ETH
Eidgenössische Technische Hochschule Zürich
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"Micronutrient Fortification of Foods: Science, Application & Management", Delhi, Jan.8, 2011

Micronutrient deficiencies: impact on health and new developments in fortification

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Micronutrient programs are extremely cost effective

2004 World Bank Report on correcting micronutrient deficiencies

"Probably no other technology today offers as large an opportunity to improve lives and accelerate development at such low cost and in such a short time"

2004/2008 Copenhagen Consensus

Ranked *"Providing micronutrients"* as the second (2004) and first (2008) best global welfare investment

Salt iodization is a very cost-effective way to deliver iodine and to improve cognition in iodine-deficient (ID) populations

- Cost of global salt iodization/yr is $0.02–0.05 per child covered
  - cost per child's death averted=$1000
  - cost per DALY gained=$34–36

(Caulfield et al, 2006)

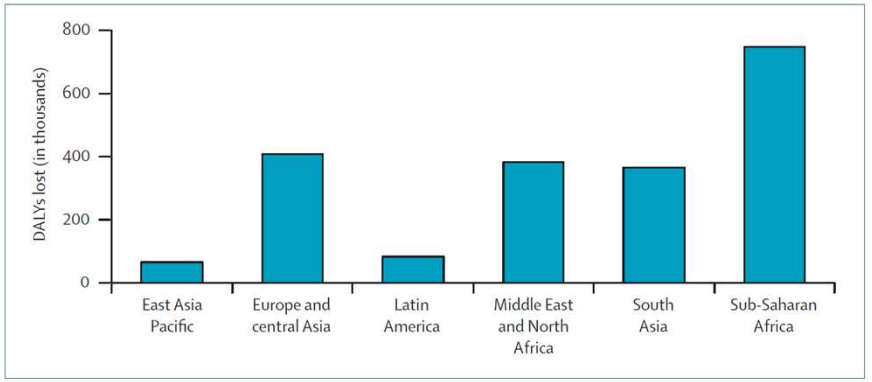


Figure 6: **Disability-adjusted life years (DALYs) (thousands) lost due to iodine deficiency in children younger than 5 years of age, by region**[77]
A DALY is calculated as the present value of the future years of disability-free life that are lost as a result of the premature deaths or cases of disability that arise in a particular year.

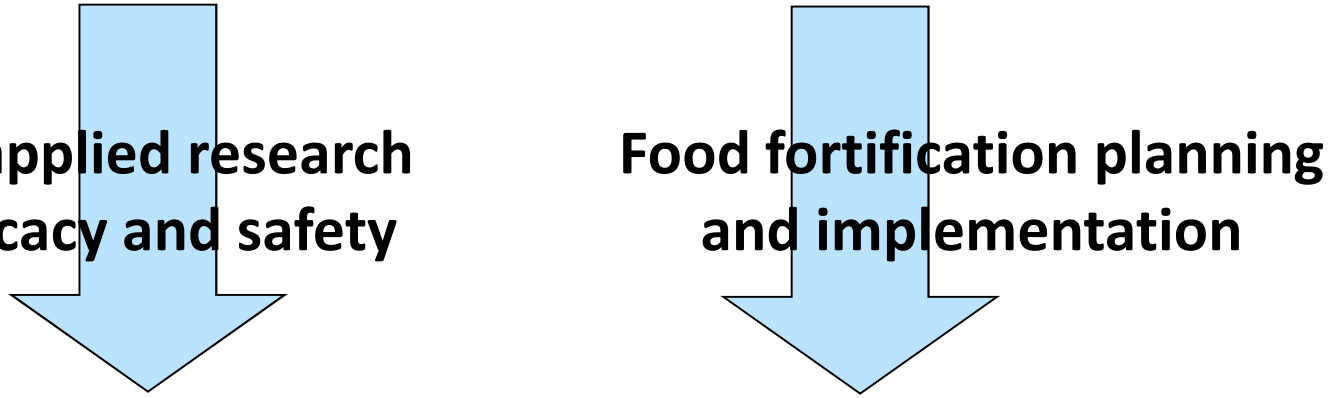
- Before widespread salt iodization, the annual losses attributable to ID in the developing world estimated at $35.7 billion, compared with an estimated $0.5 billion yearly cost for salt iodization— ie, **a 70 to 1 benefit to cost ratio** (Horton, 2006)

But investment in micronutrient research remains important

"Its important we focus on science and research again…to look for ways to bring about the widespread distribution of micronutrients and develop hardier, micronutrient-rich crops."

U.S. Secretary of State Hillary Clinton, accepting the 2010 WFP Leadership Award for fighting global hunger

Investments in food fortification and micronutrient research need to move forward in a parallel and complementary fashion



Enhanced effectiveness and safety of fortification

Micronutrient fortification research

New opportunities?

- **New compounds** –
  nanostructured iron and zinc

- **New target groups** –
  iodine for weaning infants

But we also have **new challenges:**

- iron and the **gut microflora**
- **obesity** impairs iron metabolism

New compounds –
nanostructured Fe and Zn

The concept of nanomaterials is 50 years old…

- *The principles of physics…do not speak against the possibility of maneuvering things atom by atom. It is something, in principle, that can be done; but in practice, it has not been done because we are too big.* — "There's Plenty of Room at the Bottom", 1959, Richard Feynman, Nobel Prize winner in physics

…is it time it was applied to nutrition?

The Challenge of Food Fortification with Iron

Water soluble

- Ferrous sulfate
- Ferrous gluconate

- High bioavailability
- Severe color changes

Nano-structured

Water insoluble

- Ferric phosphate
- Elemental iron

- Low bioavailability
- Minimal color changes

Flame Spray Pyrolysis

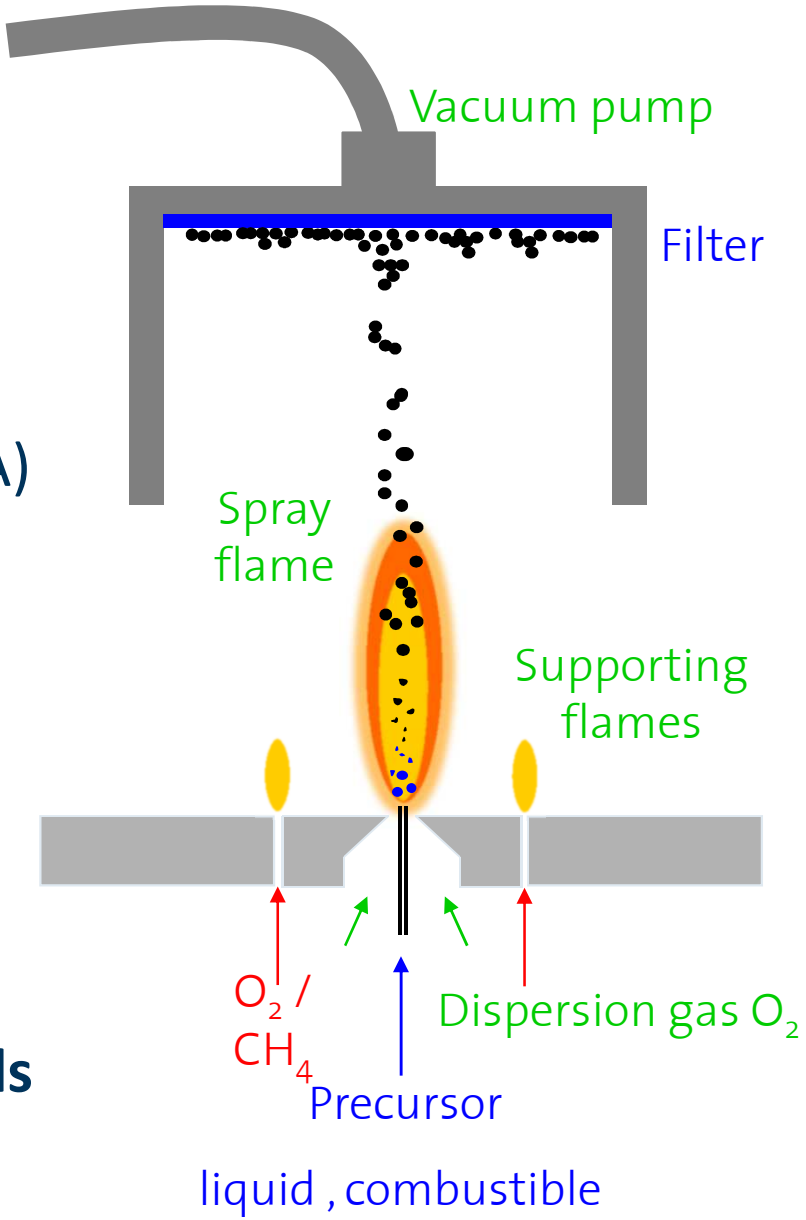
Advantages

- Versatile, scalable method
- Tailor-made compounds
- High Specific Surface Area (SSA)

Disadvantages

- Only inorganic compounds can be produced

Atomically mixed compounds

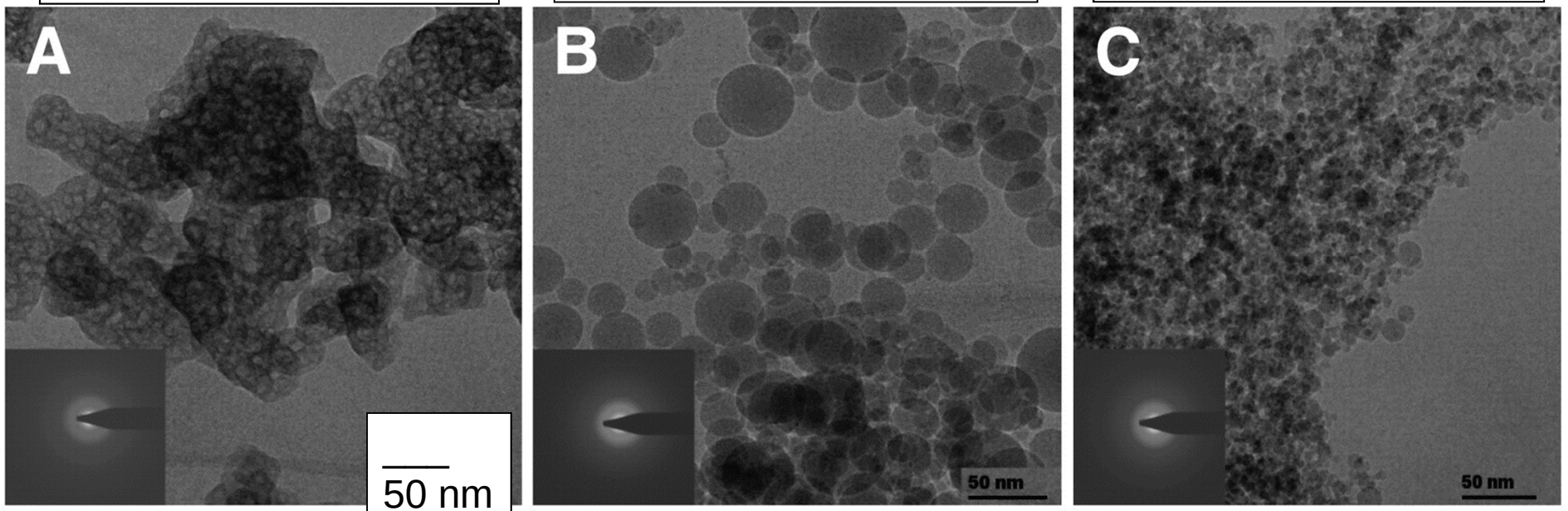


Nano-scale $FePO_4$ produced by FSP

Commercial $FePO_4$
Amorphous
Irregular, highly porous
SSA=32.6 m^2/g

'Medium' nanoscale $FePO_4$
Amorphous
Dense, spherical
SSA=68.6 m^2/g
Mean part. size= 30.5 nm

