

"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)

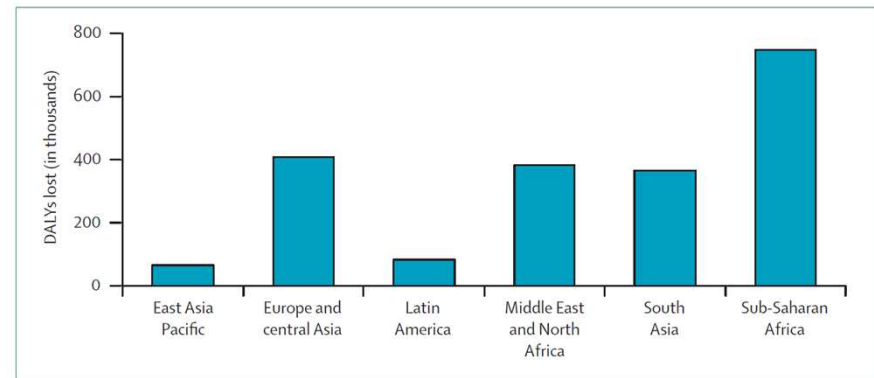


Figure 6: Disability-adjusted life years (DALYs) (thousands) lost due to iodine deficiency in children younger than 5 years of age, by region⁷⁷
A DALY is calculated as the present value of the future years of disability-free life that are lost as a result of the premature deaths or cases of disability 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)



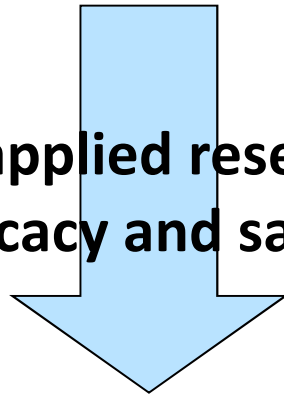
But investment in micronutrient research remains important

"It's 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."

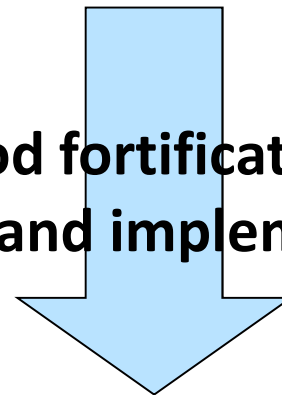
U.S. Secretary of State Hillary Clinton,
accepting the 2010 WFP Leadership
Award for fighting global hunger

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

**Basic and applied research
on MN efficacy and safety**



**Food fortification planning
and implementation**




**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

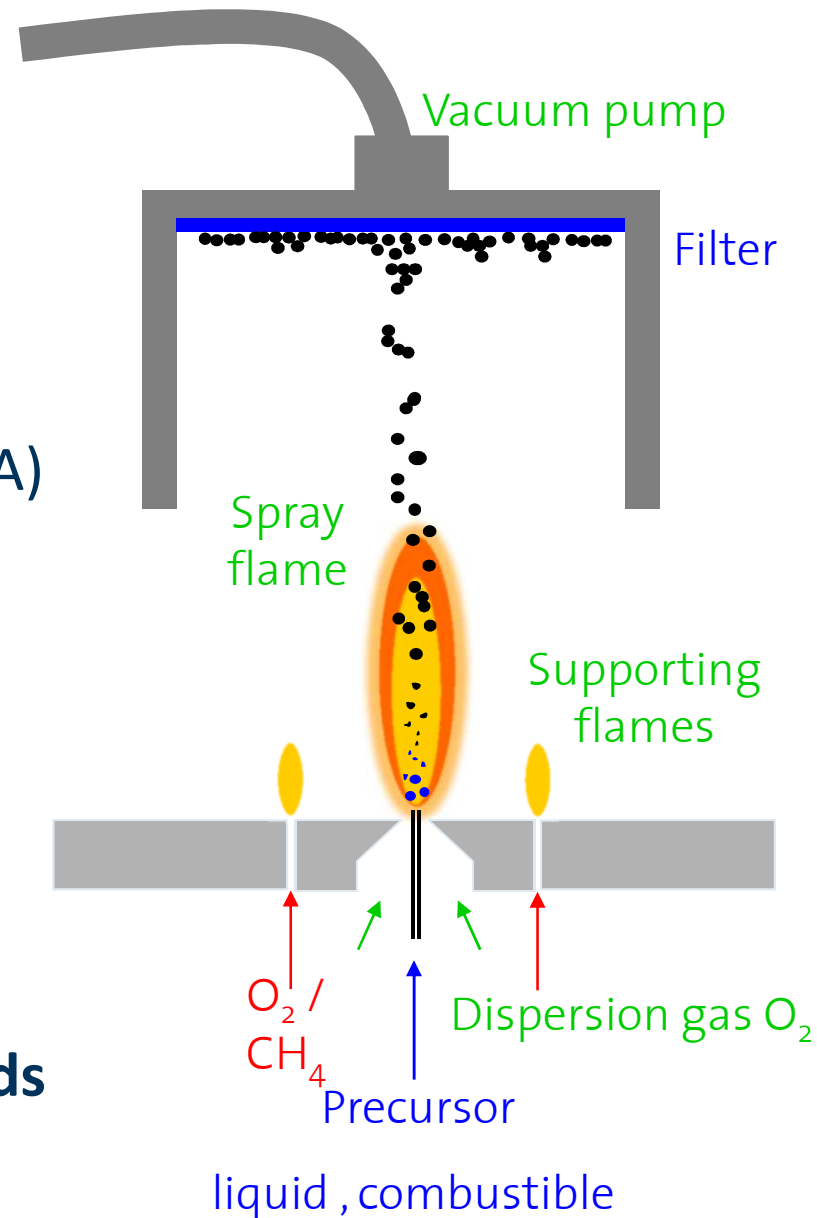
Advantages

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

Disadvantages

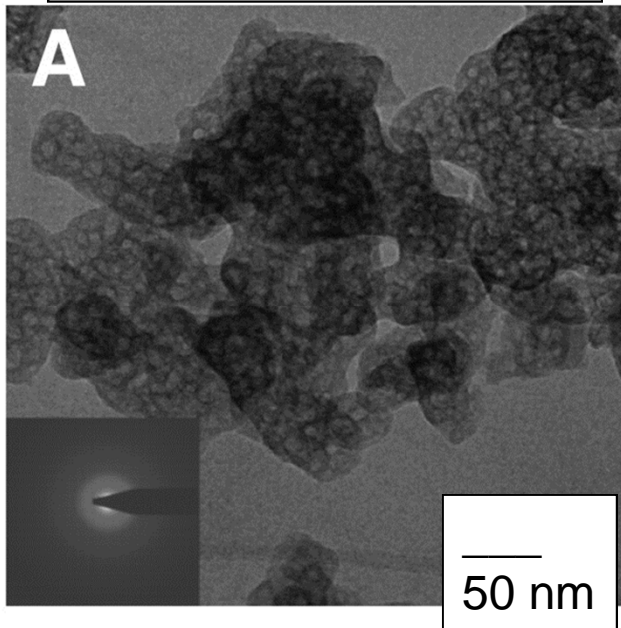
- Only inorganic compounds can be produced

Atomically mixed compounds

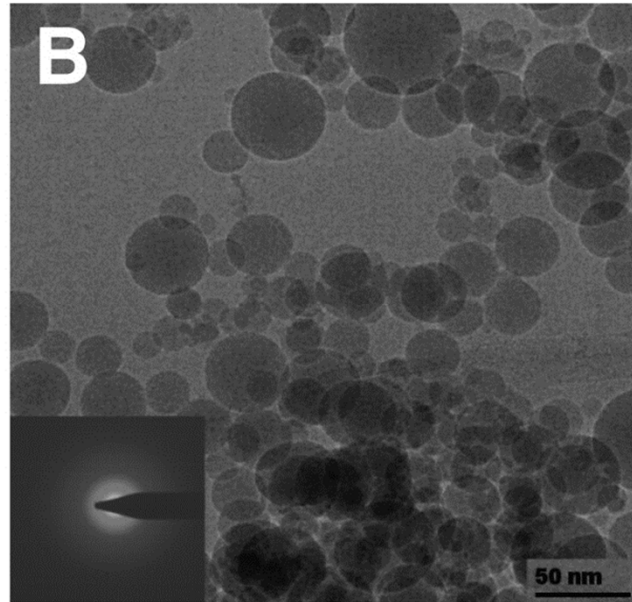


Nano-scale FePO_4 produced by FSP

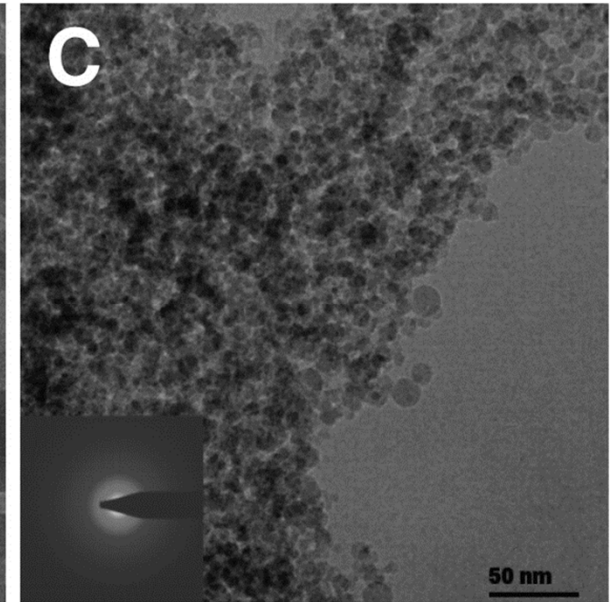
Commercial FePO_4
Amorphous
Irregular, highly porous
SSA=32.6 m^2/g



