

Plasma donor health - plasma donation frequency

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Disclosures

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No personal fees

SUPPLY

Strengthening voluntary non-remunerated plasma collection capacity in Europe

ABOUT US

What is SUPPLY?

SUPPLY is a project co-funded by the European Union's EU4Health Programme that aims to increase and strengthen the resilience of plasma collection in the EU to enable a stable and adequate supply of Plasma-derived medicinal products (PDMPs). The entire plasma chain is being assessed – from plasma donor recruitment, retention, and health, through plasma collection and processing, to demand and use of PDMPs.



SUPPLY WP5: Plasma donor protection best practices

Plasma donation is scaled up across Europe.

It is of paramount importance to ensure that plasma donation is safe prompting the questions:

- Which preventive measures should be implemented?
- How much plasma can be collected per donation?
- What is the optimal interval between two donations?
- Should there be an annual limit of plasma collected per donor?
- Should there be a lower limit for concentrations of total plasma protein and/or IgG?
- Which selection criteria are necessary to prevent adverse events?
- Should special attention and strategies be taken to mitigate the risk of adverse events among specific groups of donors

SUPPLY WP5 - Plasma donor protection best practices

Objective: To facilitate evidence-based plasma donor protection practices

Collect information on current plasma donor protection practices

Evaluate the available scientific evidence on plasma donation and health

Support tool on standardized donor vigilance data to be collected

Develop recommendations

Current plasma donor protection practices: Varied practices across participating plasma centers

Katja van den Hurk/Marloes Spekman, Sanquin

Aim:

To assess health protection practices for plasma donors in plasmapheresis across Europe and beyond.

Method:

Survey based on previous IPFA survey, covering plasma collection, donor selection, donation procedures, vigilance, registration.

Results:

18 complete responses from 17 countries.

Donation Frequency:

Annual donation limits vary from 12 donations per year (Luxembourg) to 26 (the Netherlands) to 60 (Germany) to 104 (USA).

Minimum interval between donations: 2 to 28 days.

Selection Criteria:

Suitability (e.g., veins, tolerance), weight/height/blood volume, Hb levels, medication/drug use, infectious/autoimmune diseases, blood pressure.

Varied practices across participating plasma centers

Survey results continued:

Donation Procedure:

Equipment: 10 different apheresis machines used.

Volume limit: 400 to 896 mL, with 12 organizations adjusting volume according to sex, weight, and height.

Citrate-based anticoagulants used with varying citrate percentages.

Flow rates vary.

Adverse Events:

Prevention methods: Hydration advice (12 organizations), trained staff (7 organizations), attention to new donors (5 organizations).

Vigilance systems in place; multiple adverse event recording with severity grading.

Testing:

All organizations assess total protein levels (with varying limits).

Additional tests: IgG levels, irregular blood group antibodies, blood type, liver enzymes, ferritin, HLA antibodies, blood cell counts.

WP5 Gap Analysis

Evidence gaps:

- preventive measures including the impact of the technologies used on the safety of donors
- selection criteria including total plasma protein levels, IgG, and Hb
- different donation frequencies and the effect on donor safety
- long-term health effects of plasma donation

Procedural gap:

- registration of adverse events

Focus: donation frequency

Plasma donation frequency according to the EDQM "Blood Guide"

2.4.2.6. The maximum number of plasma donations allowed is 33 per year
(*Evidence level C*).

2.4.2.10. The donation interval should be at least 1 week (see the IgG algorithm provided below).

2.4.2.14. IgG should be measured at least annually and at every 26th donation, whichever comes first (*Evidence level C, E*).

The maximum donation frequency for an individual donor should be guided by the maximum annual donation limits, based on the maximum annual donation limits of the donor's country of origin.

Donation Frequency:

Annual donation limits vary from 12 donations per year (Luxembourg) to 26 (the Netherlands) to 60 (Germany).

Guide to the
on, use and
assurance of
**BLOOD
DONORS**

SUPPLY WP5 Systematic review

Hans van Remoortel, Tine D'aes, Natalie Schroyens, Emmy De Buck, Veerle Compernelle

Research question of systematic review:

What is the impact of plasmapheresis frequency on the safety or health of donors?

Finally included:

4 observational studies

1 randomised controlled trial and 1 non-randomised trial

1 ongoing randomised controlled trial (next presentation in this session!)

The published randomised controlled trial

63 males randomised into 4 groups:

Low-frequency: 1 donation/month, n=16

High-frequency: 3 donations/month, n=16

Very high-frequency: 2 donations/week, n=16

Placebo: 1 visit/month, n=15

Outcomes:

Biochemical, haematological, clinical, physiological, exercise-related data at 1½ months and 3 months of donation.

