Findings from a 6-month efficacy trial in Maharashtra involving iron-biofortified pearl millet

Impact on iron status and physical performance

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Background- the problem

- Globally, 1 in 3 persons are estimated to be anemic (WHO 2014)
- ~50% of anemia is caused by iron deficiency (Kassebaum et al. 2014)

"Iron deficiency affects more people than any other condition, constituting a public health condition of epidemic proportions."

-World Health Organization, 2014

Anemia & iron deficiency in adolescents

Why is iron deficiency a problem in this group?

- Rapid pubertal growth: lean body mass in males, menarche in females
- Iron requirement doubles from 7-10 y to 11-14 y (WHO 2011)
- Poor diet: > 70% of Indian adolescents get < 50% of RDA for iron (NNMB 2001)

Indian national survey of anemia (ICMR 2010):

- Girls, 12-14 y: 68.7%
- Girls, 15-19 y: 55.8%
- Boys, 15-19 y: 30.2%

Background- potential solutions

Proposed solutions for alleviating the global burden of iron deficiency:

- Supplementation
- Commercial food fortification
- Home fortification- “Sprinkles”
- Dietary diversification/modification
- Biofortification of staple food crops

- Targeted
- Cost-effective
- Sustainable
- Safe

Background- overall biofortification strategy

Do the crops work to improve human health?

Efficacy trials

Provide a scientific basis for scaling up crop delivery

Background- pearl millet intake in India

- In certain regions, PM intake accounts for > 50% of total cereal consumption (Rao et al. 2006).
- At 150-250 g/d, it is a **major source of energy** in school feeding programs in rural Maharashtra.
- Consumed as flatbread (bhakri).

Pearl millet

Bhakri

Morning assembly at study school in Sarole Pathar

Prescreening:
35% anemia
> 50% iron deficiency

Study objectives

To test the efficacy of iron-biofortified PM in secondary school children.

Specifically, to determine the effect of consuming iron-biofortified PM on:

- Measures of iron status
- Resolution of iron deficiency
- Physical performance

Study design

- Randomized, controlled, masked feeding trial
- Two randomization groups:
  1. Biofortified (ICTP8203): 87 µg Fe/g PM
  2. Control (DG9444): 26 µg Fe/g PM
- Consumed PM over 6 months (140 feeding days) during lunch and dinner meals served at school

Study design

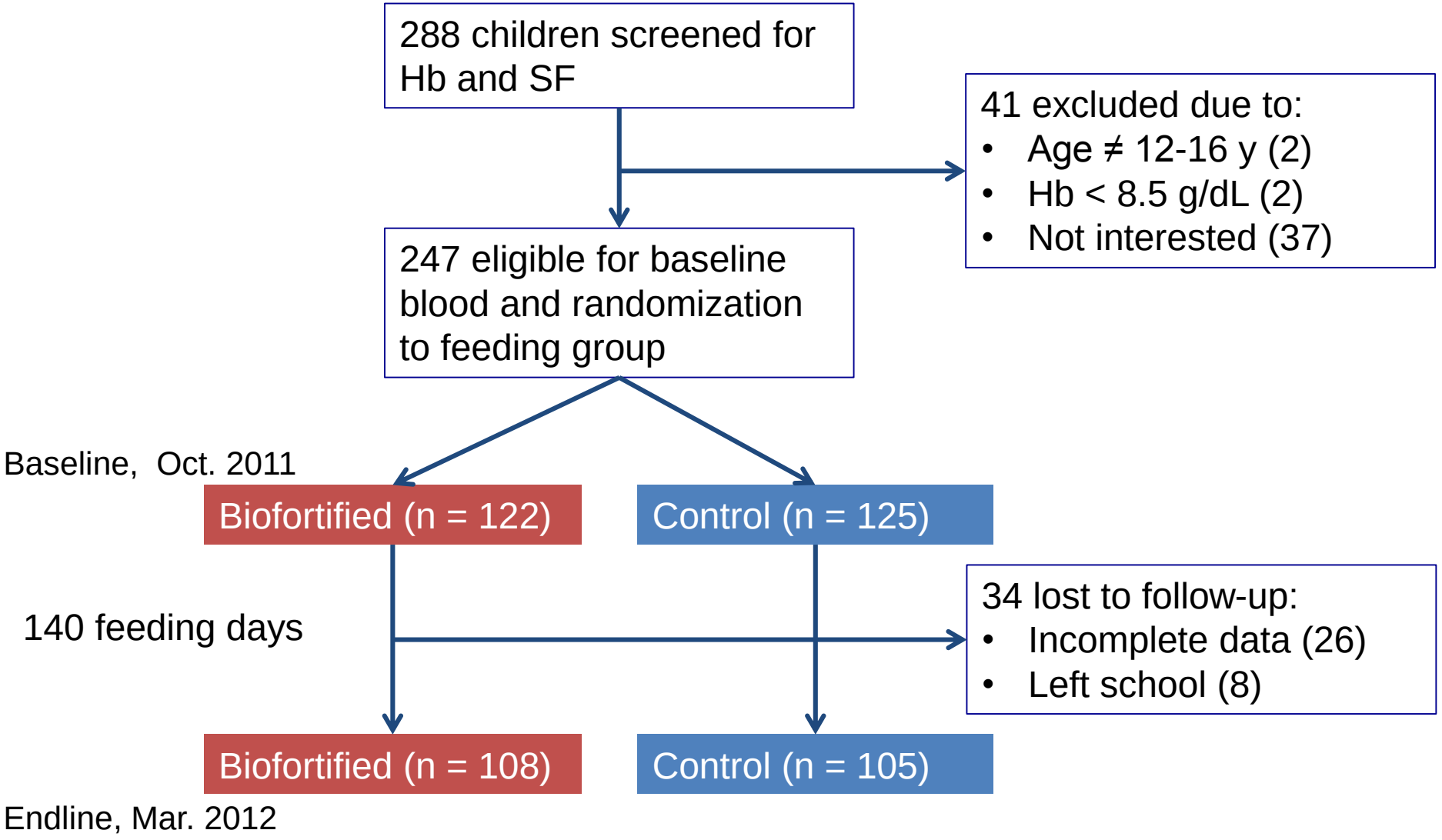
After 4 months:

- Control PM was exhausted, replaced with JKBH778: 51 µg Fe/g PM
- Shev, a savory snack made from PM flour, was introduced

Combined effect:
Control group received more Fe in last 2 months vs. first 4 months

Bag of shev

Sample selection and participant flow



Milling and storage of pearl millet

- Grain stored in air-conditioned warehouse and milled using separate machines
- Flour stored in stainless steel containers and delivered to hostels every 2-3 d

Stainless steel containers

Equipment used to mill pearl millet

Bags of grain in storage

Preparation of bhakri

- Bhakri prepared in central kitchen of school
- Each woman assigned to make only 1 type of bhakri (biofortified OR control)
- 3 daily weighings: flour women took, dough, prepared bhakri
- Preparation supervised by asst. field coordinator and one RA for each type of bhakri

Cook preparing bhakri in kitchen

Daily recording of intake

- Bhakri consumed ad libitum
- Group of 16-20 children assigned to 1 RA for monitoring meal
- Consumption for each child was recorded at every meal to the

Study subject consuming bhakri

RA handing out bhakri at lunch meal

Hematological measurements

Blood samples were obtained at 0, 4, 6 months

- Hemoglobin (Hb)
- Serum ferritin (SF)
- Serum transferrin receptor (sTfR)
- Body iron (TBI) (Cook et al. 2003)

Iron status

$$TBI\ (mg/kg) = -[\log10\ (sTfR / SF)] - 2.8229] / 0.1207$$

- C-reactive protein (CRP)
- α1-acid glycoprotein (AGP)

Inflammatory status

- SF adjusted for inflammation (Thurnham et al. 2010)

Baseline characteristics by treatment group

	Biofortified (n = 122) *Median (IQR) or %*	**Control (n = 124)** *Median (IQR) or %*
Sex (Female)	38.5%	39.5%
Age (years)	14.0 (12.1, 14.1)	14.0 (13.0, 15.0)
HAZ < -2	40.0%	38.1%
BMIZ < -2	40.0%	41.0%
CRP > 5 mg/L	3.4%	0.0%
AGP > 1 g/L	6.8%	3.4%

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Hemoglobin (g/dL)	12.5 (11.9, 13.2)	12.5 (11.8, 13.1)
< 12	28.2%	28.2%
Ferritin (ng/mL)	16.3 (10.8, 24.7)	16.4 (10.6, 24.4)
< 15	45.3%	41.0%
Transferrin receptor (mg/L)	1.5 (1.3, 1.8)	1.5 (1.3, 1.7)
> 8.3	11.1%	9.4%
Body iron < 0 mg/kg	21.4%	21.4%

Iron intake from bhakri + shev, g/d

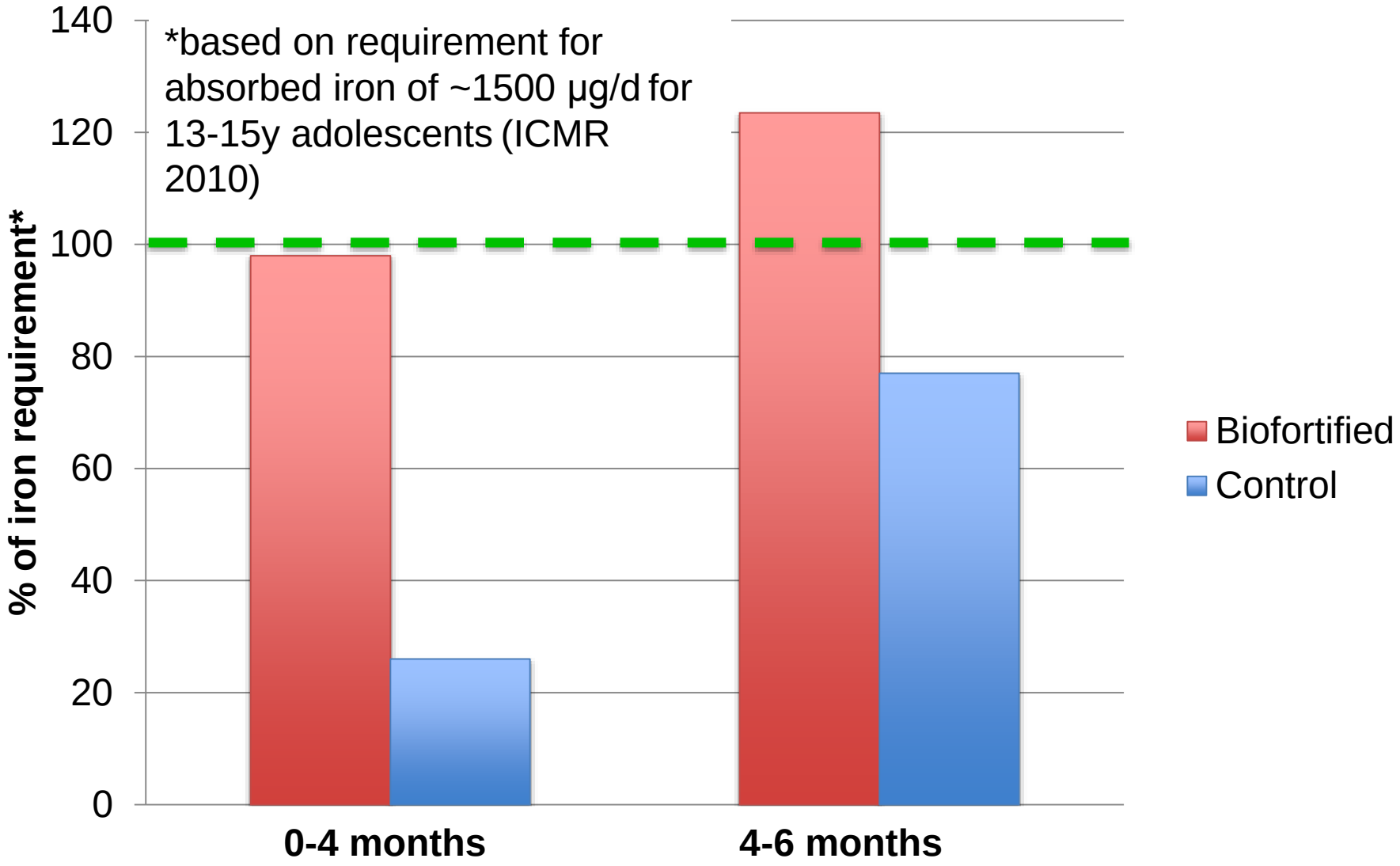
	Biofortified (n = 122) *Median (IQR)*	**Control (n = 124)** *Median (IQR)*
Total	22.0 (18.4, 25.2)	9.1 (7.7, 10.3)
Baseline to 4 months	19.6 (16.0, 24.3)	5.2 (4.4, 6.1)
4 to 6 months	24.7 (22.2, 27.3)	15.4 (13.2, 18.0)

