

Possible transfusion transmission of cerebral amyloid angiopathy

Gustaf Edgren MD PhD

Associate professor of epidemiology

Karolinska Institutet, Stockholm, Sweden

Disclosures

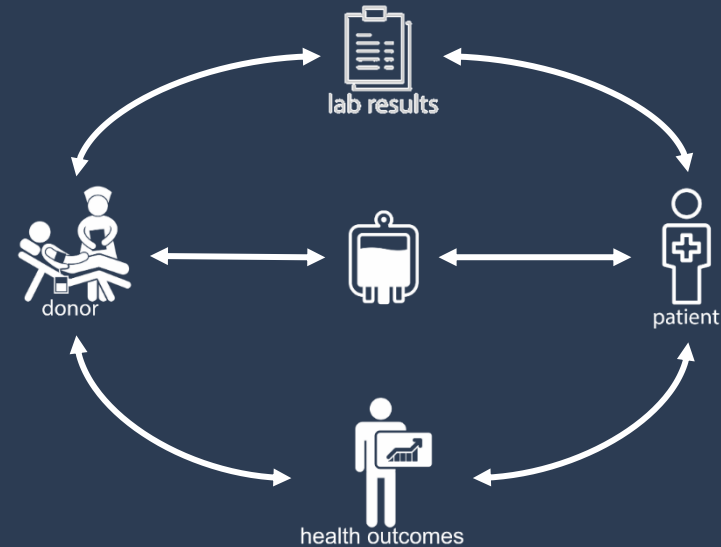
- Alas, none!

Overview

- SCANDAT background
- Using big data to study transfusion transmission?
- Transmission of neurodegenerative disease?
- Surveillance: moving into the 'agnostic' realm?

The SCANDAT database

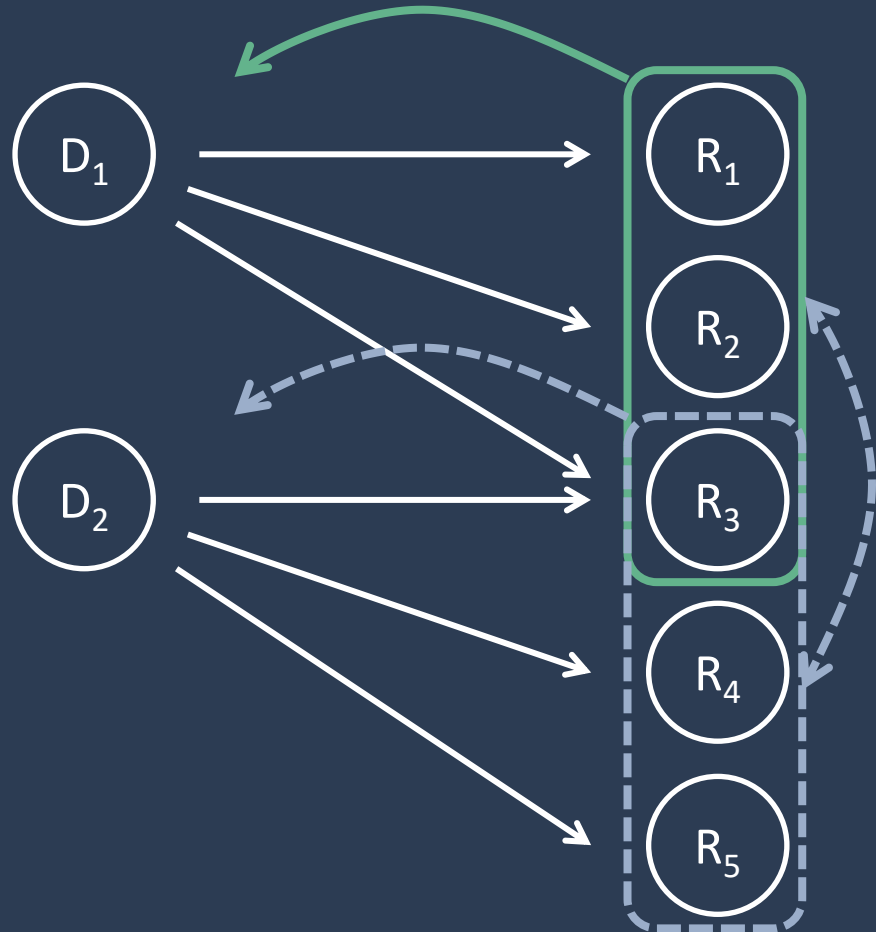
- The SCANDAT (Scandinavian Donations and Transfusions) databases are a series of databases, compiling all electronic data on blood donations and transfusions in Sweden and Denmark
- Bi-nationally (nearly) complete since mid-late 1990's
- 1.5 million blood donors, with 28 million person-years of follow-up
- 2 million transfused patients, with 13.6 million person-years of follow-up
- > 400 million laboratory test results
- Fourth update being planned



Nationwide health data registers

- Patient register
- Cancer register
- Cause of death register
- Medical birth register
- Prescription drug register
- Socio-economy data
- Multi-generation register
- Twin register
- Quality registers for intensive care, heart surgery, perioperative care, and colorectal cancer surgery

Approaches for studying transfusion transmission



Approach 1:

Is recipient disease risk associated with disease in their donors?