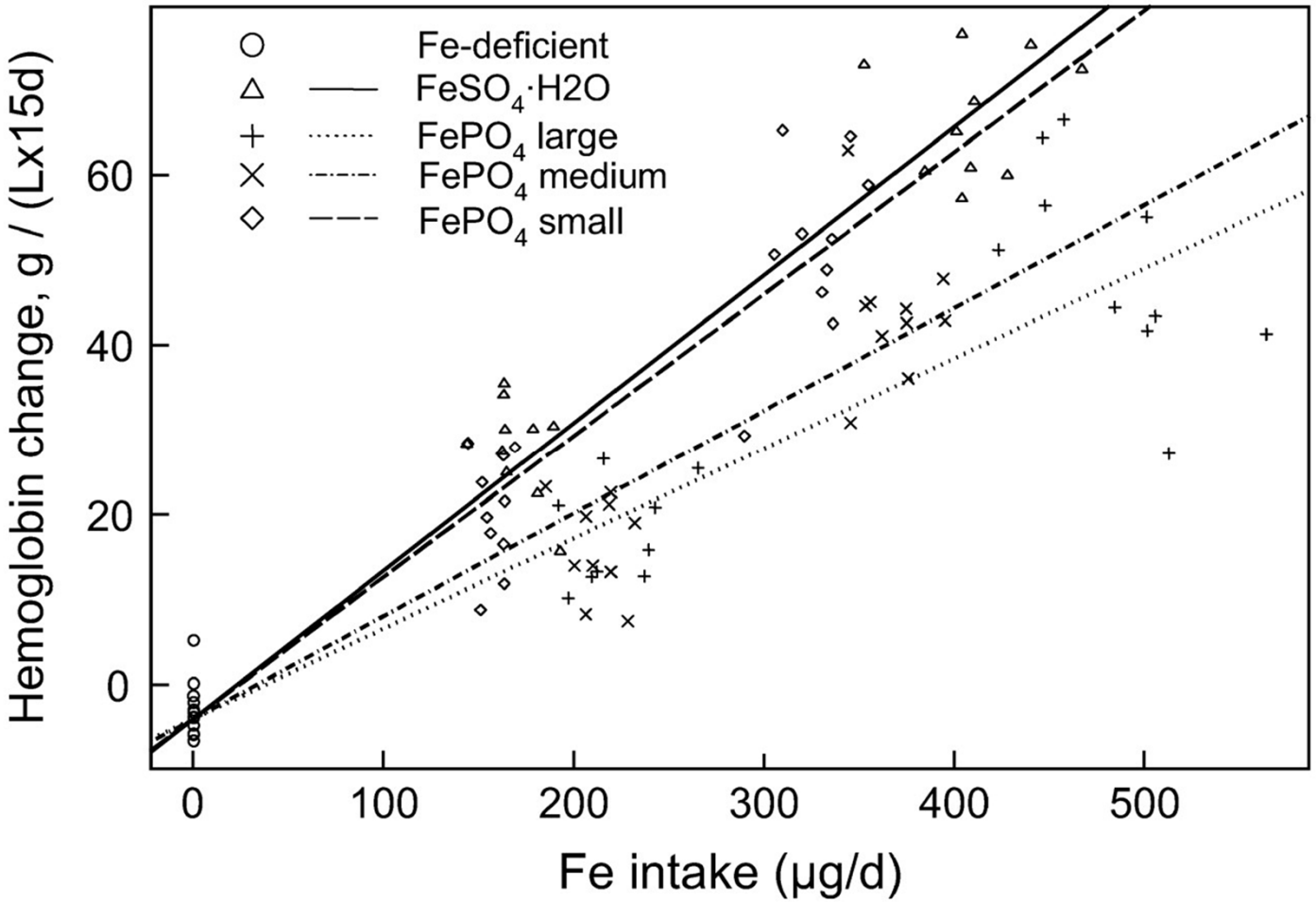
'Small' nanoscale $FePO_4$
Amorphous
Dense, spherical
SSA=194.7 m^2/g
Mean part. size= 10.7 nm



TEM and SAED (insets) images of the 3 $FePO_4$ compounds

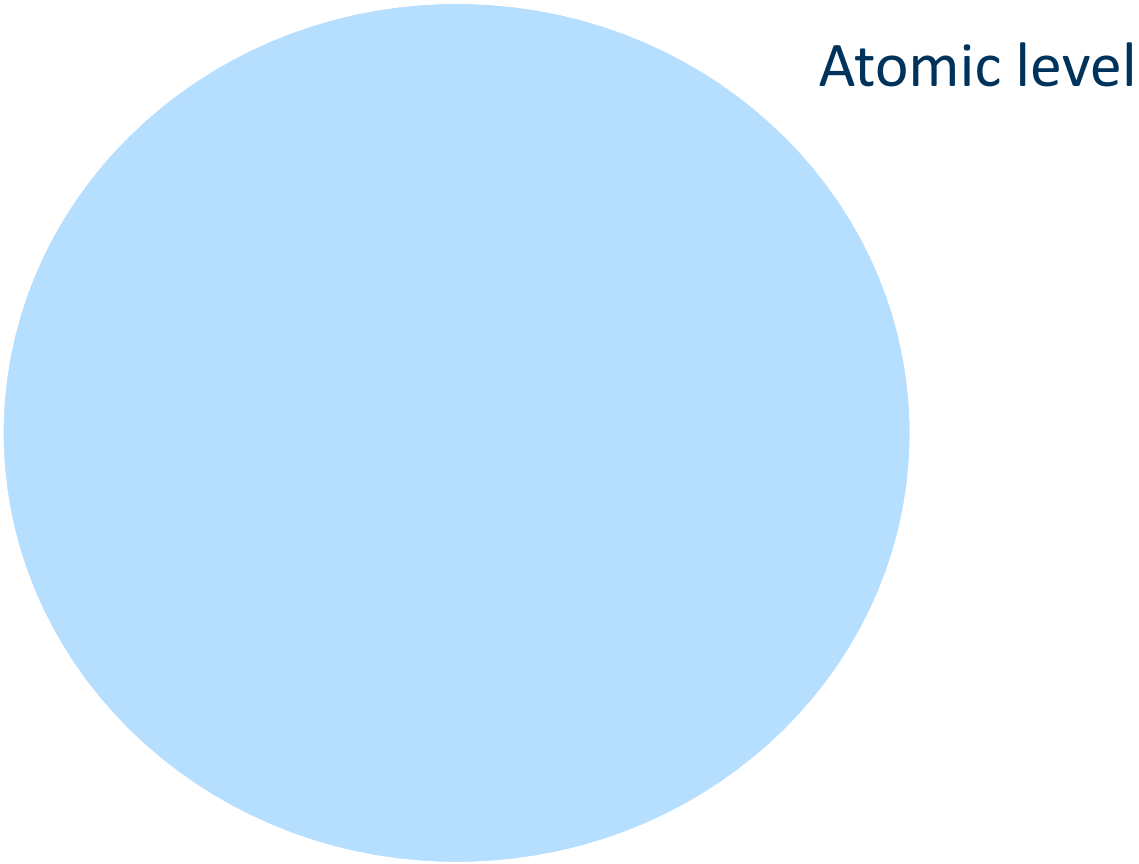
Rohner et al. J. Nutr. 2007

Nanosized $FePO_4$ is as bioavailable as $FeSO_4$ in vivo



Rohner et al. J. Nutr. 2007

Atomically mixed Nano-structured Compounds



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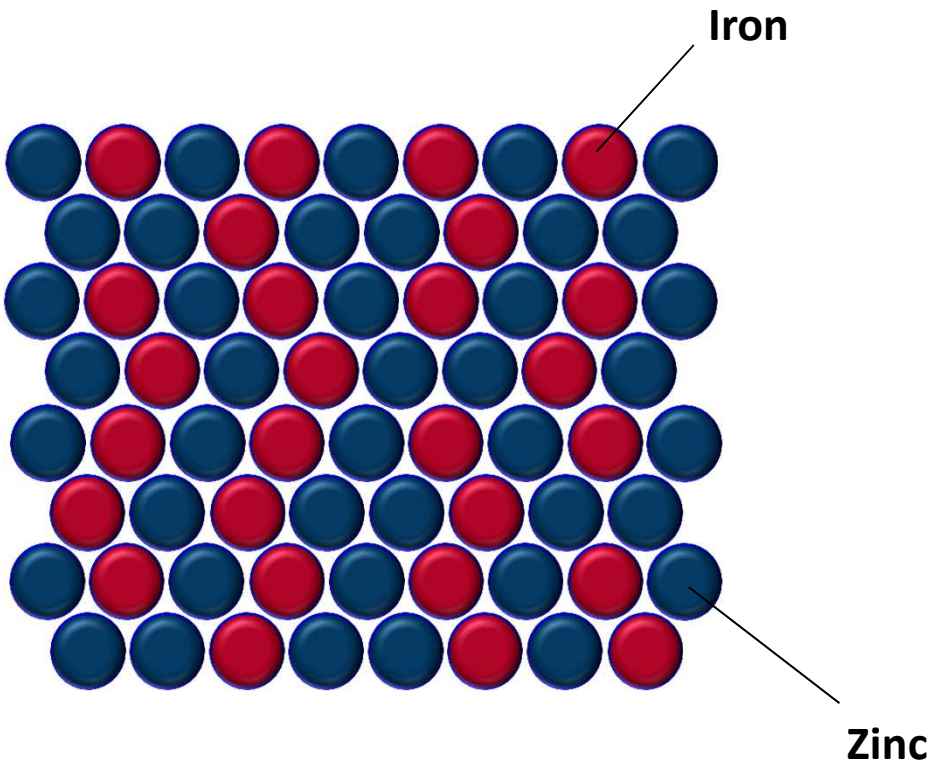

