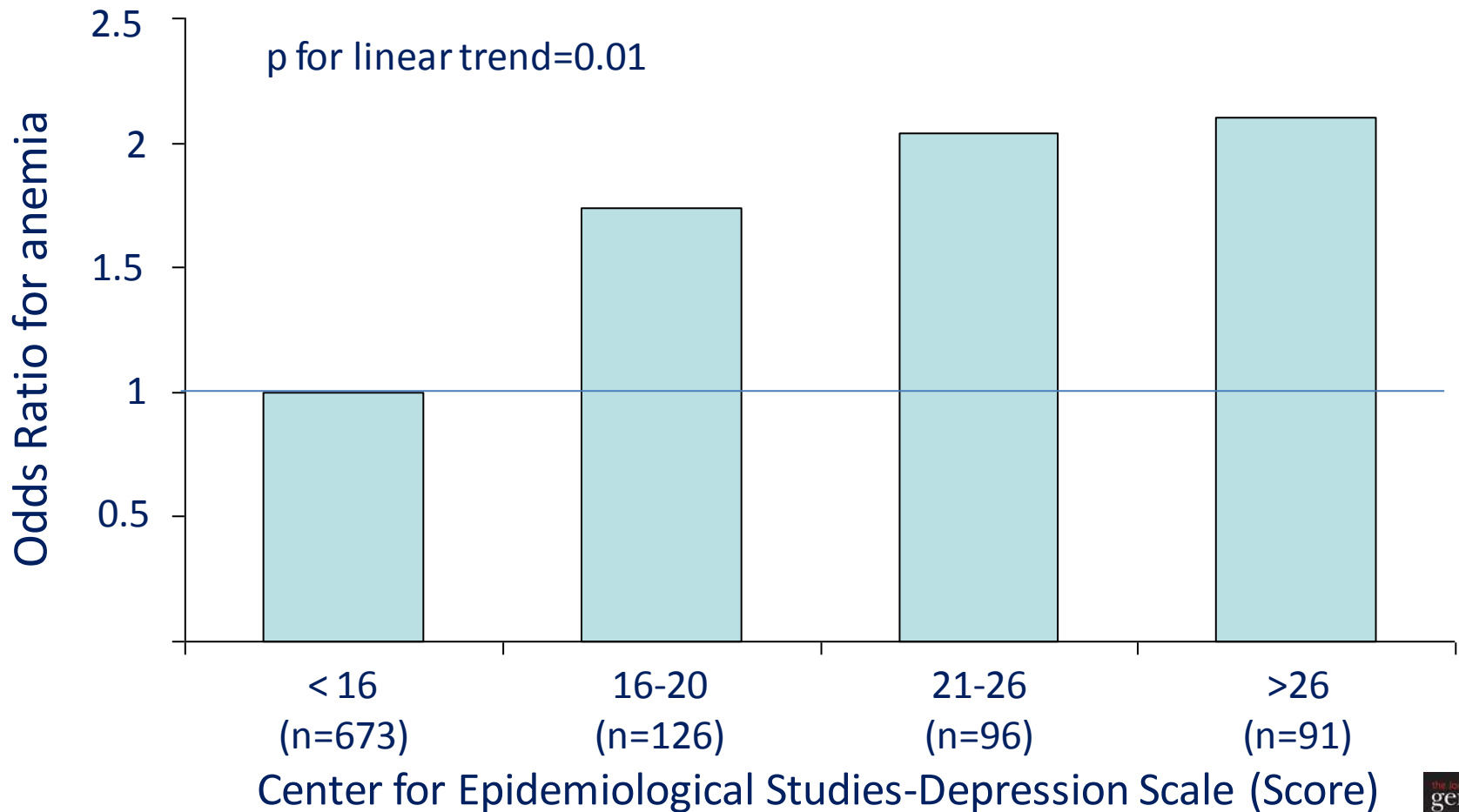
UA= Unexplained Anemia

ACI= Anemia chronic inflammation

Guralnik et al. Blood 2004



Depressione e anemia



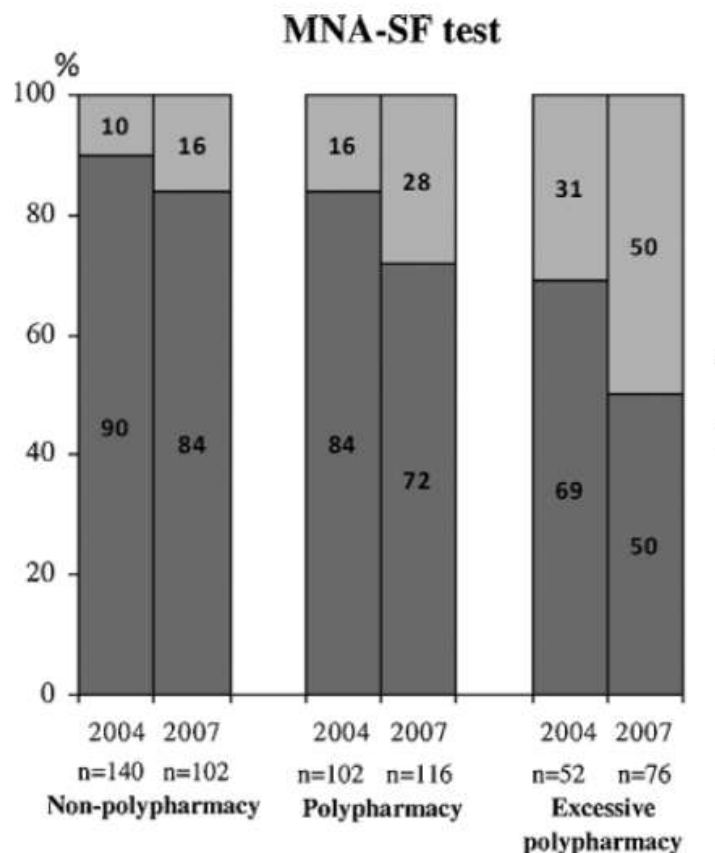
Onder G et al. JGMS 2005



Possibili cause anemia non spiegata

- Ridotta produzione eritropoietina
- Ridotta sensibilità eritropoietina
- Polipatologia
- **Politerapia**

Politerapia e stato nutrizionale



Malnourished or at risk (12–14 points in MNA-SF)
