Vitamin B_{12} (Cobalamin) deficiency and *Helicobacter Pylori* infection in children.

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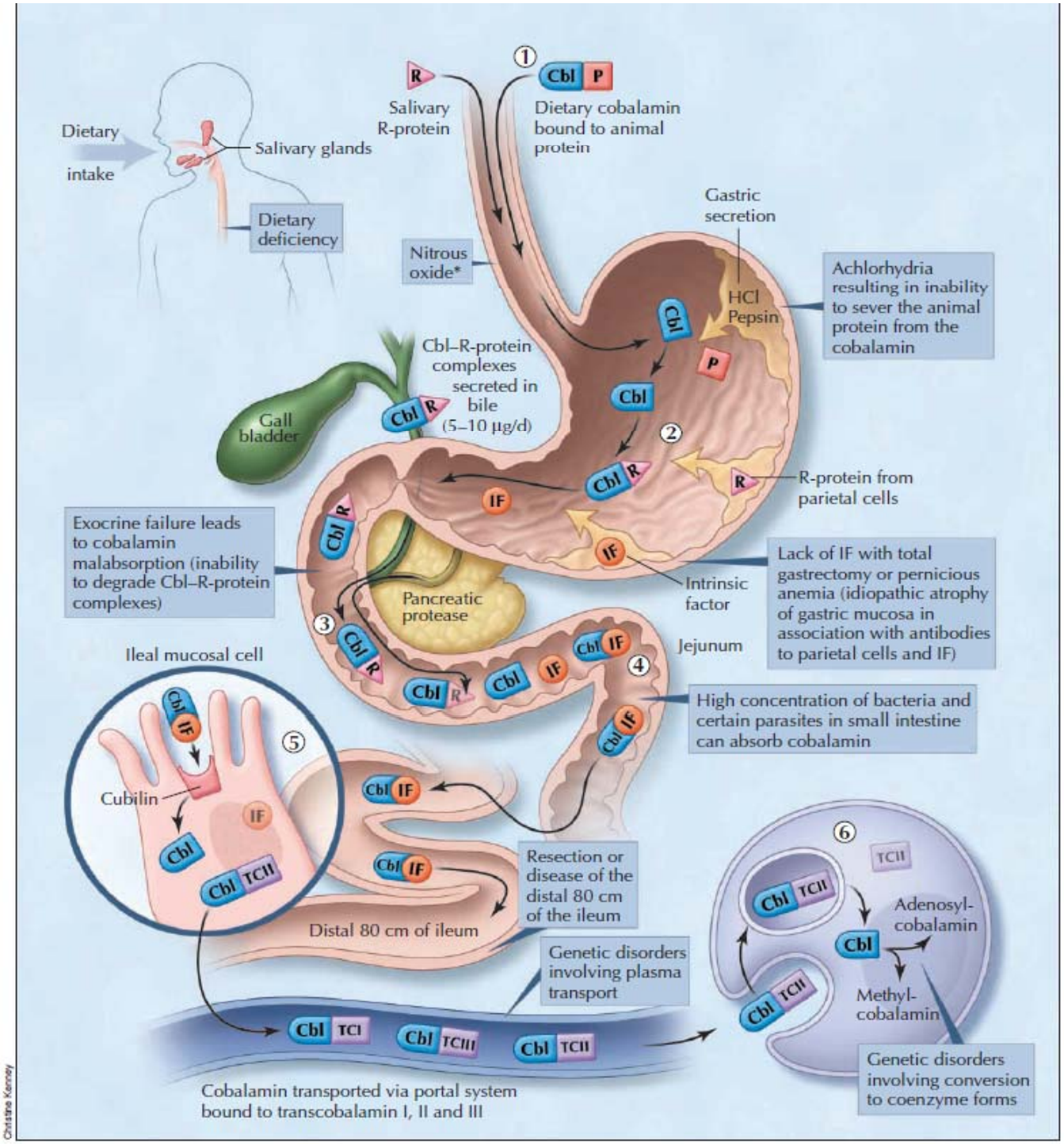
Dietary intake
Salivary glands
Dietary deficiency
R
Salivary R-protein
1
Cbl P
Dietary cobalamin bound to animal protein
Nitrous oxide*
Gastric secretion
HCl
Pepsin
Achlorhydria resulting in inability to sever the animal protein from the cobalamin
Cbl–R-protein complexes secreted in bile (5–10 µg/d)
Gall bladder
2
R-protein from parietal cells
IF
Exocrine failure leads to cobalamin malabsorption (inability to degrade Cbl–R-protein complexes)
Pancreatic protease
Intrinsic factor
Lack of IF with total gastrectomy or pernicious anemia (idiopathic atrophy of gastric mucosa in association with antibodies to parietal cells and IF)
3
Jejunum
4
High concentration of bacteria and certain parasites in small intestine can absorb cobalamin
Ileal mucosal cell
5
Cubilin
Resection or disease of the distal 80 cm of the ileum
Distal 80 cm of ileum
6
TCII
Adenosyl-cobalamin
Methyl-cobalamin
Genetic disorders involving plasma transport
TCI
TCIII
Genetic disorders involving conversion to coenzyme forms
Cobalamin transported via portal system bound to transcobalamin I, II and III
Christine Kenney

