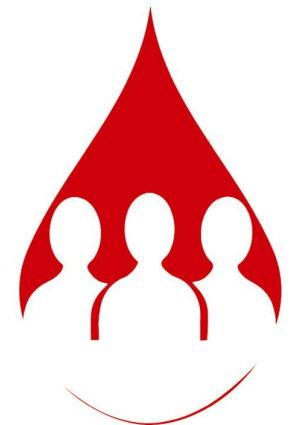


Donor Health and Vigilance, an Update

Christian Erikstrup
Chair Professor, Chief Physician
Head of Blood Production
Department of Clinical Immunology
Aarhus University Hospital



The Danish Blood Donor Study

Disclosure

- Unrestricted research grant from Abbott Diagnostics



Plasma donation and health

Demand:

- The demand for PDMPs is increasing
- COVID-19 convalescent plasma showed that new demand can appear suddenly
- Can the rest of the world rely on production in the US?
 - Is the supply safe? Will the prices increase?
 - What about ethics: paid donations, donation frequency - consequences for donor health?

Response:

- Several countries are scaling up the plasmapheresis capacity

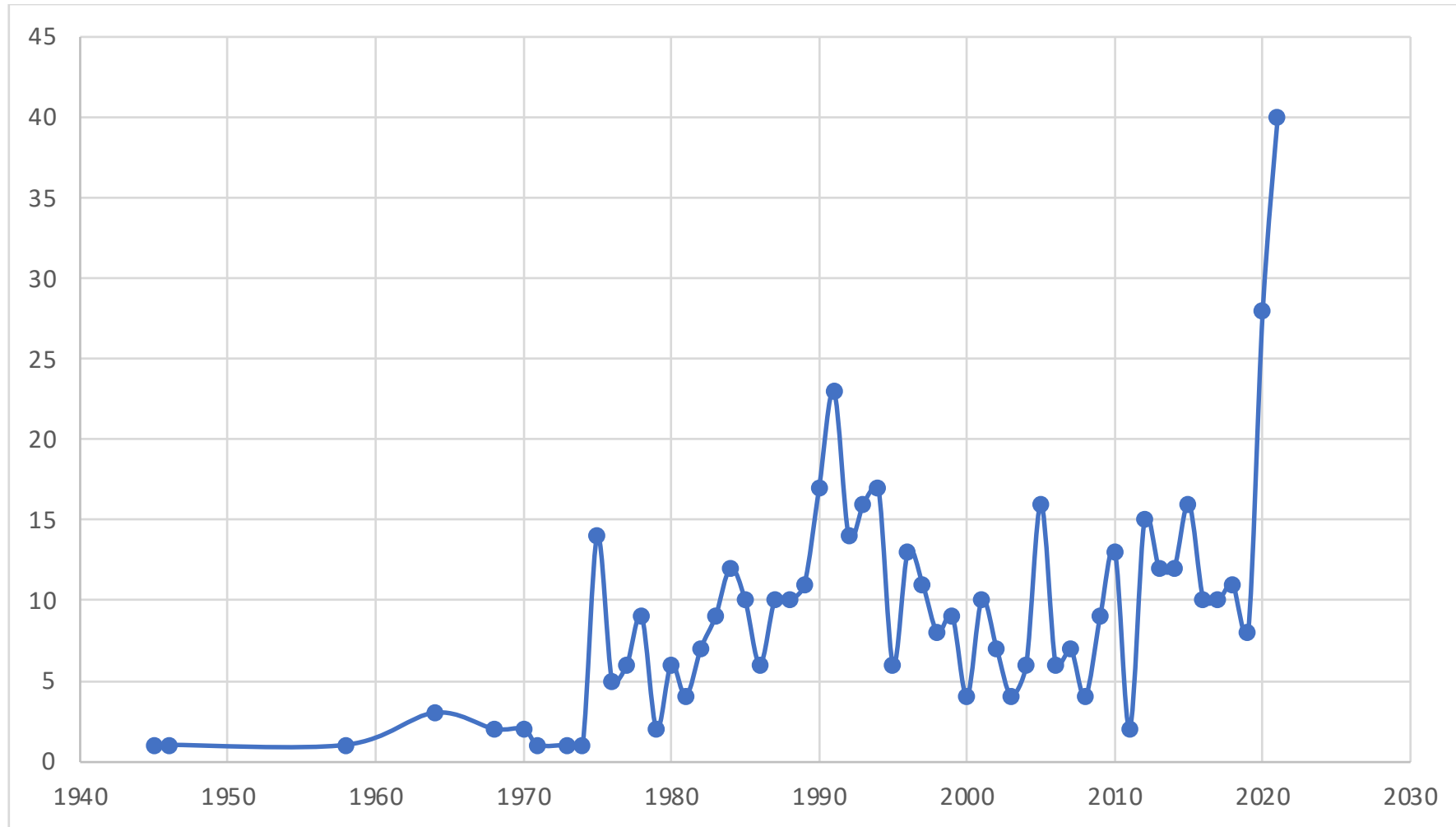
Donor vigilance:

- Collect and analyse data on short and long-term consequences for donor health
- We are obliged to mitigate the risk of deleterious health effects of plasma donation
- Unfortunately, very few studies exist on plasma donation safety/health consequences



Studies of plasma donation

pubmed - (((("donor" OR "donation") AND ("plasmapheresis"))) OR "plasma donation" OR "plasma donor") NOT transplantation



Early studies: Mostly on proteins and IgG

THE AMERICAN JOURNAL OF CLINICAL PATHOLOGY
Copyright © 1966 by The Williams & Wilkins Co.

Vol. 45, No. 4
Printed in U.S.A.