 Well-Nourished (0–11 points in MNA-SF)

Drugs associated with dry mouth	Drugs associated with ageusia/hypogeusia
Amitriptyline	ACEI
Atropine	Ampicillin
Captopril	Benzodiazepines
Chlorphenamine	Clopidogrel
Citalopam	Diltiazem
Codeine	Levodopa
Diazepam	Metformine
Enalapril	Nifedipine
Fluoxetine	Spirolactone
Levodopa	Tricyclic antidepressants
Paroxetine	

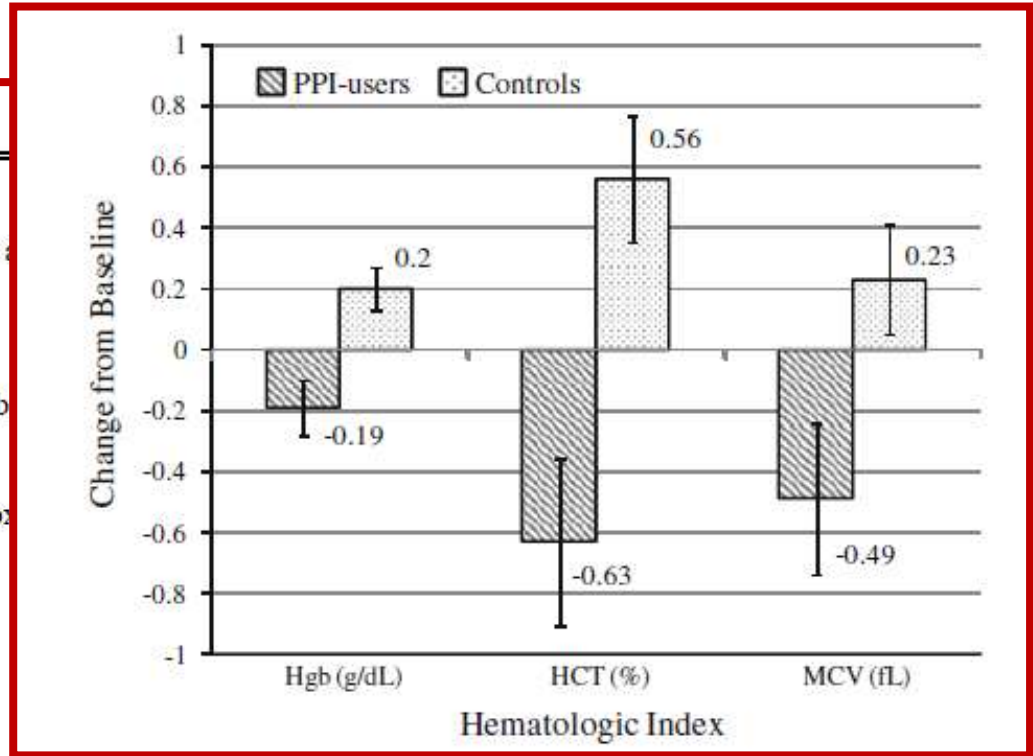
Table 4: Drugs associated with dry mouth, hypogeusia or ageusia.