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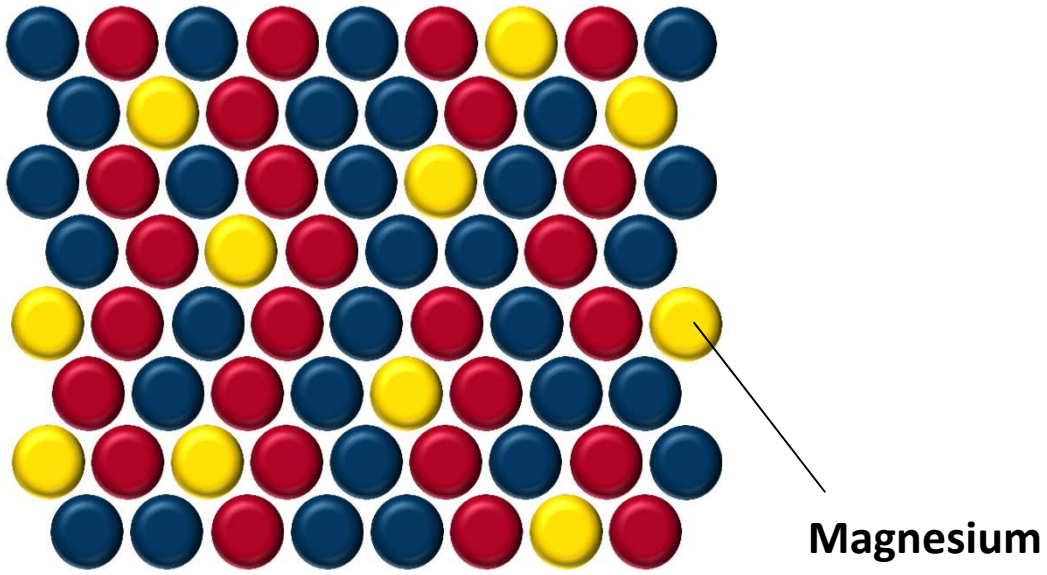
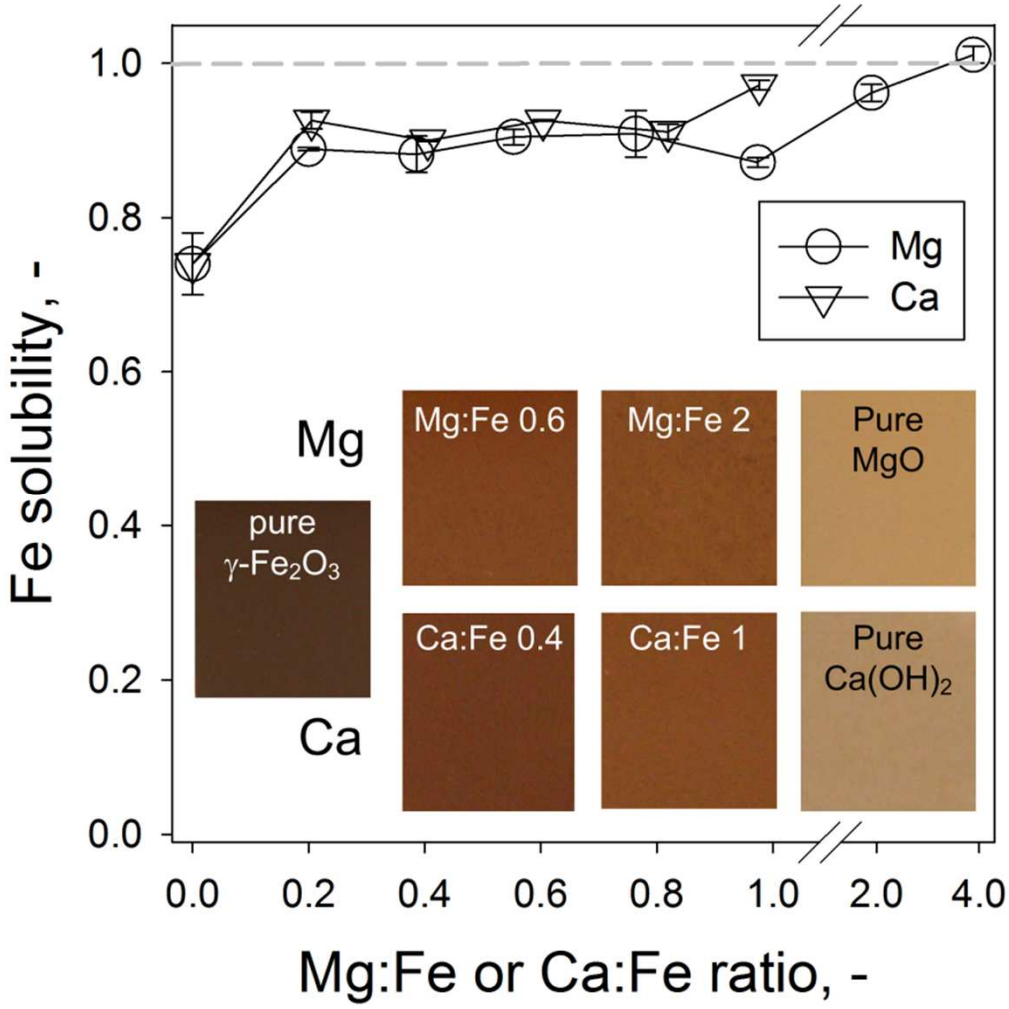
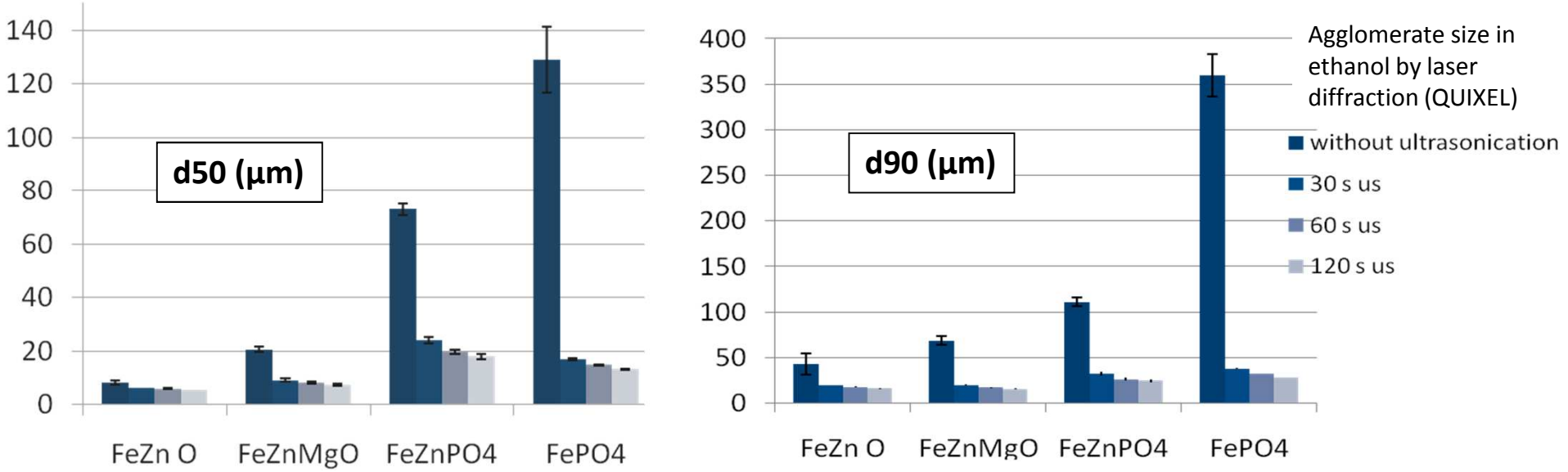


Doping with Mg or Ca improves Fe solubility and lightens compound color



Hilty FM et al. *J Food Sci*, 2010

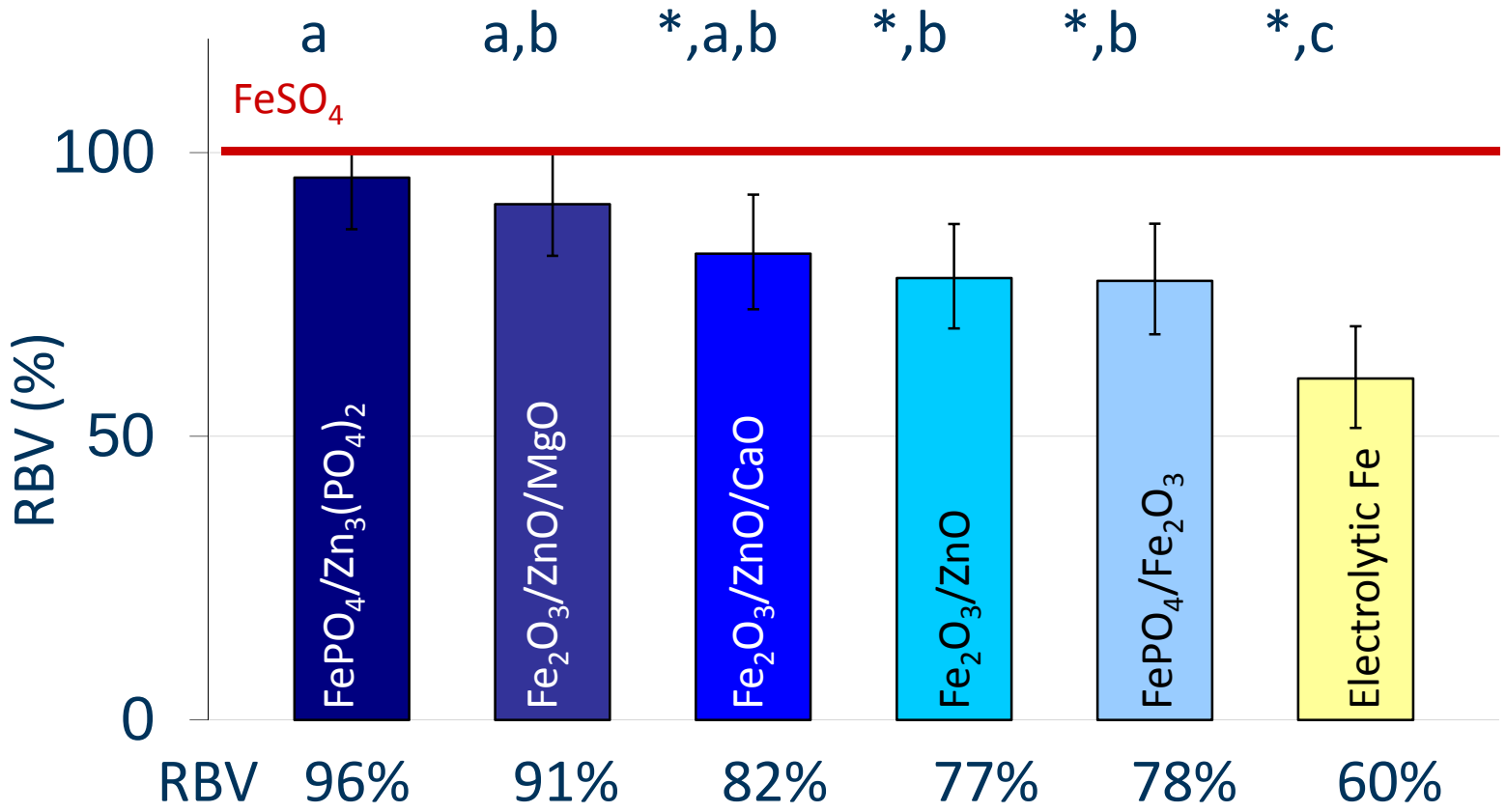
Soft agglomeration



Nanostructured cpds form soft agglomerates (size 10-130 µm) making them safer to handle (less dusting) but not reducing bioavailability

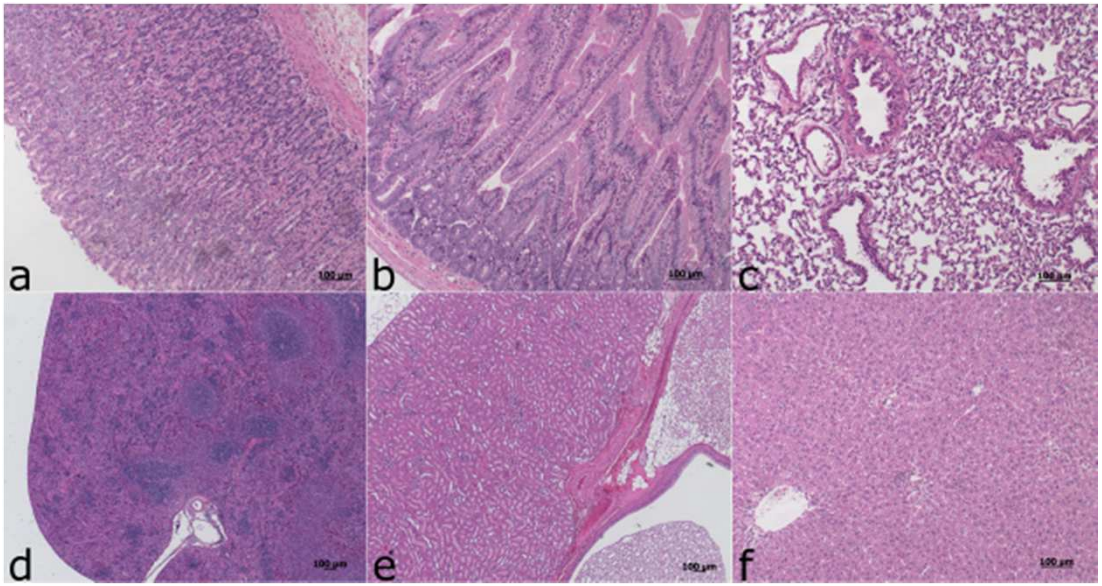
Hilty et al Nature Nanotechnol 2010

Nano-structured Fe- and Zn-containing compounds can be as bioavailable as the “gold standard” Fe sulfate



