

Workshop:

Discussion regarding deferrals based on haemoglobin/ ferritin levels

(13:30 – 15:00)

Moderator: **Rada M. Grubovic Rastvorceva**, SoHO Standards Section, EDQM

Hosts: **Mart Janssen**, Sanquin Blood Supply Foundation, the Netherlands
Amber Meulenbeld, Donor Health, Sanquin Research & Amsterdam UMC, Dept of Public and Occupational Health, the Netherlands
Katja van den Hurk, Donor Health, Sanquin Research & Amsterdam UMC, Dept of Public and Occupational Health & Amsterdam Public Health Research Institute, the Netherlands

Please note:

- *Food and drink are not permitted in the conference rooms*
- *Photography & filming during the presentations are strictly forbidden*
- *Photos and videos may only be taken by Council of Europe staff members*
- *The session will be recorded for internal purposes only*



Discussion regarding deferrals based on haemoglobin/ferritin levels

EDQM Blood Conference

Katja van den Hurk, Mart Janssen, Amber Meulenbeld

For Life.



Introduction



Katja van den Hurk
PI Donor Health
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Technology Assessment
Sanquin



Amber Meulenbeld
PhD student
Big Data Donor Health
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Contents

Introduction

The current status of iron management in donors

Limitations of current policies

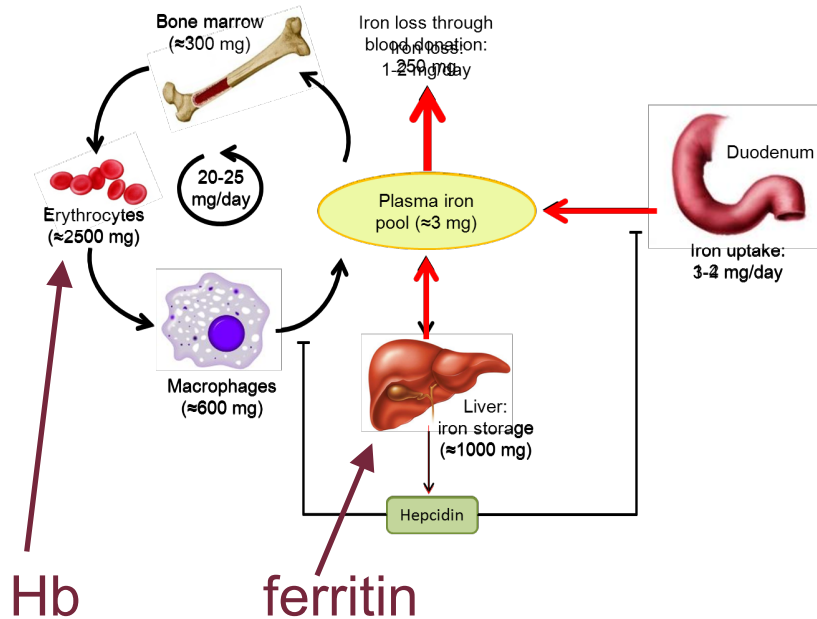
Next steps?

Interactive discussion on directions for change

Outline of an alternative donor iron management policy



Donation-induced Iron Loss



$250 \text{ mg} / 4 \text{ mg} = 62.5 \text{ days} = 9 \text{ weeks}$
 (seems optimistic, based on Schotten et al., Blood 2016, and Kiss et al., JAMA 2015)



Donation-induced iron depletion

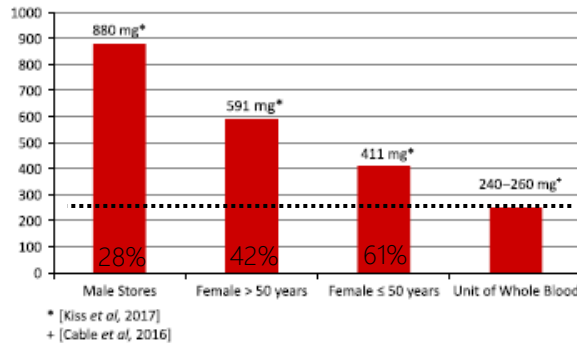
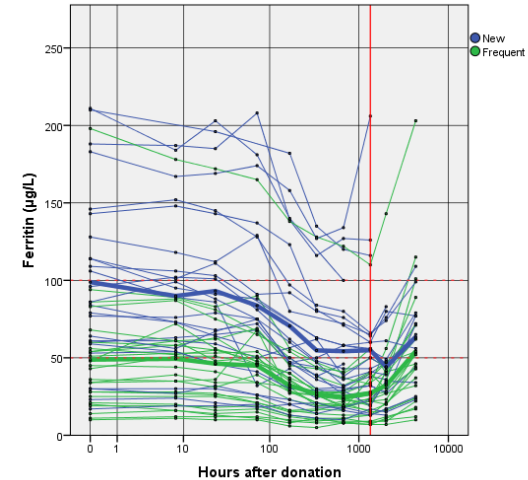
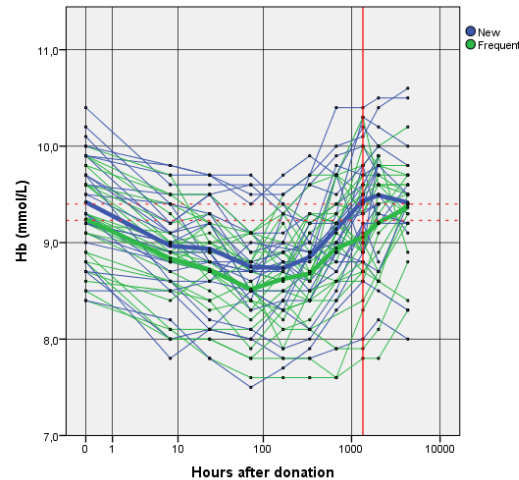


Fig 1. Iron stores in comparison to loss from the donation of one unit of whole blood (far right) reported by the indicated studies. The greatest proportionate loss (60%) is in women ≤50 years of age.

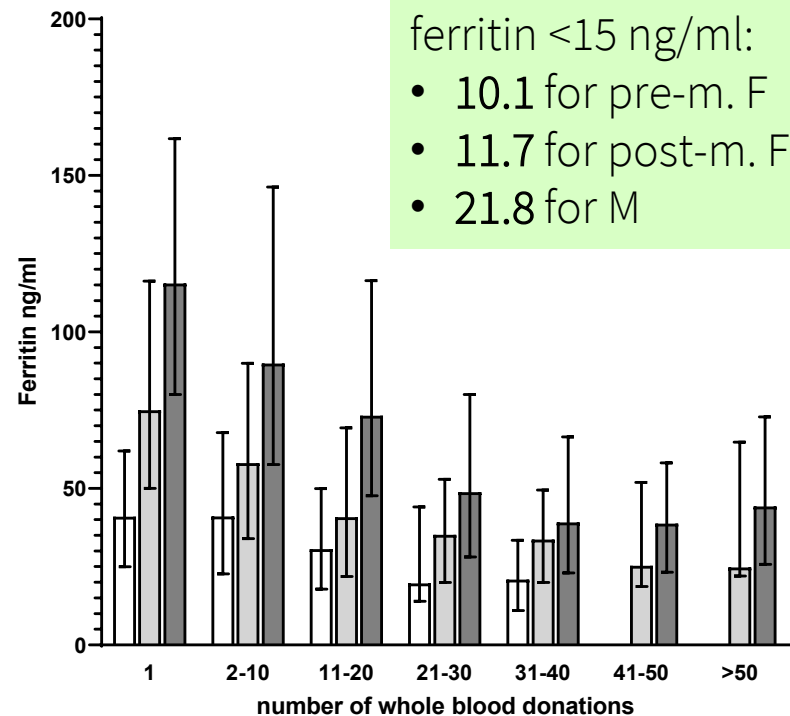
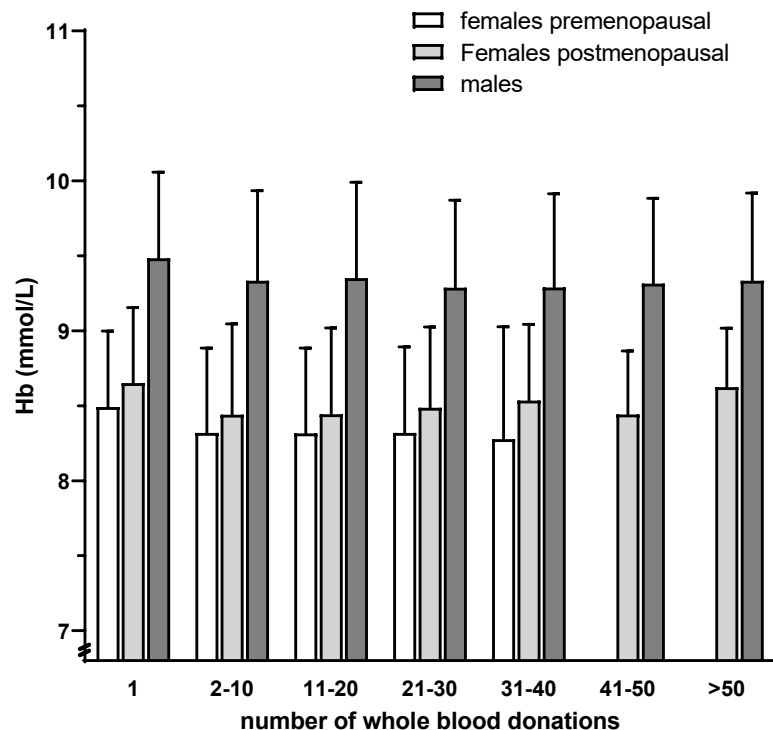


Kiss et al., Br J Haematol 2018

N. Schotten et al. Blood 2016



Ferritin and Hb before routine ferritin measurements



OR for Hb deferral if ferritin <15 ng/ml:

- 10.1 for pre-m. F
- 11.7 for post-m. F
- 21.8 for M



The origin of current Hb and ferritin thresholds

Hemoglobin: Blood Guide (21st ed)*

Females	Males
7.8 mmol/L 125 g/dL	8.4 mmol/L 135 g/dL

→ Lower may be acceptable after consultation with physician or after competent authority establishes different norms for specific population

*Guide to the preparation, use and quality assurance of blood components - European Directorate for the Quality of Medicines & HealthCare: <https://www.edqm.eu/en/blood-guide>



The origin of current Hb and ferritin thresholds

Ferritin: WHO guideline on the use of ferritin (2020)

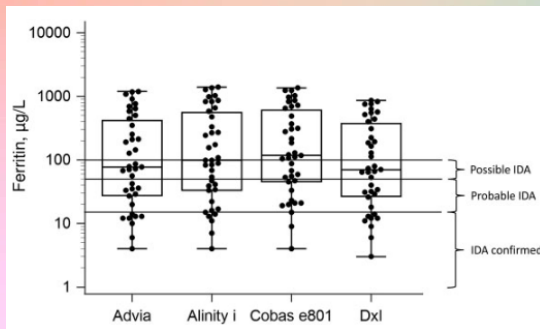
For healthy individuals: <15 ng/mL

But the certainty of evidence is **low to very low**.

However: heterogeneity in ferritin assays across blood establishments.

Assays not well-harmonized due to non-commutable WHO ferritin measurement standards.

Be careful when comparing ferritin measurements from different blood establishments!



