



Centre for  
**Heart Lung Innovation**  
UBC and St. Paul's Hospital



# Septic Shock Data Discovery Dataset

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# V A S S T dataset

## Vasopressin and Septic Shock Trial



# Dataset arising from VASST

- Septic shock 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 cytokines and other inflammatory mediators – which decrease blood pressure.
- Low blood pressure can be increased with norepinephrine or vasopressin.

## VASST hypothesis

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

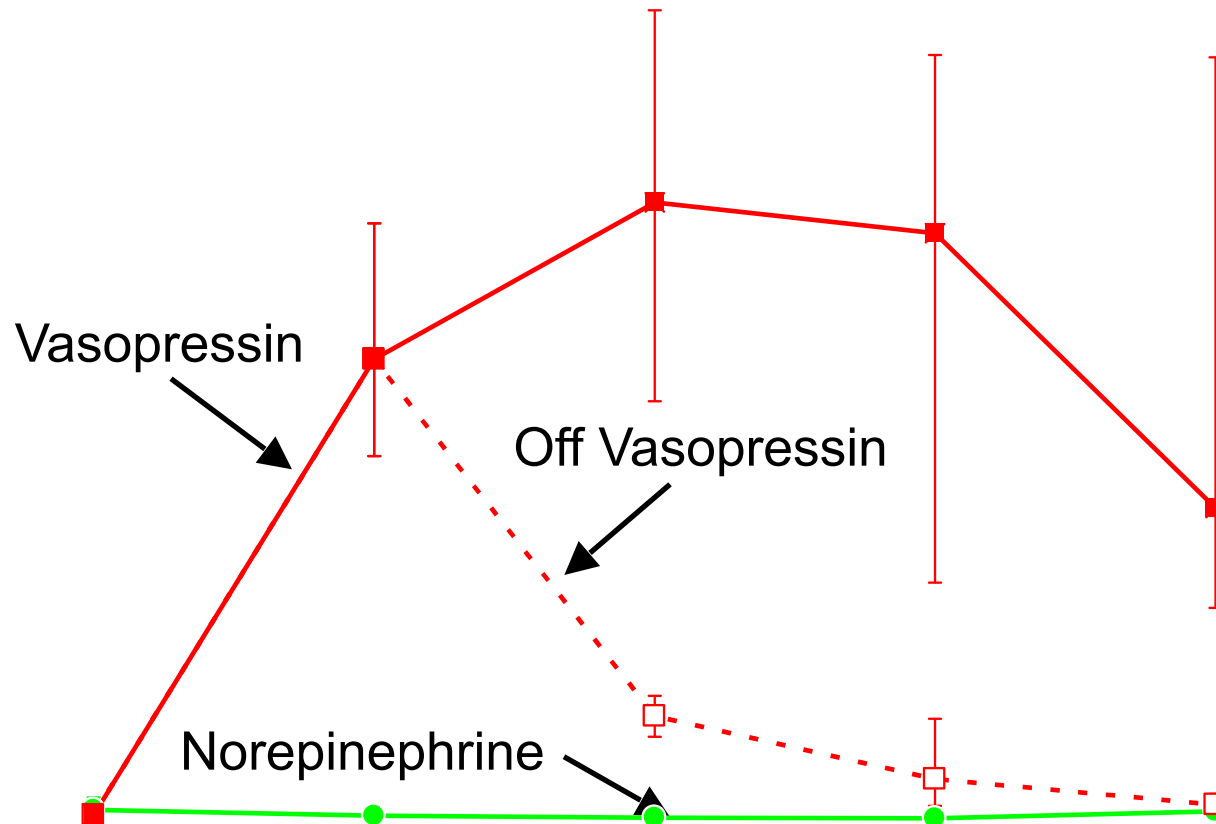
# 1) Lots of Clinical Data

>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

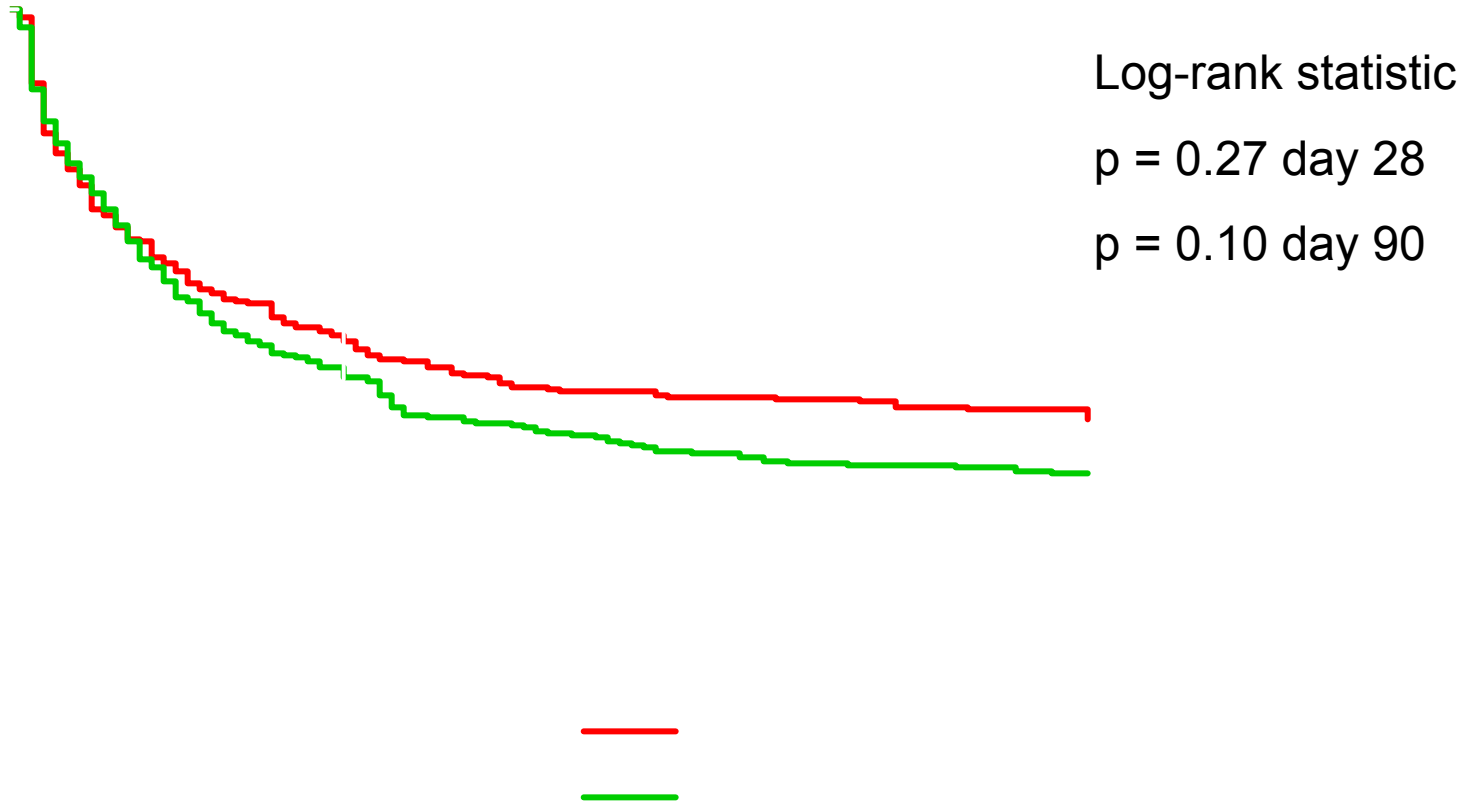
Values are n (%) or mean ± SD, as appropriate

