# Αναιμία και γήρας

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Πανεπιστημιακό Γενικό Νοσοκομείο ''ΑΤΤΙΚΟΝ''
Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών

WHO: Hemoglobin concentrations for the diagnosis of anemia and assessment of severity

- The concentration of Hb that defines the presence of anemia in the elderly would be:
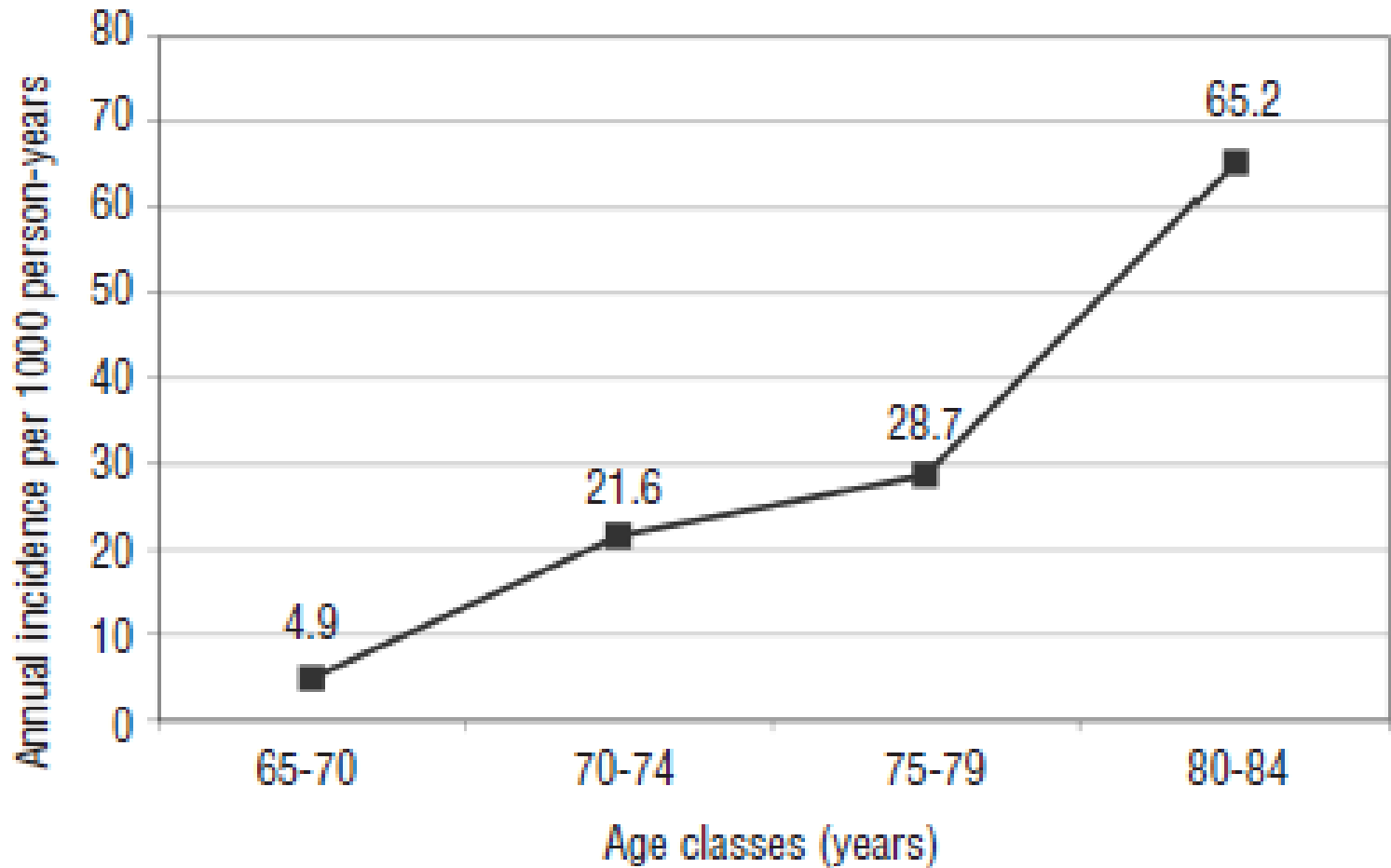 - ✓ <13 g/dl in men
  - ✓ <12 g/dl in women

Prevalence, incidence and types of mild anemia in the elderly: the "Health and Anemia" population-based study

Mild Anemia: Men (Hb=10 – 12.9), Women (Hb=10 – 11.9)
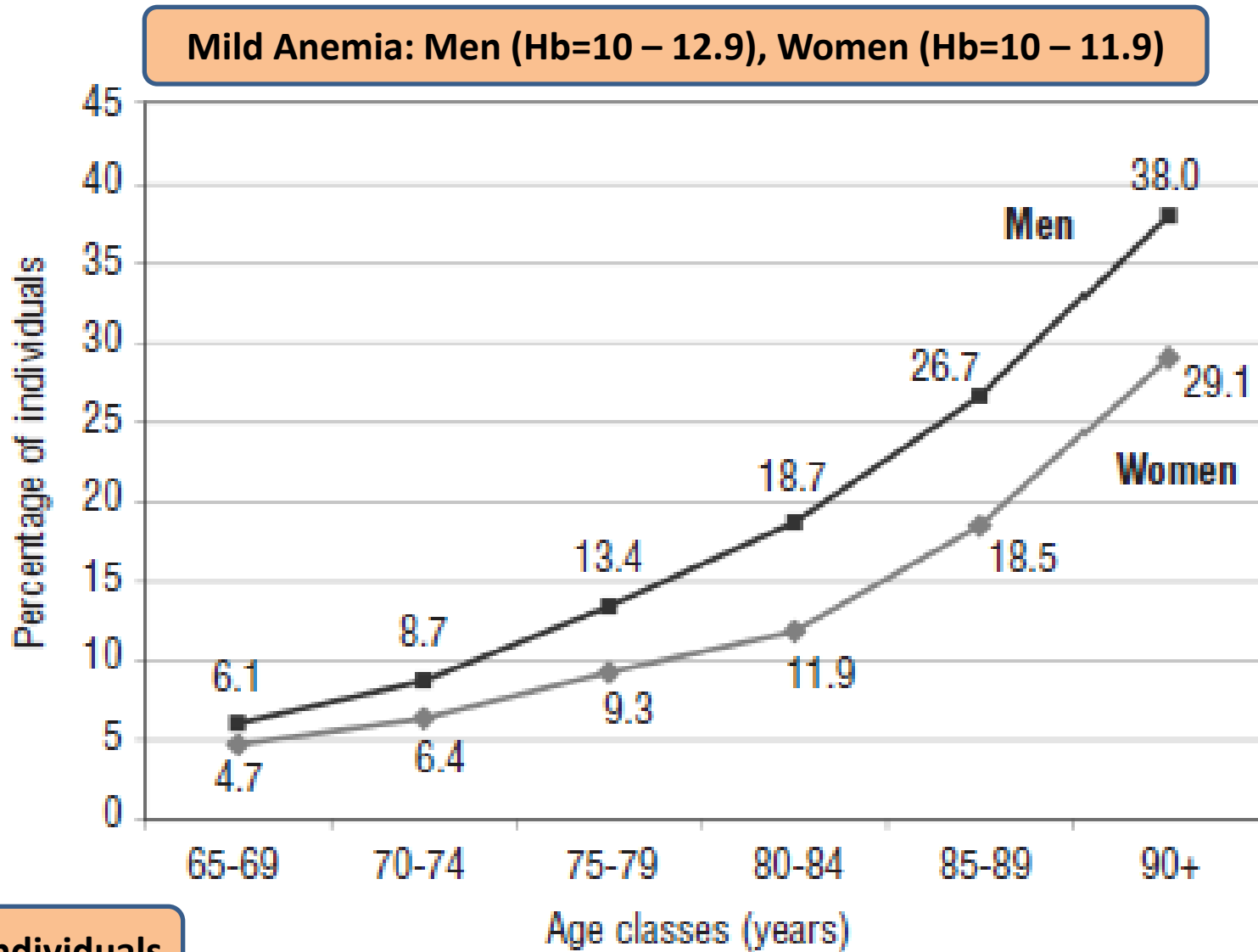
8.700 individuals

Prevalence, incidence and types of mild anemia in the elderly: the "Health and Anemia" population-based study

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8.700 individuals

Prevalence of Anemia

- Third US National Health and Nutrition Examination Survey(NHANES III, Phases 1 and 2, 1988–1994; 26,372 individuals), the prevalence of anemia in individuals:
  - ✓ ≥65 years: 10.6%
  - ✓ 65 – 74 years: 8%
  - ✓ 75–84 years: 13%
  - ✓ >85 years: 23%
  - ✓ higher among men
- EMPIRE Study-Portugal (1617 individuals):
  - ✓ >65years, men (22.2%), women (19.9%)
  - ✓ 65–79 years: 17.3%
  - ✓ ≥80 years: 31.4%

Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia

National Health and Nutrition Examination Survey (NHANES III)
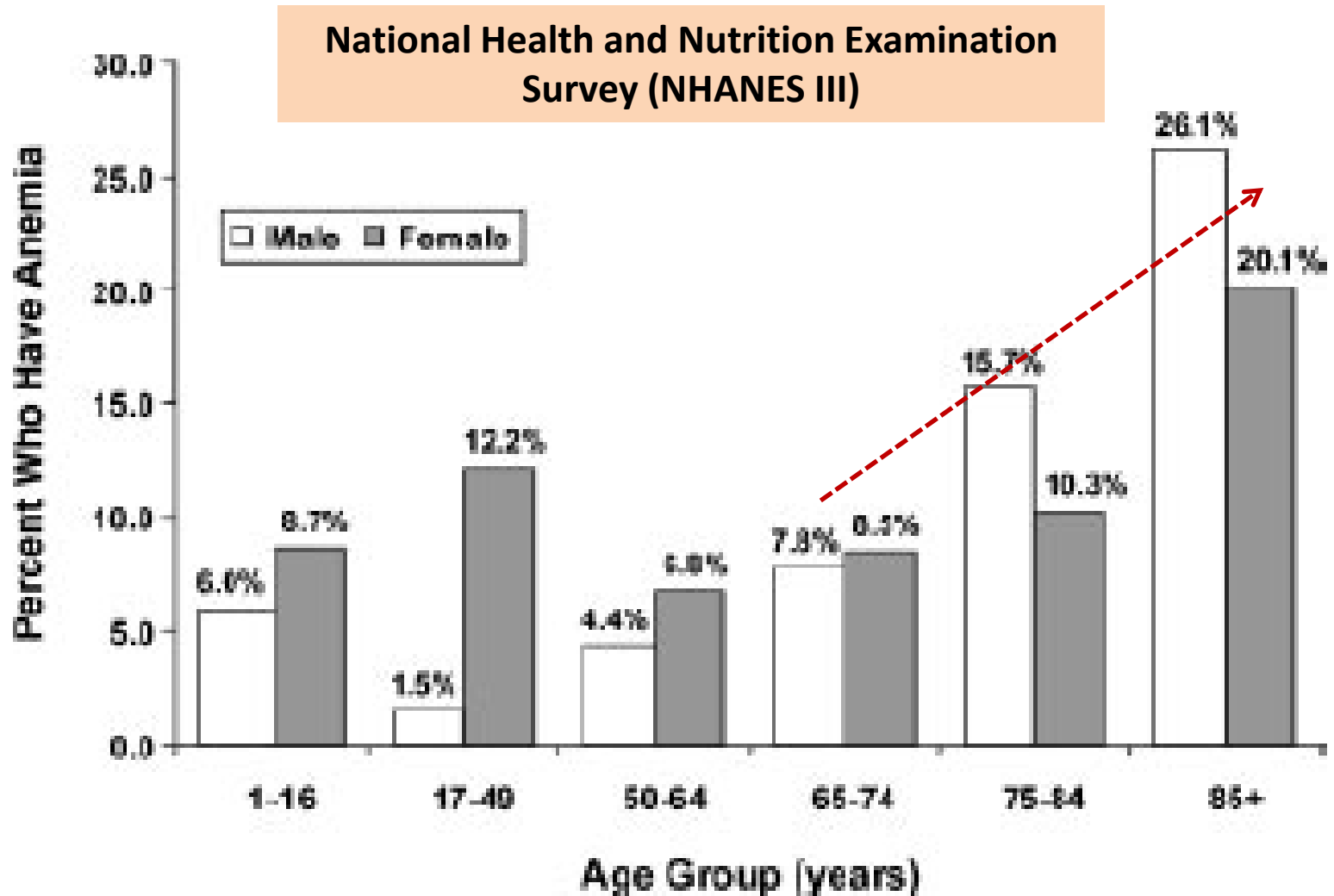
- Anemia resulting from Nutrient Deficiency
  - ✓ Iron Deficiency
  - ✓ B12 Deficiency
  - ✓ Folate Deficiency
- Anemia of Chronic Inflammation (ACI)
  - ✓ Low serum iron with normal or increased iron stores
- Anemia due to Renal Insufficiency
  - ✓ GFR < 30ml/min
- Unexplained Anemia

Differential diagnosis between Iron deficiency Anemia and Anemia of Chronic Disease

Parameters	Iron Deficiency Anemia	Anemia of Chronic Disease	Iron Deficiency Anemia and Chronic Disease
Serum Iron	↓↓	↓↓	↓↓↓
Ferritin	↓↓	↑	N
Transferrin (Total Iron Binding Capacity)	↑↑	↓	↓, N, ↑
Transferrin saturation (%)	↓↓	↓	↓↓
Soluble TFR	↑↑	N	↑

Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia

Distribution of types of anemia in persons > 65 years

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

ACI: Anemia of chronic inflammation
UA: Unexplained anemia

Σιδηροπενική Αναιμία

A. Iron deficiency

Increased iron losses

Peptic ulcer (gastric, duodenal, Cameron's esophagitis)

Benign or malignant neoplasms: colon, stomach, oesophagus, small intestine

Use of NSAIDs

Inflammatory bowel disease: ulcerative colitis, Crohn's disease

Intestinal parasitosis

Vascular disorders: angiodysplasia, hereditary haemorrhagic telangiectasia, gastric antral vascular ectasia

Genitourinary losses

Decreased absorption of iron

Celiac disease, Whipple's syndrome, lymphangiectasis, bacterial overgrowth, gastric atrophy, gastrectomy, intestinal resection or *bypass*

Medication: AntiH$_2$, PPIs, antacids, etc.

Excess fibre in the diet (especially in vegetarians), phenolic compounds in tea and coffee, soy (however, absorption of iron increases with intake of fermented foods and proteins)

Αναιμία από έλλειψη Β12, folate

B. Vitamin B deficiency$_{12}$

Inadequate intake: strict vegetarians, alcoholism, malnutrition

Gastric diseases: pernicious anaemia, gastrectomy, chronic atrophic gastritis

Diseases of the small intestine: malabsorption syndromes, ileal resection or bypass, Ileal Crohn's disease, blind loop syndrome

Pancreatic disease: pancreatic failure

Drugs: PPI and anti-H$_2$, metformin, colchicine, neomycin, cholestyramine

C. Folate deficiency

Nutritional deficiency: alcoholism, drug addiction, inadequate intake, highly cooked foods

Malabsorption: inflammatory bowel disease, celiac disease, short bowel syndrome, other small intestinal diseases

Drugs: methotrexate, trimethoprim, sulfasalazine, phenytoin

Increased requirements: haemolysis, exfoliative dermatitis

Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia

| Characteristic	Total nonanemic population 65 y and older n = 1822	ACI n = 55	UA n = 78
Mean age, y	74.9	75.0†	76.7*
Women, %	56.6	38.2*	47.4
African American, %	15.1	43.6*	30.8*
Mexican American, %	17.5	12.7	7.7
Mean hemoglobin level	14.2	11.8*	11.8*
Less than 110 g/L, %	NA	9.1	11.5
Less than 100 g/L, %	NA	3.6	1.3
Condition, %			
Hypertension	66.8	69.1	68.0
Arthritis	45.4	63.6*	56.4
Diabetes, all	18.8	32.7*	23.1
Insulin-treated diabetes	4.8	12.7	5.1
Congestive heart failure	9.0	12.7	7.7
Asthma	4.3	3.6	3.9
Stroke	9.3	16.4	11.5
Cancer, past 2 y	1.6	1.8	5.1
Cancer more than 2 y ago	6.4	5.5	11.5
Recent surgery, past 12 mo	0.4	1.8	2.6*
Hepatitis C antibody positive	1.3	3.6	3.9
Elevated CRP level, greater than 1.0 mg/dL	11.2	27.3*†	9.0
Rheumatoid factor positive, 30 IU/mL and higher	6.1	20.0*	9.0