THE LONG-TERM EFFECTS OF REPEATED PLASMAPHERESIS

LAURENCE R. SIMSON, M.D., DONNA M. LIEN, M.T. (ASCP), CAROL L. WARNER, M.T. (ASCP), AND HAROLD A. OBERMAN, M.D.

Department of Pathology, The University of Michigan, Ann Arbor, Michigan 48104

5-7 donors, up to 1 L plasma for up to 32 months.

”...serum protein levels and iron levels and blood indices...

...remained stable and within normal limits.”

Int. Arch. Allergy 41: 883-894 (1971)

The Effect of Prolonged Plasmapheresis on Immunoglobulins, other Serum Proteins, Delayed Hypersensitivity and Phyto-hemagglutinin-Induced Lymphocyte Transformation¹

J. SALVAGGIO, P. ARQUEMBOURG, J. BICKERS and D. BICE

Departments of Medicine and Microbiology
Louisiana State University Medical Center, School of Medicine,
1542 Tulane Avenue, New Orleans, La.

Prisoners, biweekly
plasmapheresis, 800 mL

”... well tolerated clinically by
normal donors with no resulting
increase in infections or delayed
wound healing”

”However, **serum immunoglobulin
... and albumin levels decreased
significantly...**”

Effects of Intensive Plasmapheresis on Normal Blood Donors

By ALLAN KLIMAN, PAUL P. CARBONE, LAWRENCE A. GAYDOS
AND EMIL J. FREIREICH

IN 1914 Abel² described the technic of plasmapheresis in animals and demonstrated that very large amounts of plasma could be withdrawn if the red cells were re-transfused. Since that time, the technic of plasmapheresis has been used extensively in the research laboratory for the study of protein

”Five donors were subjected to acute
plasmapheresis with removal of 5 litres of
plasma in 5 days. In this group, **serum protein
depletion was observed** with particular
depletion appearing at the end of the 5-day
period”

BLOOD, VOL. 23, NO. 5 (MAY), 1964

Safety and Long-term Effects of Plasmapheresis

M. A. COHEN AND H. A. OBERMAN

Transfusion
Mar.-Apr. 1970

*From the Department of Pathology, University of Michigan,
Ann Arbor, Michigan*

”No consistent clinical or laboratory value
abnormalities were found during more than
six years of plasmapheresis of donors who
gave as much as the plasma equivalent of
four units of whole blood per week.”

Loss of IgG

The Canadian Red Cross Plasmapheresis Donor Safety Program: Changes in Plasma Proteins after Long-Term Plasmapheresis

Safia Wasi, Thomas Santowski, Shelley A. Murray, Roger A. Perrault, Peter Gill
The Canadian Red Cross Society, National Reference Laboratory, Protein Chemistry Section, Ottawa, Ont., Canada

Canada planned self sufficiency – this study was performed to ascertain safety in plasma donation

Repeated plasmapheresis did not affect total protein

The mentioned studies primarily report biochemical data not clinical outcomes.

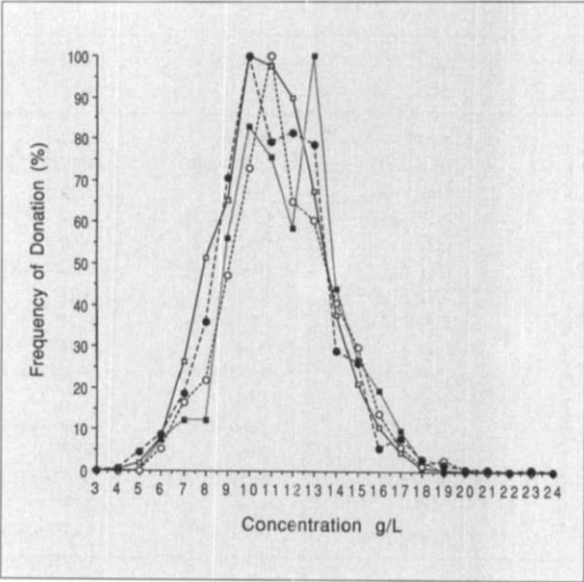


Fig. 3. Immunoglobulin G concentration distributions for first-time donations from 208 donors (population A: ■); 5,042 cumulative donations from the same 208 donors (population B: □); 1,294 donations collected over 3 months (population C: ●); and 767 donations from recent first-time donors (population D: ○).

The impact of the intensity of serum collection and the speed of deep-freezing on the quality of plasma

Peter Hellstern, Jürgen Bach, Hannelore Haubelt, Walter E. Hitzler, Sabine Mathis, and Anette Vogt

Volume 41, December 2001 **TRANSFUSION**

”In conclusion, our findings demonstrate that source plasma collected by intensive plasmapheresis shows a marked reduction in IgG levels.”

TABLE 1. ABO blood group distribution, plasma volume, citrate concentration, total protein, albumin, and IgG in the plasmas collected by intensive (n = 75) or moderate (n = 75) plasmapheresis*

	Intensive plasmapheresis	Moderate plasmapheresis	Difference (%)	p value
Number of units	75	75		
ABO blood group distribution (O/A/B/AB)	32/25/12/6	30/32/11/2		
Volume per unit (mL)	875 (685-900)	720 (710-730)	19.4	< 0.0001
Citrate (mmol/L)	14.4 (11.3-18.2)	16.4 (13.7-19.4)	12.9	< 0.0001
Total protein (g/L)	58 (45-69)	61 (54-70)	5.0	< 0.0001
Albumin (g/L)	36 (29-44)	37 (32-68)	2.7	0.007
IgG (g/L)	7.1 (2.8-11.5)	8.6 (5.2-14.5)	19.1	< 0.0001

* Results presented as median (minimum and maximum).

SIPLA

3,783 donors were switched from a moderate to an intensive plasmapheresis regimen: up to 60 times/y for 3 years

16% of donors were excluded when IgG, TSP or Hb levels fell below threshold values

It was concluded that intensive donation was safe when donors were monitored as in the study

”The incidence in severe cardiovascular diseases was lower in donors than in the general population”

Questions:

Do we know what is the acceptable decrease in IgG?