Approach 2:

Do all recipients of a given donor have a “shared” risk?

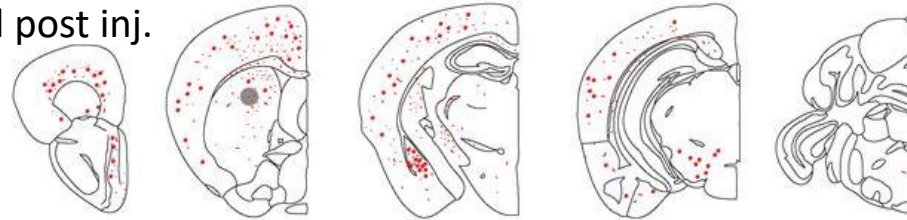
Science 338, 949 (2012);

Pathological α -Synuclein Transmission Initiates Parkinson-like Neurodegeneration in Nontransgenic Mice

Kelvin C. Luk, Victoria Kehm, Jenna Carroll, Bin Zhang, Patrick O'B
John Q. Trojanowski, Virginia M.-Y. Lee*

Parkinson's disease is characterized by abundant α -synuclein (α -Syn) neu as Lewy bodies and Lewy neurites, and the massive loss of midbrain dopa cause-and-effect relationship between Lewy inclusion formation and neur unclear. Here, we found that in wild-type nontransgenic mice, a single in synthetic α -Syn fibrils led to the cell-to-cell transmission of pathologic α -Lewy pathology in anatomically interconnected regions. Lewy pathology a progressive loss of dopamine neurons in the substantia nigra pars compa ventral tegmental area, and was accompanied by reduced dopamine level deficits. This recapitulation of a neurodegenerative cascade thus establishe transmission of pathologic α -Syn and the cardinal features of Parkinson's

30d post inj.



90d post inj.



180d post inj.



Intracerebral
inoculation of α -Syn
fibrils

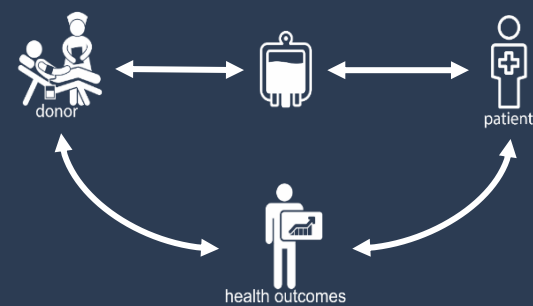
Cell-cell transmission
of α -Syn fibrils

Loss of dopamin
neurons (Lewy
pathology)

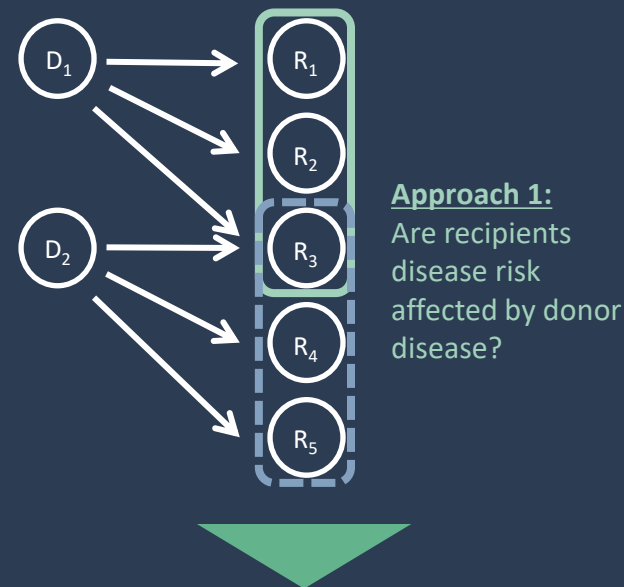
Gradual development
of motor deficits

Is dementia or liver disease infectious? (1/2)

SCANDAT database



Studying TTI:s



Approach 1:
Are recipients
disease risk
affected by donor
disease?

