Septic Shock Data Discovery Dataset

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V A S S T dataset
Vasopressin and Septic Shock Trial

Dataset arising from VASST

- <u>Septic shock</u> is organ failure and really low blood pressure due to a severe infection.
- Your body's initial immune response to severe infection is to release many <u>cytokines</u> and other inflammatory mediators – which decrease blood pressure.
- Low blood pressure can be increased with norepinephrine or vasopressin.

<u>VASST hypothesis</u>

Low dose vasopressin infusion, in addition to conventional vasopressors, will decrease 28-day mortality in human septic shock, compared to norepinephrine infusion alone.

1) Lots of Clinical Data
>2000 fields/patient

	Norepinephrine (n=382)	Vasopressin (n=396)
Age, years	61.8 ±16	59.3 ±16.4
Male sex	229 (59.9)	246 (62.0)
Caucasian	320 (83.8)	336 (84.6)
Co-morbidities		
Ischemic heart disease	65 (17.0)	68 (17.1)
COPD	72 (18.8)	55 (13.9)
Chronic renal failure	48 (12.6)	40 (10.1)
Cancer	104 (27.2)	85 (21.4)
Pre-existing steroid use	86 (22.5)	82 (20.7)
Recent surgery	132 (34.6)	151 (38.0)
Time from eligibility to infusion, hrs	11.5 ± 9.4	11.9 ± 8.9

Values are n (%) or mean ± SD, as appropriate

Plasma vasopressin levels
(n = 107)

Vasopressin

Off Vasopressin
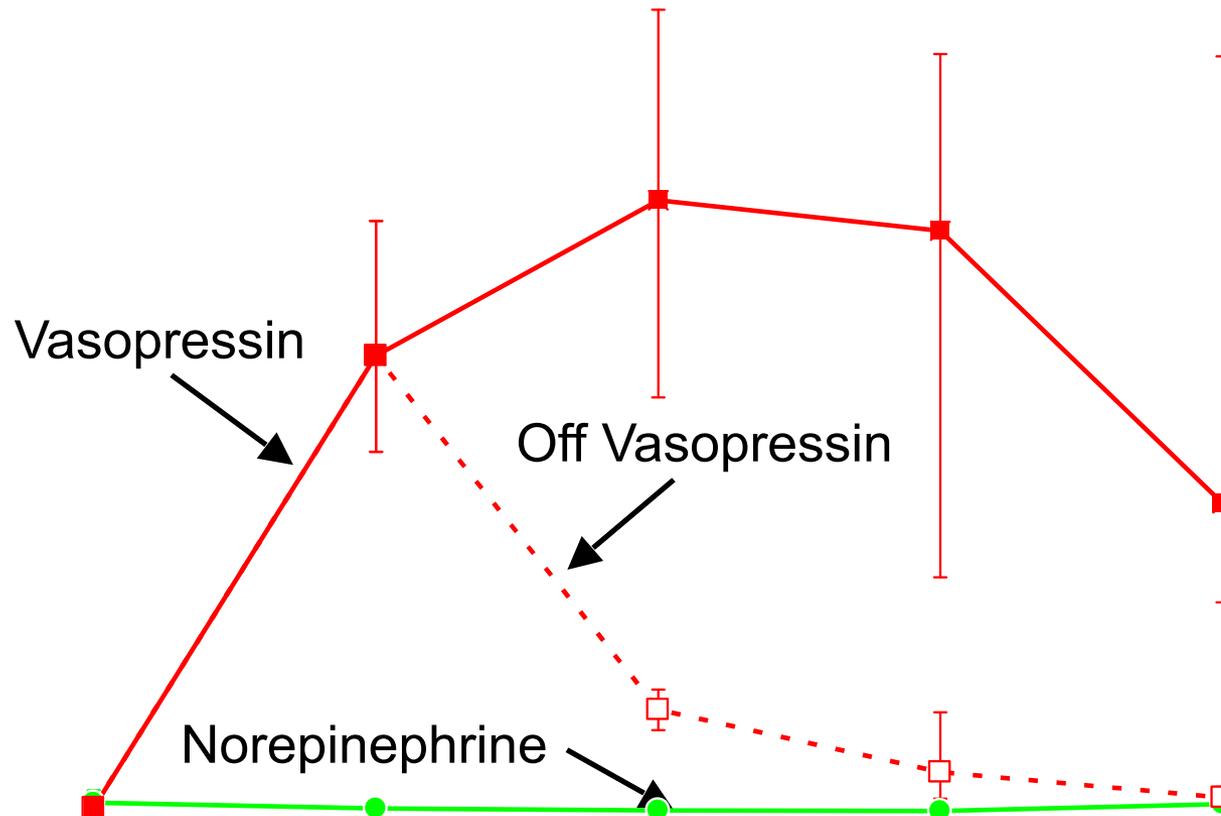
Norepinephrine

Kaplan-Meier survival curve
All patients

Log-rank statistic

p = 0.27 day 28

p = 0.10 day 90
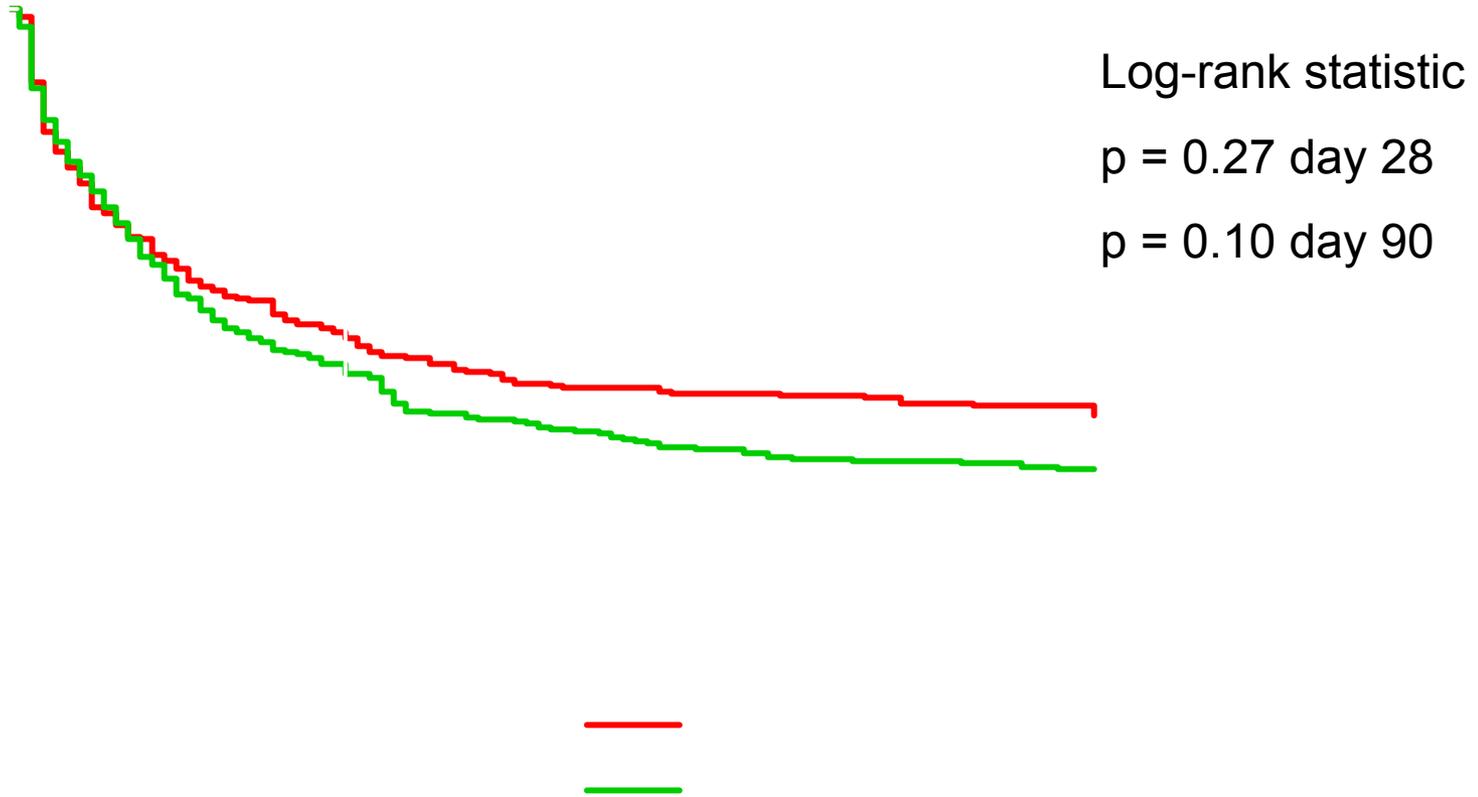
Kaplan-Meier survival curve
Less severe shock

