BURGERSTEIN FOUNDATION
MICRONUTRIENTS FOR HEALTH

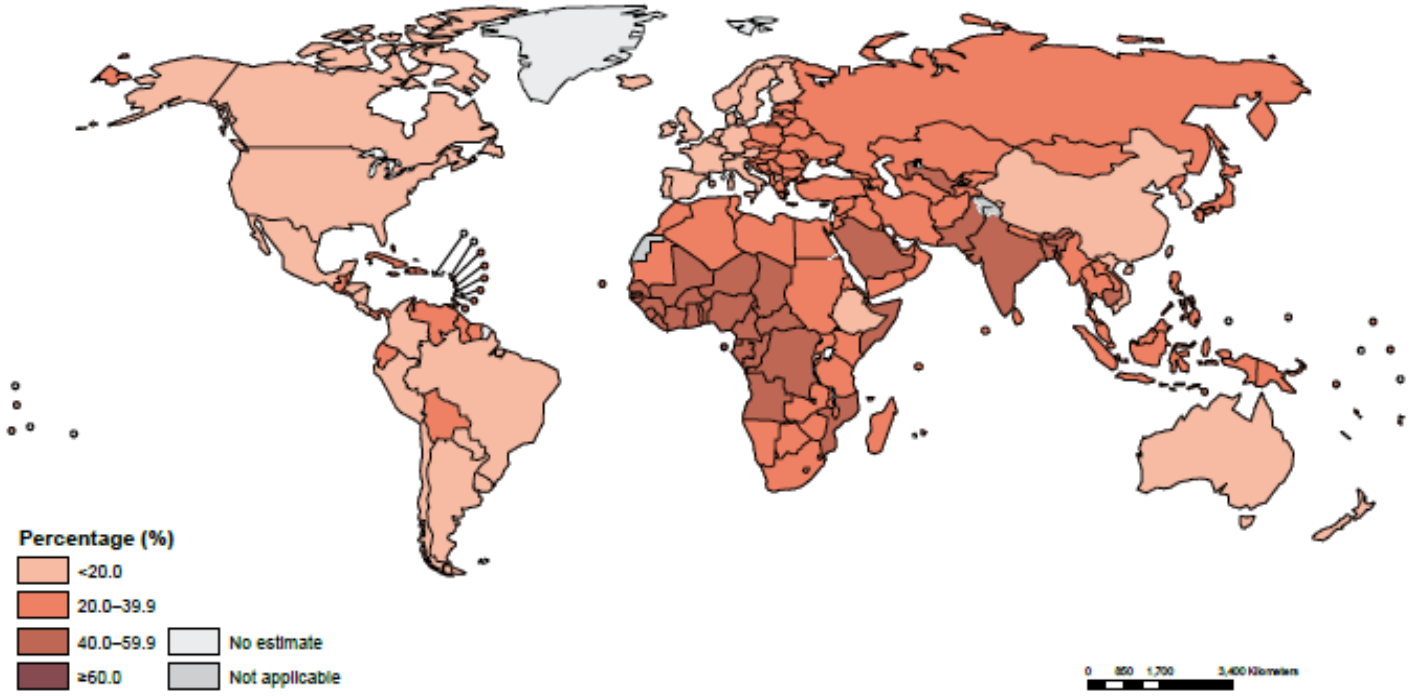
Ärztekongress 2023
Mikronährstoffe in der Medizin

Oral iron every second day?

What is the best way to take oral iron supplements?

Prof. Dr.med. Michael Zimmermann
Department of Health Sciences and Technology, ETH Zurich, Switzerland
University of Oxford, John Radcliffe Hospital, Oxford, UK

Iron deficiency (ID) and anemia are major global health problems, affecting >20% of women in most countries



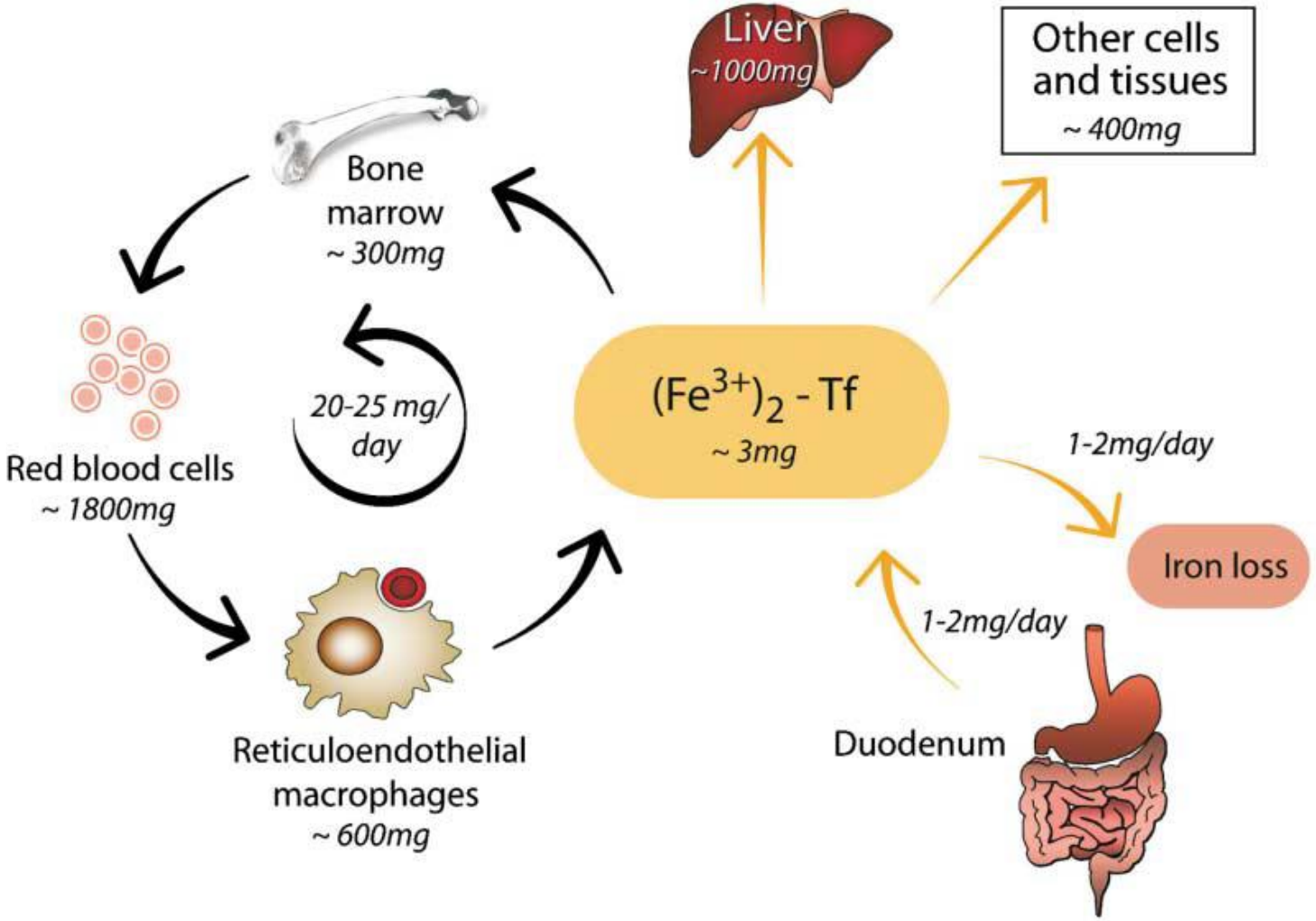
WHO global estimates of the prevalence of anemia in women of reproductive age in 2011
WHO, *The global prevalence of anaemia in 2011*. 2015.

Global Burden of Disease: ID 14th leading cause of disability worldwide

Leading causes 2017	Mean percentage change in number of DALYs, 2007–17	Mean percentage change in age-standardised DALY rate, 2007–17
1 Neonatal disorders	-18·2	-21·9
2 Ischaemic heart disease	17·0	-10·4
3 Stroke	13·6	-12·5
4 Lower respiratory infections	-26·8	-33·6
5 Diarrhoeal diseases	-27·8	-35·5
6 COPD	21·2	-6·3
7 Low back pain	17·3	-2·7
8 Headache disorders	15·3	0·7
9 Diabetes	29·5	1·9
10 Congenital defects	-9·6	-14·8
11 Depressive disorders	14·1	-3·1
12 HIV/AIDS	-53·9	-58·8
13 Malaria	-35·4	-40·2
14 Dietary iron deficiency	-5·0	-14·6
15 Alzheimer's disease	36·1	-0·9

Lancet, 392:1859-922; 2018

200 billion erythrocytes are produced every day, requiring more than $2x10^{15}$ iron atoms *every second*

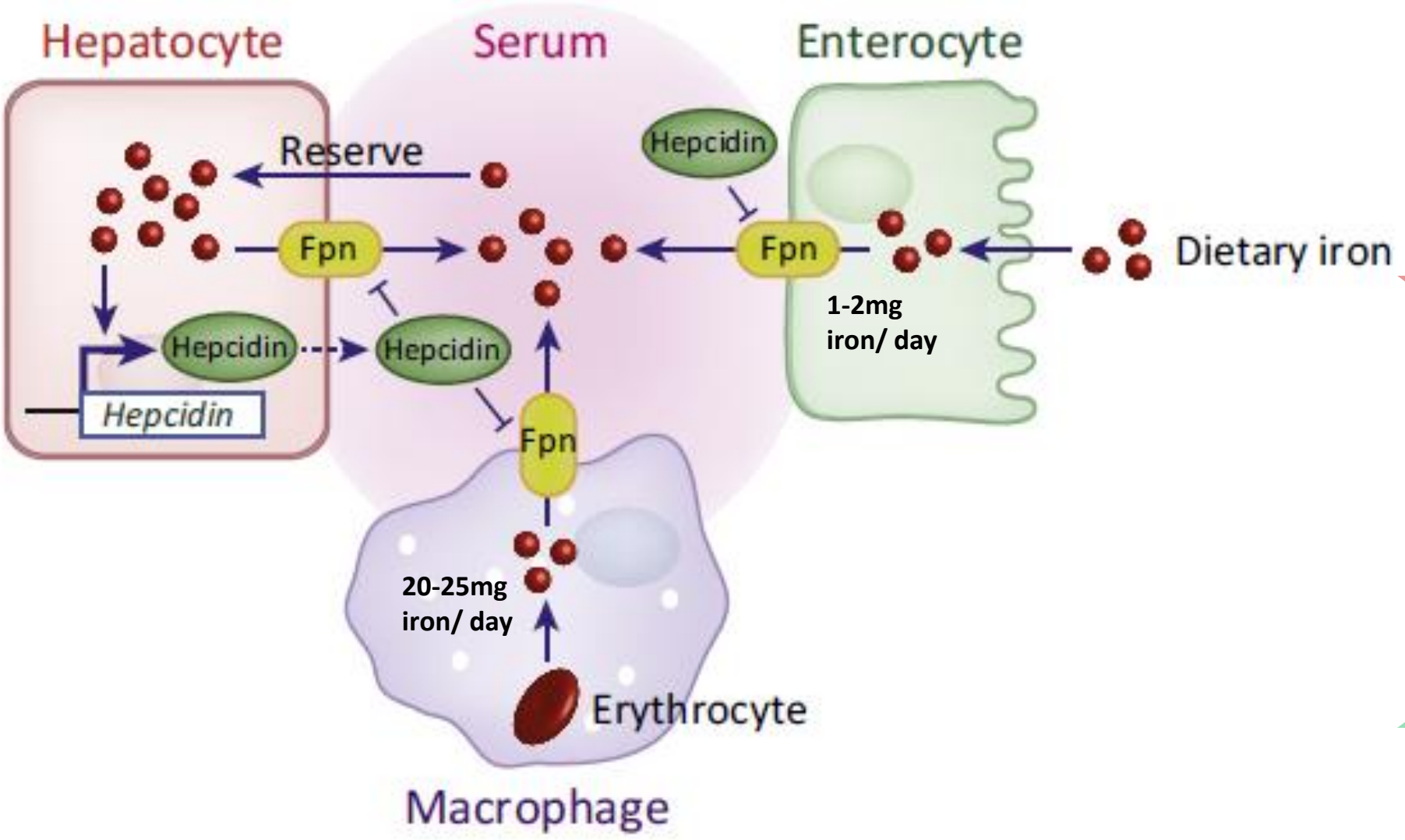


90% of the daily iron needs are generated from **recycling iron** from erythrocytes

The **diet** provides **1-2 mg iron/day**, to compensate for iron losses

Hentze et al., Cell, 2004

Hepcidin: the central regulator of systemic iron homeostasis



High hepcidin

Low iron circulation

Low iron absorption

Low hepcidin

High iron circulation

High iron absorption

Bogdan et al., Trends Biochem Sci, 2016

How should we give oral iron?

- daytime?
- away from meals?
- with a glass of orange juice?