Fractional iron absorption in iron-deficient Beninese women (Cercamondi et al. 2013):

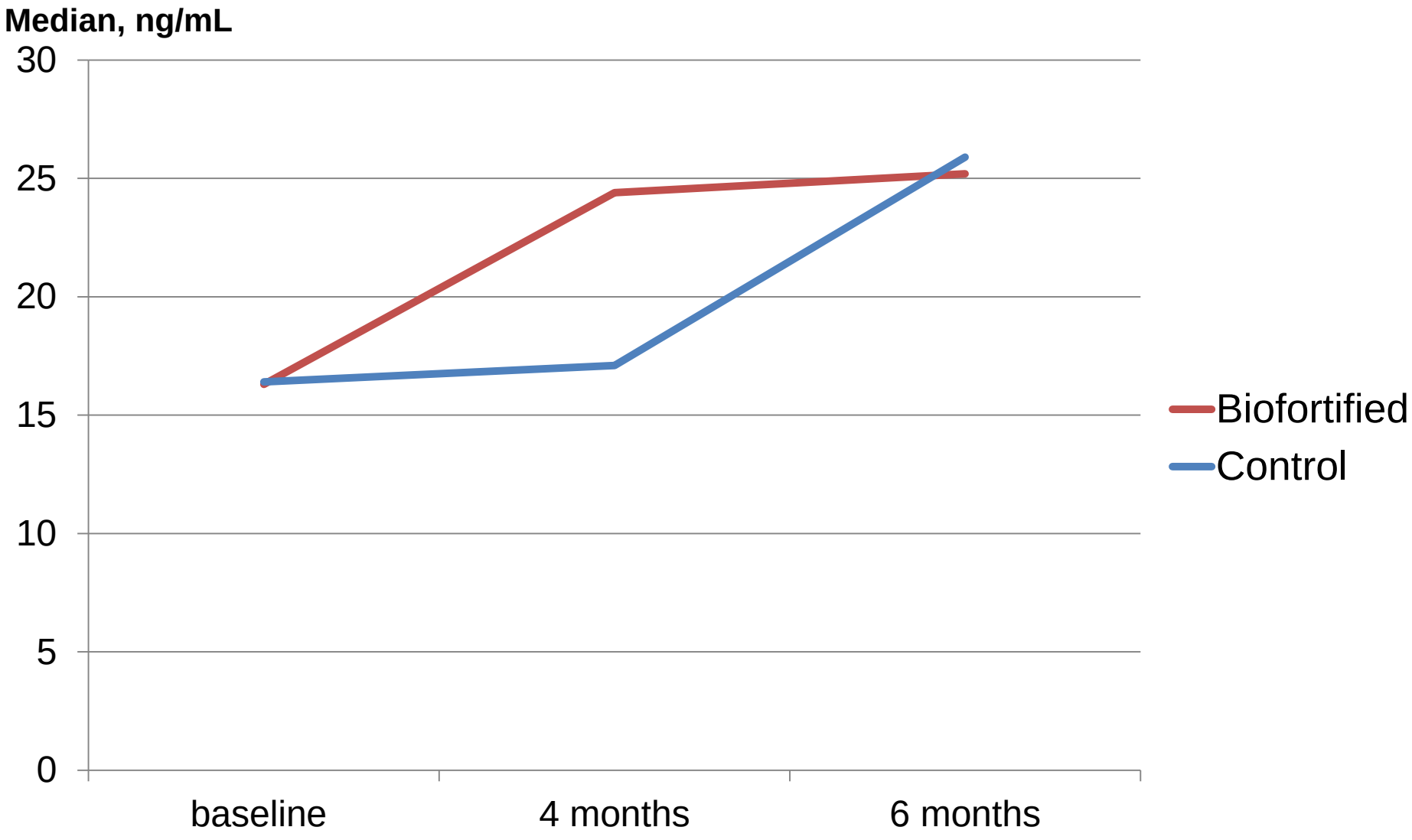
- Biofortified (ICTP8203): 7.5%
- Control (DG9444): 7.5%