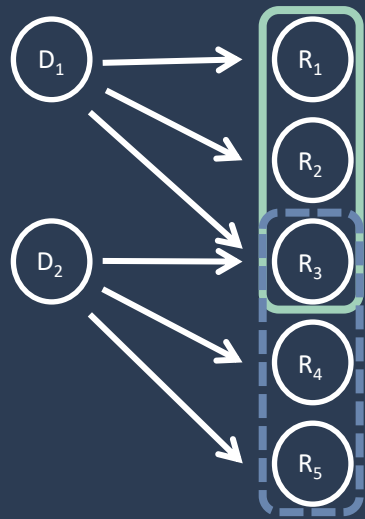
No transmission of neurodegenerative disease

	Donor diseased		Donor not diseased	
Disease	Events	Hazard ratio (95% CI) [†]	Events	Hazard ratio (95% CI) [†]
All dementia, overall	1,949	1.04 (0.99-1.09)	99,356	1.00 (ref)
<5 year latency in donor	157	1.05 (0.90-1.23)	99,356	1.00 (ref)
Alzheimer's disease, overall	173	0.99 (0.85-1.15)	20,378	1.00 (ref)
<10 year latency in donor	9	0.73 (0.38-1.41)	20,378	1.00 (ref)
Parkinson's disease, overall	113	0.94 (0.78-1.14)	11,024	1.00 (ref)
<10 year latency in donor	47	1.10 (0.83-1.47)	11,024	1.00 (ref)

No transmission of hepatotropic agent after 1992

	Donor diseased		Donor not diseased	
Time period	Events	Hazard ratio (95% CI) [†]	Events	Hazard ratio (95% CI) [†]
Before 1992	375	1.21(1.09-1.36)	5,033	1.00 (ref)
<5 year latency in donor	51	1.61(1.21-2.14)	5,033	1.00 (ref)
After 1992	66	0.91(0.70-1.17)	7,573	1.00 (ref)
<5 year latency in donor	16	0.94(0.56-1.58)	7,573	1.00 (ref)

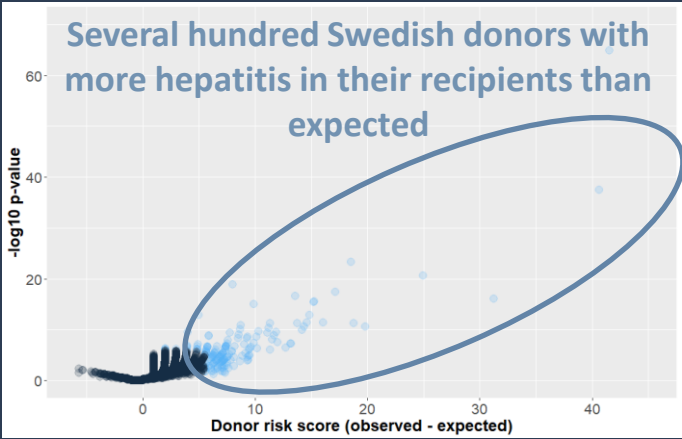
Is dementia or liver disease infectious? (2/2)



Approach 2:
Do all recipients
of one donor
have a ‘shared’
increased risk?

”Risky” donors?

$$\text{Donor risk score}_n = \sum_{k=1}^{n-1} \text{observed}_k - \sum_{k=1}^{n-1} \text{expected}_k$$



Still no transmission of dementia...

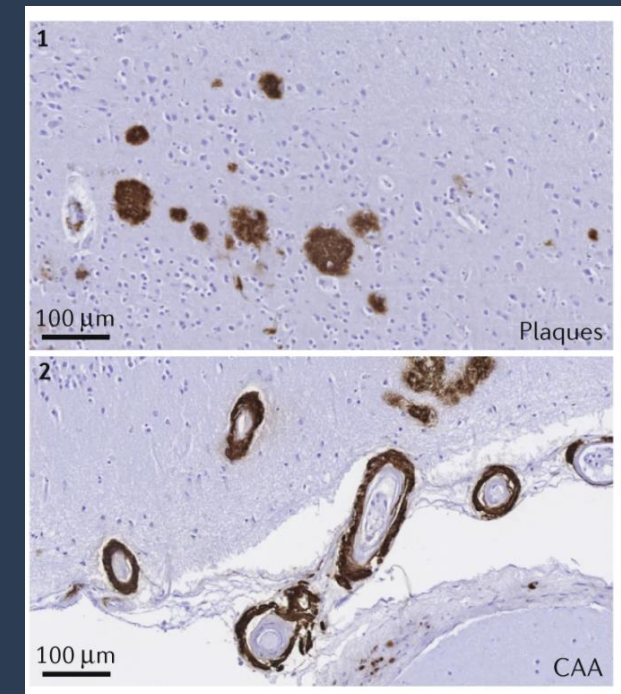
Maximum Disease Excess Score Among Blood Donors, by Disease*	Events	Hazard Ratio (95% CI)†
Dementia (any type)		
<0	36,118	1.00 (ref)
0‡	17,093	1.00 (0.97–1.03)
0.1–2.5	47,070	1.01 (0.99–1.03)
2.6–5.0	1005	1.07 (0.98–1.16)
>5.0	19	1.17 (0.66–2.08)
Alzheimer disease		
<0	10,416	1.00 (ref)
0‡	4666	1.01 (0.97–1.05)
0.1–2.0	5428	1.00 (0.96–1.04)
>2.0	41	1.00 (0.73–1.36)