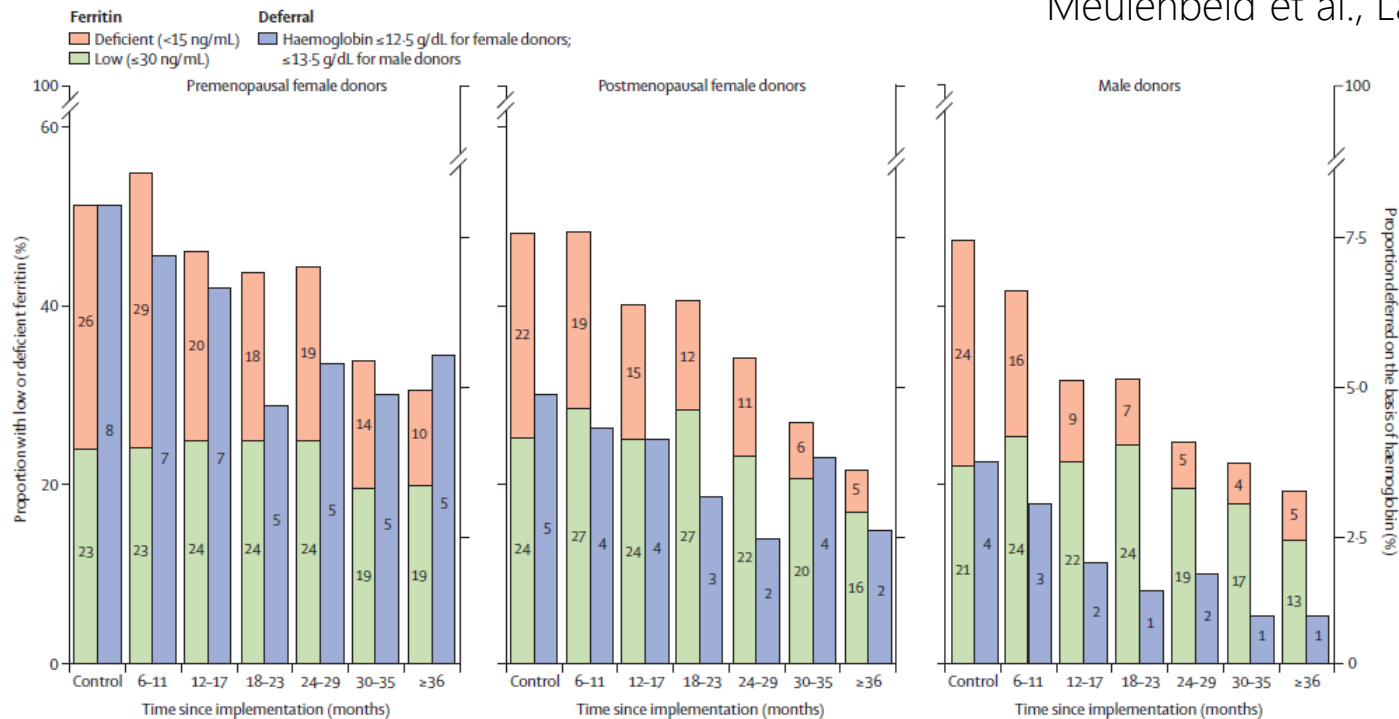
*WHO guideline on use of ferritin concentrations to assess iron status in individuals and populations
– World Health Organization: <https://www.who.int/publications/i/item/9789240000124>



Effectiveness of iron management strategies on donor recovery

Ferritin-guided donation intervals

Meulenbeld et al., Lancet, 2024





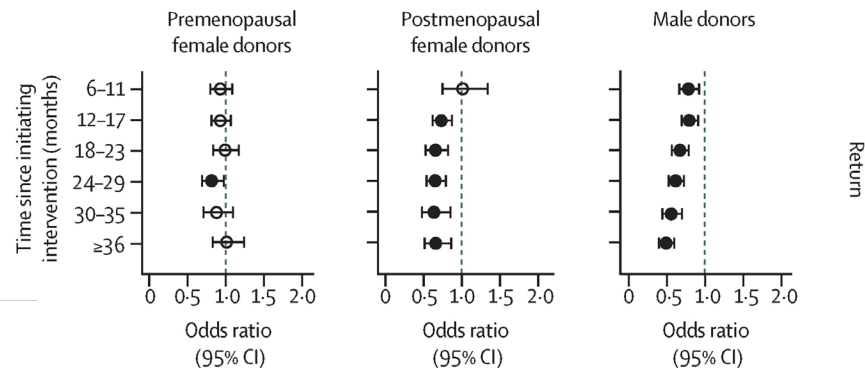
Effectiveness of iron management strategies on donor recovery

Ferritin-guided donation intervals FIND'EM trial

Meulenbeld et al., Lancet, 2024

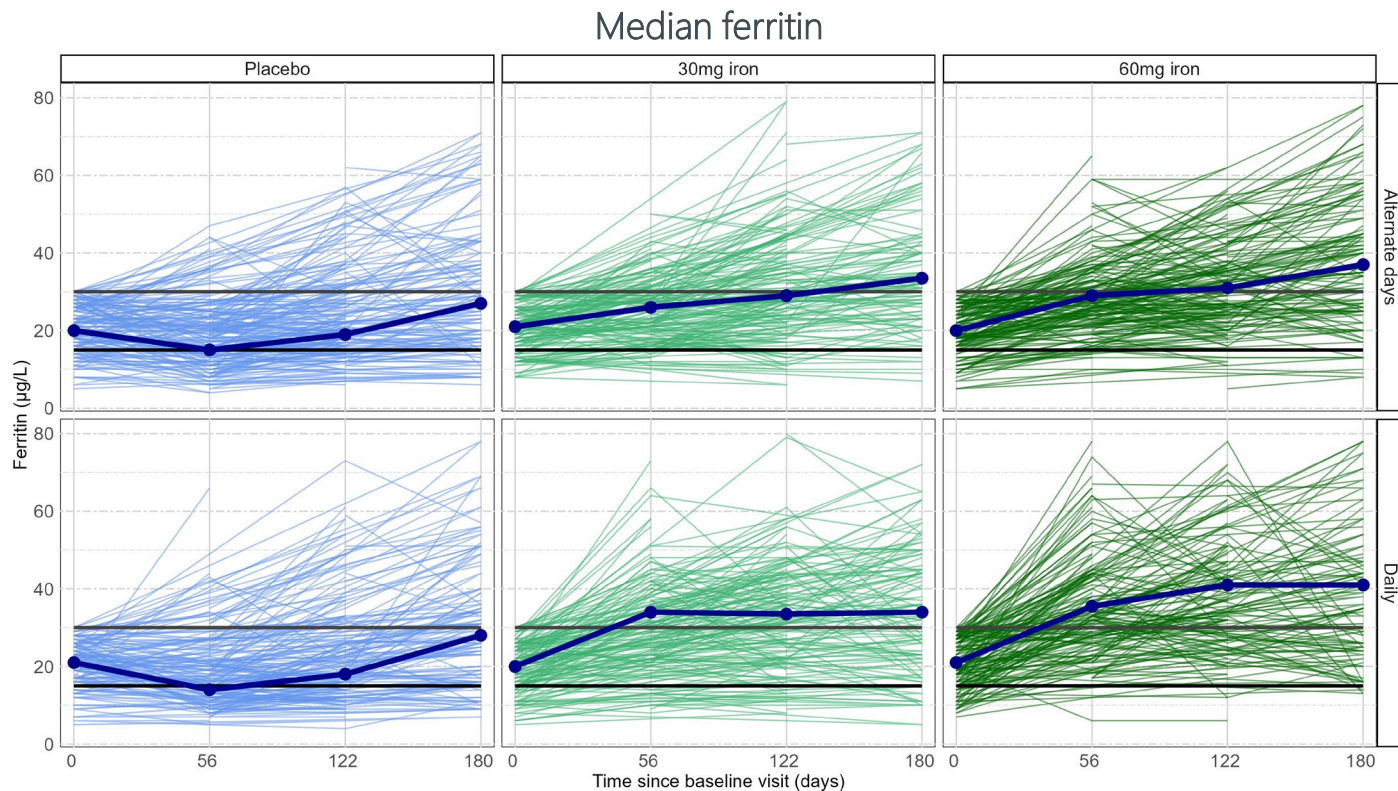
Effectively increase ferritin and Hb,
decrease iron deficiency and for males also
Hb-deferrals.

But...