Anemia of Chronic Inflammation
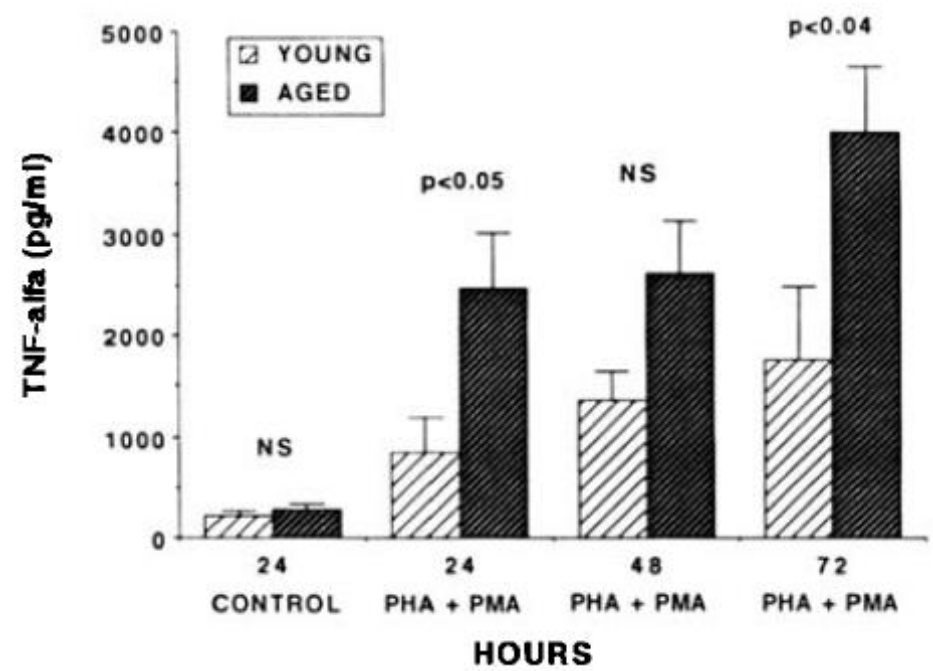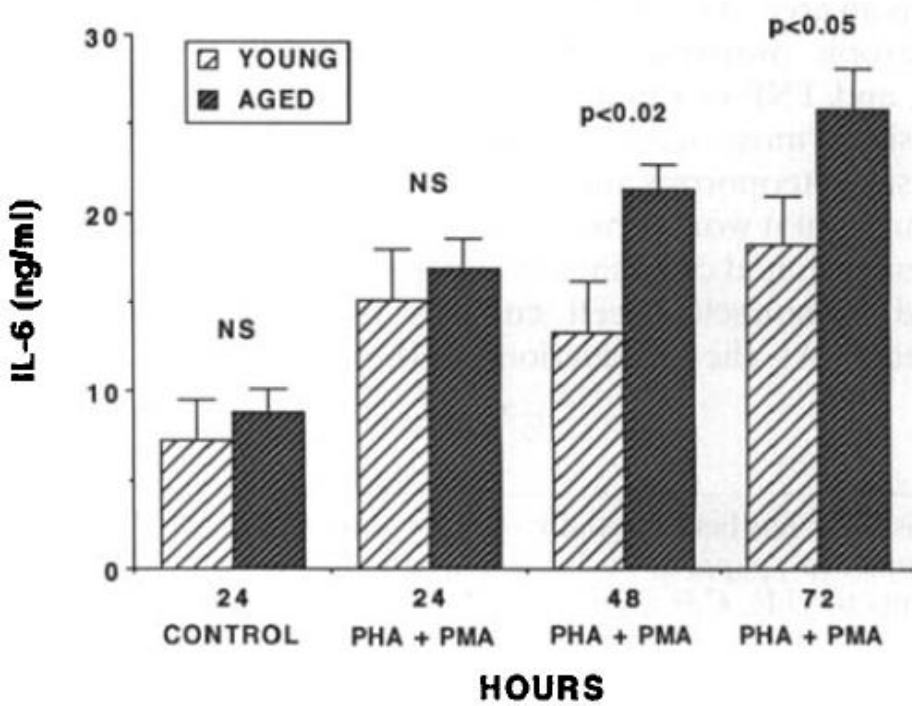- **Low serum iron**
- **Normal iron stores**

Anemia of Chronic Inflammation
- **More Arthritis**
- **More Diabetes (DM)**
- **More Insulin-treated DM**
- **More CHF**
- **More Stroke**
- **Increased CRP**

Is aging an inflammatory process?
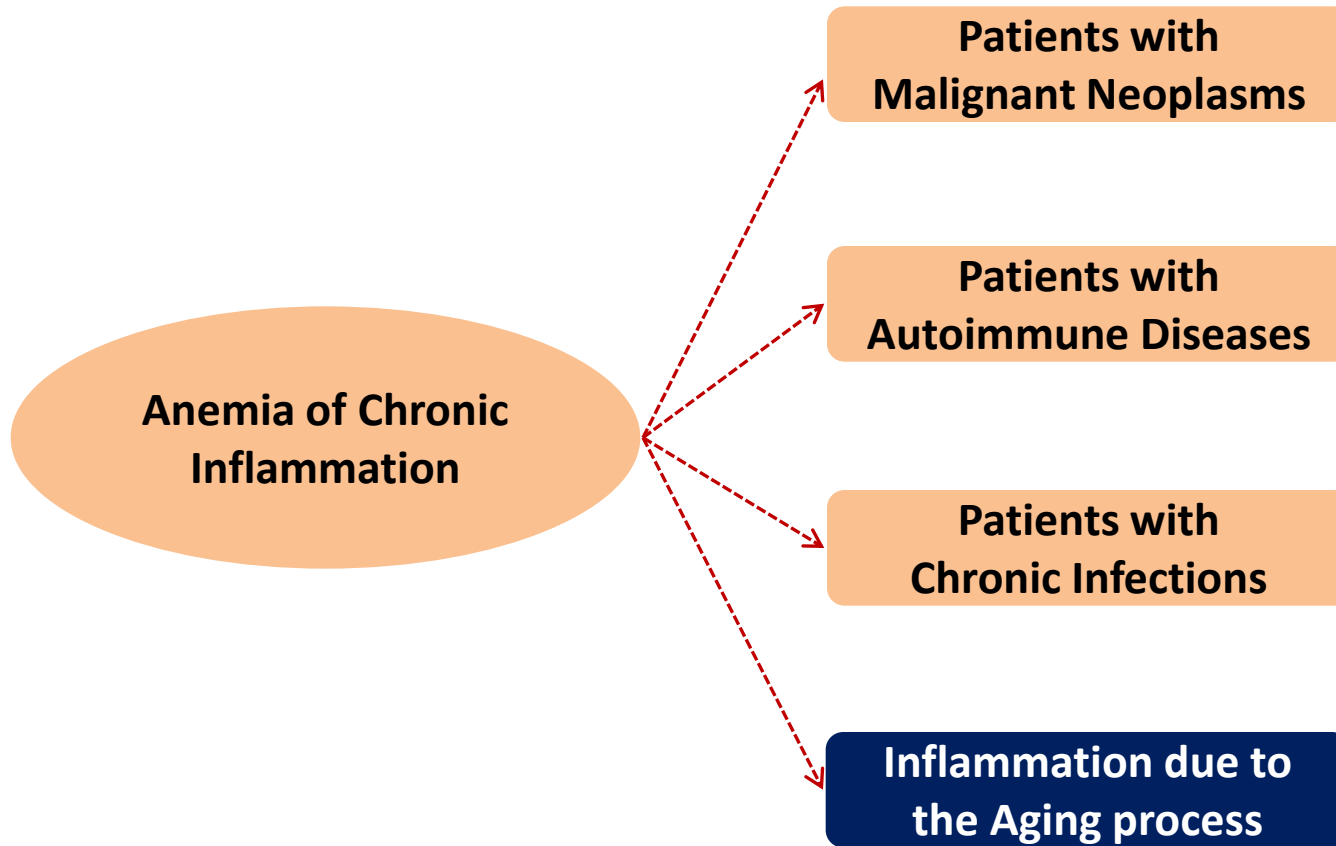
Increased cytokine production in mononuclear cells of healthy elderly people*
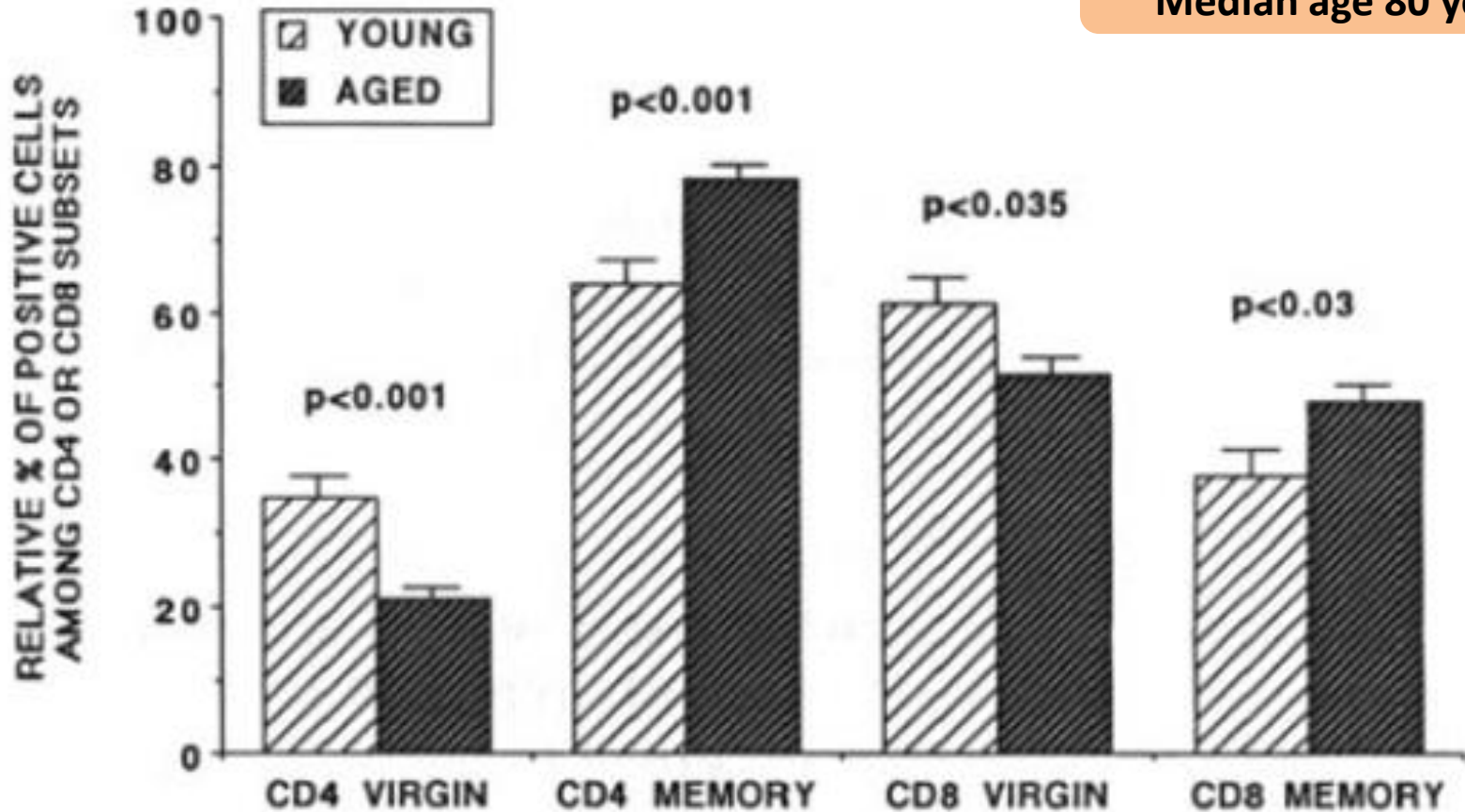