Calculate how much iron is absorbed and % of requirement met

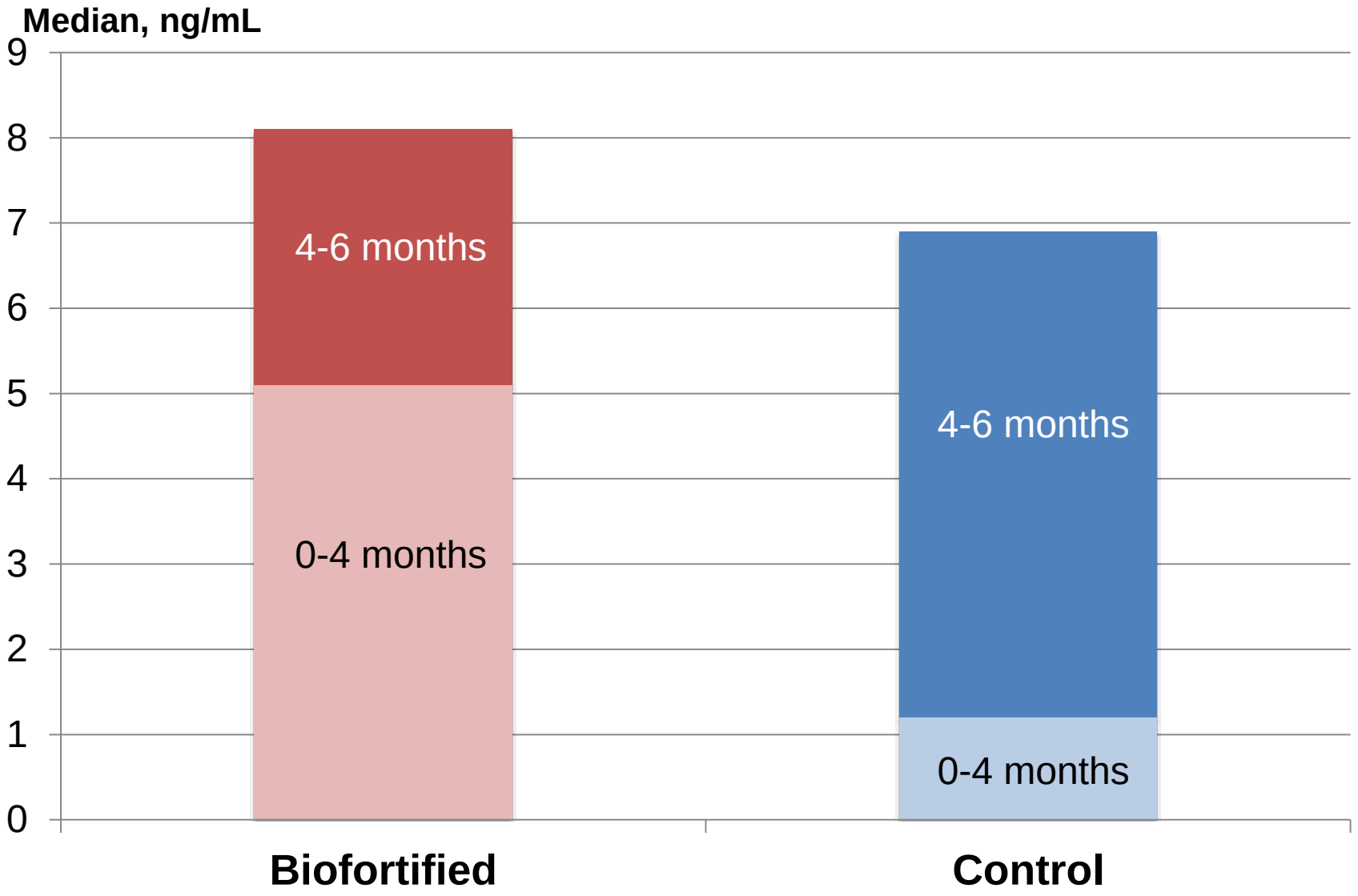
Iron requirements were met by biofortified pearl millet



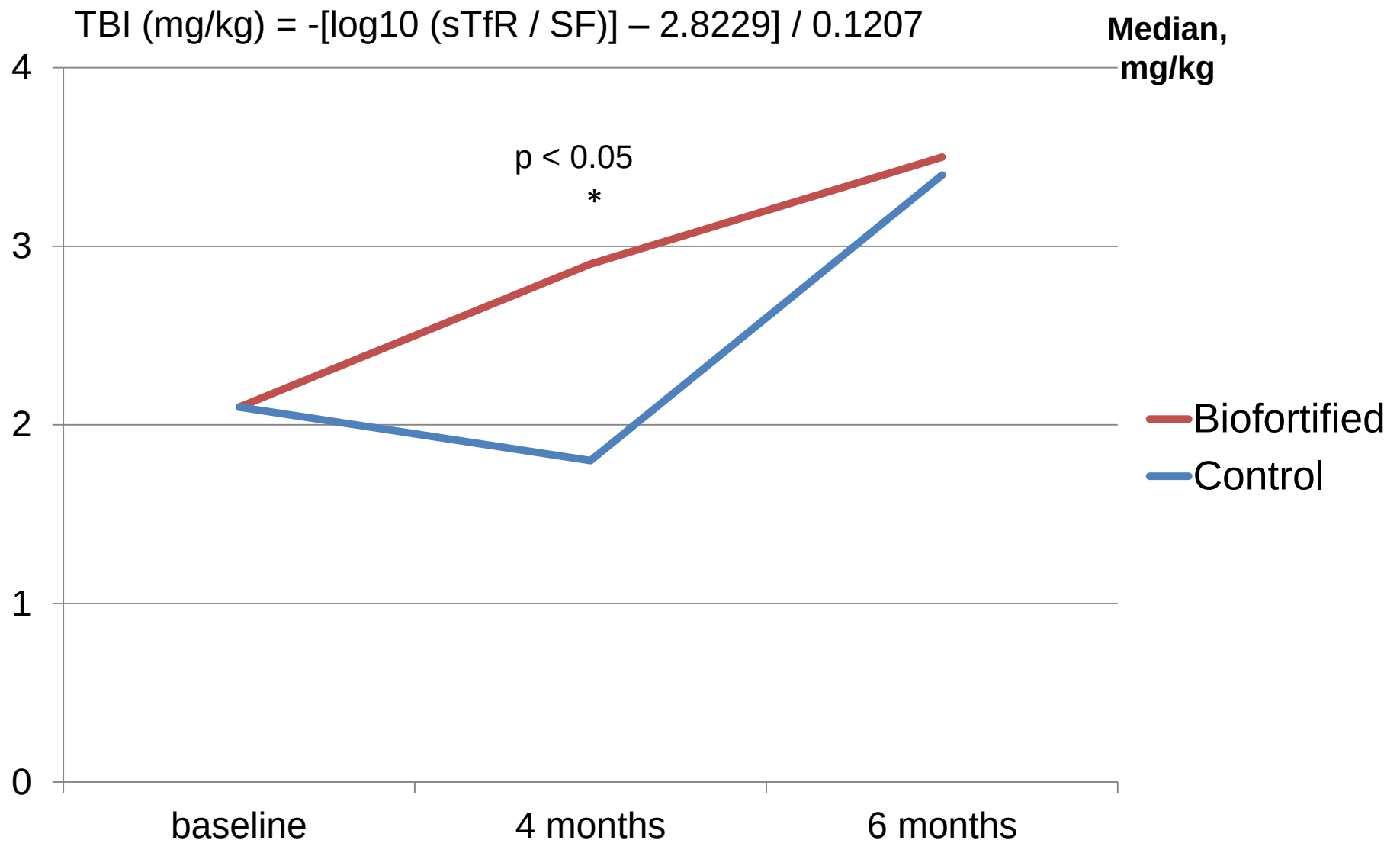
Effect on serum ferritin (SF)