Ortolani et al. J Gerontol Geriat Res 2013

Jyrrka et al PDS 2011

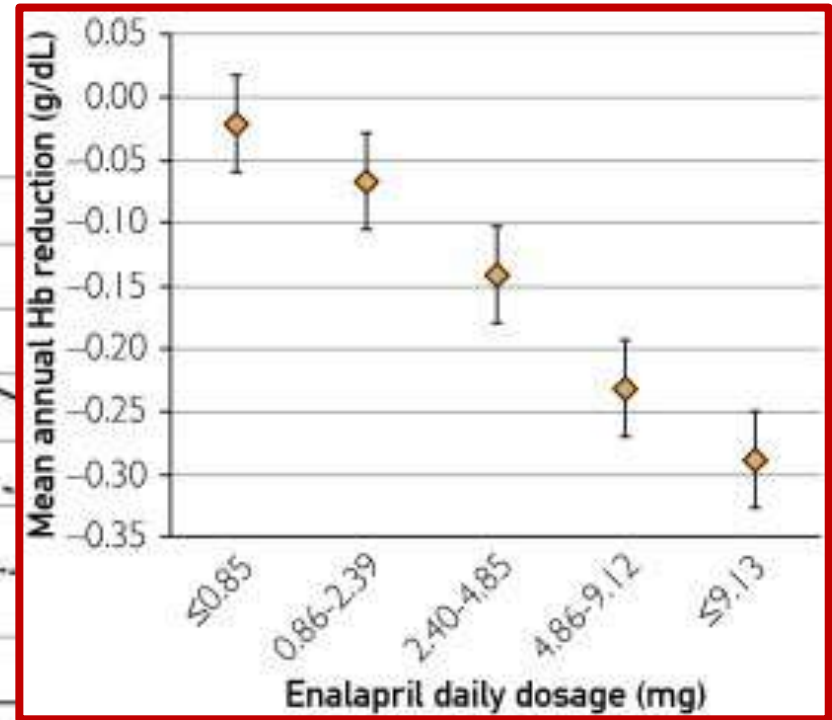
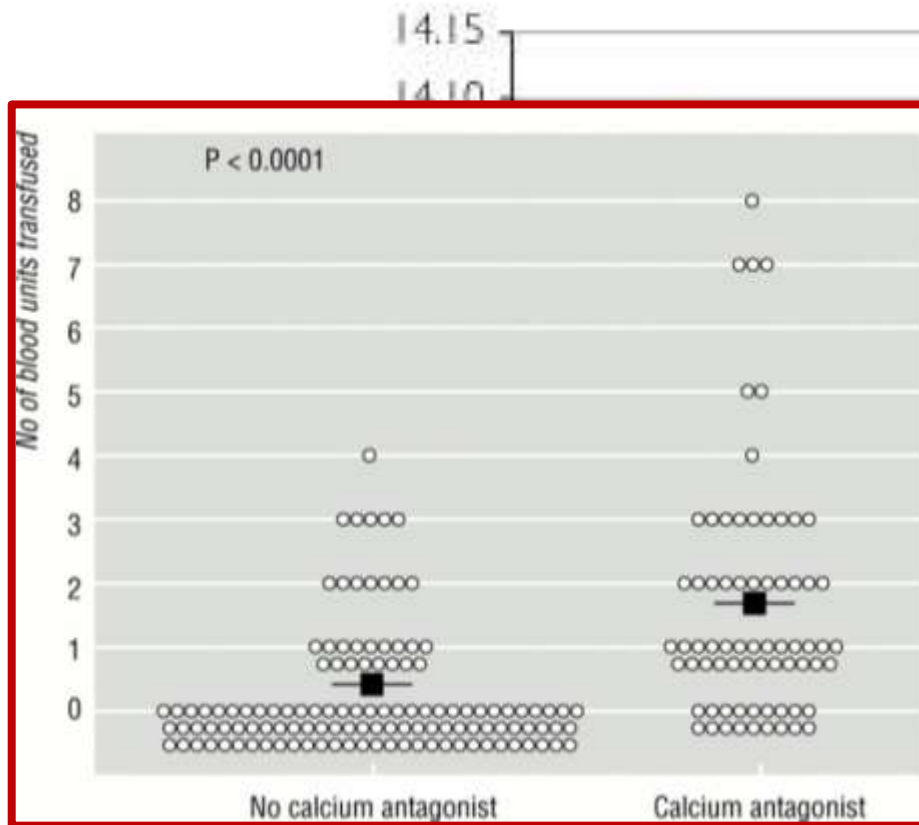
Farmaci e anemia

Red Cell Disorder	Common Medications
Megaloblastic Anemia	Alkylating agents [6]
	Antimetabolite chemotherapeutic agents [6,25,26]
	Methotrexate
	Other dihydrofolate reductase inhibitors
	Pyrimethamine [28]
	Trimethoprim-sulfamethoxazole
	Oral contraceptives [29]
	Anticonvulsants [30]
	Phenobarbital
	Phenytoin
	Primidone
	Others
	Metformin [31]
Sulfasalazine [6]	
Triamterene [27]	



Sarzynski et al. Dig Dis Sci 2011

Anti-ipertensivi e anemia



Possibili cause anemia non spiegata

- Ridotta produzione eritropoietina
- Ridotta sensibilità eritropoietina
- Polipatologia
- Politerapia
- **Deficit ormonali**
 - Androgeni
 - Tiroide

Possibili cause anemia non spiegata

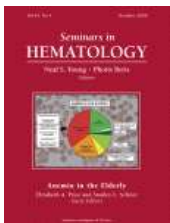
- Ridotta produzione eritropoietina
- Ridotta sensibilità eritropoietina
- Polipatologia
- Politerapia
- Deficit ormonali
- **Mielodisplasia**

Mielodisplasia

The red blood cells are typically **macrocytic** and examination of the peripheral blood smear may indicate abnormalities in **WBC or platelets**.