Background

- HP infection has been implicated, in several recent studies, in the etiology of iron deficiency anemia (IDA).
- Recently it was suggested that in adults, HP infection is a possible trigger for autoimmune gastritis, in a form of molecular mimicry.
- Thus, it is plausible that HP is involved in the early stages of pernicious anemia (PA), leading to severe gastric atrophy and contributing to depletion of vitamin B_{12} stores.

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Variable hematologic presentation of autoimmune gastritis: age-related progression from iron deficiency to cobalamin depletion

Chaim Hershko, Aaron Ronson, Moshe Souroujon, Itzhak Maschler, Judith Heyd and Julian Patz

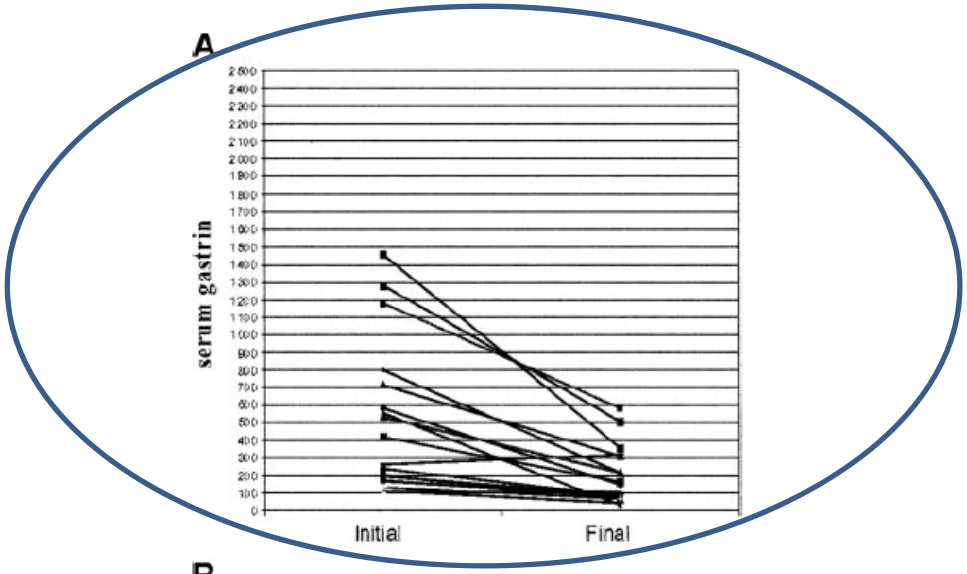
Table 1. Autoimmune gastritis: mode of presentation, associated findings, and results of endoscopy