Effect on change in serum ferritin (SF)

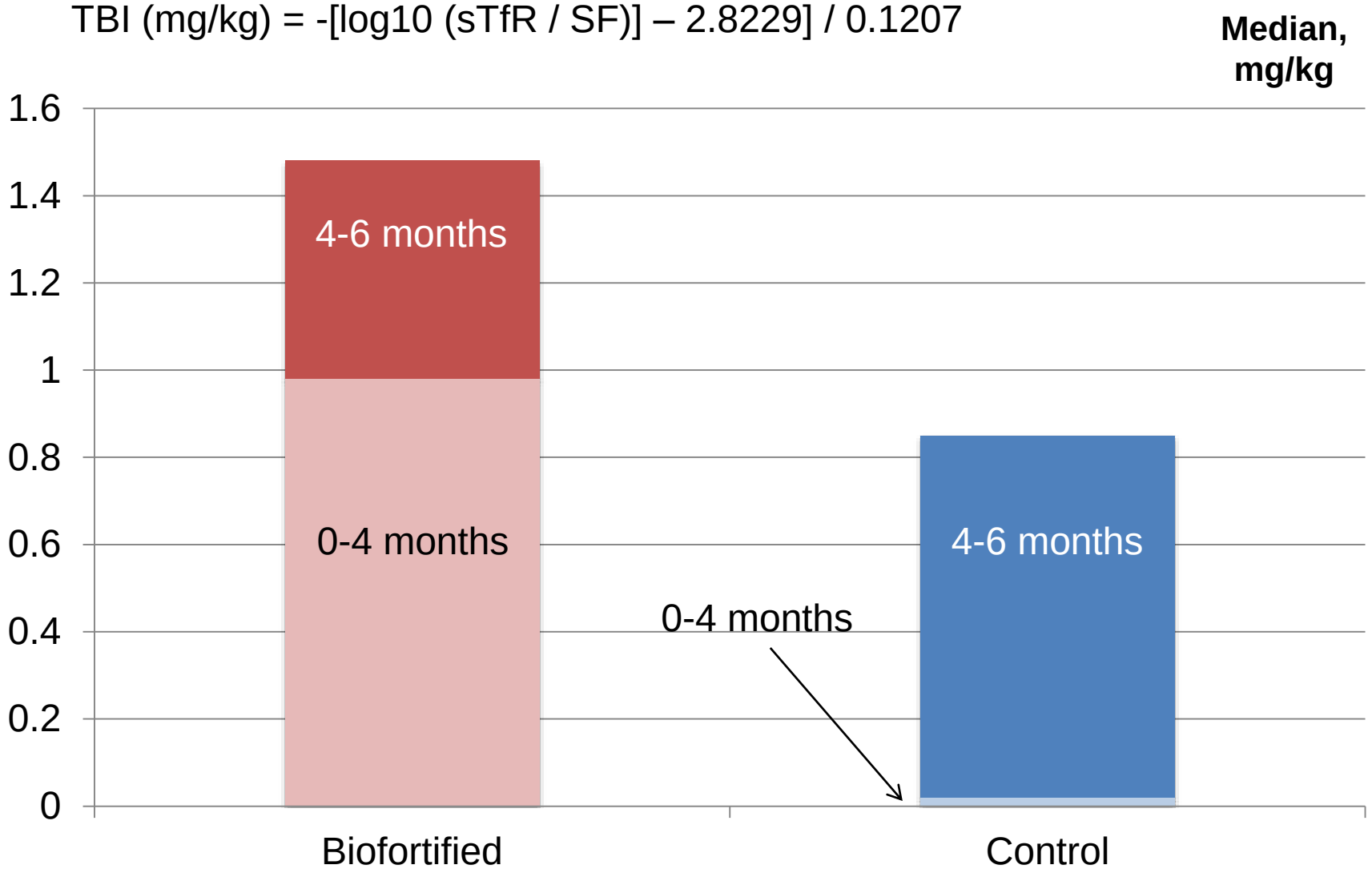


Effect on total body iron (TBI)

