UNIVERSITY OF DUBLIN

Low vitamin B12 status in our elderly citizens: Trying to see the wood through the trees!

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Identifying the problem

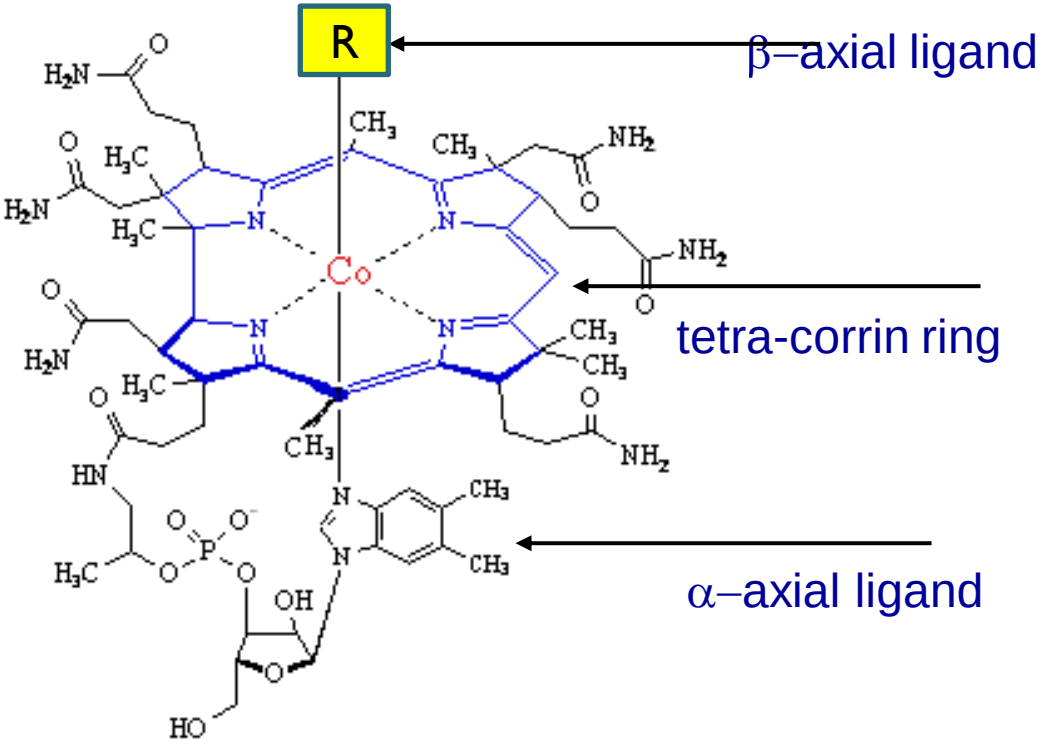
- Low vitamin B12 blood status has been estimated to affect more than 30% of people over 60 years of age.
- It is not clear what proportion of those with low B12 will eventually develop clinically relevant consequences.
- It is possible that some of the symptoms we attribute to "normal" aging –memory loss, cognitive decline, decreased mobility, etc. – are partly caused by B12 deficiency.

Symptoms of B12 deficiency

FACTS:

- Vitamin B_{12} deficiency can be slow to develop, causing symptoms to appear gradually and intensify over time.
- Older individuals rarely have classical features of macrocytic anaemia and neuropathy.
- The condition can be overlooked or confused with non-specific symptoms of fatigue and cognitive impairment that can be attributed to "old age".

What is Vitamin B12?



R = CH_2CONH_2
R'=$CH_2CH_2CONH_2$

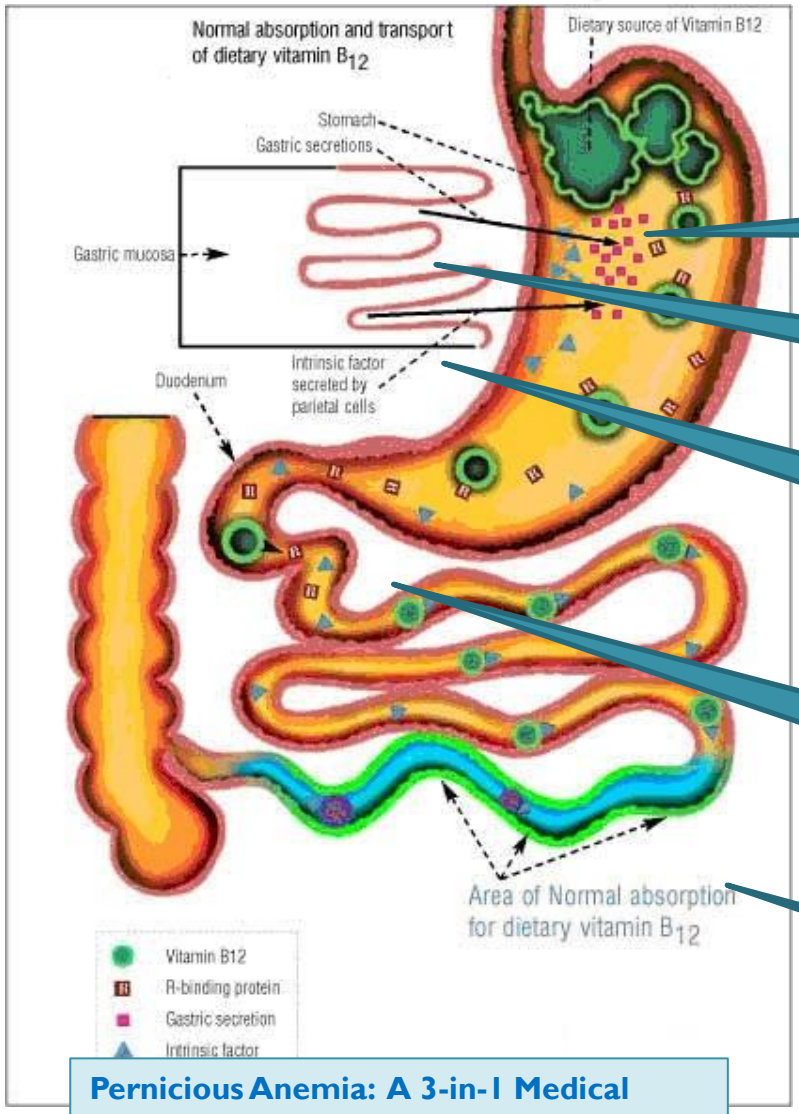
R =

- OH: Hydroxycobalamin
- CH3: Methylcobalamin
- Ado: 5'Deoxyadenosylcobalamin
- CN: Cyanocobalamin

"Nature's most beautiful cofactor"..J.Stubbe 1994

Why is vitamin B12 deficiency a particular problem in older persons?

Malabsorption!!!



Low acid secretion: Gastric enzymes don't function properly. B12 not released from food