Is it really enough just to defer donors with low levels of IgG/protein?

A prospective multicentre study on the safety of long-term intensive plasmapheresis in donors (SIPLA)

T. Schulzki,¹ K. Seidel,² H. Storch,³ H. Karges,² S. Kiessig,³ S. Schneider,⁴ U. Taborski,⁵ K. Wolter,³ D. Steppat,² E. Behm,³ M. Zeisner³ & P. Hellstern⁶ for the SIPLA study group

¹RBSD SRK Graubünden, Chur, Switzerland

²ZLB Plasma Services, Marburg, Germany

³Baxter Deutschland, Heidelberg, Germany

⁴Institut für Herzinfarktforschung, Ludwigshafen, Germany

⁵Deutsche Gesellschaft für Humanplasma, Ludwigshafen, Germany

⁶Institute of Hemostaseology and Transfusion Medicine, Ludwigshafen, Germany

Table 4 Initial and final immunoglobulin G, total serum protein and Hb values and number of donors below respective thresholds in the 923 donors who completed the study

	Initial values	Final values	P-value
Females, <i>n</i> = 193			
IgG, g/l	8.8 (5.3–16.4)	8.0 (4.7–18.8)	< 0.0001 ^a
Number of donors with IgG below 5.8 g/l	2	7	0.17 ^b
TSP, g/l	68 (58–77)	69 (58–81)	0.45 ^a
Number of donors with TSP below 60 g/l	1	6	0.12 ^b
Hb, g/l	133 (120–162)	134 (116–160)	0.35 ^a
Number of donors with Hb below 115 g/l	0	0	1.0 ^b
Males, <i>n</i> = 730			
IgG, g/l	8.7 (5.5–16.0)	7.9 (5.0–17.0)	< 0.0001 ^a
Number of donors with IgG below 5.8 g/l	2	32	< 0.0001 ^b
TSP, g/l	69 (60–82)	70 (60–88)	0.10 ^a
Number of donors with TSP below 60 g/l	0	0	1.0 ^b
Hb, g/l	147 (121–171)	149 (117–184)	0.001 ^a
Number of donors with Hb below 115 g/l	0	0	1.0 ^b

Data are expressed as median values (minimum–maximum).

^aWilcoxon matched pairs test; ^bFisher's exact test.

IgG, immunoglobulin G; TSP, total serum protein; Hb, haemoglobin.



The Healthy Donor Effect (HDE)

HDE is a selection bias analogous to the Healthy Worker Effect

HDE can mask deleterious effects of blood or plasma donation

Observational studies are challenged by HDE

BLOOD DONORS AND BLOOD COLLECTION

Healthy donor effect: its magnitude in health research among blood donors

Femke Atsma, Ingrid Veldhuizen, André Verbeek, Wim de Kort, and Femmie de Vegt

TRANSFUSION Volume 51, August 2011

Eur J Health Econ (2015) 16:733–745

DOI 10.1007/s10198-014-0625-1

ORIGINAL PAPER

Healthy donor effect and satisfaction with health

The role of selection effects related to blood donation behavior

Edlira Shehu · Annette Hofmann · Michel Clement ·
Ann-Christin Langmaack

TRANSFUSION
MEDICINE

Official Journal of
the British Blood Transfusion Society



Transfusion Medicine | SHORT COMMUNICATION

The healthy donor effect impacts self-reported physical and mental health – results from the Danish Blood Donor Study (DBDS)

A. S. Rigas,¹ A. Skytthe,² C. Erikstrup,³ K. Rostgaard,⁴ M. S. Petersen,³ H. Hjalgrim,^{4,5} H. Ullum,¹ K. O. Kyvik^{6,7}
& O. B. Pedersen⁸

COVID-19 Convalescent Plasma

Wuhan Blood Center: Adverse events were reported among 5.2% of donors to 309 donations of convalescent plasma.

More frequent than at routine plasmapheresis donation.

Short time since COVID-19 was associated with higher risk.

37,104 donations in 9 US blood centers:

38 adverse events per 1,000 donations

Conclusion: safety comparable to routine plasmapheresis

Received: 19 November 2020 | Revised: 18 January 2021 | Accepted: 22 January 2021

DOI: 10.1002/jca.21882

RESEARCH ARTICLE



Donor tolerability of convalescent plasma donation

Rui He^{1,2} | Hui Lin³ | Songli Xie³ | Qilu Lv^{1,2} | Yujie Kong^{1,2} | Ling Li^{1,2} | Haixia Xu^{1,2} | Jue Wang^{1,2} | Wenjuan Li⁴ | Peng Fang⁴ | Yanyun Wu⁵ | Zhong Liu^{1,2}

Received: 20 May 2021 | Revised: 14 June 2021 | Accepted: 14 June 2021

DOI: 10.1111/trf.16572

BLOOD DONORS AND BLOOD COLLECTION

TRANSFUSION

The safety of COVID-19 convalescent plasma donation: A multi-institutional donor hemovigilance study

Joseph H. Cho¹ | Srijana Rajbhandary² | Nancy L. van Buren³ | Mark K. Fung⁴ | Maha Al-Ghafry⁵ | Joy L. Fridey⁶ | Beth A. Dy⁷ | Alyssa Ziman⁸ | George B. Schreiber⁹ | Richard R. Gammon¹⁰ | Rita Reik¹⁰ | James R. Stubbs¹¹ | Camille M. van Buskirk¹¹ | Hany Kamel¹² | Mary J. Townsend¹² | Michelle P. Zeller¹³ | Jerome L. Gottschall¹

Adverse events

Plasma volume and risk of adverse events:

Hartmann et al. Personalized collection of plasma from healthy donors: A randomized controlled trial of a novel technology-enabled nomogram. *Transfusion*. 2021;61(6):1789–98.