	Macrocytic, n = 29	Normocytic, n = 48	Microcytic, n = 83
Age, y, ± SD (M/F)	62 ± 15 (17/12)	58 ± 17 (18/30)	41 ± 15 (18/65)
Anemic, no. (%)	18 (62)	19 (40)	83 (100)
Low B_{12} level, no. (%)	29 (100)	44 (92)	38 (46)
Iron deficiency, no. (%)	3 (10)	24 (50)	83 (100)
Thyroid disease, no. (%)	3 (10)	14 (29)	15 (18)
Hypothyroid, no.	3	12	12
Graves disease, no.	0	1	2
Hashimoto thyroiditis, no.	0	1	1
Vitiligo, no. (%)	2 (7)	0 (0)	0 (0)
Diabetes mellitus, no. (%)	1 (3)	4 (8)	7 (8)
Neurologic complications, no. (%)	5 (17)	2 (4)	0 (0)
Gastric histology, total no.	13	24	32
Atrophic gastritis, no. (%)	9 (69)	13 (54)	13 (41)
Chronic gastritis, no. (%)	2 (15)	9 (38)	18 (56)
MALT lymphoma, no. (%)	1 (8)	1 (4)	0 (0)
Neoplasia, no., type (%)	1, adenocarcinoma (8)	1, polyp (4)	1, polyp (3)

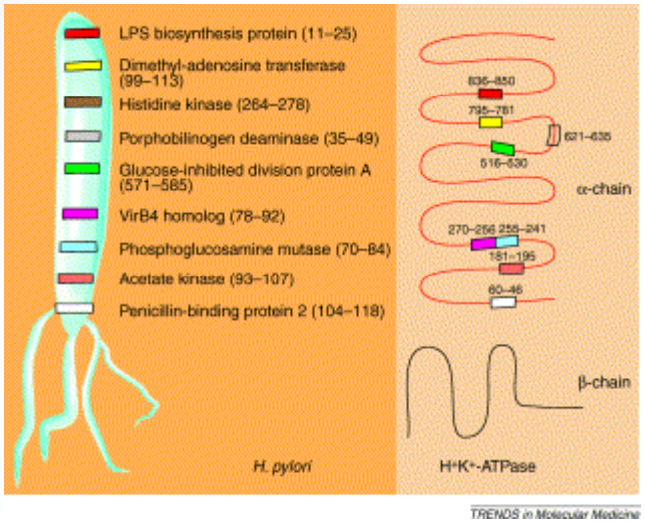
Table 3. Effect of age on presenting features of autoimmune gastritis

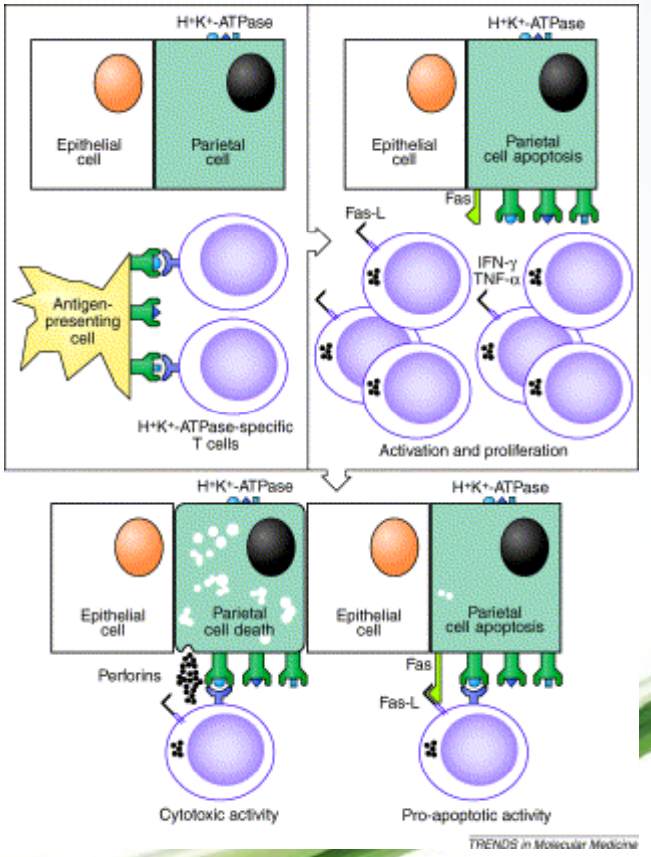
Age, y	No.	Sex, M/F	Hemoglobin level, g/L	MCV, fl	Serum iron level, μM	TIBC, μM	Ferritin level, μg/L	B_{12} level, pM	Gastrin level, pM	*H pylori*, no. positive/total (%)
Younger than 20	8	2/6	96 ± 18 (9.6 ± 1.8 g/dL)	67.6 ± 9.0	6.1 ± 3.2 (33.8 ± 18.1 μg/dL)	56.7 ± 3.62 (317.0 ± 20.2 μg/dL)	3.5 ± 2.2	289.1 ± 132.0 (391.9 ± 178.9 pg/mL)	166.6 ± 118 (349.3 ± 247.4 pg/mL)	7/8 (87.5)
20-40	40	7/33	101 ± 21 (10.1 ± 2.1 g/dL)	78.1 ± 15.2	6.9 ± 6.3 (38.6 ± 35.2 μg/dL)	60.3 ± 8.5 (337.0 ± 47.7 μg/dL)	9.9 ± 16.6	140.0 ± 87.4 (189.6 ± 118.4 pg/mL)	222.8 ± 156.2 (467.1 ± 327.5 pg/mL)	16/34 (47.1)
41-60	58	15/43	106 ± 24 (10.6 ± 2.4 g/dL)	81.8 ± 16.9	8.7 ± 6.5 (48.4 ± 36.3 μg/dL)	60.0 ± 9.1 (333.8 ± 50.9 μg/dL)	17.2 ± 22.3	116.8 ± 58.4 (158.3 ± 79.2 pg/mL)	310.4 ± 224.3 (650.7 ± 470.2 pg/mL)	18/48 (37.5)
Older than 60	54	28/26	115 ± 25 (11.5 ± 2.5 g/dL)	95.0 ± 16.0	12.5 ± 6.3 (69.8 ± 35.1 μg/dL)	54.3 ± 10.6 (303.6 ± 59.0 μg/dL)	36.8 ± 40.5	79.9 ± 48.3 (108.3 ± 65.4 pg/mL)	381.6 ± 299.2 (800.0 ± 627.3 pg/mL)	4/32 (12.5)