Hilty et al Nature Nanotechnol 2010

Safety Indicators: Tissue histology after iron repletion with nanocompounds



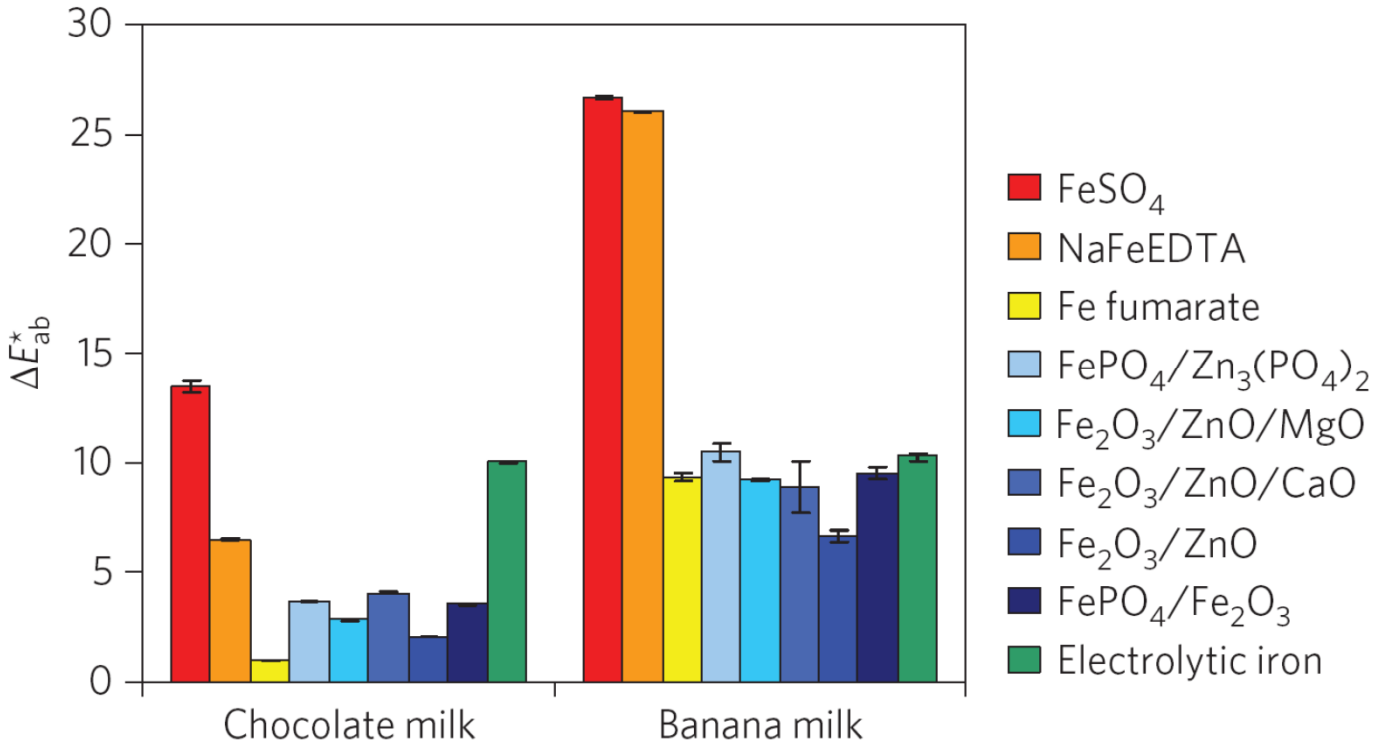
Tissues tested:

- Stomach
- Duodenum
- Ileum
- Jejunum
- Colon
- Liver
- Spleen
- Brain
- Lung
- Heart
- Kidney
- Stomach
- Testis
- Lymphatics

- **No significant stainable iron was detected in any organ**
- **No significant Fe detected in the mucosa/submucosa of GI tract, or gut-associated/mesenteric lymphatics**
- **No discernible histological abnormalities**

Rohner et al. J Nutr 2007, Hilty et al Nature Nanotechnol 2010

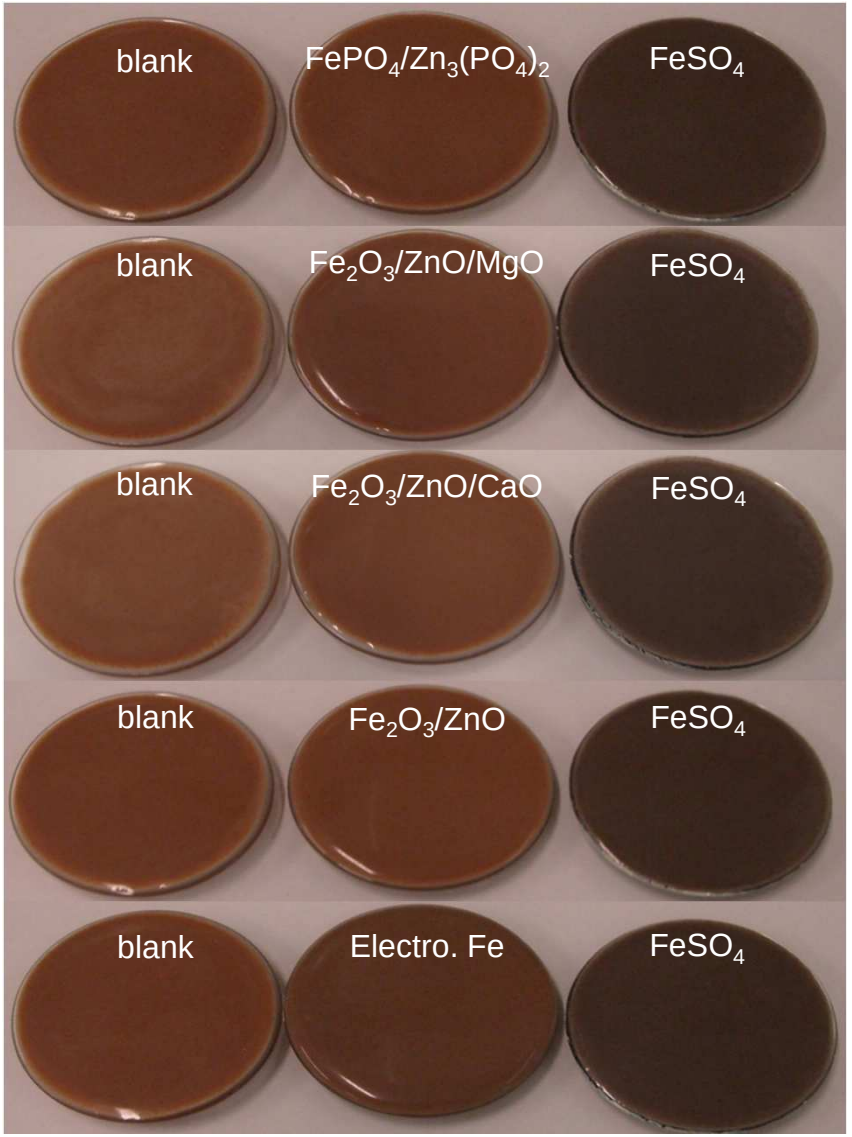
Color changes in polyphenol-containing screening foods



Hilty et al Nature Nanotechnol 2010

Figure 4 | Sensory performance of nanostructured iron-containing compounds in comparison with commercially available $FeSO_4$, NaFeEDTA, ferrous fumarate and electrolytic iron in chocolate and banana milk, two sensitive food matrices at 10 mg Fe per 100 g food. The colour change after 120 min compared to a non-fortified sample is given as ΔE^*_{ab}.

Sensory Changes in Chocolate Milk



Hilty et al Nature Nanotechnol 2010

Summary: nano Fe and Zn compounds

At neutral pH (foods)

form soft agglomerates in the **µm** range
have very low solubility
light native colour

→ **superior sensory qualities** in difficult-to-fortify foods

At low pH (GI tract)

agglomerates open up
nm scale particles with very high SSA
good solubility

→ **good bioavailability**

Perspective

Reducing mineral (and vitamin?) compounds to nanoscale modifies their functional characteristics and may open up new possibilities in nutrition

New target groups –

I deficiency in weaning infants

Iodine status in infants

Why critical?

Iodine deficiency during infancy
may irreversibly impair development

Iodine status in infants

Why critical?

Iodine & thyroid hormone requirements per kg body weight are higher than at any other time in life

- Thyroidal iodine content at birth is only ~300 µg
- High T4 turnover: 5-6 µg/kg body weight/d

WHO : if children and pregnant women are iodine sufficient, generally assumed infants are also sufficient

But weaning infants may be at risk of iodine deficiency, because iodized salt contributes little dietary iodine during this period

Newborn

Weaning period

BM iodine (40-140 µg/L) from iodized salt	Home-prepared complementary foods very low in iodine	No added salt or cow‘s milk in the 1st year

To fill this gap, iodine fortified into infant formula milk (IFM) and complementary foods (CF) is likely important

Newborn **Weaning period**

BM iodine (40-140 µg/L) from iodized salt

Iodine in IFM

EU: Max 35 µg/100 kcal. No minimum (CEC 2006)

USA: Content unpredictable (Pearce et al. 2004)

No added salt or cow's milk in the 1st year

Criteria for assessing iodine nutrition in a population based on median urinary iodine (UI)

Median UI (µg/L)	Iodine nutrition
Measured in school-aged children	
<20	Severe iodine deficiency
20-49	Moderate iodine deficiency
50-99	Mild iodine deficiency
100-199	Optimal
200-299	More than adequate

WHO, 2007

Why not measure UI in newborns?

- Access to newborns in the first few days after birth is high in many countries
- **But the challenge is sample collection**

- Develop and test a noninvasive, pad collection system for spot urine sampling
- Tested in a national sample of term Swiss infants (n=1224), 1 to 5 days old

Collecting infant urine samples

3 ml spot sample by noninvasive pad collection

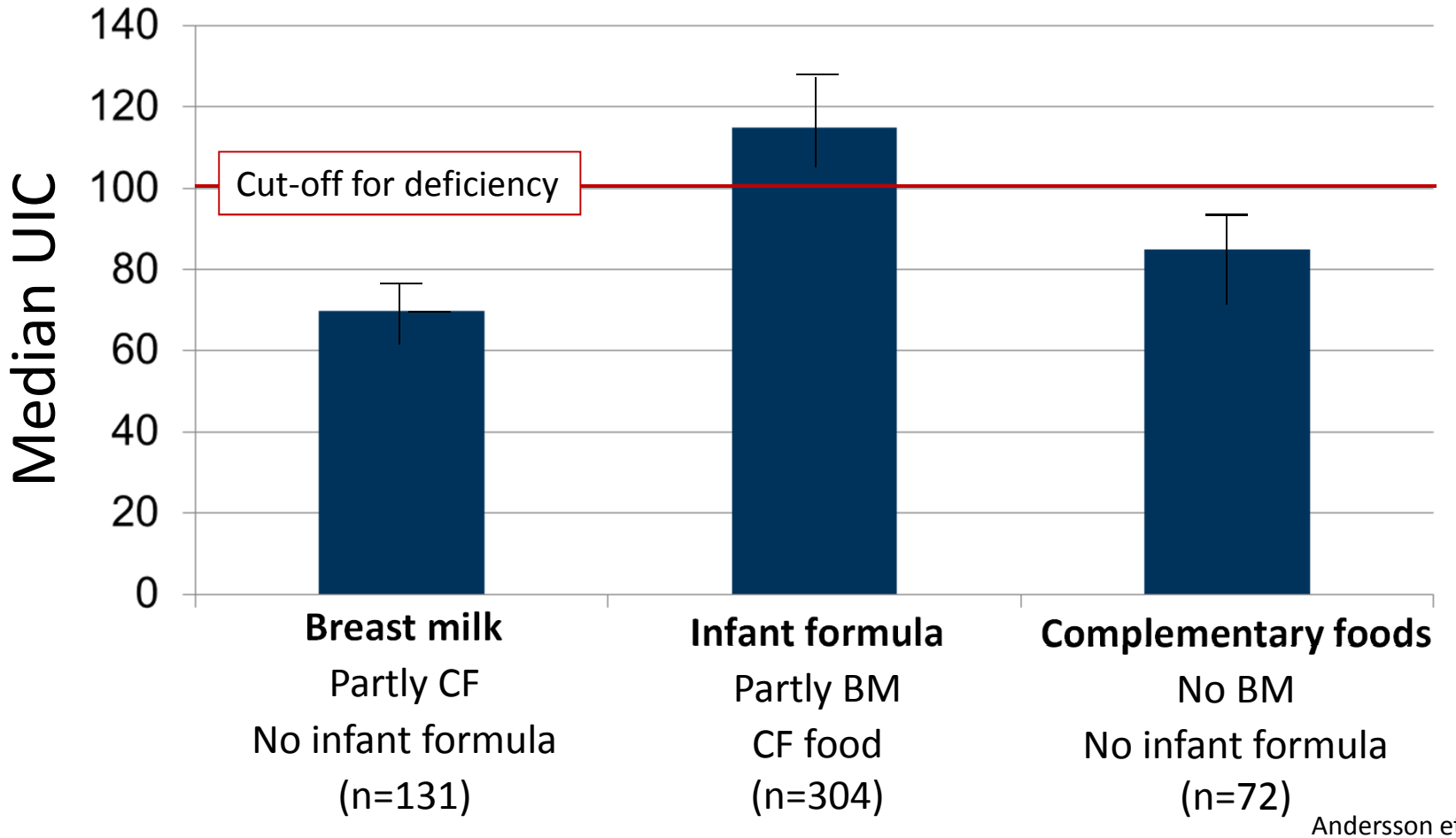
Swiss iodized salt program provides adequate iodine for children and pregnant women but infants are borderline iodine deficient