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



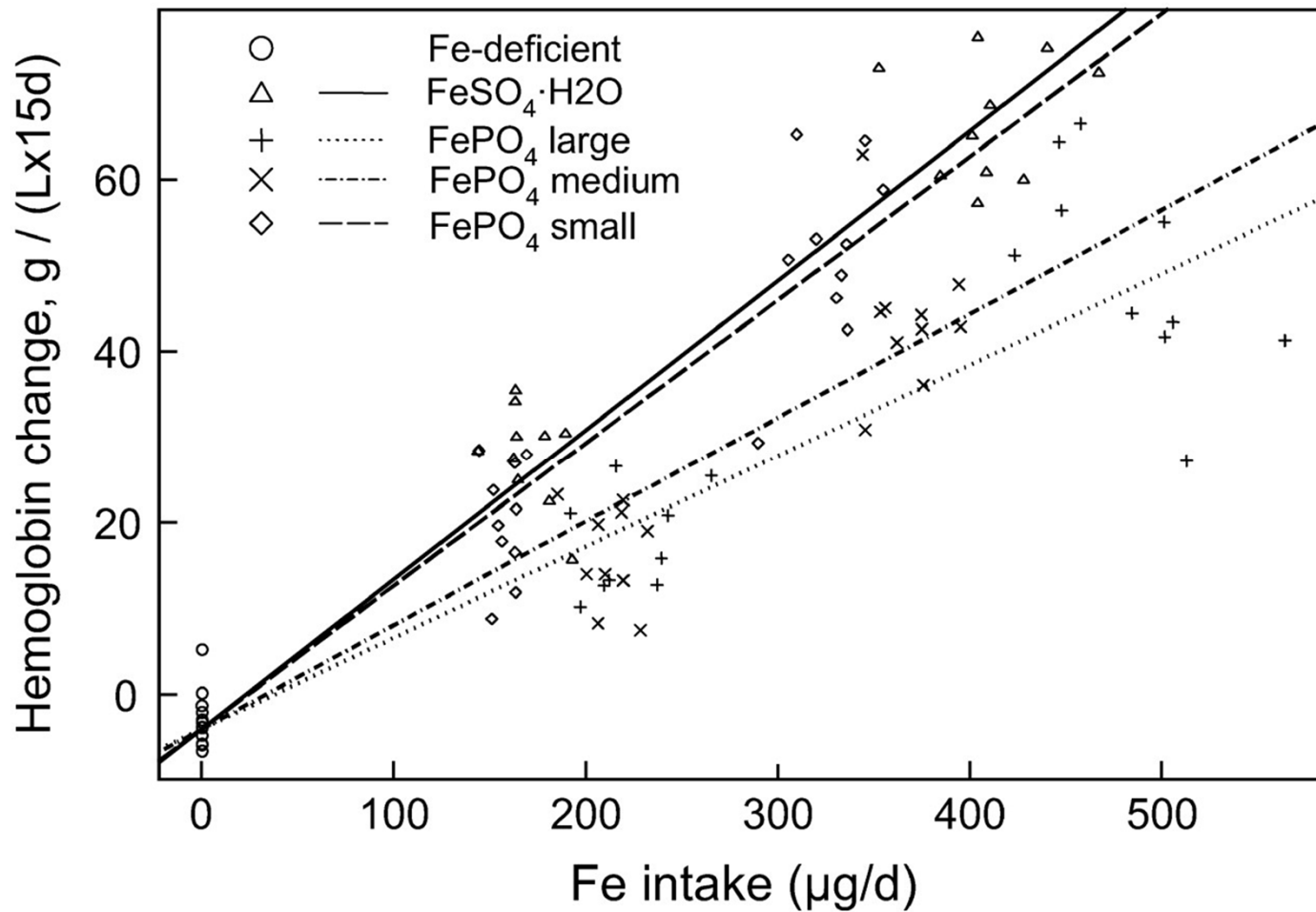
'Small' nanoscale FePO_4
Amorphous
Dense, spherical
SSA=194.7 m^2/g
Mean part. size= 10.7 nm