Results:

Few adverse events were reported. Donation frequency had no effect on blood pressure, body composition or exercise performance.

Biochemical parameters (hemoglobin, ferritin, immunoglobulin levels...) were severely impacted when plasmapheresis was repeated twice a week, mildly impacted with a frequency of three times per month and not impacted with a frequency of once a month.

Received: 11 July 2023 | Revised: 3 November 2023 | Accepted: 7 November 2023

DOI: 10.1111/vox.13569

ORIGINAL ARTICLE

Vox Sanguinis  International Society of Blood Transfusion

Effects of plasmapheresis frequency on health status and exercise performance in men: A randomized controlled trial

Alexandre Mortier¹ | Jina Khoudary² | Sophie van Dooslaer de Ten Ryen¹ |
Camille Lannoy¹ | Nicolas Benoit¹ | Nancy Antoine¹ | Sylvie Copine¹ |
Hans Van Remoortel^{3,4}  | Philippe Vandekerckhove^{2,4} | Veerle Compennolle^{2,5} |
Louise Deldicque^{1,6} 

IgG levels

IgG levels decreased 38% with 2 donations/week
IgG levels decreased 16% with 3 donations/month

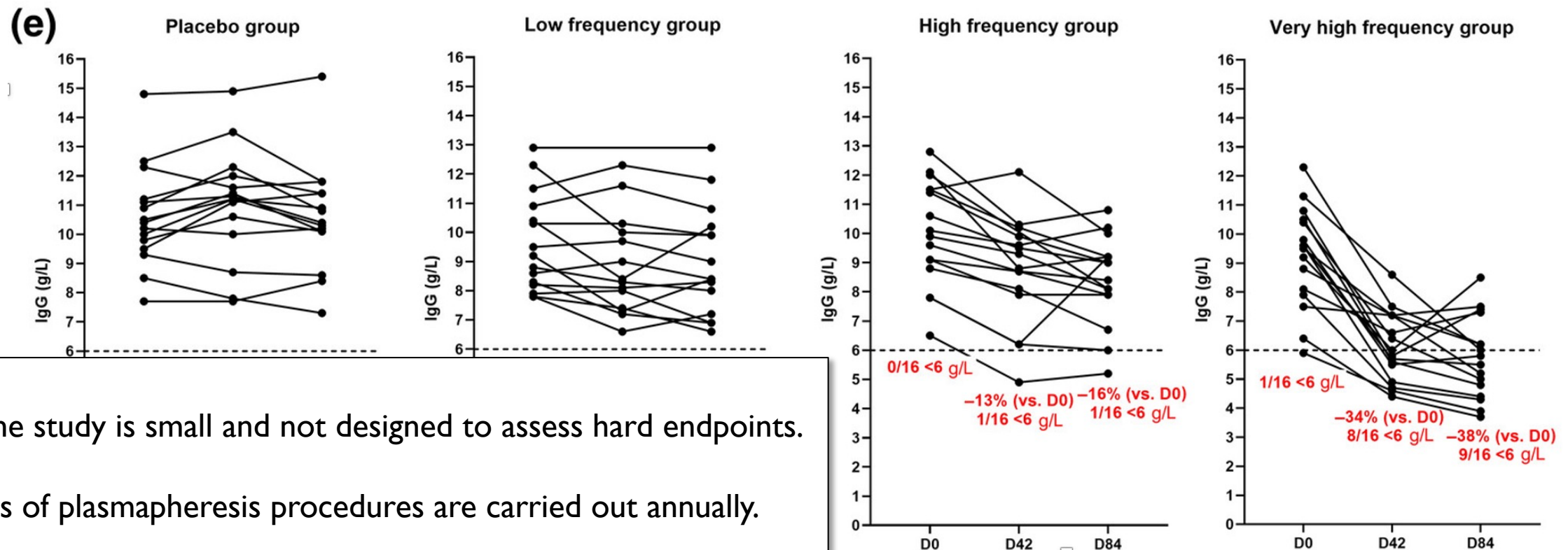
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Louise Deldicque^{1,6} 



This fine study is small and not designed to assess hard endpoints.
Millions of plasmapheresis procedures are carried out annually.

Concerns about papers by the PPTA published in Transfusion

Fransen M, et al. Effects of donation frequency on U.S. source plasma donor health. Transfusion 2023

Self-reported health-related quality of life (SRQL) was assessed in 5,608 plasmapheresis donors from 14 US centers.