Young healthy donors:
Median age 25 years

Elderly healthy donors:
Median age 80 years

Increased cytokine production in mononuclear cells of healthy elderly people*

Young healthy donors: Median age 25 years

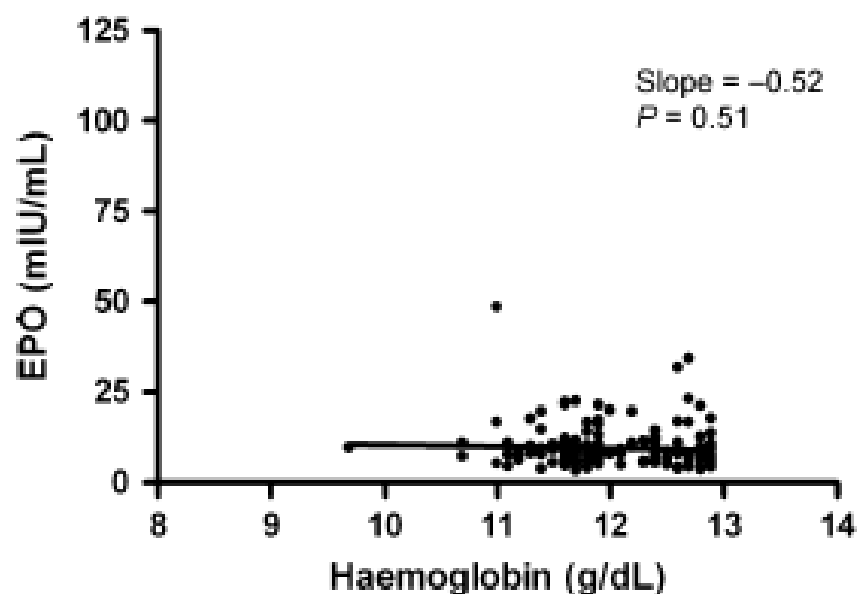Elderly healthy donors: Median age 80 years

Unexplained Anemia

- 10% - 30% of individuals > 65 years with anemia
- The percentage depends on the robustness of diagnostic methodology
- Most individuals present with mild anemia
- Hb < 11.0gr/dl in approximately 10%
- Hb < 10.0gr/dl in approximately 1.5%
- Multifactorial origin
- Myelodysplastic syndromes?

Erythropoietin, GDF15, IL6, hepcidin and testosterone levels in a large cohort of elderly individuals with anaemia of known and unknown cause
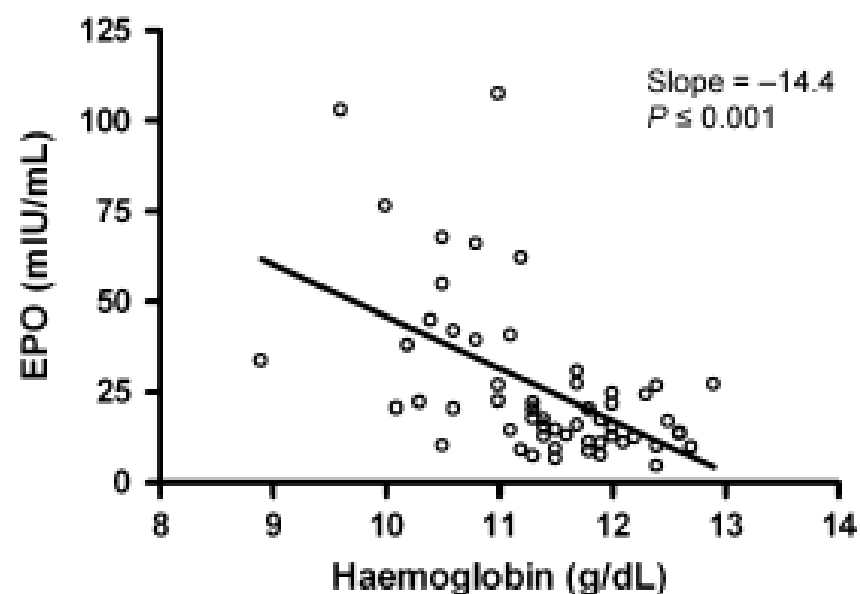
	Control		Anaemia of unknown aetiology (AUE)		
	n		n		P-value
IL6 (pg/mL)					
Men	24	1.4 ± 1.4	34	1.5 ± 1.3	NS
Women	23	1.7 ± 1.6	23	1.4 ± 1.4	NS
EPO (mIU/mL)					
Men	80	7.4 ± 2.9	72	10.0 ± 7.0**	0.003
Women	83	7.1 ± 2.7	80	8.6 ± 4.0**	0.005
Testosterone (ng/mL)					
Men	79	9.8 ± 7.7	72	7.6 ± 4.0**	0.03
Hepcidin (ng/mL)					
Men	25	132 ± 79	34	152 ± 69	NS
Women	23	148 ± 74	23	192 ± 105	NS