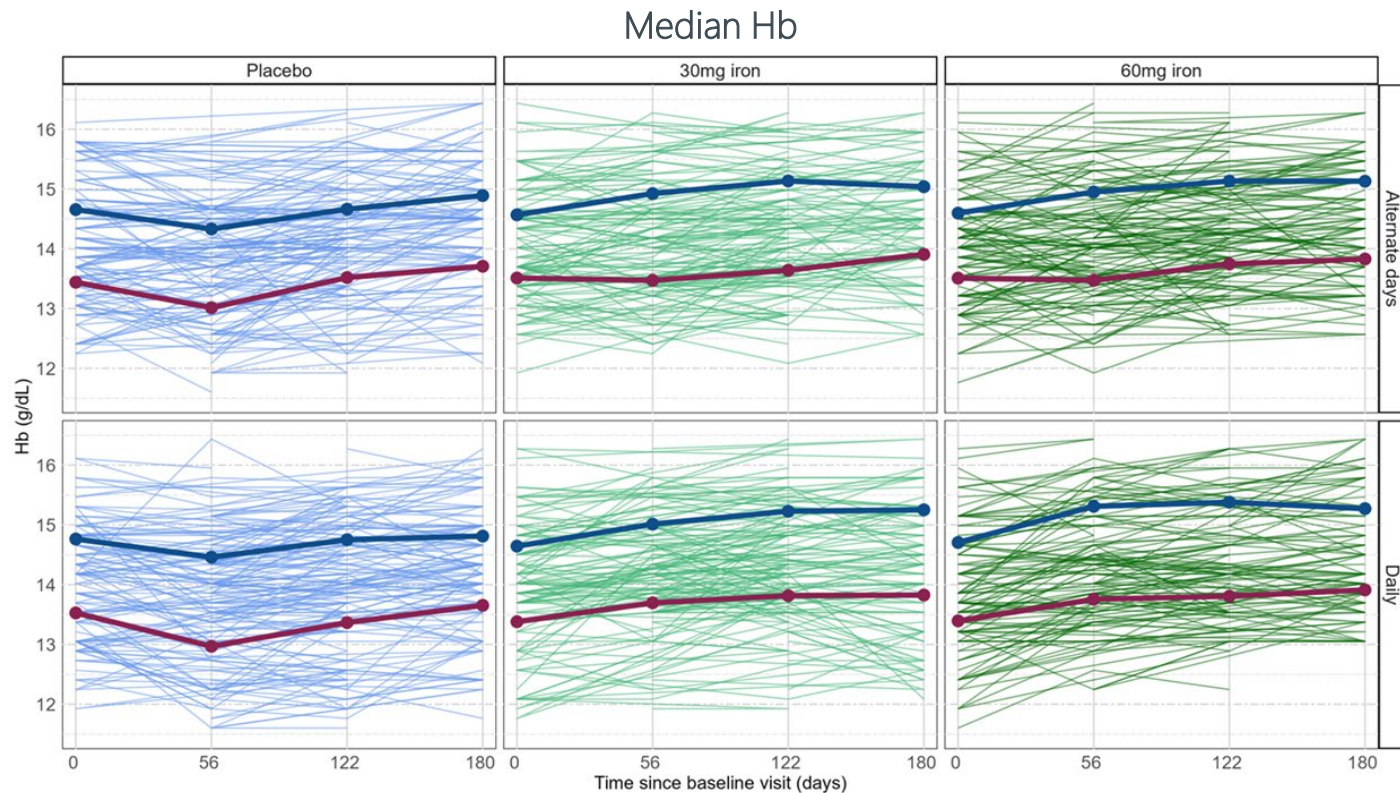


Ferritin-guided iron supplementation FORTE trial





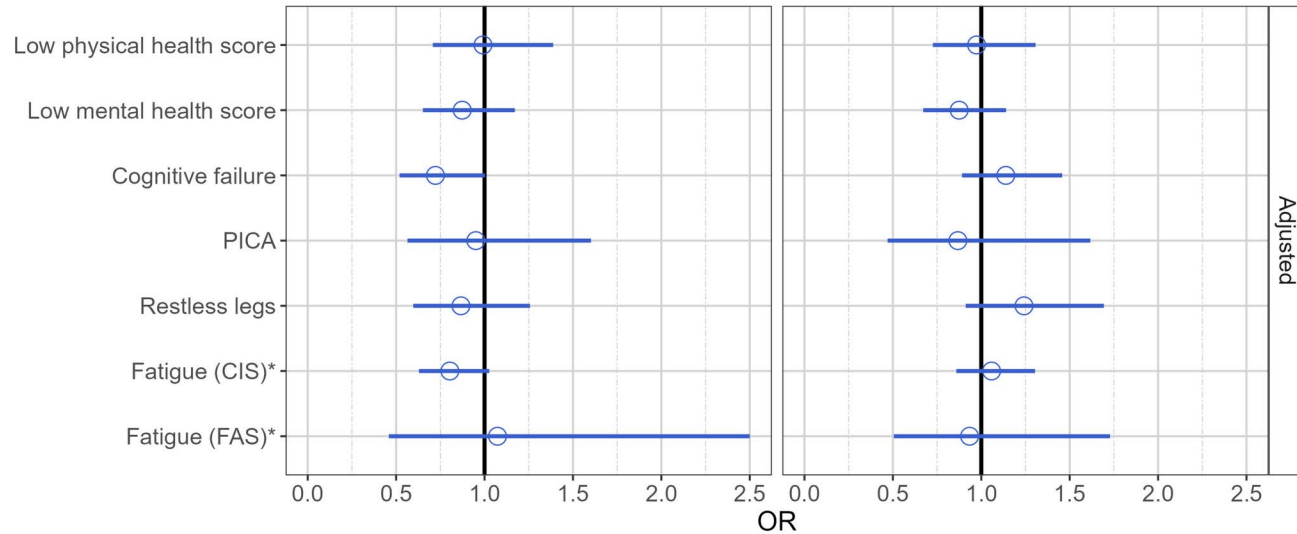
Ferritin-guided iron supplementation FORTE trial



Iron deficiency symptoms

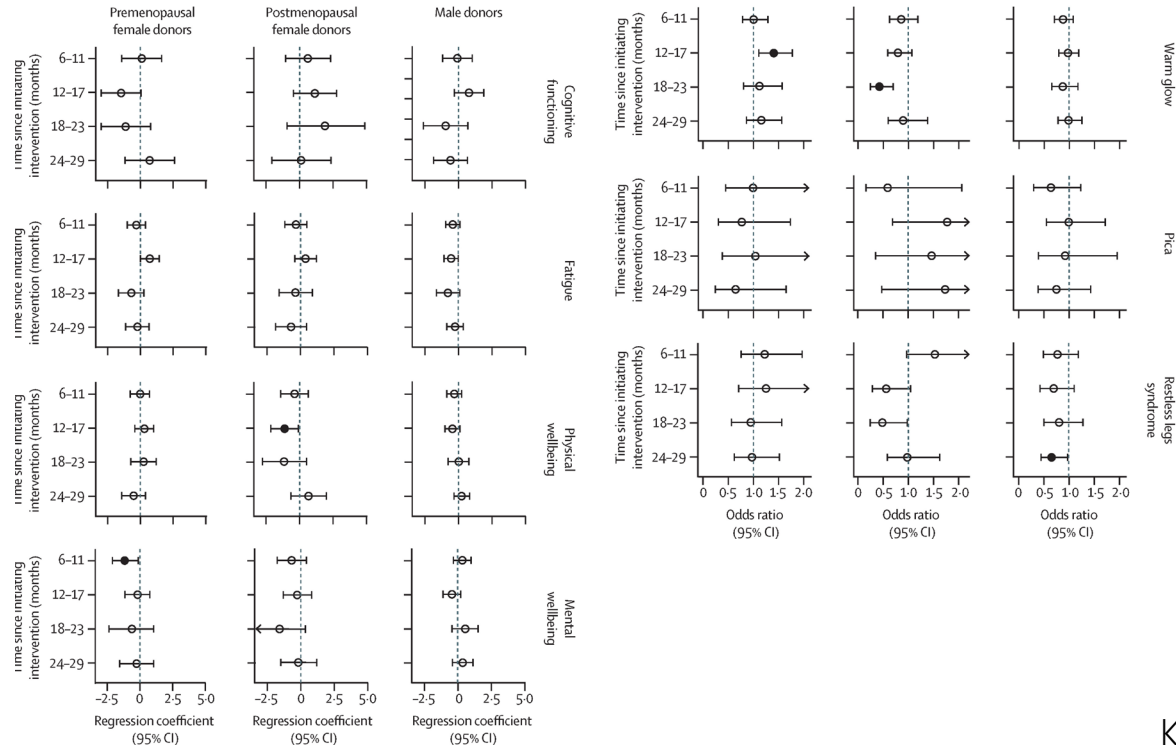


Associations between ferritin levels and ID symptoms in non-anemic donors



Karregat et al., Transfusion, 2024
Meulenbeld et al., Lancet, 2024

Iron deficiency symptoms



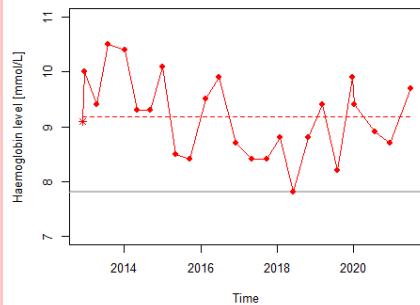
Seems to be no effect of low ferritin or ferritin improvement on donor symptoms, but...

- Donors with symptoms may drop out of our populations over time
- Confounding by healthy donor effect
- Objective measures needed because of warm glow

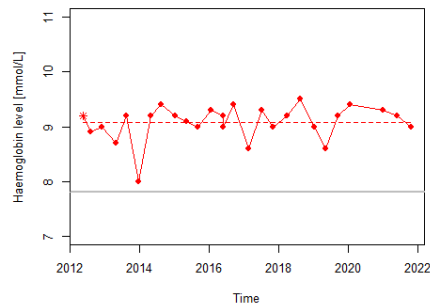


Group 1

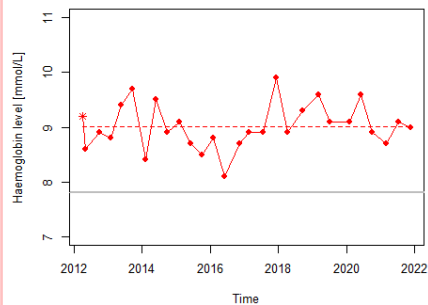
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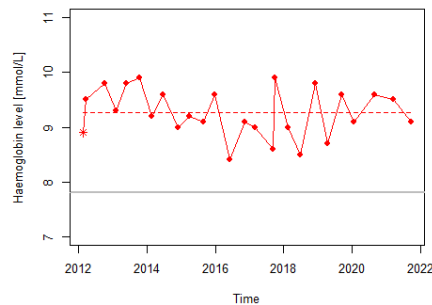
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Donor ID = 84272885 (F)

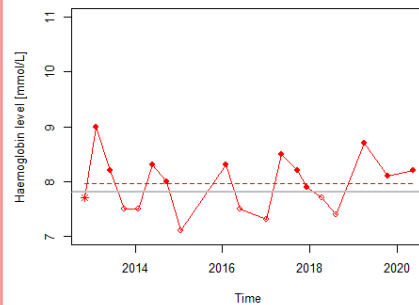


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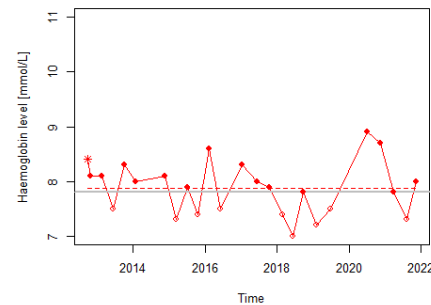


Group 2

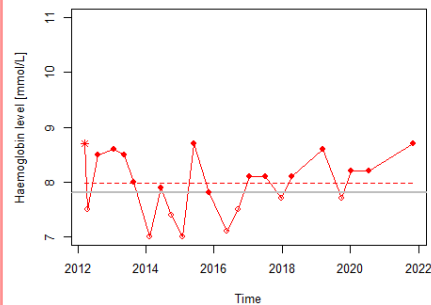
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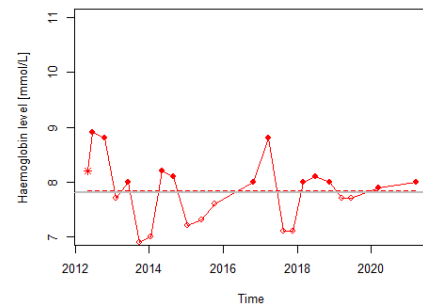
Donor ID = 70900742 (F)



Donor ID = 61774446 (F)



Donor ID = 75540159 (F)