Log-rank statistic

p = 0.05 day 28

p = 0.03 day 90
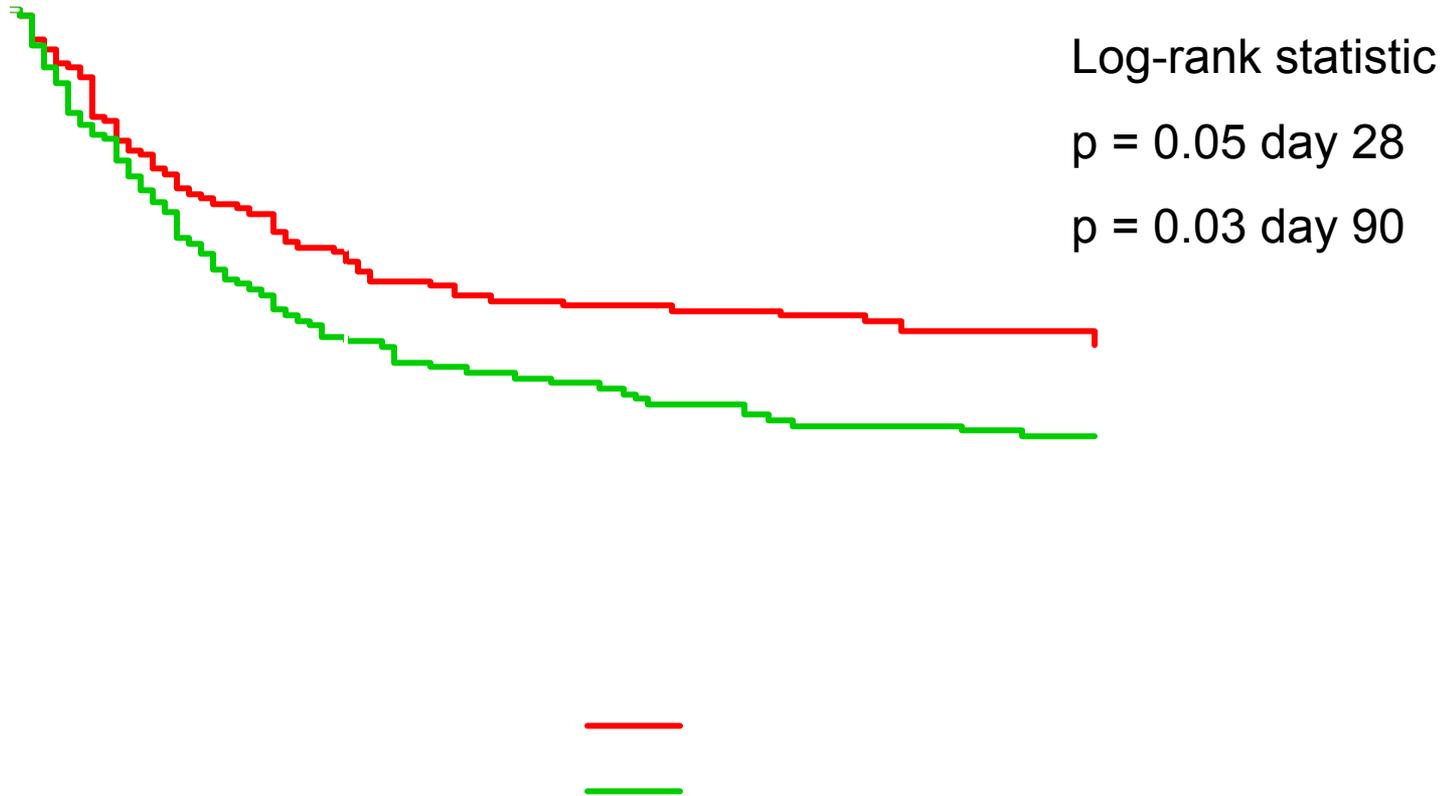
Serious adverse events

	Norepinephrine (n=382)	Vasopressin (n=397)	p
Myocardial infarction / ischemia	7 (1.8)	8 (2.0)	1.00
Cardiac arrest	8 (2.1)	3 (0.8)	0.14
Tachyarrythmia	3 (0.8)	4 (1.0)	1.00
Bradyarrythmia	3 (0.8)	4 (1.0)	1.00
Mesenteric ischemia	13 (3.4)	9 (2.3)	0.39
Digital ischemia	2 (0.5)	8 (2.0)	0.11
Cerebrovascular accident	1 (0.3)	1 (0.3)	1.00
Hyponatremia	1 (0.3)	1 (0.3)	1.00
Other	2 (0.5)	5 (1.3)	0.45
Total	40 (10.5)	41 (10.3)	1.00

2) 50+ cytokines

Russell et al. AJRCCM 2013; 188 (3): 356-364.

Baseline cytokines
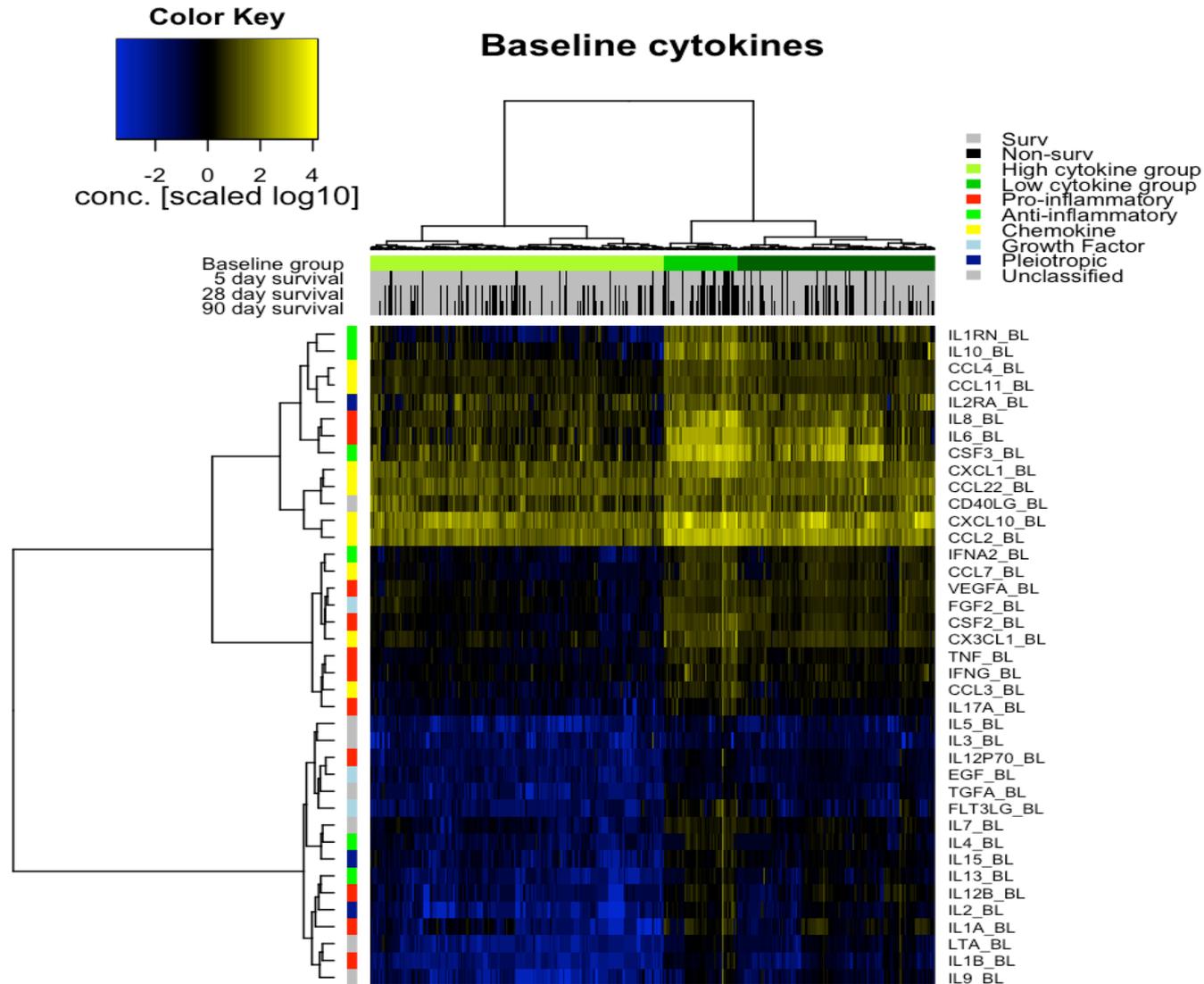
How cytokine data might be used