Bone marrow examination including cytogenetic studies may be required for accurate diagnosis.

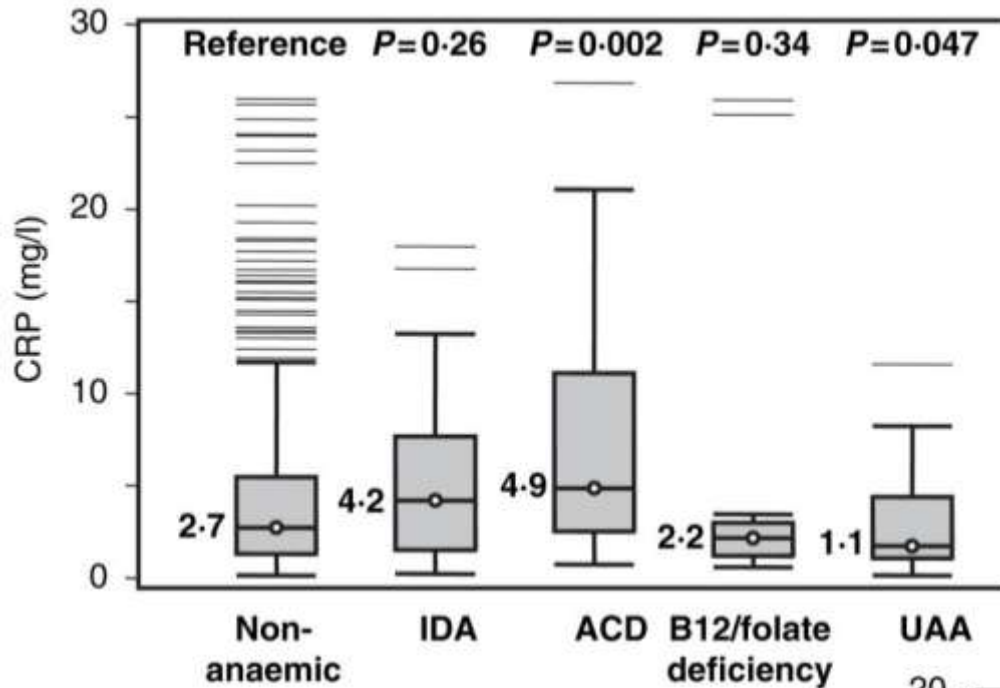
... some cases of MDS will present with anemia alone ... anemia in these circumstances may have other features of UA, it might be considered UA for some time.



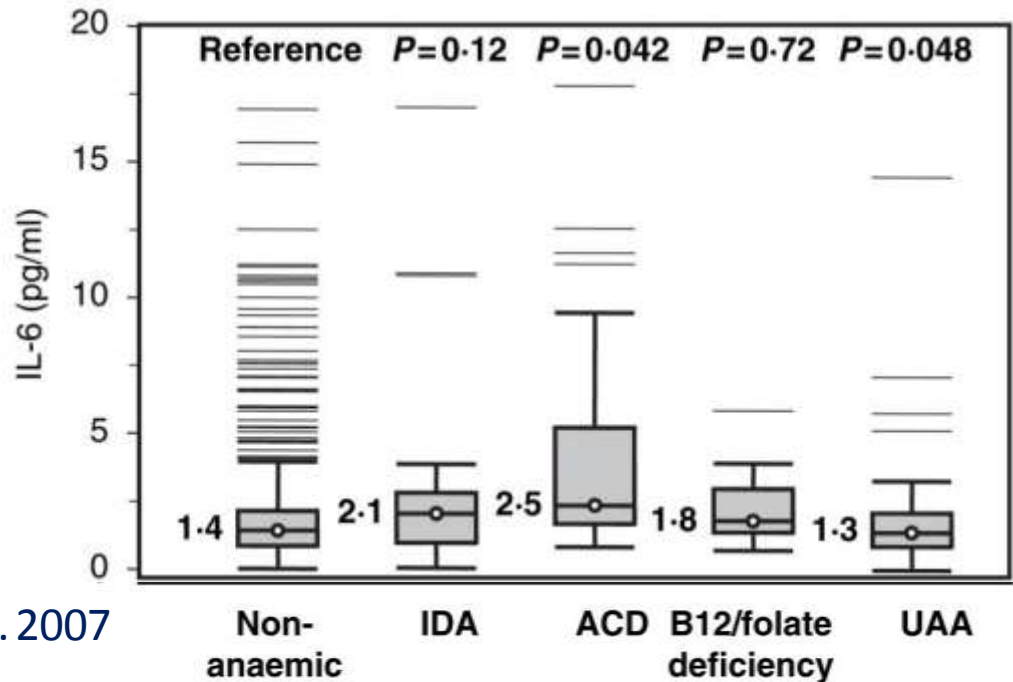
Possibili cause anemia non spiegata

- Ridotta produzione eritropoietina
- Ridotta sensibilità eritropoietina
- Polipatologia
- Politerapia
- Deficit ormonali
- Mielodisplasia
- **Infiammazione**