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

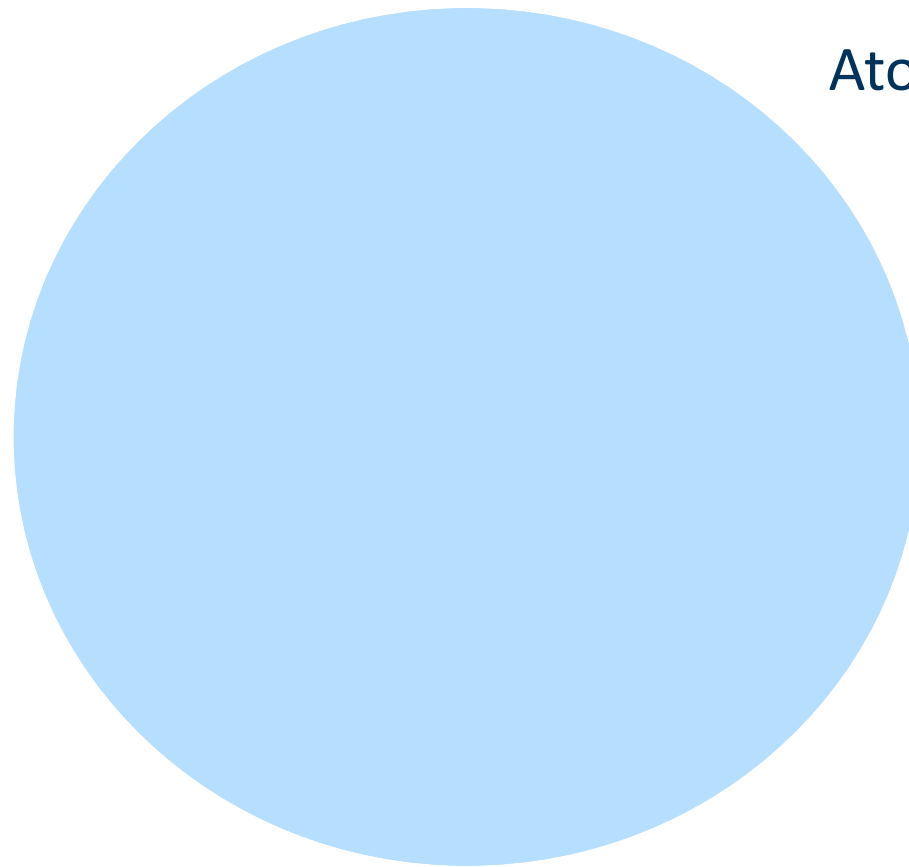
Rohner et al. J. Nutr. 2007

Nanosized FePO_4 is as bioavailable as FeSO_4 in vivo



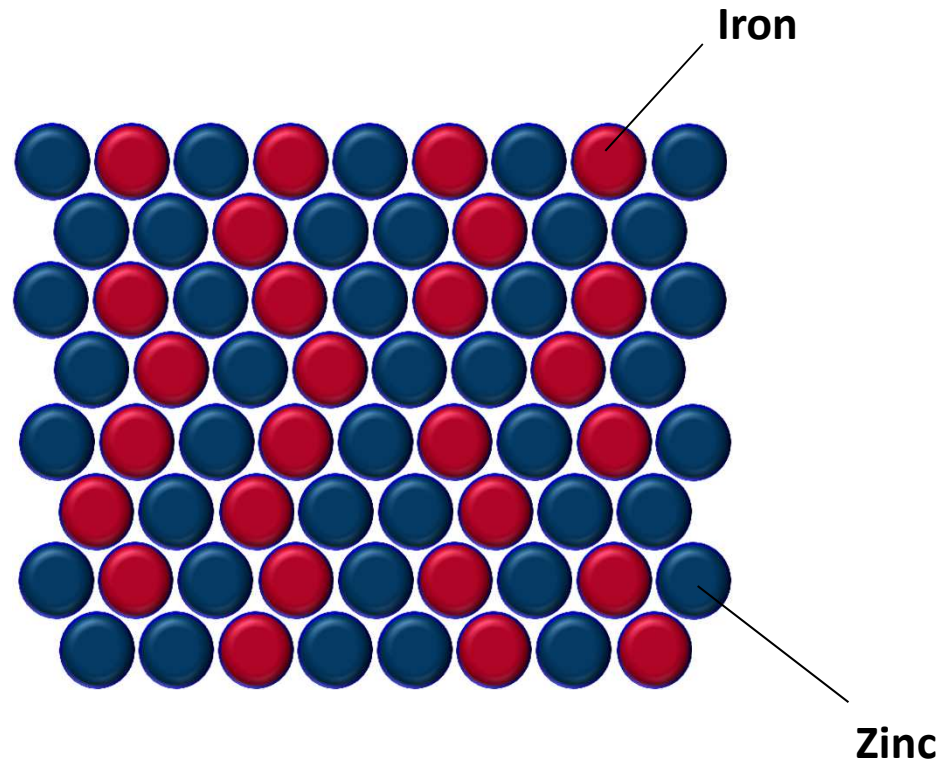
Rohner et al. J. Nutr. 2007

Atomically mixed Nano-structured Compounds

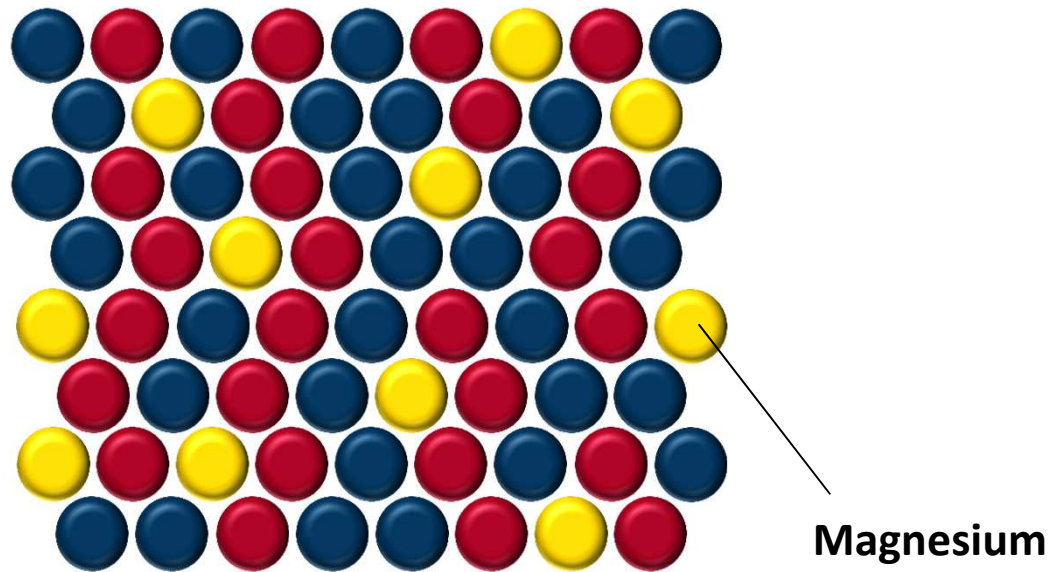


Atomic level

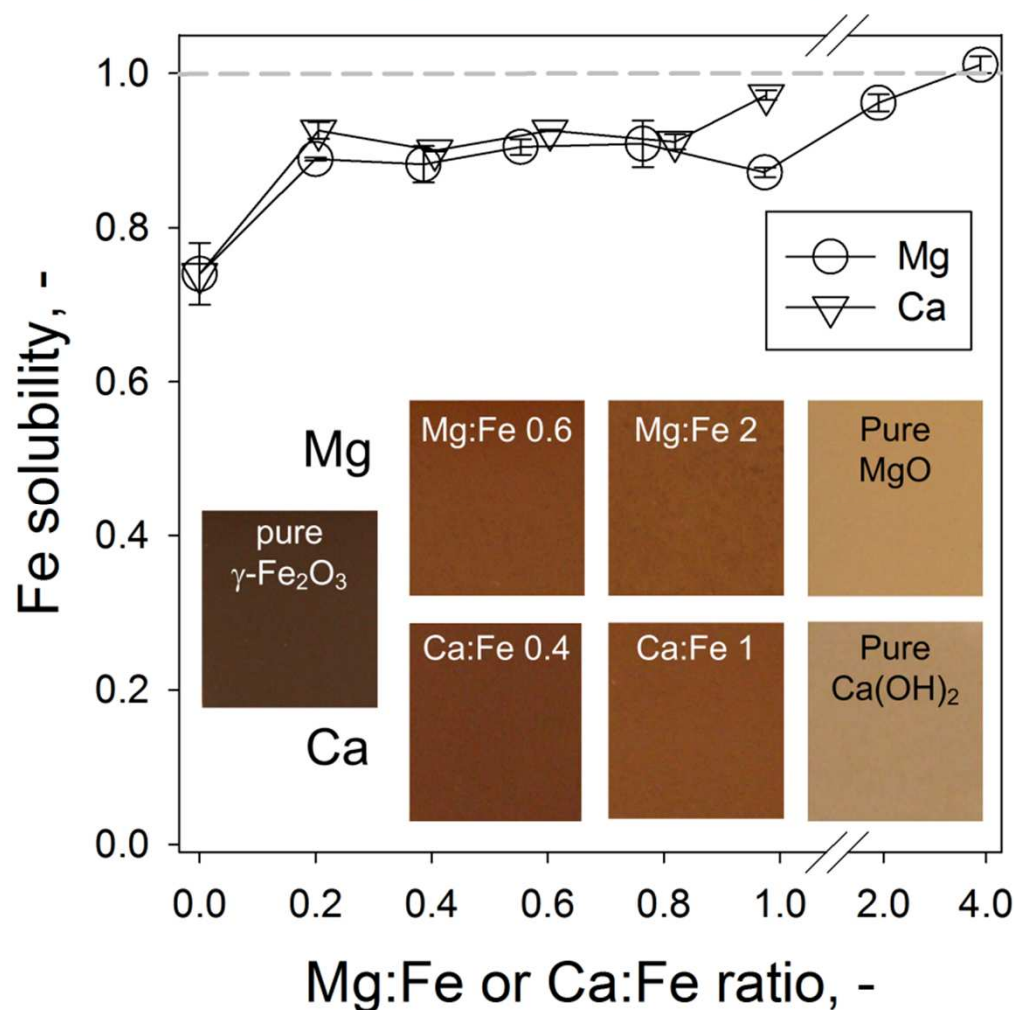
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Atomically mixed Nano-structured Compounds

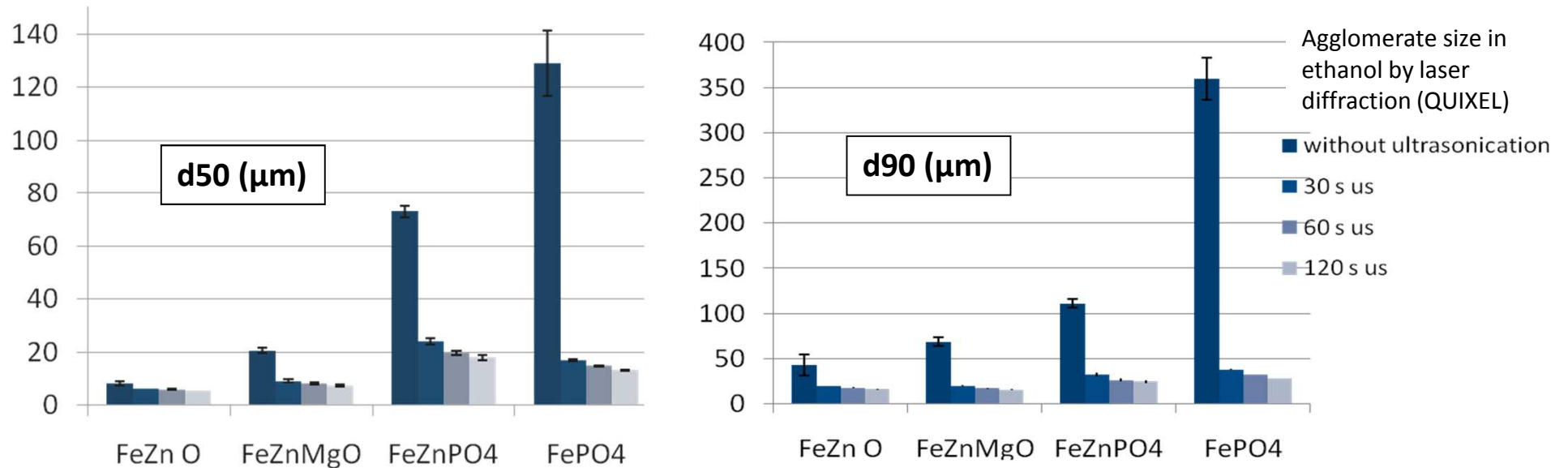


Doping with Mg or Ca improves Fe solubility and lightens compound color



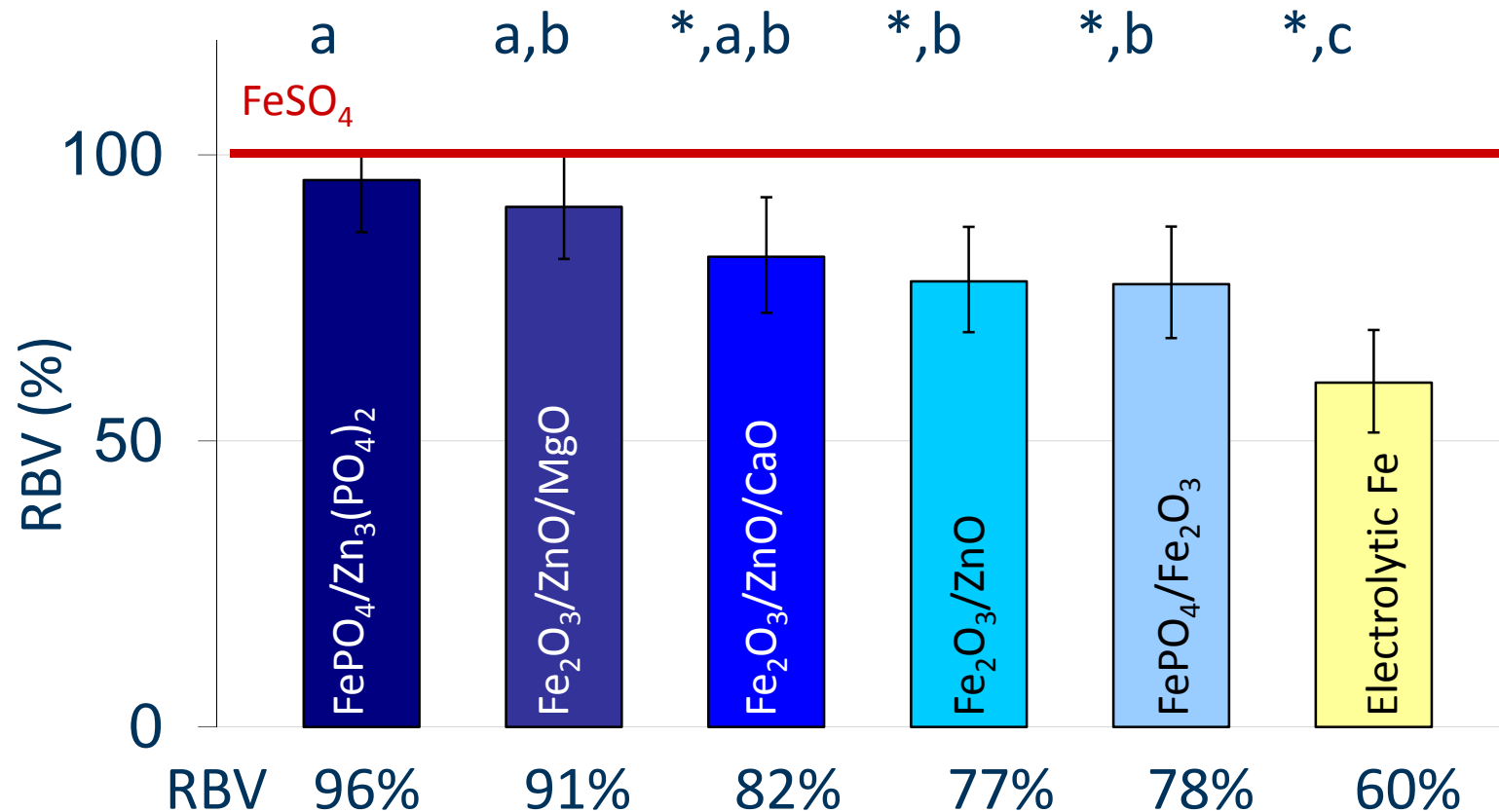
Hilty FM et al. *J Food Sci*, 2010

Soft agglomeration



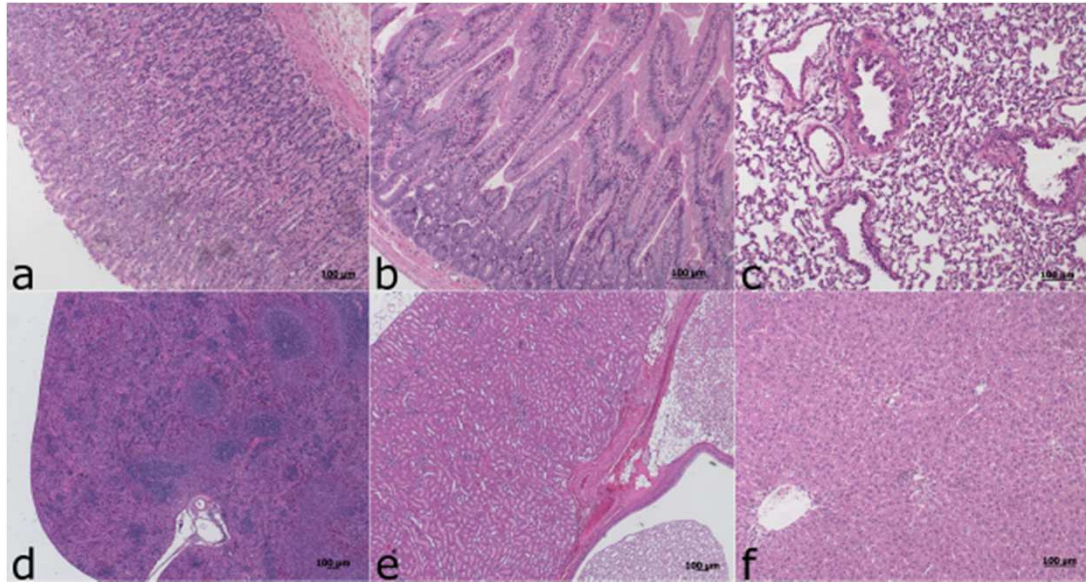
Nanostructured cpds form soft agglomerates (size 10-130 μm) making them safer to handle (less dusting) but not reducing bioavailability

