The Danish Blood Donor Study
- Platform and results

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Is blood donation healthy?

Blood donor mortality reduced by 30% compared to the general population

High frequency donor mortality was lower than mortality for low frequency donors

SCANDAT2
25 million donations from 1.6 million donors to 2.2 million patients
1. Blood donation improves health
2. Blood donors are more healthy – therefore they can/will donate.
Why establish a cohort of blood donors?

• Necessary for the study of health impact of blood/plasma donation
• Very cost efficient setup
• Feasible for the study of generic research questions?
## Infrastructure for large population studies

<table>
<thead>
<tr>
<th>Access to participants:</th>
<th>Mail, phone, homepage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collection sites:</td>
<td>Close to participants</td>
</tr>
<tr>
<td>Educated staff:</td>
<td>Information, interviews, samples</td>
</tr>
<tr>
<td>Transport:</td>
<td>Time, temperature</td>
</tr>
<tr>
<td>Laboratories:</td>
<td>Sample handling, analysis</td>
</tr>
<tr>
<td>Storage Facilities:</td>
<td>-80C freezers, preferably automated</td>
</tr>
</tbody>
</table>
### Blood bank/donor organisation infrastructure

<table>
<thead>
<tr>
<th>Feature</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access to participants</td>
<td>250,000 blood donations annually</td>
</tr>
<tr>
<td>Collection sites</td>
<td>200 sites nationally</td>
</tr>
<tr>
<td>Educated staff</td>
<td>Nurses, technicians, physicians, public relations experts</td>
</tr>
<tr>
<td>Transport</td>
<td>Look-back samples from each donation</td>
</tr>
<tr>
<td>Laboratories</td>
<td>Sample handling and analysis</td>
</tr>
<tr>
<td>Storage Facilities</td>
<td>-20C automated freezer, -80C freezers</td>
</tr>
</tbody>
</table>
Do the donors want to participate?
Extending the gift of donation

Donor gift 1

Blood donor → Blood donation → Blood for transfusion → Patient

Donor gift 2

Blood donor → Blood sample/questionnaire → Medical research → Future patients

Now part of the strategy for the Danish Blood Donor Association in the recruitment of donors
Inclusion of donor

- Blood donors are informed about the study at signup or while being bled
- Nearly everybody (>95%) accepts
- Routine tubes are marked for retrieval
- Donor signs consent form, fills questionnaire
- Samples are sent to blood center scanned and stored in bio bank
Consent

Permission to store samples in bio bank (plasma and DNA)

Permission to collect questionnaires

Permission to collect data from national registers
National Patient Register
   ICD-10 codes from all contacts with hospitals
National Prescription Register
   ATX codes from all filled prescriptions
Socioeconomic data

Permission to contact donor again
Questionnaire v1

- Self reported health (Short Form 12)
- Smoking status
- Alcohol consumption
- Physical activity
- Diet
- Iron intake
- Height, weight, and waist
- Contraception
- Menopausal status.
Questionnaire v2
Electronic questionnaire:

LimeSurvey

Folding questions and the possibility for sub-group targeted questions

- Asthma/allergy
- RLS
- Depression
- ADHD – trait
Status

Initiated March 2010

>105,000 blood donors have been included

Work dataset has just been updated - merged and uploaded to Statistics Denmark: approx. 92,000 participants; 375,000 person-years of follow-up by Dec 31 2015

All baseline samples transferred to automated sample management system

DNA purified from 55,000 samples

>500,000 plasma archive samples from every donation available for research

14 articles published – many in the pipeline
Examples - Donor health
Blood donation and iron deficiency

Ferritin levels among donors predicted by donation frequency, sex and age. Limited effect of diet.
(Rigas et al, Transfusion, 2014)

No effect of iron depletion on self reported health
(Rigas et al, Transfusion, 2015)
Low ferritin was the strongest predictor of low hemoglobin

The Danish Blood Donor Study

Is it safe to donate?

(Kotze et al, Transfusion, 2015)
Low hemoglobin and risk of infection

• Low Hb is associated with poor general health and linked to anemia of chronic disease
  => increased risk of infection?
• Iron is needed by replicating microorganisms
  => decreased risk of infection?
• Association between Hb and risk of infection among healthy individuals not yet investigated.
• 497,390 donors; 5,458,499 donations; window: 3 months after each donation; 1,339,362 person years of follow-up

Conclusions:
• Hb below deferral guidelines was not associated with risk of hospital contact due to infection.
• Hb below deferral guidelines was associated with a slightly reduced risk of filling a prescription for anti-microbials:
  Men: HR: 0.91, 95%CI: 0.88-0.94; similar for women (Kotze et al, in revision)
Ferritin-guided iron supplementation – a semi cluster randomized approach

• 2 regions:
  ferritin $< 30 \mu g/ml \Rightarrow 100$ iron tablets
  ferritin $< 60 \mu g/ml \Rightarrow 20$ iron tablets

• 2 regions:
  ferritin $< 15 \mu g/ml \Rightarrow 60$ iron tablets
  ferritin $< 40 \mu g/ml \Rightarrow 20$ iron tablets

• 1 region:
  no intervention
  ferritin to be measured retrospectively

End points:

• Infections, cardiovascular disease, fecal microbiome changes etc.
The healthy donor effect depends on the disease

37,808 participants and 44,917 randomly chosen controls from the general population matched for age, sex, and region of Denmark.