Random assignment to current nomogram or “novel percent plasma nomogram”.

Primary endpoint: hypotensive adverse events

Conclusion: increased plasma collection – not increase in hypotensive adverse events.

Questions we have to ask:

Is it sufficient to assess hypotensive events?

Is it sufficient to assess only acute or sub acute events?



Donor vigilance

In this study, Burkhardt et al report data from +1 million whole blood donations and +340,000 plasma donations

Adverse events were more frequent in plasma than in whole blood donations



Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci



Donor vigilance data of a blood transfusion service: A multicenter analysis

T. Burkhardt ^a, B. Dimanski ^b, R. Karl ^{b,c}, U. Sievert ^d, A. Karl ^{a,d}, C. Hübler ^e,
T. Tonn ^{e,f}, I. Sopvinik ^g, H. Ertl ^a, R. Moog ^{g,*}

^a German Red Cross Blood Donor Service North-East, Institute Plauen, Germany

^b Institute Berlin, Germany

^c Institute Potsdam, Germany

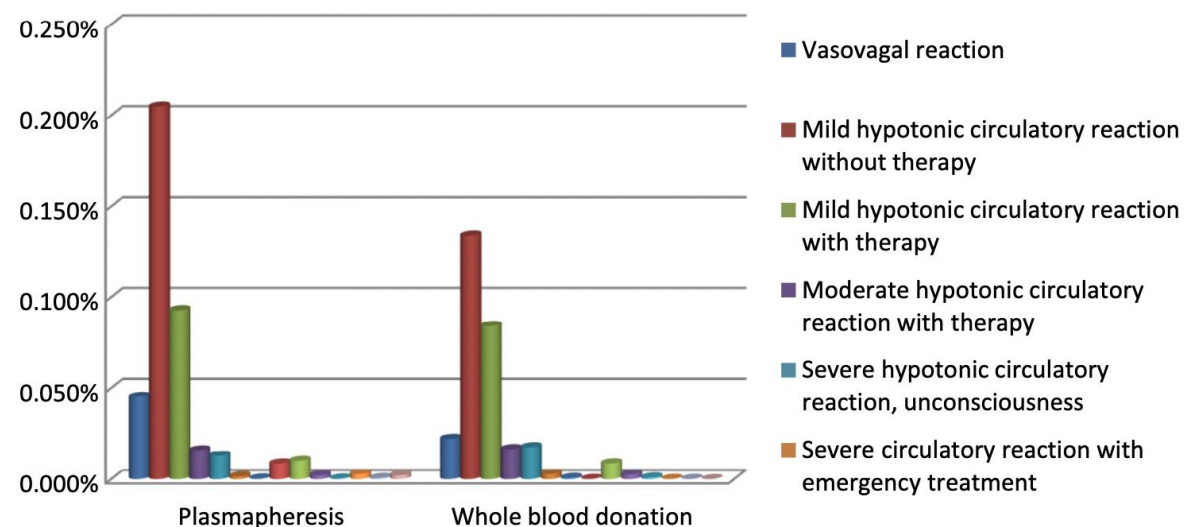
^d Institute Chemnitz, Germany

^e Institute Dresden, Germany

^f Medical Faculty Carl Gustav Carus Technische Universität Dresden, Germany

^g Institute Cottbus, Germany

*T. Burkhardt et al. / Transfusion
and Apheresis Science 53
(2015) 180–184*



Short and long-term effects

Data must be standardised to be used in multinational studies and facilitate comparisons between blood centers

Acute effects of donation:

Standard for Surveillance of Complications Related to Blood Donation (ISBT, IHN, AABB, 2014)
endorsed by the ABO and EBA

AABB grading tool

Long-term effects:

Immunoglobulins?

Ferritin, hemoglobin?

DEXA, other calcium measures on sub group?

Long-term clinical data? Risk of infection? Risk of cardiovascular disease?



Due diligence? – An example from whole blood donation

Low ferritin due to blood donation

Iron Stores in Blood Donors

Toby L. Simon, MD; Philip J. Garry, PhD; Elizabeth M. Hooper

• A high frequency of donations by some blood donors has prompted concern about iron depletion. Five hundred sixteen female and 505 male donors were examined by measurements of hemoglobin, hematocrit, plasma iron, total iron-binding capacity, and ferritin values and detailed histories of iron ingestion, pregnancy and menstrual status, and past blood donations. Hemoglobin, hematocrit, and serum iron studies, unlike ferritin, are not sensitive indicators of body iron depletion. Reduced ferritin was found in 8% of male and 23% of female donors. Menstruation lowered iron stores in women. The total number of lifetime donations was not as predictive of decreased iron stores as frequency per year. Even casual iron supplementation reduced the impact of blood donation on iron stores. Administration of iron to donors, especially women, should be studied by blood programs.