SRQL was compared between donors grouped according to donation frequency. No differences in SRQL between the donor frequency groups compared with new donors.

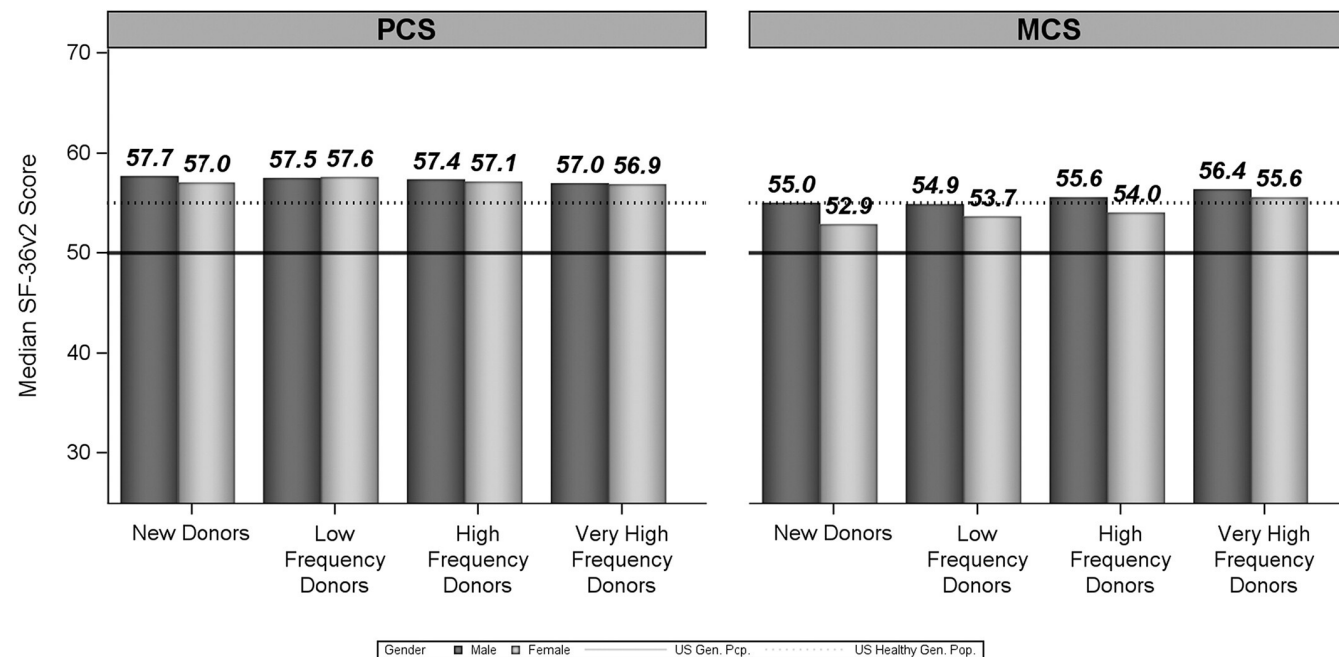
Conclusion:

Remunerated, high-frequency donations are safe.

We disagree:

The study is not designed to answer this question.

The Healthy Donor Effect cannot be neglected.



Continued: Concerns about papers by the PPTA published in Transfusion

Fransen M et al. Why do US source plasma donors stop donating? Transfusion 2023

545 plasmapheresis donors from 14 US centers, not returning for at least six months, responded to a survey about their reasons for stopping donations.

The authors report that factors categorized as “convenience” were the primary reasons donors stopped donating (e.g., schedule conflicts/lack of time) (n = 377, 69.1%)

Self-reported health concerns with a possible or uncertain relationship to plasmapheresis were less frequent (45.5%).

The authors concluded that these results provide additional evidence supporting the safety of frequent plasmapheresis (up to 104 plasma donations/year) to assure donor health.

We disagree:

45.5% with possible health issues is far from negligible and does not support the authors’ conclusion.

Several methodological flaws in both articles.

Very-low quality evidence that should not be used to substantiate claims regarding the safety of repeated plasmapheresis.

Absence of evidence is not equal to evidence of absence.

Received: 6 November 2023

Accepted: 6 November 2023

DOI: 10.1111/trf.17601

COMMENTARY

TRANSFUSION

Very-high frequency plasmapheresis and donor health –absence of evidence is not equal to evidence of absence

Hans Van Remoortel^{1,2} | Katja van den Hurk^{3,4} | Veerle Compernelle^{5,6} |
Peter O’Leary⁷ | Pierre Tiberghien^{7,8,9} | Christian Erikstrup^{10,11}

SIPLA

3,783 donors were switched from a moderate to an intensive plasmapheresis regimen: up to 60 donations per year for 3 years.