22,198 donors received at least one prescription during 48,492 person-years

(Hansen et al, unpublished)
Blood donor prevalence increases with income category

Lower proportion of donors in lower and highest income categories
(Burgdorf et al, submitted)

Donors who were: unemployed, retired, receiving social security, or of foreign origin were more often low frequency donors
(Christensen et al, unpublished)

New collaboration with behavioral economists: modelling of e.g. risk behavior from register data
Blood donation is heritable

Additive genetic and shared environmental effects: 0.53 (95% CI, 0.33-0.73) and 0.28 (95% CI, 0.10-0.45), respectively, of the variance in the motivation to donate blood.

The heritability of blood donation: a population-based nationwide twin study

Ole Birger Pedersen,1 Skytte Axel,5 Klaus Rostgaard,3 Christian Erikstrup,2 Gustaf Edgren,6 Kaspar René Nielsen,7 Henrik Ullum,4 Kirsten Ohm Kyvik,8 and Henrik Hjalgrim3
Obesity and risk of infection

Among 37,808 participants:
1,233 participants had hospital contact due to infection during 106,609 person-years of observation; adjusted for age, sex, smoking

15,856 participants filled a prescription of antimicrobials during 58,834 person-years of observation

<table>
<thead>
<tr>
<th>Site of infection</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Infections overall</td>
<td>575</td>
<td>1.44 (1.13-1.84)</td>
</tr>
<tr>
<td>Abscesses</td>
<td>105</td>
<td>2.28 (1.40-3.70)</td>
</tr>
<tr>
<td>Respiratory tract infections</td>
<td>144</td>
<td>1.60 (1.00-2.55)</td>
</tr>
</tbody>
</table>

Epidemiology, 2015

Original Article

Phenoxyemethylpenicillin

Men

Body Mass Index (kg/m²)

18.5≤BMI<25  25≤BMI<30  BMI≥30
ABO and CRP

Non-O blood groups explain >30% of venous thromboembolic events.

New study: Non-O - higher risk of low-grade inflammation (CRP>3 mg/mL) among women

<table>
<thead>
<tr>
<th></th>
<th>Women (N=7,376)</th>
<th></th>
<th>Men (N=8,224)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>CI</td>
<td>p</td>
</tr>
<tr>
<td>Non 0 vs. 0</td>
<td>1.27</td>
<td>(1.09-1.47)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>A vs. 0</td>
<td>1.22</td>
<td>(1.04-1.43)</td>
<td>0.01</td>
</tr>
<tr>
<td>B vs. 0</td>
<td>1.21</td>
<td>(0.93-1.56)</td>
<td>0.15</td>
</tr>
<tr>
<td>AB vs. 0</td>
<td>2.06</td>
<td>(1.46-2.91)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current smoking, Yes/No</td>
<td>1.25</td>
<td>(1.00-1.50)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

(Stilling et al, unpublished)
Studies within the study

• A nasal swab has been obtained from 2,500 donors; aim 10,000

• Primary aim: to study the associations of *S. aureus* colonisation with morbidity (infections, metabolic disorders, autoimmune diseases)

• Secondary aims:
  Nasal microbiome and donor morbidity
  *S. aureus*/nasal microbiome and recipient outcome

• First finding: *S. aureus* colonisation more prevalent than previous studies: 50%
Other studies

- Genetic testing and iron depletion
- Predictors of hemoglobin
- Attention-Deficit/Hyperactivity Disorder ADHD spectrum in healthy Danes
- Combined oral contraception and low-grade inflammation
- Blood screening for cytokine autoantibodies
- HLA and infections
- Environmental factors and HLA in Allergy/Asthma
- Self perceived health and infections among IgA deficiency donors
New data: Sysmex
Prediction of chronic lymphatic leukemia

• Sysmex and hemoglobin measurements:
  Full white cell differential: 65,000 measurements /y
  Red cell parameters: approx. 150,000 measurements /y

Proof of concept:

• One small donation facility: 118,430 lymphocyte measurements from 15,448 donors during 13 years
Conclusions

• We bleed donors with CLL

No evidence of transmission of chronic lymphocytic leukemia through blood transfusion

Henrik Hjalgrim,1 Klaus Rostgaard,1 Senthil K. Vasan,2 Henrik Ullum,3 Christian Erikstrup,4 Ole B. V. Pedersen,5 Kaspar R. Nielsen,6 Kjell-Einar Tistlestad,7 Mads Melbye,1 Olof Nyrén,2 and Gustaf Edgren2,8

Blood 2015

• Donors should be informed and offered counselling
• New medicine – early intervention may be feasible for some mutations
• Sysmex data – immense possibilities
Upcoming:

GWAS: 16,000 samples to be typed this year
Dept. of Clinical Immunology, Aarhus University Hospital:
• Kathrine Agergaard Kaspersen
• Sebastian Kotzé
• Mikkel Steen Petersen
• Bjarne Møller
• Khoa Manh Dinh
• Christina Stilling
Dept. of Clinical Immunology, Naestved Hospital:
• Ole Birger Pedersen
Dept. of Clinical Immunology, Aalborg University Hospital:
• Kaspar René Nielsen
The Blood Donors in Denmark
• Jesper Villumsen
• Poul Erik Herner Petersen
Dept. of Clinical Immunology, Copenhagen University Hospital:
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• Erik Sørensen
• Lise Wegner Thørner
• Kristoffer Sølvsten Burgdorf
• Andreas Striboldt Rigas
• Jakob Hjorth Von Stemann
Dept. of Epidemiology Research, Statens Serum Institut:
• Henrik Hjalgrim
• Klaus Rostgaard
Dept. of Clinical Immunology, Odense University Hospital:
• Mie Topholm Bruun
Dept. of Clinical Microbiology, Aarhus University Hospital:
• Lise Tornvig Erikstrup
Give blood, save lives, create knowledge