Hematologic Values for Entire Donating Population				
	Women (N=516)	Men (N=505)	Menstruating Women (N=410)	Nonmenstruating Women (N=106)
Hemoglobin value, g/dL, mean±SD	13.2±1.1	15.1±1.2	13.1±1.0	13.5±1.1
Hematocrit reading, %, mean±SD	40.1±3.0	44.6±3.5	40.0±2.9	40.7±3.3
Ferritin value,* ng/mL, mean±SD	26 21±12	51 38±22	23 20±11	38 27±16
PSAT,† mean±SD	23.3±10.8	27.2±10.9	23.1±11.0	24±9.6
% with ferritin value <12 ng/mL	23.4	7.7	25.4	16.2
% with ferritin value <12 ng/mL, PSAT <16%	13.4	2.9	14.6	8.6

Iron depletion in whole blood donation

European
Conference of
Donor Health
and
Management
(ECDHM)

Special Session 3 “Donor iron management: Pros and cons of existing strategies”

Friday, 17 th September – Special Session 3	
1.30 pm – 3.00 pm	Donor Iron Management: Pros and Cons of Existing Strategies <i>Panel leader: Katja van den Hurk / Organizer: Katja van den Hurk and Johanna Castrén</i>
1.30 pm – 2.00 pm	Donor iron deficiency mitigation policy in Finland <i>Johanna Castrén</i>
2.00 pm – 2.30 pm	Donor iron deficiency mitigation policy in Denmark <i>Christian Erikstrup</i>
2.30 pm – 3.00 pm	Donor iron deficiency mitigation policy in the Netherlands <i>Katja van den Hurk</i>

Research in iron deficiency in whole blood donors has still not led to conclusions.

Oral iron supplementation is not associated with short-term risk of infections: results from the Danish Blood Donor Study

Kathrine Agergård Kas
Lise Tornvig Erikstrup,²
Kaspar

BLOOD D

Predictors of hem
the

Sebastian R. Kotzé,¹ Ole B. Pedersen,² Mikkel S. Petersen,¹ Erik Sørensen,³ Lise W. Thøner,³
Cecilie J. Sørensen,¹ Andreas S. Rigas,³ Henrik Hjalgrim,⁴ Klaus Rostgaard,⁴ Henrik Ullum,³
and Christian Erikstrup¹

IRON RELATED



737 Dan
Blood D

BLOOD DONORS AND BLOOD COLLECTION

Elevat



Efficiency and safety of varying the frequency of whole blood donation (INTERVAL): a randomised trial of 45 000 donors



Emanuele Di Angelantonio*, Simon G Thompson*, Stephen Kaptoge*, Carmel Moore*, Matthew Walker, Jane Armitage, Willem H Ouweland,
David J Roberts†, John Danesh†, on behalf of the INTERVAL Trial Group†

SWAY-III (REDS-III) Program

Kaspar Nielsen, Ragn Thorslund, Gustav Edgren,^{6,7} Kl
Henrik Hjalgrim,^{8,10} and He

¹ Lise W. Thøner

BLOOD DONORS AND BLOOD COLLECTION

Prevalence and determinants of declining versus stable hemoglobin levels in whole blood donors

Kazem Nasserinejad,¹ Joost van Rosmalen,¹ Katja van den Hurk,² Mireille Baart,²
Trynke Hoekstra,^{3,4} Dimitris Rizopoulos,¹ Emmanuel Lesaffre,^{1,5} and Wim de Kort^{2,6}



Why we have to keep monitoring risks to our donor

Plateletpheresis: concerns were raised already in the 80ies

20% decrease in lymphocyte count after 10 weekly plateletpheresis procedures

Recent findings show that plateletpheresis using a leukocyte reduction chamber (Trima Accel) is associated with CD4 and CD8 T-cell lymphopenia



TRANSFUSION MEDICINE

Plateletpheresis-associated lymphopenia in frequent platelet donors

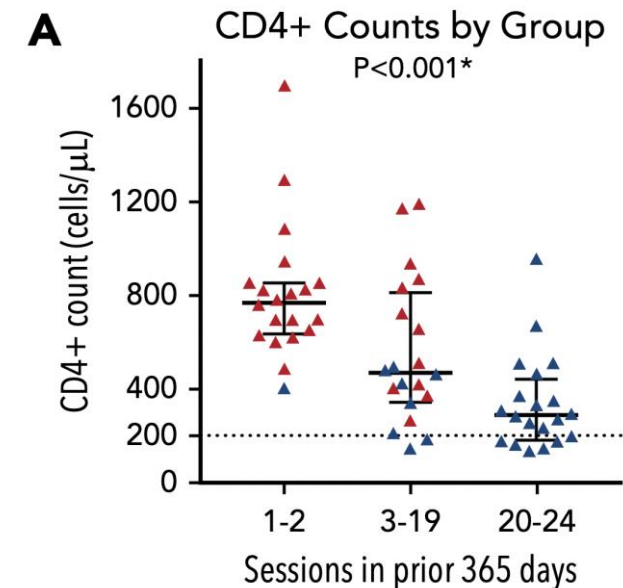
John M. Gansner,¹ Mahboubah Rahmani,² A. Helena Jonsson,³ Brooke M. Fortin,⁴ Idayat Brimah,⁵ Martha Ellis,⁶ Robin Smeland-Wagman,⁶ Zhihan J. Li,⁷ Jason M. Schenkel,⁸ Michael B. Brenner,³ Revital Yefidoff-Freedman,¹ Steven R. Sloan,^{8,9} Nancy Berliner,¹ Nicolas C. Issa,¹⁰ Lindsey R. Baden,¹⁰ Dan L. Longo,¹ Duane R. Wesemann,³ Donna Neuberg,¹¹ Deepak A. Rao,³ and Richard M. Kaufman⁸

THE JOURNAL OF AABB
TRANSFUSION
transfusion.org

The safety of weekly plateletpheresis: effect on the donors' lymphocyte population

J.A. Koepke M.D., W.M. Parks, J.A. Goeken, G.G. Klee, R.G. Strauss

First published: January-February 1981 | <https://doi.org/10.1046/j.1537-2995.1981.21181127485.x> | Citations: 44



Frequent platelet donations and lymphopenia

Platelet pheresis using a leukocyte reduction chamber was confirmed to be associated with CD4 T-cell lymphopenia

...but also with increased risk of infection

This example shows how clinical findings can be coupled with register-based research

It also underlines why we must monitor health effects: crucially, we should not forget earlier findings/hypotheses not verified or falsified due to lack of statistical power

Received: 31 August 2020 | Revised: 25 September 2020 | Accepted: 25 September 2020