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



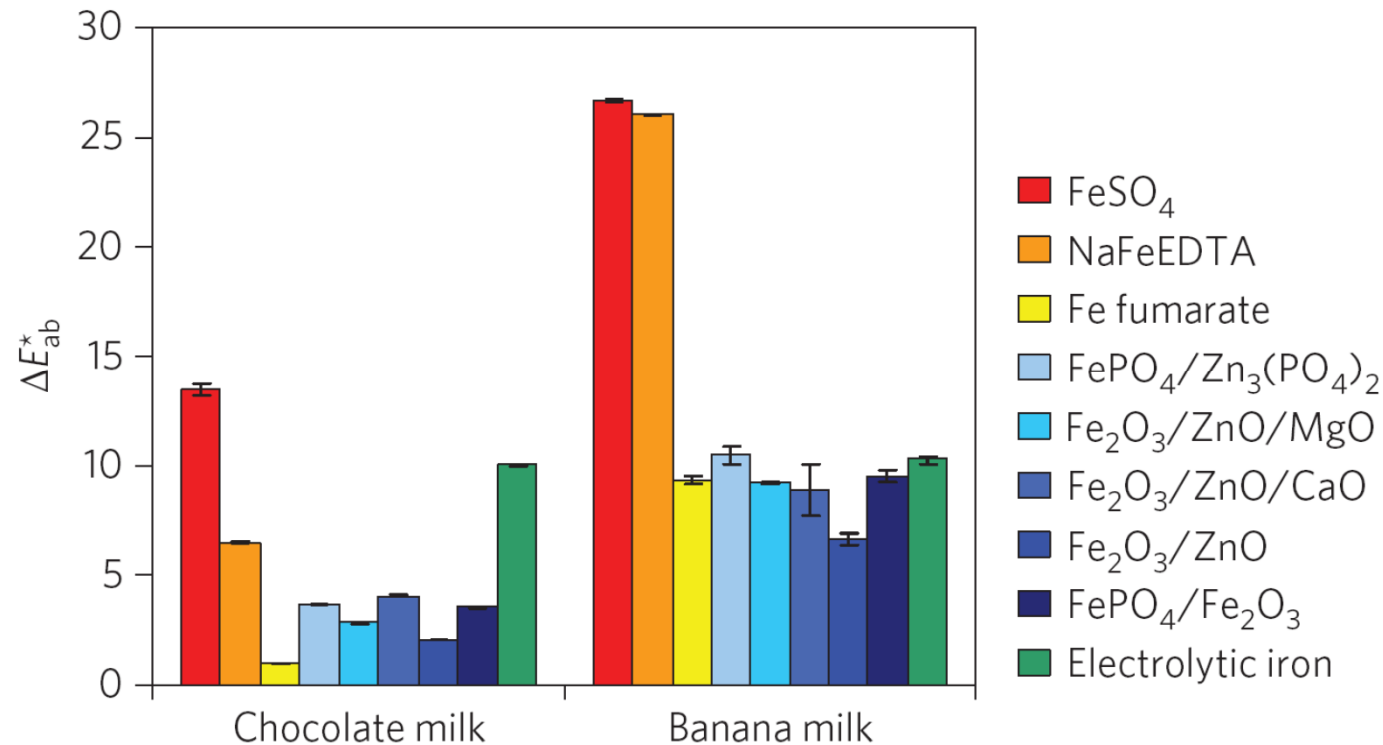
Tissues tested:

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

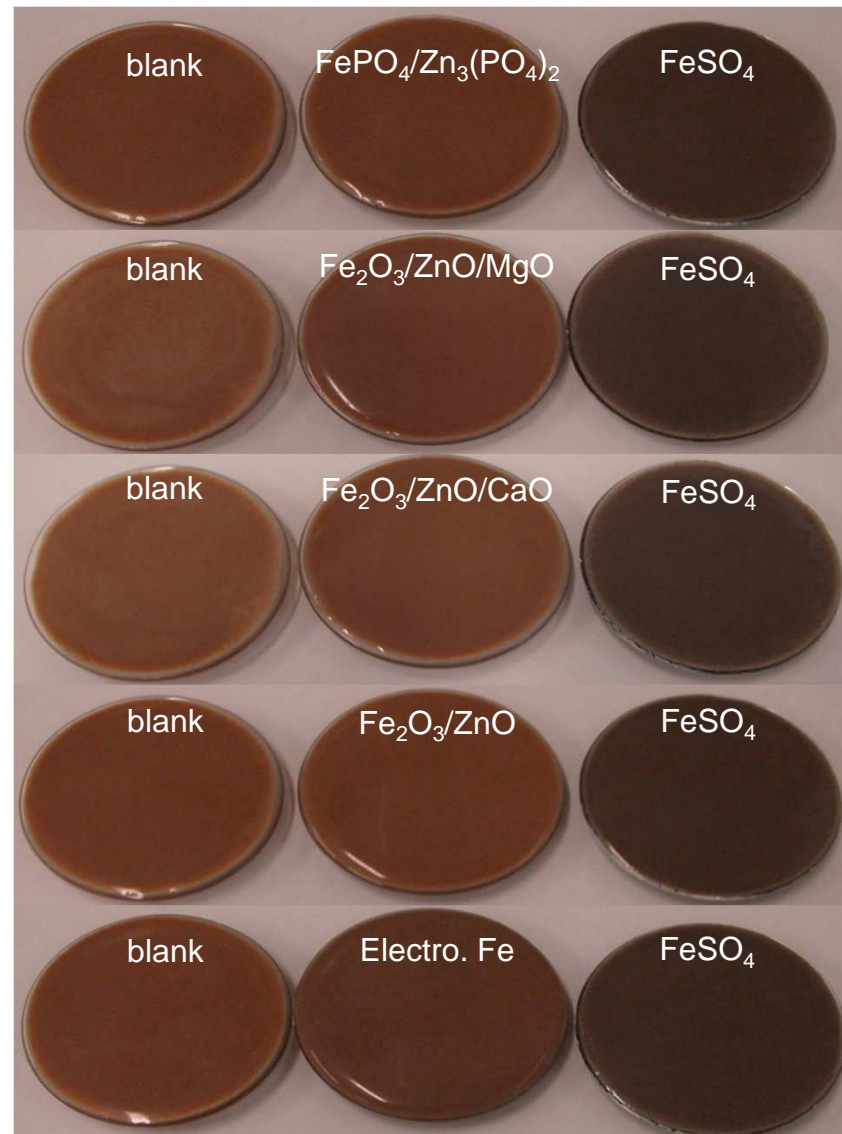
Color changes in polyphenol-containing screening foods



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 $\sim 300 \mu\text{g}$
- High T4 turnover: 5-6 $\mu\text{g/kg}$ 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 $\mu\text{g/L}$)
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 $\mu\text{g/L}$)
from iodized salt**

Iodine in IFM
EU: Max 35 $\mu\text{g}/100$ 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 ($\mu\text{g/L}$)	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



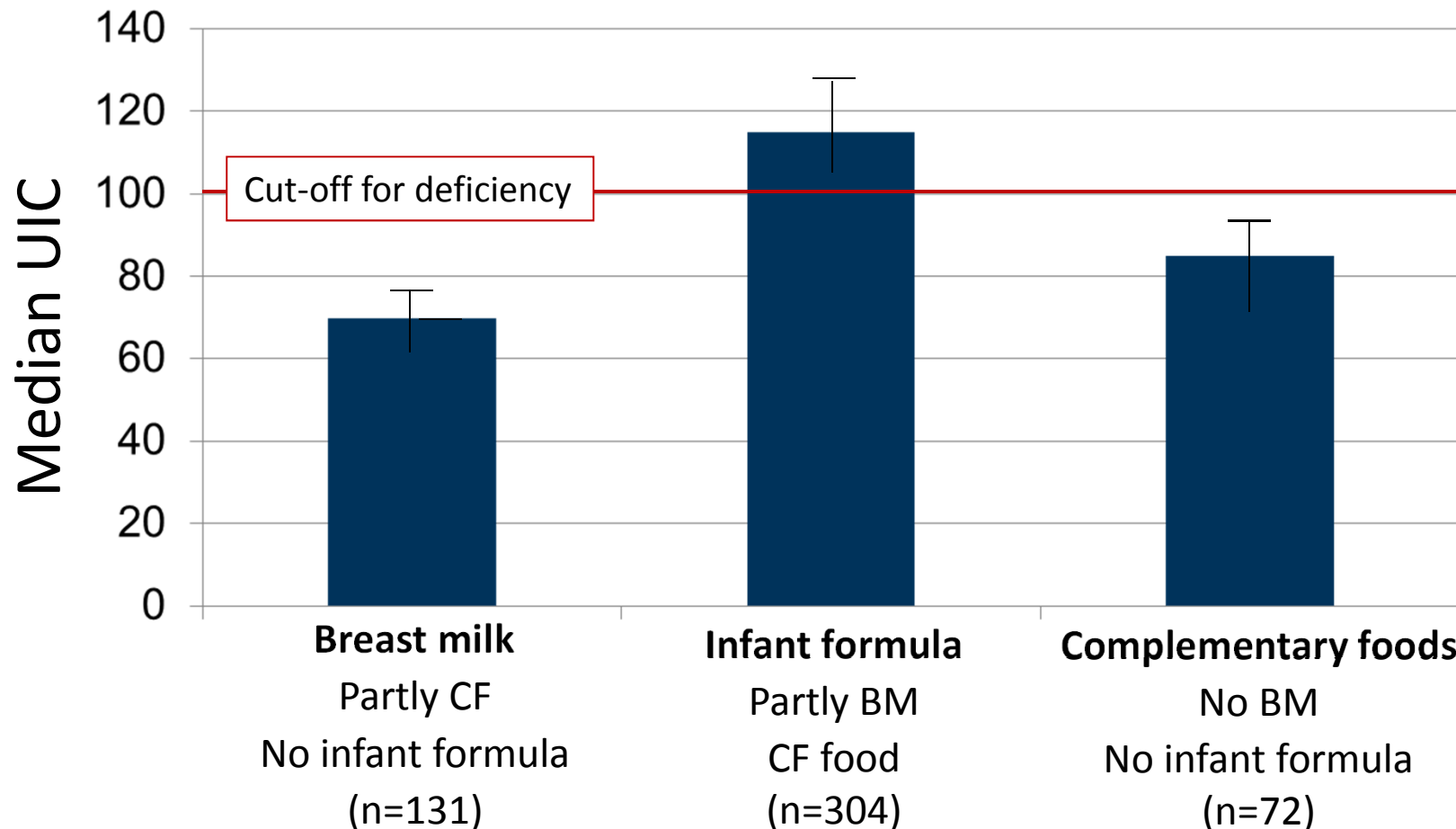
Swiss iodized salt program provides adequate iodine for children and pregnant women **but** infants are **borderline iodine deficient**