Medications / helicobacter Gastric surgery

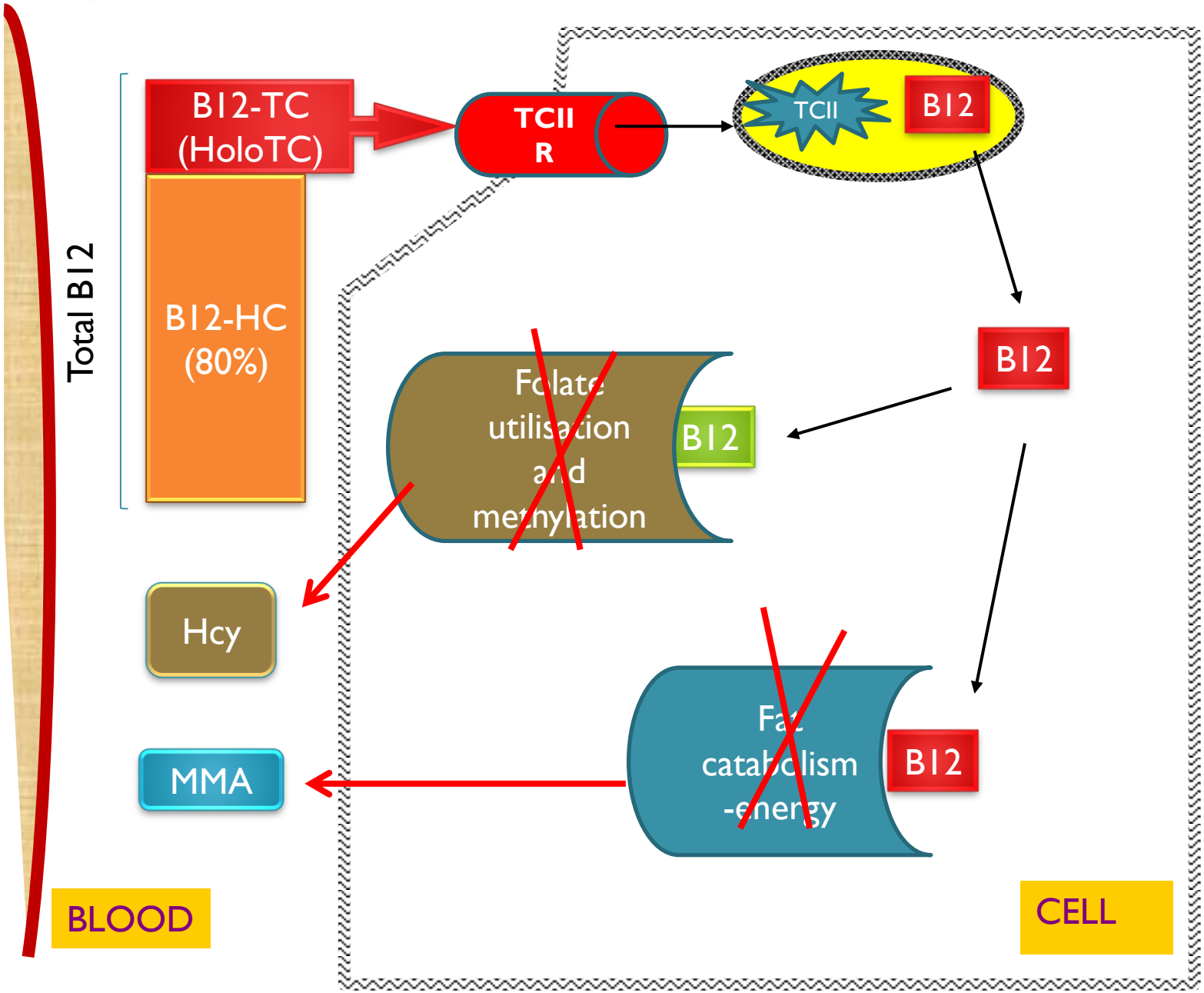
Parietal cell disease: IF deficiency – severe (PA) 1-2%

Pancreatic conditions affect enzymes that release B12 from HC in the duodenum

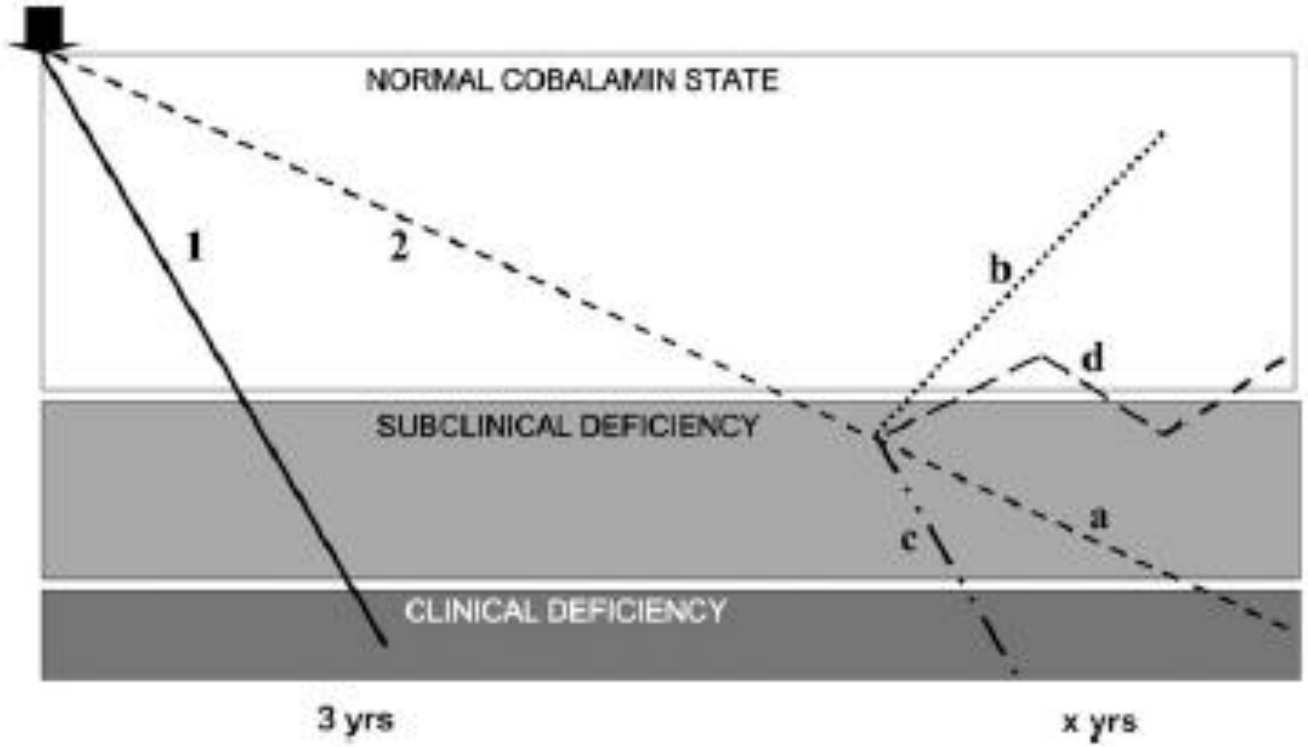
Bacterial overgrowth

Pernicious Anemia: A 3-in-1 Medical Reference: Icon Health Publications 2004

Why do we need it?



Progression of B12 deficiency



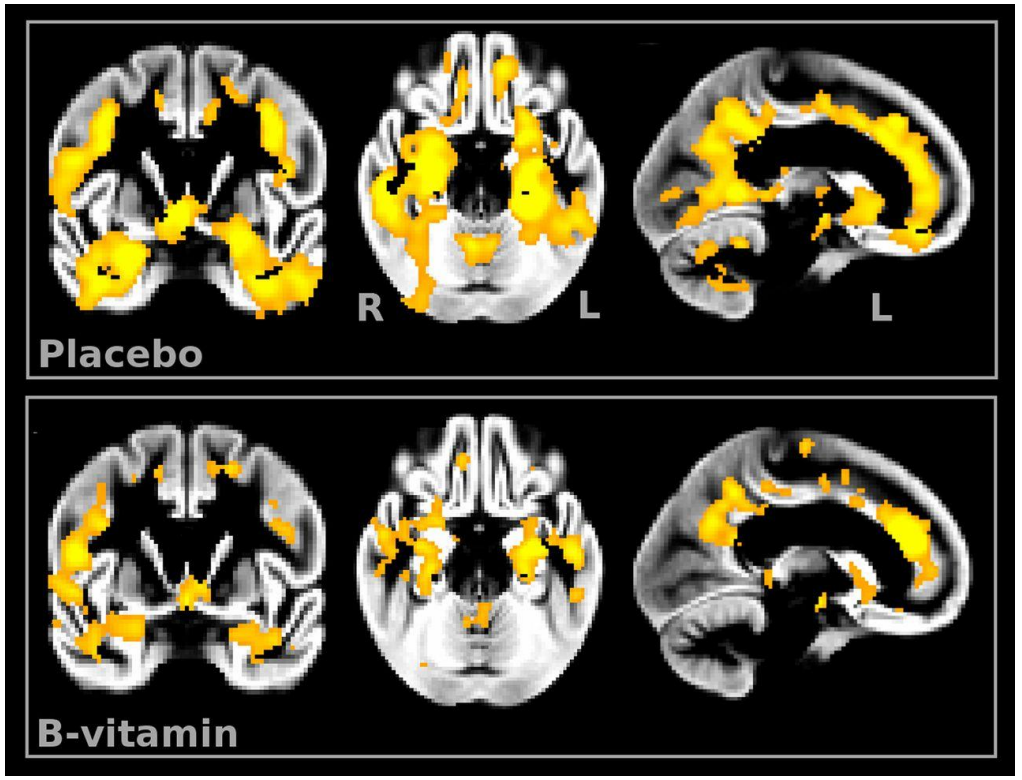
1 Severe malabsorption due to pernicious anaemia

2. Unexplained B12 deficiency due to food malabsorption and other factors
   - (a) on a path to clinical deficiency
   - (b) remission due to unknown reasons
   - (c) accelerates into clinical disease
   - (d) fluctuates at borderline deficiency with unknown consequences

Carmel R. Am J Clin Nutr 2011

Preventing Alzheimer's disease-related gray matter atrophy by B-vitamin treatment

Gwenaëlle Douaud[a,b,1], Helga Refsum[b,c,d], Celeste A. de Jager[c], Robin Jacoby[e], Thomas E. Nichols[a,f,g], Stephen M. Smith[a], and A. David Smith[b,c]



Regional loss of GM volume in placebo and B-vitamin groups.