DOI: 10.1111/trf.16175

BLOOD DONORS AND BLOOD COLLECTION

TRANSFUSION

Frequent platelet donation is associated with lymphopenia and risk of infections: A nationwide cohort study

Jingcheng Zhao¹ | Erin Gabriel² | Rut Norda³ | Petter Höglund^{4,5} | Lindsey Baden⁶ | Beatrice A. Diedrich^{5,7} | Per Marits^{5,7} | Sara L. Enoksson^{5,7} | John M. Gansner⁸ | Richard Kaufman⁹ | Paul W. Dickman² | Gustaf Edgren^{1,10}



European Blood Alliance - Donor Studies Special Interest Group

A forum for the discussion of blood donor studies

- what (standardised) data we need for plasma donor vigilance
- suggestions on how to initiate proper European plasma donor vigilance

Why is plasma donor vigilance important?

No comprehensive surveillance of donor health is performed on a European basis

Most previous studies are on biochemical markers and some on acute adverse reactions

In the blood banks we must design relevant studies - we must assess also long-term health outcomes

The industry must share available data

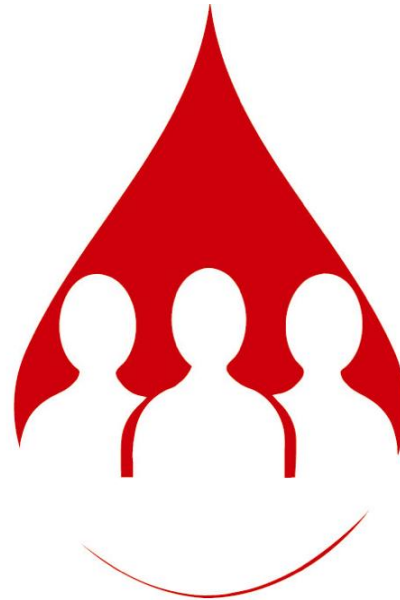
We owe it to the donors to carefully monitor health effects of plasma donation through research.

Strengthening voluntary non-remunerated plasma collection capacity in Europe (SUPPLY):

May hopefully help to put plasma donation health on the agenda

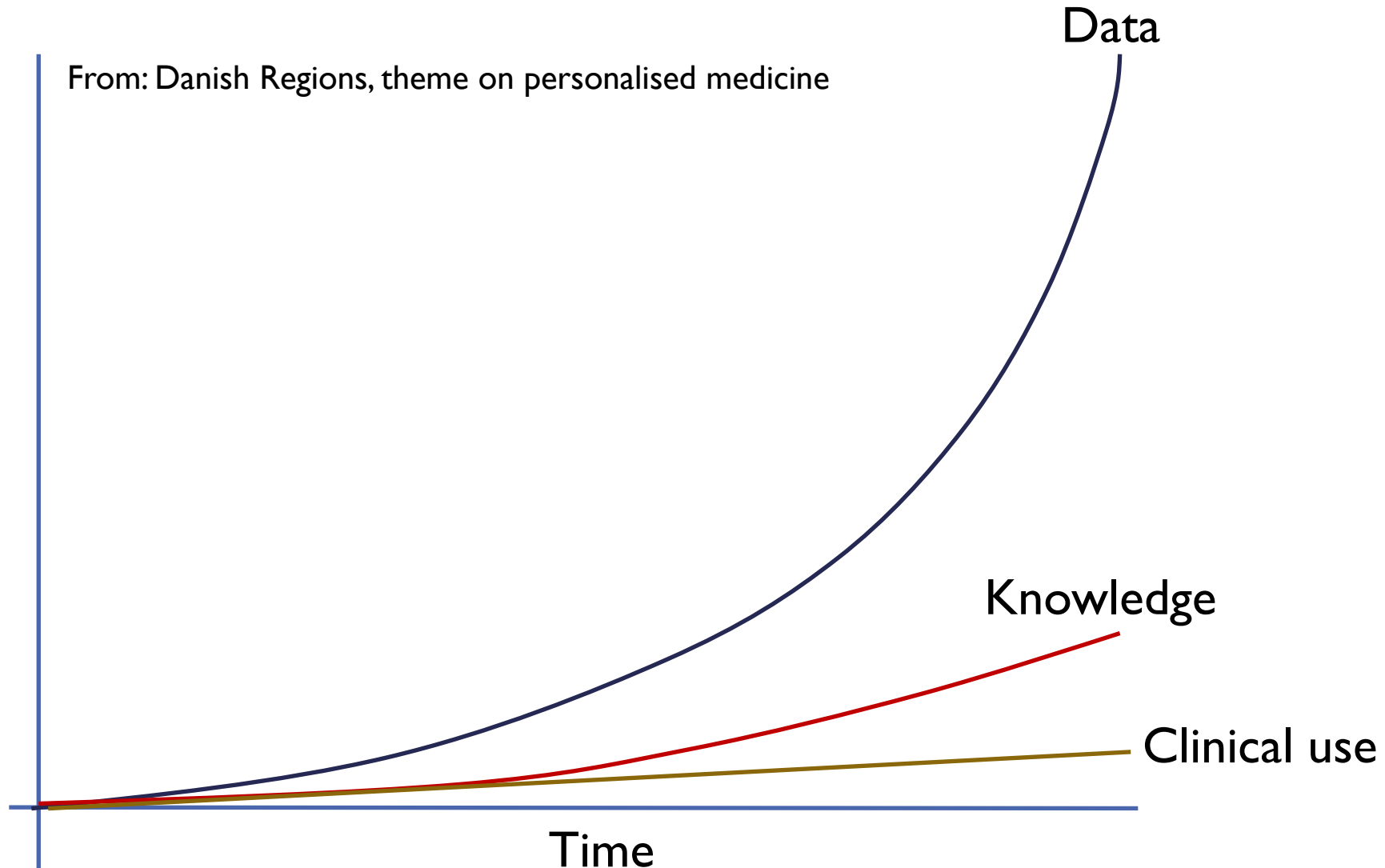


Thanks to our blood and plasma donors!