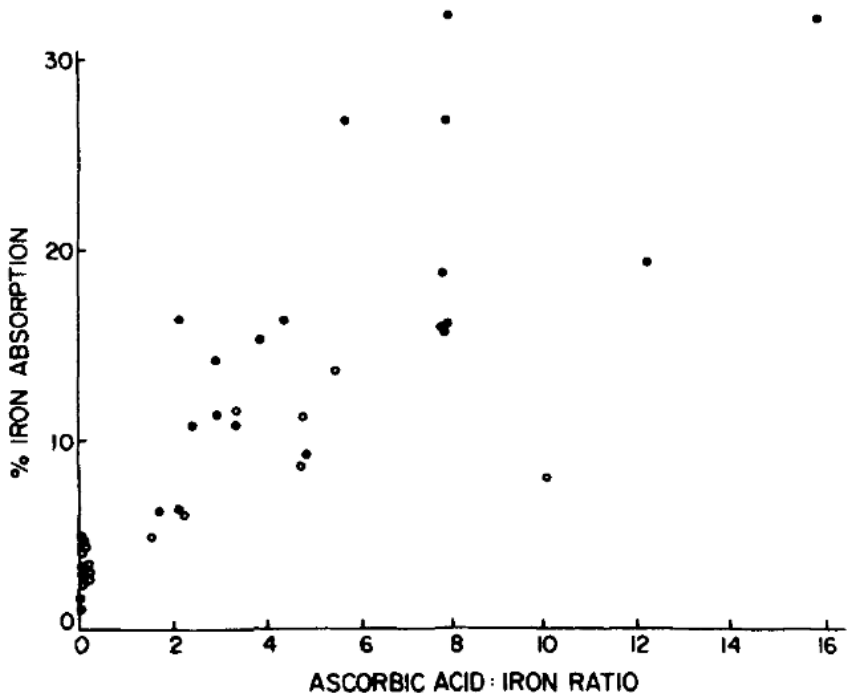
How often should we give oral iron?

- daily?
- every other day?

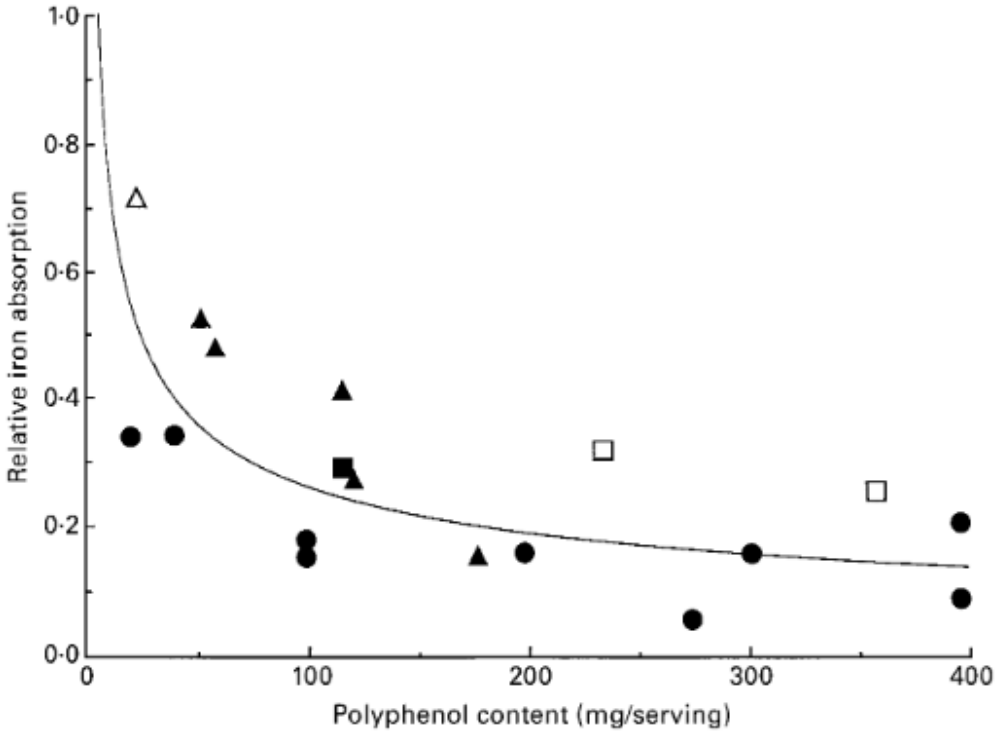
Experts often recommend to take oral iron in the morning away from meals with vitamin C

but this is based on studies with **iron fortificants and food iron**

Vitamin C increases absorption of nonheme iron in foods



Bread and polyphenol-rich drinks reduce iron absorption from foods



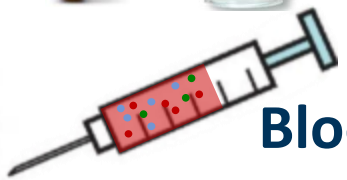
Lynch SR et al., Ann N Y Acad Sci 1980

How do we measure iron absorption?

Stable Isotopes

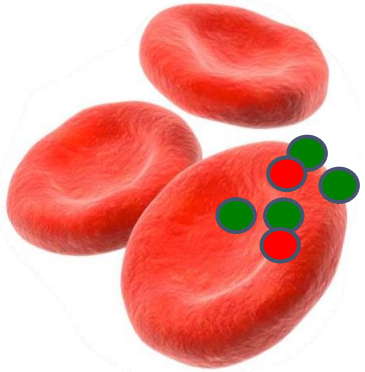
Isotope abundance	
^{54}Fe	5.8%
^{56}Fe	91.8 %
^{57}Fe	2.1 %
^{58}Fe	0.3 %

oral isotope (oral absorption)
labeled (0.5-2 mg **^{57}Fe**)

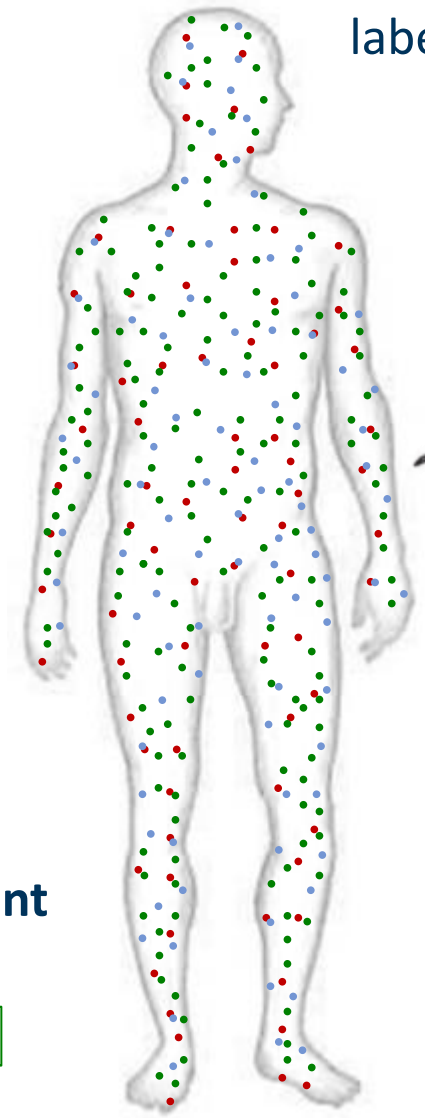


Blood sample after 14 days

Shift in enrichment ratios of the **^{57}Fe** and **^{54}Fe** into the 'natural' **^{56}Fe** in the red blood cells



Naturally abundant in the body (^{56}Fe**)**

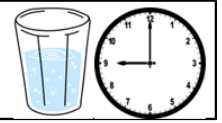


Stable iron isotope study

- Healthy women aged 18 – 45 y
- Non-anemic: Hb > 12 g/dL
- Iron deficient: ferritin ≤ 30 µg/L
- No inflammation: CRP < 5 mg/L