Anemia e parametri infiammatori



IDA, iron deficiency anaemia
ACD, anaemia of chronic disease
UAA, unexplained anaemia



Possibili cause anemia non spiegata

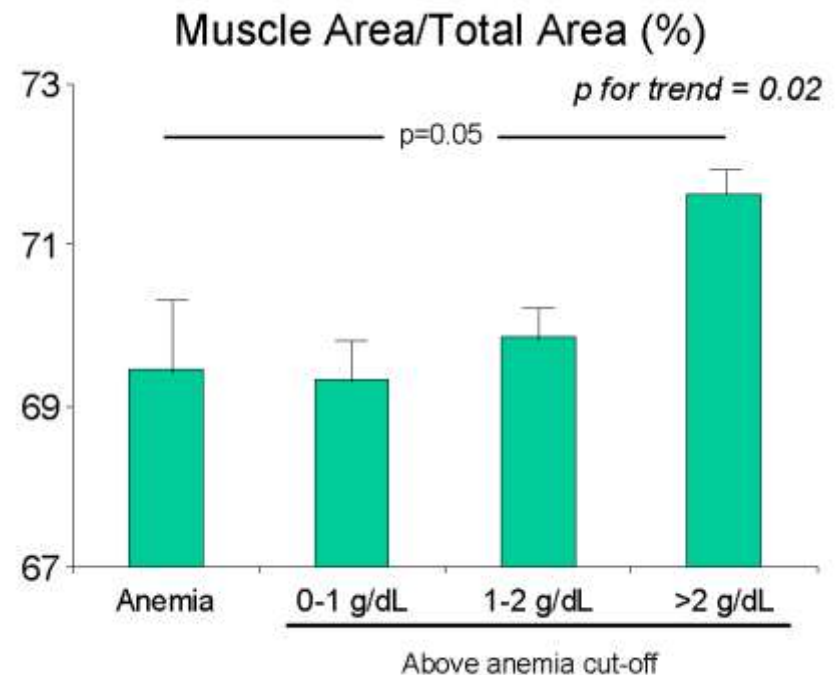
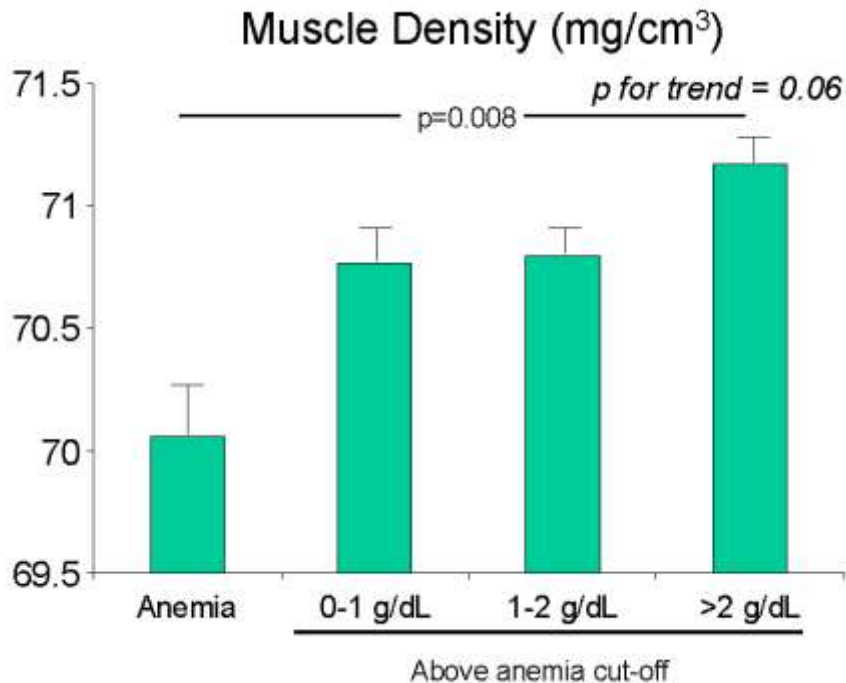
- Ridotta produzione eritropoietina
- Ridotta sensibilità eritropoietina
- Polipatologia
- Politerapia
- Deficit ormonali
- Mielodisplasia
- Infiammazione
- **Sarcopenia**