Data is not enough:

Data volume is growing – our use of the data is trailing behind



The precautionary principle has been used extensively in whole blood collection

Example not related to donor safety – risk of transfusion-transmitted infections: Deferrals are expensive

The combined costs of deferrals for blood establishments and donors was estimated to €1,449,055 (€669,439-€3,145,961) per quality-adjusted life year gained

(Cost-effectiveness of questionnaires in preventing transfusion-transmitted infections, de Kort et al, Transfusion 2014)

Maybe more importantly:

Increased deferrals => increased frequency of donations in remaining donors

If we were all whole blood donors we only had to give a couple of donations throughout our lifetime to ensure the blood supply.



Trends in return behavior after an adverse event in Australian whole blood and plasma donors

Amanda Thijsen ¹, Barbara Masser,^{2,3} Carley N. Gemelli ⁴, and Tanya E. Davison⁴

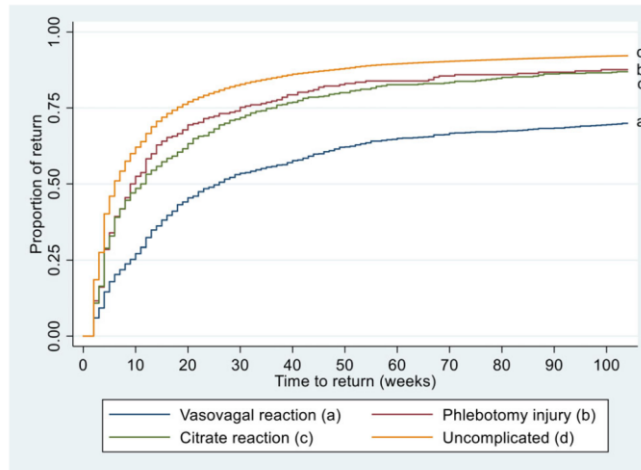


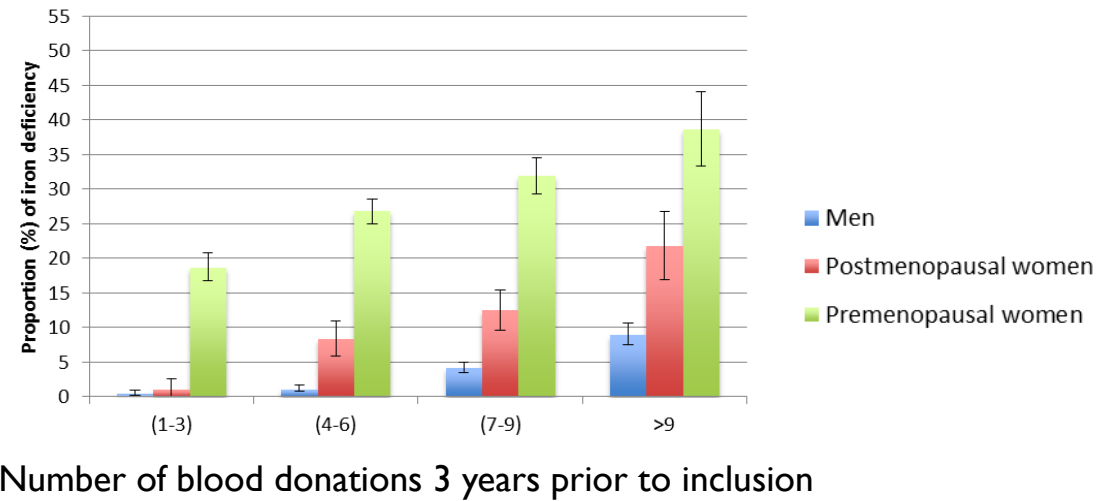
Fig. 1. Time taken to return for plasma donors by DAE type.



IRON RELATED

Predictors of iron levels in 14,737 Danish blood donors: results from the Danish Blood Donor Study

Andreas Stribolt Rigas,¹ Cecilie Juul Sørensen,² Ole Birger Pedersen,³ Mikkel Steen Petersen,²
Lise Wegner Thøner,¹ Sebastian Kotzé,² Erik Sørensen,¹ Karin Magnussen,¹ Klaus Rostgaard,⁴
Christian Erikstrup,² and Henrik Ullum¹



Frequent blood donation and offspring birth weight—a next-generation association?

Andreas S. Rigas,¹ Ole B. Pedersen,² Erik Sørensen,¹ Lise W. Thøner,¹ Margit H. Larsen,¹ Louis M. Katz,³
Kaspar Nielsen,⁴ Kjell Titlestad,⁵ Gustaf Edgren,^{6,7} Klaus Rostgaard,⁸ Christian Erikstrup,⁹
Henrik Hjalgrim,^{8,10} and Henrik Ullum¹

A combination of studies using data from
The Danish Blood Donor Study and
SCANDAT