Donor intake



Donor intake

First donation

Three to
six weeks

Time →

Donor intake



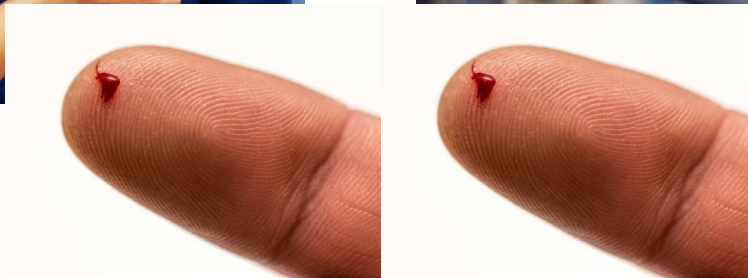
2 measurements



First donation

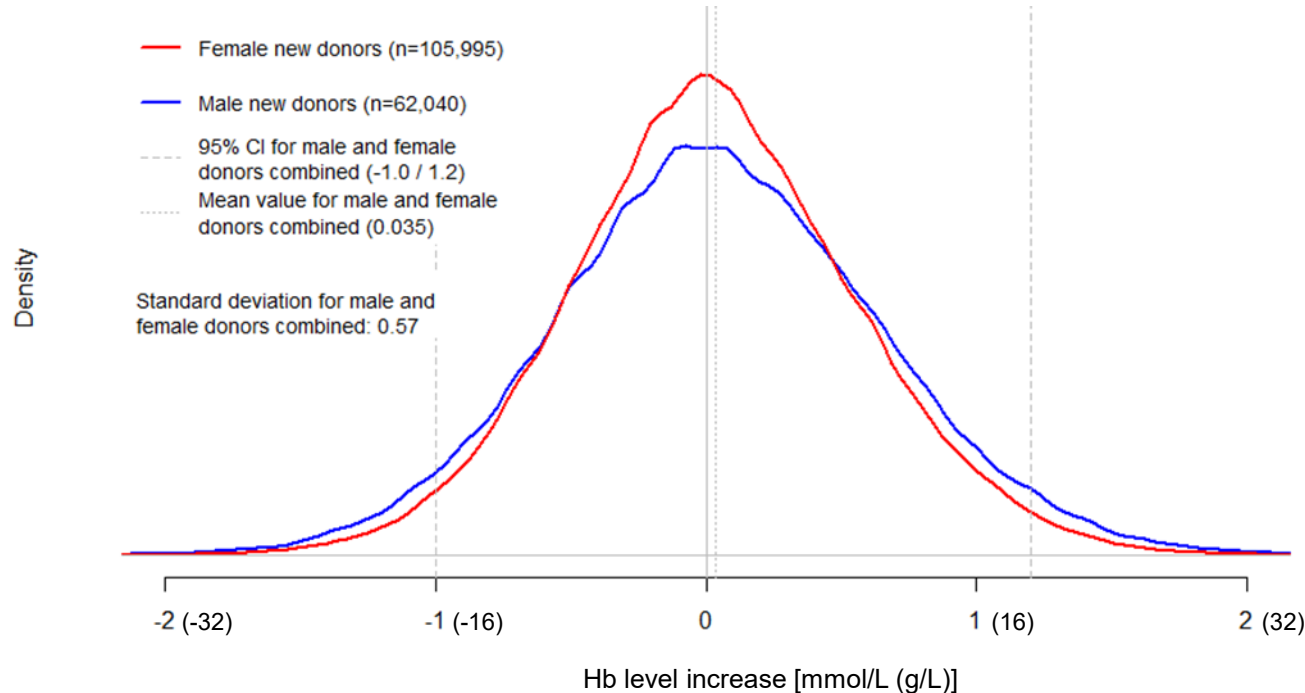


no intervention



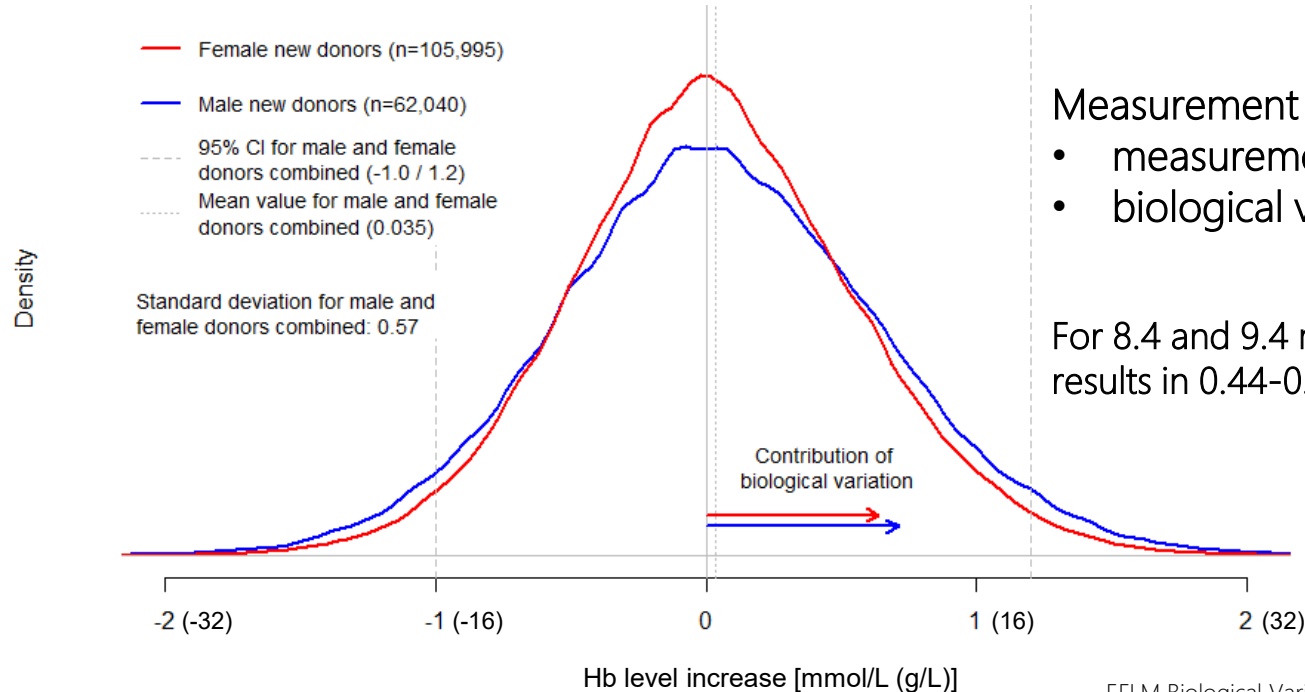


Variability in observed Hb levels (measured within 6 weeks after intake)





Variability in observed Hb levels (measured within 6 weeks after intake)



Measurement variation

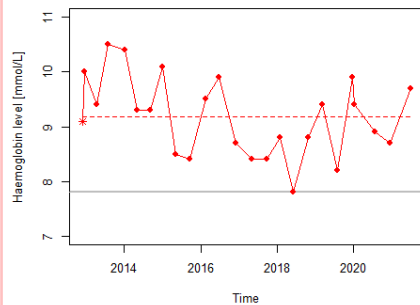
- measurement variation
- biological variation (2.7%)

For 8.4 and 9.4 mmol/L (F/M) this results in 0.44-0.49 mmol/L or 7-8 g/L

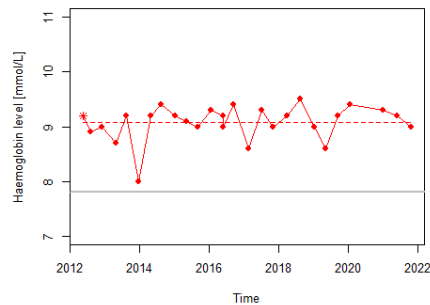


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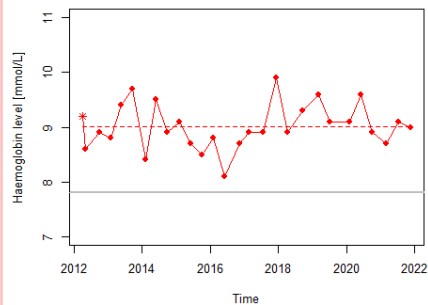
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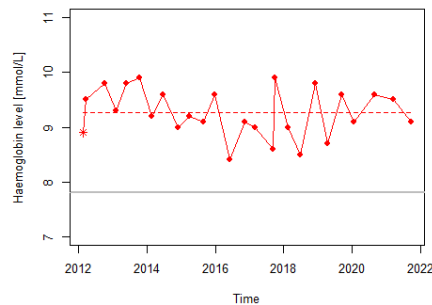
Donor ID = 46838916 (F)



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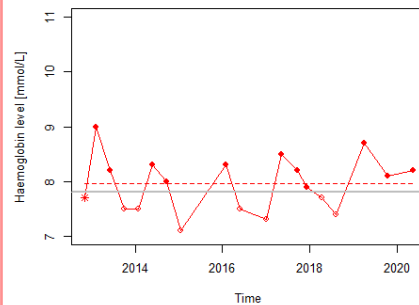


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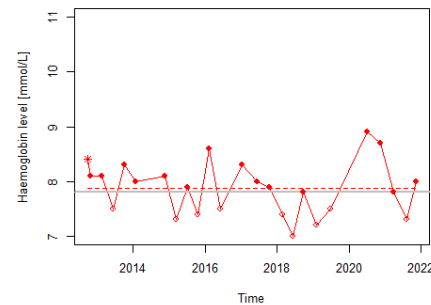


Group 2

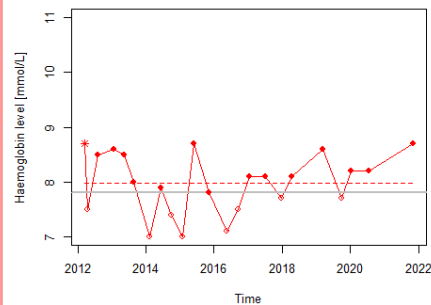
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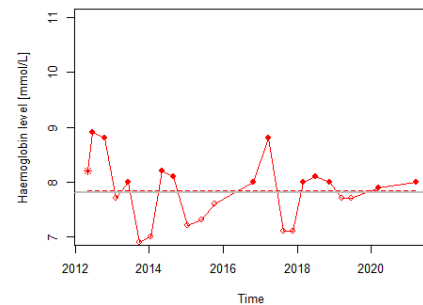
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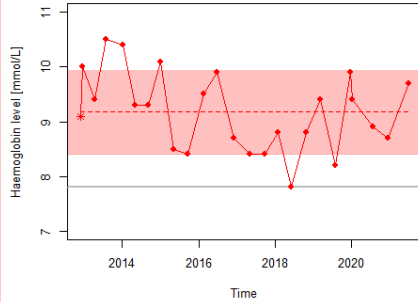
Donor ID = 75540159 (F)



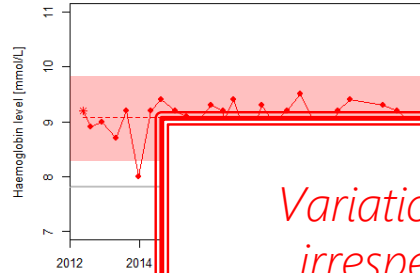


Group 1

Donor ID = 1698270 (F)



Donor ID = 46838916 (F)

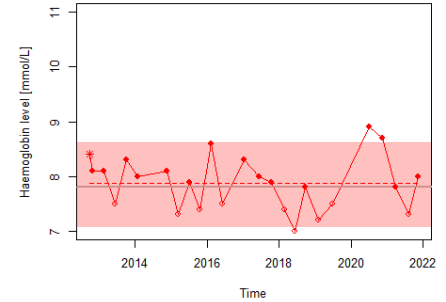


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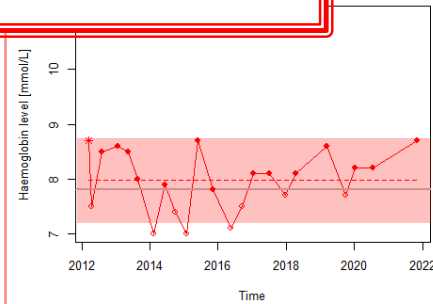
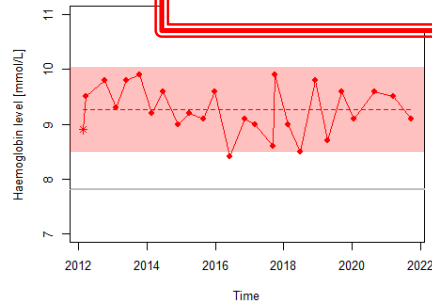
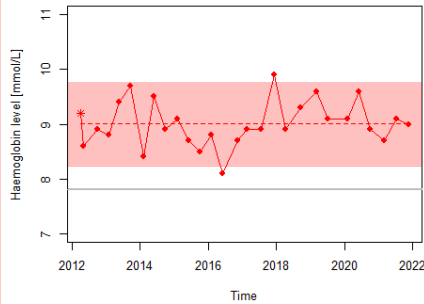


Group 2

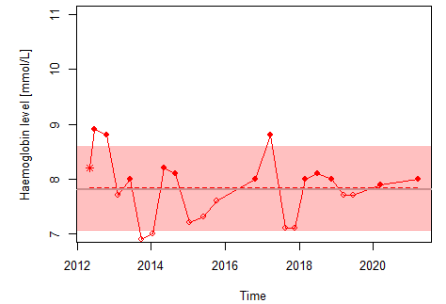
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Donor ID = 84272885 (F)



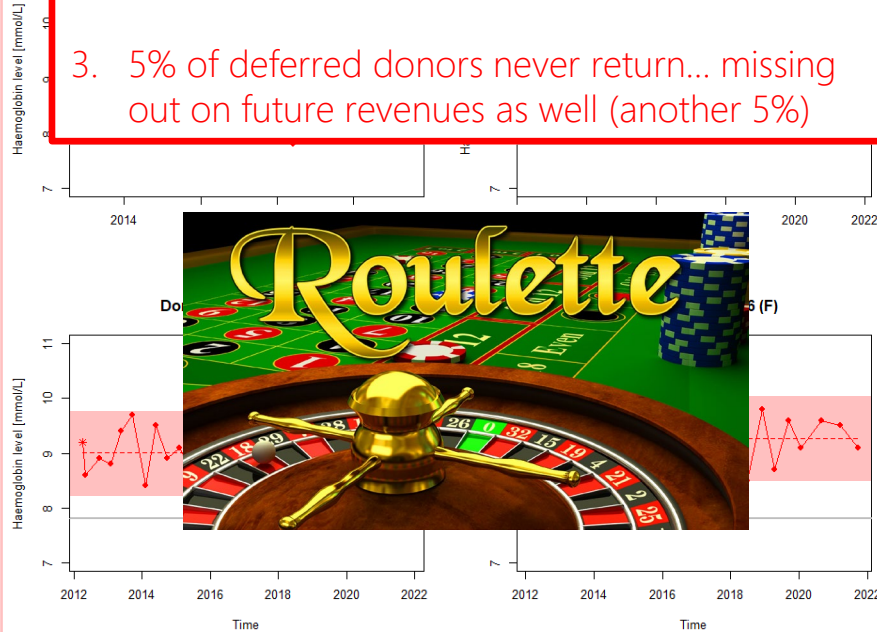
Donor ID = 75540159 (F)



*Variation is present,
irrespective of the
donation!!*



1. Current onsite Hb-deferral is a chance process
2. In the Netherlands we lose 5% of donations
3. 5% of deferred donors never return... missing out on future revenues as well (another 5%)



There is room for improvement
in donor deferral strategies...