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

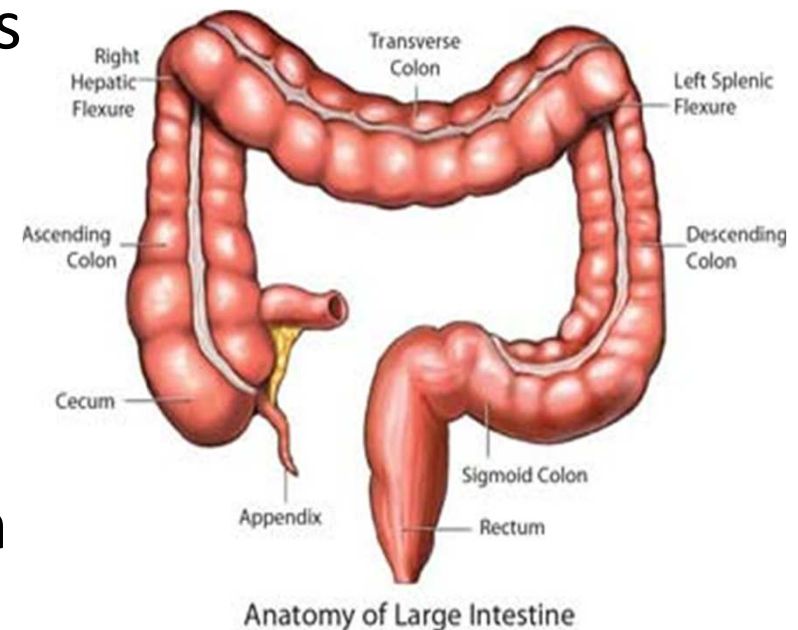


Iron fortification common in SSAfrica

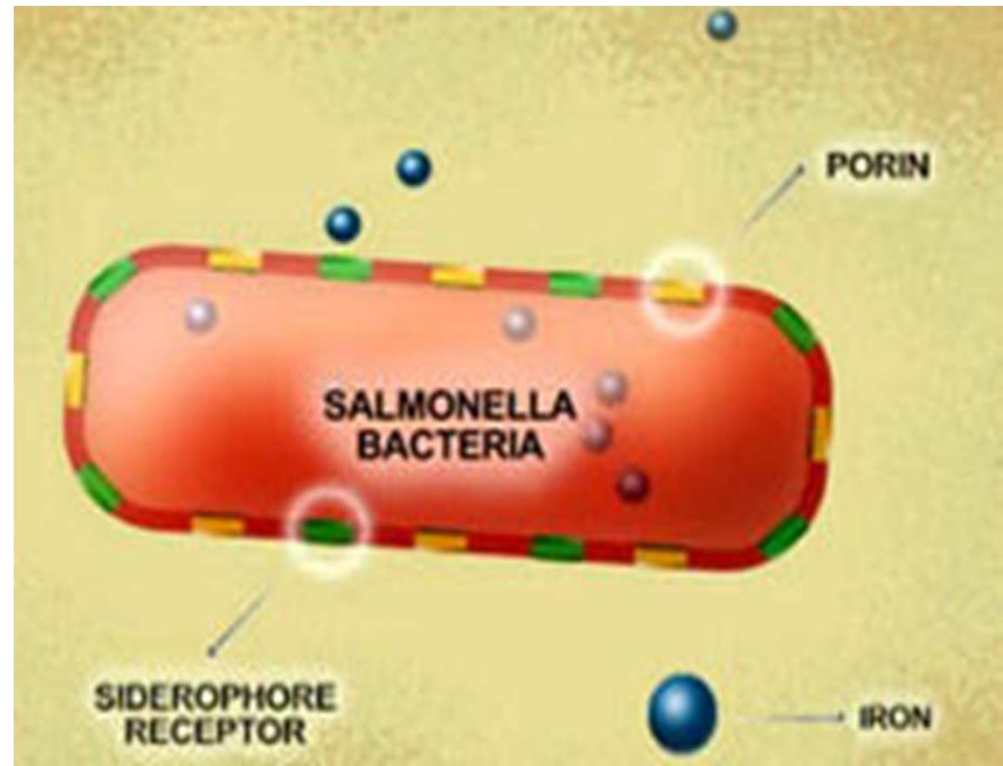
- Iron fortification being widely introduced in developing countries
- Flour fortification in place or planned in ≈ 80 countries; incl. $\frac{1}{4}$ of population of SS Africa
- Most common fortificants are elemental Fe powders despite low bioavailability
 - absorption of these poorly-soluble forms 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



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

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

Many dominant fibrinolytic strains (e.g. *Bacteroides*) **require Fe for growth, H₂ and SCFA production**

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



Colonic Fe supply may influence balance of gut microbiota



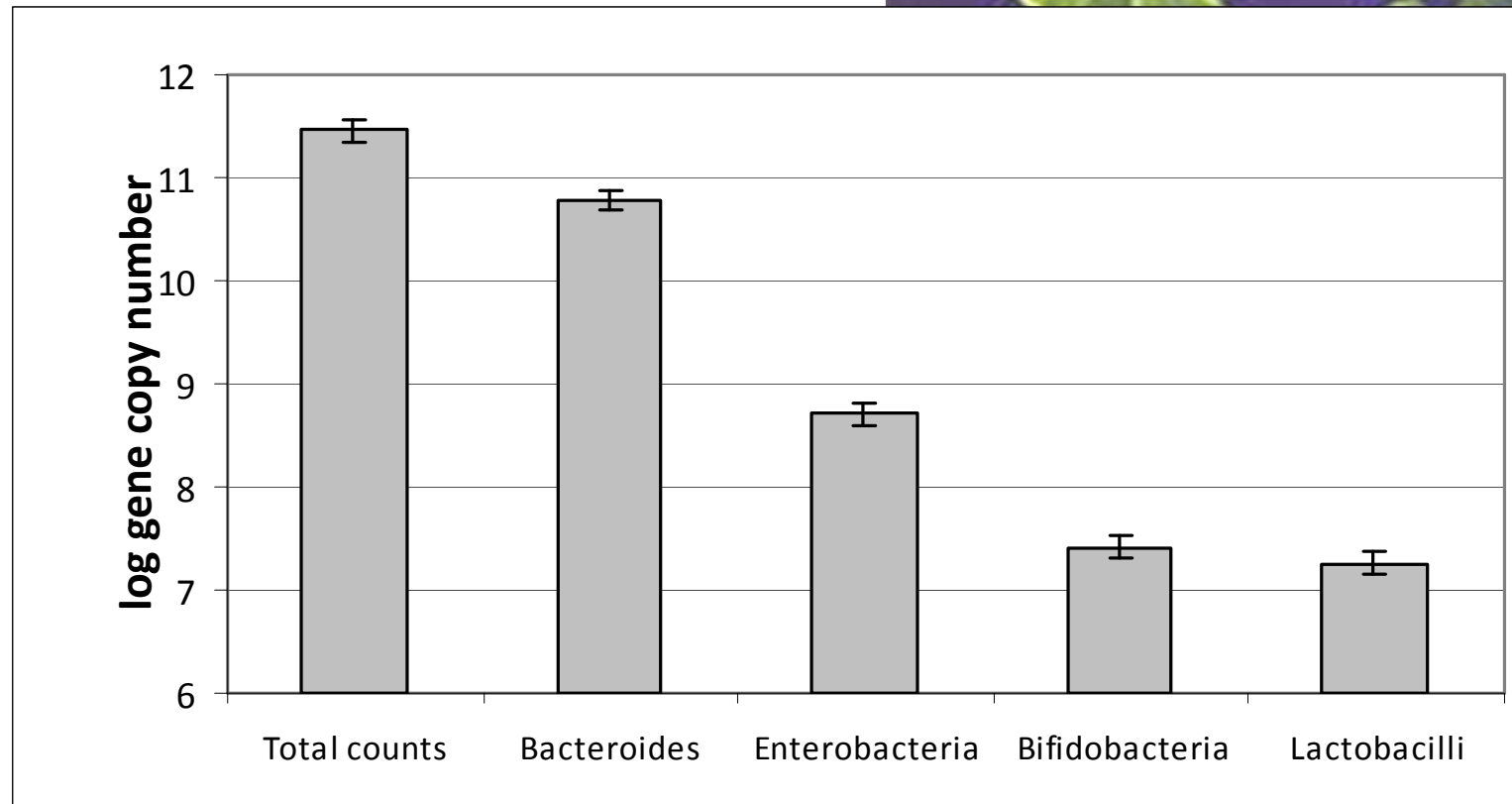
- Increase in unabsorbed dietary Fe through fortificants or supplements **could modify the colonic microbiota equilibrium and favor growth of pathogenic strains over ‘barrier’ strains**
 - If true, would be an important adverse effect; diarrhea the cause of death of 1 in 6 <5 y-olds in SS Africa