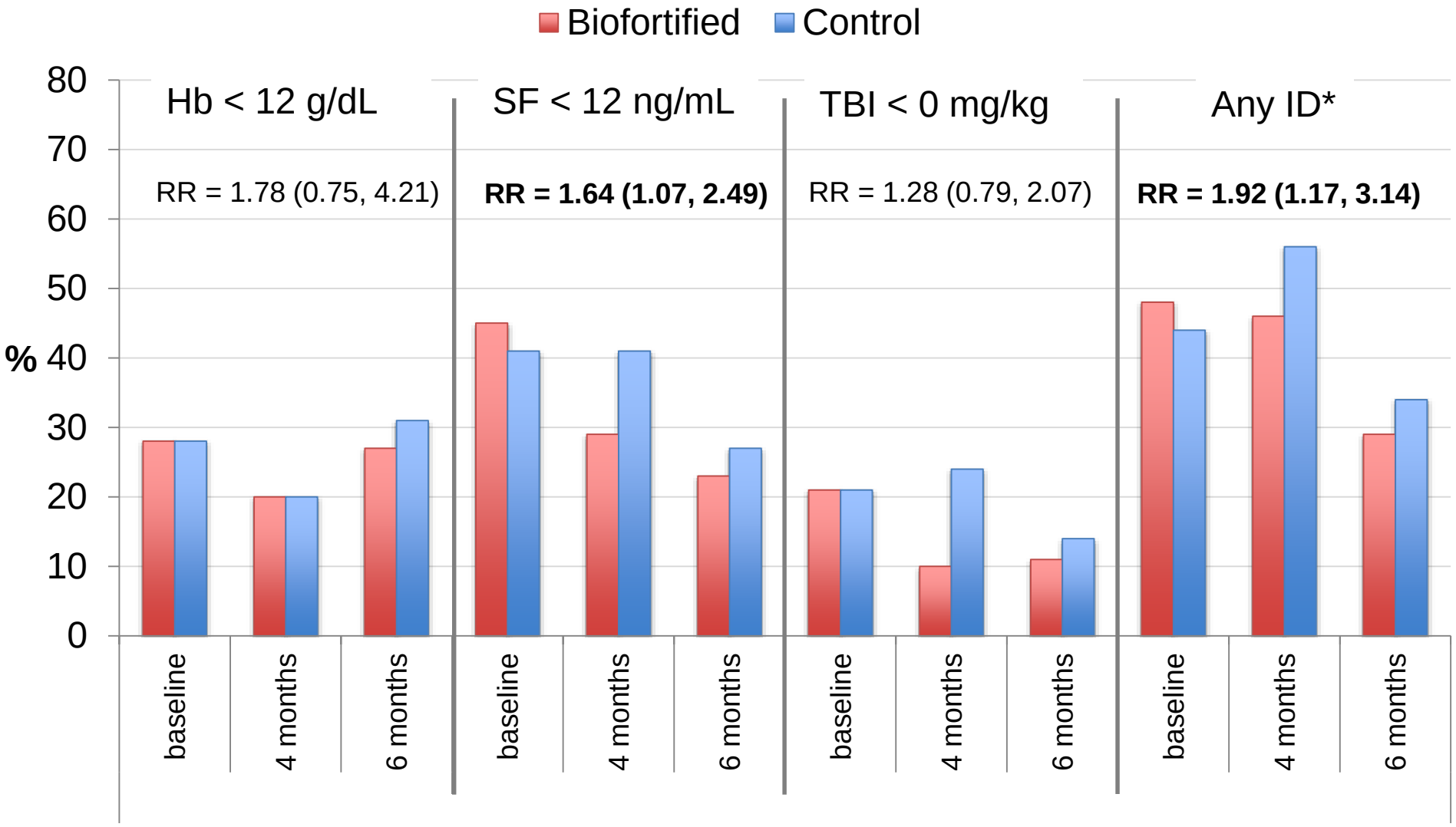


Effect on change in total body iron (TBI)