Median UI by age/population group in Switzerland

Age group	Infants 3-4 d	Infants 6 mo	Infants 12 mo	School children	Pregnant women
N	368	279	228	916	648
UIC	**91**	**91**	**103**	120	162
(95% CI)	(82, 99)	(79, 103)	(92, 116)	(120, 128)	(144, 177)

Andersson et al., JCEM 2010

In industrialized countries with iodized salt programs, weaning infants need iodine-fortified complementary foods to avoid deficiency



Andersson et al., JCEM 2010

Perspective

Good micronutrient epidemiology can identify vulnerable populations for targeted fortification

New challenges

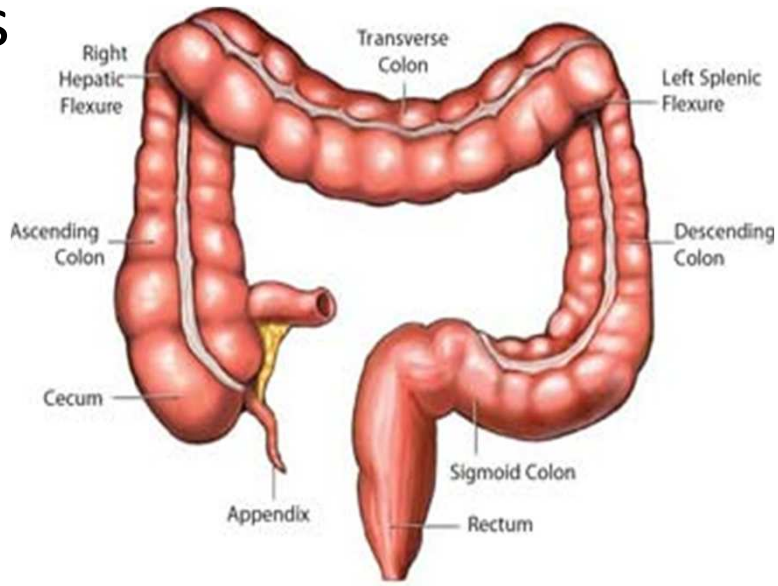
Iron and the gut microflora

Iron fortification common in SSAfrica

- Iron fortification being widely introduced in developing countries
- Flour fortification in place or planned in ≈80 countries; incl. ¼ of population of SS Africa
- Most common fortificants are elemental Fe powders despite low bioavailability
  - absorption of these poorly-soluble forms of iron is often as low as <2-3%

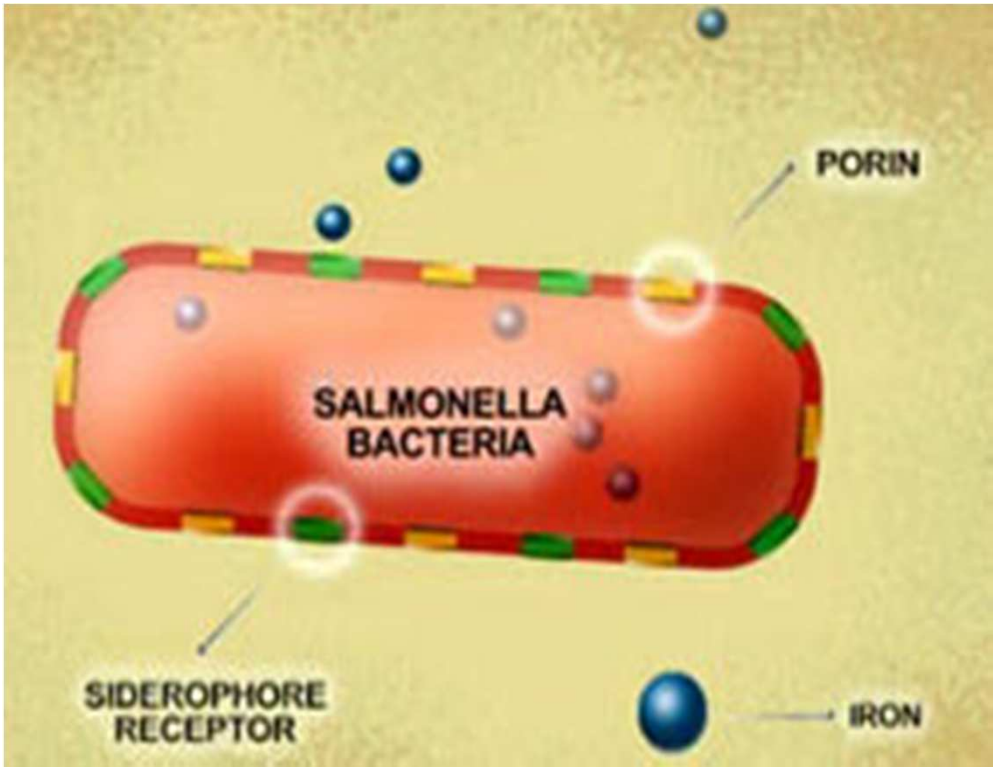
Colonic iron and the gut microflora

- Low absorption of Fe fortificants results in >90% passing into the colon
- Most body Fe tightly bound to proteins limiting supply to potential pathogens
- But no system for sequestration of dietary Fe in gut



Anatomy of Large Intestine

Intense competition for unabsorbed dietary iron among the gut microflora



- Fe a **growth-limiting nutrient** for many gut bacteria
  - colonization depends on ability to acquire iron and other essential growth nutrients

Iron is essential for most, but not all, gut microflora

Lactobacilli, beneficial 'barrier' bacteria, help prevent colonization by enteric pathogens, **do not require Fe**

Many dominant fibrinolytic strains (e.g. Bacteroides) **require Fe for growth, H_2 and SCFA production**

Enteric gram-negative bacteria (e.g. *Salmonella*, *Shigella*, *E. coli*) **effectively compete for Fe and acquisition plays essential role in virulence** and colonization

Colonic Fe supply may influence balance of gut microbiota

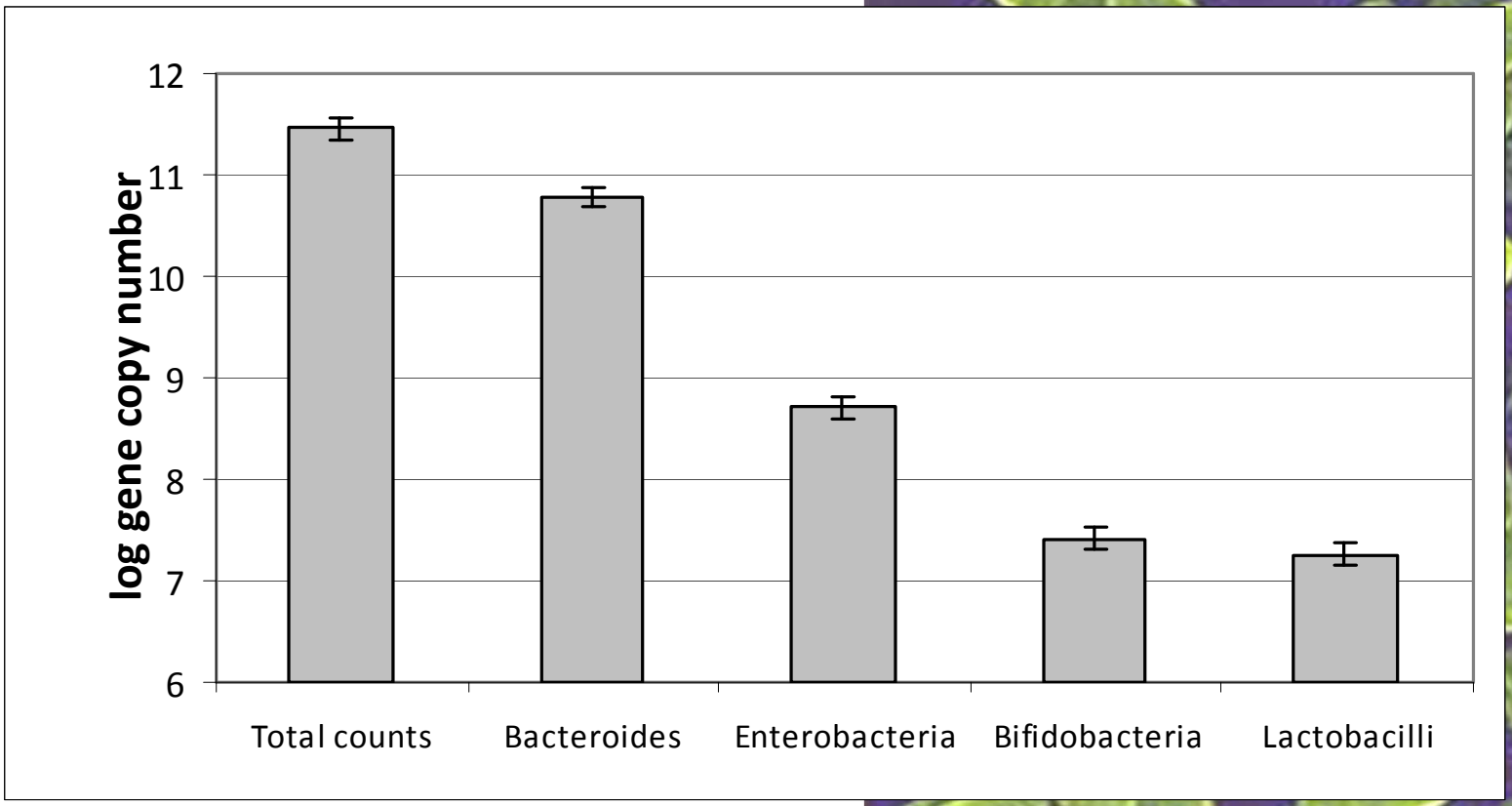
- Increase in unabsorbed dietary Fe through fortificants or supplements **could modify the colonic microbiota equilibrium and favor growth of pathogenic strains over 'barrier' strains**
  - If true, would be an important adverse effect; diarrhea the cause of death of 1 in 6 <5 y-olds in SS Africa

Effects of iron fortification on the gut microbiota in African children

- Double-blind RCT
- 6-14 y-old Ivorian children (n=139)
- received Fe-fortified biscuits w20 mg Fe/d 4x/wk as electrolytic iron or nonfortified biscuits for 6 months
- Stool samples at baseline