Erythropoietin, GDF15, IL6, hepcidin and testosterone levels in a large cohort of elderly individuals with anaemia of known and unknown cause
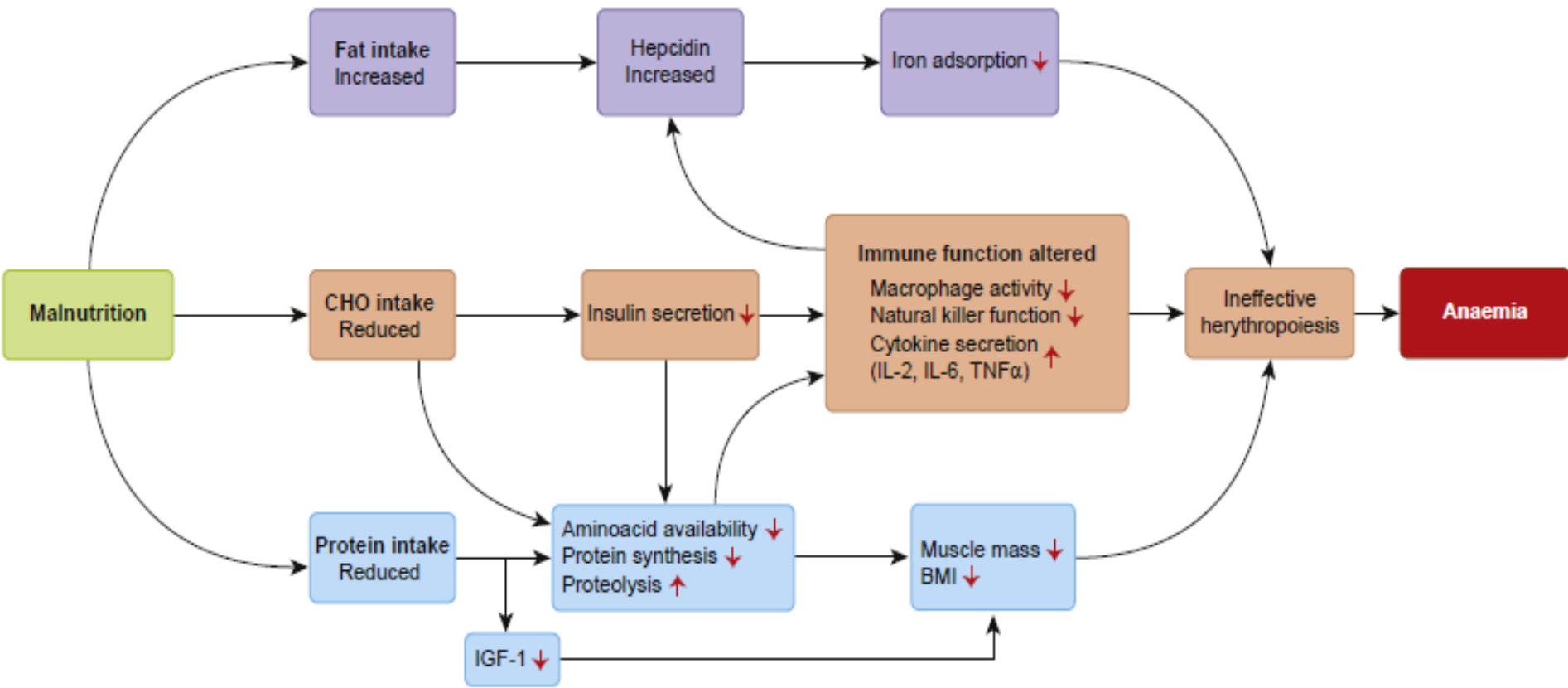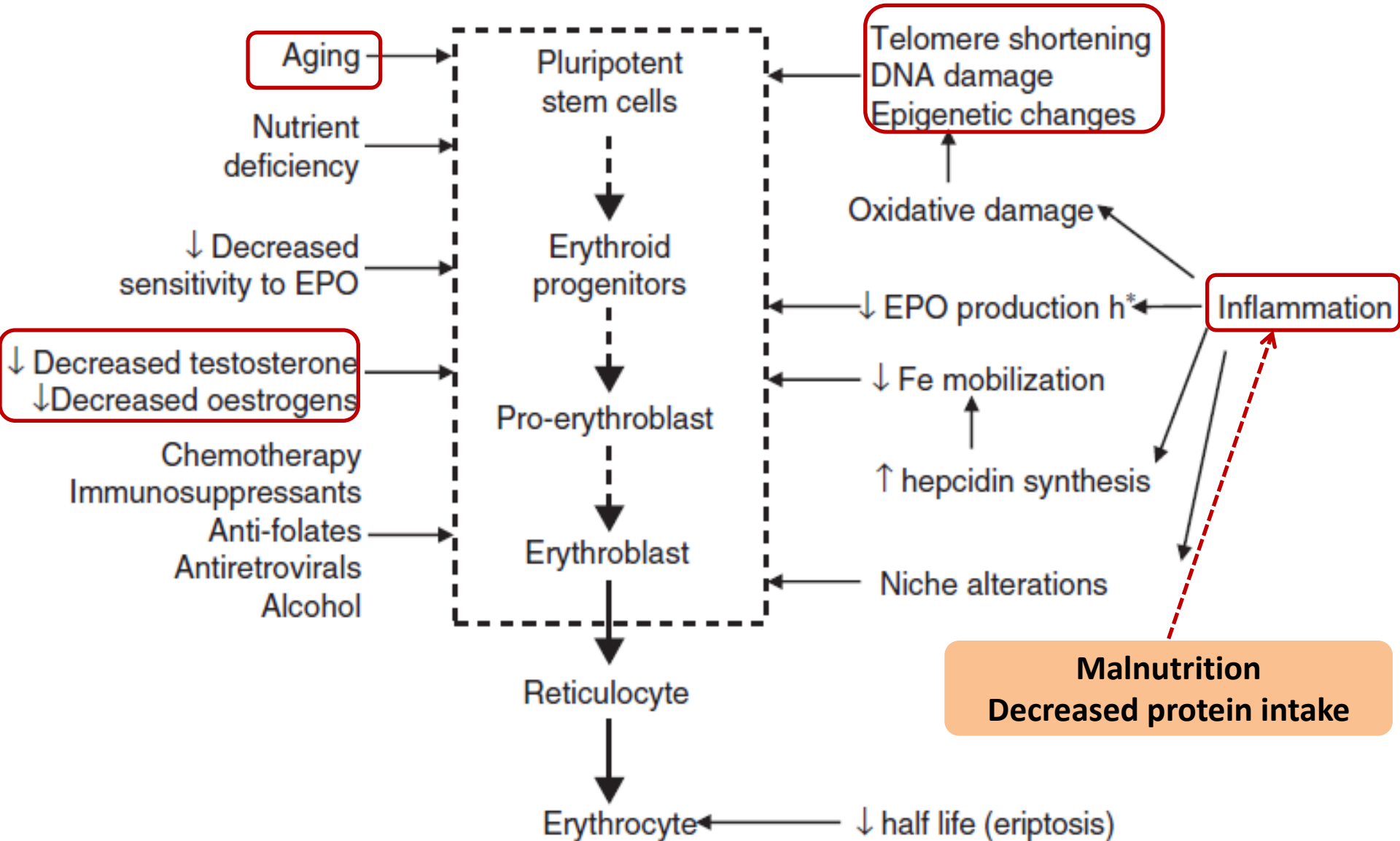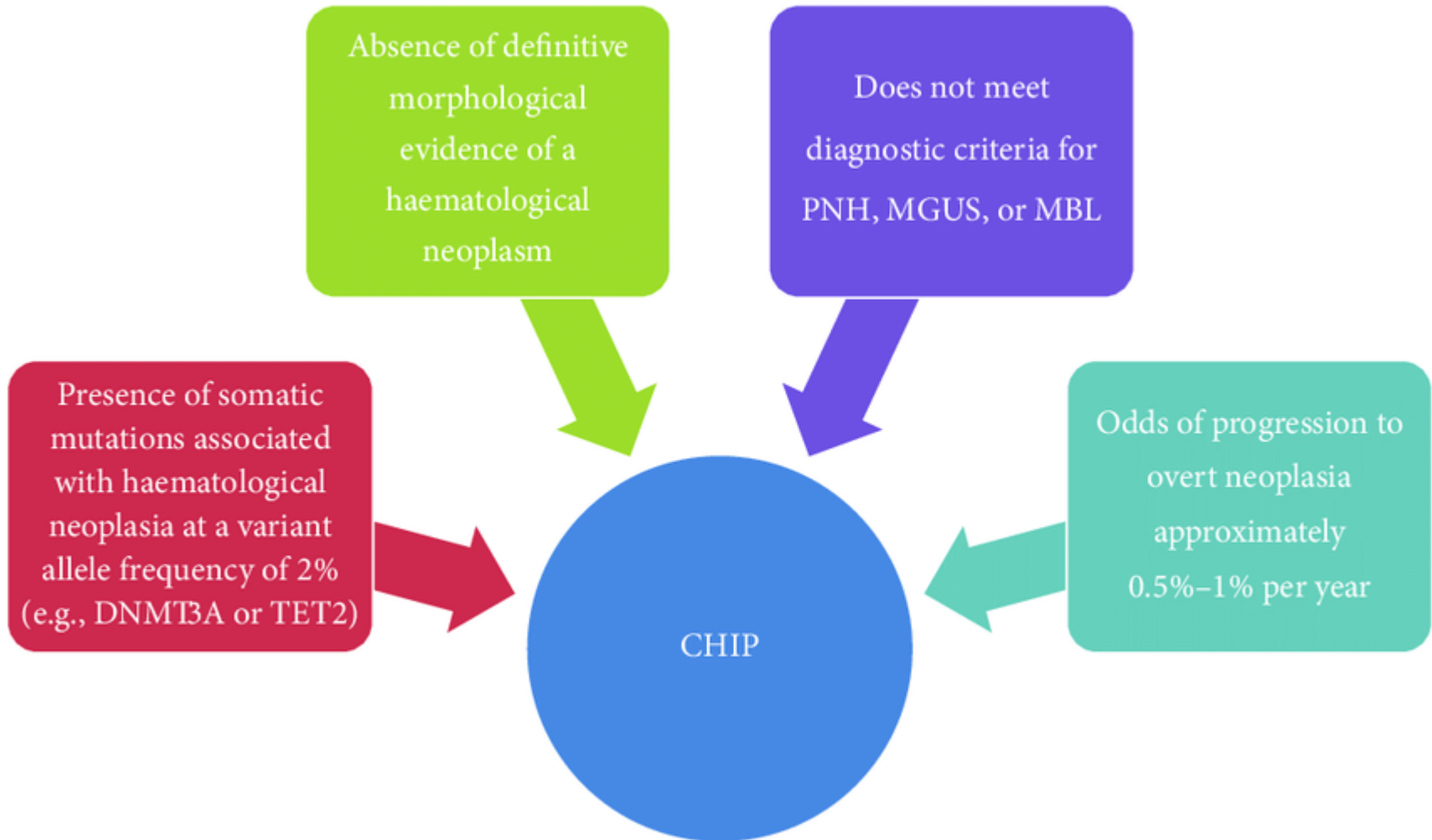

European Journal of Haematology 87 (107–116)