Image from www.angiopoietin.de
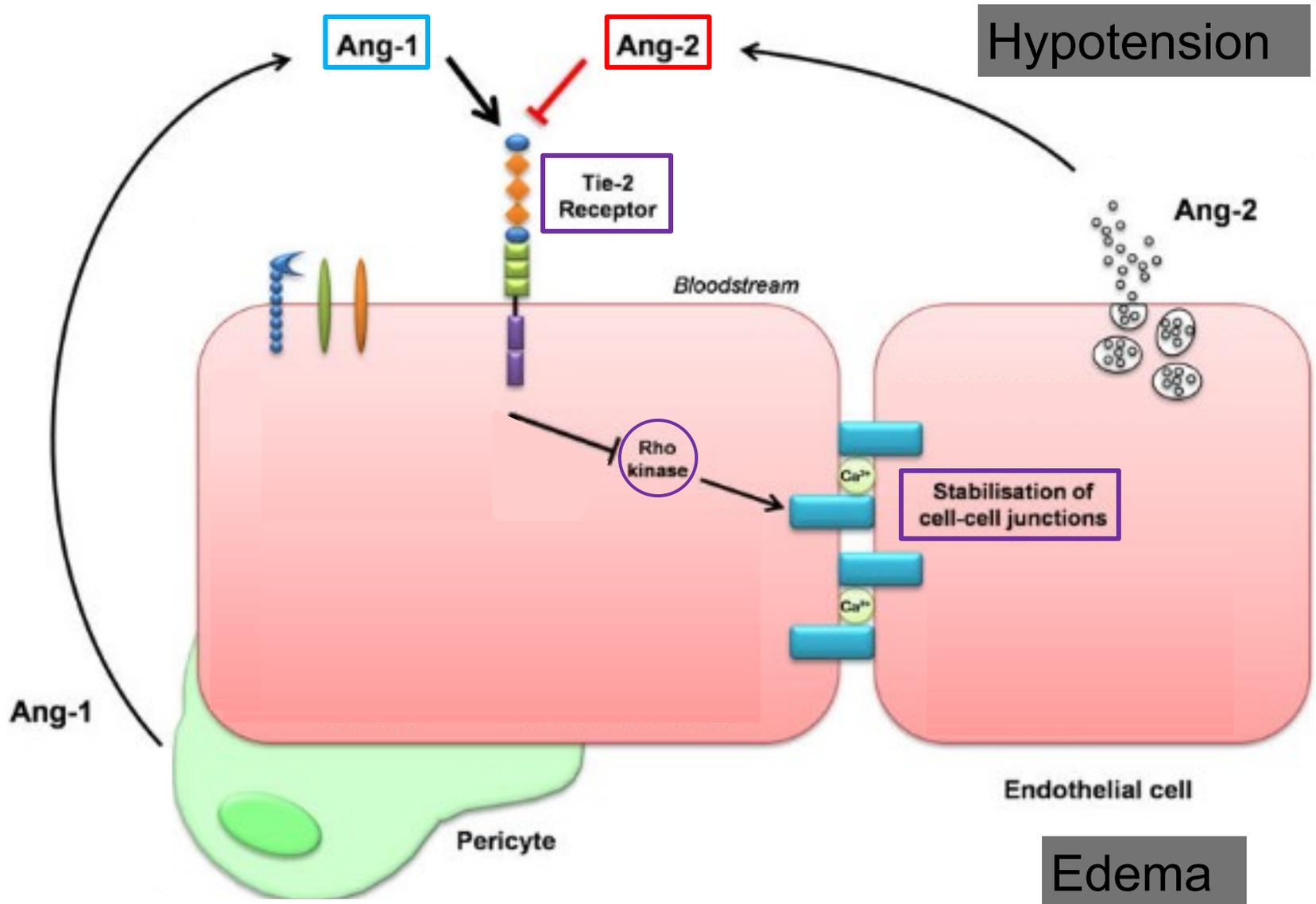
Plasma Ang-2 Levels Associated with Fluid Overload

Ang-2 level and baseline fluid overload

spearman r=0.1843
P=0.0008

% Fluid Overload / Log Ang-2
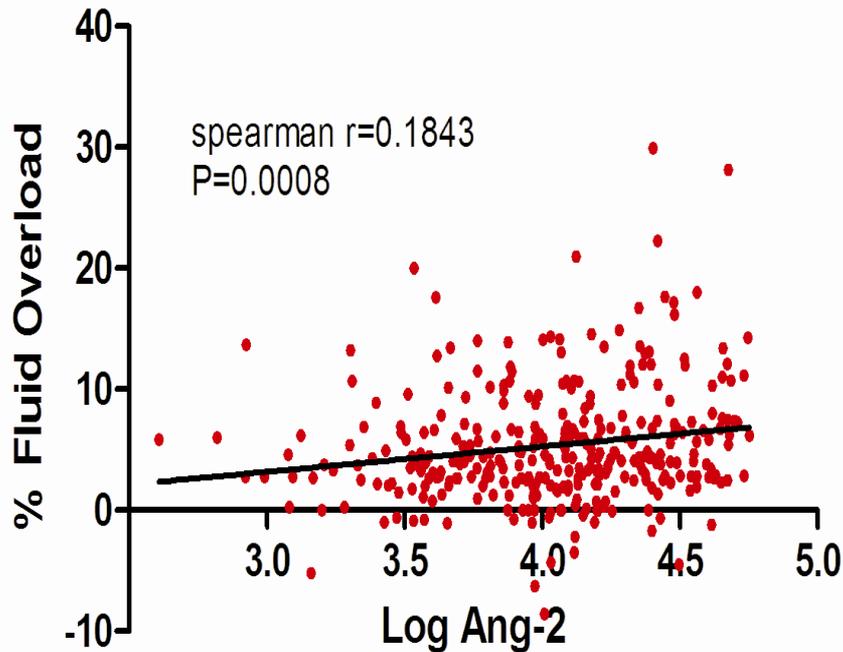
Ang-2 Level and 6h Fluid Overload

spearman r=0.1252
P=0.0234

% Fluid Overload / log Ang-2
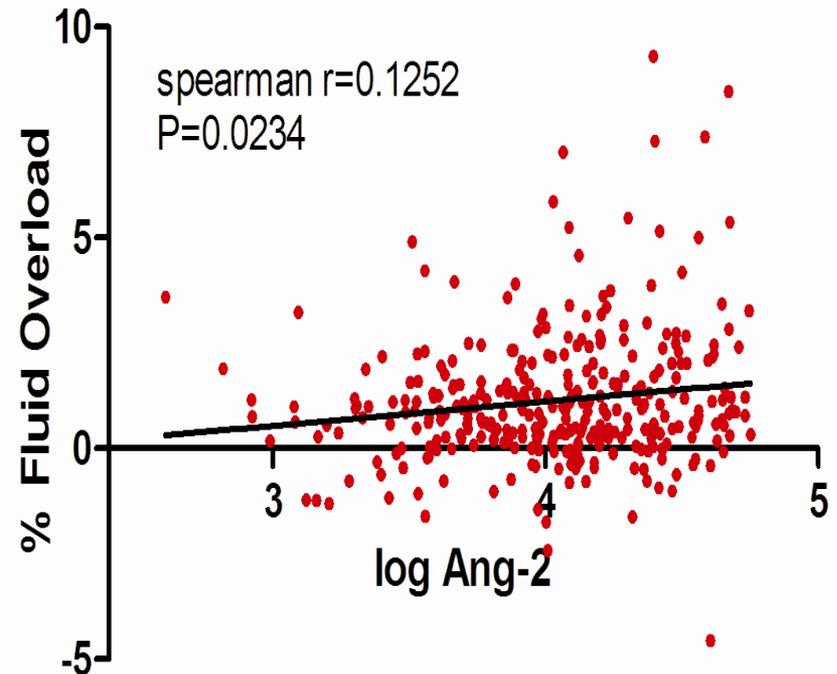
$$\%FO = (\text{intake-output})/\text{weight} \times 100\%$$