Sarcopenia e anemia

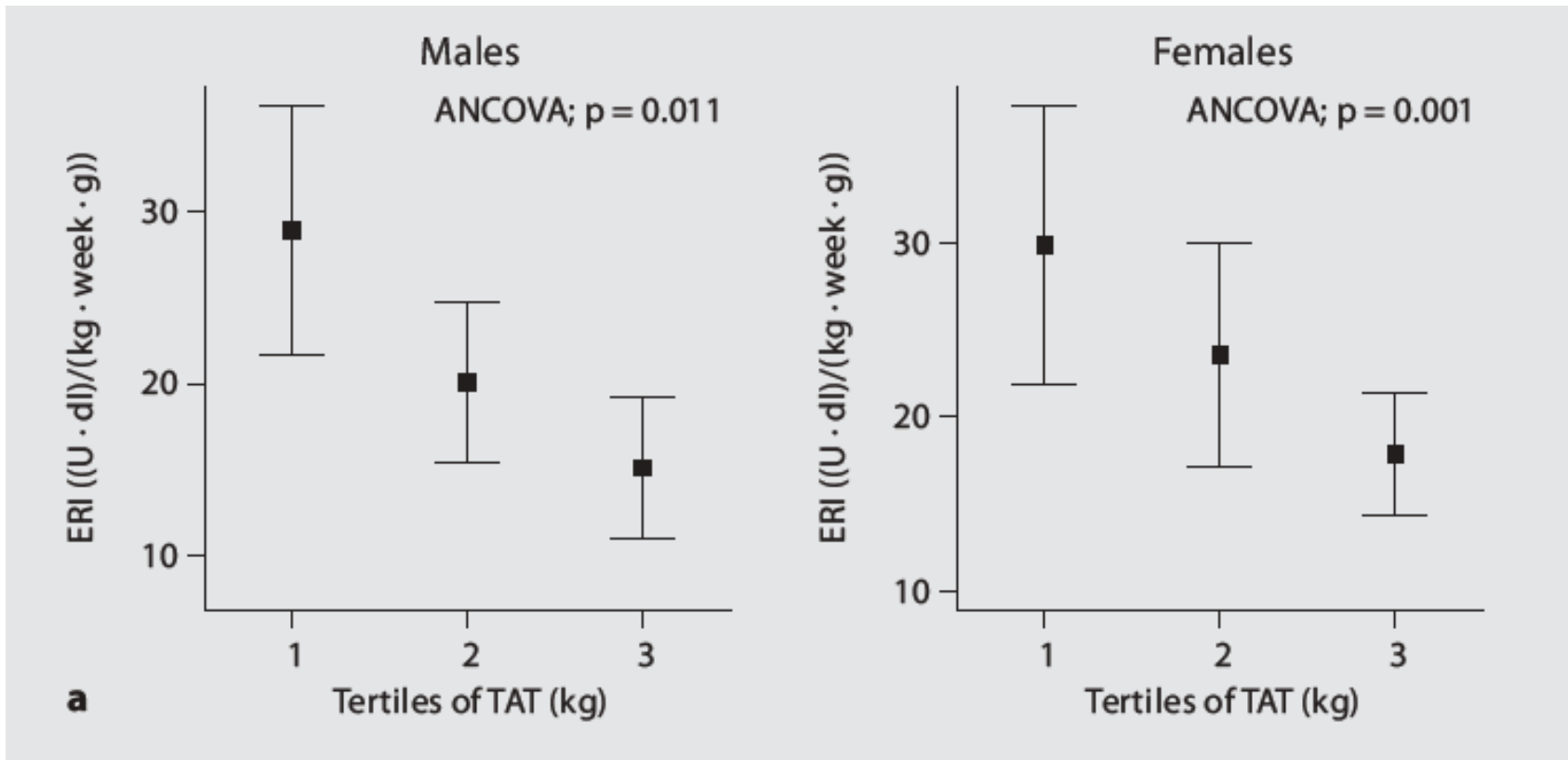
A related concept is anemia as it occurs in sarcopenic elderly ... One hypothesis raised (without specific scientific corroboration as of yet) is that the **decrease in muscle mass may bring about changes in red blood cell mass, oxygen utilization, and perhaps EPO production.** In such patients, their anemia may represent a physiological response to sarcopenia.