Role of nutrition on anemia in elderly

Pathogenesis of Unexplained Anemia of the Elderly

Clonal Hematopoiesis of Indeterminate Potential (CHIP)

Absence of definitive morphological evidence of a haematological neoplasm

Does not meet diagnostic criteria for PNH, MGUS, or MBL

Presence of somatic mutations associated with haematological neoplasia at a variant allele frequency of 2% (e.g., DNMT3A or TET2)

Odds of progression to overt neoplasia approximately 0.5%–1% per year

CHIP

DNMT3A is frequently mutated in CHIP

Clonal Hematopoiesis of Indeterminate Potential (CHIP)

	'Non-clonal' ICUS	CHIP	CCUS	Lower Risk MDS	Higher Risk MDS
Clonality	–	+	+	+	+
Dysplasia	–	–	–	+	+
Cytopenias	+	–	+	+	+
BM Blast %	< 5%	< 5%	< 5%	< 5%	< 19%
Overall Risk	Very Low	Very Low	Low (?)	Low	High
Treatments	Obs/BSC	Observation	Obs/BSC/GF	Obs/BSC/GF IMiD/IST	HMA/HCST
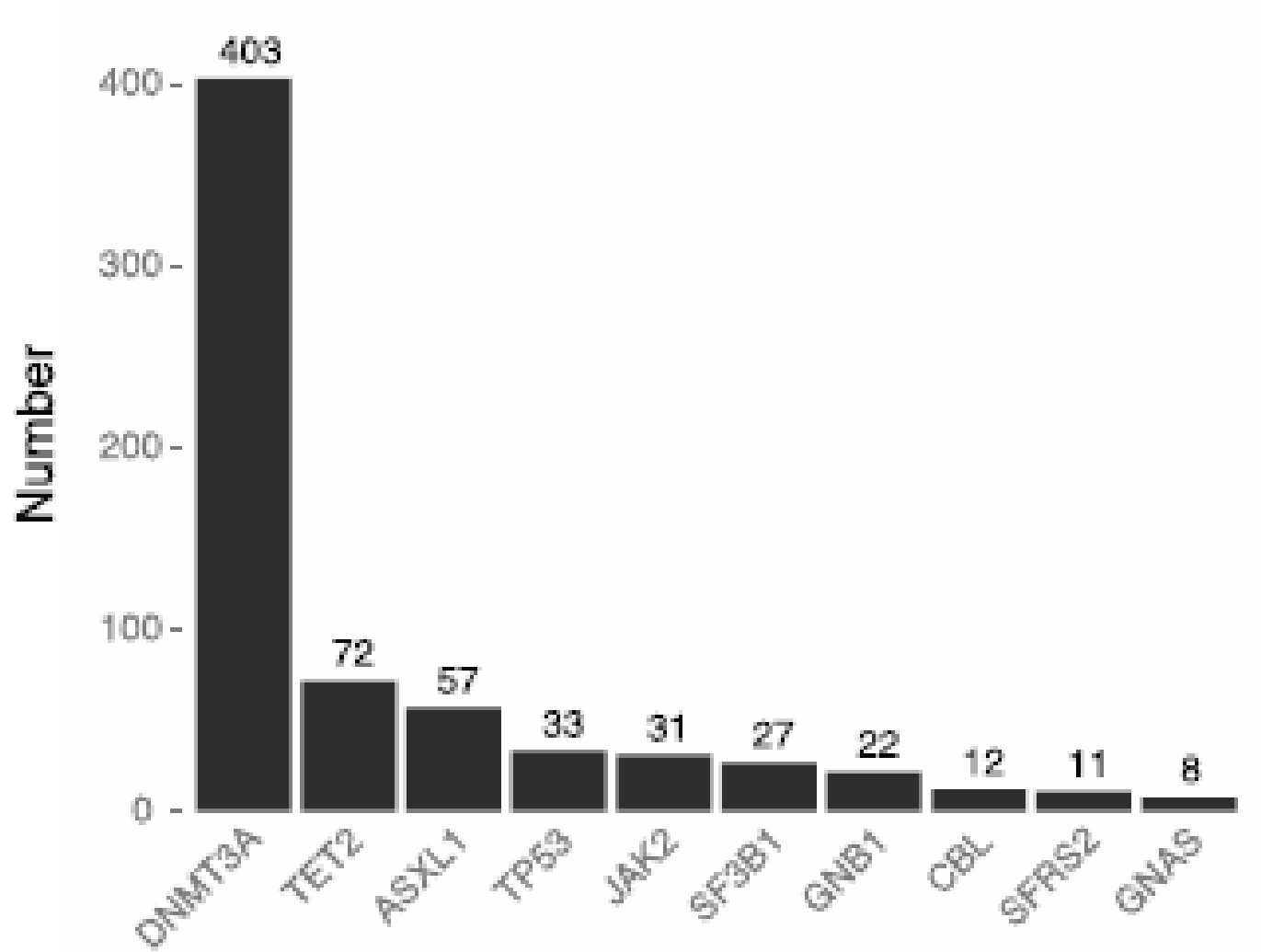
Traditional ICUS

MDS by WHO 2008

Clonal Cytopenias

Clonal Hematopoiesis of Indeterminate Potential (CHIP)

Jaiswal et al., *NEJM* 2014
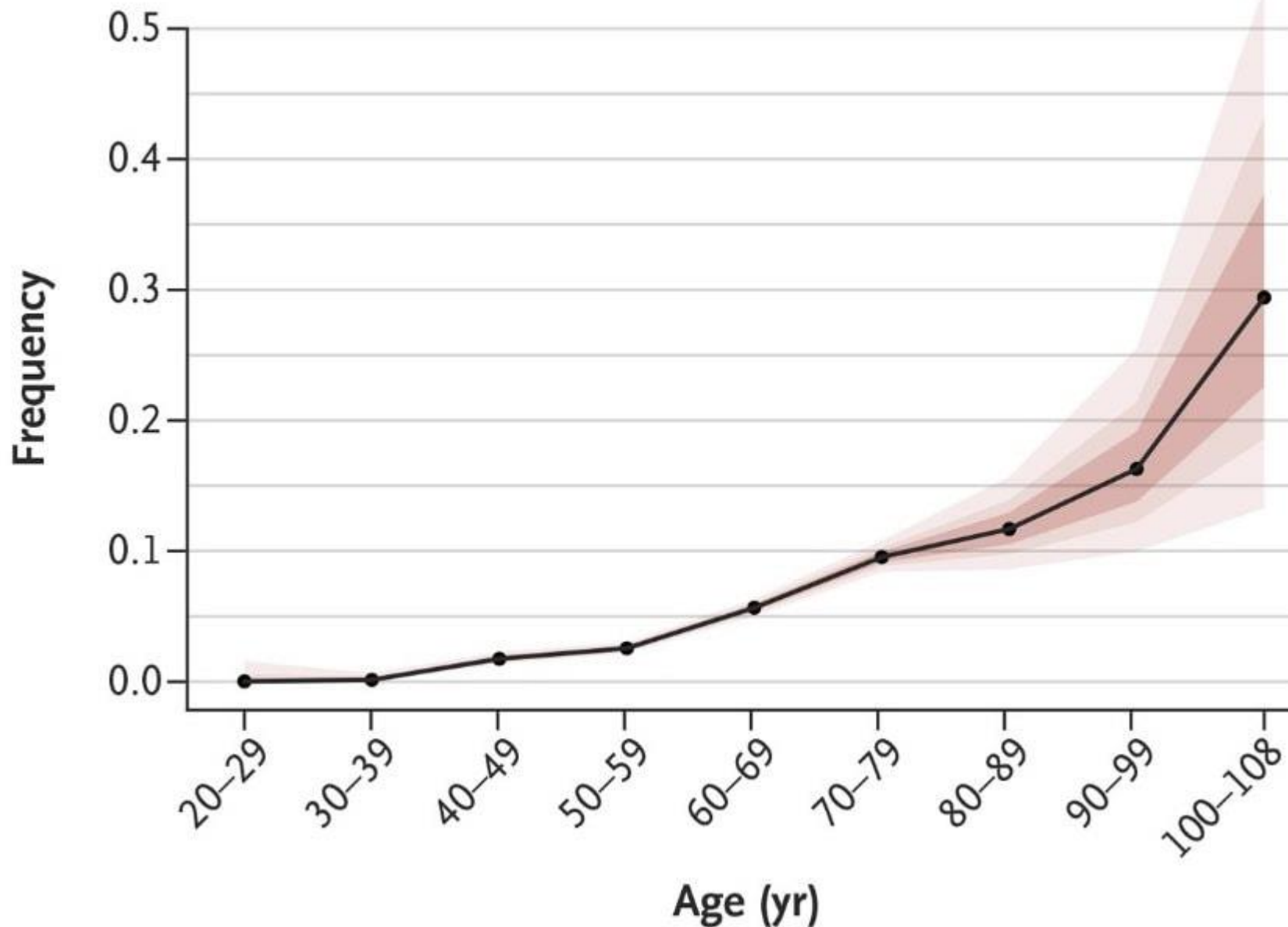
Clonal hematopoiesis is associated with higher risk of heart attack and stroke