  (before intro of Fe) and after 6 months

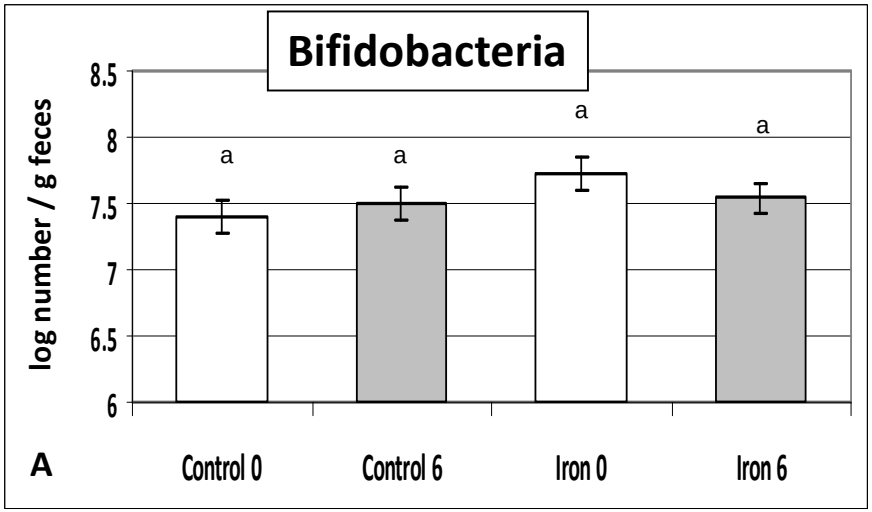
At baseline, far more fecal Enterobacteria than Lactobacilli or Bifidobacteria

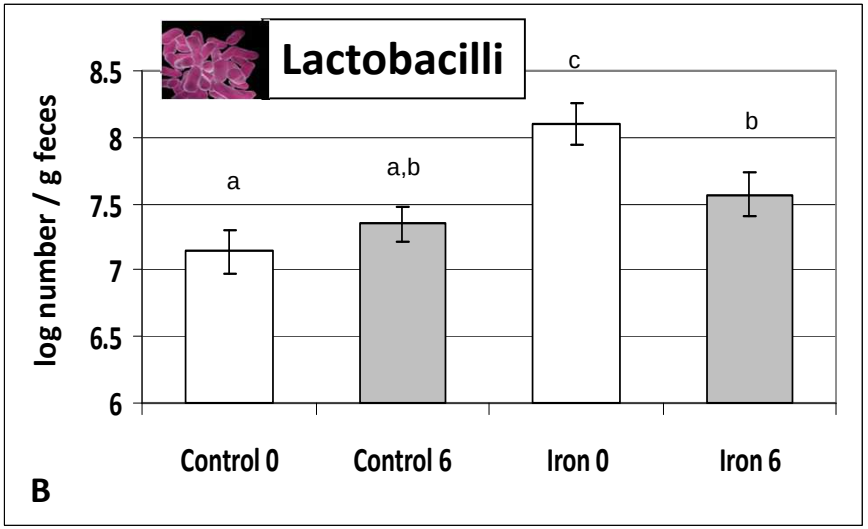


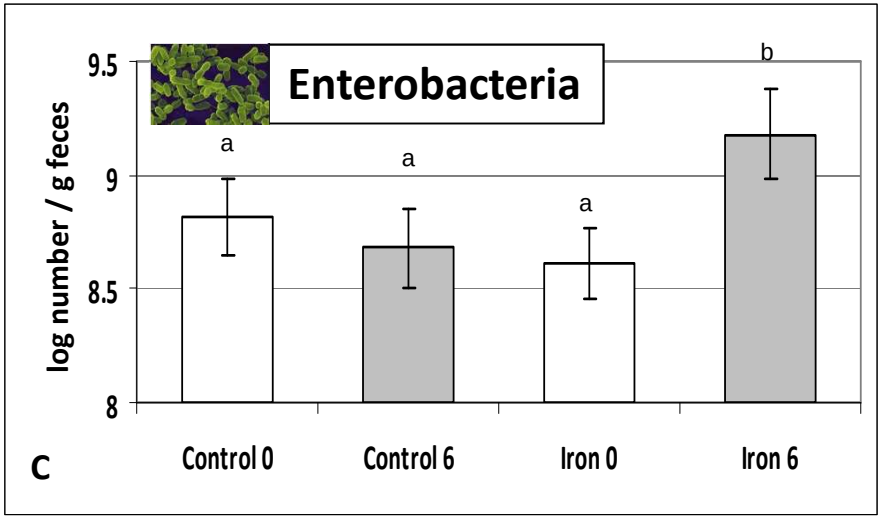
log gene copy number/g feces by RT PCR
Values are means ± SE.

(Zimmermann et al. 2010)

Fe fortification increased fecal Enterobacteria and decreased Bifidobacteria and Lactobacilli







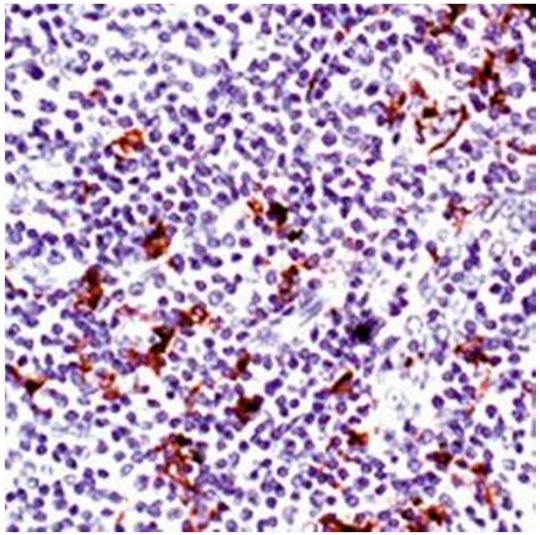
Values are means ± SE.
Means without a common letter differ, P <0.05.

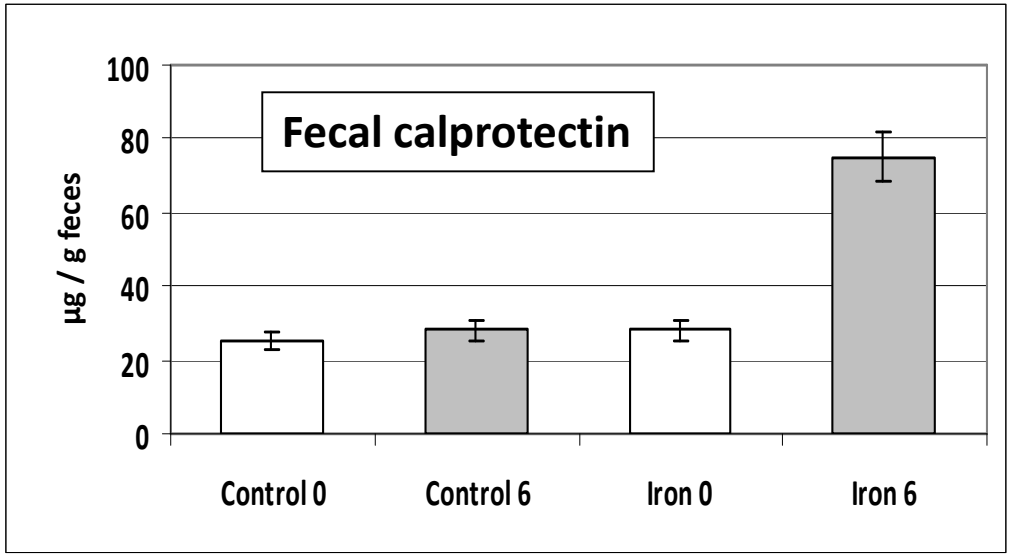
(Zimmermann et al. 2010)

Fe fortification increased gut inflammation

- At 6 months, more children positive for *Salmonella* spp. in Fe than control grp (23% vs 16%, N.S.)
- No increase in diarrhea with Fe
- Fe increased fecal calprotectin ($p<0.01$); correlated with increase in fecal Enterobacteria

(Zimmermann et al. 2010)





Perspectives

New methods of characterizing the gut microbiome will provide new insights into the links between micronutrients and health

new challenges –
double burden,
iron and obesity

Obesity increases risk for iron deficiency in vulnerable groups

- In NHANES III, overweight toddlers and children (n=9000) had double the risk of ID (Tsat, FEPP, SF)
  (Nead et al., Pediatrics, 2004)

- Increased ID (TfR) in obese women in Mexico, Spain and the USA (Lecube et al., Obesity, 2006; Menzie et al JADA 2008; Yanoff et al IJO, 2007; Cepeda et al AJCN 2010)

Why the link?

Why the link?

- Lower dietary intake from poor dietary choices?

  Maybe, but:

  - Low serum iron in obese U.S. adults not predicted by lower iron intake or iron bioavailability (Menzie et al., 2008)

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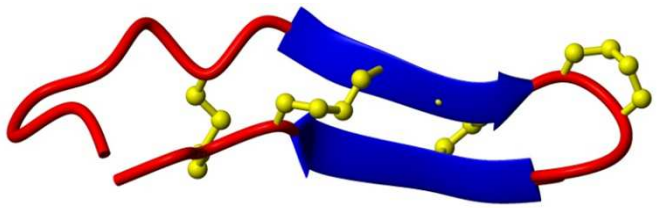
- Higher requirements, larger blood volume?

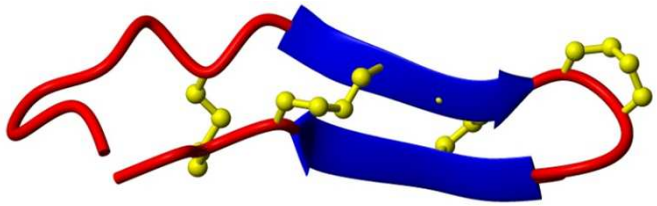
- **Reduced absorption/increased iron sequestration due to low-grade adiposity-related inflammation?**

Inflammation in obesity

- Obesity is an **inflammatory** disease
  - Increased macrophage inflitration of adipose tissue
    - Leads to increased IL-6 and leptin production by adipose tissue
  - both stimulate **hepcidin** synthesis



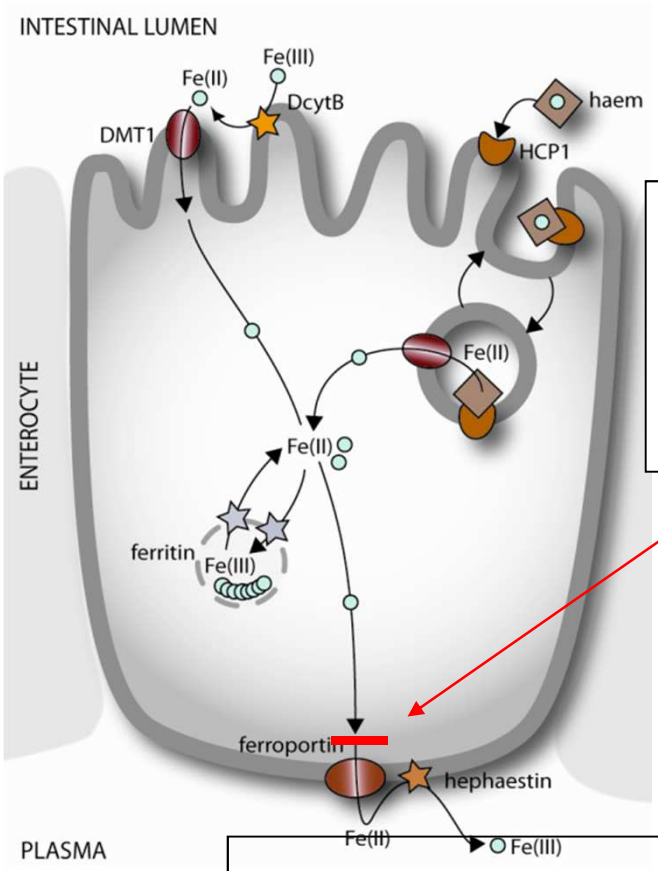
Hepcidin



- Key regulator of body iron metabolism
  - reduces intestinal iron absorption and iron release from macrophages and liver
  - Produced mainly by liver, but also small amounts by the stromal fraction of adipose tissue