*We can and should
be doing better!!*

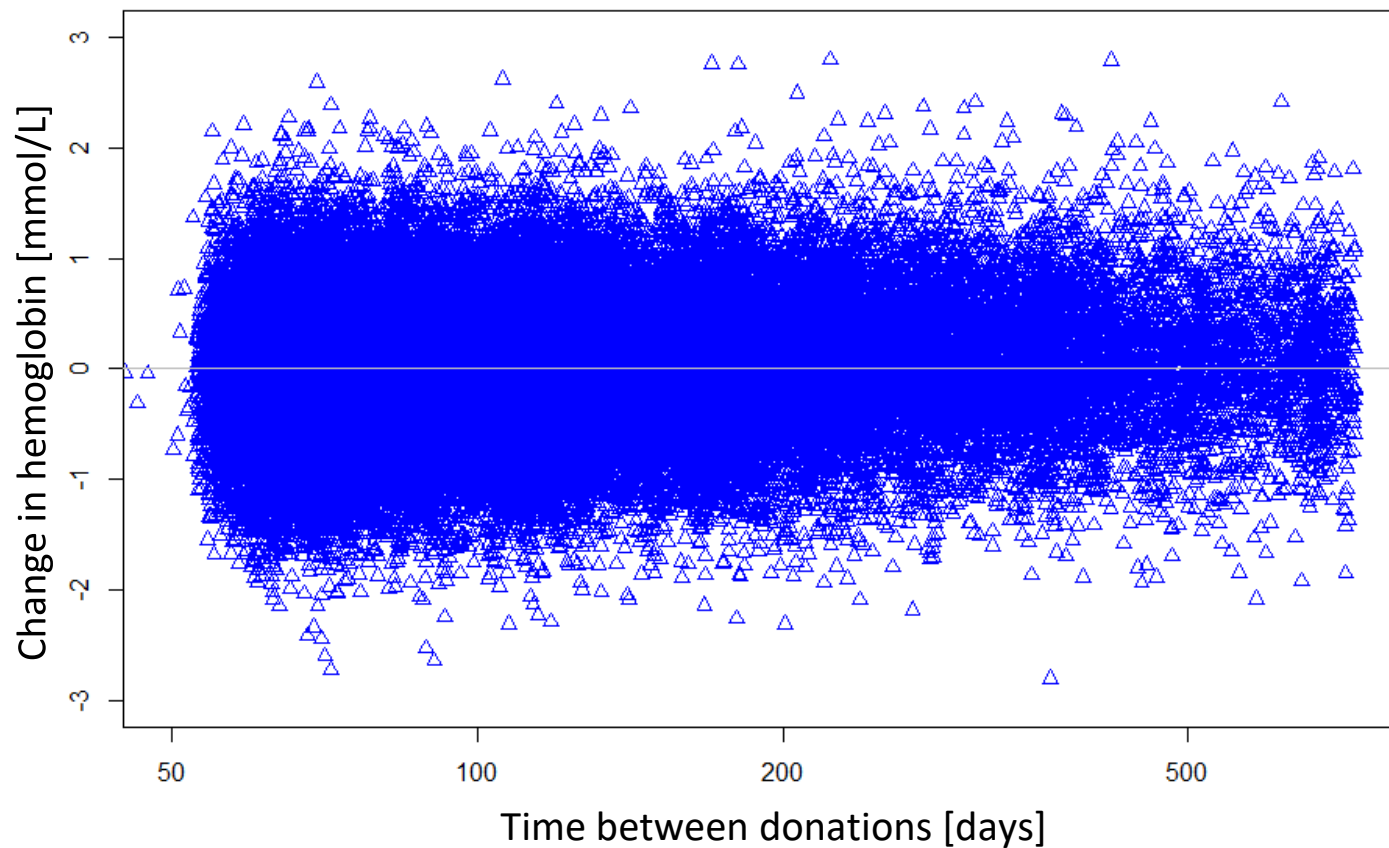


Why the majority of on-site repeat donor deferrals are completely unwarranted...

MP Janssen, Transfusion. 2022 Oct;62(10):2068-2075. doi: 10.1111/trf.17085.