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



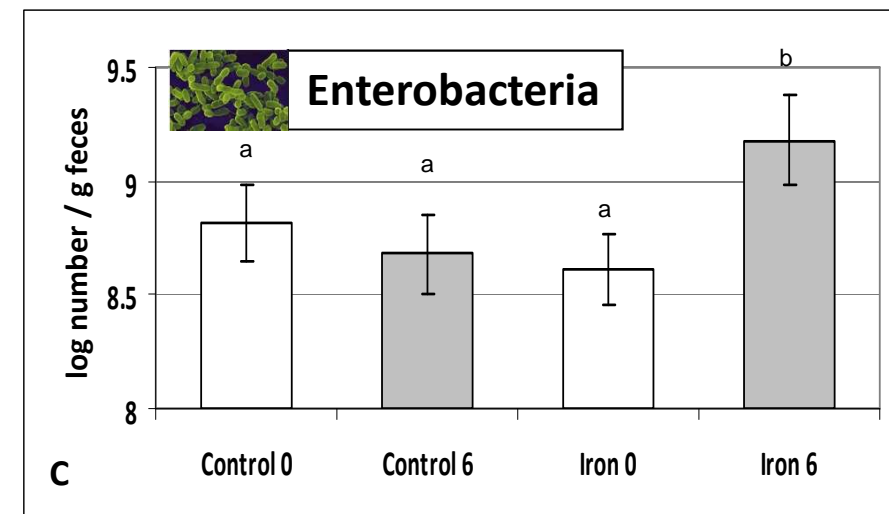
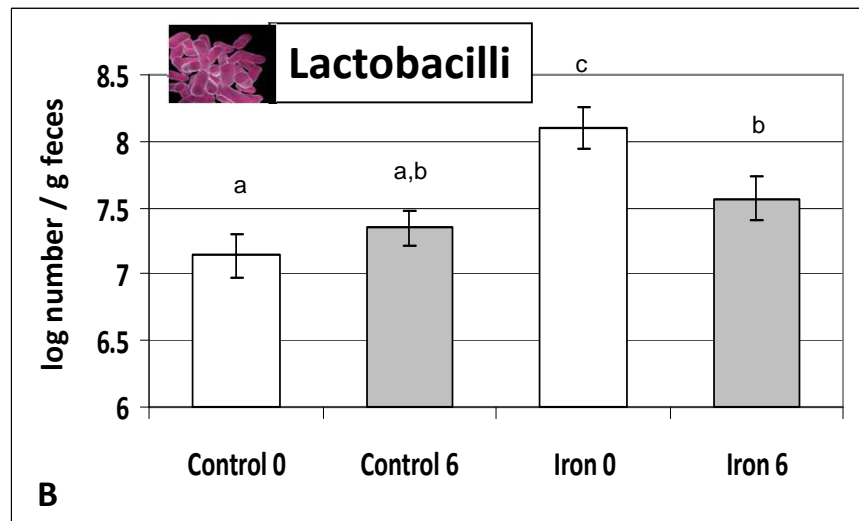
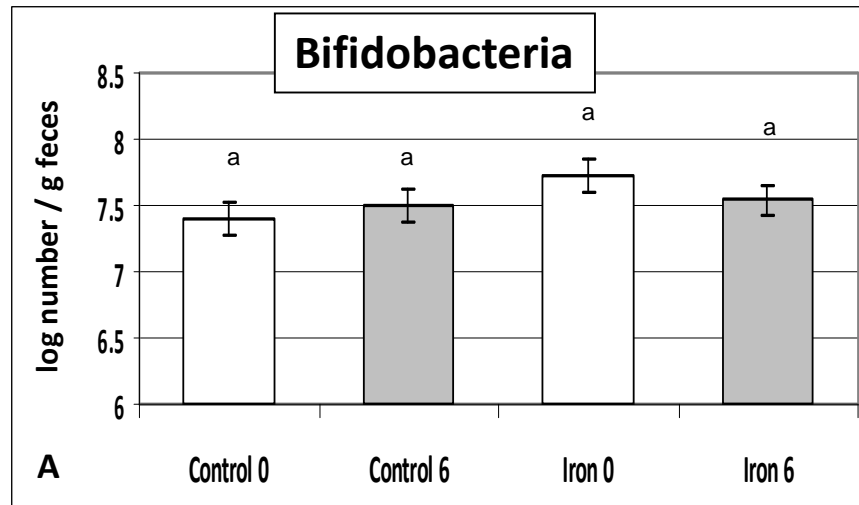
**At baseline, far more fecal
Enterobacteria than Lactobacilli
or Bifidobacteria**



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

(Zimmermann et al. 2010)

Fe fortification increased fecal Enterobacteria and decreased Bifidobacteria and Lactobacilli



Values are means \pm SE.

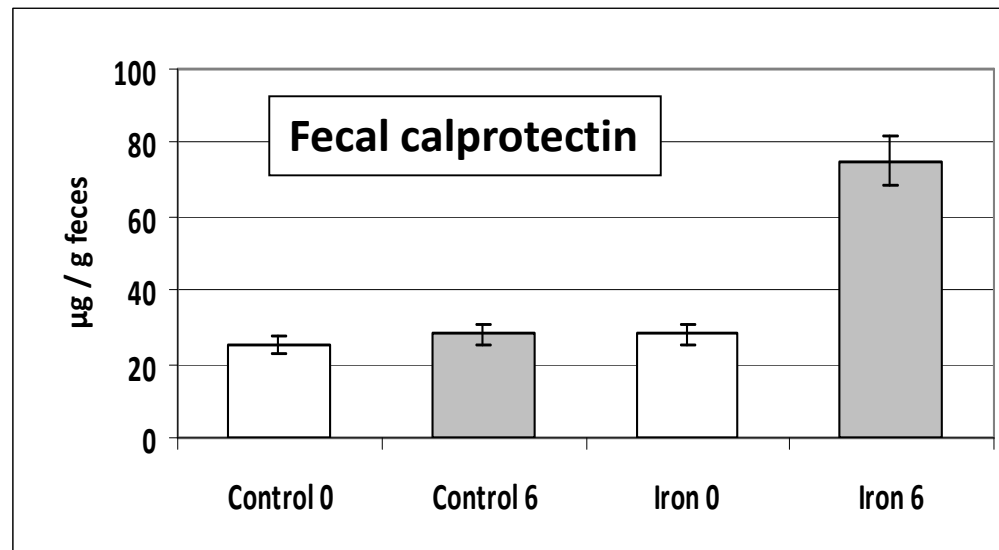
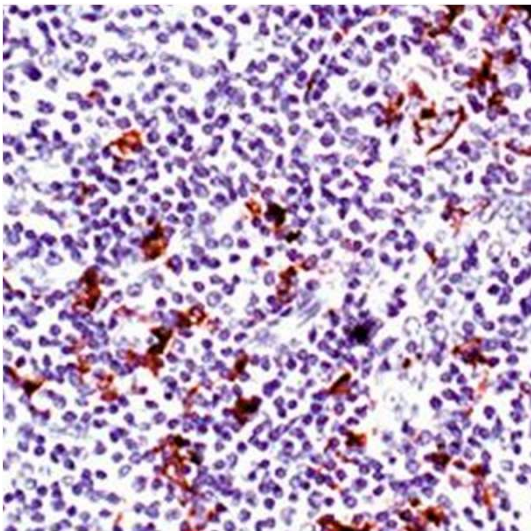
Means without a common letter differ, $P < 0.05$.

(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?

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- 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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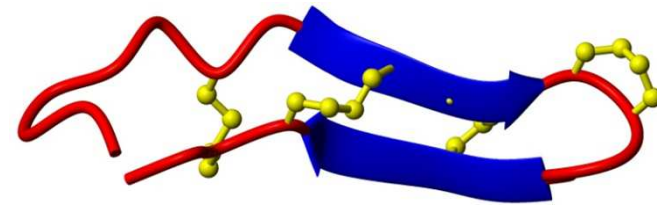
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Maybe, but:

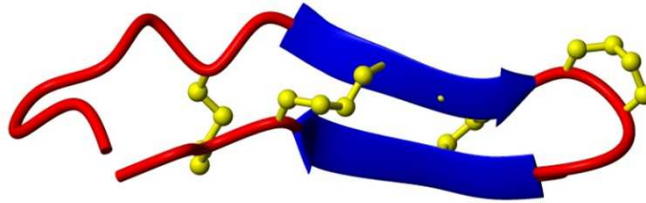
- Low serum iron in obese U.S. adults not predicted by lower iron intake or iron bioavailability (Menzie et al., 2008)
- Higher requirements, larger blood volume?
- **Reduced absorption/increased iron sequestration due to low-grade adiposity-related inflammation?**