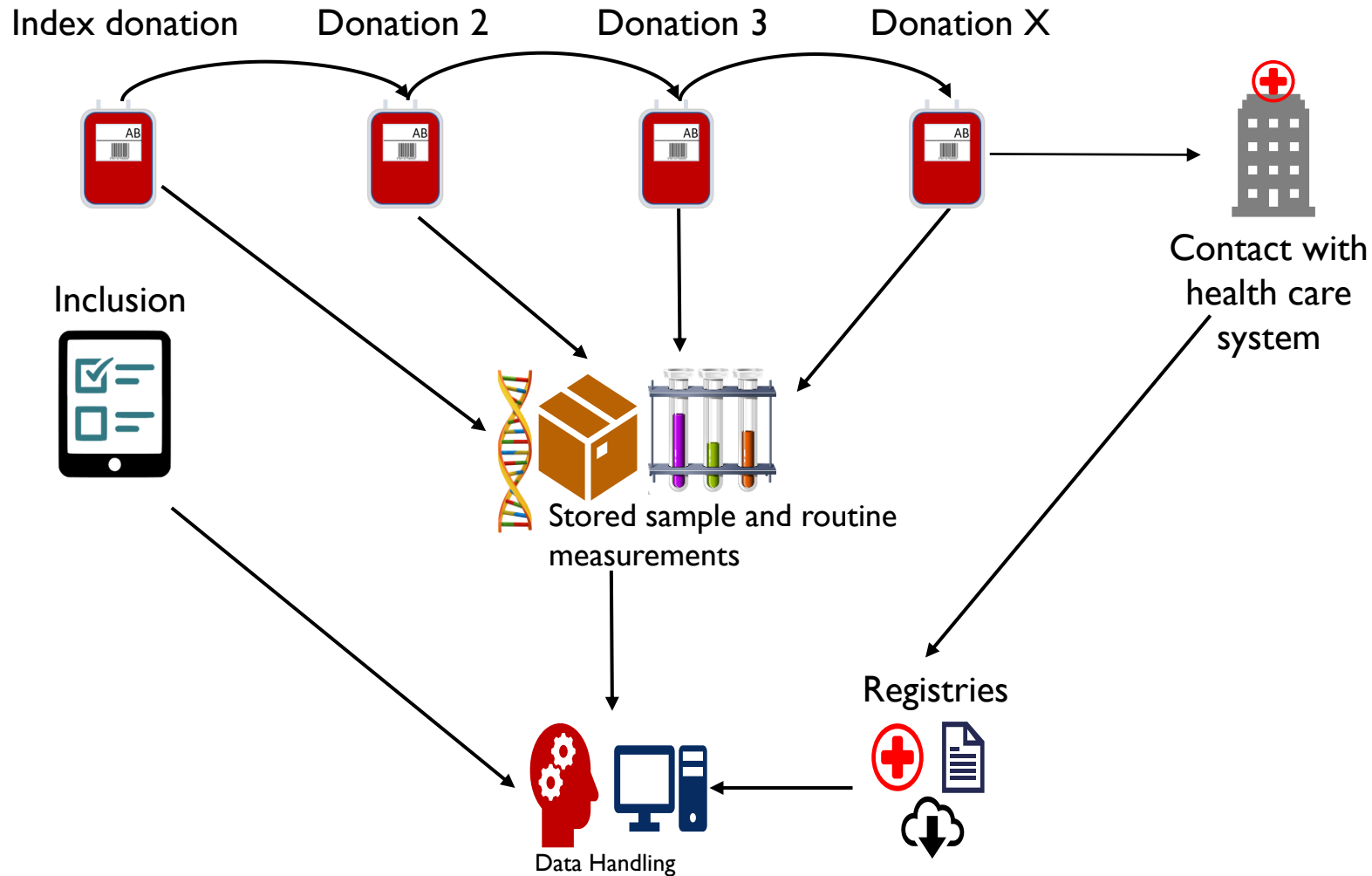
Oral iron supplementation is not associated with short-term risk of infections: results from the Danish Blood Donor Study

Kathrine Agergård Kaspersen,¹ Khoa Manh Dinh,¹ Susan Mikkelsen,¹ Mikkel Steen Petersen,¹
Lise Tornvig Erikstrup,² Ole Birger Pedersen,³ Erik Sørensen,⁴ Henrik Hjalgrim,^{5,6} Andreas Rigas,⁴
Kaspar Rene Nielsen,⁷ Henrik Ullum,⁴ and Christian Erikstrup¹



The Danish Blood Donor Study

130,000 whole blood and plasma donors included in a prospective cohort and bio bank



Why donor health studies are challenging to perform

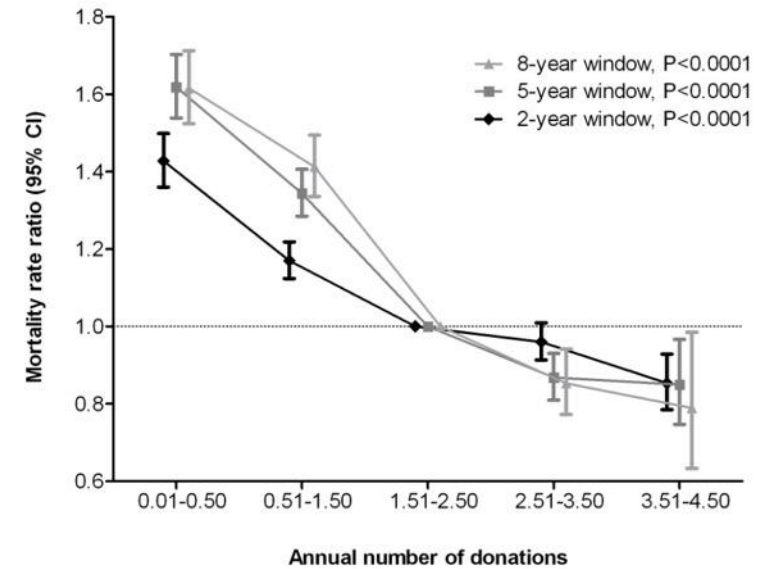
- The Healthy Donor Effect

Scandinavian Donation and Transfusion Database (SCANDAT):

25 million donations from

1.6 million donors to

2.2 million patients



Mortality among blood donors
is 30% lower than in the background population

The mortality is even lower among frequently donating donors

Explanations:

1. Blood donation improves health
2. Blood donors are healthy - therefore they donate



What is personalised donor care?