Data are mean ± 1 SD.



Gastric autoimmunity: the role of *Helicobacter pylori* and molecular mimicry





Trends in Molecular Medicine, *Volume 10, Issue 7*, *1 July 2004*, *Pages 316-323*
Mario M. D'Elios, Ben J. Appelmelk, Amedeo Amedei, Mathijs P. Bergman, Gianfranco Del Prete

כללית 100 שנה
הכי טובה למשפחה

In Pediatric Patients:

- Atrophic gastritis in young children and adolescents,
  - 173 children, 58 from Korea (median age, 14 years), 115 from Colombia (median age, 13 years).
  - HP+ in 85% of Colombia children vs 17% of Korean children ($p<0.01$).
  - Mucosal atrophy was present in 16 children from Columbia (16% HP+), median age, 15 years (7-17).

O Ricuarte et al, J Clin Pathol 2005

- Organ-specific autoantibodies in children with HP infection.
  - 124 dyspeptic children, 56 HP+, 68 HP-
  - The frequency of organ-specific autoantibodies was higher in patients with *H. pylori* infection than in uninfected patients (χ^2-test $p < .0001$). Specifically **gastric autoantibodies** were significantly **higher**: seven of the 56 *H. pylori*-positive children were PCA-positive and one was IFA-positive (χ^2-test $p = .0004$).

Guariso G et al, Helicobacter 2004

Association Between Gastric Atrophy and *Helicobacter pylori* Infection in Japanese Children: A Retrospective Multicenter Study

- 196 patients, 1-16 years, 131 HP+, 65 HP-.
- Prevalence of atrophy in the antrum in (HP+) was10.7%, and 0% in (HP-), ($p<0.01$) and in corpus 4.3% and 0%, respectively ($p=0.2$).
- *H. pylori*-induced gastric inflammation can cause atrophy in Japanese children, predominantly in the antrum.

Minoura et al, Digestive Diseases and Sciences 2006.

Antibodies to H+/K+-ATPase of gastric parietal cells in children with Helicobacter pylori associated chronic gastritis

- 54 children, 3-15y, abs were found in 27.7% of children, concomitant autoimmune diseases, pangastritis, pre-atrophic morphology, were discovered more often in antibody + patients.