# Plasma vasopressin levels (n = 107)



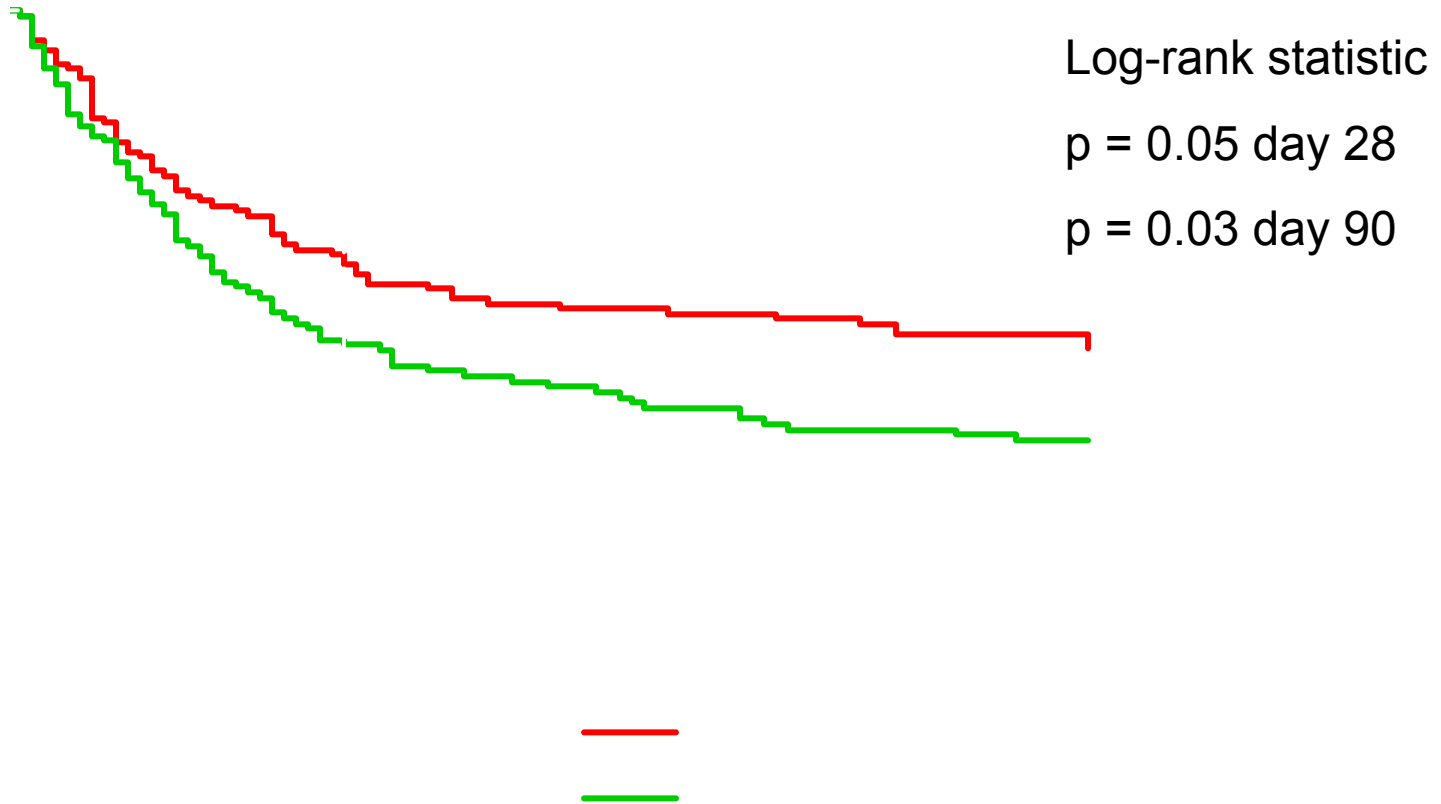
# Kaplan-Meier survival curve

## All patients



# Kaplan-Meier survival curve

## Less severe shock



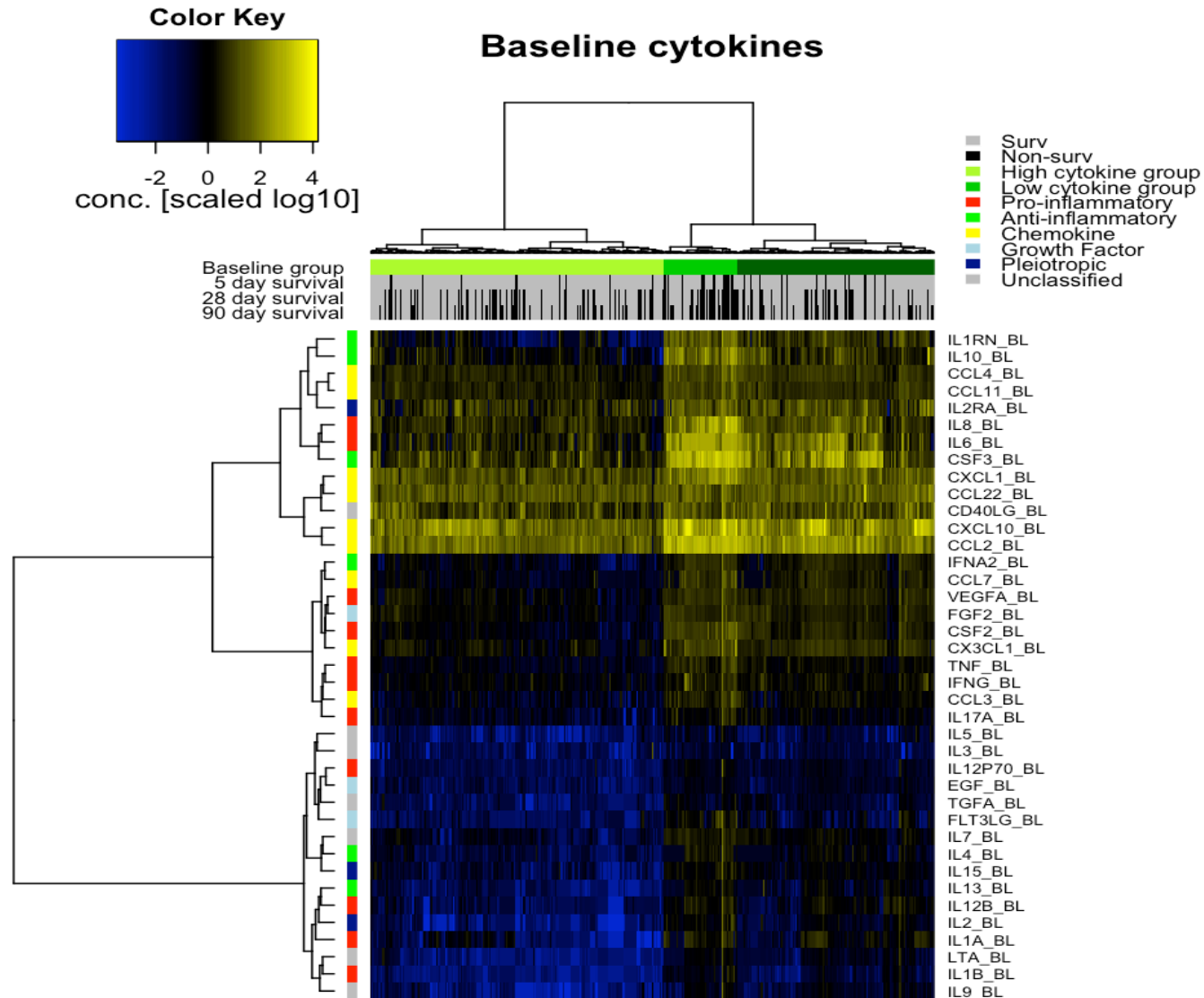
# Serious adverse events

	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
Tachyarrhythmia	3 (0.8)	4 (1.0)	1.00
Bradycardia	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