No control group!

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”.

ORIGINAL PAPER

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

¹*RBSD SRK Graubünden, Chur, Switzerland*

²*ZLB Plasma Services, Marburg, Germany*

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⁵*Deutsche Gesellschaft für Humanplasma, Ludwigshafen, Germany*

⁶*Institute of Hemostaseology and Transfusion Medicine, Ludwigshafen, Germany*

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 often challenged by HDE.

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

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

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

Why observational 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

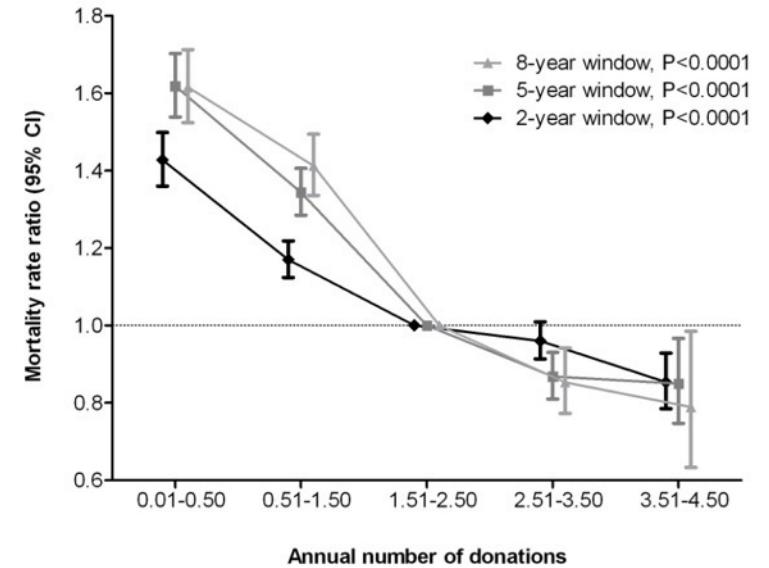
Mortality among blood donors
is 30% lower than in the background population

The mortality is even lower among frequently donating donors

Explanations:

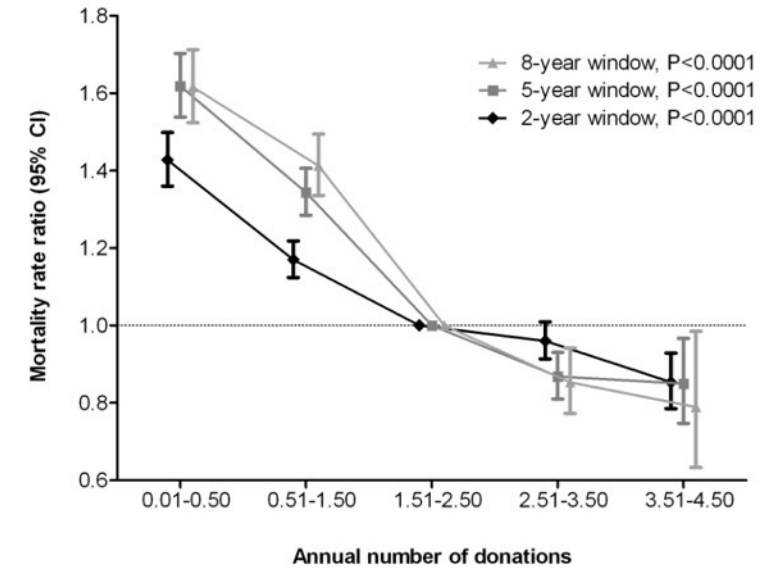
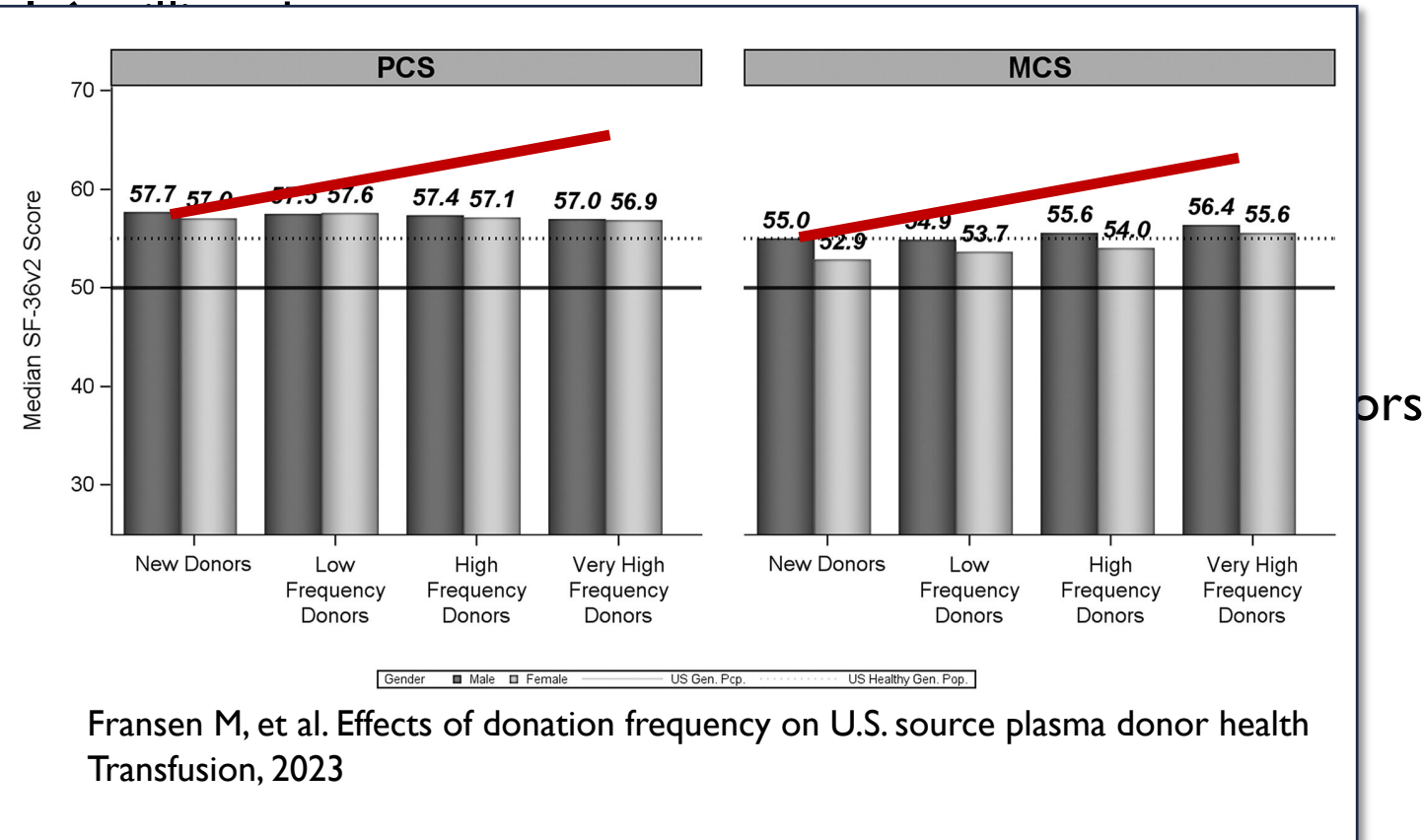
Blood donation improves health

Blood donors are healthy - therefore they donate



Why observational donor health studies are challenging to perform - The Healthy Donor Effect

Scandinavian Donation and Transfusion Database (SCANDAT):
25 million donations from



Healthy Donor Effect complexity

- Physical and mental wellbeing

Danish National Health Survey was linked to donor data

339,912 respondents to the National Health Survey

49,138 (14%) were active or lapsed blood donors

Short-form-12 physical and mental self-reported health scores were compared between donors and non-donors

Received: 4 February 2022 | Revised: 29 September 2022 | Accepted: 29 September 2022