3) We don't have gene expression (mRNA), but we have it in some datasets

Calvano et al. Nature 2005;437:1032-7.
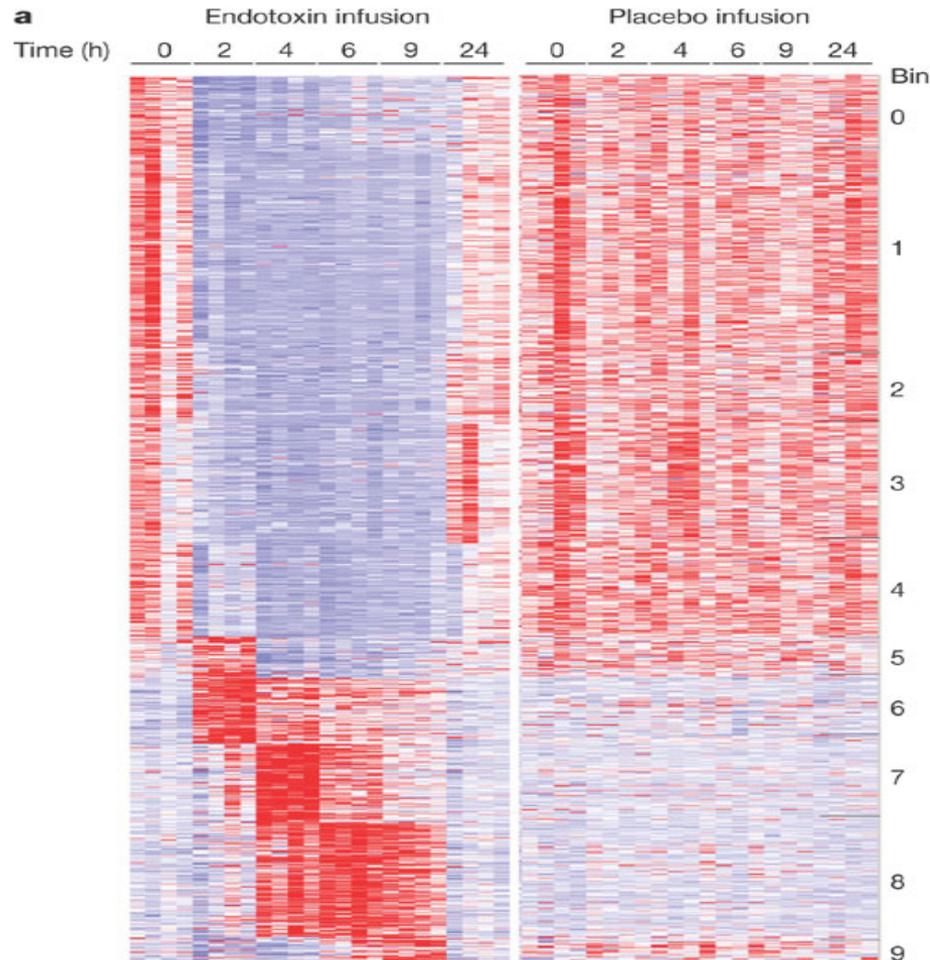
4) 1M Single Nucleotide Polymorphisms (SNP) genotypes
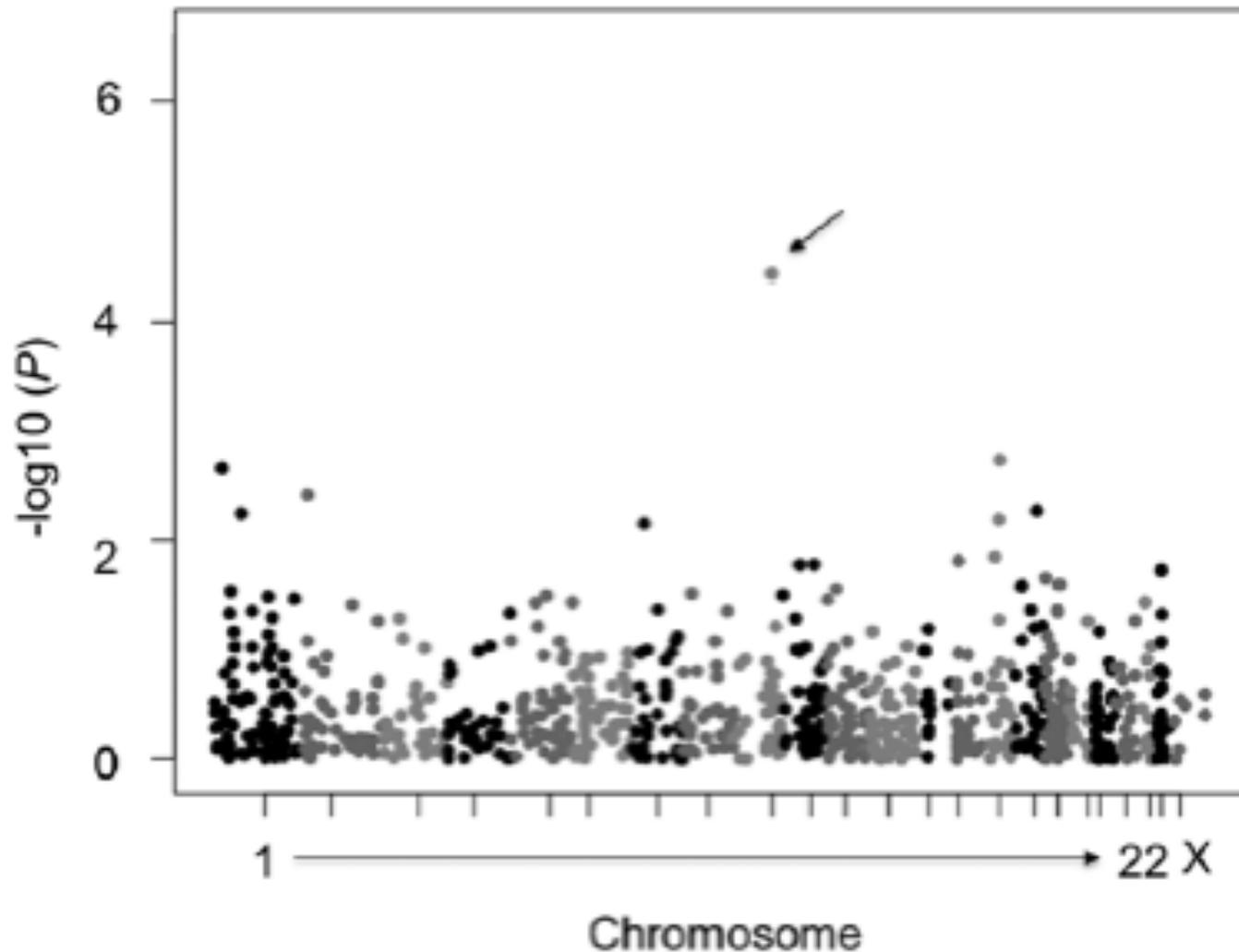
Association plot of non-synonymous SNPs with 28-day mortality

What can be done with the data

- Clinical associations
  - Obesity associated with decreased survival
- Gene association studies
  - ADRB2, AGTRAP, SVEP1, IL17, PCSK9, etc
- Causal inference
  - Instrumental variables, Mendelian Randomization
- Mechanism of action
  - Inhibition, over-expression
- New discoveries
  - Link to other datasets, AI to discover patterns

Example clinical association
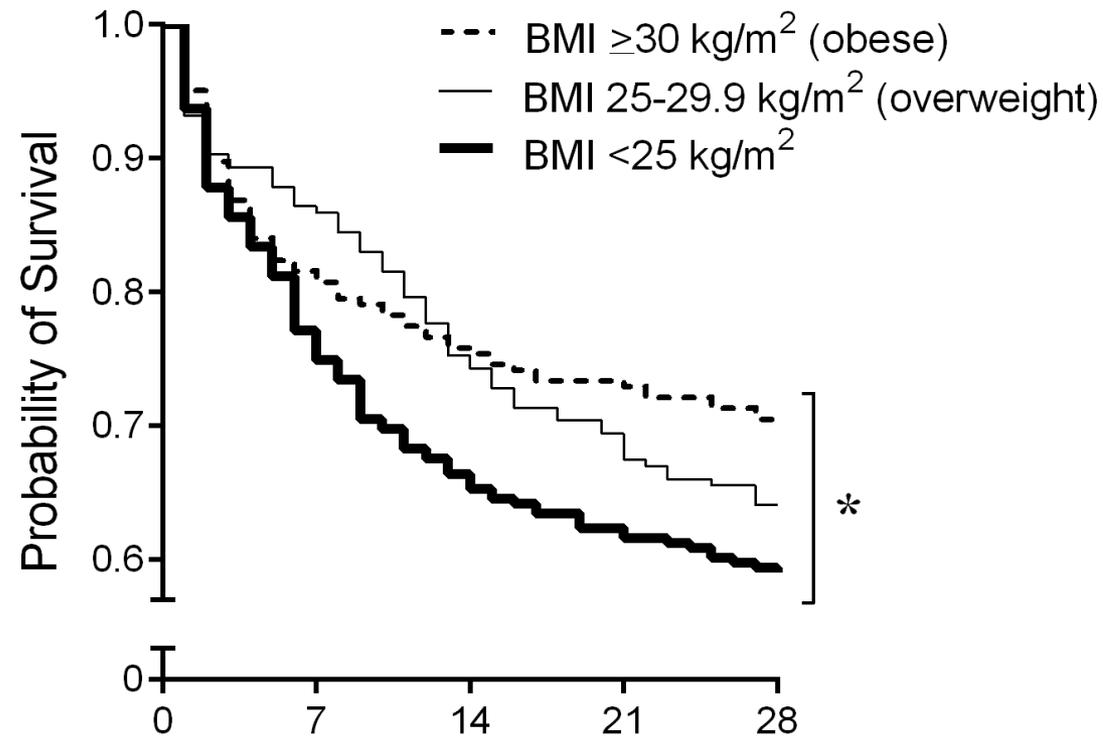
Example gene association
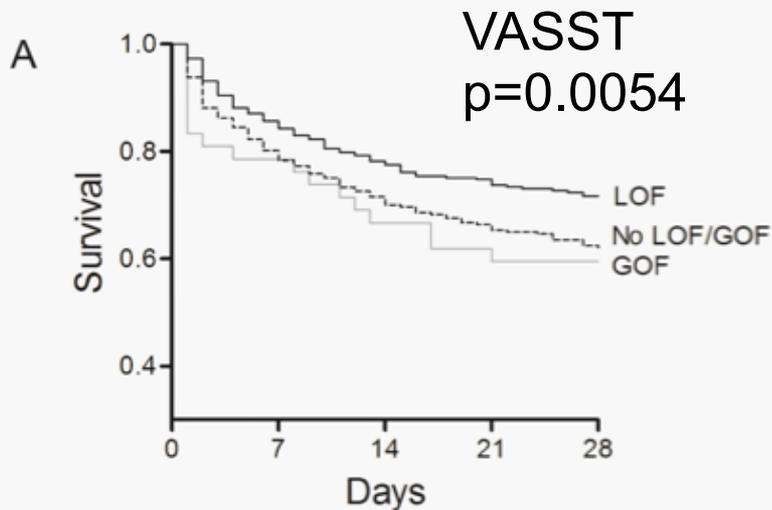
A — VASST p=0.0054