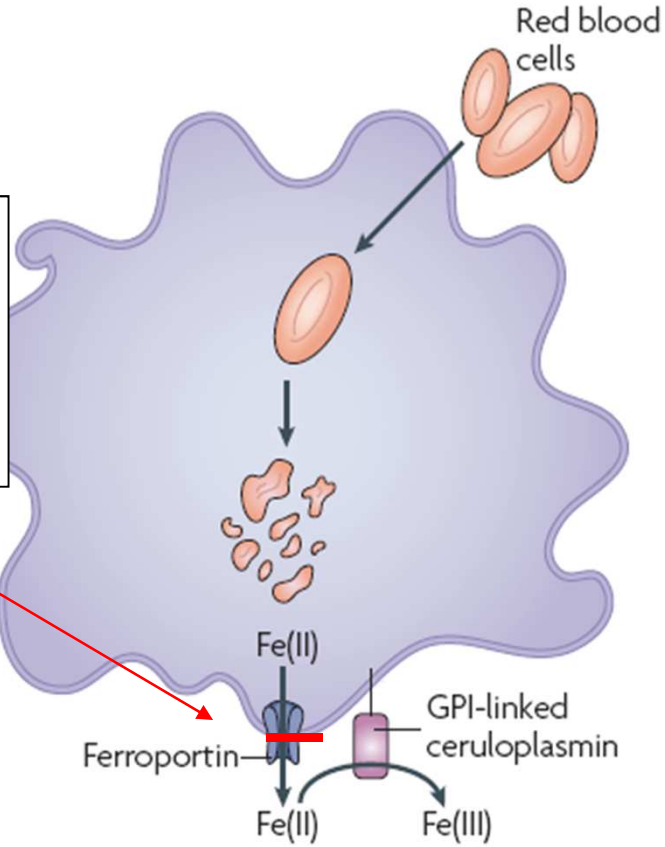
In obesity : ↑ IL6, CRP, leptin

Enterocyte



Hepcidin ↑ from hepatocytes and adipose tissue

Macrophage



Reduced systemic iron availability

Could increased inflammation and/or leptin concentrations in obesity increase hepcidin and thereby reduce iron availability from dietary sources and/or from body stores?

→ **Could this explain poor iron status in obesity?**

Overweight vs. normal weight children

	Normal weight	overweight
n	33	85
BMI (kg/m^2)	16.6 ± 2.1 [a]	24.1 ± 3.8 [b]
BMI-SDS	-0.42 ± 1.07 [a]	1.76 ± 0.42 [b]
Serum ferritin (ng/ml)	41.15 ± 24.5 [a]	45.3 ± 20.2 [a]
Transferrin receptor (mg/l)	3.94 ± 0.77 [a]	4.40 ± 0.88 [b]
Body iron (mg/kg)	6.4 ± 2.5 [a]	6.6 ± 1.8 [a]
Iron deficient based on an elevated sTfR; no.(%)	2 (6)	17 (20)
Hepcidin (mM)	1.4 (0.4-6.1) [a]	2.0 (1.2-5.4) [b]
CRP (mg/l)	0.03 (0.01-0.42) [2,a]	0.13 (0.03-2.25) [b]
IL-6 (pg/ml)	0.25 (0.05-1.81) [a]	0.58 (0.10-2.10) [b]
Leptin (ng/ml)	2.00 (0.11-24.16) [a]	18.72 (1.78-62.87) [b]

[1] mean ± SD, all such values, [2] median (min. – man.) all such values

Means or medians not sharing a common superscript letter are significantly different from each other at $p<0.05$ (independent samples t-test)

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20% of overweight show mild Fe deficient erythropoesis

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Serum ferritin (ng/ml)		45.3 ± 20.2 [a]
Transferrin receptor (mg/l)	3.94 ± 0.77 [a]	4.40 ± 0.88 [b]
Body iron (mg/kg)	6.4 ± 2.5 [a]	6.6 ± 1.8 [a]
Iron deficient based on an elevated sTfR; no.(%)	2 (6)	17 (20)
Hepcidin (mM)	1.4 (0.4-6.1) [a]	2.0 (1.2-5.4) [b]
CRP (mg/l)	0.03 (0.01-0.42) [2,a]	0.13 (0.03-2.25) [b]
IL-6 (pg/ml)	0.25 (0.05-1.81) [a]	0.58 (0.10-2.10) [b]
Leptin (ng/ml)	2.00 (0.11-24.16) [a]	18.72 (1.78-62.87) [b]

20% of overweight show Fe deficient erythropoesis

Elevated hepcidin and inflammation

[1] mean ± SD, all such values, [2] median (min. – max.) all such values

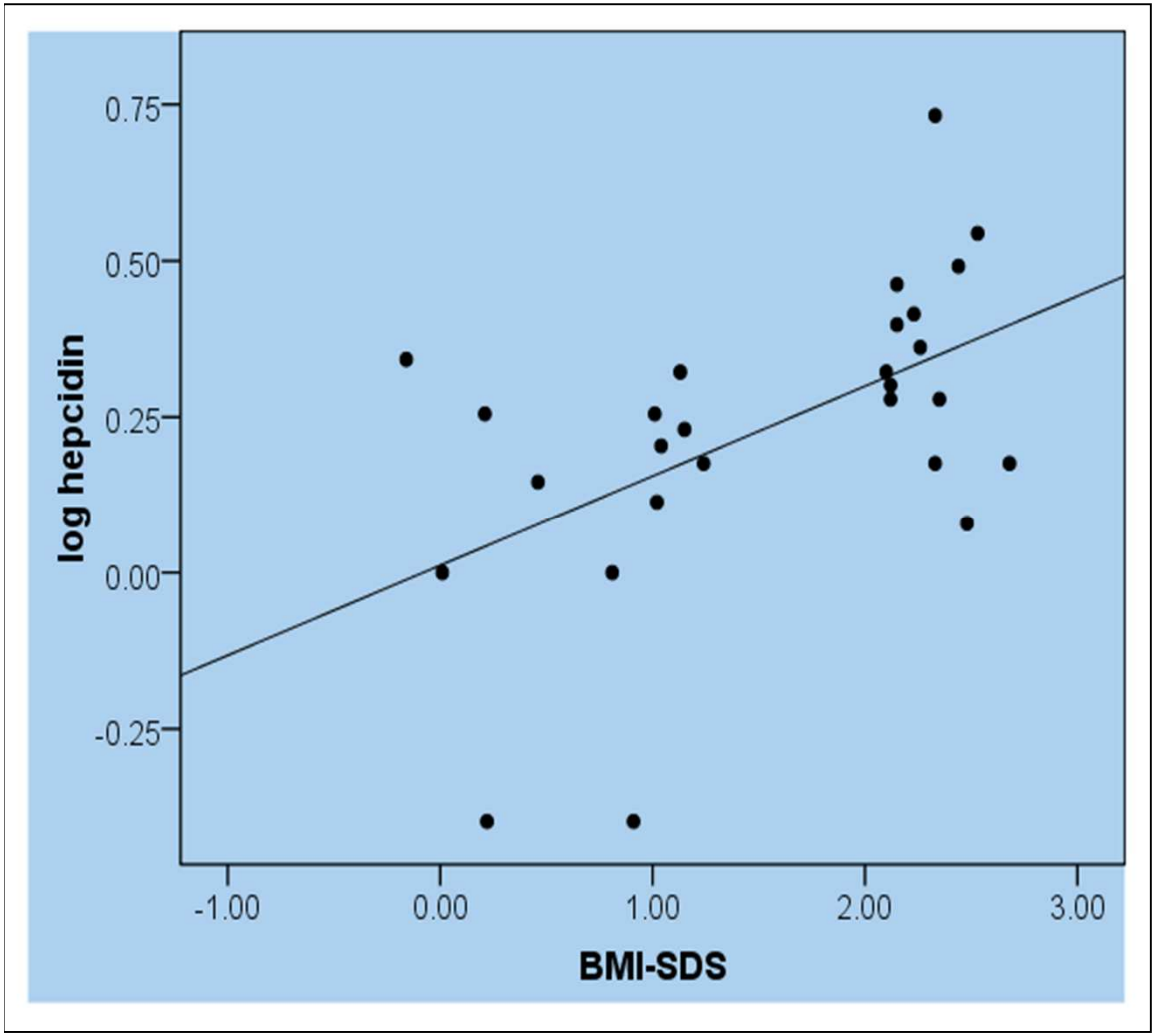
Means or medians not sharing a common [illegible]ly different from each other at p<0.05 (independent

- Dietary iron intake and bioavailability were comparable in overweight and normal weight children
- BMI-SDS was positively correlated to the intake of heme iron, total bioavailable iron and meat products.

	Dietary iron intake (mg)	% non-heme Fe bioavailability
Overweight	10.2 ± 2.8	7.0 ± 1.1
Normal weight	10.0 ± 2.6	6.7 ± 1.1

Aeberli et al., IJO 2009

Hepcidin levels higher in obese children



- Serum hepcidin correlated with BMI-SDS (p=0.020)
- sTfR correlated with BMI-SDS (p=0.027) but not iron intake or iron bioavailability

Aeberli et al., IJO 2009

Does adiposity in women and children in transition countries predict iron absorption and/or iron deficiency?

In Mexico, sharply higher rates of ID in obese women and children are correlated with inflammation rather than iron intakes

- National nutrition survey (1999)
- Overweight young women and SA children had **odds ratios for iron deficiency of 1.92 and 3.81** compared to normal weight population
- Correlated with CRP but not with dietary iron intakes or bioavailability