Douaud G et al. PNAS 2013;110:9523-9528

VITACOG STUDY

Recruited 156 older persons with mild cognitive impairment

Carried out a randomized placebo controlled trial over 24 months

Treatment FA 0.8 mg; B12 0.5 mg; B6 20 mg

MRI scans before and after treatment

B-vitamin treatment significantly reduced regional loss of GM ($P < 0.05$ FWE-corrected).

Anthropometric details

Demographic details

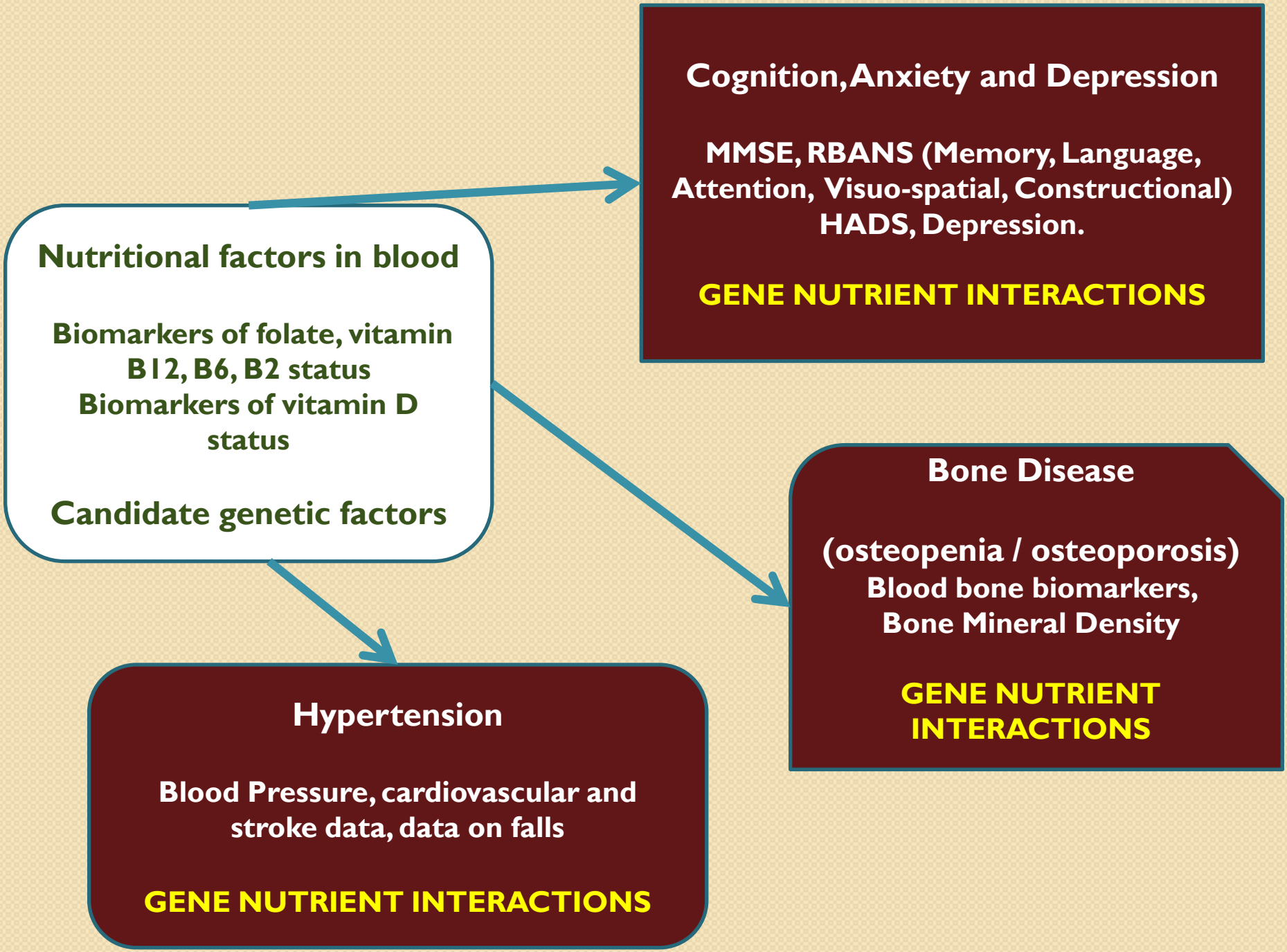
Lifestyle variables
Smoking, alcohol, dietary habits, sun exposure

Medications, supplements, fortified foods

Clinical parameters
BP, liver function, kidney function, haematology, lipids, electrolytes

Medical history,
Heart disease, stroke, diabetes, hypertension, falls, anxiety, depression

Measures of frailty
Physical self maintenance, daily living activities, mobility


Cognition, Anxiety and Depression
MMSE, RBANS (Memory, Language, Attention, Visuo-spatial, Constructional)
HADS, Depression.
GENE NUTRIENT INTERACTIONS
Nutritional factors in blood
Biomarkers of folate, vitamin B12, B6, B2 status
Biomarkers of vitamin D status
Candidate genetic factors
Bone Disease
(osteopenia / osteoporosis)
Blood bone biomarkers,
Bone Mineral Density
GENE NUTRIENT INTERACTIONS
Hypertension
Blood Pressure, cardiovascular and stroke data, data on falls
GENE NUTRIENT INTERACTIONS

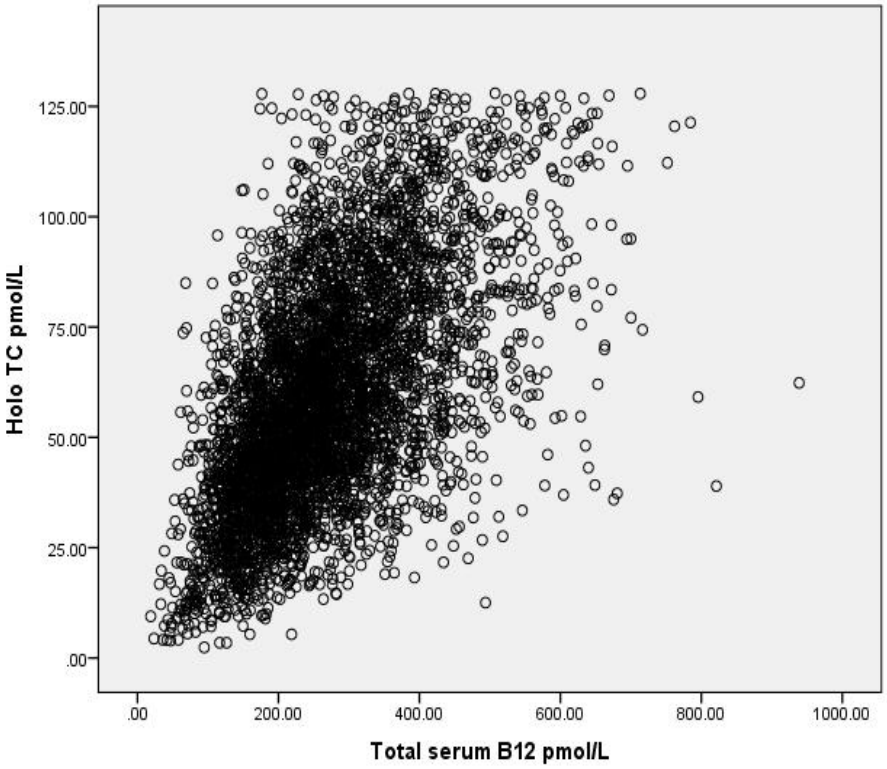
Aims

- To compare the total serum B12 with serum holoTC (Active B12™) as a marker of vitamin B12 status