And no hepatitis transmission after 1992!

Maximum disease excess score among contributing blood donors	Events	Hazard ratio (95% CI)†
Before 1992 (i.e. pre HCV screening)		
< 0.0 recipients	2,421	1.00 (ref)
0.0, i.e. no prior donations	2,582	0.98(0.93-1.04)
0.1-2.5 recipients	4,619	1.07(1.01-1.13)
2.6-5.0 recipients	373	1.40(1.24-1.58)
>5.0 recipients	56	2.93(2.19-3.92)
After 1992 (i.e. post HCV screening)		
< 0.0 recipients	7,208	1.00 (ref)
0.0, i.e. no prior donations	6,079	0.98(0.95-1.02)
0.1-2.5 recipients	8,878	1.03(1.00-1.07)
2.6-5.0 recipients	199	0.92(0.79-1.08)
>5.0 recipients	0	0.00 (n.e.)

No evidence of dementia being transmissible, but what about other amyloid- β pathologies?

- Cerebral amyloid angiopathy is a common cause of intracerebral hemorrhage, closely related to Alzheimer's disease
- CAA is characterized by multiple lobar intracerebral hemorrhages (ICH) and cerebrovascular amyloid- β deposits
- Estimated to co-occur in majority of Alzheimer's disease cases, and vice versa.
- Second most common cause of spontaneous ICH in older patients, after hypertension
- Lifetime risk of moderate-to-severe CAA estimated to be about 25%, high prevalence particularly >80y



Human-to-human transmission of amyloid- β pathology demonstrated in recipients of cadaveric growth hormone

Cadaveric growth hormone contaminated with prions for Creutzfeldt-Jakob Disease (CJD)



Intramuscular injections

Autopsy study of 8 patients who died due to iCJD between 36-51y, where half had moderate to severe CAA despite young age.

Shown to contain A β_{40} , A β_{42} and tau proteins



Inoculated into mice models and led to CAA

nature

Evidence for human transmission of amyloid- β pathology and cerebral amyloid angiopathy

Zane Jaunmuktane¹, Simon Mead^{2,3,4}, Matthew Ellis², Jonathan D. F. Wadsworth^{2,3}, Andrew J. Nicoll^{2,3}, Joanna Kenny^{2,4}, Francesca Launchbury⁴, Jacqueline Linehan¹, Angela Richard-Loendt⁴, A. Sarah Walker¹, Peter Rudge^{2,4}, John Collinge^{1,4} & Sebastian Brandner^{1,2,3}

nature

Transmission of amyloid- β protein pathology from cadaveric pituitary growth hormone

Silvia A. Purro¹, Mark A. Farrow¹, Jacqueline Linehan¹, Tamsin Nazari¹, David X. Thomas¹, Zhicheng Chen², David Mengel², Takashi Saito³, Takaomi Saido³, Peter Rudge¹, Sebastian Brandner^{1,4}, Dominic M. Walsh^{1,2} & John Collinge^{1*}

Variant CJD – a prion illness - has been shown to be transmissible by human-to-human blood transfusions

- Prion illnesses are “infections caused by self-propagating misfolded proteins” called prions
- Variant CJD caused by ingesting beef with bovine spongiform encephalopathy (“mad cow disease”)
- Four cases of probable transfusion-transmission of vCJD between 2004-2007
- Donor deferral policies were enacted in several countries for residents or transfusion recipients in geographies affected by the BSE epidemic

THE LANCET

Volume 363, Issue 9407, 7 February 2004, Pages 417-421

🕒 Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion

THE LANCET

Volume 364, Issue 9433, 7 August 2004, Pages 527-529

Preclinical vCJD after blood transfusion in a *PRNP* codon 129 heterozygous patient

THE LANCET

Clinical presentation and pre-mortem diagnosis of variant Creutzfeldt-Jakob disease associated with blood transfusion: a case report



Fourth case of transfusion-associated vCJD infection in the United Kingdom

“Prion-like” transmissivity of amyloid- β pathologies

	Prion illnesses transmission	Amyloid- β pathology transmission
 Dura mater grafts	Yes 	Yes 
 Neurosurgical instruments	Yes 	Likely 
 Cadaveric pituitary hormone	Yes 	Yes 
 Blood transfusion	Yes 	?