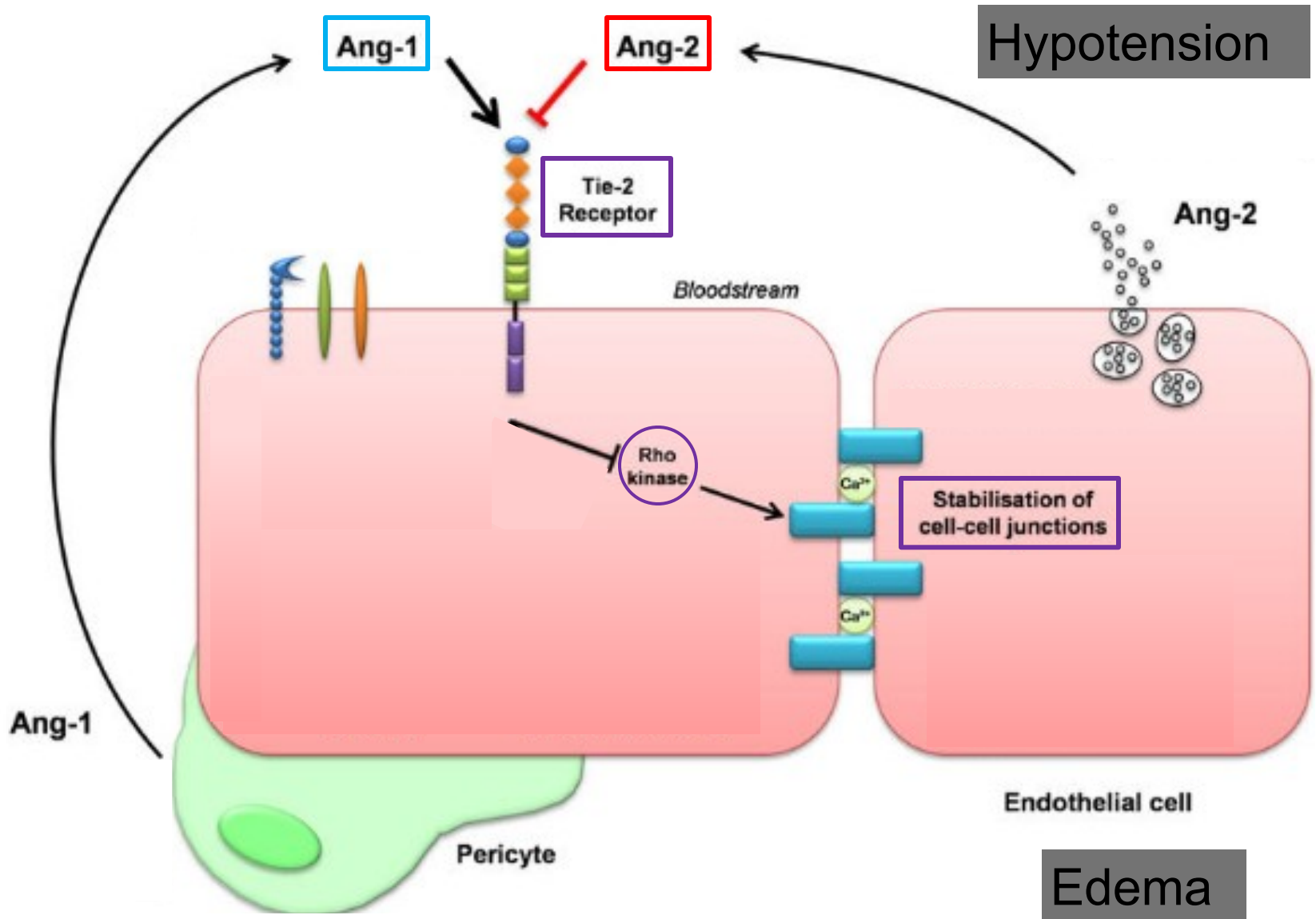


# 2) 50+ cytokines

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

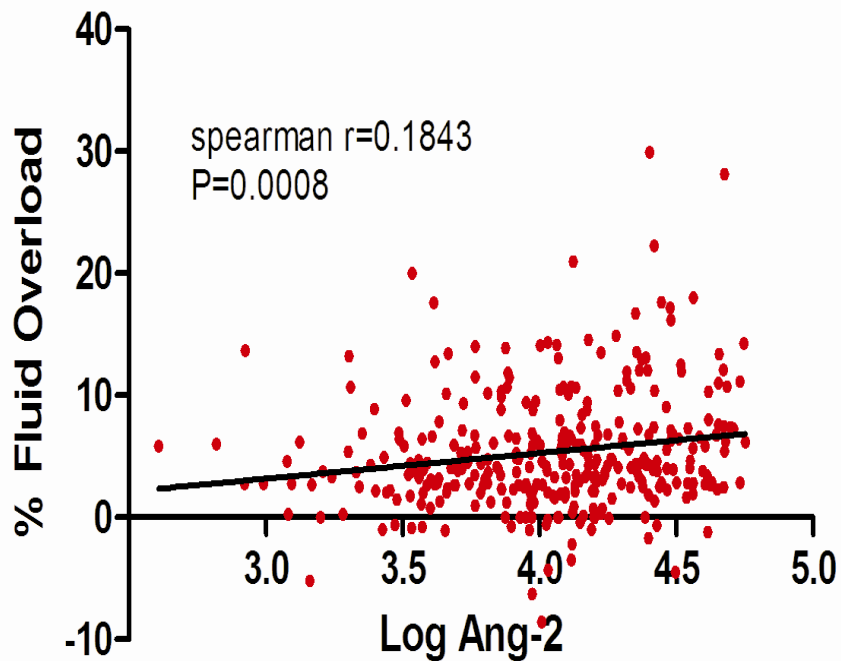


# How cytokine data might be used

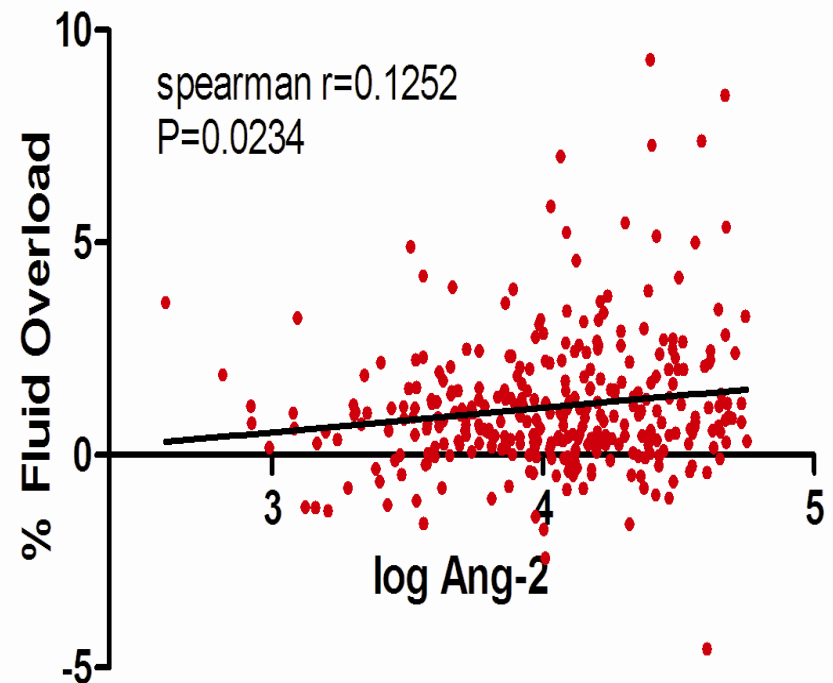