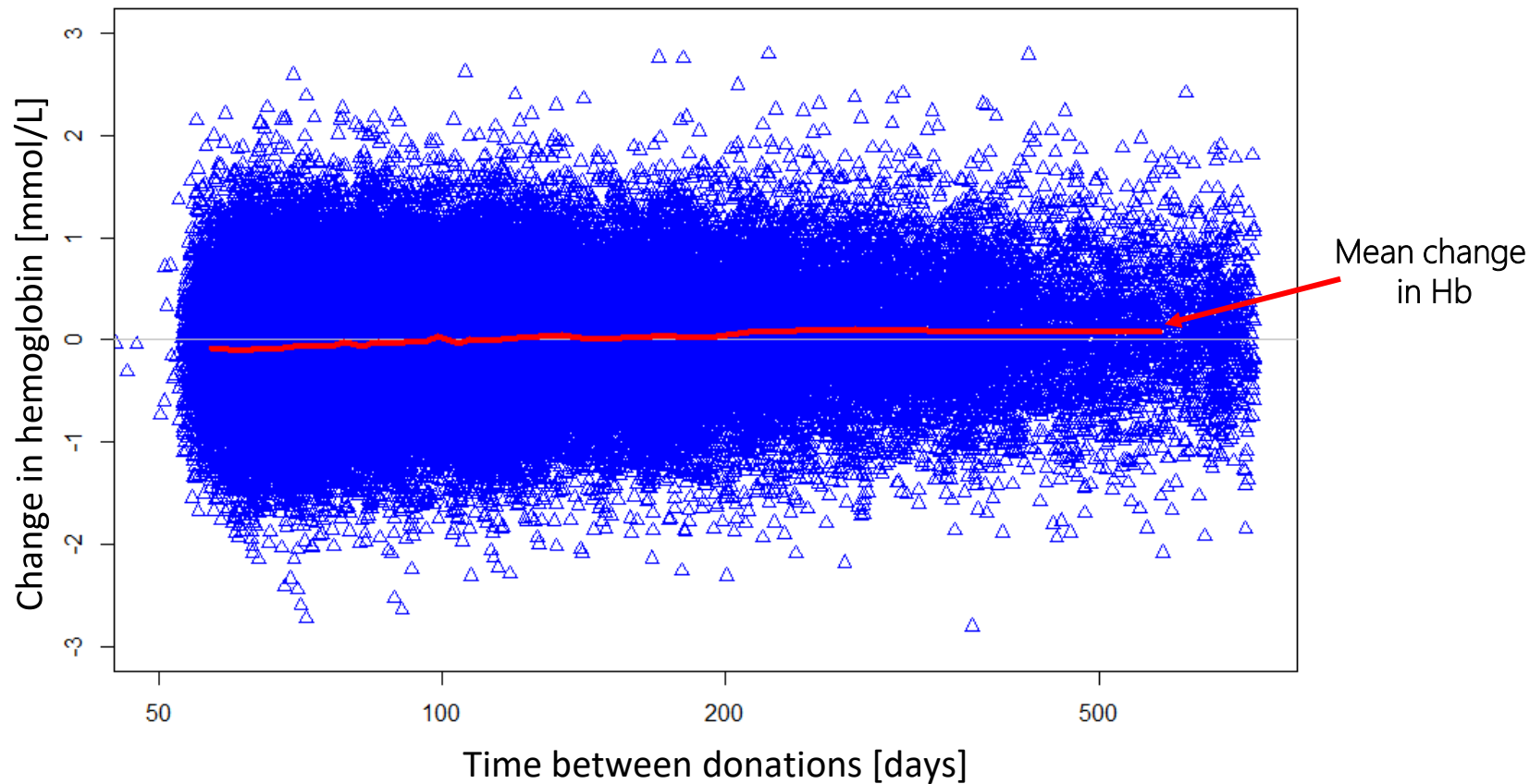


Change in hemoglobin between donations in 1,881,317 male donors



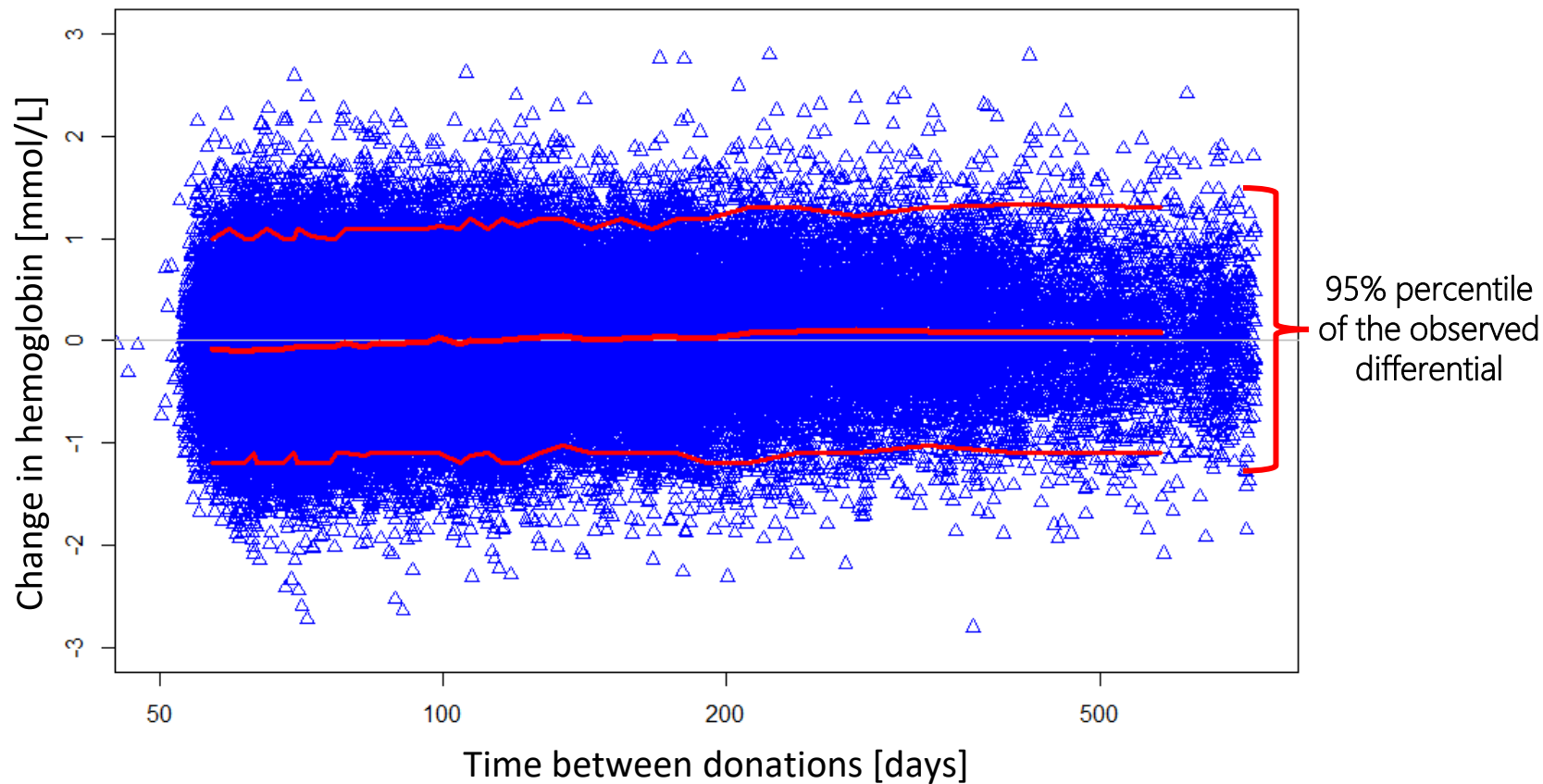


Change in hemoglobin between donations in 1,881,317 male donors



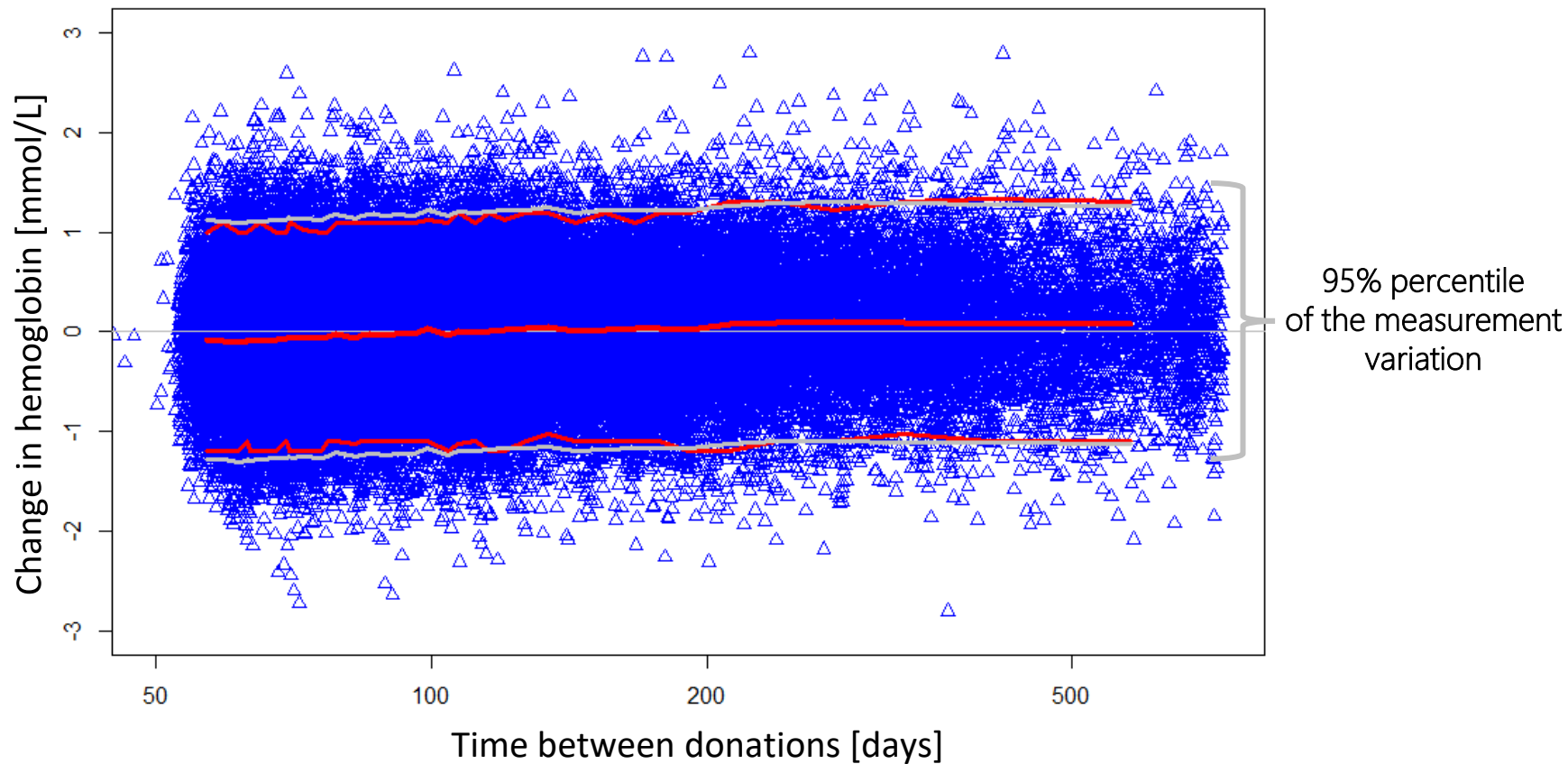


Change in hemoglobin between donations in 1,881,317 male donors



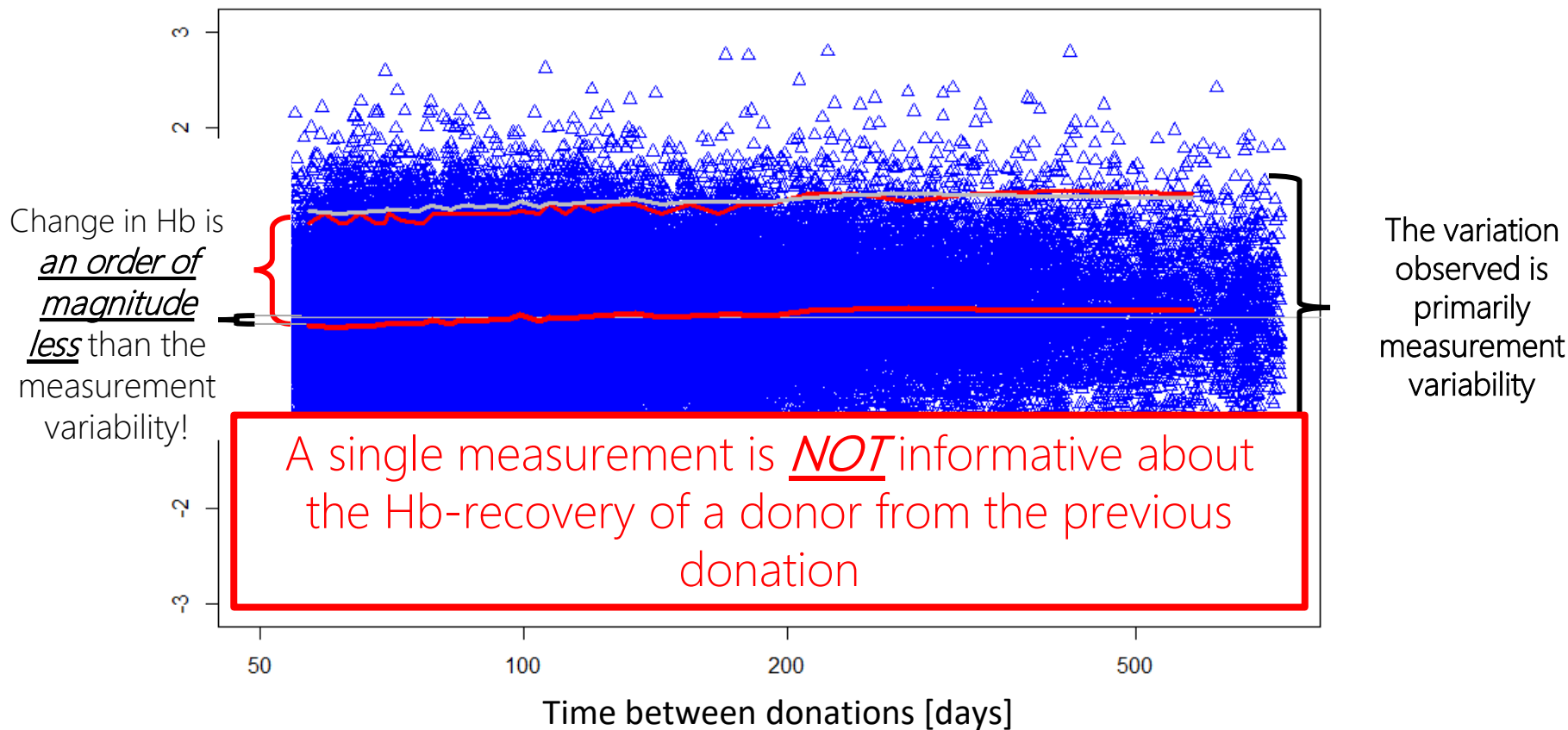


Change in hemoglobin between donations in 1,881,317 male donors





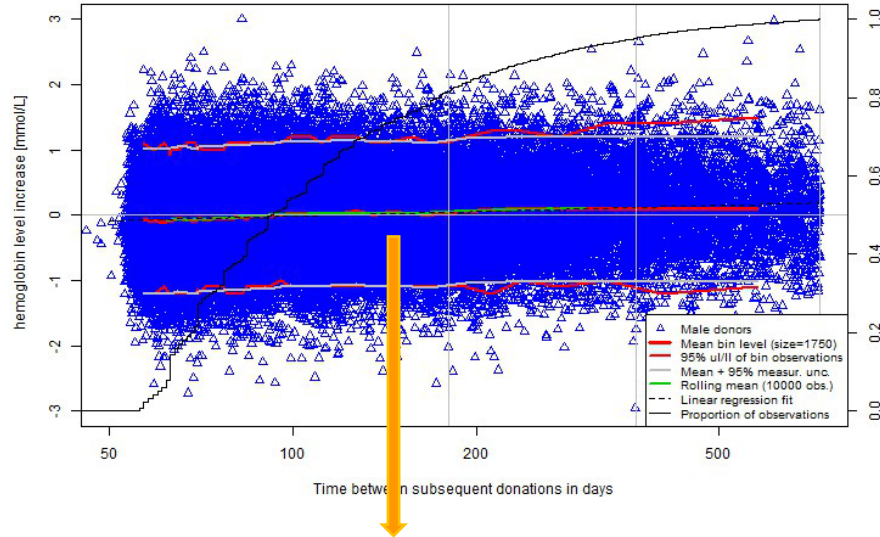
Change in hemoglobin between donations in 1,881,317 male donors





Change in Hb and ferritin in between donations

Hemoglobin change in male repeat donors (n=1,881,317)