Methodological considerations – CAA is rarely diagnosed

Recurring spontaneous ICH may be suitable proxy

- CAA is second most common cause of spontaneous ICH in older patients
- Among patients with CAA-related ICH, the risk of ICH recurrence is about 10% a year
- The risk of recurrence is 7-fold compared to other causes of ICH



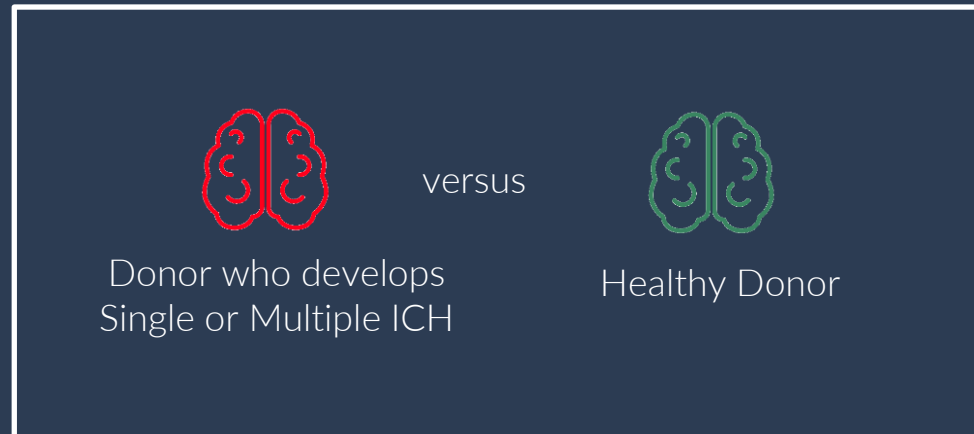
Our approach

- Recurring spontaneous ICH as proxy for CAA
- Use patient register to identify inpatient episodes with a diagnosis of spontaneous ICH (without brain tumors, trauma, or vascular malformation)
- Single ICH serves as additional control (where prevalence of CAA is expected to be much lower)

Approach to assess possible transmissivity

What is the risk of developing spontaneous ICH in recipients?

Donor-recipient disease concordance



“ Does disease in donors predict disease in the recipient?



Stratified Cox proportional hazards regression using transfusion exposure during first 180-days since first transfusion

Validation cohort and 'negative control'



Ischemic stroke shares many of the same etiologies as spontaneous ICH (hypertension, atherosclerosis) but is not strongly related to CAA

Can we replicate findings from Sweden in Denmark?

Increased risk of ICH in recipients who received blood from donors who eventually developed multiple but not single ICH

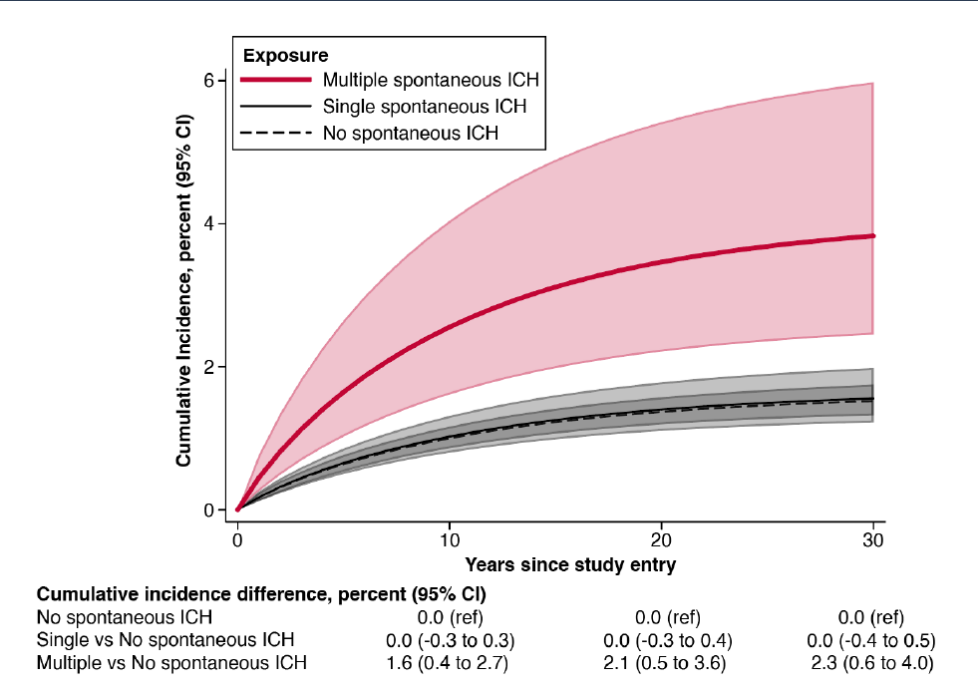
Cause-specific hazard ratios for ICH in recipients