# Plasma Ang-2 Levels Associated with Fluid Overload

**Ang-2 level and baseline fluid overload**



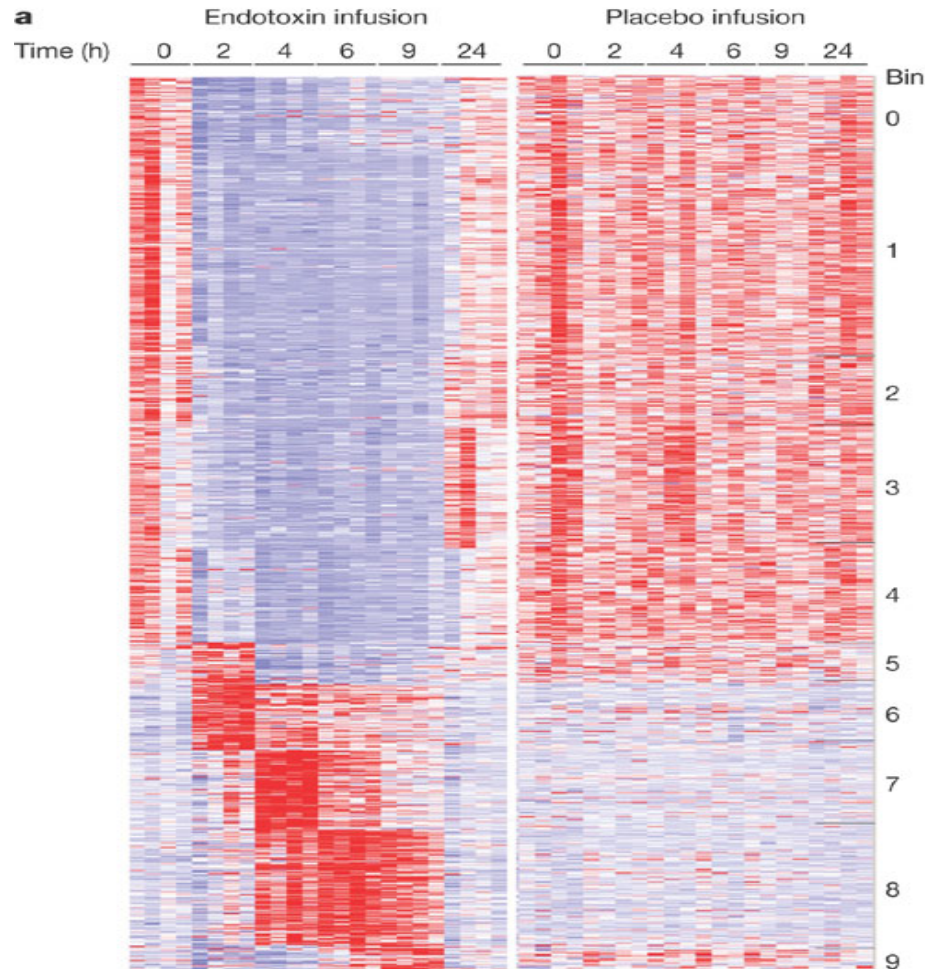
**Ang-2 Level and 6h Fluid Overload**



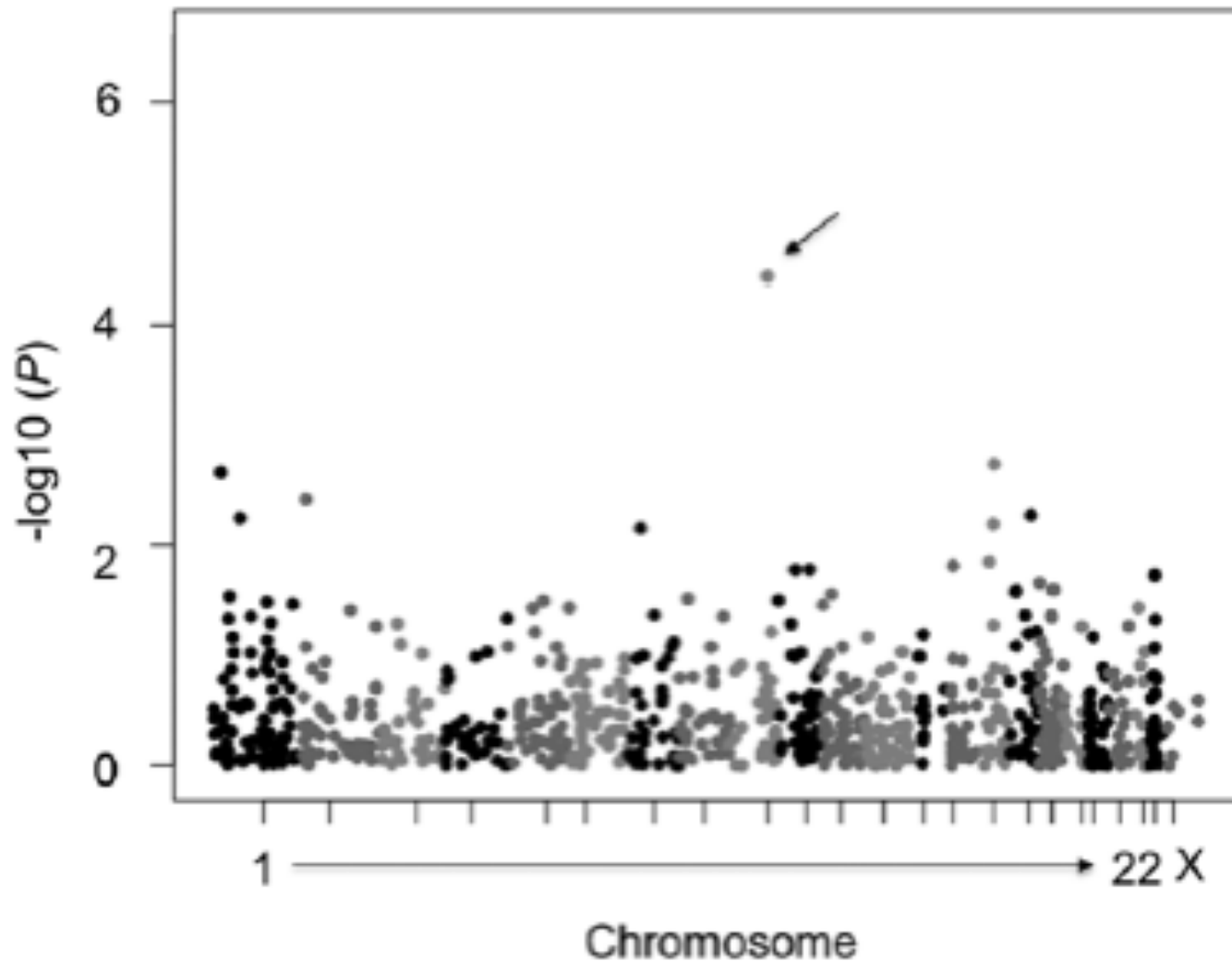
$$\%FO = (\text{intake-output}) / \text{weight} \times 100\%$$