all subjects received 100 mg oral iron in six conditions

n = 35 iron-deficient women enrolled

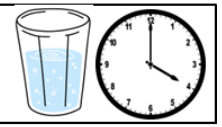
Day 1: 100 mg ^{57}FeFum 

Day 3: 100 mg ^{54}FeFum  80 mg AA

Day 5: 100 mg ^{58}FeFum 

Day 22: 100 mg ^{54}FeFum  500 mg AA

Day 24: 100 mg ^{58}FeFum 

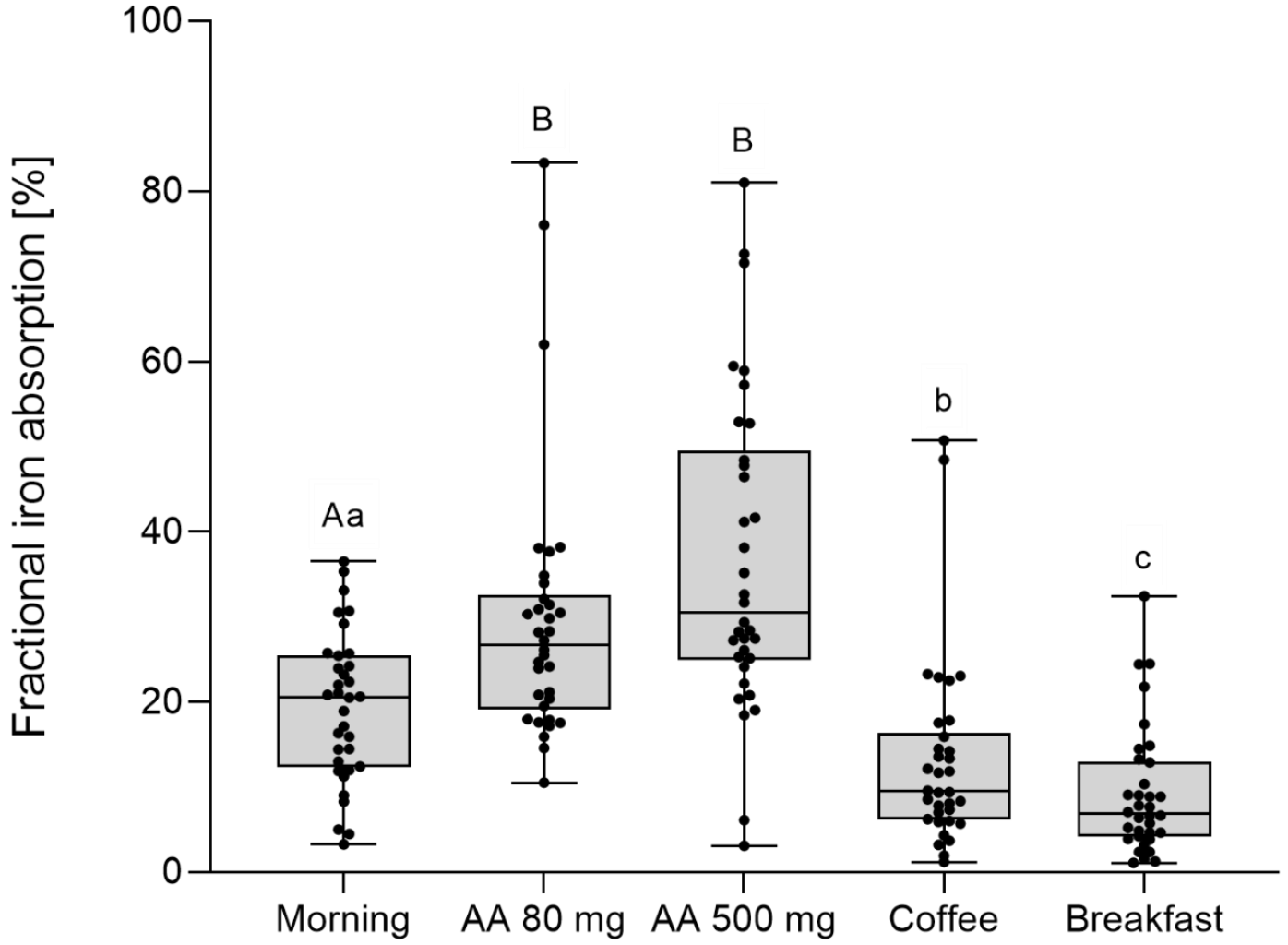
Day 26: 100 mg ^{57}FeFum 

Day 43: venipuncture

n = 34 women included into analysis

Effects of vitamin C and breakfast on oral iron absorption

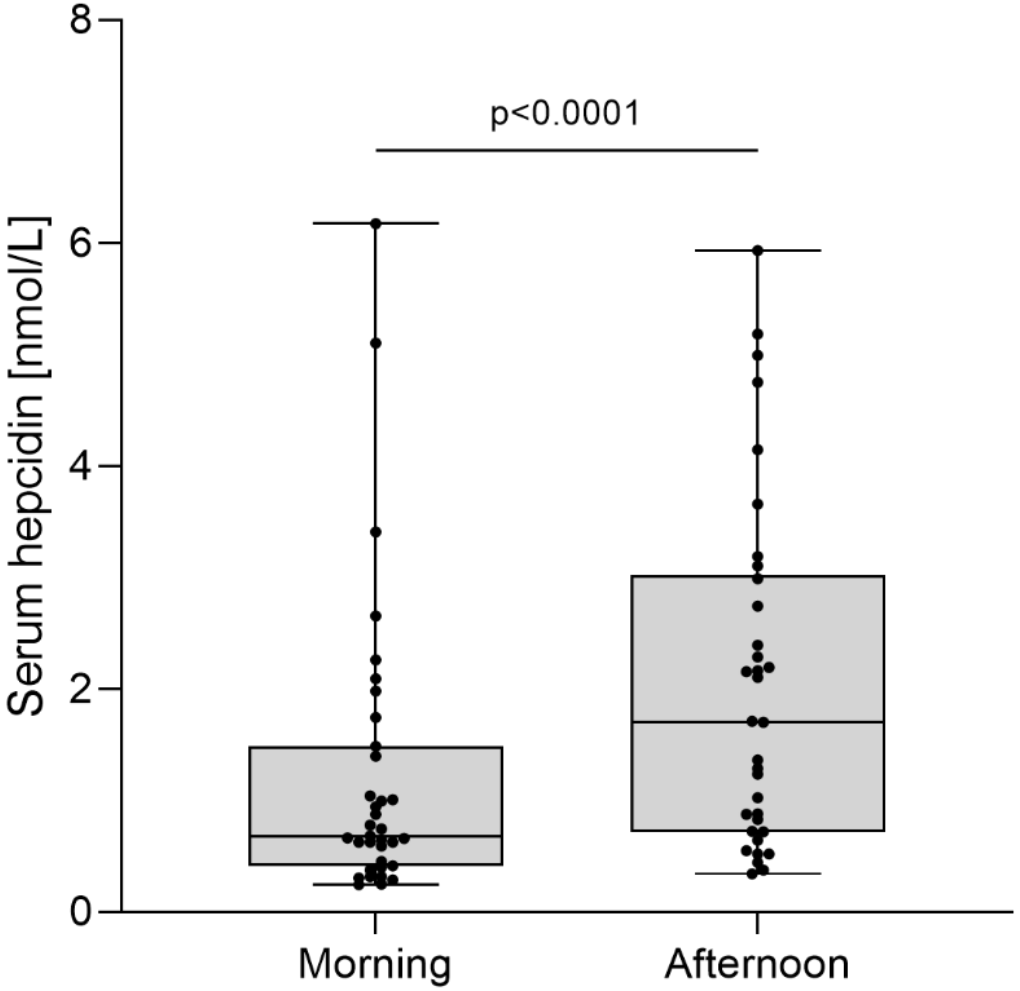
- 80mg vit C increased FIA by 30% but 500mg vit C did not further increase FIA
- coffee decreased FIA by 54%
- coffee with breakfast decreased FIA by 66% despite ~90mg of vit C in the meal

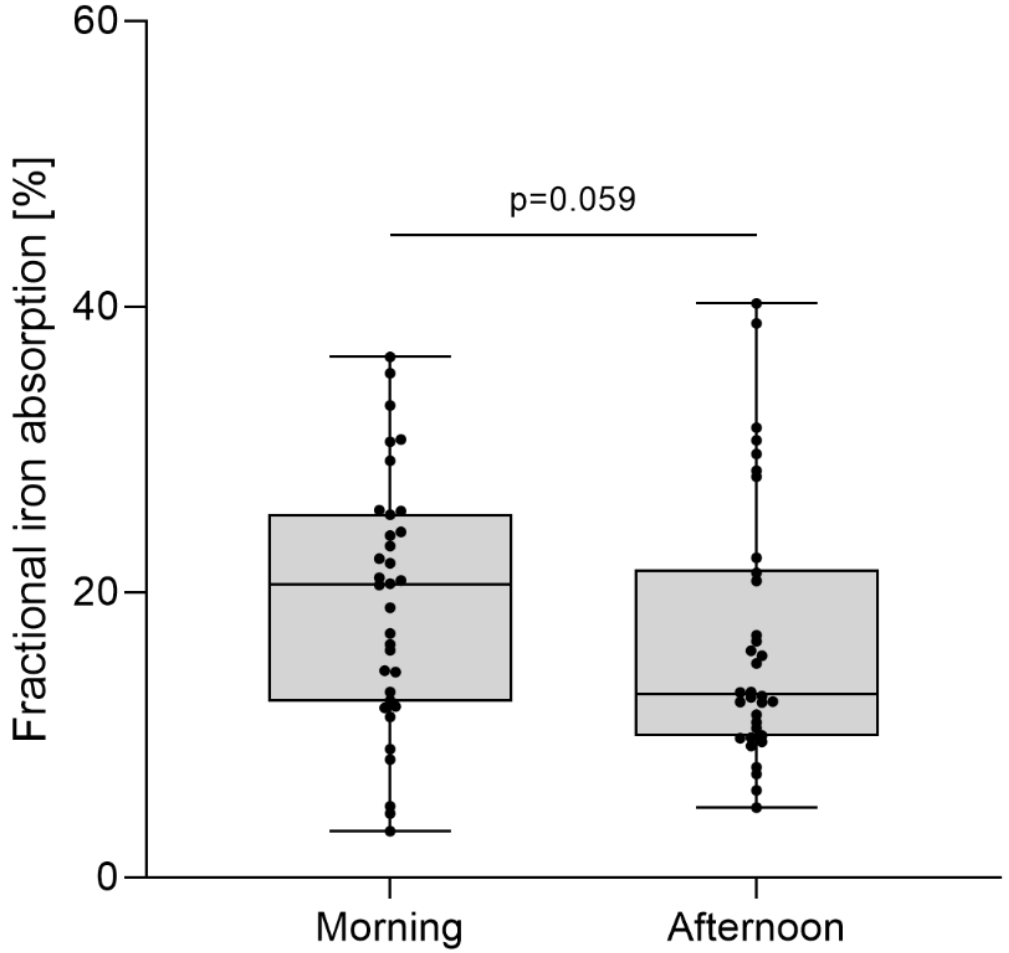


Von Siebenthal et al, Am J Hematol 2023, in press

Boxes with different subscript letter differ significantly

Serum hepcidin was lower and iron absorption was 60% higher in the morning compared to the afternoon





Von Siebenthal et al, Am J Hematol 2023, in press

In iron deficient women given a dose of 100 mg oral iron, compared to a dose given only with water:

- 80 mg AA increased iron absorption but increasing the AA dose to 500 mg did not further increase absorption
- consumption with coffee decreased iron absorption
- consumption with breakfast including coffee decreased iron absorption further, despite the presence of ~90 mg of AA in the meal
- consumed in the afternoon, iron absorption was lower in the afternoon compared to the morning

➡ Compared to taking a 100mg iron dose in the morning with coffee/ breakfast, taking it only with orange juice results in **a ~4-fold increase in absorption**, and provides **~20 more mg** of absorbed iron per dose

Oral iron every second day?

How often should we give oral iron to maximize absorption, compliance and efficacy?

We all know how to treat iron-deficiency anemia, right?

- Oral treatment starts with tablets of ferrous sulfate or a similar compound, each containing about 65-70 mg of elemental iron, preferably taken on an empty stomach three times a day[1,2]

- Benchmark for successful treatment is a 2 g/dL Hb increase in 3 weeks

[1] Brittenham GM. Disorders of iron homeostasis: iron deficiency and overload. In: Hematology: Basic Principles and Practice. 6th ed. New York: Elsevier; 2013
[2] Schrier SL, Auerbach M. UpToDate: Treatment of the Adult with Iron Deficiency Anemia. Philadelphia, PA: Wolters Kluwer; 2015.

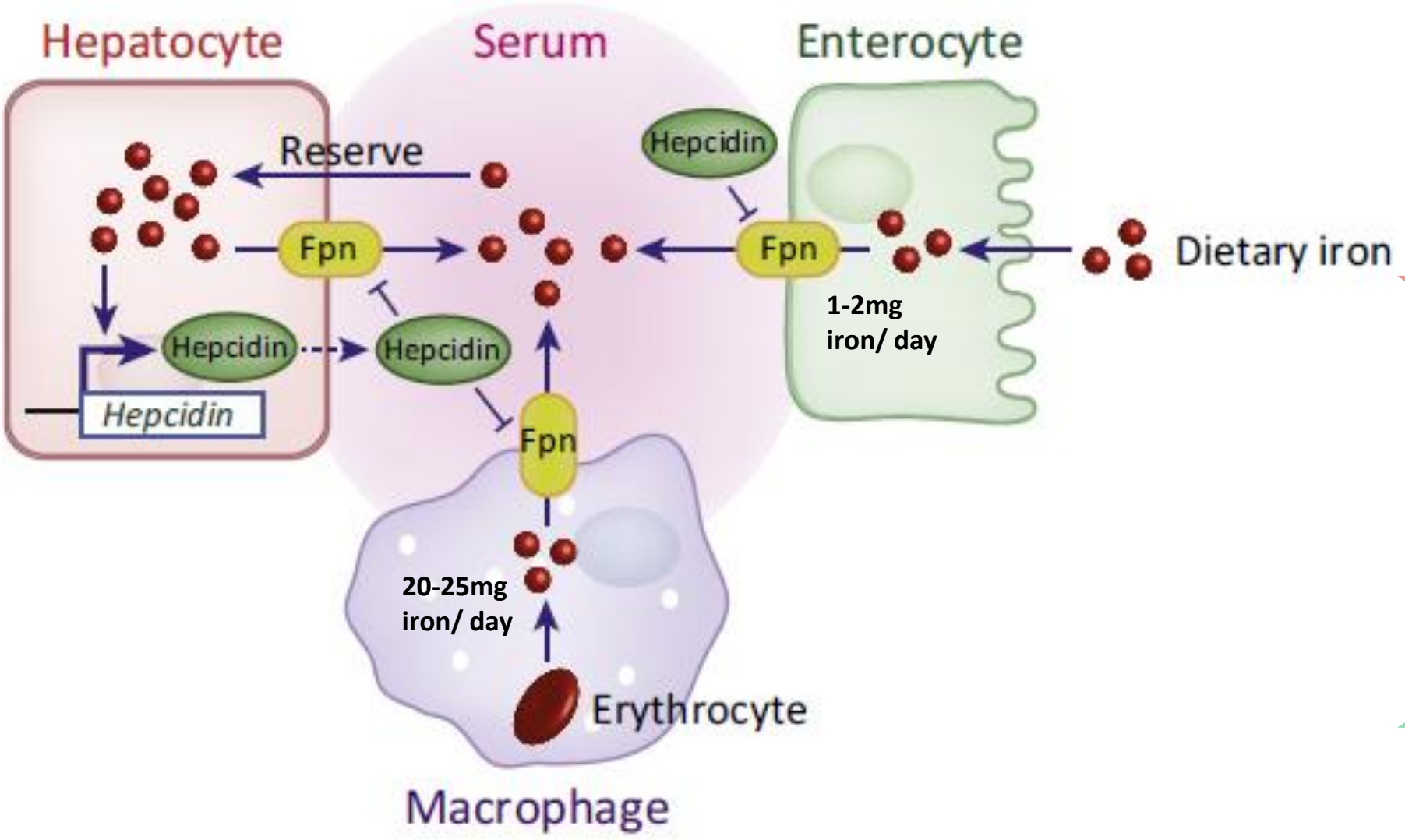
Problems with current regimens of oral iron supplementation

- Oral iron supplements are poorly absorbed
  - Fasting **9% (8-20%)**; with food: **2.2% (1-13%)**[1]

- Constipation, epigastric discomfort
- Poor compliance to supplementation schedules
  - Large amounts of unabsorbed Fe
  - Potential negative effects on the gut microbiome[2,3]