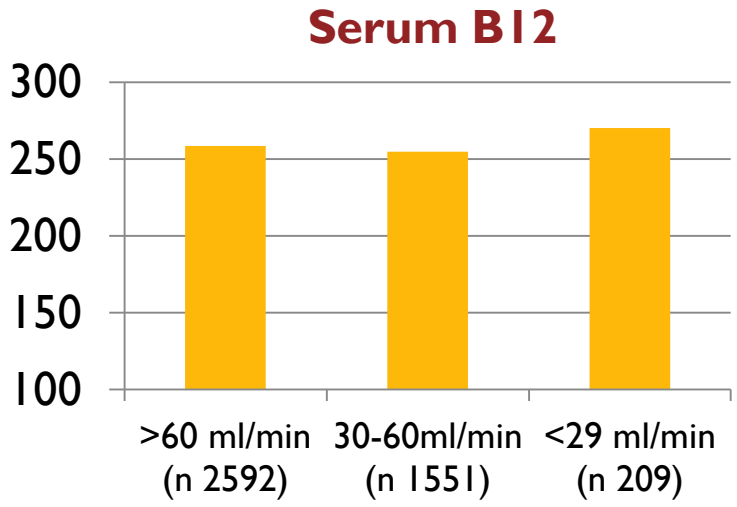
- To assess common trends in B12 blood status in the TUDA cohort
  - Age
  - Medications
  - Cognitive Function

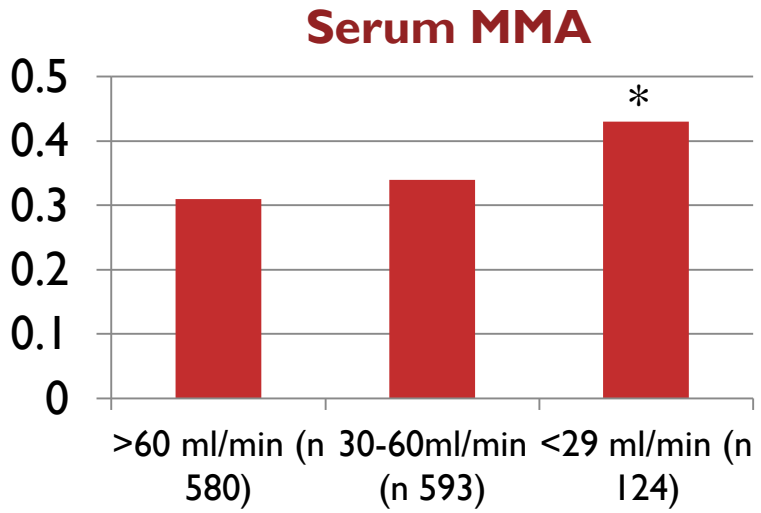
Correlation of holoTC with serum total B12

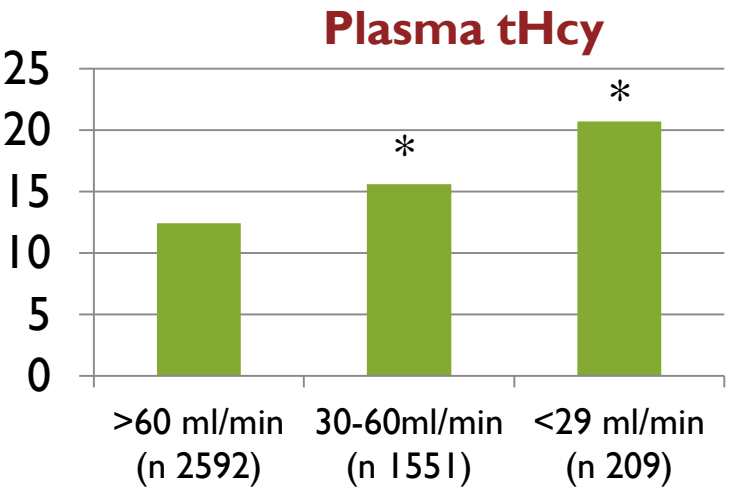
r=0.60; *P*<0.001

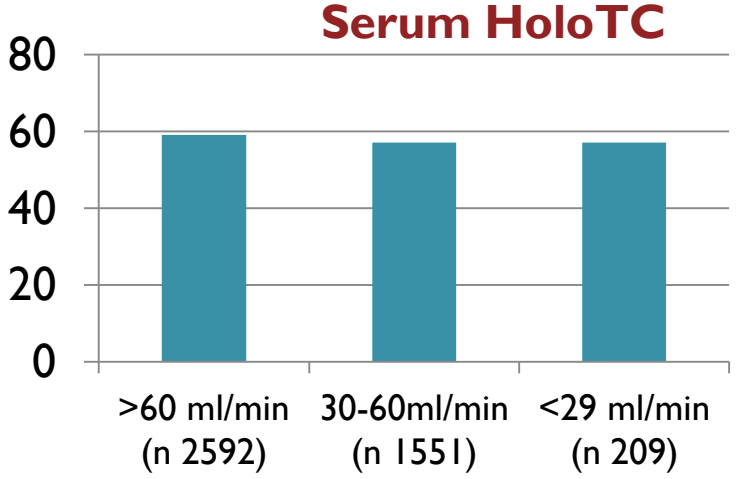


Effect of renal function on markers of B12

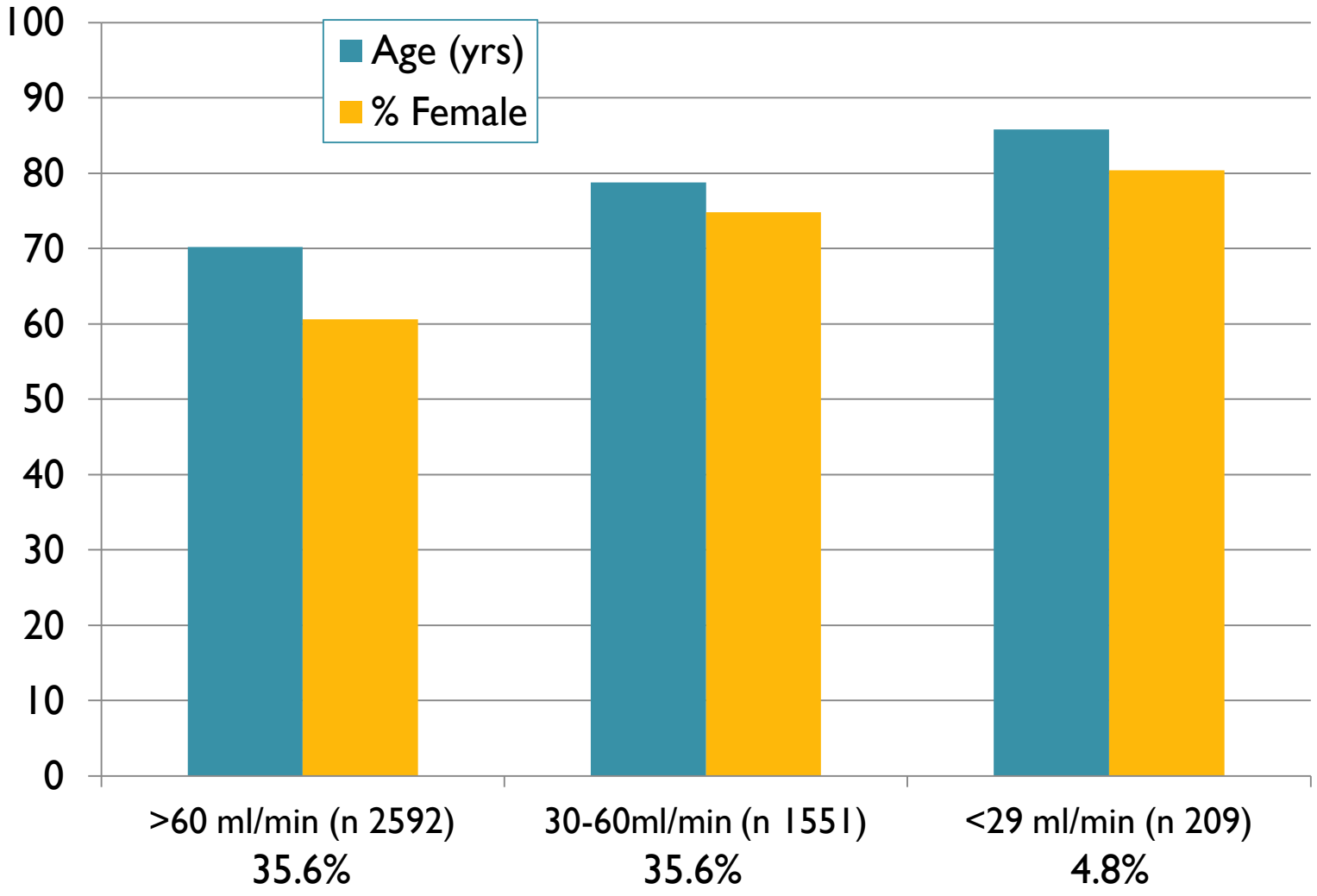








Prevalence of renal impairment



Participant Characteristics

	Males (n 1416)	Females (n 2753)	P	Males v Females
Age (yrs)	72 (66, 78)	73 (67, 79)	0.005	↓
BMI (kg/m^2)	28 (25, 31)	27 (24, 31)	<0.001	↑
Hemoglobin (g/dL)	14.2 (13.1, 15.1)	13.0 (12.2, 13.8)	<0.001	↑
S. Folate (nmol/l)	21.8 (14.3, 33.4)	25.7 (16.4, 44.1)	<0.001	↓
eGFR (ml/min)	73.9 (58.4, 91.4)	63.4 (50.4, 78.7)	<0.001	↑
tHcy (µmol/L)	14.1 (11.7, 17.5)	13.1 (10.8, 16.5)	<0.001	↑
MMA (µmol/L)	0.34 (0.24,0.54)	0.32 (0.23,0.48)	0.085	