B — SPH p=0.022
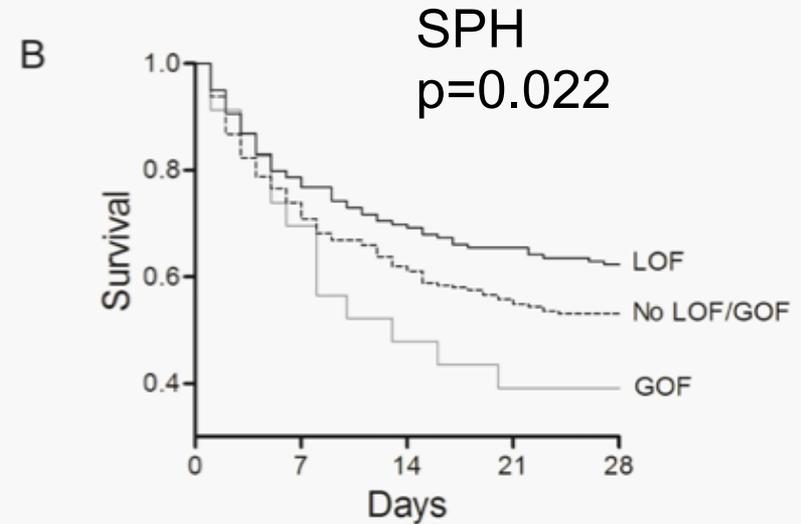
Example causal inference
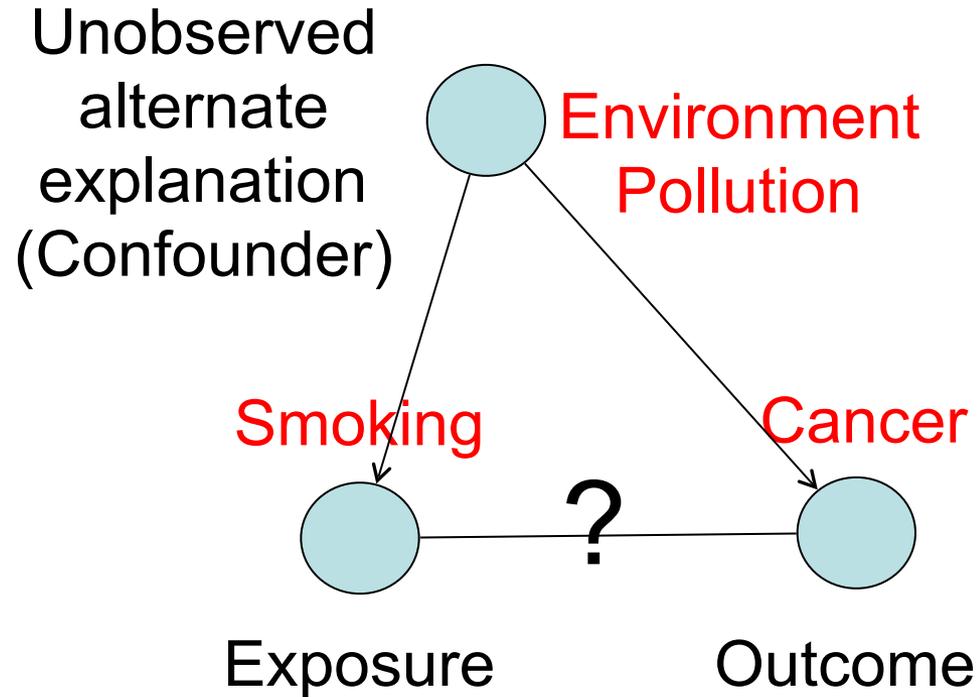
Instrumental Variables ➜ Cause
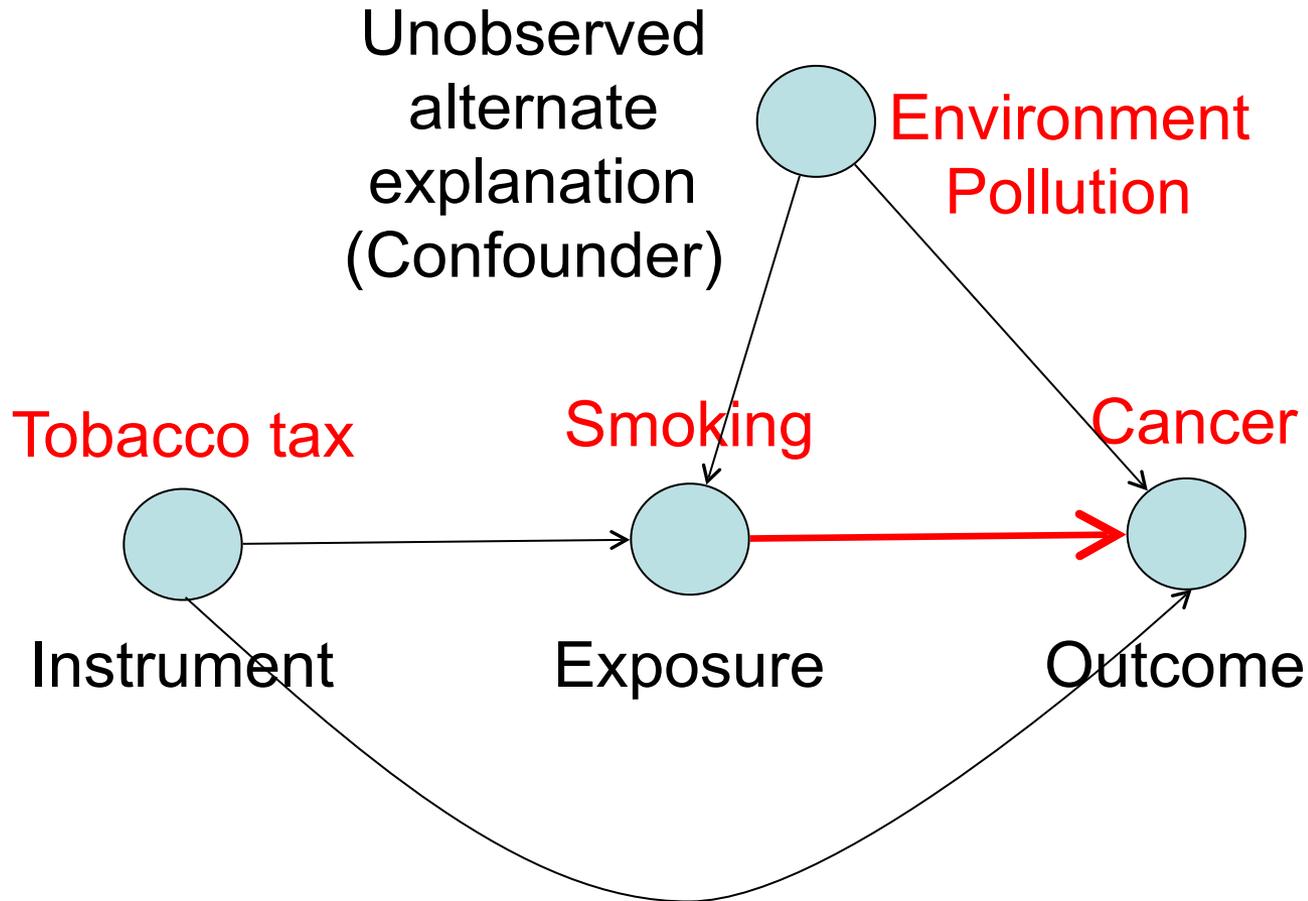
Mendelian Randomization