Inflammation in obesity

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



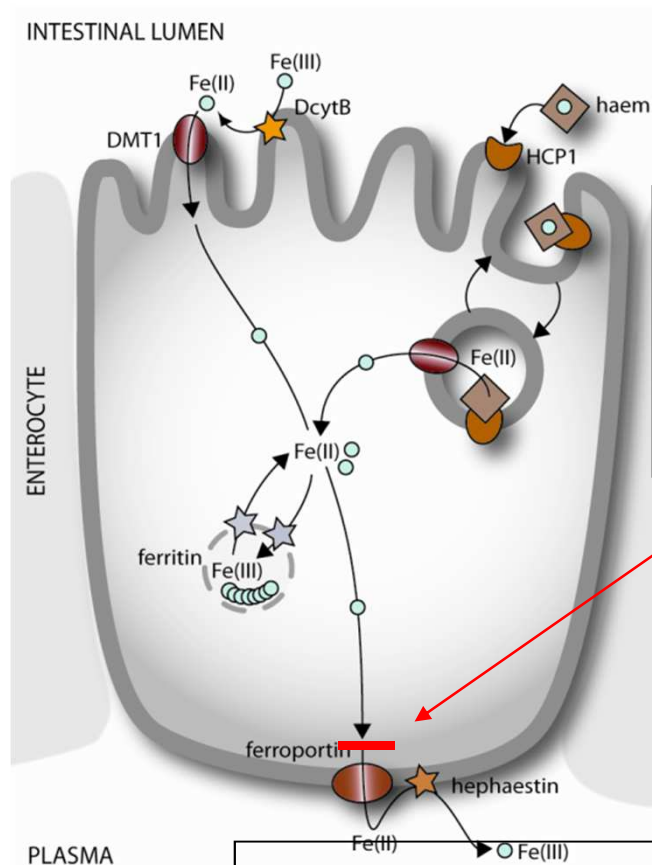
Hepcidin



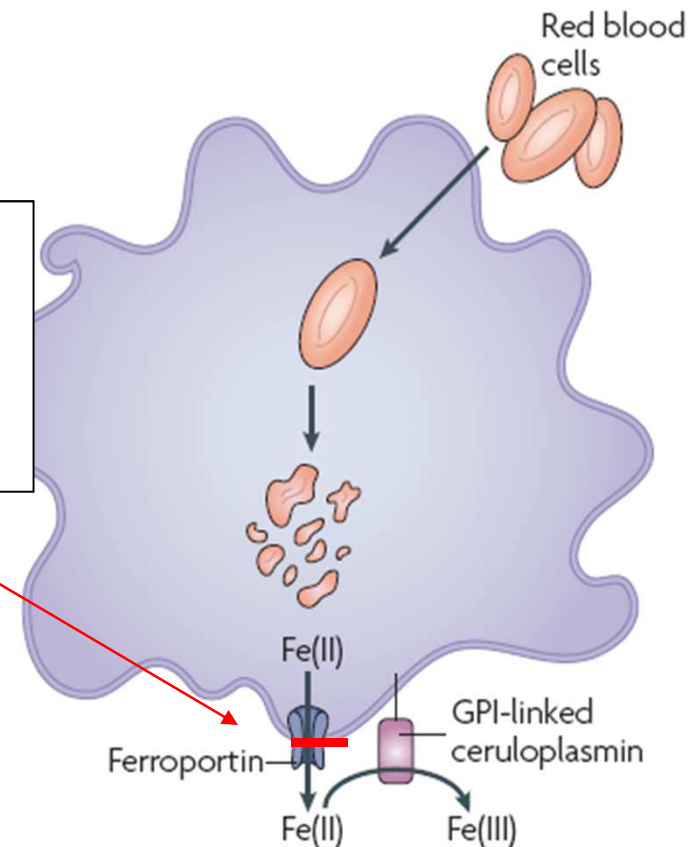
- Key regulator of body iron metabolism
 - reduces intestinal iron absorption and iron release from macrophages and liver
 - Produced mainly by liver, but also small amounts by the stromal fraction of adipose tissue

In obesity : ↑ IL6, CRP, leptin

Enterocyte



Macrophage



Hepcidin ↑ from hepatocytes and adipose tissue

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. – max.) 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 erythropoiesis

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

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

20% of overweight show Fe deficient erythropoiesis

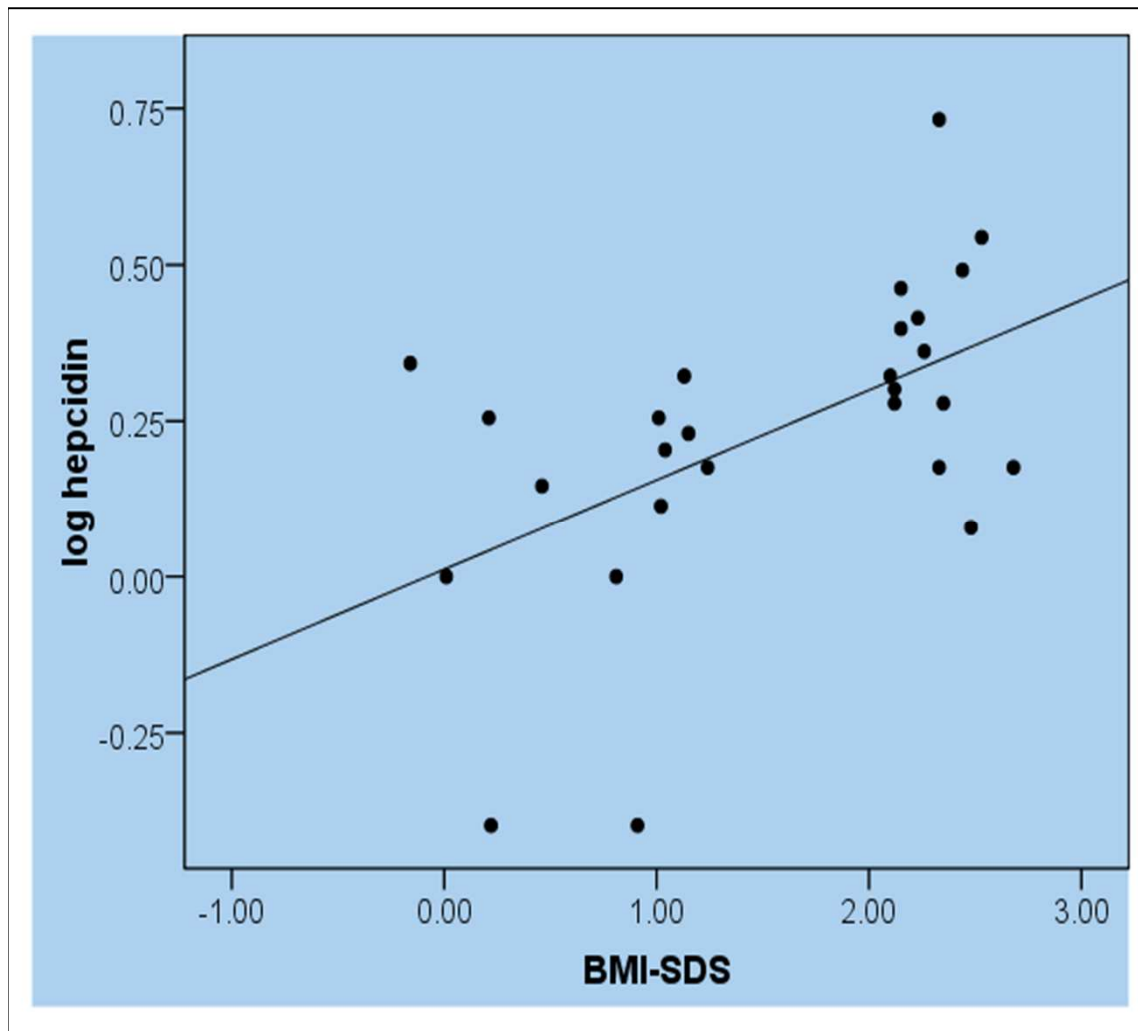
Elevated hepcidin and inflammation

- 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 \pm 2.8	7.0 \pm 1.1
Normal weight	10.0 \pm 2.6	6.7 \pm 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