[1]Cook&Reddy, AJCN,1995; [2] Zimmermann et al, AJCN 2010; [3] Jaeggi et al 2015

Hepcidin: the central regulator of systemic iron homeostasis



High hepcidin

Low iron circulation

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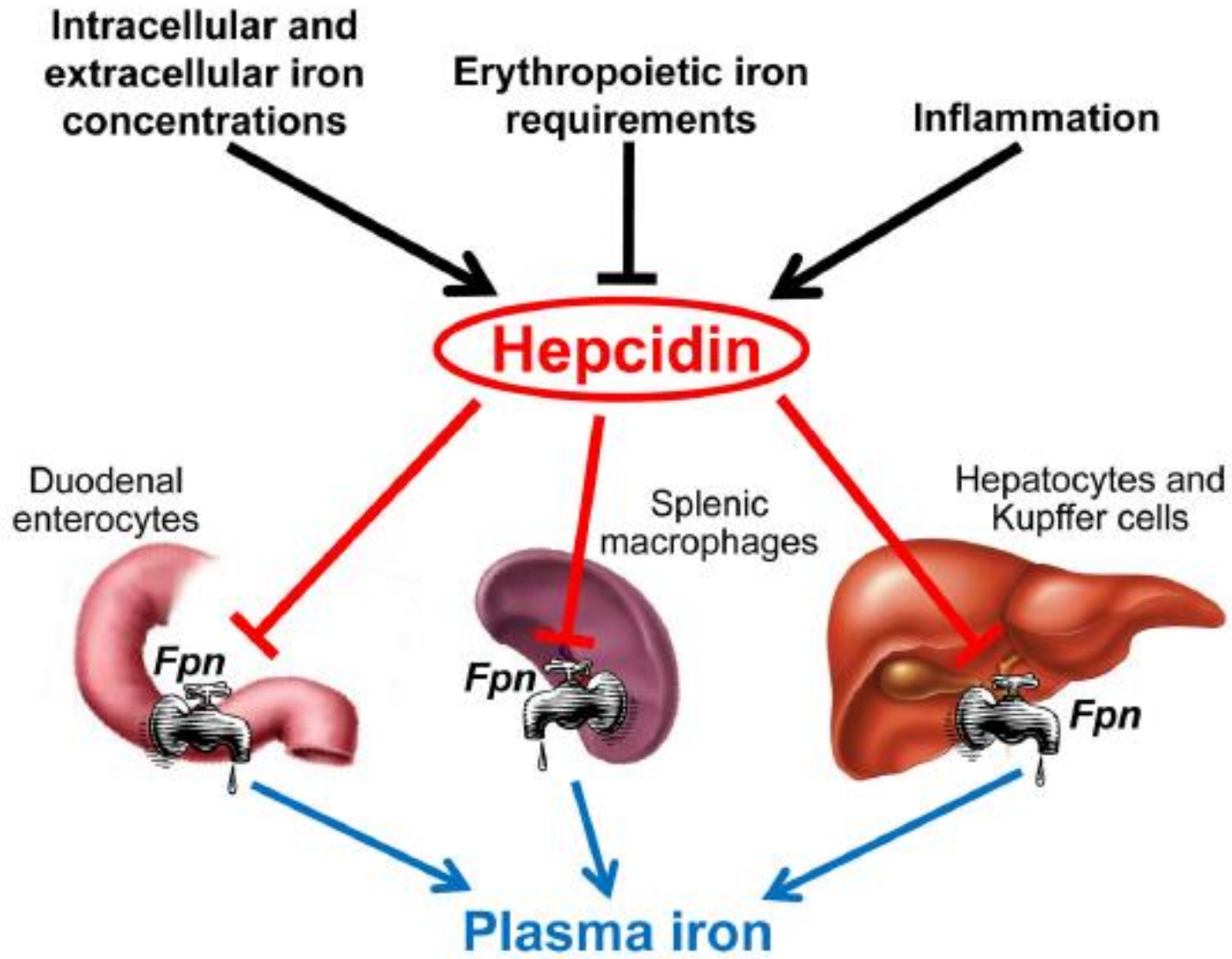
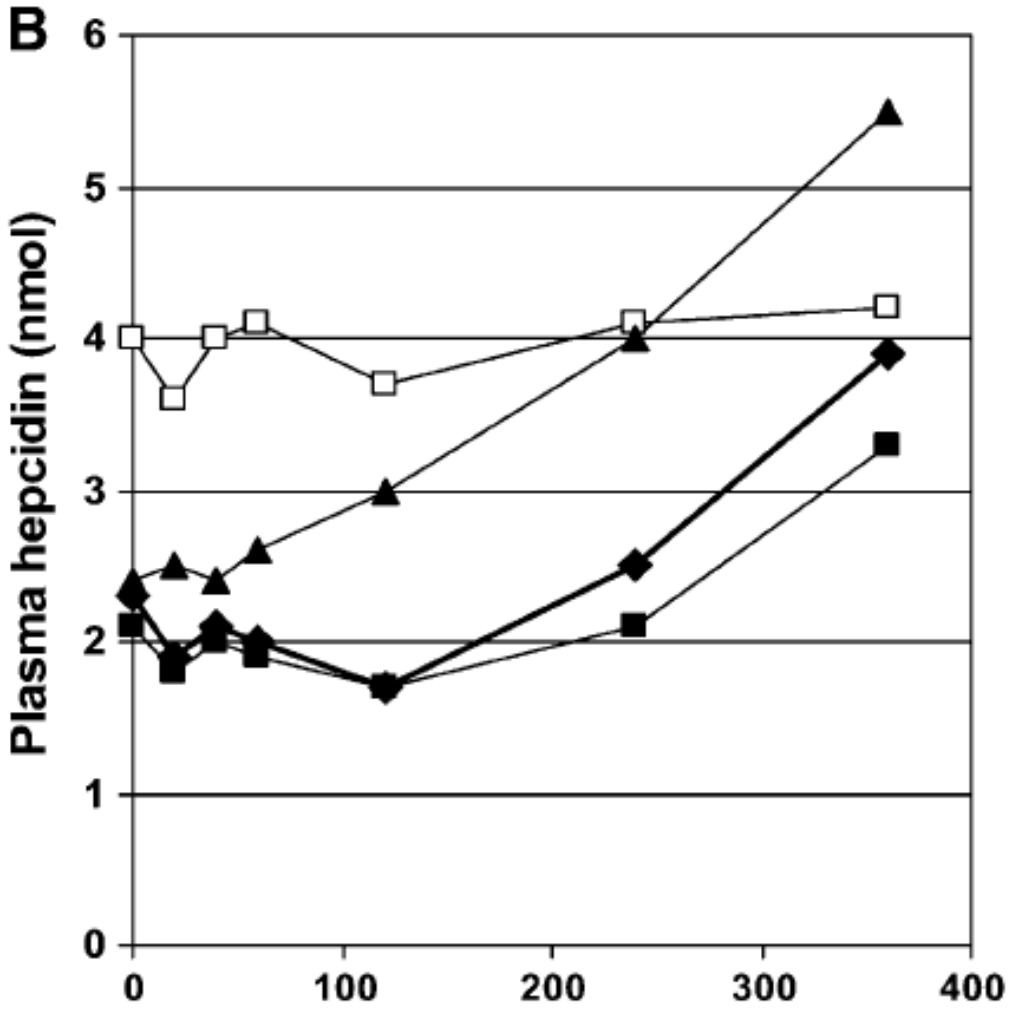
Bogdan et al., Trends Biochem Sci, 2016

Hepcidin is regulated by:



A single oral dose of iron induces an acute hepcidin rise

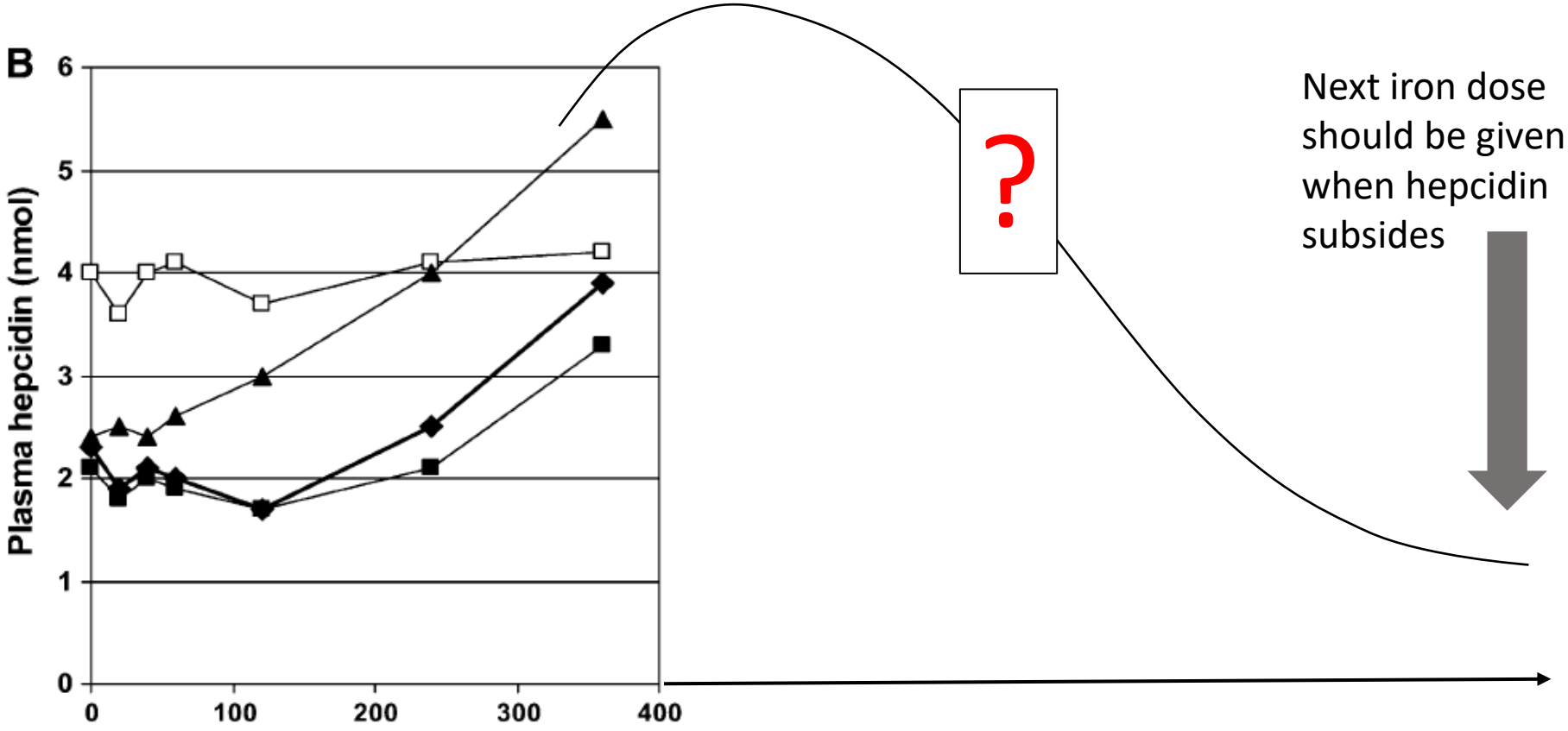


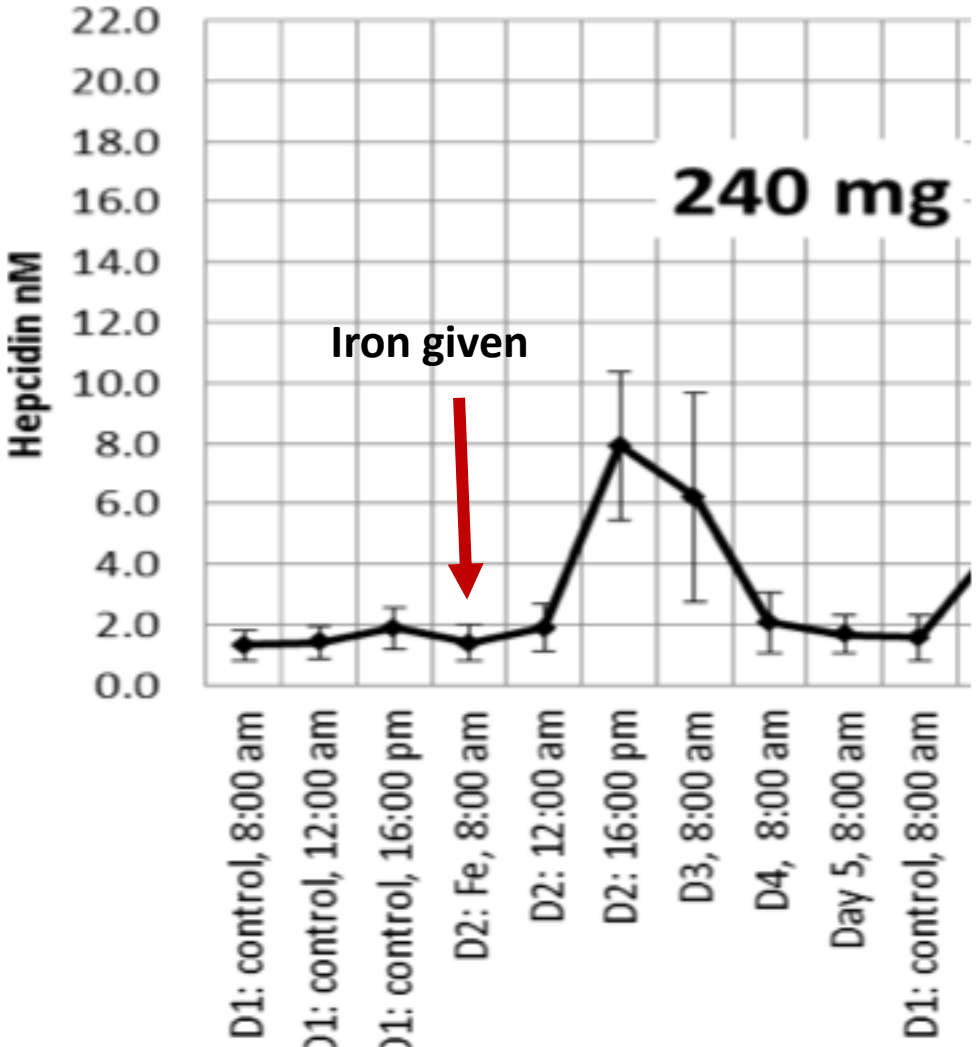
Time (min) after 60 mg oral iron dose

Zimmermann et al., AJCN, 2009

High plasma hepcidin sharply reduces iron absorption

What is the profile of the Fe-induced hepcidin response, and could we use this to devise a supplementation schedule to maximize absorption?