Mendelian Randomization

Meyer et al. Am J Respir Crit Care Med. 190(6):656-664, 2014
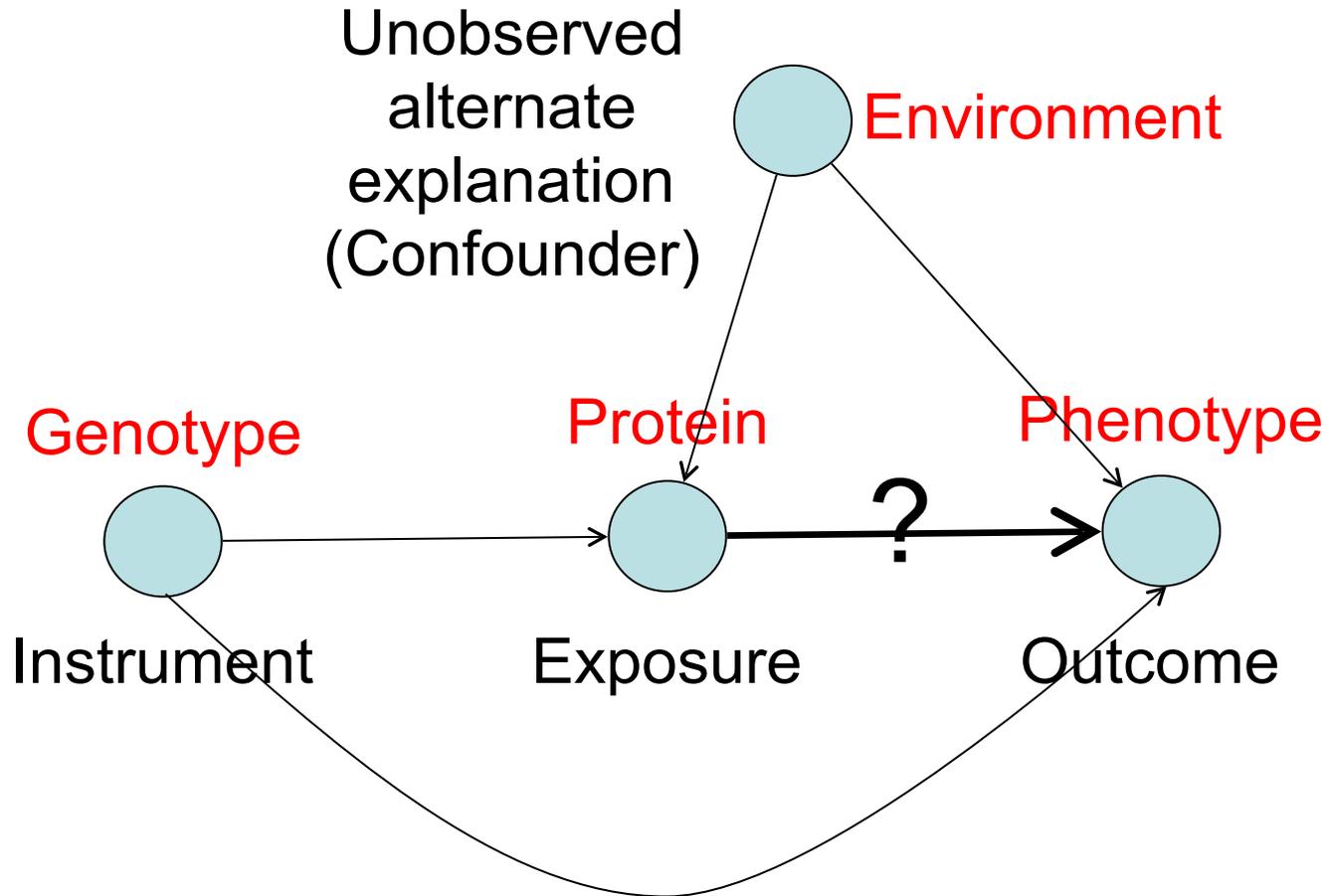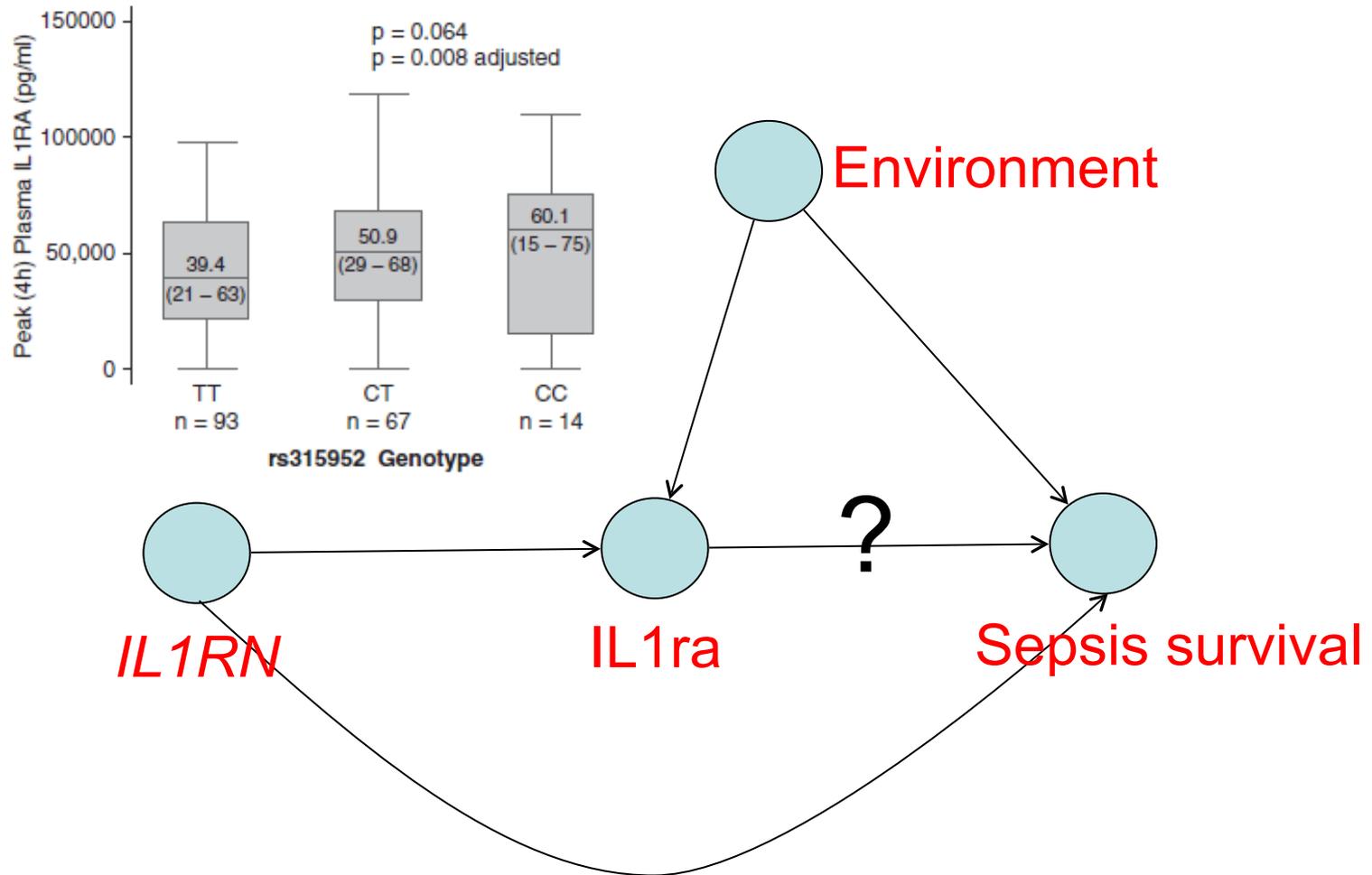
IL1RN genotype ~ Sepsis survival
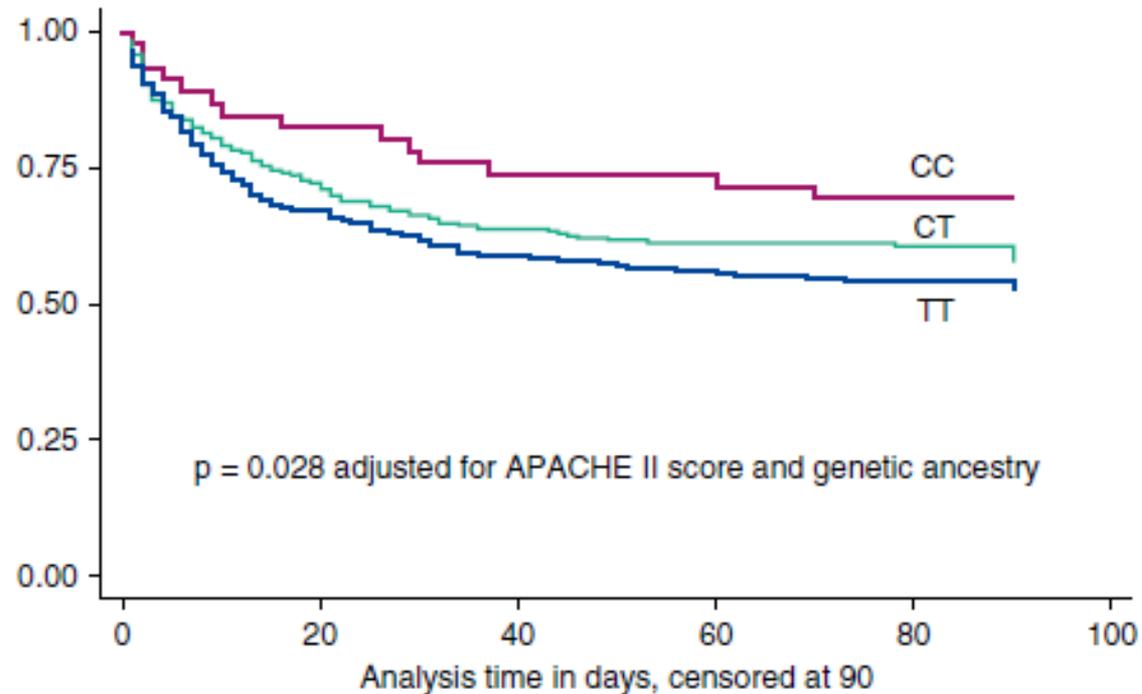
Meyer et al. Am J Respir Crit Care Med. 190(6):656-664, 2014