Coronary heart disease

- No mutation, n=2,912
- Mutation, n=118

p=0.009

HR 2.0, 95% CI 1.2-3.4, p=0.018

Stroke

- No mutation, n=3,094
- Mutation, n=123

p=0.005
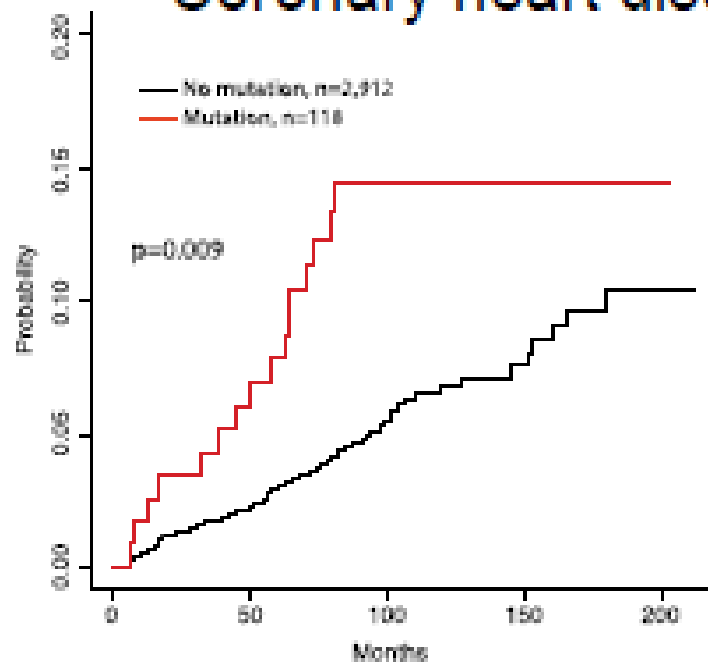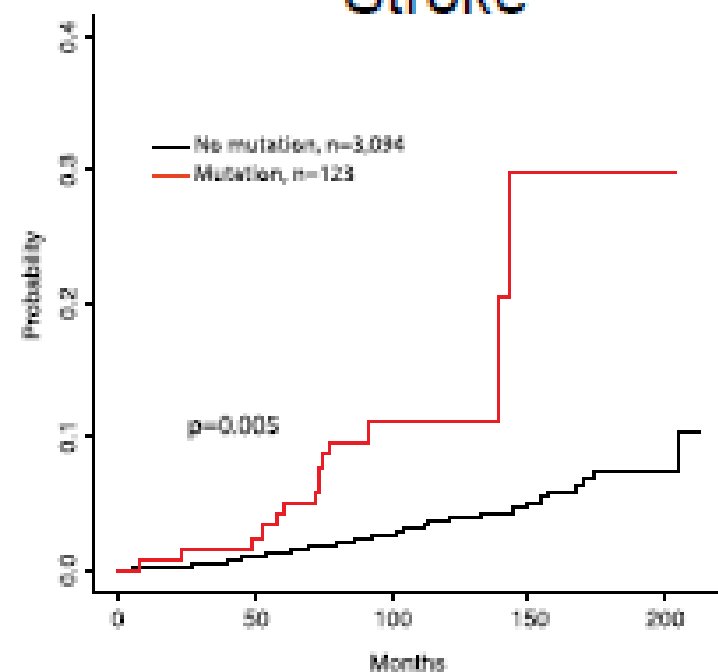
HR 2.6, 95% CI 1.4 to 4.8, p=0.003

Regression models were adjusted for age, sex, BMI, lipids, blood pressure, and smoking

Mechanism of Cardiovascular Events in Clonal Hematopoiesis

Clonal expension in marrow

Mutant monocytes

Wild-type monocytes

Circulating clonal monocytes infiltrate myocardium
- NLRP3 inflammasome activated; 1L-1β secreted
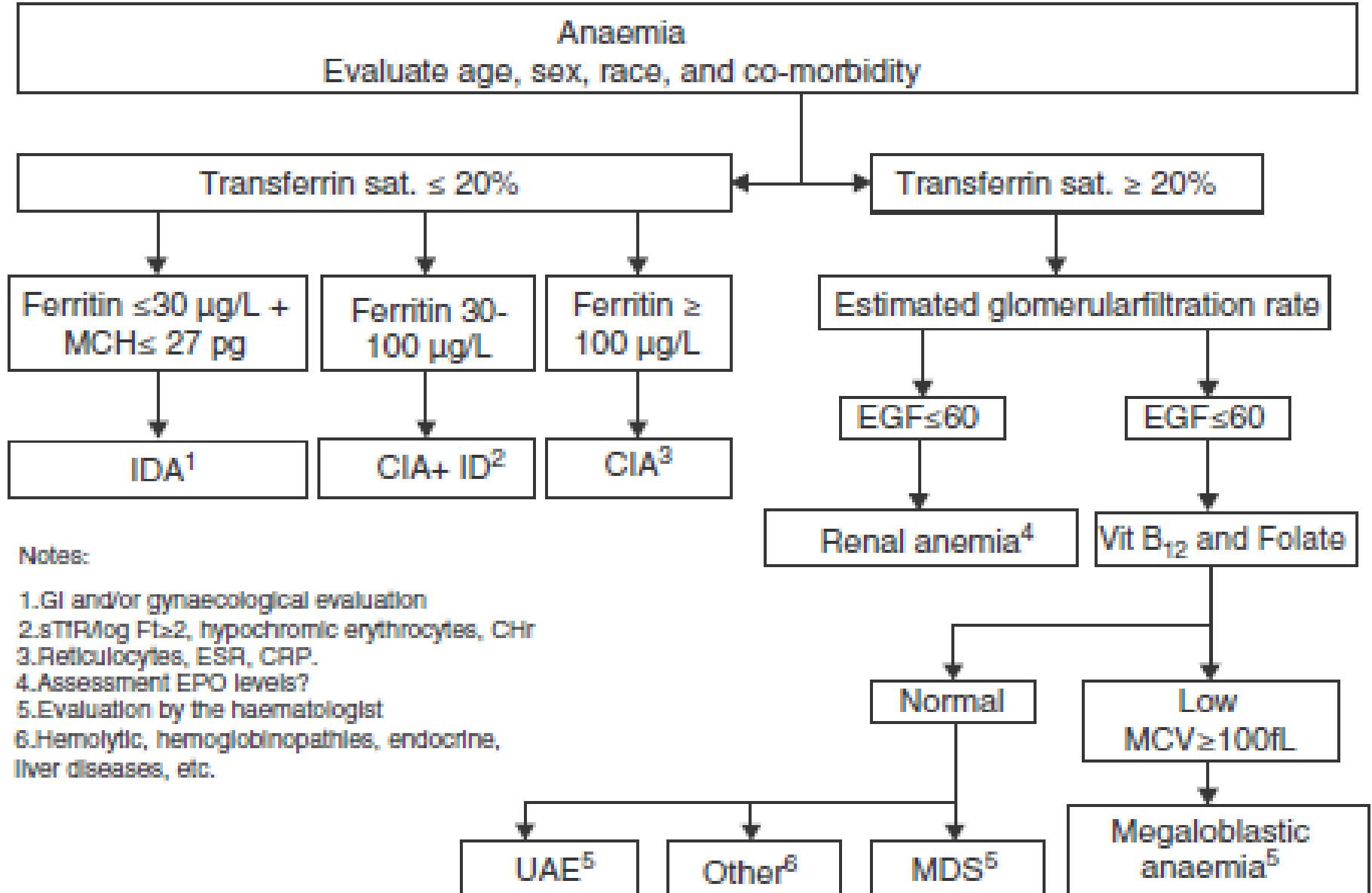- Disordered cardiac remodeling
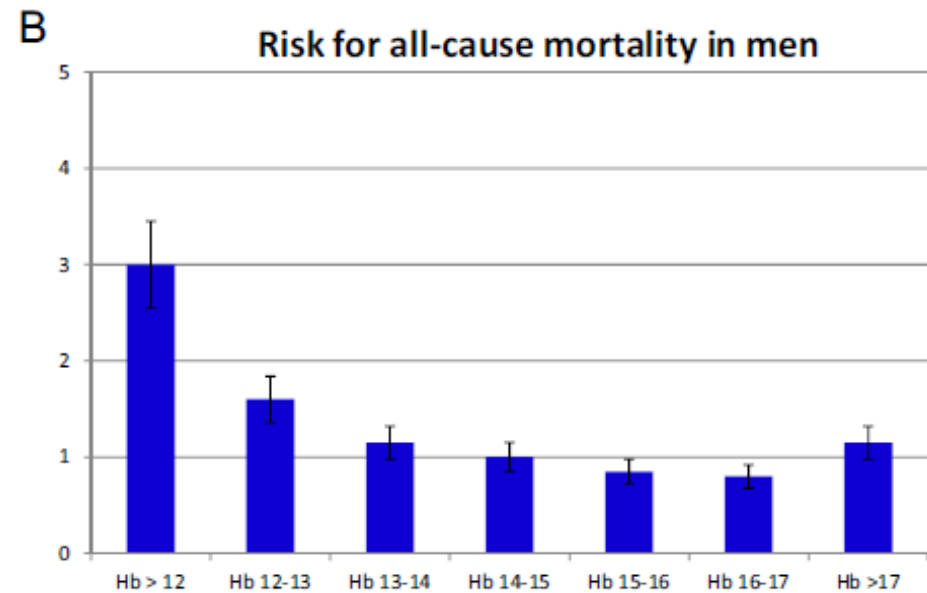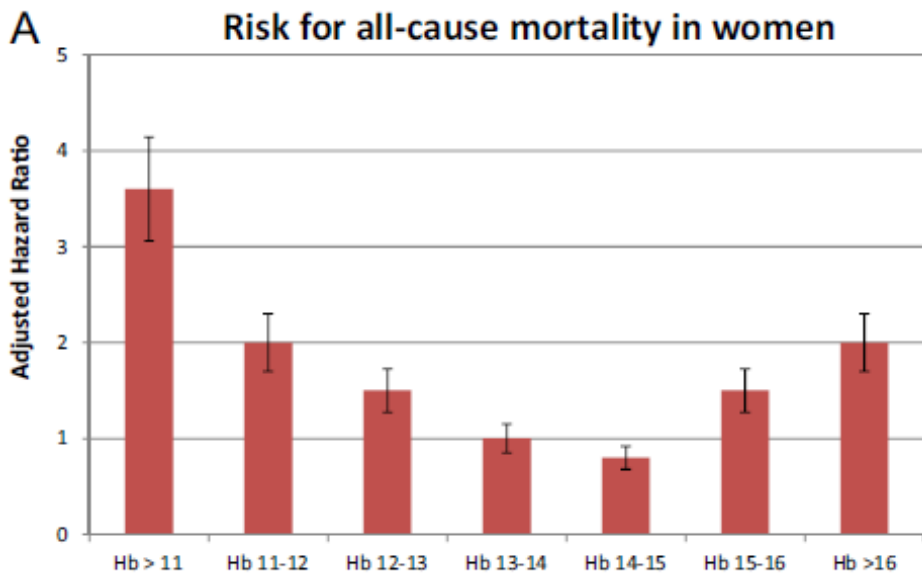- Heart failure develops or worsens