Change in plasma hepcidin after a single oral dose of iron

Hepcidin increases >5 fold after a single dose

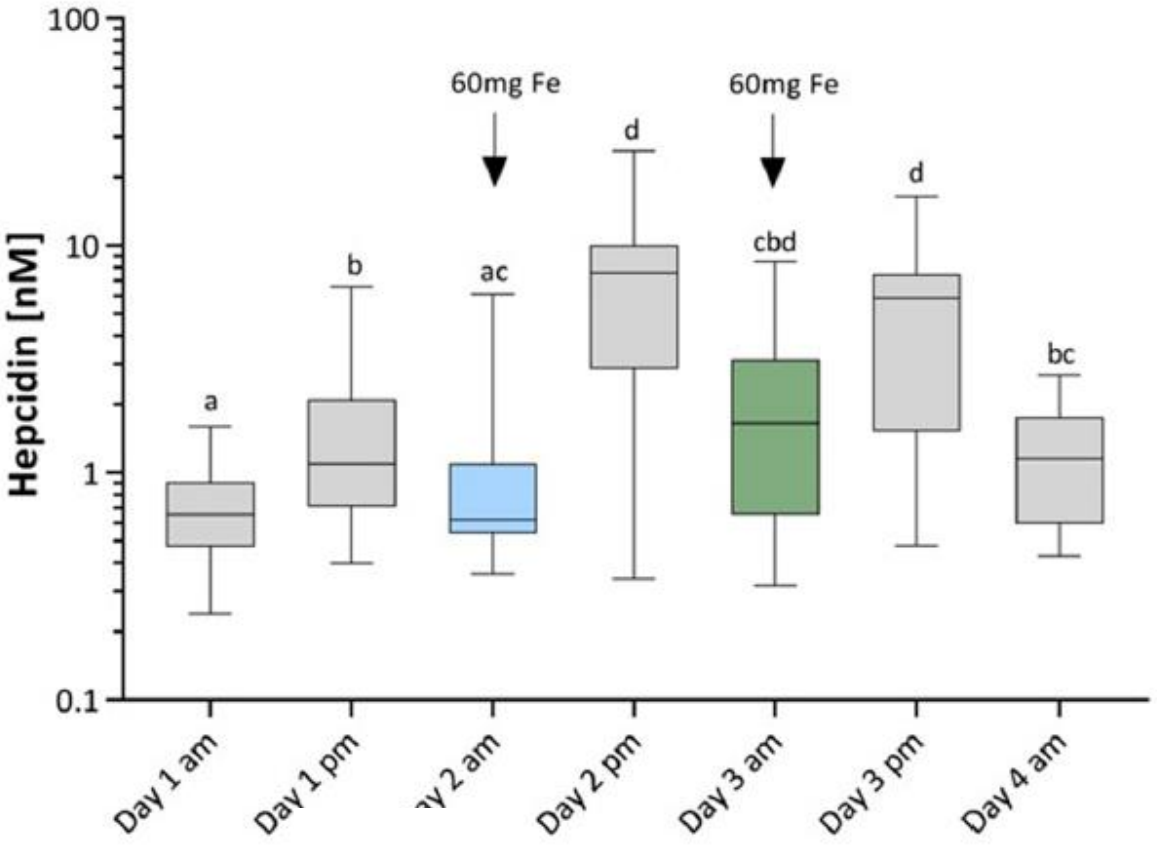
- Peaks at 8h
- Elevated at 24h, but not 48h

Moretti et al. Blood 2015

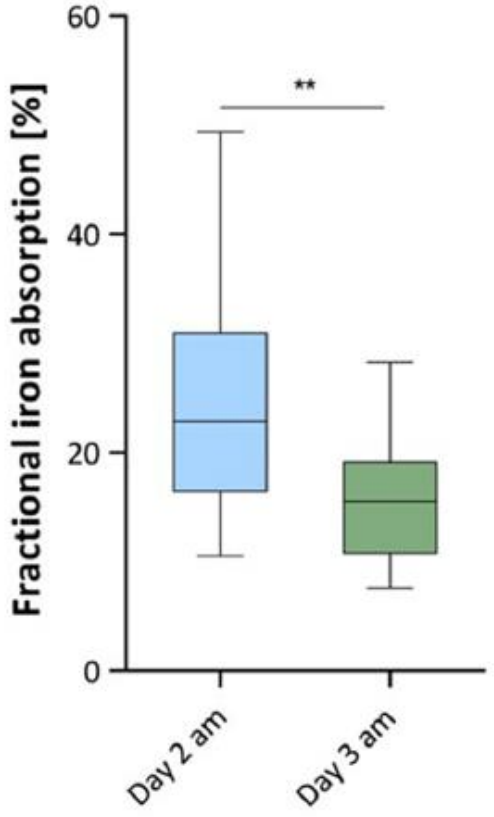
In ID women, 60mg oral iron increases hepcidin after 24 h and decreases iron absorption from the next days dose by 35%

Doses are given both at 8.00 a.m. on consecutive days 2 and 3; with day 1 as control day

Hepcidin profiles (n=16) during the observation period; boxes with different subscript letter differ significantly ($p < 0.05$).



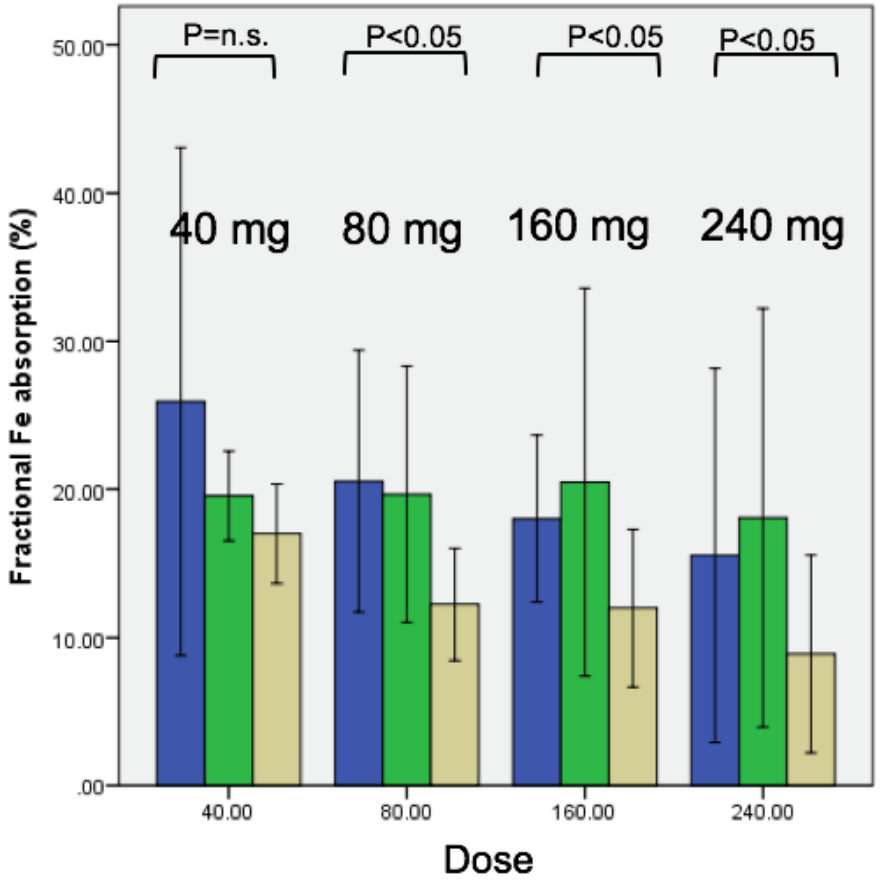
Fractional iron absorption measured on days 2 and 3 from the 60-mg Fe dose. $^{**}p < 0.01$.



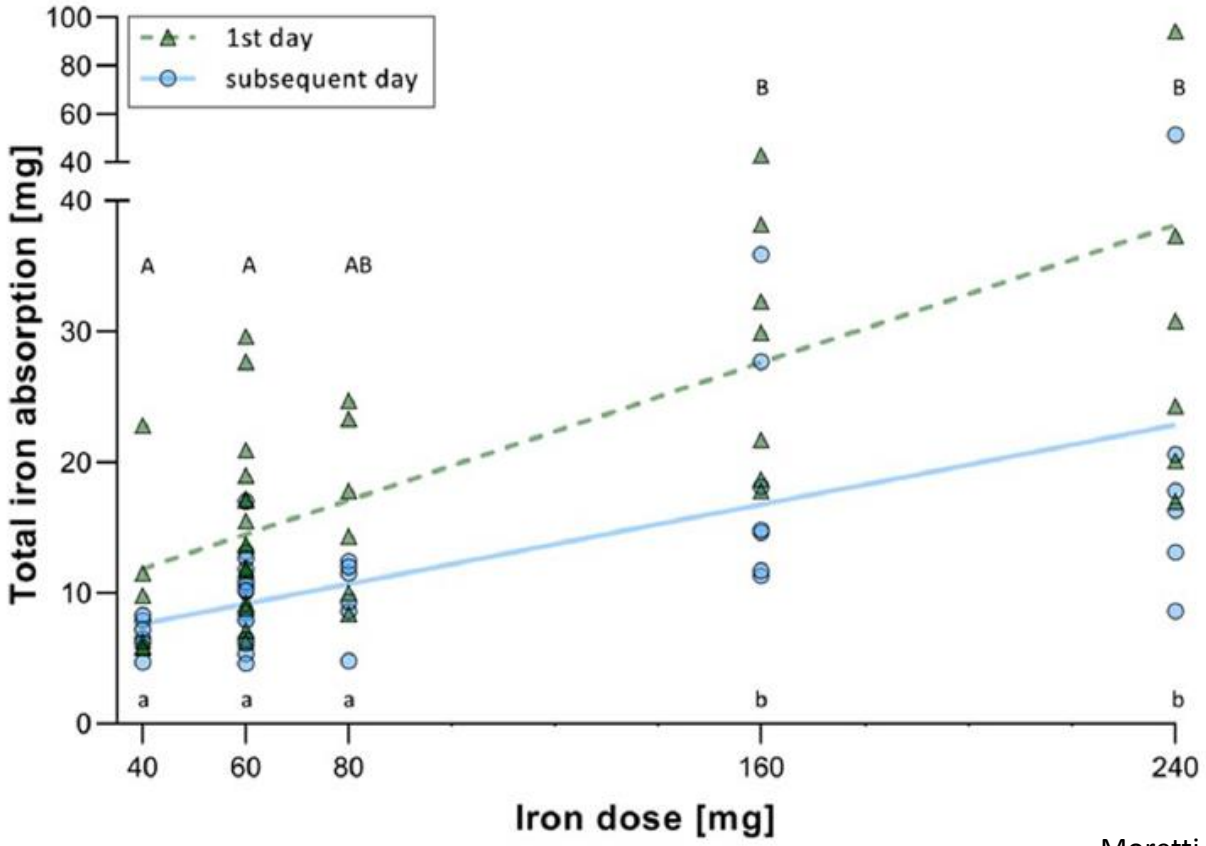
Moretti et al. Blood 2015

In ID women, daily dosing results in a 30-50% decrease in absorption from the next morning's dose

Doses of 40-240 mg Fe given on two consecutive mornings: at doses of iron >40 mg, 30-50% decrease in fractional absorption from the next day's dose