TBI (mg/kg) = -[log10 (sTfR / SF)] – 2.8229] / 0.1207

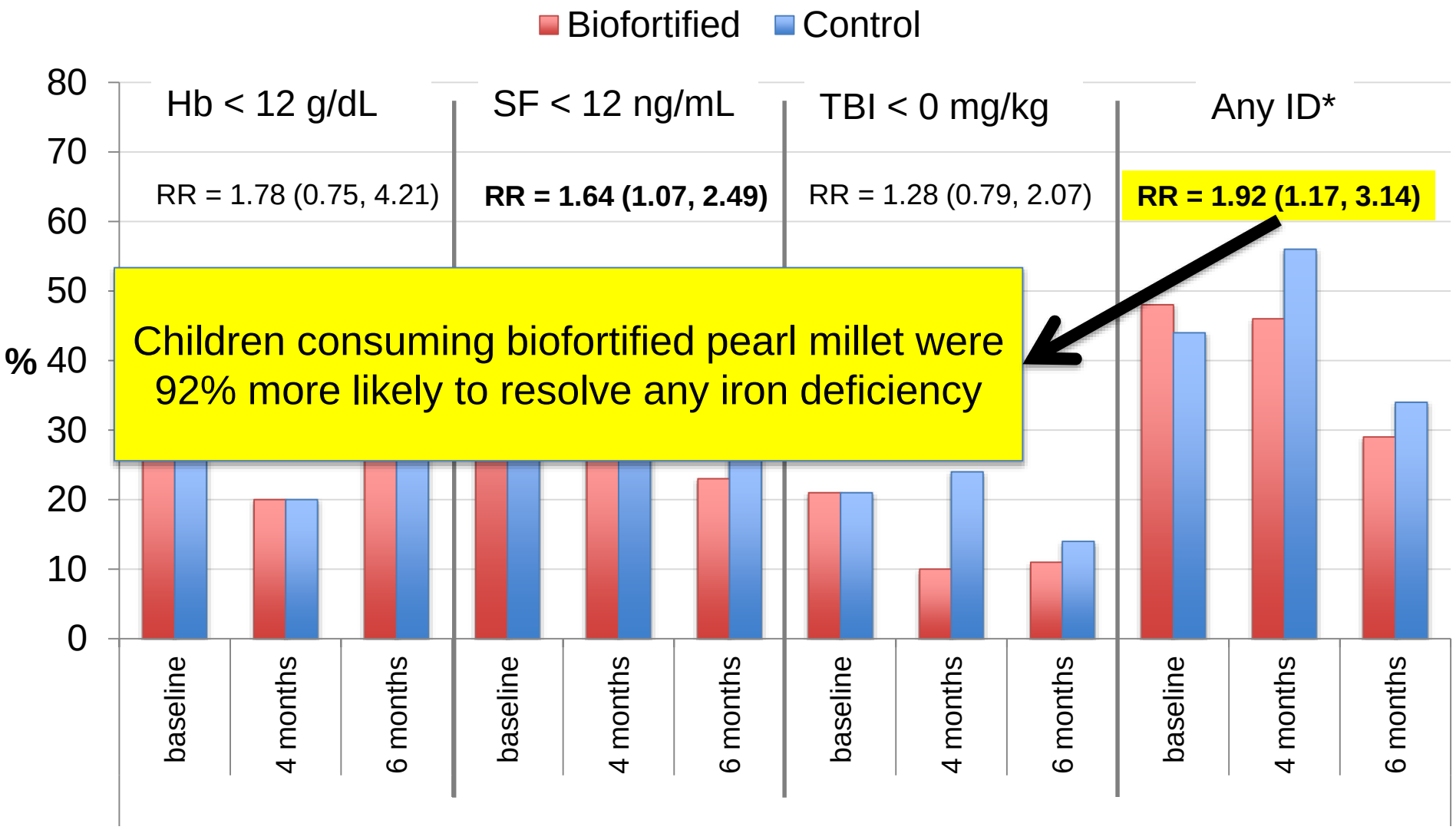


Effect on prevalence of anemia and iron deficiency



*SF < 12 ng/mL or sTfR > 8.3 mg/L or TBI < 0 mg/kg

Effect on prevalence of anemia and iron deficiency



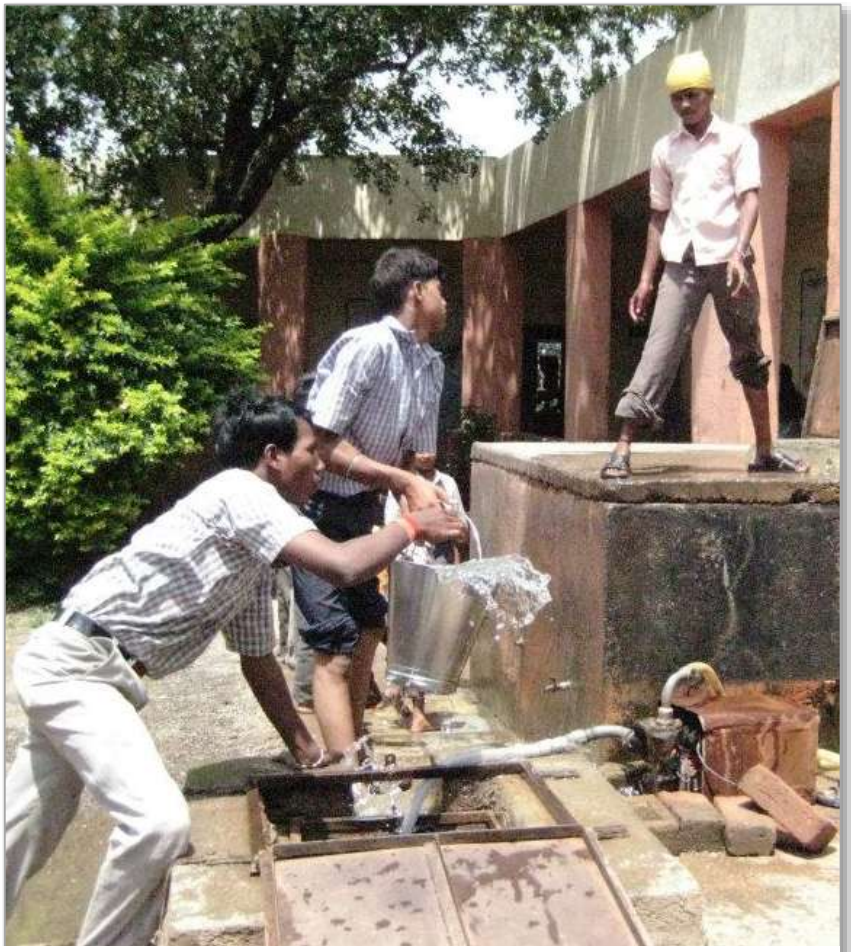
*SF < 12 ng/mL or sTfR > 8.3 mg/L or TBI < 0 mg/kg

How should efficacy of biofortified crops be assessed?

- Efficacy is typically assessed in terms of impact on biomarkers
- Benefits of consuming biofortified crops may extend beyond improvements in ferritin or body iron
- Can biofortified crops improve quality of life?
- Demonstration of an effect of biofortified crops on functional outcomes will allow for a comprehensive assessment of cost-benefit

Can iron-biofortified PM benefit physical performance?

- Laboratory studies have shown that ID compromises physical performance (Haas & Brownlie 2001)
- ID has been linked to fatigue, impaired aerobic capacity, and low work productivity
- Iron supplementation at therapeutic doses has been shown to improve measures of physical performance
- It is unknown whether low dose iron via consumption of biofortified crops can have similar benefits



Boys fetching water at study site

Physical performance- objective & sampling technique

Objective: To determine whether consumption of iron-biofortified pearl millet for 6 months can improve physical performance in Indian school children

Sample selection: subsample (n=135) of subjects in feeding trial, selected for low iron status

Physical performance measures were performed at 0 and 6 months, before and after feeding trial

Physical performance- measures

1. Aerobic capacity (VO_2max)
   - Assesses maximal oxygen uptake at peak exertion on a physical test
   - Measures heart rate, O_2 and CO_2 at progressive workloads on a cycle ergometer
   - Primary determinant is Hb