DOI: 10.1111/trf.17190

BLOOD DONORS AND BLOOD COLLECTION

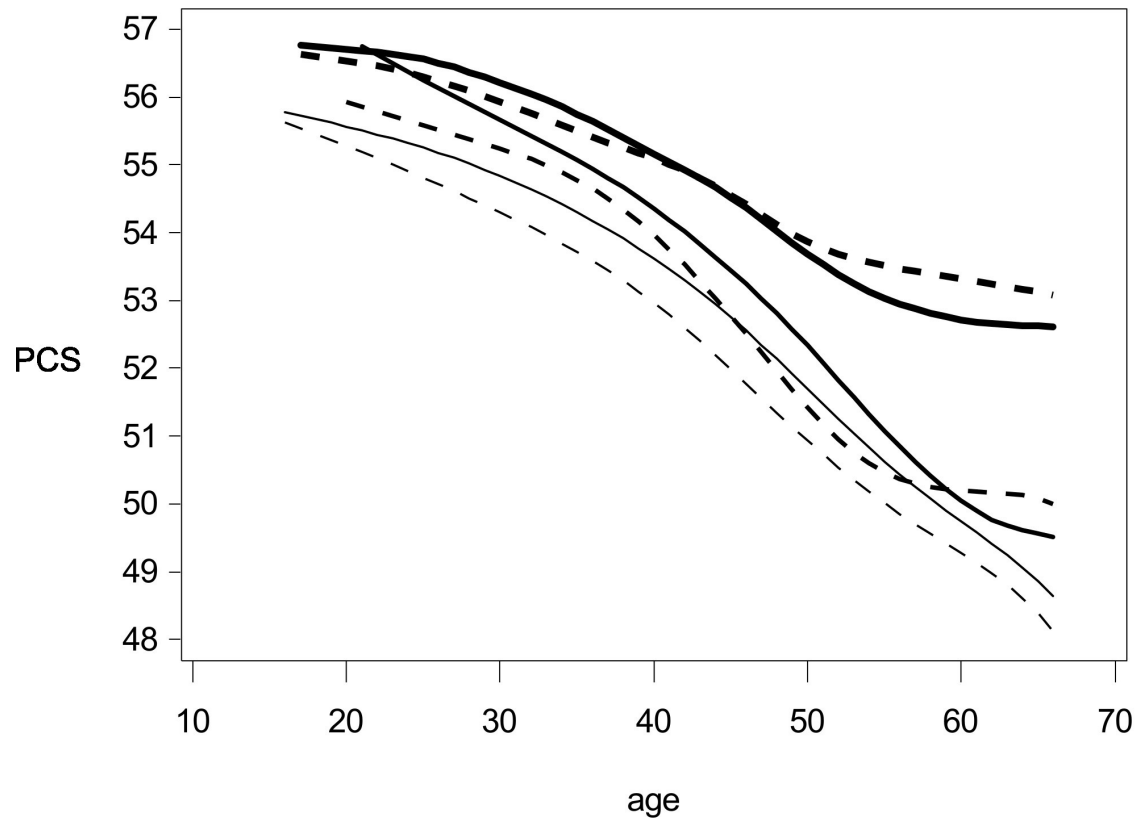
TRANSFUSION

The healthy donor effect and survey participation, becoming a donor and donor career

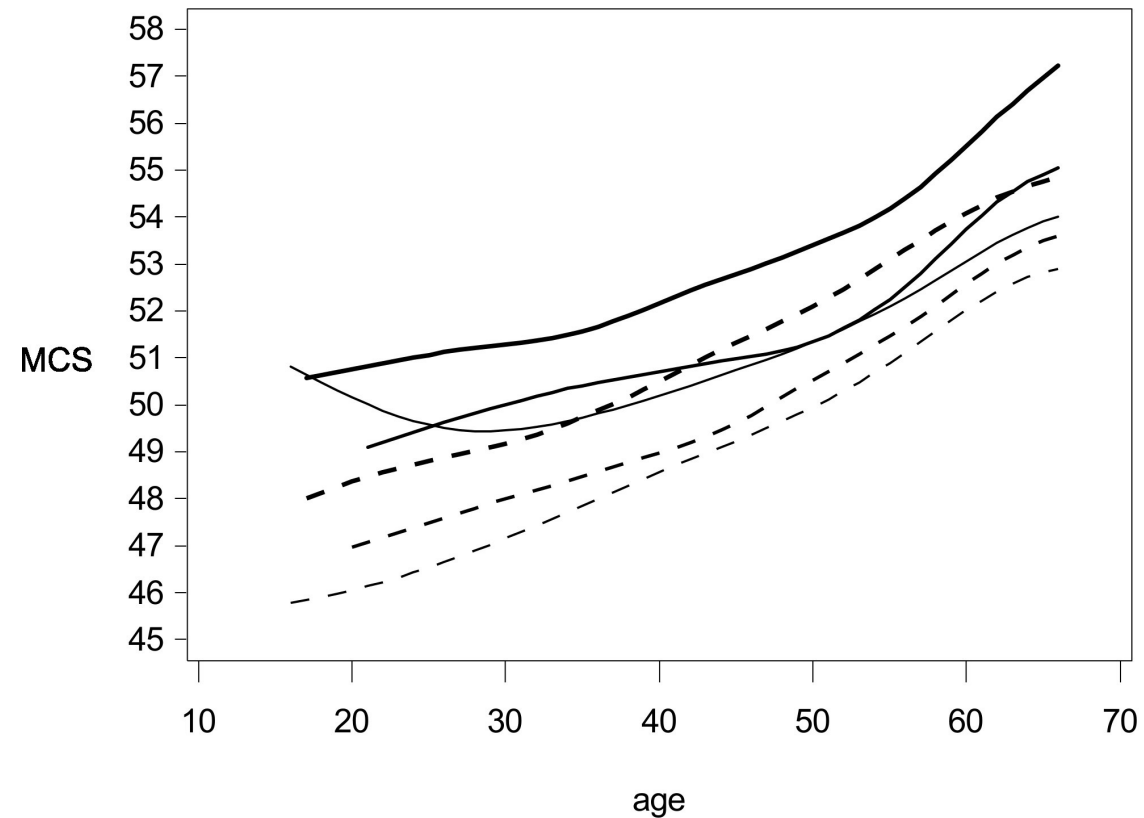
Thorsten Brodersen^{1,2}  | Klaus Rostgaard^{3,4} | Cathrine Juel Lau⁵ |
Knud Juel⁶ | Christian Erikstrup⁷ | Kasper Rene Nielsen⁸ |
Sisse Rye Ostrowski^{9,10} | Kjell Titlestad¹¹ | Susanne G. Sækmose¹ |
Ole B. V. Pedersen¹ | Henrik Hjalgrim^{3,4,10,12}