Anemia e sarcopenia



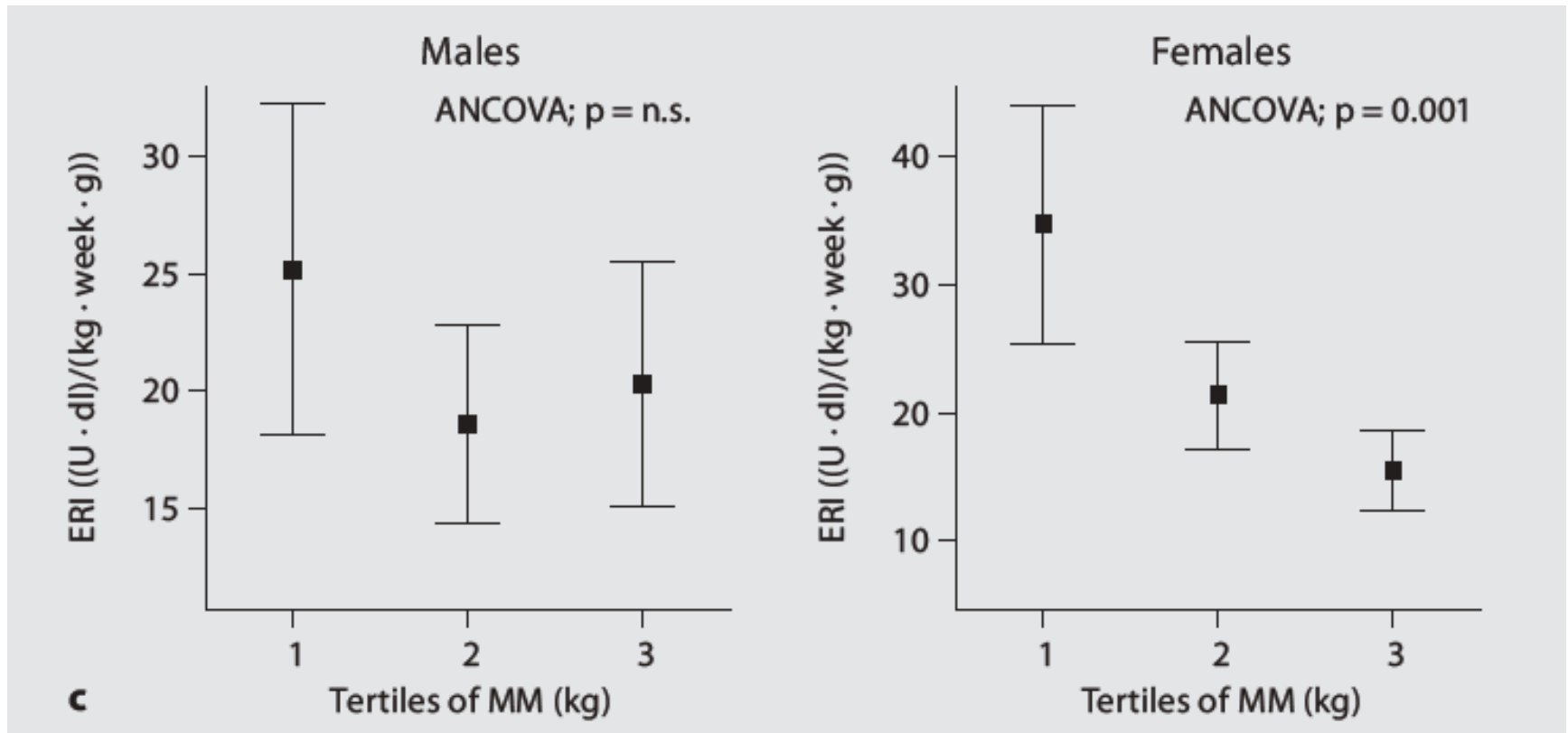
Composizione Corporea e anemia



ERI= Erythropoietin resistance index
TAT=Total Adipose Tissue



Composizione Corporea e anemia



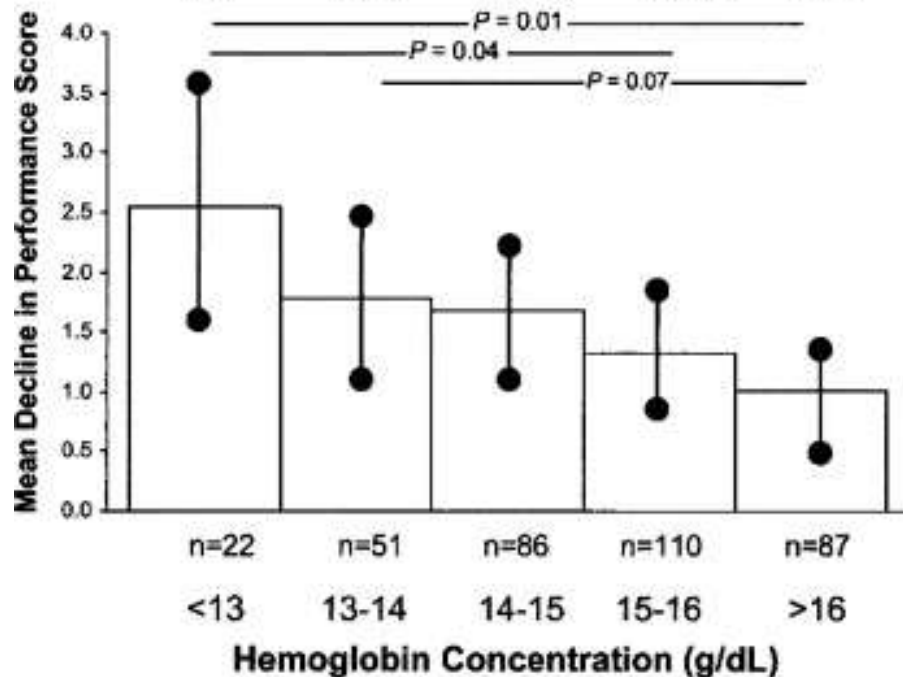
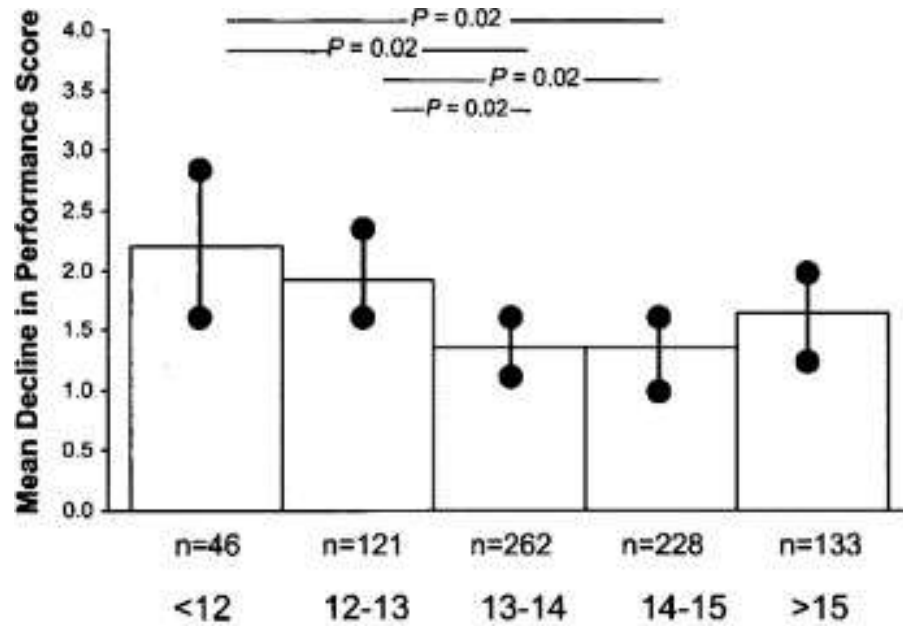
ERI= Erythropoietin resistance index
MM=Muscle Mass