Values are medians (inter-quartile range). Difference between sexes are assessed using an independent T-test on transformed data where applicable.

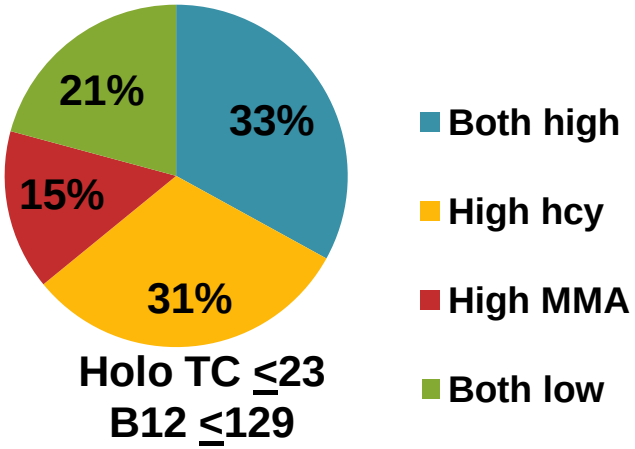
Participant B12 Status

	Total	Male	Female
Total B12 (pmol/L)	256 (189,340)	247 (182,315)	262 (194,352)
<129 (pmol/L) % (n)	7.8 (323)	8.8 (123)	7.4 (200)
<148 (pmol/L) % (n)	12.1 (489)	13.7 (189)	11.2 (300)
HoloTC (pmol/L)	58.4 (40.1,72.6)	54.5 (40.1,72.6)	60.6 (43.0,82.7)
<23 (pmol/L) % (n)	6.2 (255)	6.7 (94)	5.9(161)
<30 (pmol/l) % (n)	11.5 (476)	12.6 (178)	10.9 (298)
<35 (pmol/L) % (n)	16.5 (682)	18.1 (255)	15.7 (427)

Values are medians(inter-quartile range).

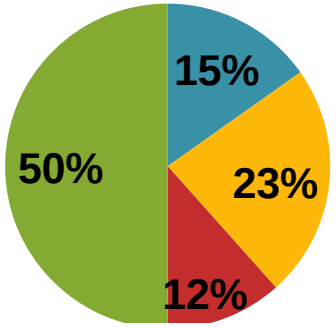
MMA>0.75µmol/L; tHcy>20µmol/L

N=106 (2.5% of cohort)



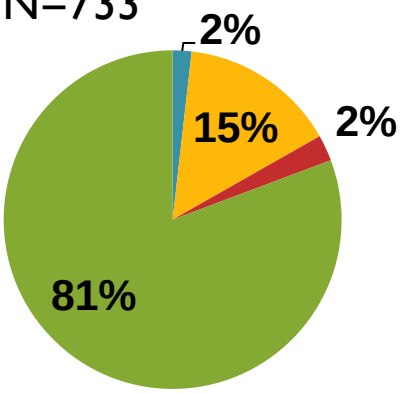
Holo TC ≤23
B12 ≤129

N=138 (3.3% of cohort)



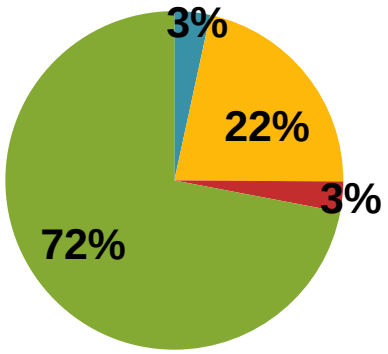
Holo TC ≤23
B12 >129

N=733



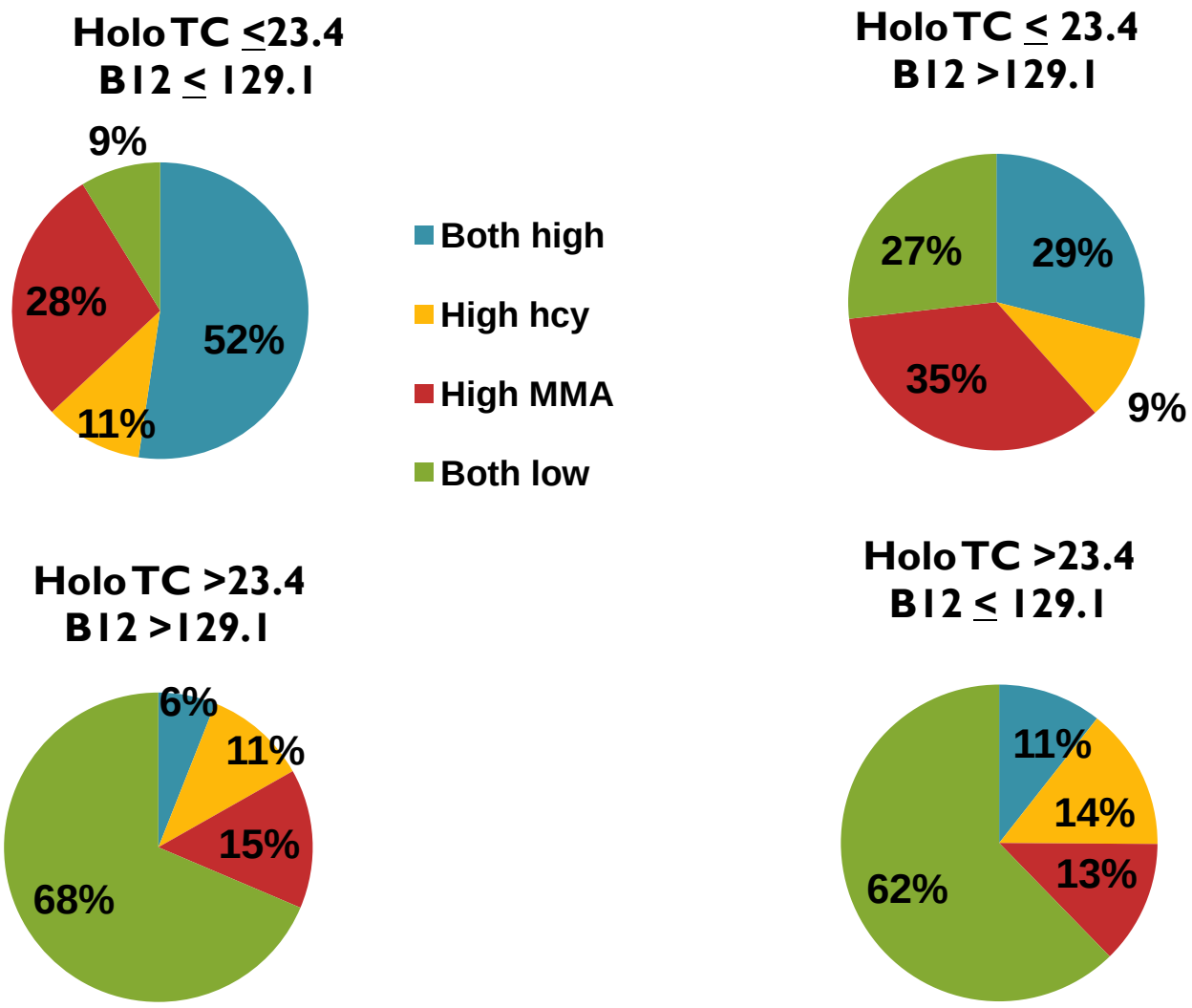
Holo TC >23
B12 ≥129

N=207 (4.9% of cohort)