Mendelian Randomization
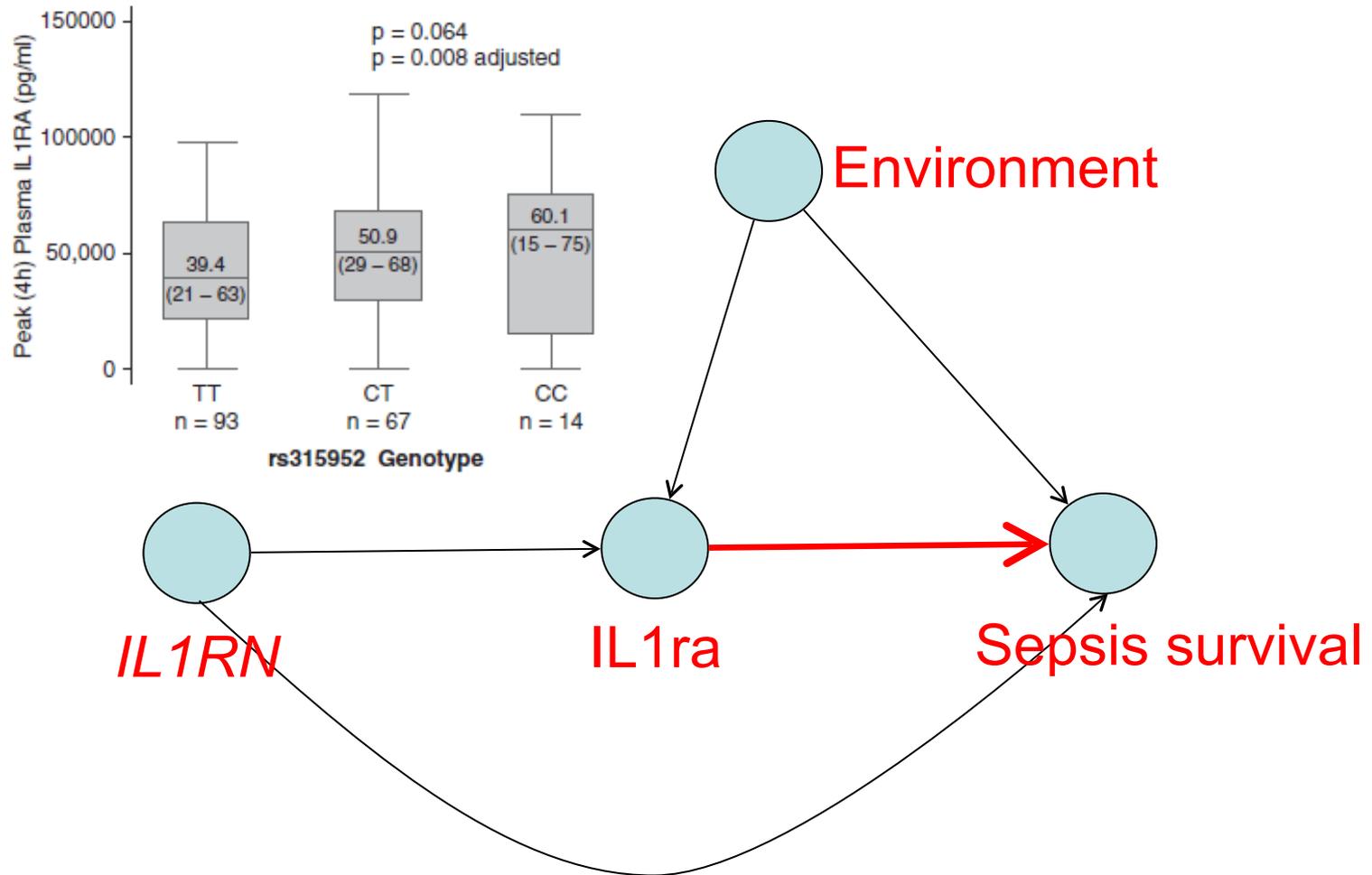
Example mechanism of action
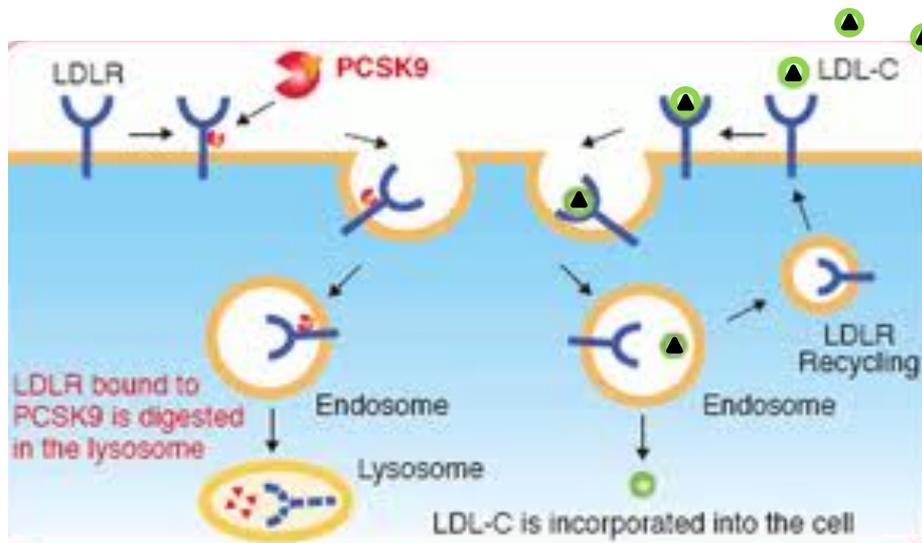
Lipopolysaccharide (LPS) Gram - endotoxin

Lipoteichoic acid (LTA) Gram +

Could PCSK9 inhibition increase pathogen lipid clearance?