Kotanko et al Blood Purif 2008



Anemia e performance fisica

L'anemia è associata ad outcomes negativi di salute, ma...



Penninxet al Am J Med 2003

Tipo anemia e mortalità

Factor	Hazard ratio	<i>p</i> value
Nutritional	2.34	<0.01
Chronic renal	1.70	<0.01
Chronic inflammation	1.48	<0.01
Unexplained	1.26	<0.01
None	1.00	Reference

Shavelle et al. Int J Hematol. 2012



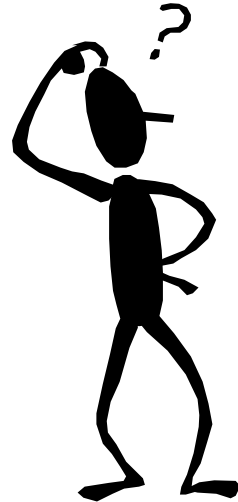
An increased risk for mortality was observed in subjects with **explained anaemia [HR: 1.93 (95% CI: 1.47-2.52)]**, but not in subjects with **unexplained anaemia [HR: 1.19 (95% CI: 0.85-1.69)]**. Adjusted analyses did not change the observed associations for both explained and unexplained anaemic subjects.

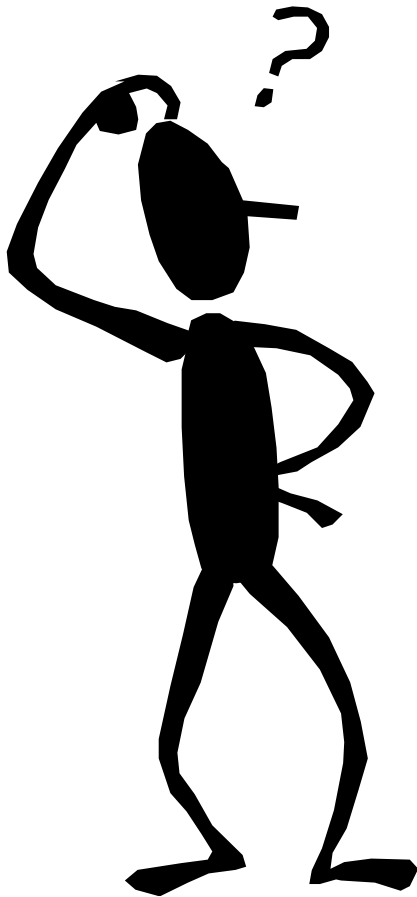
Willems et al Age Ageing 2012



Conclusioni

- L'anemia è comune negli anziani
- L'anemia non spiegata è responsabile di circa 1/3 dei casi di anemia
- L'eziologia dell'anemia non spiegata non spiegata è spesso multifattoriale





- Definizione di anemia?
- Esistono anemie dell'anziano?
- Impatto anemia e miglioramento outcomes con terapie? → EPO
- Screening anemia negli anziani?
- Linee guida per management anemia?

Grazie per l'attenzione