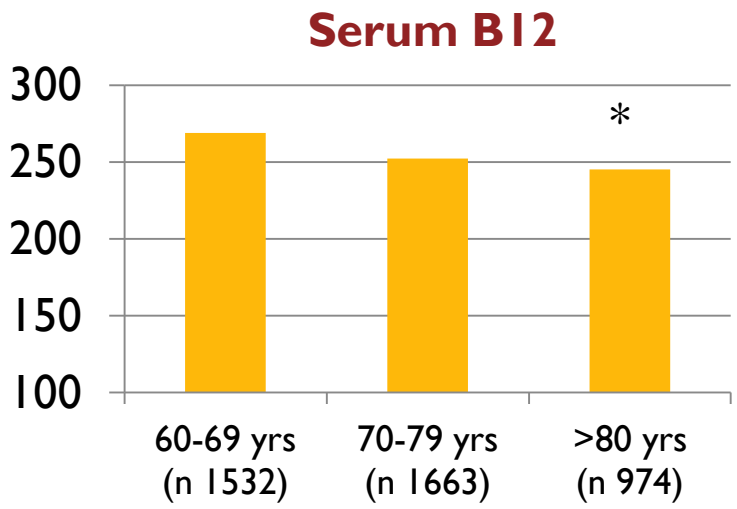


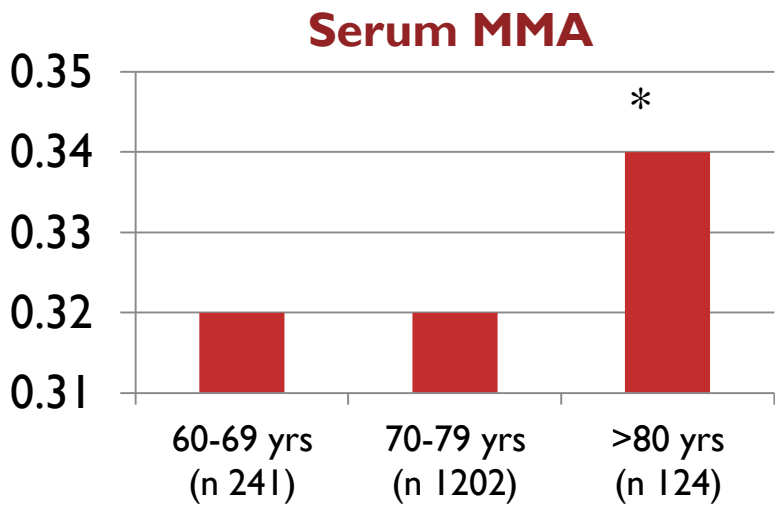
Holo TC >23
B12 ≤129

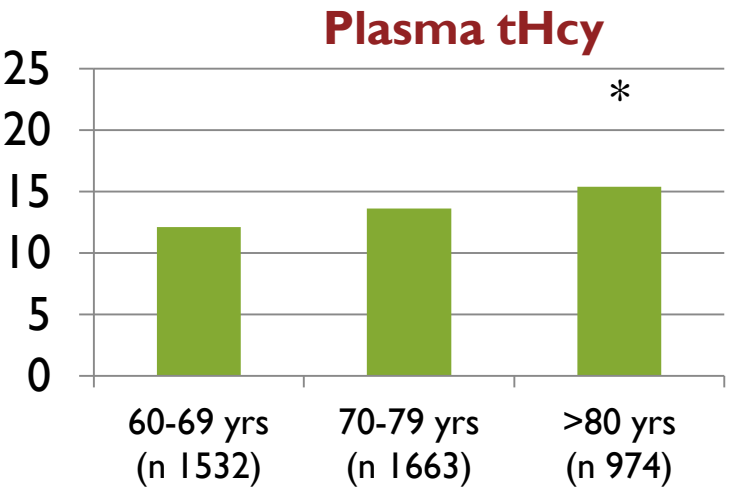
MMA>0.45µmol/L; tHcy>20µmol/L

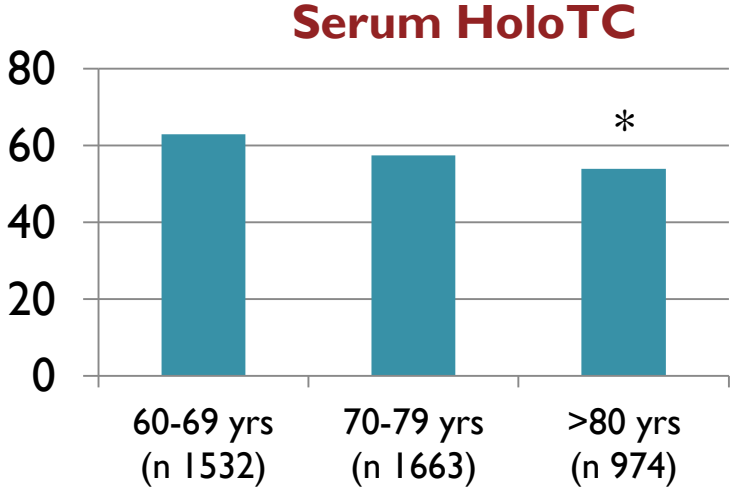


Effect of age on markers of B12

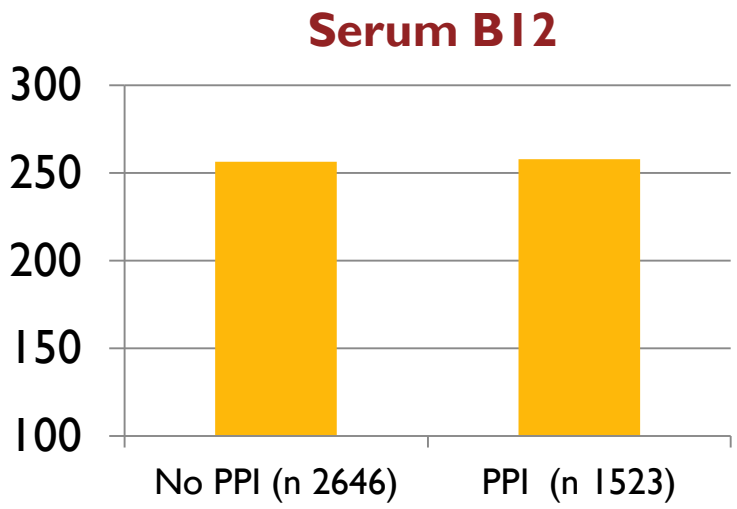


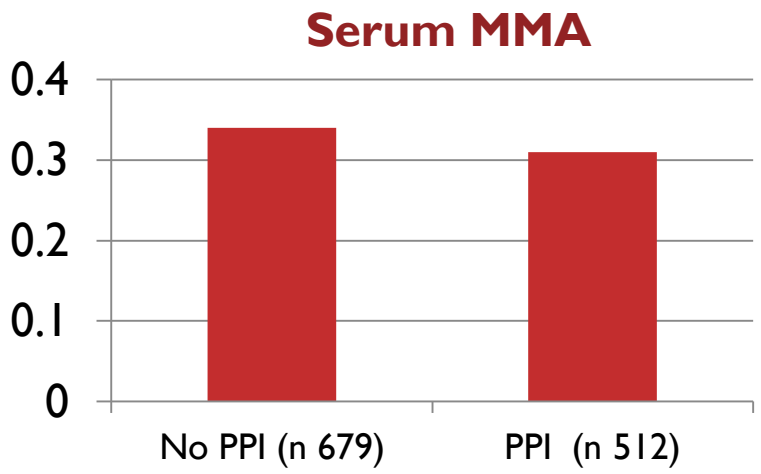


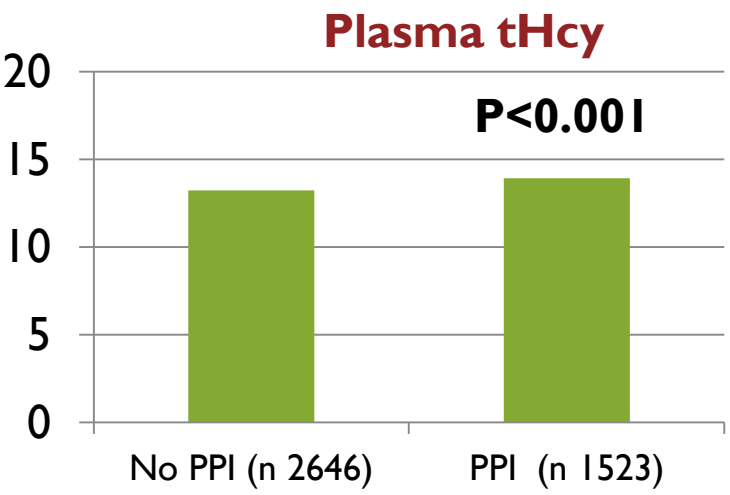


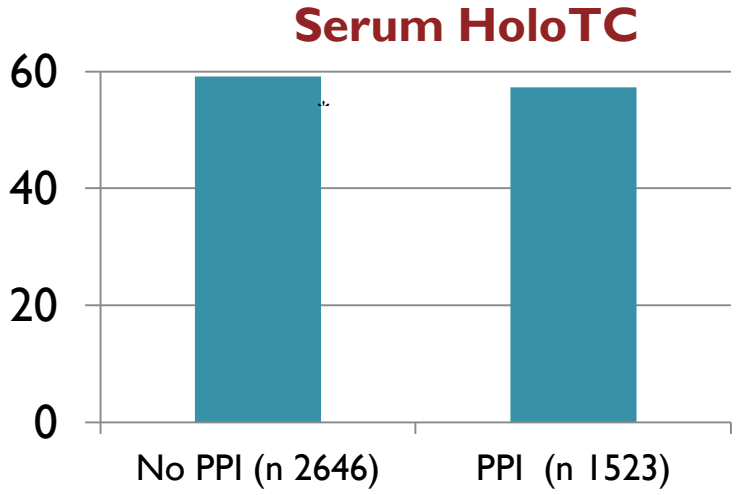


Effect of PPI on markers of B12

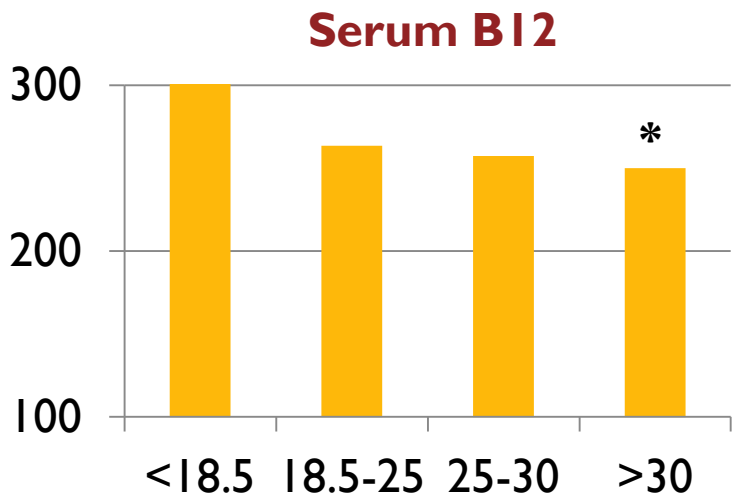


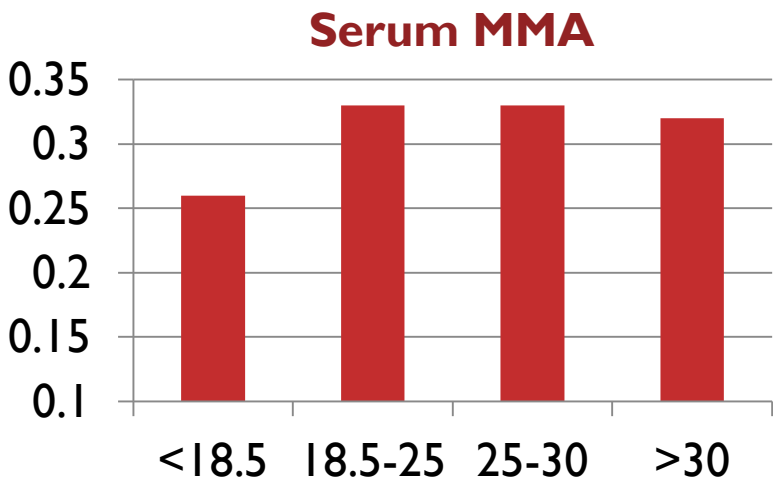