### 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

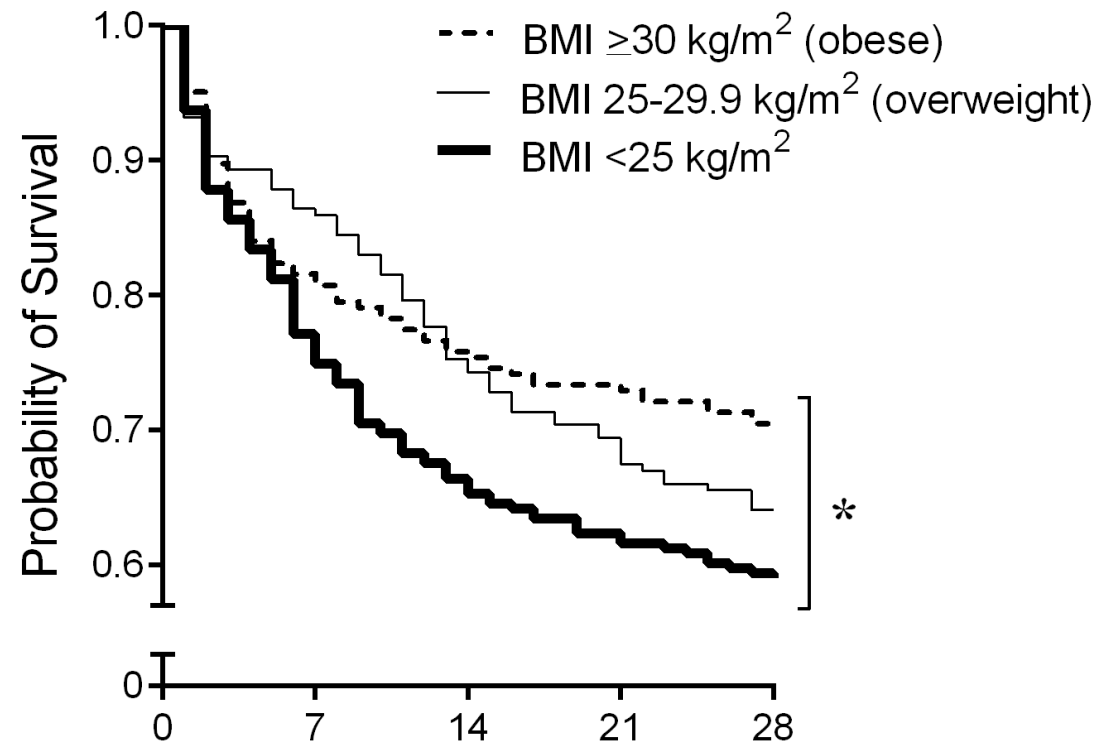


Association plot of non-synonymous SNPs with 28-day mortality

# 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

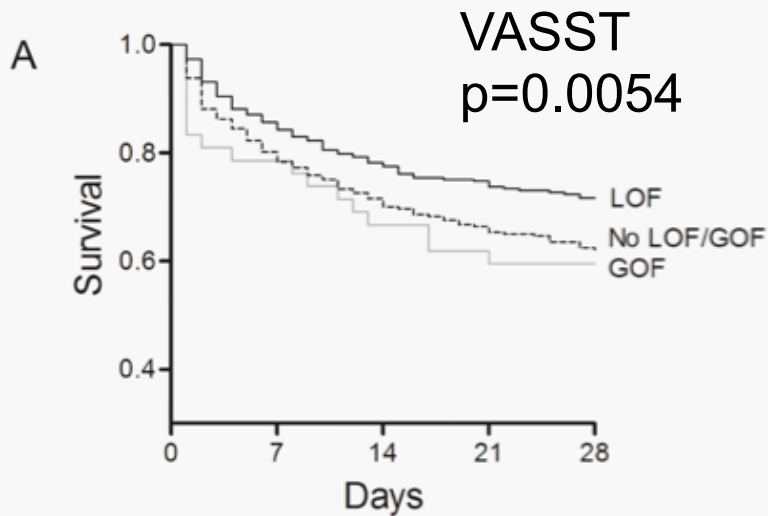
# Example clinical association



Number at Risk

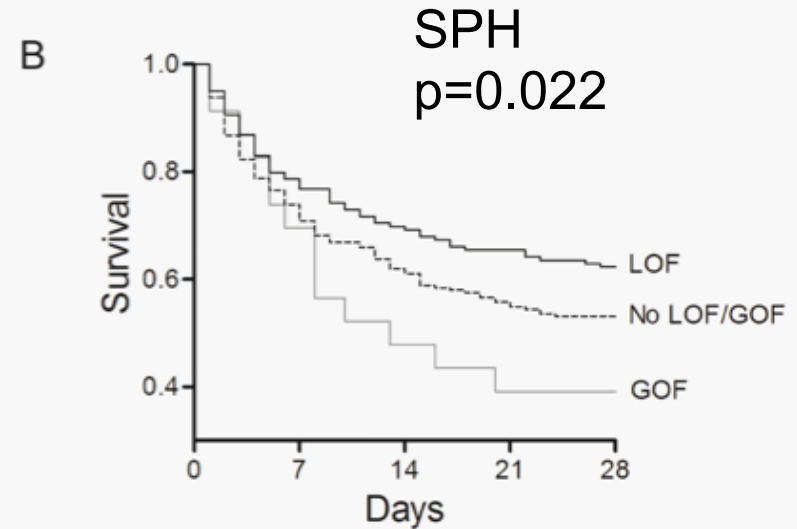
	0	7	14	21	28
BMI $\geq 30$ kg/m <sup>2</sup>	245	201	187	179	174
BMI 25-29.9 kg/m <sup>2</sup>	209	181	160	143	135
BMI $< 25$ kg/m <sup>2</sup>	276	220	183	169	162

# Example gene association



Number at Risk:

LOF	293	251	229	219	210
No LOF/GOF	282	222	198	184	173
GOF	44	33	28	26	25

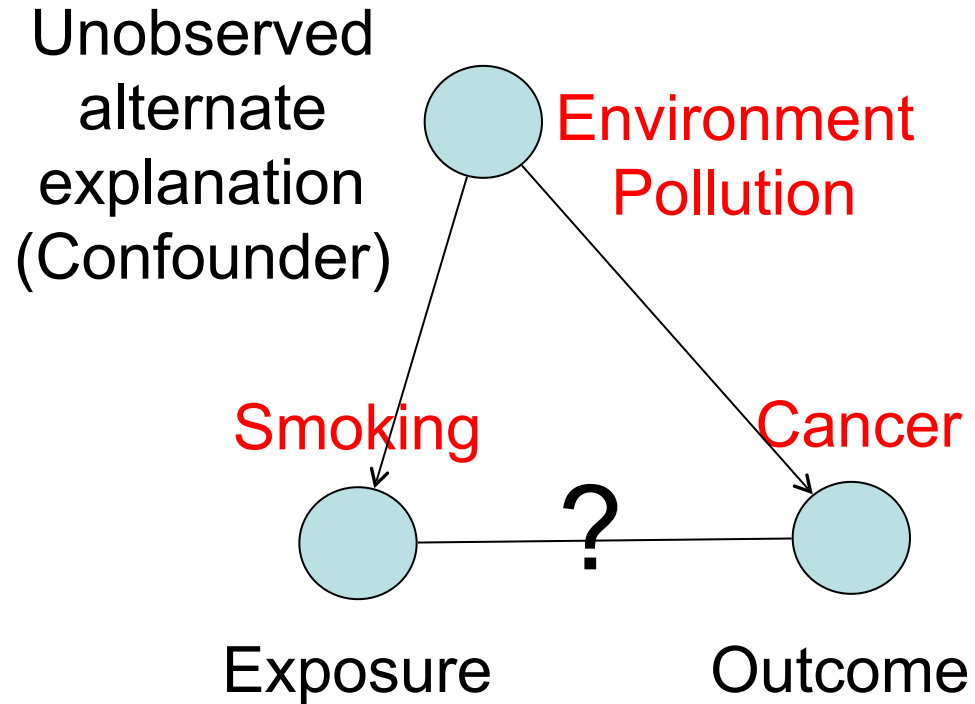


Number at Risk:

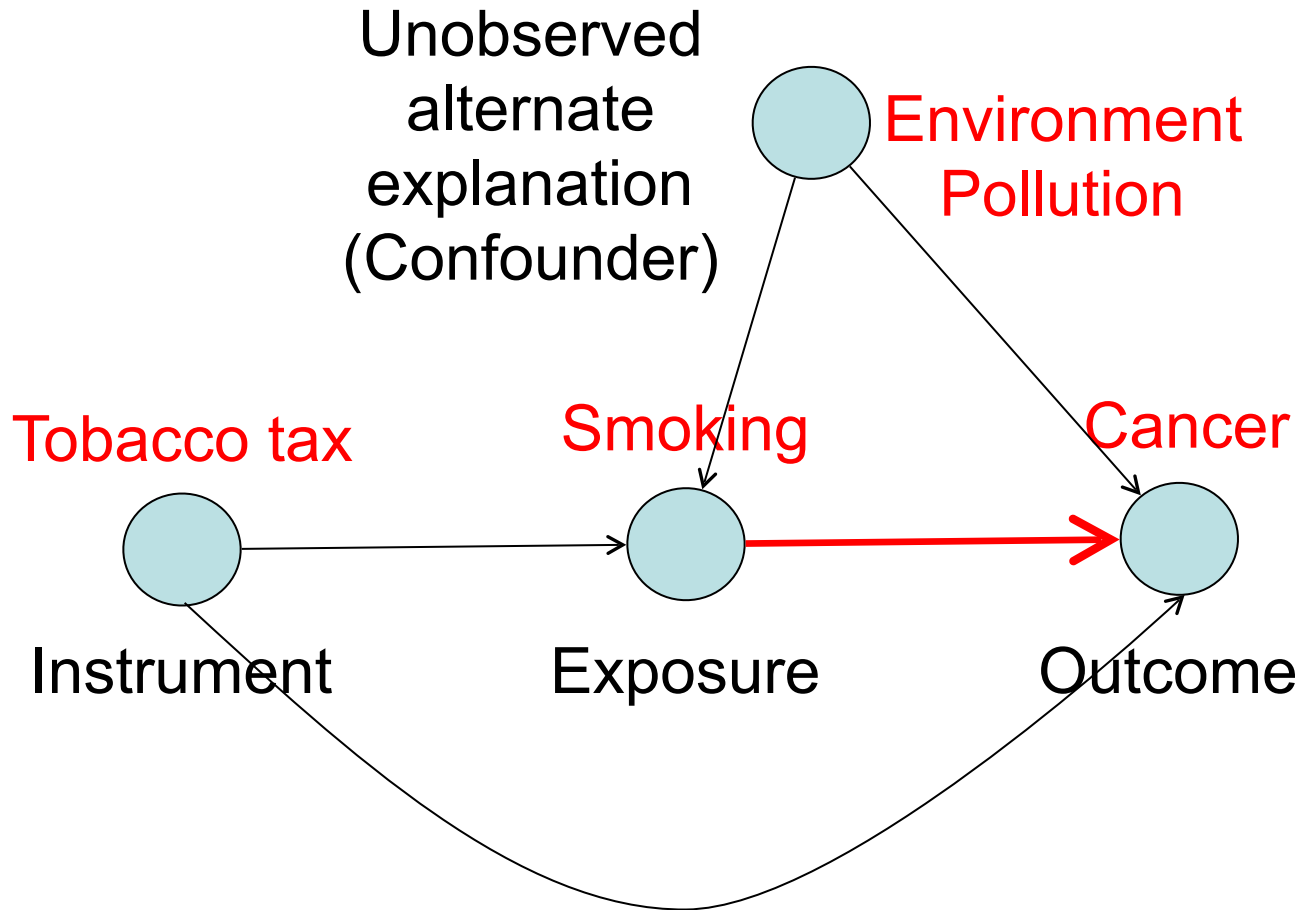
LOF	159	125	111	104	99
No LOF/GOF	226	167	140	126	120
GOF	23	16	11	9	9