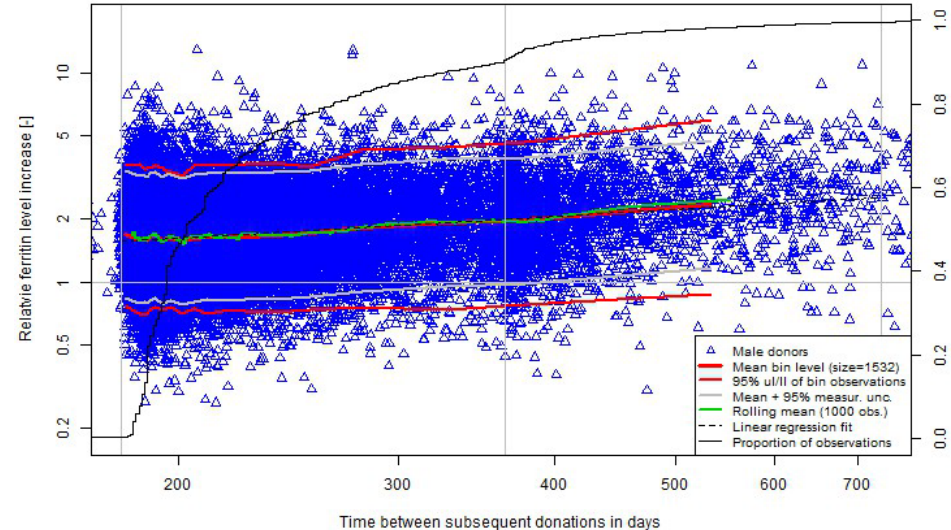


Variance is for 100% explained
by measurement variation

Variance is for 73% explained by
measurement variation



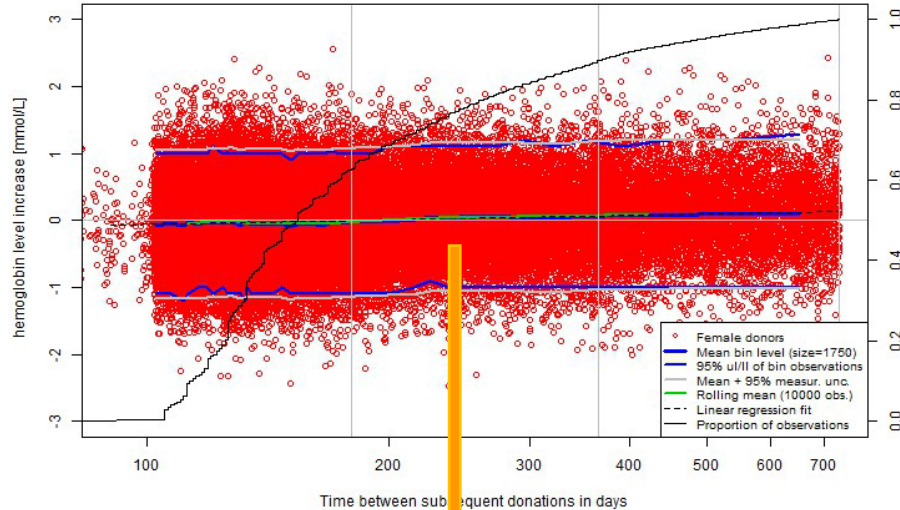
Relative ferritin change in male repeat donors with ferritin levels
between 15 and 30 ng/mL (n=30,639)





Change in Hb and ferritin in between donations

Hemoglobin change in female repeat donors (n=1,524,661)

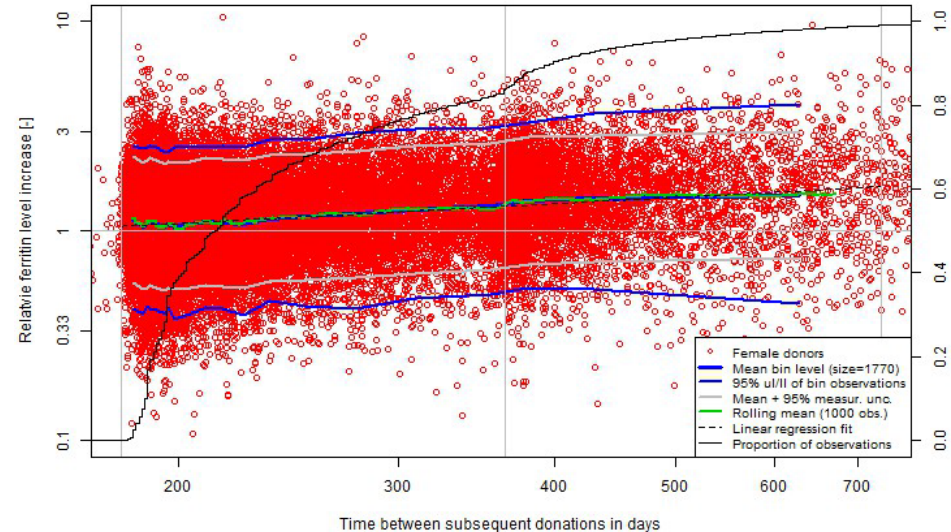


Variance is for 100% explained by measurement variation

Variance is for 59% explained by measurement variation



Relative ferritin change in female repeat donors with ferritin levels between 15 and 30 ng/mL (n=35,392)



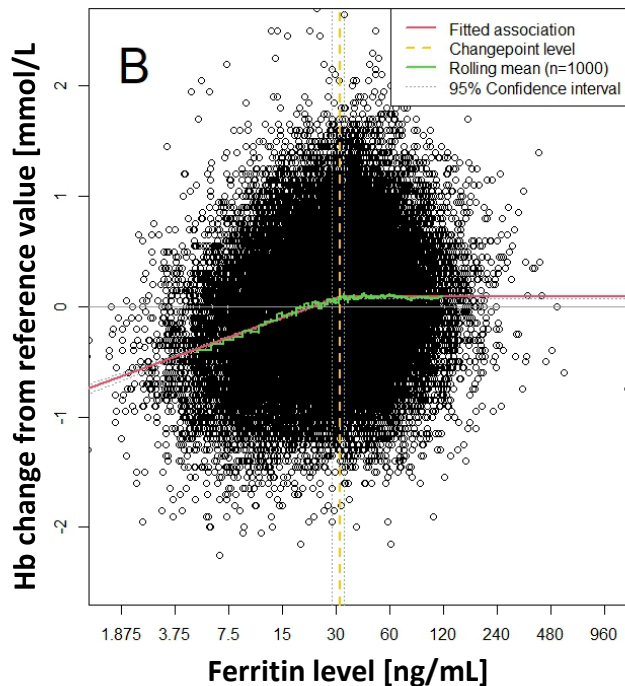
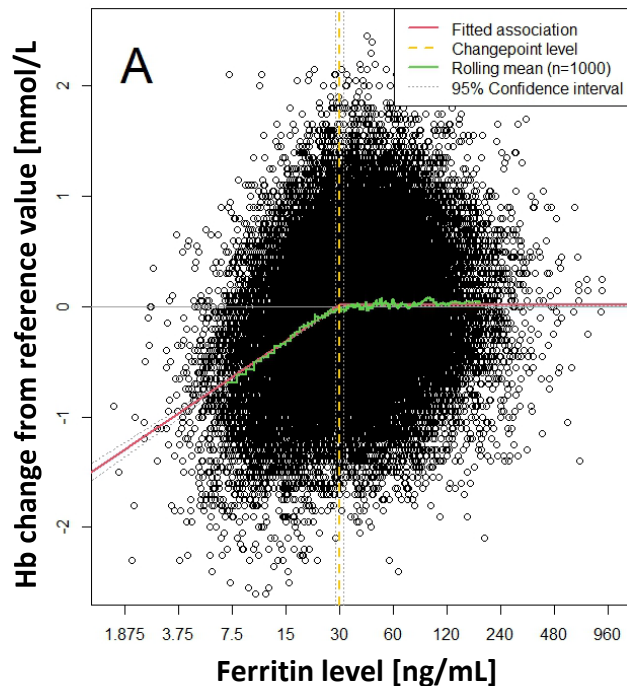


Association between ferritin and Hb

Male donors (n=50,390)

Female donors (n=49,864)

Change in
Hb since
first
donation

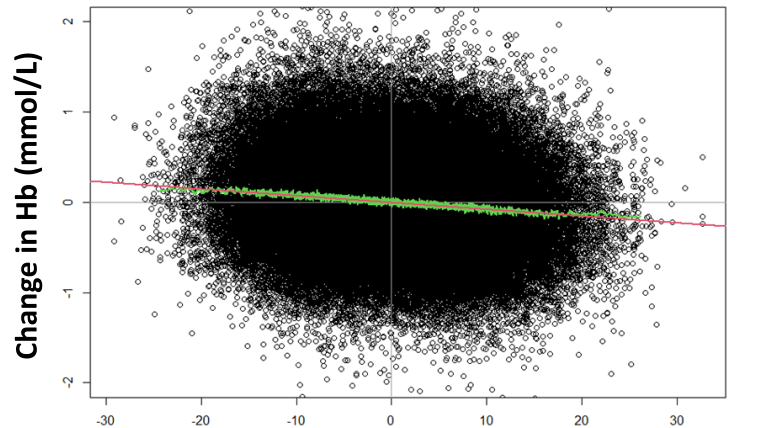


$$\text{Hb change} = \Delta\text{Hb} = \text{Current Hb} - \text{Reference Hb}$$



Effect of ambient temperature and time of donation

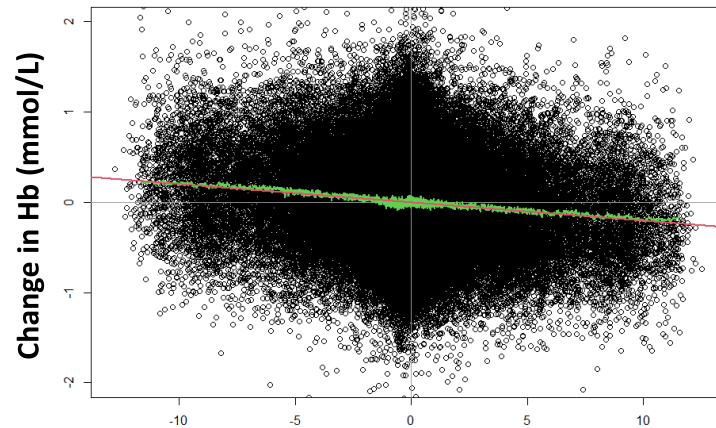
Effect of change in ambient temperature at donation



Change in ambient temperature between donations [°C]

-0.15 mmol/L per 20°C

Effect of change in hour of donation during the day



Change in time of donation between donations [hrs]

-0.16 mmol/L per 8 hours



NEXT STEPS – more tailoring?

Current policies still based on *"one size fits all"*

Promising leads for further improvement:

- Individual donor characteristics
 - SNPs
 - Menopause / heavy menstrual bleeding
 - Dietary iron intake
- Individual changes in Hb and/or ferritin levels