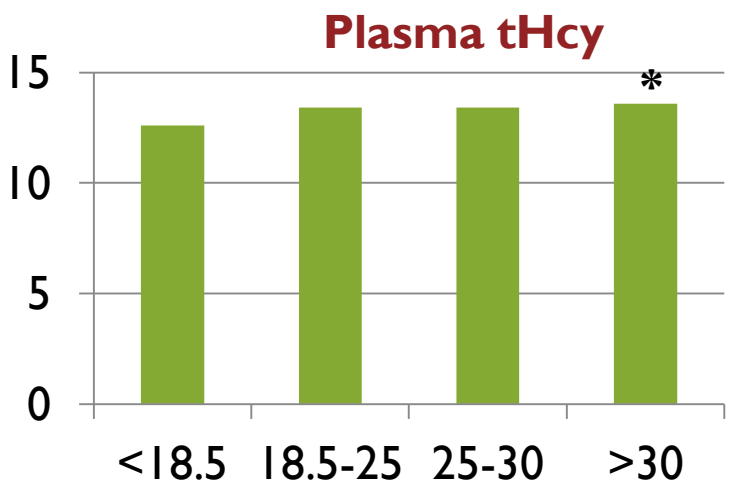


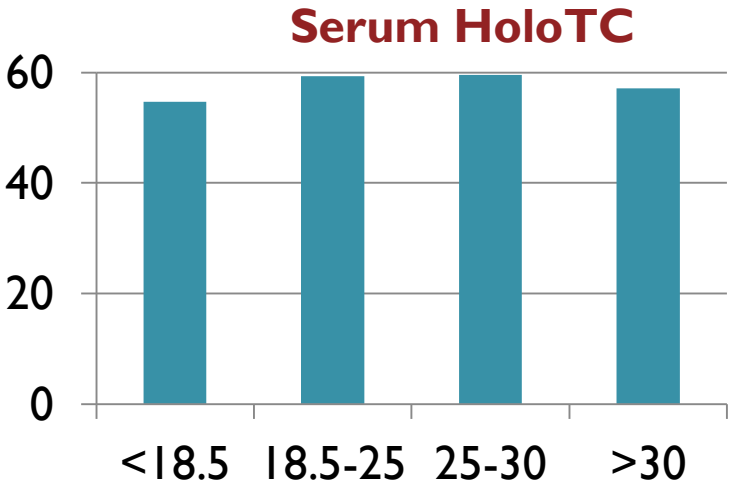


Effect of BMI on markers of B12

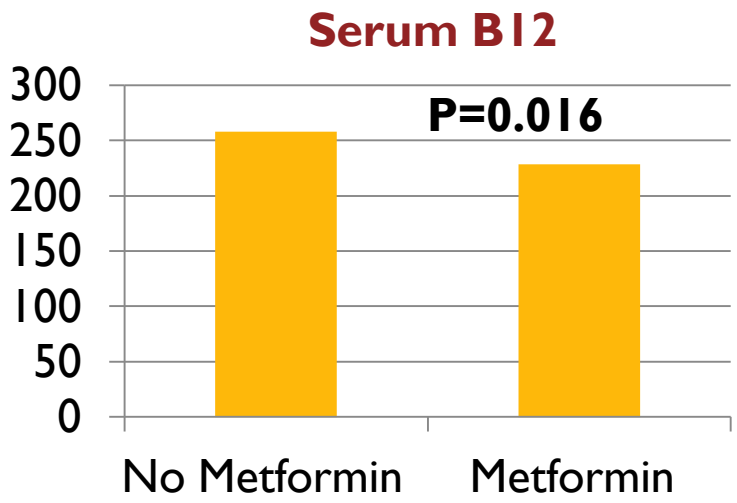


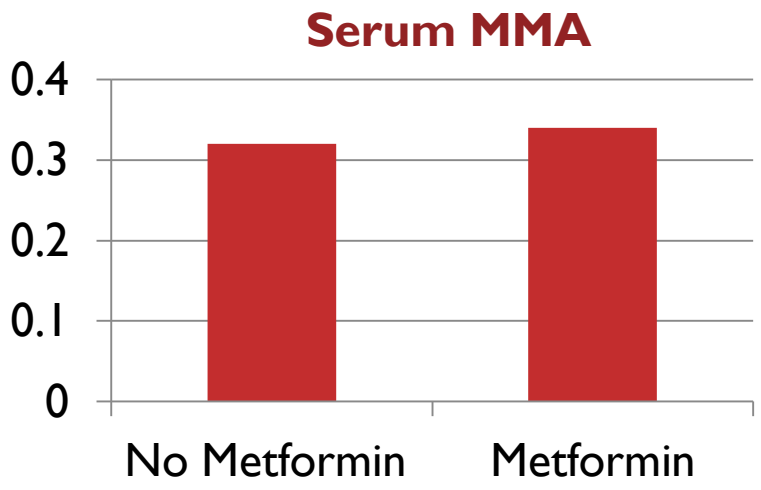


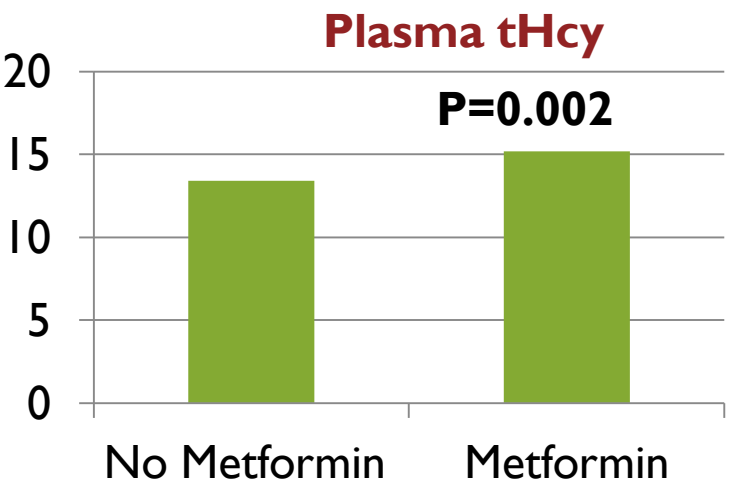


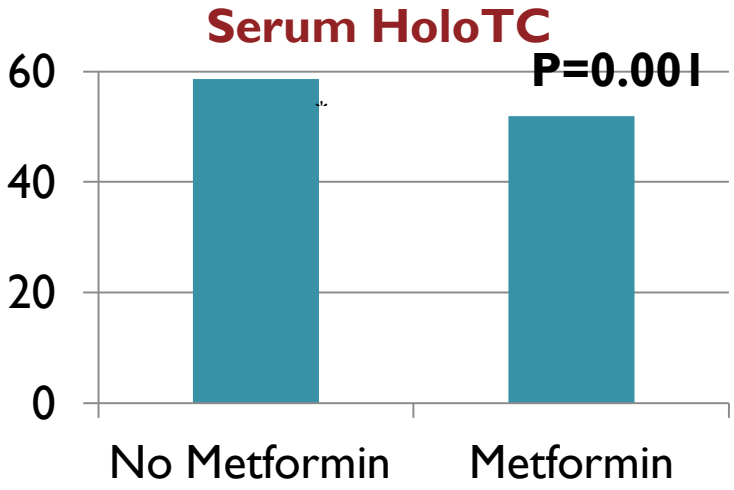


Effect of Metformin on markers of B12

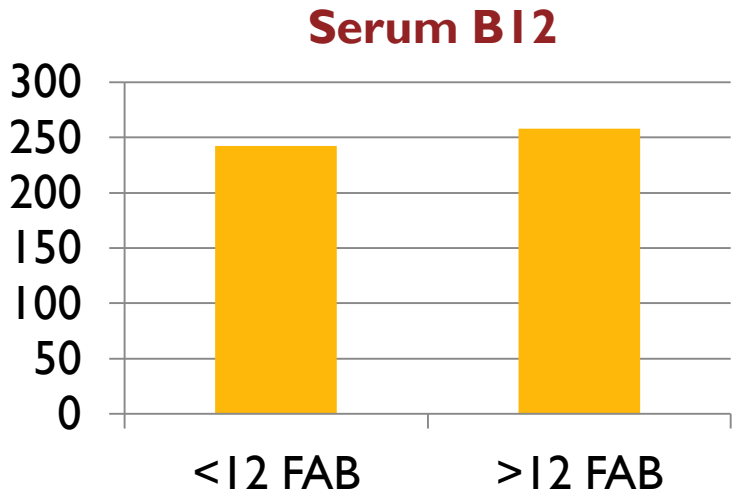


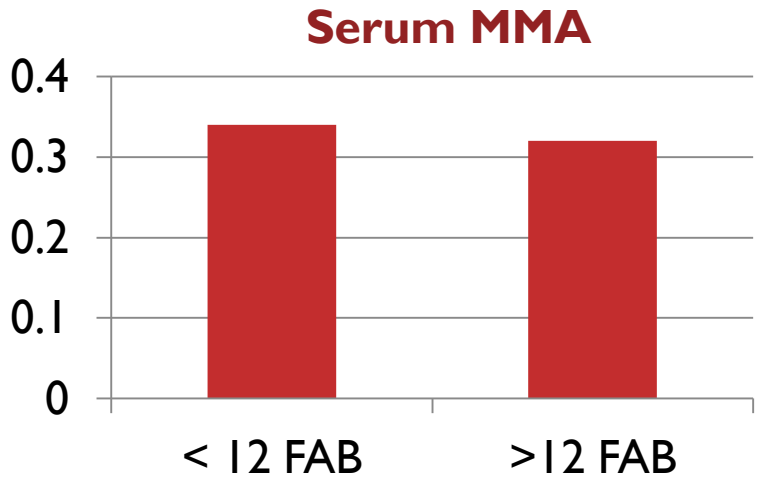


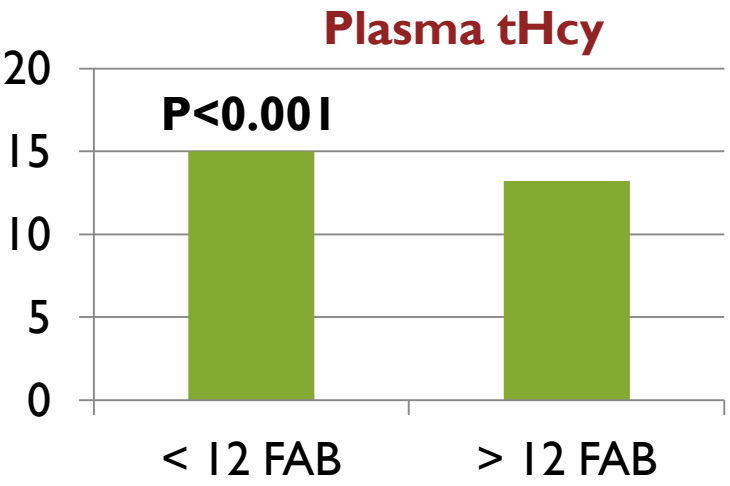


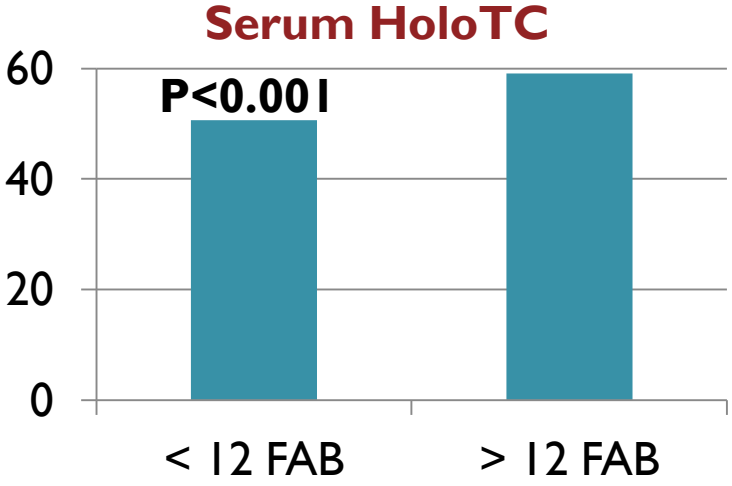


Frontal assessment battery (FAB)& markers of B12









Conclusions

- Low serum HoloTC concentrations more often correlate with biomarkers of deficiency than the serum total B12
- The degree to which the non-TC fraction of serum B12 is affected by medications and ancillary conditions needs further understanding
- Complex interactions between B12 status markers and renal impairment, medications and age need to be carefully considered when assessing associations between B12 and clinical conditions of older age

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