Eksp Clin Gastroenterol. 2003

Table 1

Parietal Cell Antibodies and Helicobacter pylori in Children

Kolho, Kaija-Leena; Jusufovic, Jasminka; Miettinen, Aaro; Savilahti, Erkki; Rautelin, Hilpi

Journal of Pediatric Gastroenterology and Nutrition 2000.

	Median age (yr) (range)	Sex (F/M)	No. PCA positive
H. pylori–infected (n = 71)	9.5 (2–16)	35/36	
Finnish (n = 25)	13 (3–16)	11/14	0
Other white (n = 11)	9 (2–13)	6/5	0
Nonwhite (n = 35)	8 (2–15)	19/16	0
H. pylori infection possible (n = 8)			
Finnish (n = 8)	12 (6–15)	3/5	1 (titer 5000)
No *H. pylori* infection (n = 130)	8 (1–18)	67/63	
Finnish (n = 121)	8 (1–18)	65/56	1 (titer 6250)
Other white (n = 2)	9.5 (8–11)	1/1	0
Nonwhite (n = 7)	2 (1–14)	1/6	1 (titer 1250)
Celiac disease: all Finnish[a] (n = 61)	5 (1–17)	39/22	0

Children considered *Helicobacter pylori*–infected had positive findings in at least two of the following: serum antibodies, culture or *Helicobacter* seen on histology of gastric biopsy specimens. Children with positive serology but no other positive diagnostic findings were considered possibly infected. Children with no *H. pylori* infection were screened by serology and found negative. PCA, parietal cell antibodies.

[a] One child with positive serology for *H. pylori* (histology negative).

Objective

- to determine the prevalence of cobalamin deficiency in children with HP gastritis compared to healthy children without HP gastritis.

Methods

- 80 consecutive children (ages 2-18) referred to the Pediatric Gastroenterology and Nutrition Unit, Meyer Children's Hospital, for endoscopy were enrolled.
- Children known to have chronic diseases were excluded.
- HP infection was determined by Giemsa staining of gastric samples.
- Assessment of gastritis as well as gastric atrophy was documented by assessment of antrum and corpus biopsies.
- Laboratory work up included a complete blood count, serum iron, transferrin, ferritin, vitamin B_{12}, anti-parietal antibodies and gastrin levels. The study group included HP positive children and HP negative children served as controls.

Results

	HP Positive	HP Negative	Total	P value
Age (years): Mean±SD [Median]	11.5±3.35 [11]	11.18±4.04[12]	11.3±3.78 [11.5]	0.91
Sex	Female 17 (56.67%) Male 13 (43.33%)	Female 24 (48%) Male 26 (52%)	Female 41 (51.25%) Male 39 (48.75%)	0.45
Ethnicity	(J) 16 (53.33%) (A) 14 (46.67%)	(J) 32 (64%) (A) 18 (36%)	(J) 48 (60%) (A) 32 (40%)	0.34

Results

Variable	HP Negative	HP Positive	Total
Iron	81.02±41.16 [76.5]	87.36±41.14 [91]	83.56±40.98 [81]
Ferritin	33.27±27.68 [23]	31.37±21.41 [29]	32.54±25.32 [26]
B_{12}	502.12±242.56 [445]	530.03±268.12 [510]	512.72±251.24 [462]
Hemoglobin	13.08±1.63 [13.2]	12.93±1.5 [12.95]	13.02±1.57 [13.1]
Gastrin* **p<0.01 ***	53.95±55.71 [43.5]	72.13±81.3 [60]	60.98±66.74 [52]