A Sweden (Main)			B Denmark (Validation)		
Exposure	Events / Personyears; IR	Adjusted Hazard Ratio (95% CI)	Events / Personyears; IR	Adjusted Hazard Ratio (95% CI)	
180-day exposure period					
No sICH	5185 / 4,611,866 ; 1.12	1.00 (ref)	1901 / 1,751,337 ; 1.09	1.00 (ref)	
Single sICH	67 / 49,583 ; 1.35	1.06 (0.84 to 1.36)	23 / 16,916 ; 1.36	1.06 (0.70 to 1.60)	
Multiple sICH	18 / 5704 ; 3.16	2.73 (1.72 to 4.35)	6 / 2127 ; 2.82	2.32 (1.04 to 5.19)	

Adjusted for hospital/geographical region, calendar year, age, sex, age and sex interaction, number of transfusions, transfusion indication, and ABO and RhD blood group. All numerical covariates were treated as restricted cubic splines with 5 equally spaced knots.

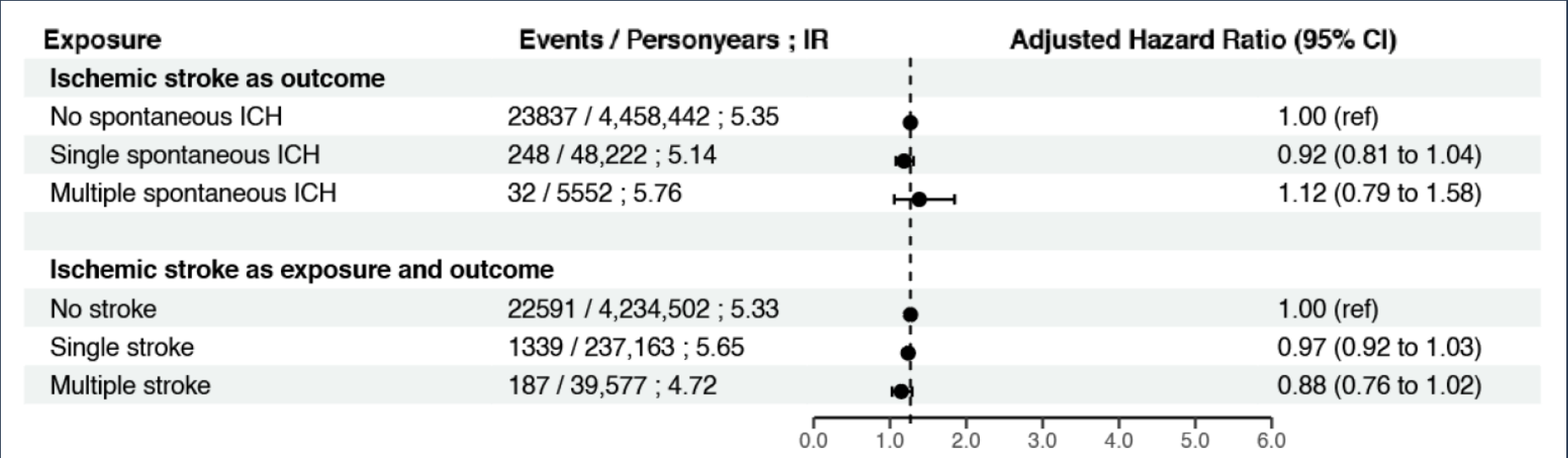
Receiving blood from a donor who eventually developed multiple ICH is associated with a 3x higher risk of developing ICH

Standardized cause-specific cumulative incidence for spontaneous ICH



Adjusted for competing events by death, additional transfusions, and primary cerebral tumor. Estimated using a 180-day exposure window with Swedish cohort only, with the baseline hazard modeled as a restricted cubic spline with 5 knots.