Self-reported health, SF12 physical and mental component score (PCS and MCS) by age, sex, and donor status

————



———— active M ——— lapsed M ——— never M
- - - active F - - - lapsed F - - - never F



———— active M ——— lapsed M ——— never M
- - - active F - - - lapsed F - - - never F

Securing data: 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?

Describe requirements for a support tool on standardized donor vigilance data to be collected

Tool Requirements for Donor Vigilance:

Record and analyze plasma donor protection practices

Standardize adverse event classification

”The support tool designed is the first approach to lay the foundations for the further development and design of an EU-wide collection of data, risks and side effects.”

Torsten Tonn/Thomas Burkhardt/
Knut Gubbe, German Red Cross

Adverse Reaction	
Donation ID	XXXXXXX
internal code	SR 04
Typ of advers reaction	Vasovagale reaction with LOC > 60 sec
Time of occurrence	during pd
medicine used?	yes
OMR/EMR	yes
Degree of severity	2
donor information	
age	45
sex	f
Donation type	Plasma (SP/FFP?)
First time donor?	no
No plasma donation in the op	24
total number of plasma donations	112
body weight	82
body height	178
donation/equipment information	
target volume plasma in ml	850
collected volume in ml	340
anticoagulant used in ml	83

Long-term effects

- National health registers

National Patient Register:

Hospital contacts (admission or outpatient visit) registered with ICD-10 diagnosis code, date in, date out

Prescription Register:

Redeemed drugs registered with ATC-codes, dose, packing size, date

Socioeconomic registers:

Education level, income level, area of home address...

Near 100% coverage

Future possibilities?

The European Health Data Space

Aim

The EHDS seeks to provide rules, common standards and practices, infrastructures and a governance framework for both primary use (using personal electronic health data to provide health services to an individual) and secondary use (using electronic health data for broader needs such as health research or public policy) of public health data. To that end, it (1) strengthens patient control over their data; (2) establishes rules for electronic health records (EHR) systems in order to promote reliability, security and interoperability; (3) establishes rules for secondary use of health data; and (4) establishes mandatory cross-border infrastructures, one for primary use and the other for secondary use.

Marcus et al. The European Health Data Space. SSRN Journal. 2022;
Available from: <https://www.ssrn.com/abstract=4300393>

Maybe this can open national registers for donor studies in the EU

The Healthy Donor Effect – a role for observational studies?

The Danish Blood Donor Study extended to all donors in Denmark:

30,910 first-time plasma donors.

Outcome: hospital contact due to infection or prescription of antibiotics.