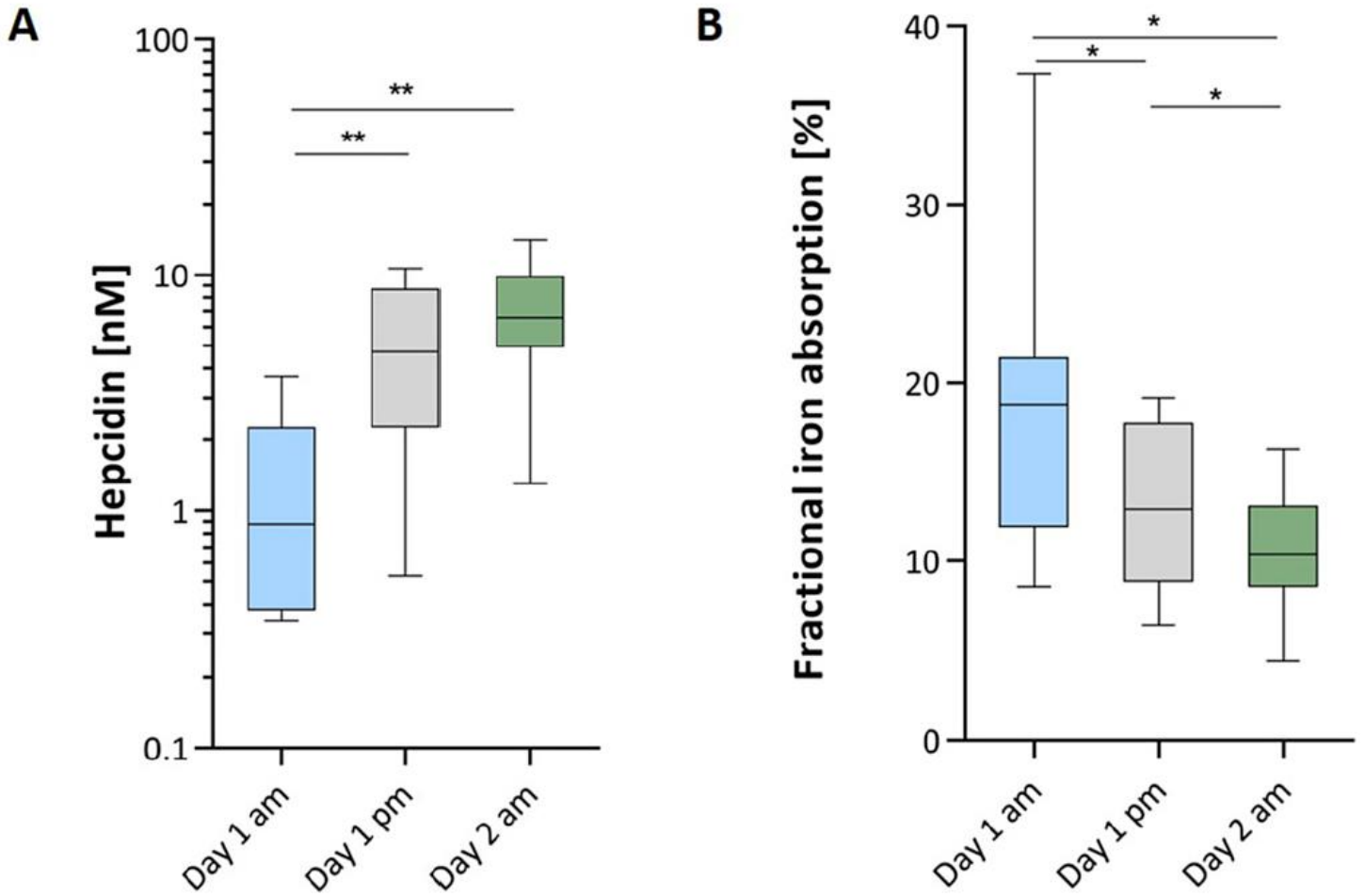
Total iron absorption in relation to the dose administered on the first day (broken line, Δ) and on the second day (continuous line, o). At doses of 60 mg and higher, the first and second dose absorptions differed ($p < 0.01$)



Moretti et al. Blood 2015

What about splitting doses?
In ID women given twice daily dosing of 60 mg Fe, the normal afternoon hepcidin increase is increased by the morning dose, decreasing absorption of the afternoon and next day‘s doses

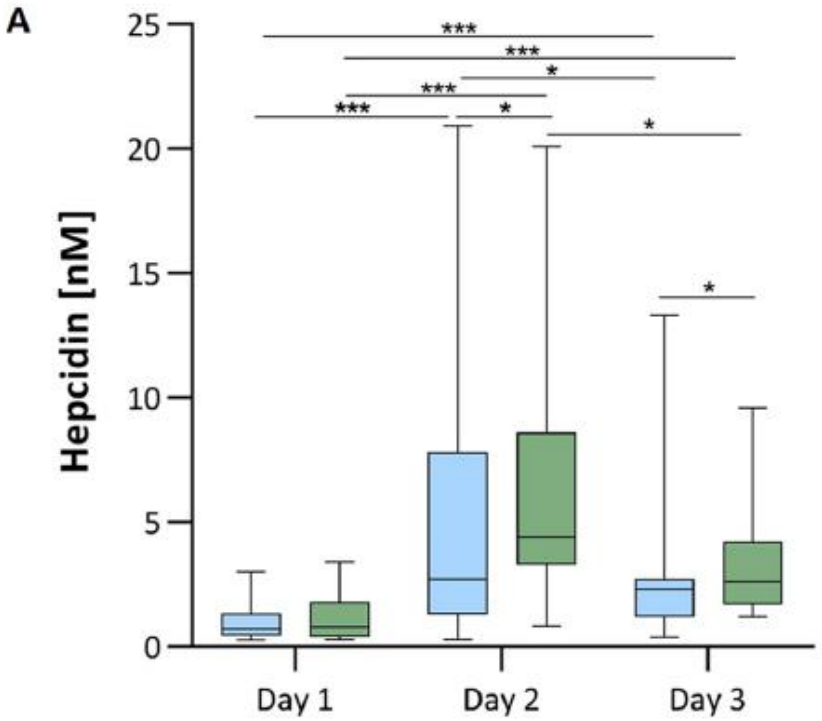
In iron-deficient women (n = 13), twice-daily iron administration at 10.00 a.m. and at 5.00 p.m. results in increased hepcidin (A) on the consecutive day and decreased iron absorption (B) of the afternoon dose and the next morning’s dose

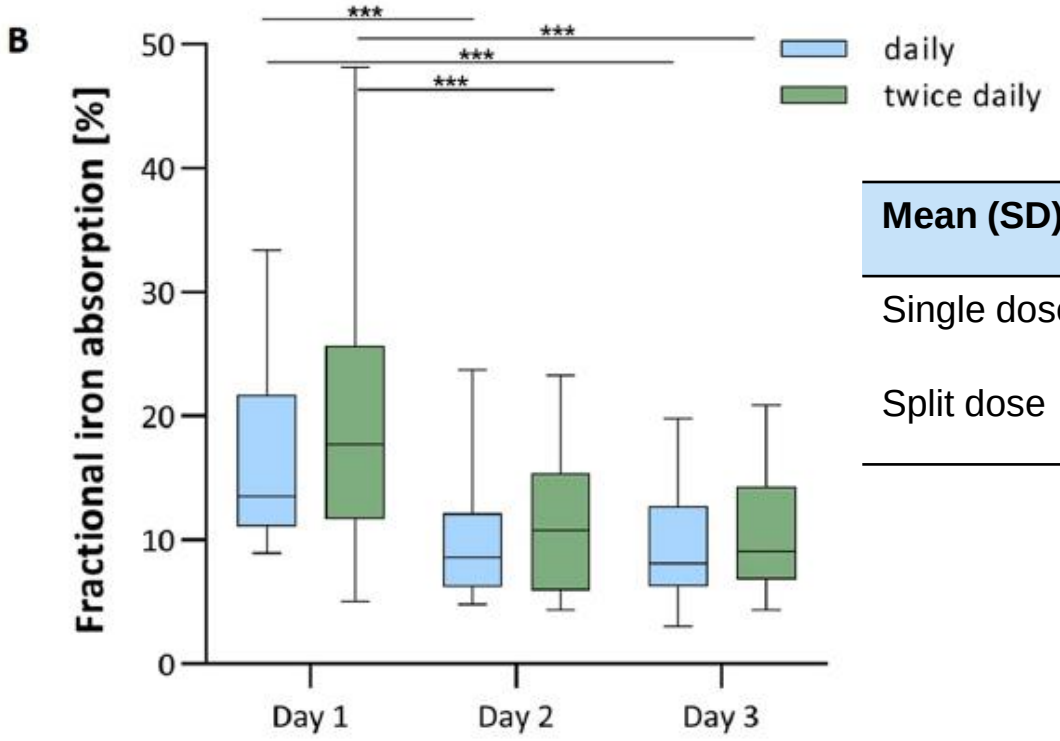


Moretti et al. Blood 2015

In ID women, no difference in iron absorption from a single morning dose (1 x 120 mg) vs. twice daily dosing (2 x 60 mg)

In iron deficient women (n = 20) receiving single morning iron doses (120 mg) or split morning and afternoon doses (each 60 mg) for 3 days, there were no significant differences in iron absorption but twice-daily divided doses resulted in a higher serum hepcidin. *p < 0.05, ***p < 0.001.

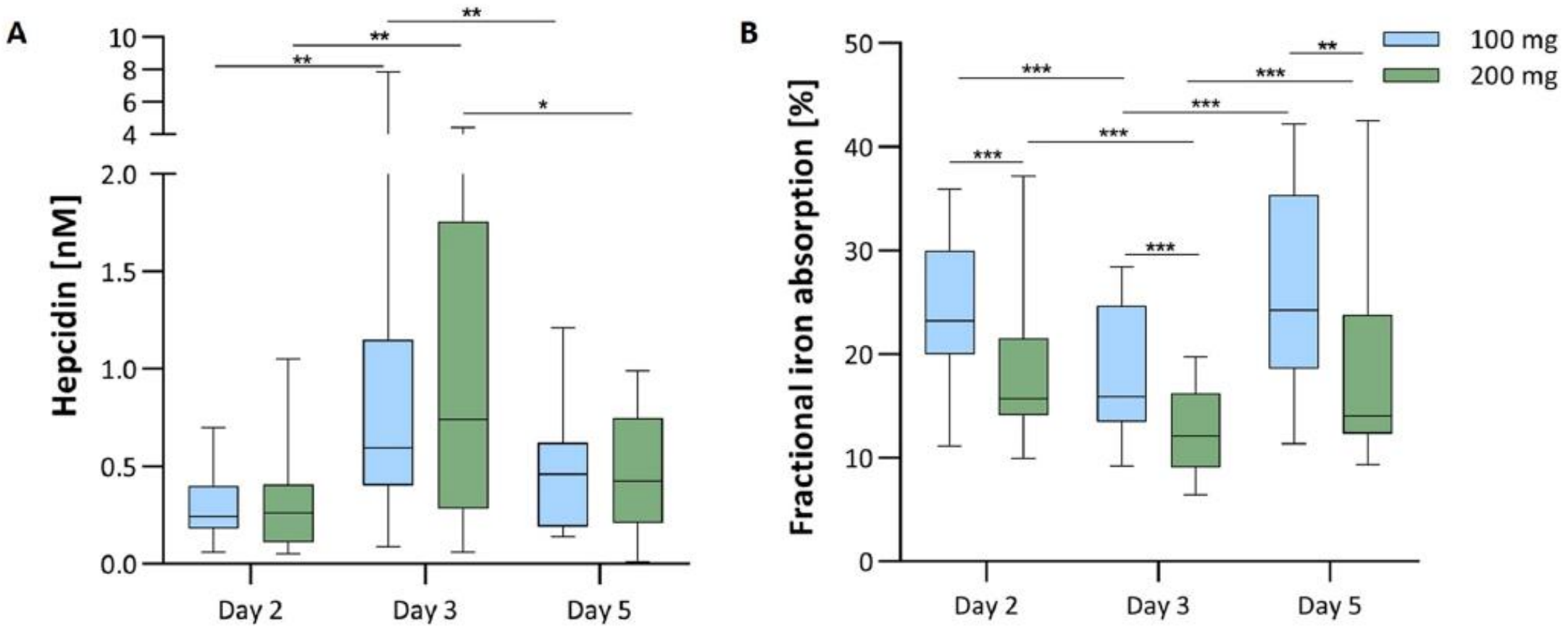




Mean (SD) total Fe absorption (mg)	
Single dose	40.7 (26.7, 62.2)
Split dose	44.7 (28.0, 71.5)

Stoffel et al. Lancet Hematology 2018

In women with IDA, hepcidin increases 24h after 100 or 200 mg oral iron doses, but subsides by 48h: thus, alternate day dosing of increases absorption by 35-47%