Negative control: no effect seen for ischemic stroke



Adjusted for hospital/geographical region, calendar year, age, sex, age and sex interaction, number of transfusions, transfusion indication, and ABO and RhD blood group. All numerical covariates were treated as restricted cubic splines with 5 equally spaced knots.

So?

- We observe a modest and consistent association between occurrence of spontaneous, unprovoked intracerebral haemorrhage in donors and their recipients
- Possibly explainable by CAA transmission, but speculative given observational data
- Depending on how computed, the population attributable risk is $<1\%$, but CAA prevalence is much higher than exposure in our data
- Independent replication would be fantastic, but not known whether there are other, sufficiently large databases
- Mechanistic studies are being planned

Is it possible to 'search' agnostically for unknown TTIs?

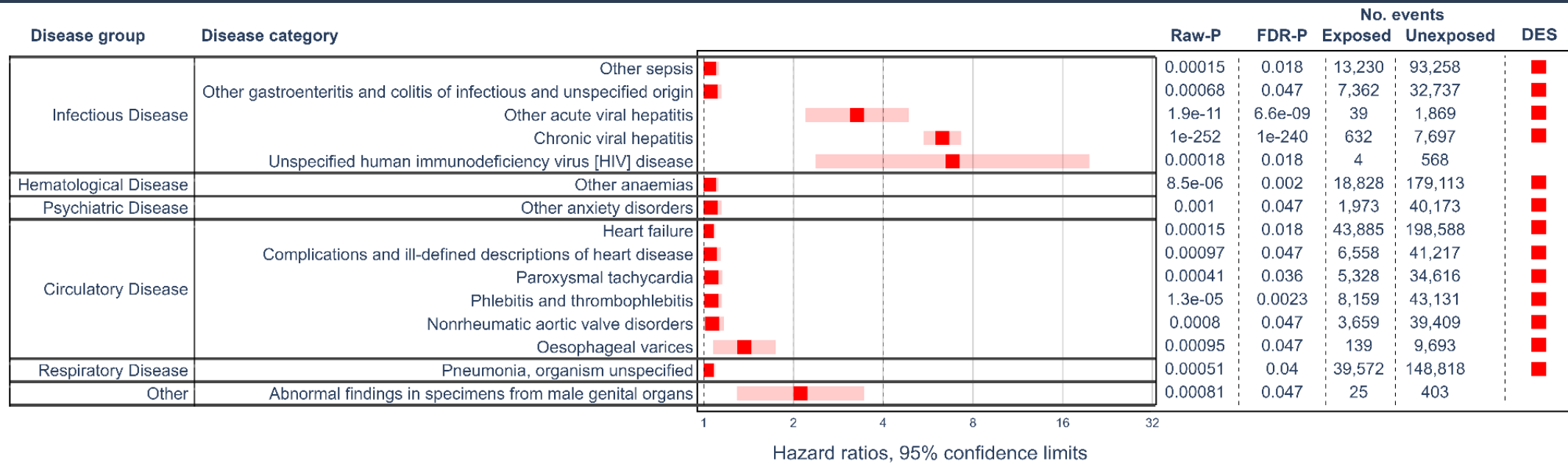
- We have demonstrated that it is possible to study transfusion transmitted disease using retrospective data
- But, rather than looking at individual diseases, can we not look at all diseases at the same time?
- By applying agnostic statistical methods to large-scale transfusion data, we want to be able to find unknown TTIs
- Perhaps use also as a surveillance tool?