Pcsk9 knockout mice
↑ LPS clearance, ↓ inflammation

Walley KR et al. Science Translational Medicine. 6(258):258ra143
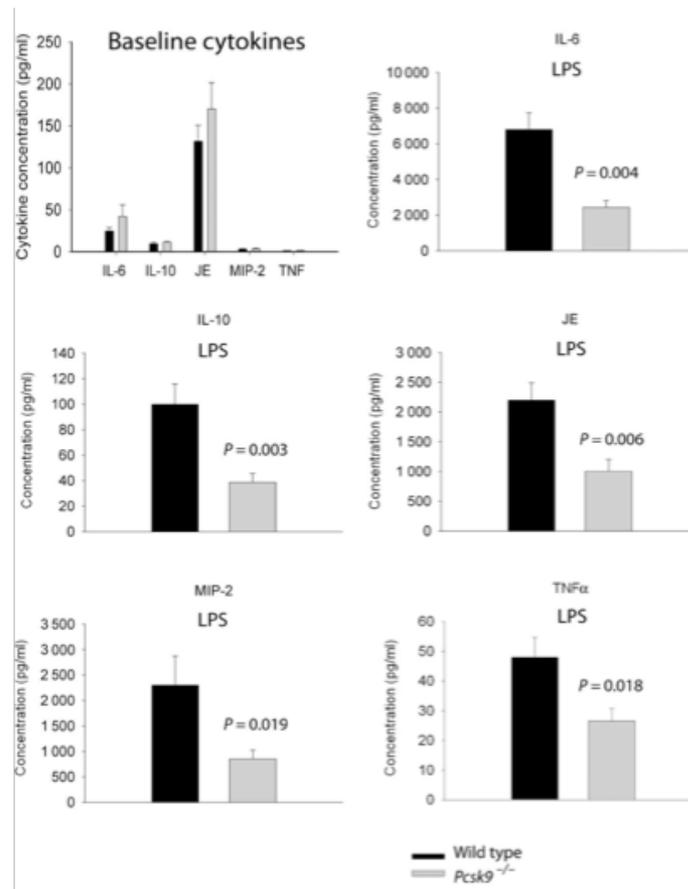
Pcsk9 knockout mice
↓ physiologic response
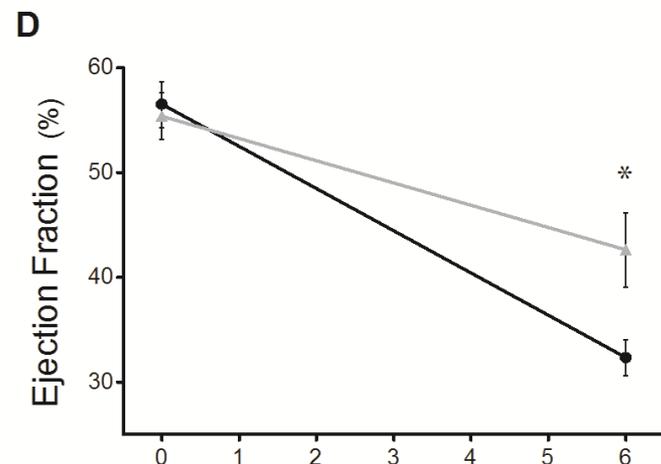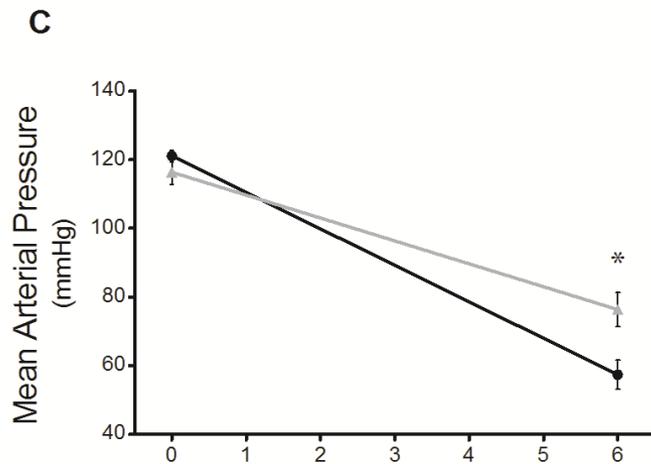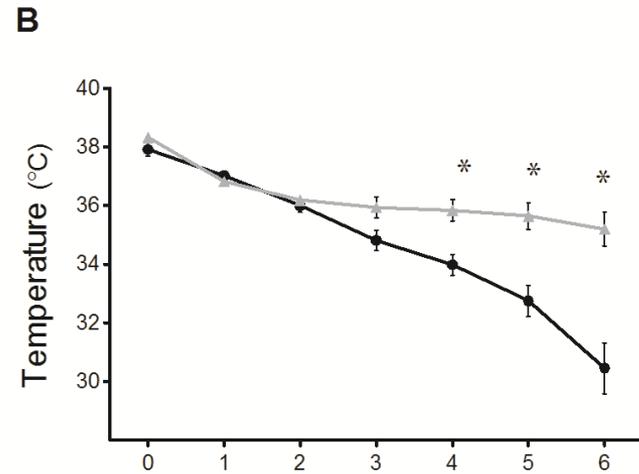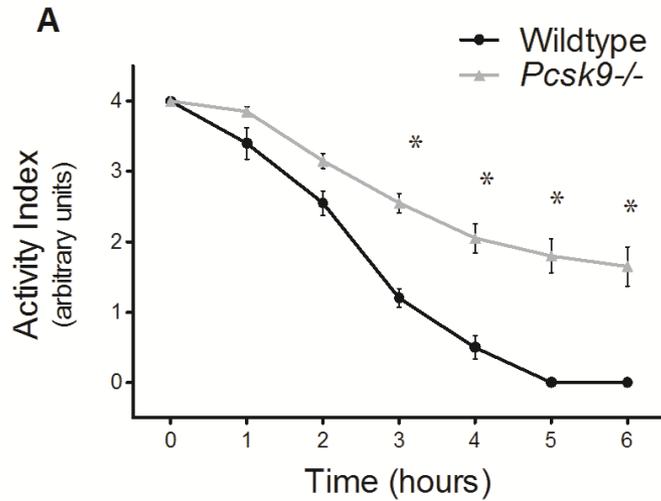
# PCSK9 antibody: ↑ CLP survival
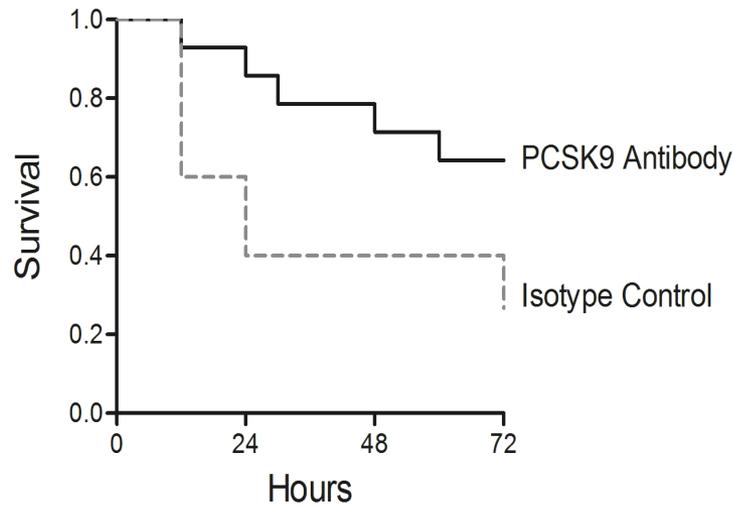
p=0.034
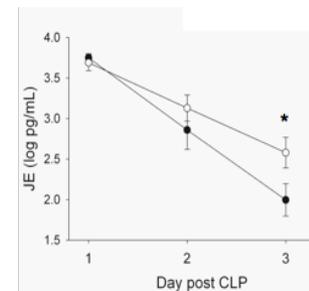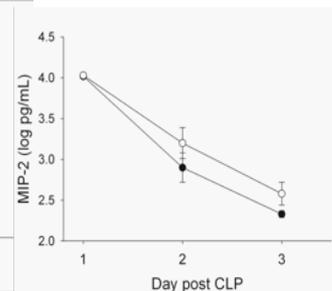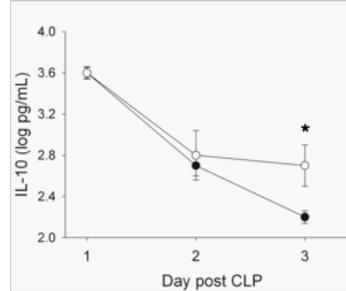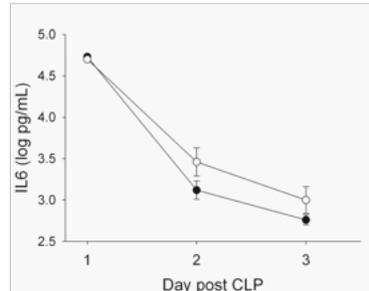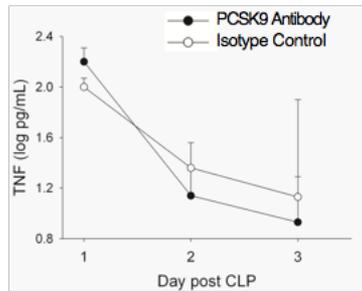
TNFα (p=0.027), IL-6 (p=0.051), IL-10 (p=0.068), JE (p=0.0085) and MIP-2 (p=0.040)

LPS uptake by hepatocytes

Topchiy E, et al. PLoS One. 2016 May 12;11(5):e0155030

27
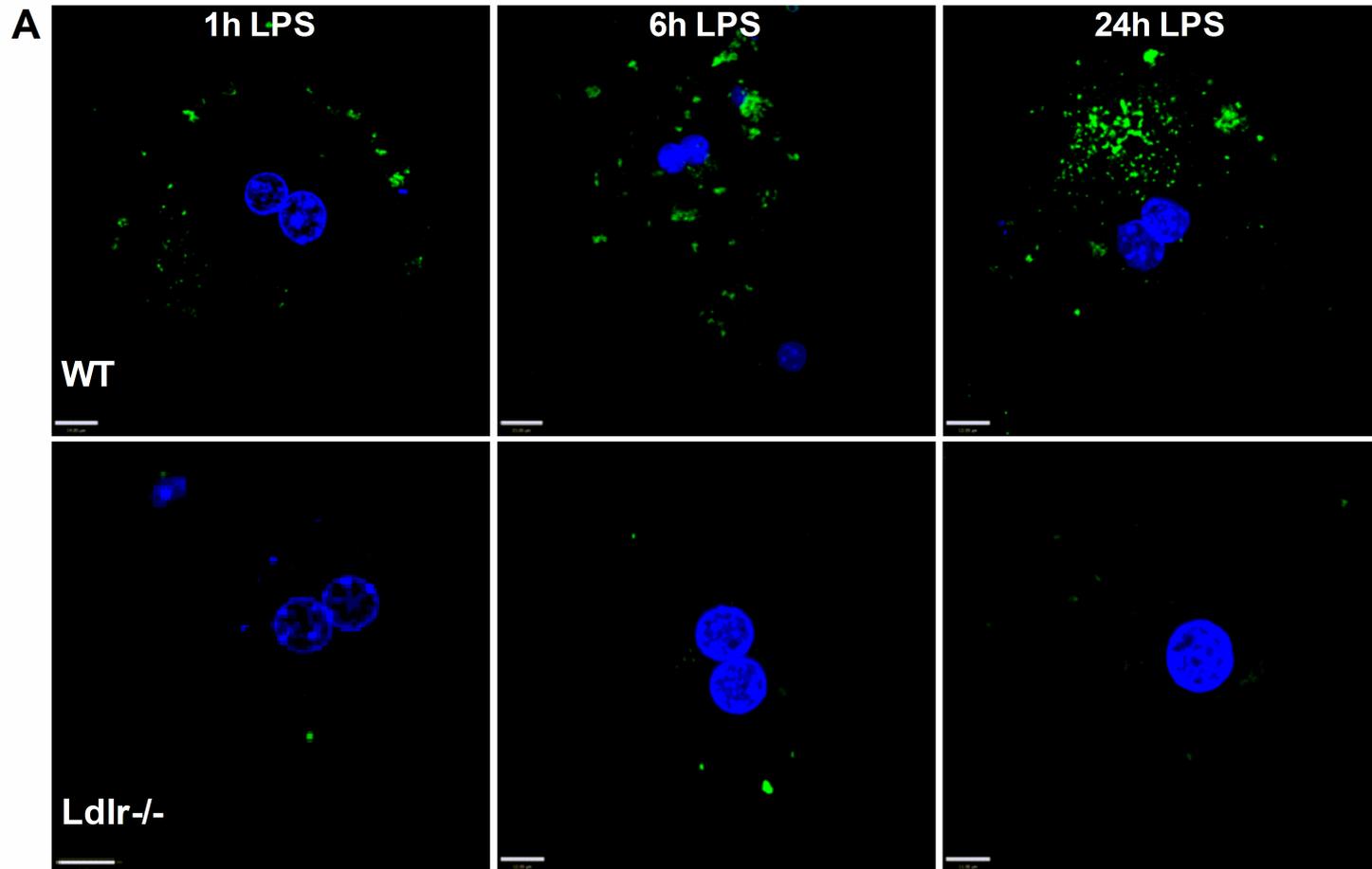
Example link to other datasets

Example new approaches

- Took all fields from electronic health record
- Coloured according to how abnormal
- Used image recognition to find patterns associated with adverse outcome
  - Laboratory data, high frequency data
- Also looked to see where the algorithm spent the most time
  - Laboratory data, patient vital signs

UBC co-investigators
John Boyd
Jim Russell

U Penn co-investigators
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Jane Ferguson

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