*p <0.05, **p <0.01, ***p <0.001

Stoffel et al. Hematologica 2020

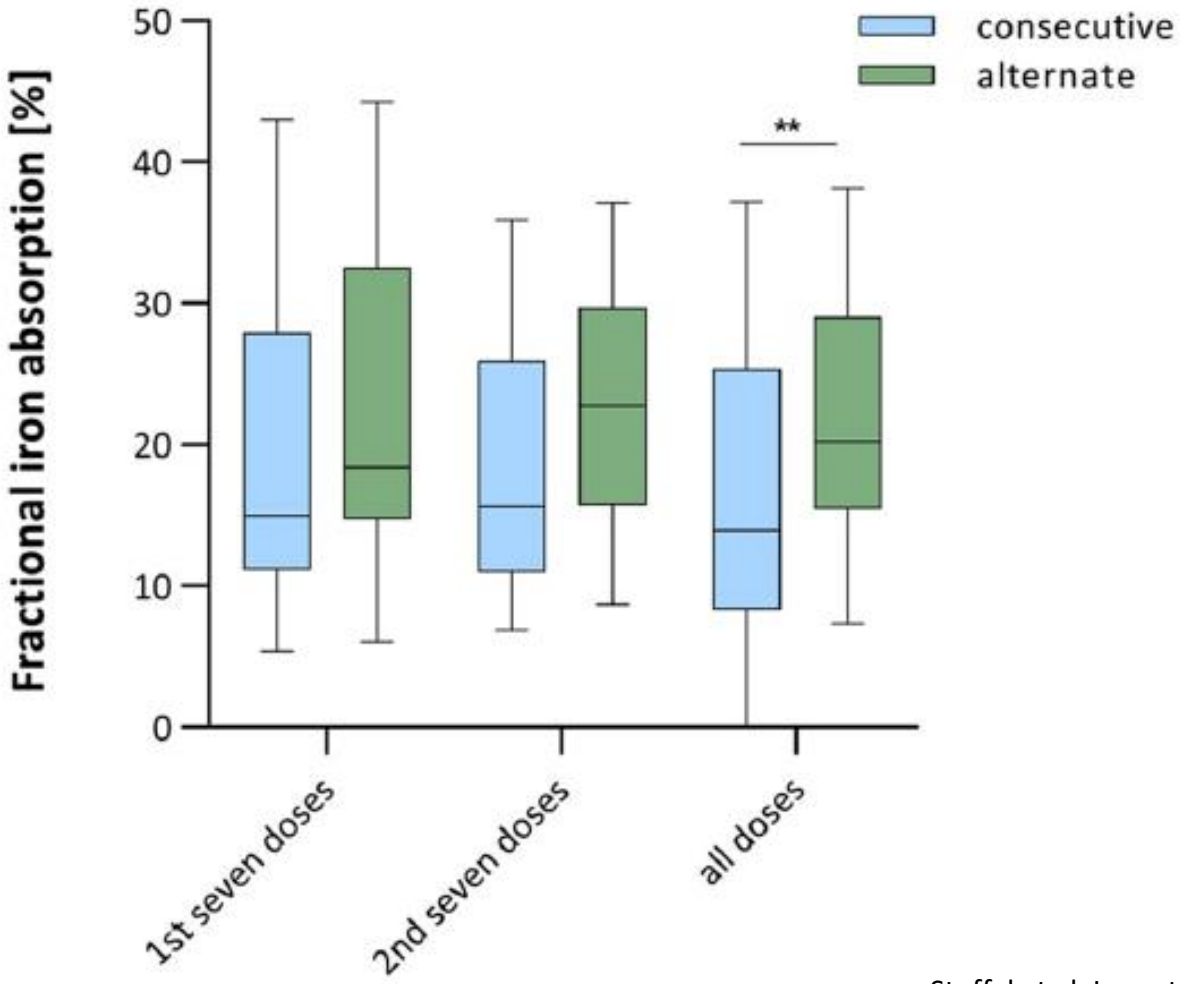
In ID women, 14 doses of 60 mg given on alternate days deliver 20 mg more total absorbed iron than when given daily

Alternate day dosing increases fractional and total iron absorption by 30%

Total iron absorbed (mg)	
daily	67.1 (39.3, 114.3)
alternate	87.6 (55.6, 137.9)

Mean (SD)

33% less GI side effects in the alternate day group

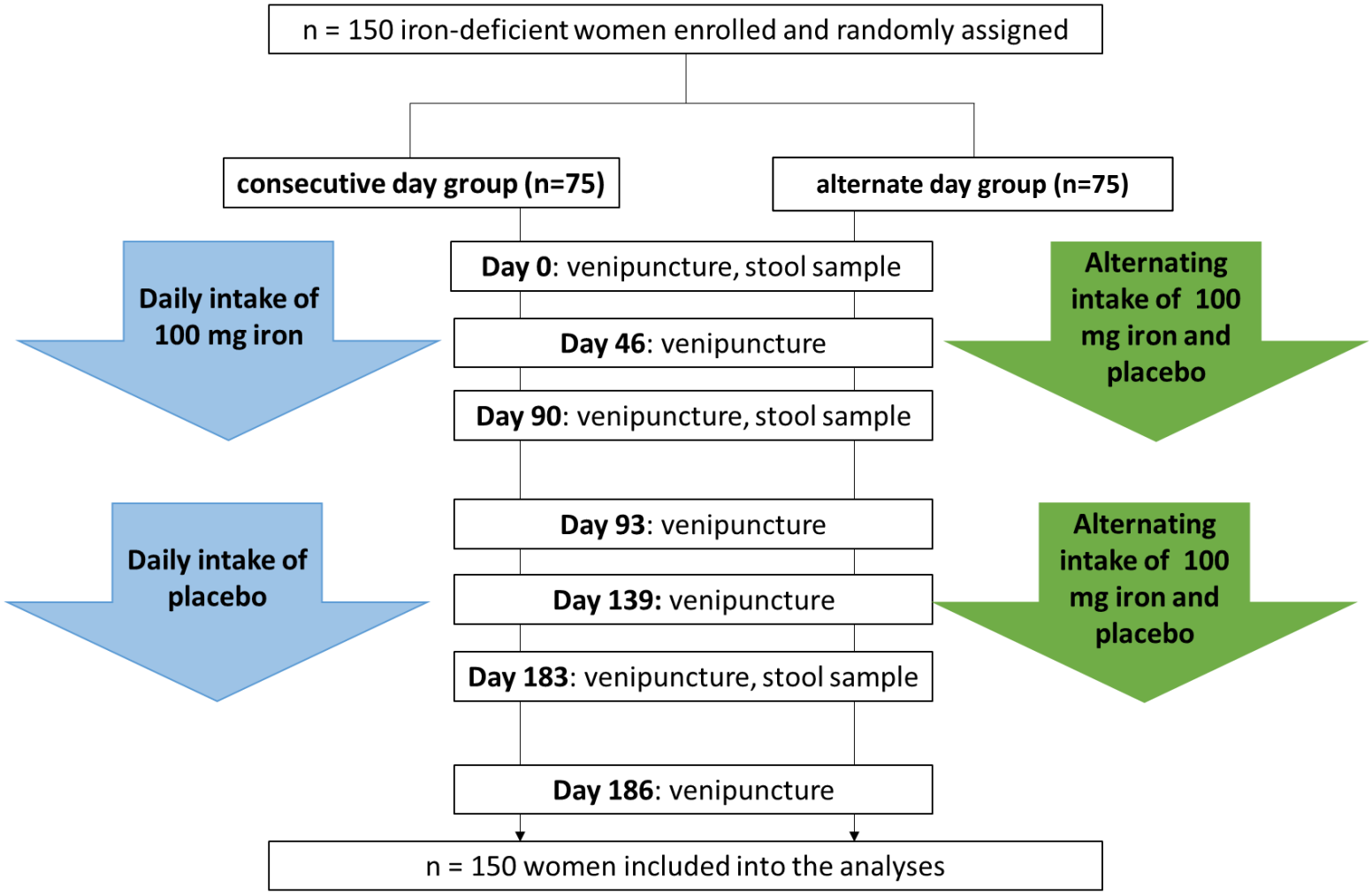


Stoffel et al. Lancet Hematology 2018

Randomized double-blind placebo-controlled study of daily vs. alternate day 60 mg iron supplementation

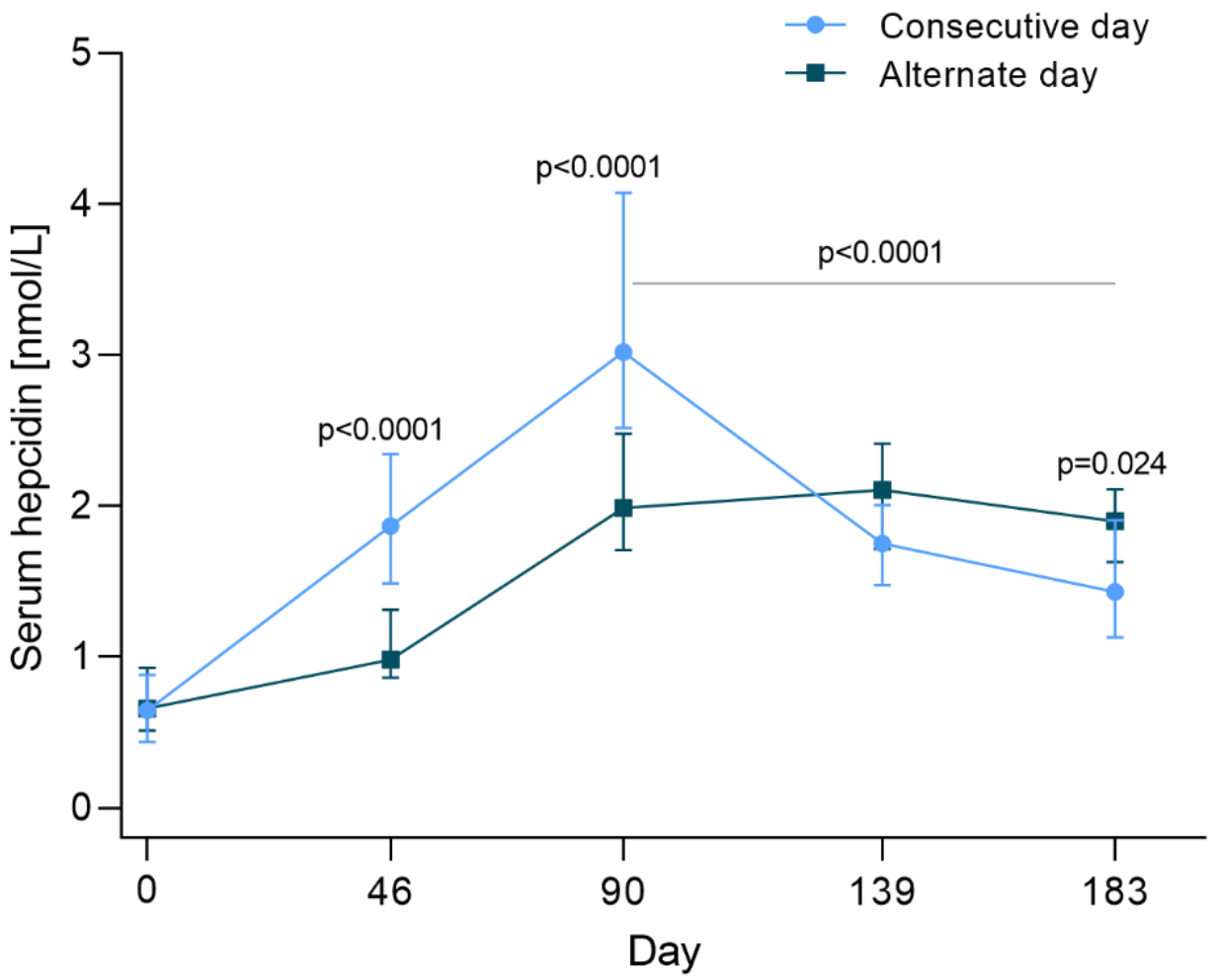
- Healthy women aged 18 – 45 y
- BMI 18.5–26.5 kg/m²
- Non-anemic: Hb > 11 g/dL
- Iron deficient: PF ≤ 30 µg/L
- No inflammation: CRP < 5 mg/L

'Real-time' assessment of GI side effects during the study using a specifically-designed app