Approach

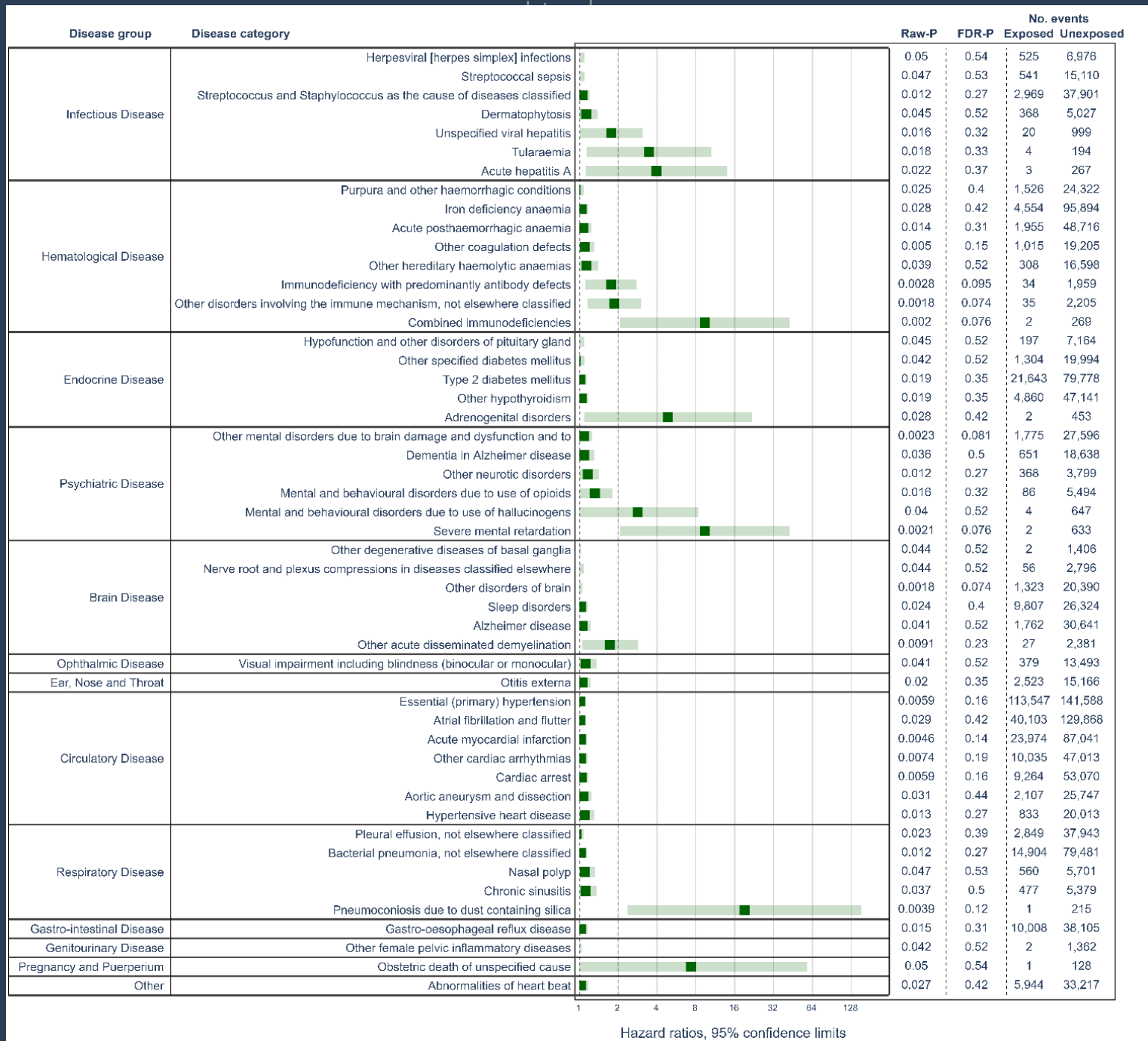
- 1.7 million transfused patients, median follow-up of 4.5 years
- 1,155 different, unique outcomes (ICD-8—10)
- Two-pronged approach, with adjustment for multiple testing:



Anything exciting?



Non-FDR-significant associations



$-\log_{10}(\text{FDR-adjusted p-value})$

P 0.05

245

9

7

5

Infectious Disease

Malignant Disease
Hematological Disease

Endocrine Disease

Psychiatric Disease

Brain Disease

Ophthalmic Disease
Ear, Nose and Throat

Circulatory Disease

Respiratory Disease

Gastro-intestinal Disease
Dermatological Disease
Musculoskeletal Disease

Genitourinary Disease
Pregnancy and Puerperium

Other

Other gastroenteritis and colitis of infectious and unspecified origin

Other sepsis

Chronic viral hepatitis

Other acute viral hepatitis

Unspecified human immunodeficiency virus HIV disease

Other anaemias

Other anxiety disorders

Nonrheumatic aortic valve disorders

Paroxysmal tachycardia

Heart failure

Complications and ill-defined descriptions of heart disease

Phlebitis and thrombophlebitis

Oesophageal varices

Pneumonia, organism unspecified

Abnormal findings in specimens from male genital organs

Acknowledgements



Gustaf Edgren MD PhD
gustaf.edgren@ki.se



Jingcheng Zhao MD PhD
jingcheng.zhao@ki.se



Anne Brynolf MD
anne.brynolf@ki.se



Torsten Dahlén MD PhD
torsten.dahlen@ki.se



Lucas Ekström MD
lukas.ekstrom@ki.se

For more information about our transfusion epidemiology research
please visit www.scandat.se