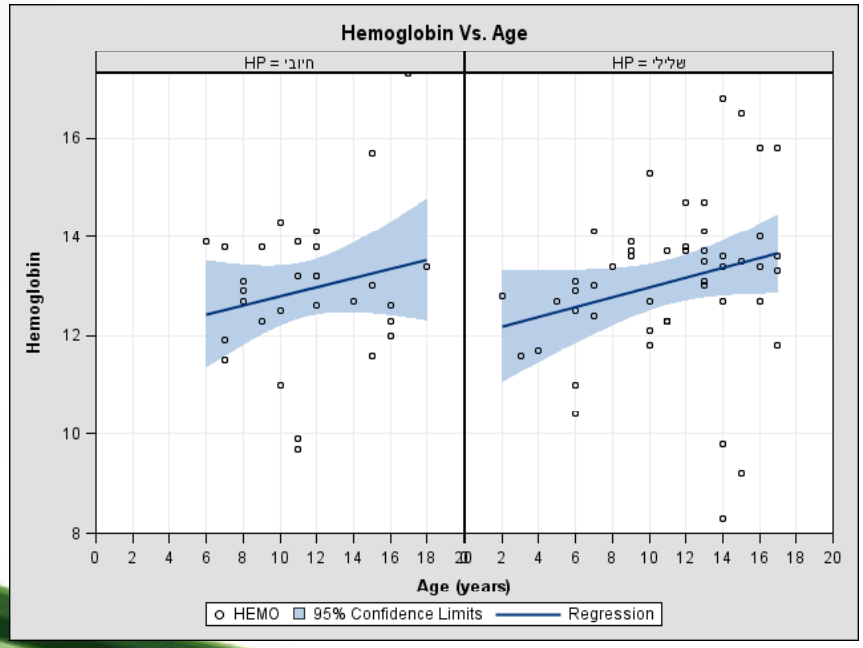
IDA was found in 6 children (7.5%), 3 (6%) in the HP positive group, 3 (10%) in the group without HP

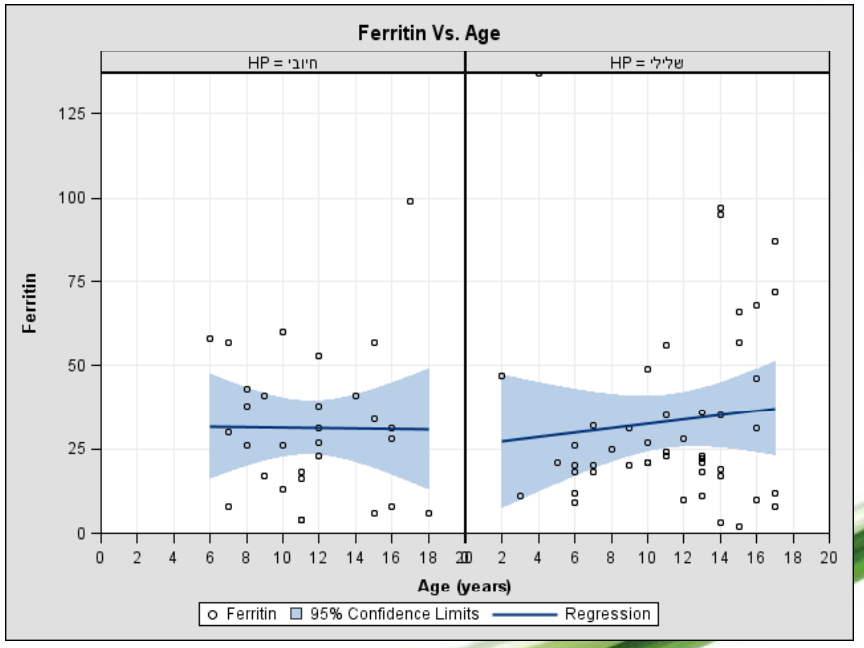
Anti Parietal Abs or gastric atrophy were not found

Results


B12 Vs. Age
HP = חיובי
HP = שלילי
B12
1250
1000
750
500
250
0 2 4 6 8 10 12 14 16 18 20
Age (years)
B12
95% Confidence Limits
Regression

Results


Hemoglobin Vs. Age
HP = חיובי
HP = שלילי
Hemoglobin
Age (years)
HEMO
95% Confidence Limits
Regression


Ferritin Vs. Age
HP = חיובי
HP = שלילי
Ferritin
Age (years)
Ferritin
95% Confidence Limits
Regression

Conclusions

- Our results suggest that currently, neither IDA nor vitamin B_{12} deficiency were associated with HP infection in Israeli children.

- Whether the high gastrin levels in the HP positive group are associated with development of gastric atrophy should be determined.