SNPs

INTERVAL, DBDS, deCODE genetics
Bell S, Comm Biol, 2021

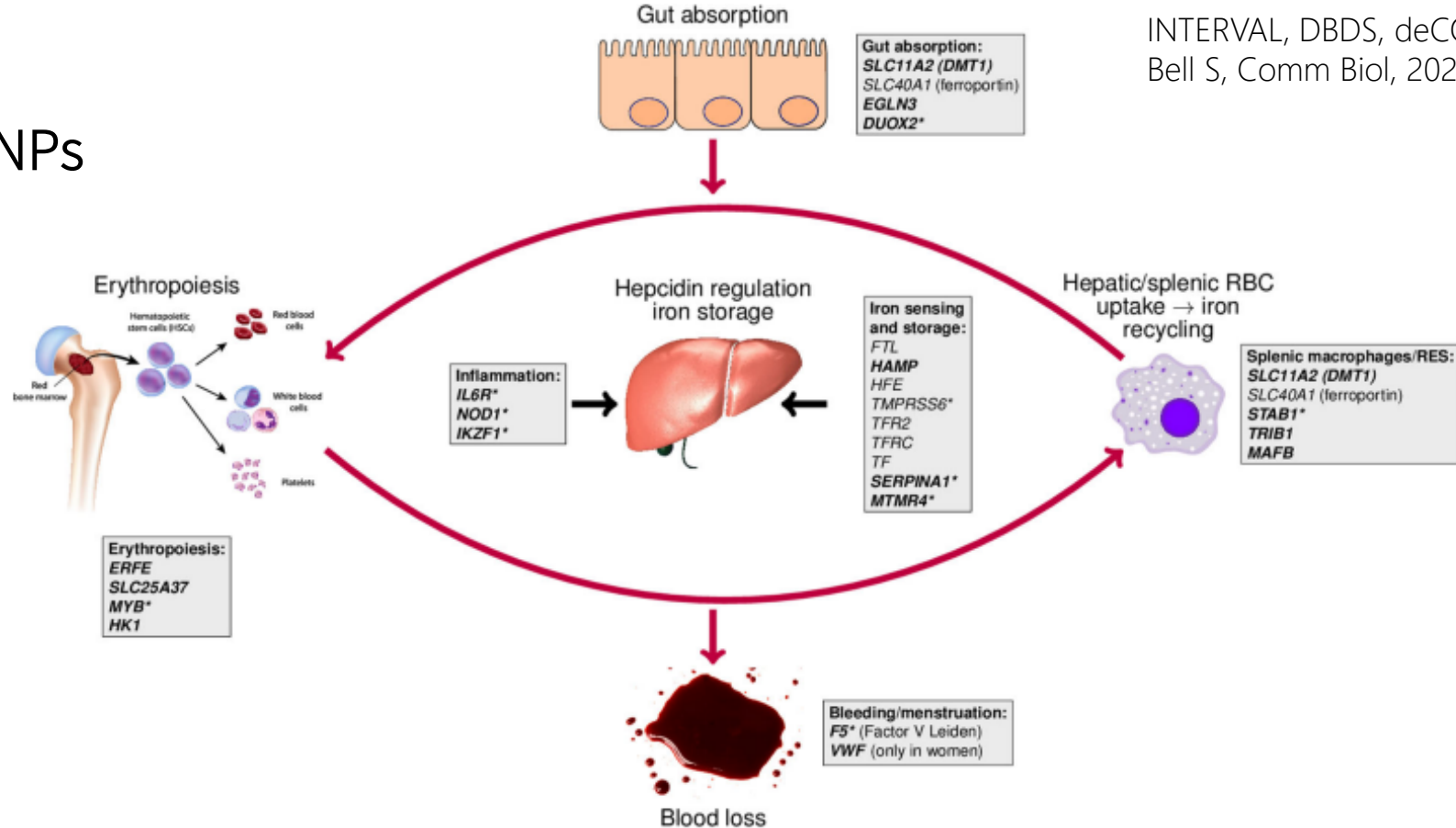


Fig. 4 Iron homeostasis loci in the context of systemic iron homeostasis, categorization into main physiological processes. Novel loci are in bold font.

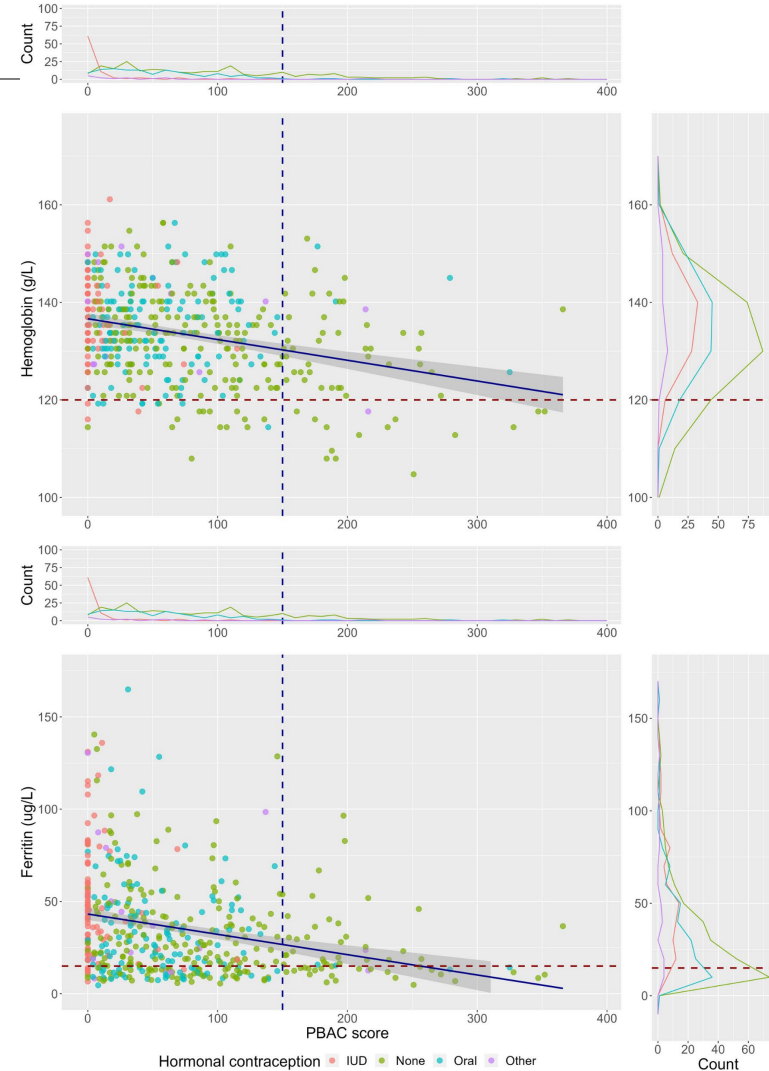
*Gene with a predicted probability of being causal (based on a variant-to-gene algorithm, see "Methods") larger than 50%. The liver, blood spot, and erythropoiesis/hematopoiesis cartoons were bought from Shutterstock (standard license), the macrophage is from Wikimedia Commons (<https://commons.wikimedia.org/wiki/File:Macrophage.svg>).



Menopause and menstrual blood loss

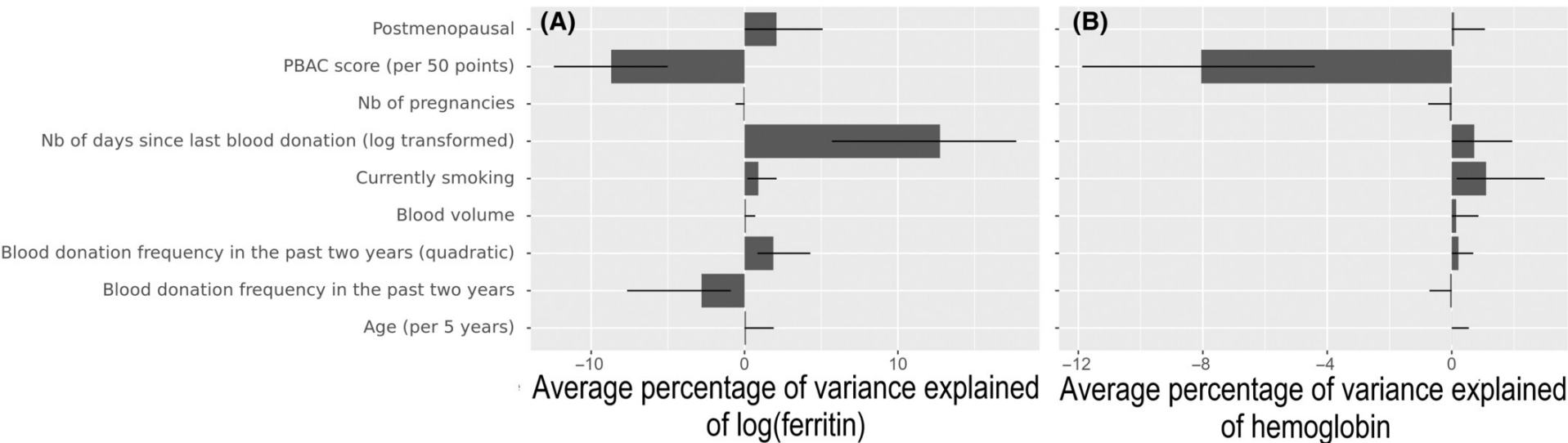
Hb deferral rates female whole blood donors:

- 2016:
 - Hb deferral rates were **9.1 and 5.6%** for females aged <45 and ≥ 45 years, respectively.
 - Iron deficiency (ID) rates were **25.8 and 9.4%**, respectively (both $p < 0.001$).
- 2023:
 - Hb deferral rates **4.8 and 2.6%**,
 - ID rates **14.7 and 6.2%** (both $p < 0.001$).





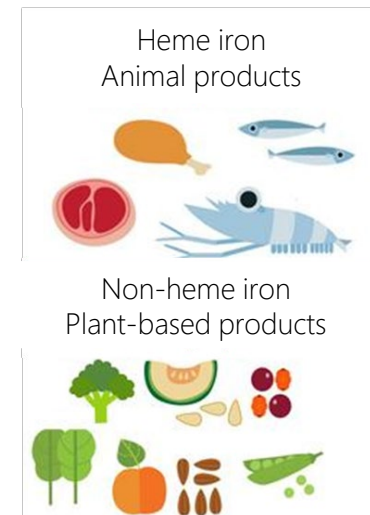
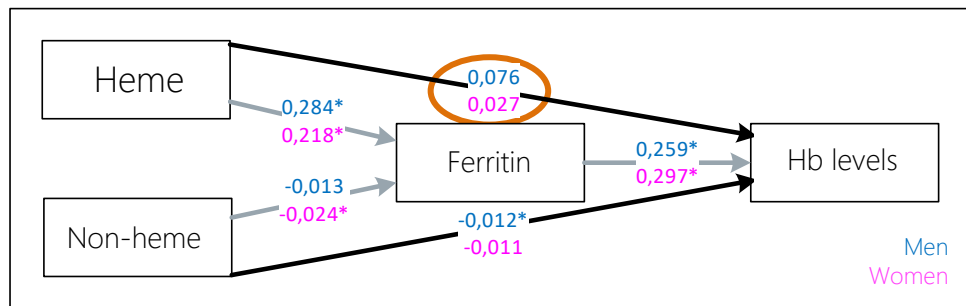
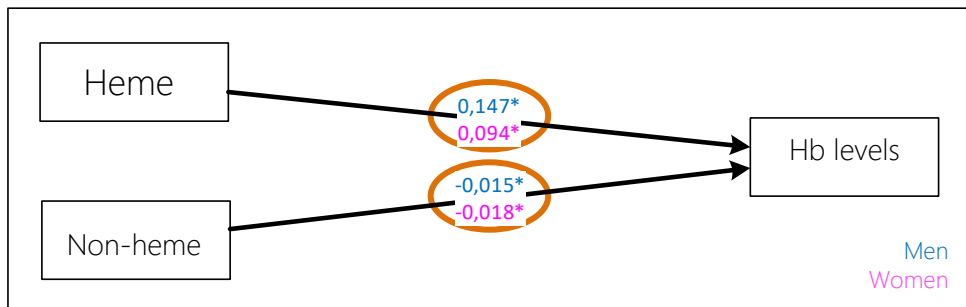
Menstrual blood loss (PBAC score): explains ferritin and Hb variance



Relative importance analysis (RIA) of a linear model of ferritin (A) and Hb (B). RIA estimates the average percentage of variance in the outcome variable explained by each covariate. A positive value represents a positive correlation, and a negative value represents a negative correlation. The bootstrapped 95% CIs are characterized by the black lines.



Dietary heme iron intake



Indirect effect		
♂	Heme	0.073 (0.046 to 0.106)
	Non-heme	-0.003 (-0.008 to 0.000)
♀	Heme	0.065 (0.031 to 0.100)
	Non-heme	-0.007 (-0.013 to -0.002)



To summarize

- Changes in hemoglobin levels between donations are small, variation in measurement outcomes is large
- Long-term frequent donation may lead to reduced Hb and ferritin levels -> extended donation intervals or iron supplementation mitigates this
- Single deferral thresholds do not protect donors against cumulative loss of iron
- Impact of donations differs between donors -> depending on donor characteristics, lifestyle and previous Hb and ferritin levels



Key questions for a new donor deferral strategy

1. How to handle variation in measurement outcomes?
2. How to balance the risk of unnecessary deferral against the risk of donating with too low iron/Hb levels?
3. What is or should be our targets when striving for donor health?
4. How much uncertainty is acceptable?
5. How should we personalize strategies?





Sanquin

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