Study subject on cycle ergometer

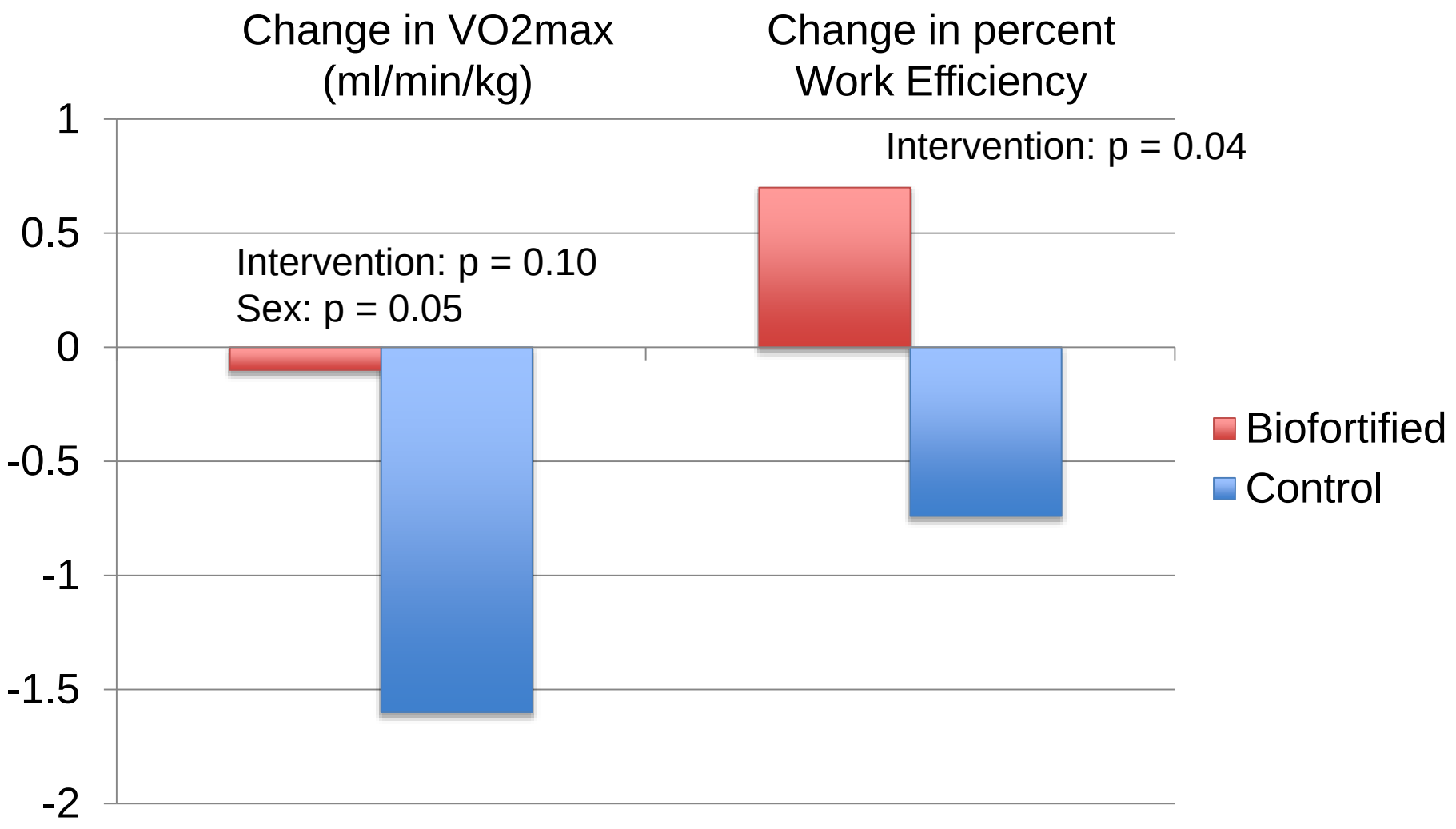
Physical performance- measures

2. Work efficiency

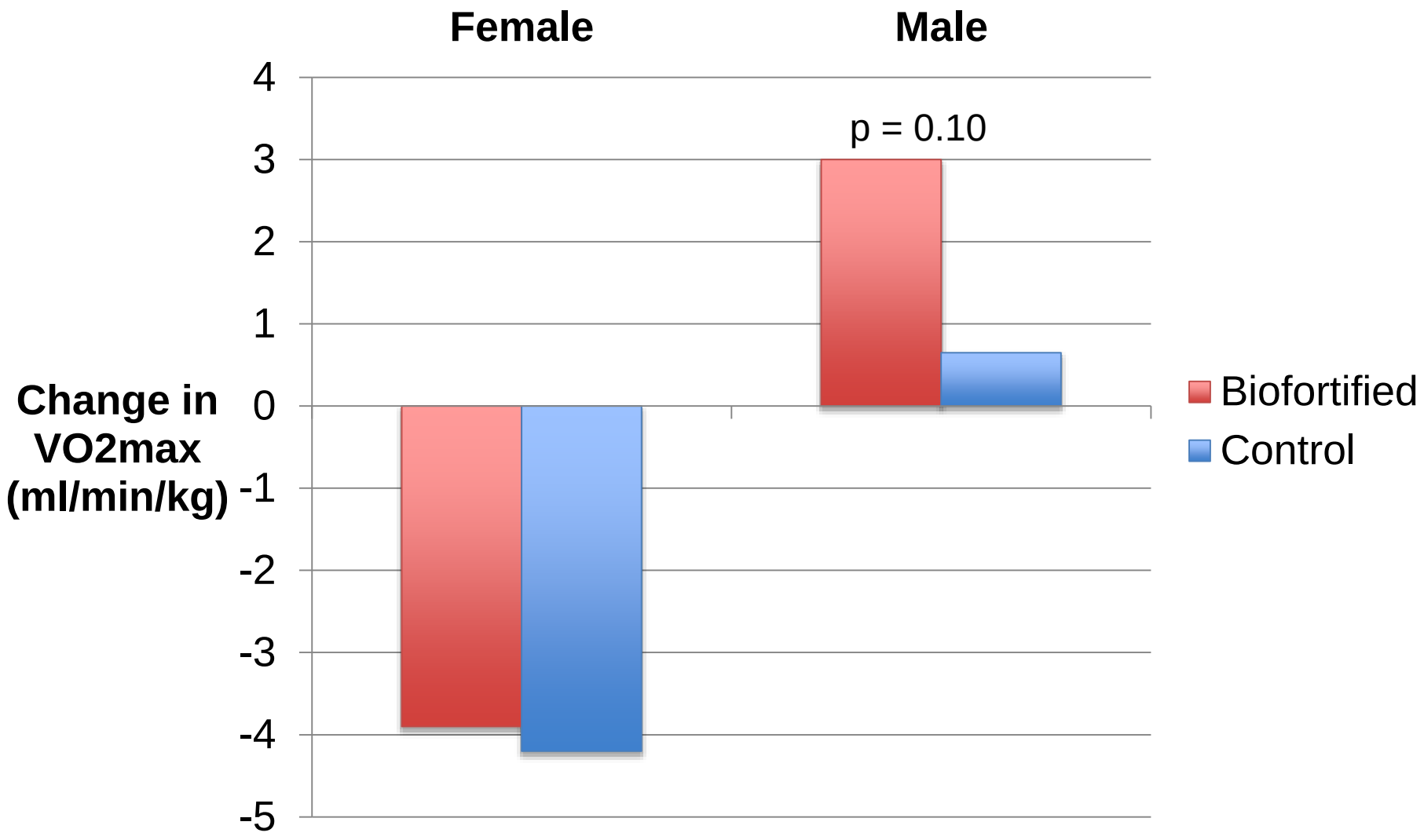
- Amount of physiological energy required to perform a given amount of physical work
- Uses ratio of energy expended (from O_2 and CO_2) to work performed (watts output on ergometer)
- More sensitive to tissue oxidative capacity (ferritin)

Study subject on cycle ergometer

Effect of biofortified pearl millet on physical performance



Sex differences in change in VO_2max



Summary of findings

In this randomized efficacy trial involving consumption of iron-biofortified vs. control pearl millet by 247 Indian school children ages 12-16 y:

- Baseline anemia (28% Hb < 12 g/dL) and iron deficiency (43% SF < 15 ng/mL) were present

- Iron-biofortified pearl millet:
  - improved iron status by 4 months
  - resolved iron deficiency by 6 months, with greater resolution among those who were more deficient at baseline
  - improved physical work efficiency

These findings suggest that iron-biofortification of pearl millet is an efficacious approach, and should be evaluated for effectiveness.

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