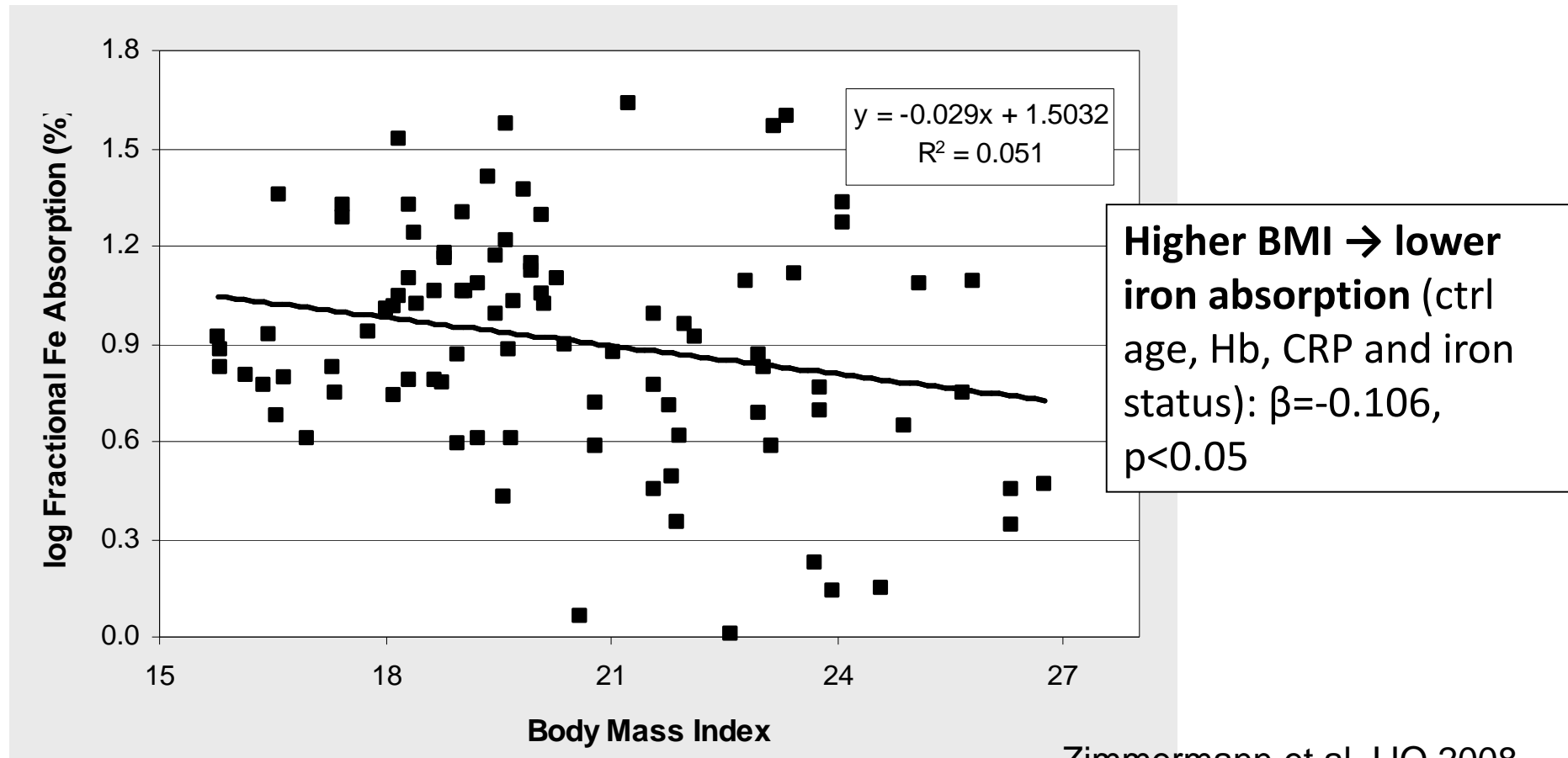
Cepeda Lopez et al, AJCN 2010

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



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

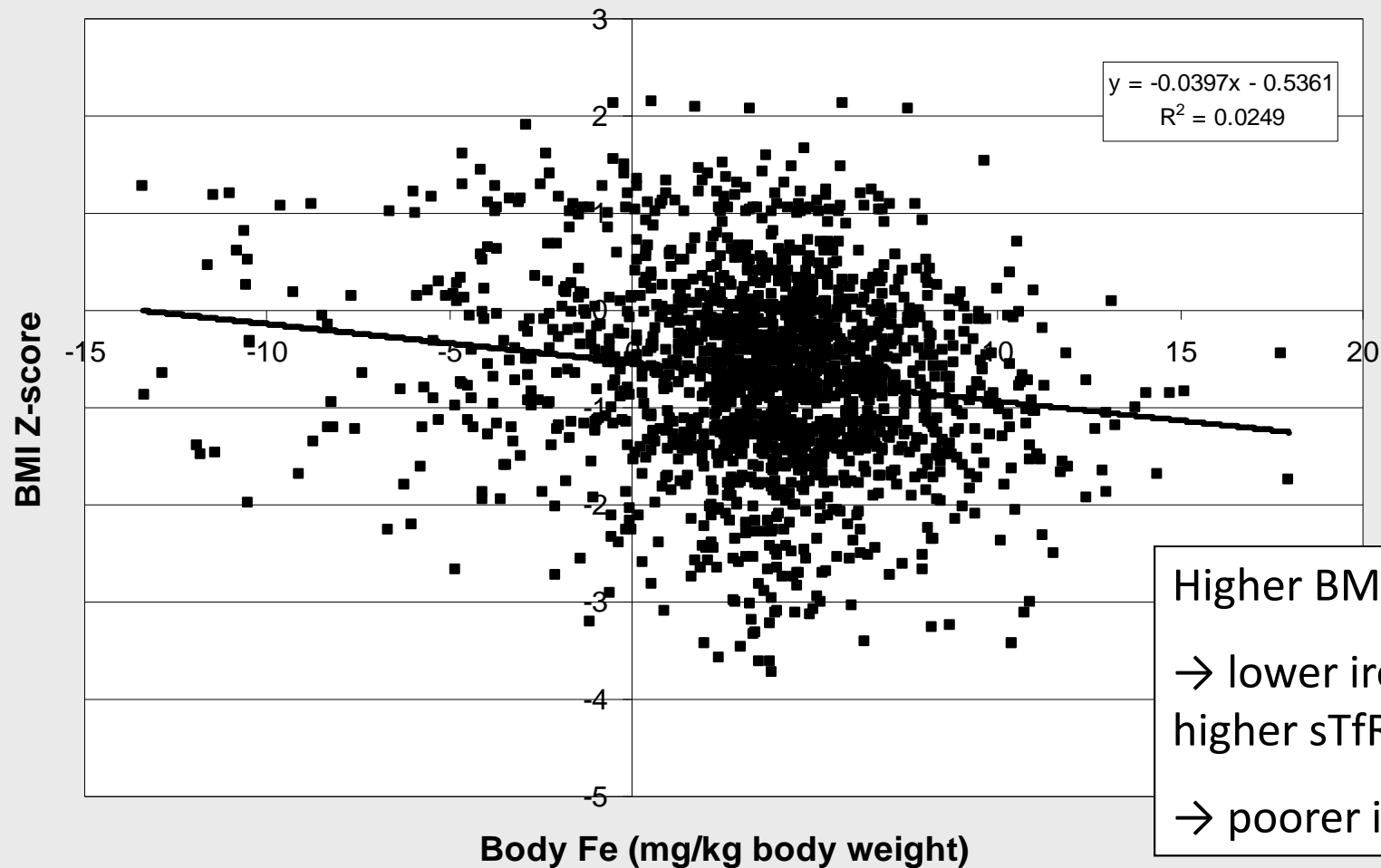
Higher BMI → higher CRP concentration
($r=0.227$, $p<0.001$)

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

Iron fortification in overweight children

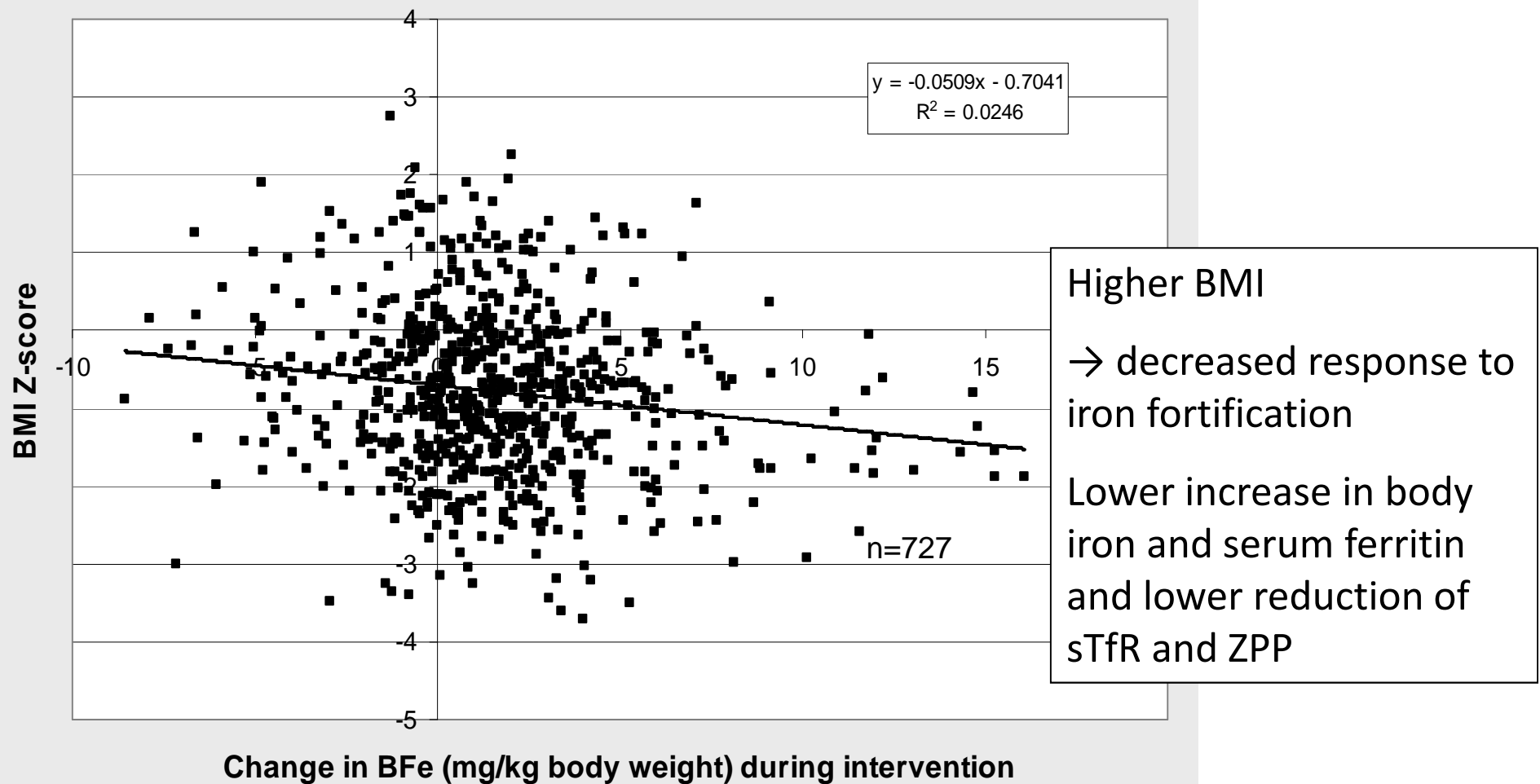
- 4 efficacy trials of iron fortification in children (5-16 y) from Morocco and India (n=1688)
- Iron fortification with encapsulated ferrous sulfate/fumarate or micronized FePP
- Hb, SF, sTfR, ZPP measured at baseline and after 7–9 months
- prevalence of overweight was 6%; prevalence of iron deficiency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

Children with higher BMI have lower iron stores



Zimmermann et al. IJO 2008

Children with higher BMI have a blunted response to iron fortification



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

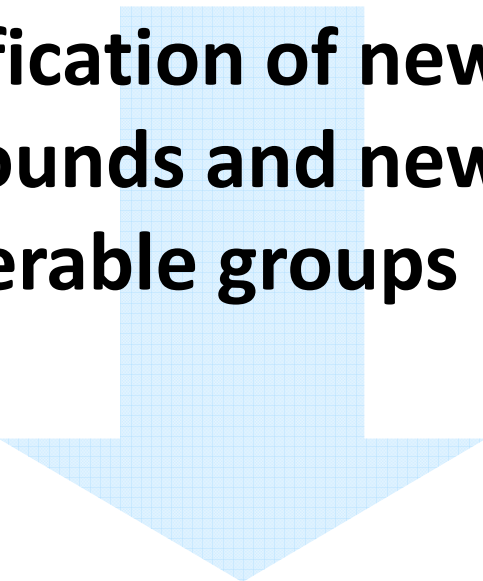
Perspectives

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

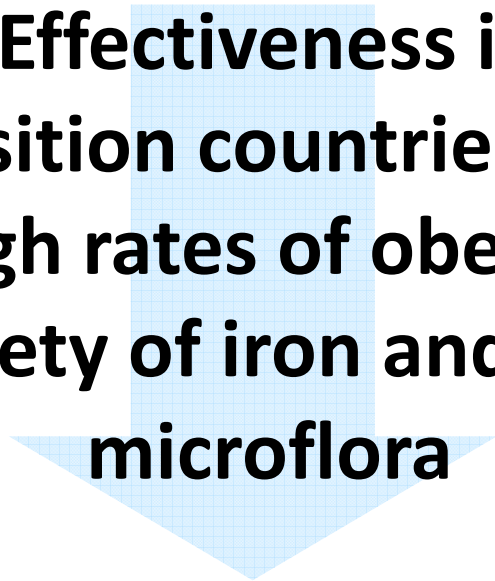
Interactions of the 'double burden' of malnutrition may have adverse consequences

**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