Circulating clonal monocytes traffic to atherosclerotic plaques
- Differentiate to macrophages and infiltrate endothelium/plaque
- NLRP3 inflammasome activated; 1L-1β secreted
- Increased P-selectin upregulation recruits more macrophages
- Atherosclerotic plaque thickens or ruptures

Diagnostic approach

Anaemia
Evaluate age, sex, race, and co-morbidity

Transferrin sat. ≤ 20%

Transferrin sat. ≥ 20%

Ferritin ≤30 µg/L + MCH≤ 27 pg

Ferritin 30-100 µg/L

Ferritin ≥ 100 µg/L

Estimated glomerularfiltration rate

EGF≤60

EGF≤60

IDA^1

$CIA+ ID^2$

CIA^3

Renal anemia[4]

Vit B_{12} and Folate

Normal

Low
MCV≥100fL

UAE^5

$Other^6$

MDS^5

Megaloblastic anaemia[5]

Notes:

1. GI and/or gynaecological evaluation
2. sTfR/log Ft≥2, hypochromic erythrocytes, CHr
3. Reticulocytes, ESR, CRP.
4. Assessment EPO levels?
5. Evaluation by the haematologist
6. Hemolytic, hemoglobinopathies, endocrine, liver diseases, etc.

Anemia: Risk for all-cause mortality

Treatment

- Treatment of the underlying disorder
- Patients in need for transfusion rarely have unexplained anemia
- Treatment with ESA (erythropoietin stimulating agents)
1. Patients with renal failure
2. Patients without renal failure?
   - ✓ Only in the context of a clinical trial
   - ✓ Therapeutic target: Hb≈10gr/dl

Complications Associated With Erythropoietin-Stimulating Agents in Patients With Metastatic Breast Cancer
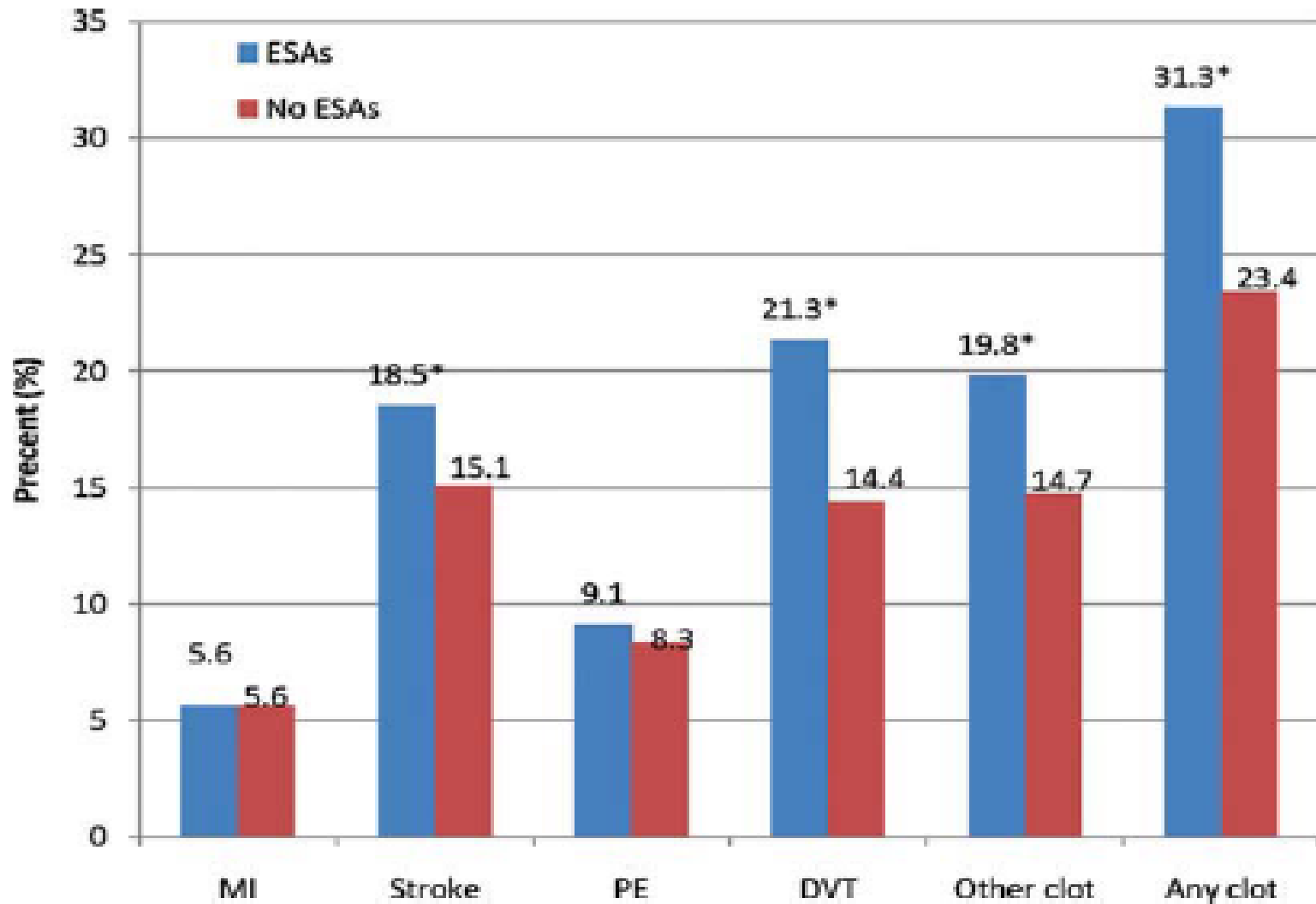
Studies of Epo for the treatment of chemotherapy induced anemia with a detrimental effect on survival of cancer patients

Study	Neoplasm	Treatment	ESA	Hb Goal
Henke et al[19]	Head and neck	Radiotherapy	Epoetin β	>14 (women) >15 (men)
Hedenus et al[18]	Lymphomas	Chemotherapy	Darbepoetin α	>14 (women) >15 (men)
Leyland Jones et al[17]	Breast	Chemotherapy	Epoetin α	>14
Wright et al[16]	Non-small cell lung cancer	Radiotherapy	Epoetin α	>14
Overgaard et al[15]	Head and neck	Radiotherapy	Darbepoetin α	>15.5
PREPARE[14]	Breast	Chemotherapy	Darbepoetin α	>13
Thomas et al[13]	Cervix	Chemoradiotherapy	Darbepoetin α	>14
Smith et al[12]	Solid tumors	No antineoplastic treatment	Darbepoetin α	>13

Anemia in elderly

- Chronic inflammation
- Malnutrition: reduced protein intake
- Sex hormone deficiency
- Treat the underlying disorder not the hemoglobin