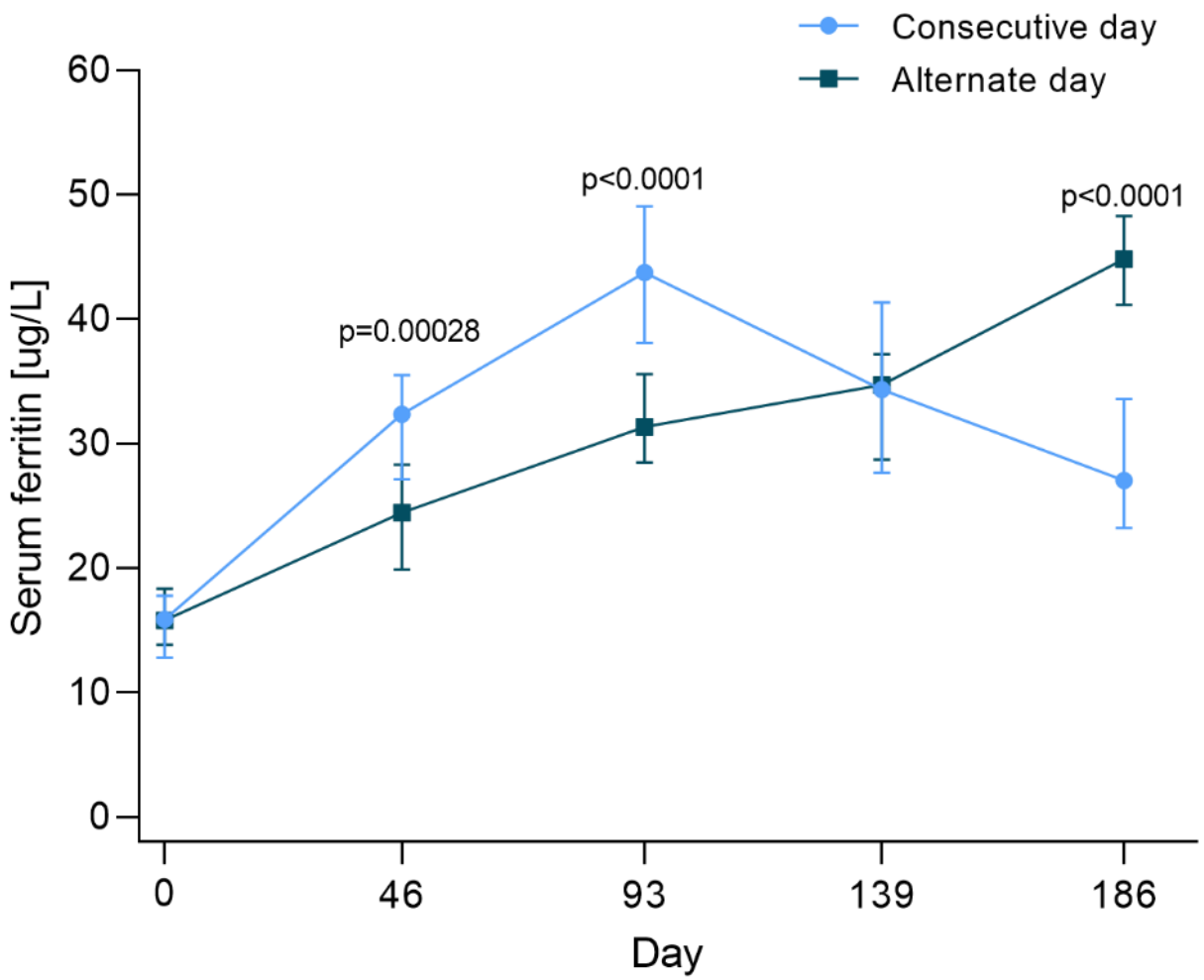
Von Siebenthal et al, Blood 2023, in press

Alternate day dosing resulted in lower serum hepcidin compared to daily dosing



Von Siebenthal et al, Blood 2023, in press

Comparable serum ferritin increases between the daily and alternate-day groups

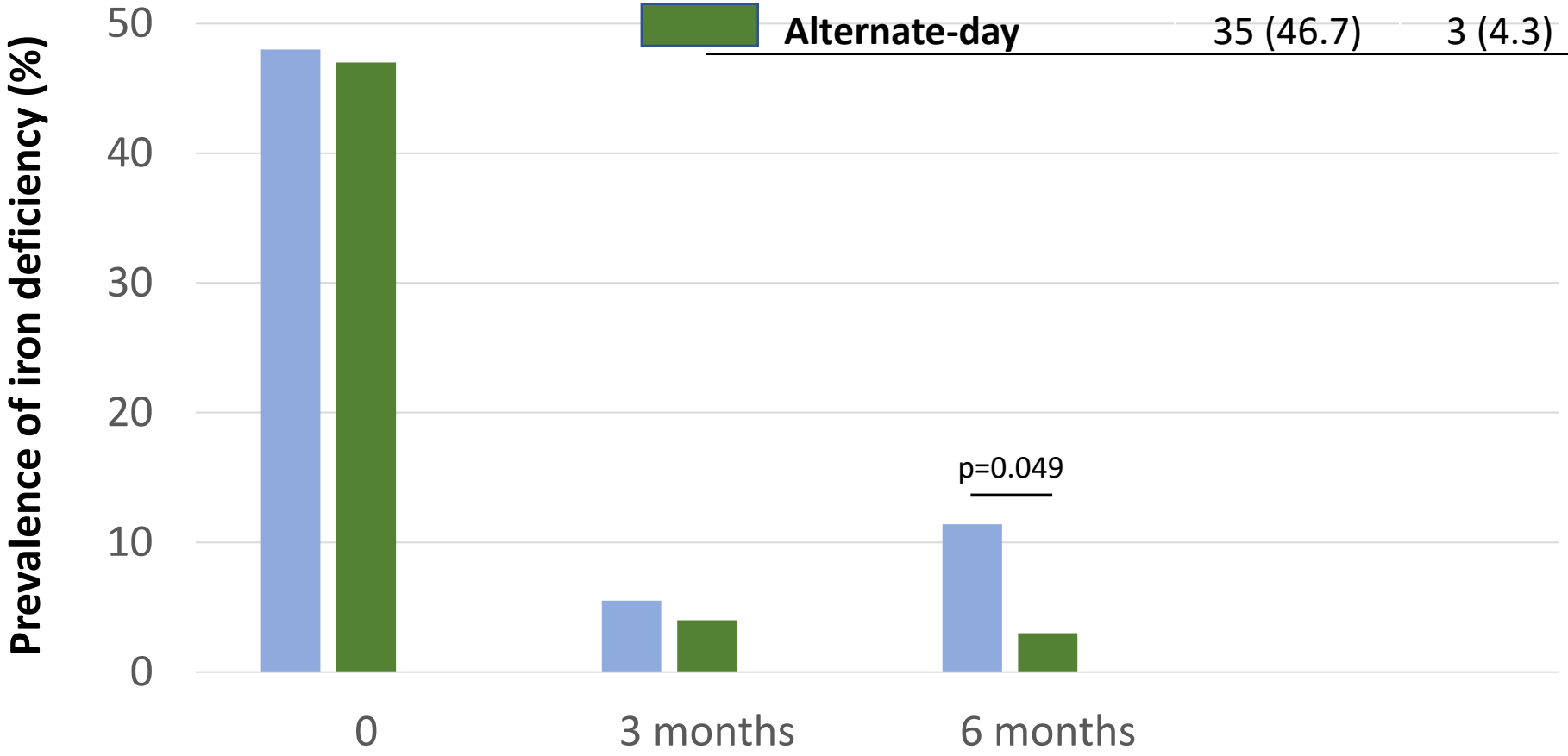


Von Siebenthal et al, Blood 2023, in press

Comparable reductions in iron deficiency after 3 months; more sustained reduction at 6 months in the alternate day group

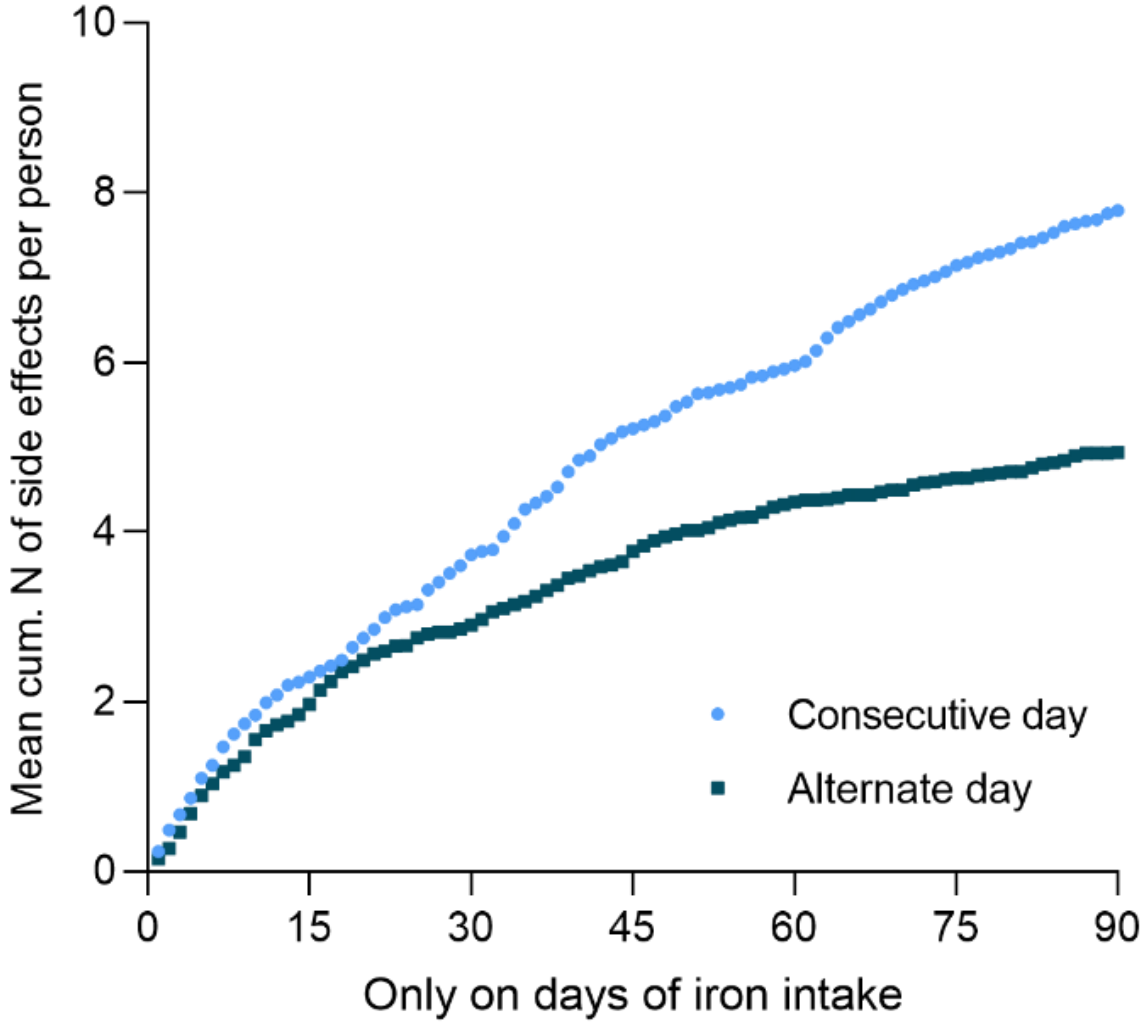
Iron deficiency, n (%)	Day 0	3 months	6 months
Consecutive-day	36 (48.0)	4 (5.5)	8 (11.4)*
Alternate-day	35 (46.7)	3 (4.3)	2 (3.0)

*p<0.05



Von Siebenthal et al, Blood 2023, in press

At equal total iron doses, 56% more GI side effects on days of iron intake in the consecutive-day group



Incidence rate ratio (95% CI): 1.56 (1.38, 1.77)

Von Siebenthal et al, Blood 2023, in press

What is the best way to take oral iron supplements?

Ferrous iron supplements should be consumed:

In the morning (not divided)

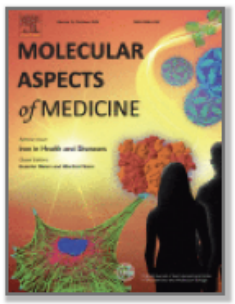
Away from meals or coffee

With an vit C-rich food or beverage

Every other day

Molecular Aspects of Medicine

Volume 75, October 2020, 100865



Oral iron supplementation in iron-deficient women: How much and how often?

Nicole U. Stoffel [a] ✉, Hanna K. von Siebenthal [a] ✉, Diego Moretti [a, b] ✉, Michael B. Zimmermann [a] ✉

inside blood commentary

22 OCTOBER 2015 | VOLUME 126, NUMBER 17

CLINICAL TRIALS AND OBSERVATIONS

Comment on Moretti et al, page 1981

So you know how to treat iron deficiency anemia

Stanley L. Schrier STANFORD UNIVERSITY SCHOOL OF MEDICINE

In this issue of *Blood*, Moretti et al[1] provide data that challenge the entrenched oral treatment of iron deficiency anemia. The paper shows how the newer understanding of hepcidin and iron metabolism in general can lead to very practical improvements in the management of iron deficiency anemia, a disorder that may affect as many as 1 billion people.

dose of iron will cause an increase in plasma iron, which in turn will cause an increase in hepcidin, which in turn will interfere with iron absorption of the next dose of iron.

Using elegant technology based on their skills with 3 isotopes of iron, so that subjects could be their own controls, they measured total and fractional iron absorption in several scenarios testing varying doses of oral iron administered over a variety of schedules. Per prediction, they found that ingesting a substantial single dose of oral iron, when absorbed, led to an increase in plasma iron, which in turn led to an increase in hepcidin. The measured increase in hepcidin then impaired iron absorption from subsequent doses of oral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Swiss National Science Foundation


SFEFS

If you’re in a hurry, alternate day dosing of twice the dose results in higher total iron absorption compared to daily dosing

In women with ID/IDA (n = 64), total iron absorption from 80 mg, 120 mg, 160 mg, 200 mg and 240 mg given on alternate days (dashed line) is higher than total iron absorption from 2 x 40 mg, 2 x 60 mg, 2 x 80 mg, 2 x 100 mg and 2 x120 mg, respectively, given on consecutive days. Overall, across all doses, **alternate day dosing of twice the dose** resulted in higher total iron absorption compared to consecutive day dosing.

The two lines indicate linear regressions on total iron absorption from daily or alternate day dosing.