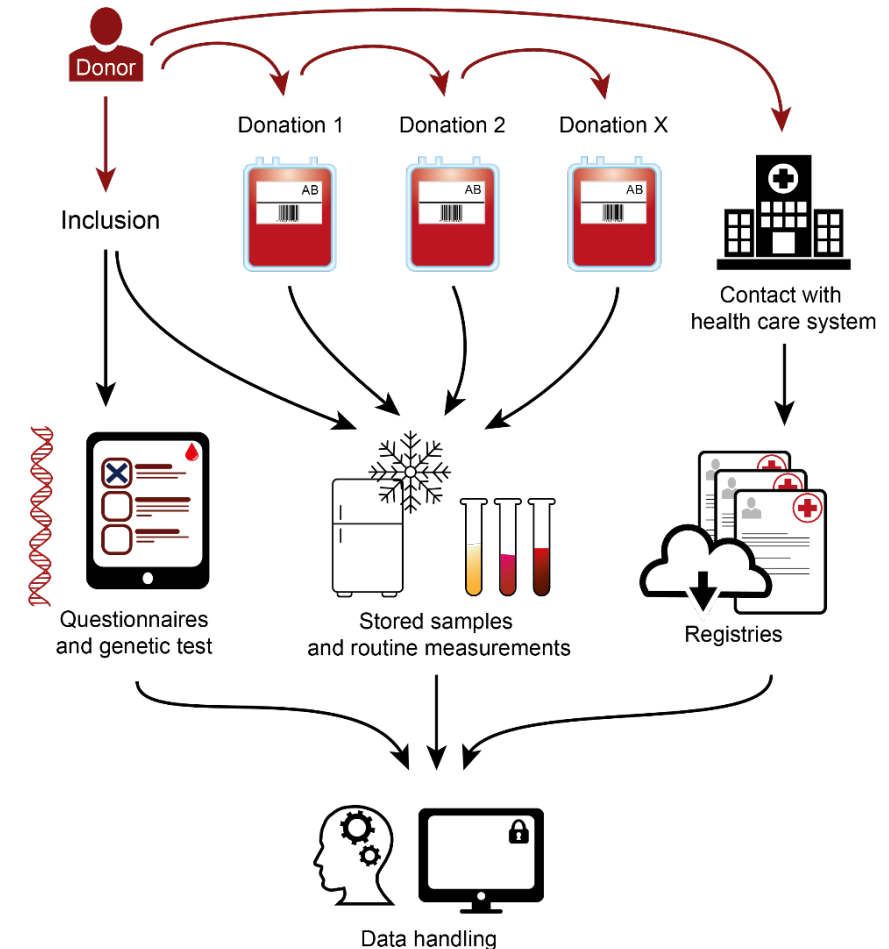
Various designs have been implemented. The latest model is using features from target trial emulation.

The risk of experiencing an infection decreased with number of plasma donations:

Hazard ratio: 0.96 (0.94-0.97).

Will we be able to accurately assess the effect of the exposure without an appropriate control group?

We need large randomised trials!



WP5 Recommendations on protection of plasma donors

Adherence to the Blood Guide (21st edition 2023) until further evidence is acquired.

However: **a maximum of two plasma donations per month**, pending sufficient evidence confirming the safety of higher donation frequencies. This recommendation is based on expert opinion and reflects the view of a majority of WP5 members.*

* Alternative recommendation, supported by two WP5 members: a maximum of two plasma donations per month, unless a donor health and IgG management system is established by the respective blood establishment.

IgG levels should be monitored. Evidence of optimal IgG algorithms and test intervals are lacking.

Urgent initiation of prospective studies to examine the health consequences of plasma donation at varying frequencies.

Implementation of a register for standardized haemovigilance data on a mandatory basis.

Recommendations are based on the use of the precautionary principle, placing donor safety first while awaiting further evidence.

Absence of evidence is not evidence of absence

The precautionary principle is used extensively to mitigate even theoretical risks for the recipients of blood.

Can we accept that donor health criteria, e.g., donation frequency, are based on expert opinions?

Observational studies may help but the Healthy Donor Effect poses a challenge.

It is possible to perform very large randomised trials assessing the impact of donation frequency
– example The INTERVAL study from the UK



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‡*

We need large studies to also assess rare and long-term effects of plasma donation: are there consequences of a low IgG?
Of other plasma factors? For how long?

DONOR STUDIES WORKING GROUP

A forum where we can discuss and plan plasma donor health studies

The Donor Studies Working Group focuses on sharing experiences and insights from blood donor studies to enhance the understanding of blood donor health, recruitment, and retention. These studies may also evaluate generic health questions using blood donors as representatives of the general population. The working group seeks to develop the concept of blood donor studies further to identify more efficient ways of recruiting donors and assess the health impacts of blood and plasma donations.

<https://europeanbloodalliance.eu/working-groups/donor-studies-working-group/>

WP5 SUPPLY members

Hans van Remoortel

Tine D'aes

Natalie Schroyens

Emmy De Buck

Veerle Compernelle



Belgian
Red Cross



Evidence-based
by **CEBaP**

Torsten Tonn

Thomas Burkhardt



German
Red
Cross

Susan Mikkelsen



Katja van den Hurk

Marloes Spekman



Elodie Pouchol

Pascale Richard



Pierre Tiberghien

Peter O'Leary

Petar Kos

Gaia Mori