Cepeda Lopez et al, AJCN 2010

Iron absorption/utilization in normal and overweight women

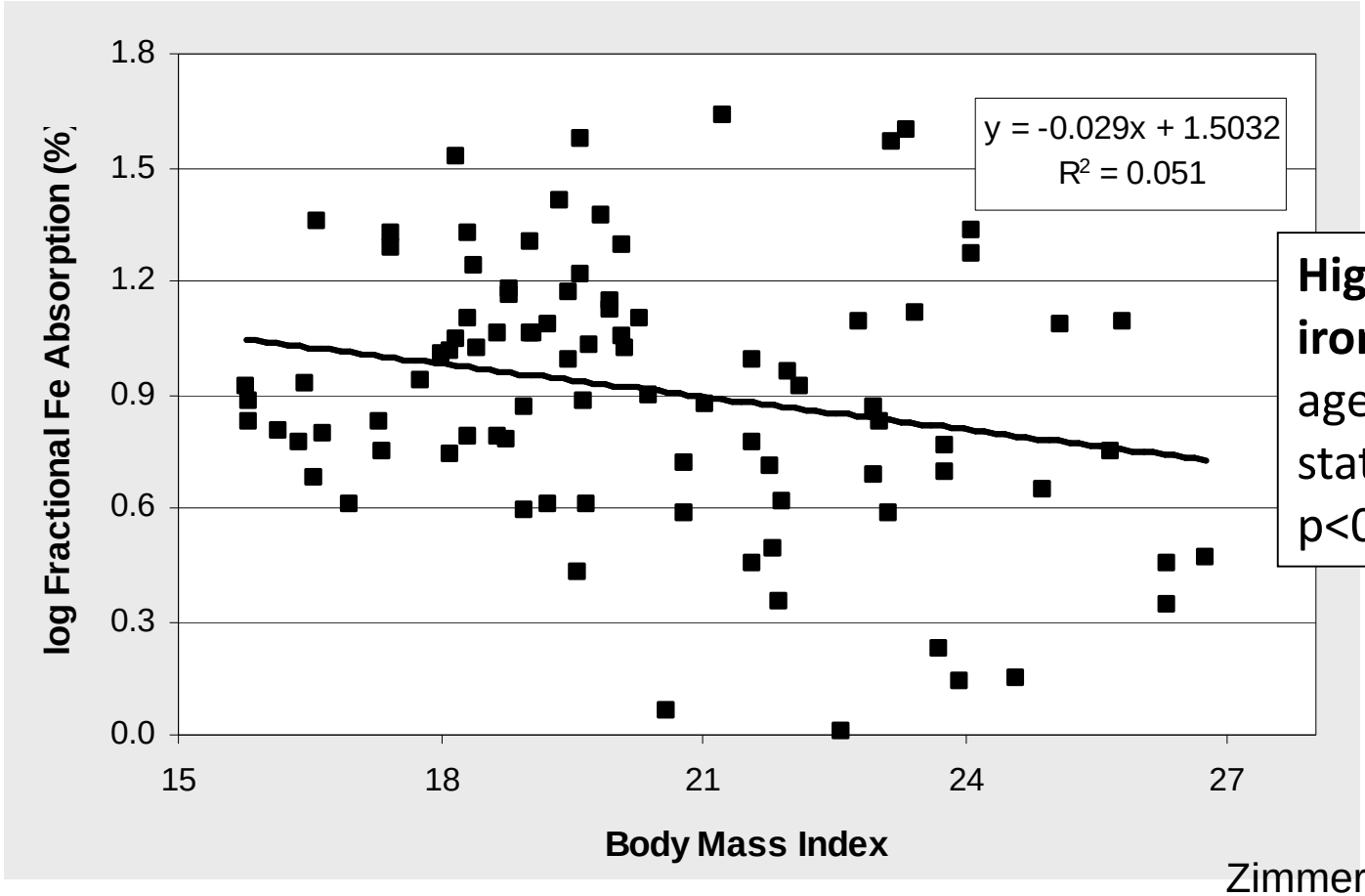
- Apparently healthy premenopausal Thai women

- 22% of the women were overweight
- 20% were iron deficient

- Consumed rice and veggie test meals, with 4 mg of isotopically labeled fortification iron as [57Fe/58Fe]-ferrous sulfate

Zimmermann et al. IJO 2008

Overweight women have reduced iron absorption/utilization from a labelled test meal



Higher BMI → lower iron absorption (ctrl age, Hb, CRP and iron status): β=-0.106, p<0.05

Zimmermann et al. IJO 2008

Overweight women have more low-grade inflammation, and this predicts iron bioavailability

Higher BMI → higher CRP concentration (r=0.227, p<0.001)

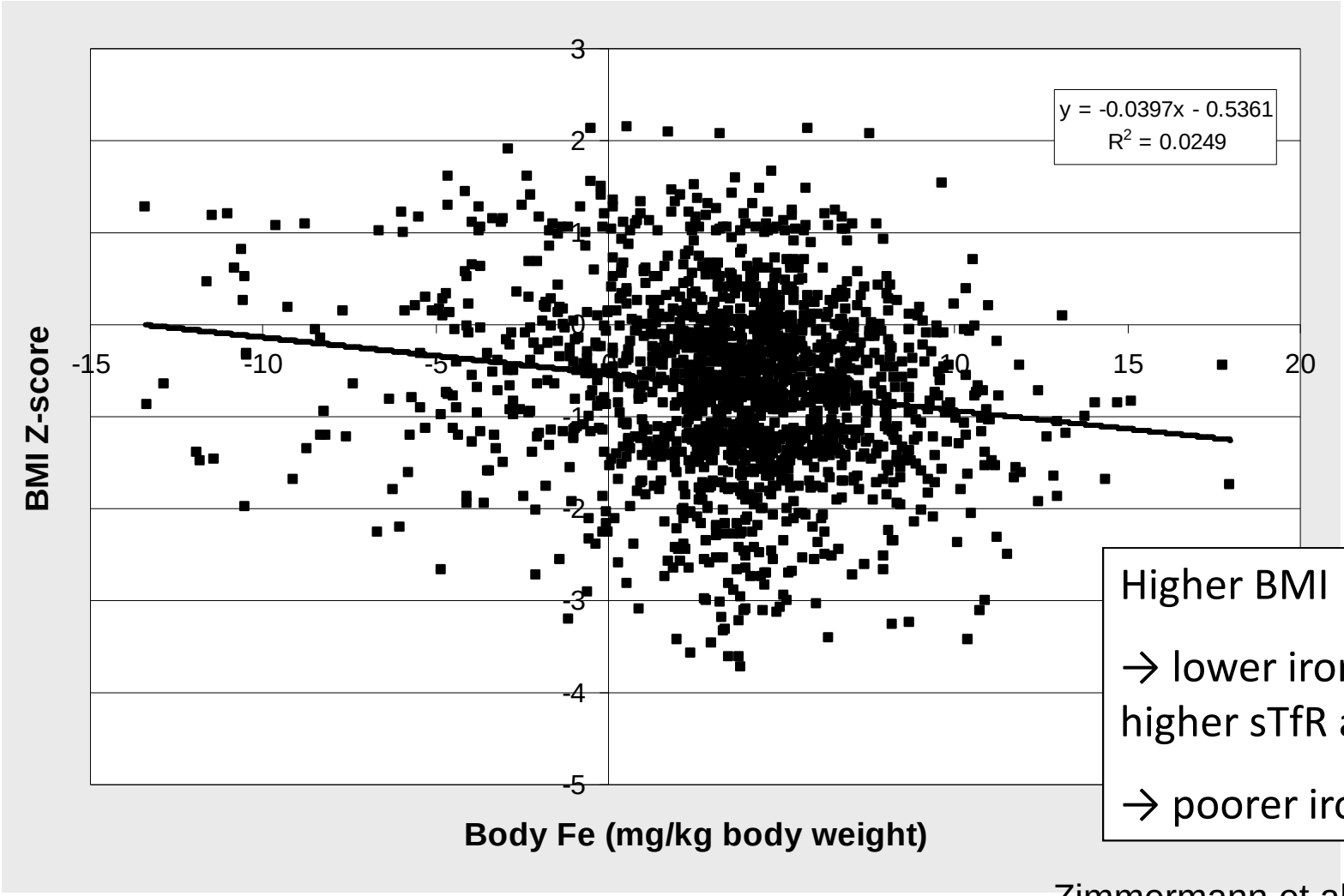
Higher CRP → lower iron absorption (ctrl for age, Hb and BMI: β=-0.422, p<0.001)

Zimmermann et al. IJO 2008

Iron fortification in overweight children

- 4 efficacy trials of iron fortification in children (5-16 y) from Morocco and India (n=1688)
- Iron fortification with encapsulated ferrous sulfate/fumarate or micronized FePP
- Hb, SF, sTfR, ZPP measured at baseline and after 7–9 months
- prevalence of overweight was 6%; prevalence of iron deficiency 42%: anemia 33%

Children with higher BMI have lower iron stores



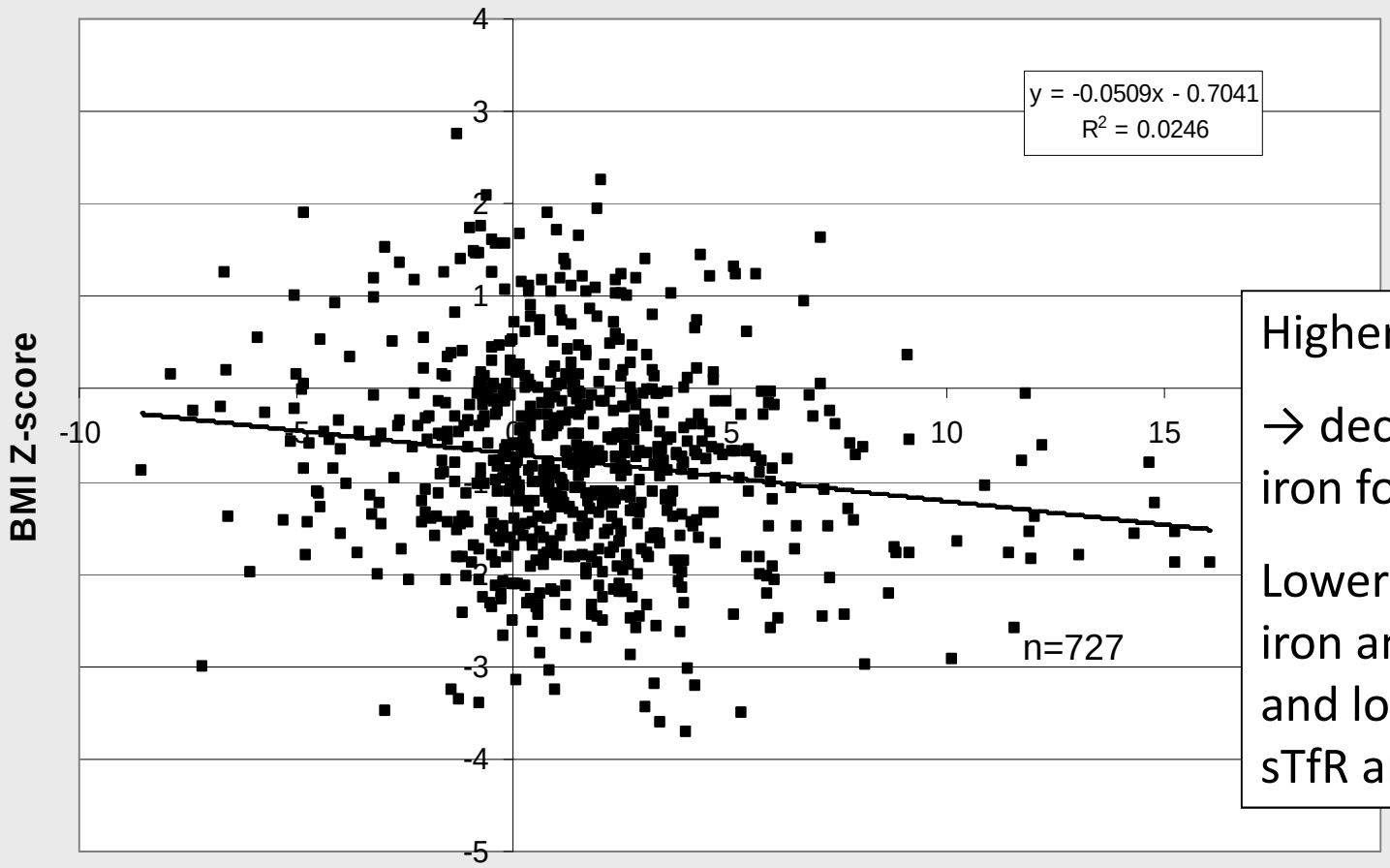
Higher BMI

→ lower iron stores, higher sTfR and ZPP

→ poorer iron status

Zimmermann et al. IJO 2008

Children with higher BMI have a blunted response to iron fortification



Higher BMI

→ decreased response to iron fortification

Lower increase in body iron and serum ferritin and lower reduction of sTfR and ZPP

Zimmermann et al. IJO 2008

Conclusions

- Adiposity in women and children predicts decreased iron absorption, iron deficiency and a reduced response to iron fortification

- Overweight may increase risk for iron deficiency via low-grade inflammation that increases hepcidin and reduces systemic iron availability

Perspectives

In transition countries, current surge in overweight may impair efforts to control iron deficiency

Interactions of the ‘double burden’ of malnutrition may have adverse consequences

Investments in food fortification and micronutrient research need to move forward in a parallel and complementary fashion

Identification of new compounds and new vulnerable groups

Effectiveness in transition countries with high rates of obesity
Safety of iron and gut microflora

Enhanced effectiveness and safety of fortification

Thank you

For more information:

Reviews:

Nutritional iron deficiency
Zimmermann et al., Lancet 2007

Iodine deficiency disorders
Zimmermann et al., Lancet 2008