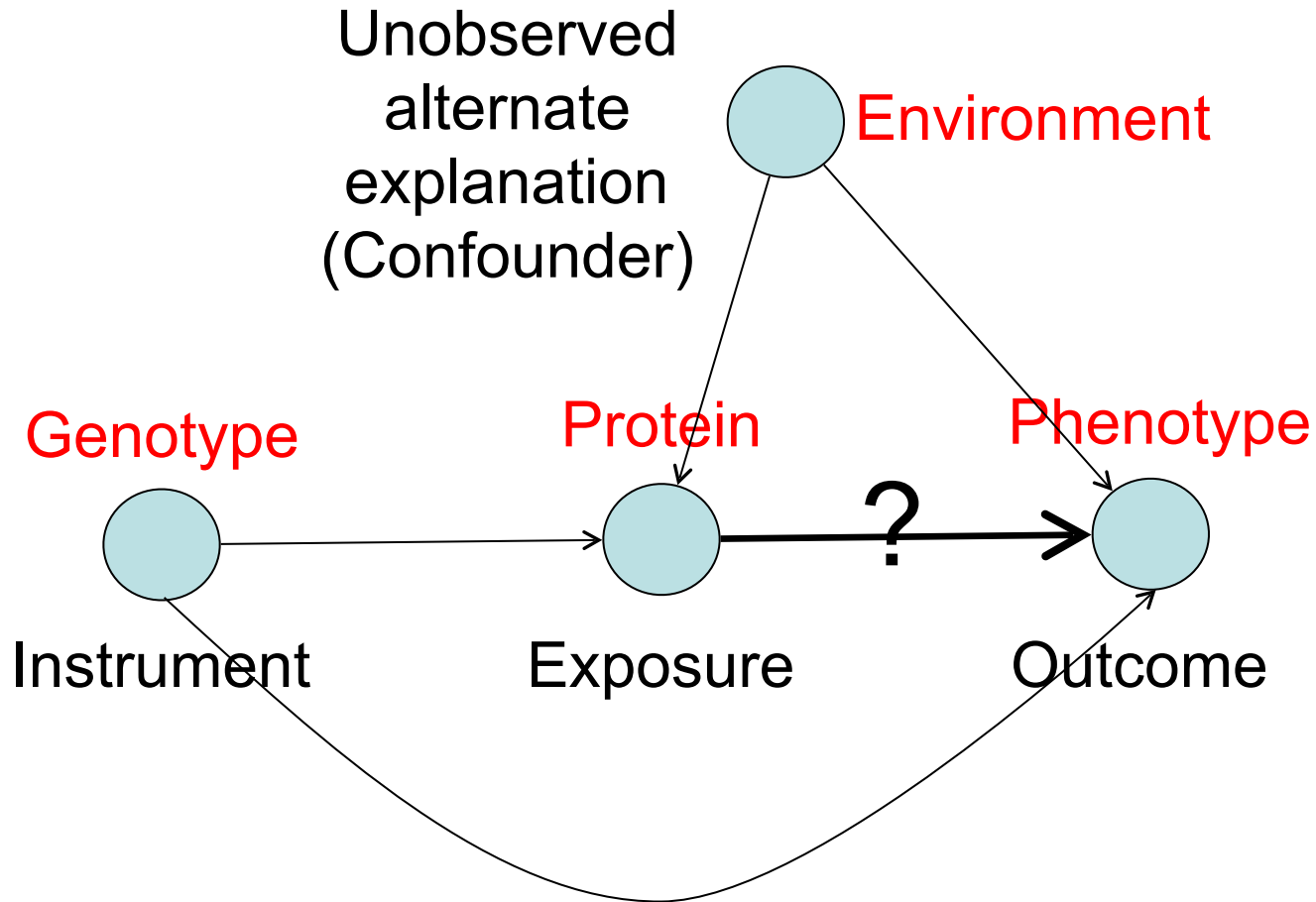
# Example causal inference



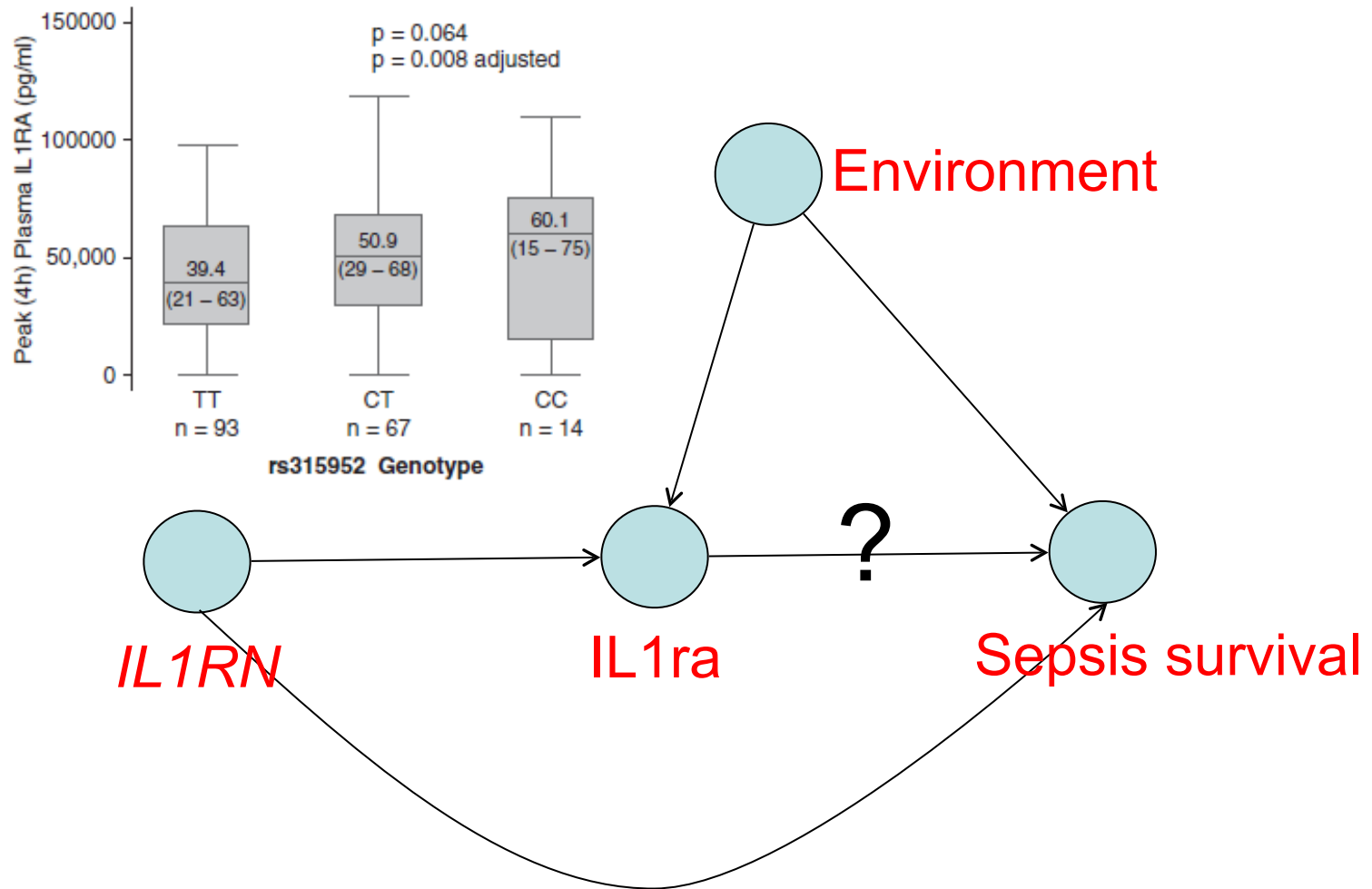
# Instrumental Variables → Cause



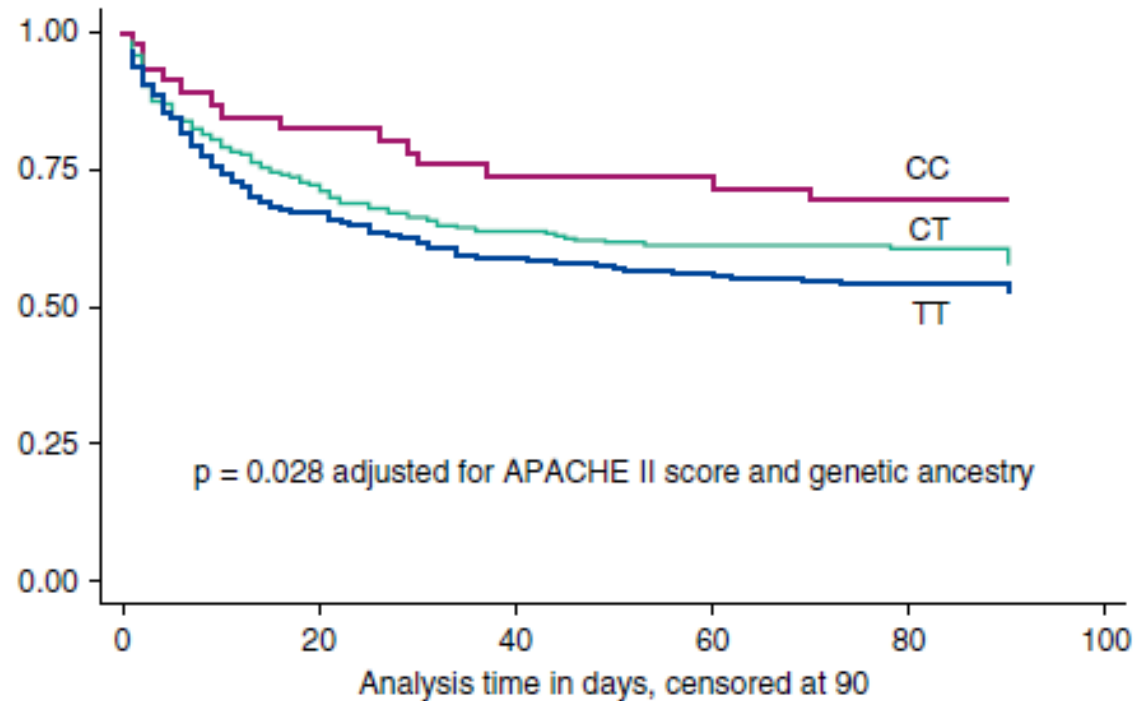
# Mendelian Randomization



# Mendelian Randomization



# IL1RN genotype ~ Sepsis survival

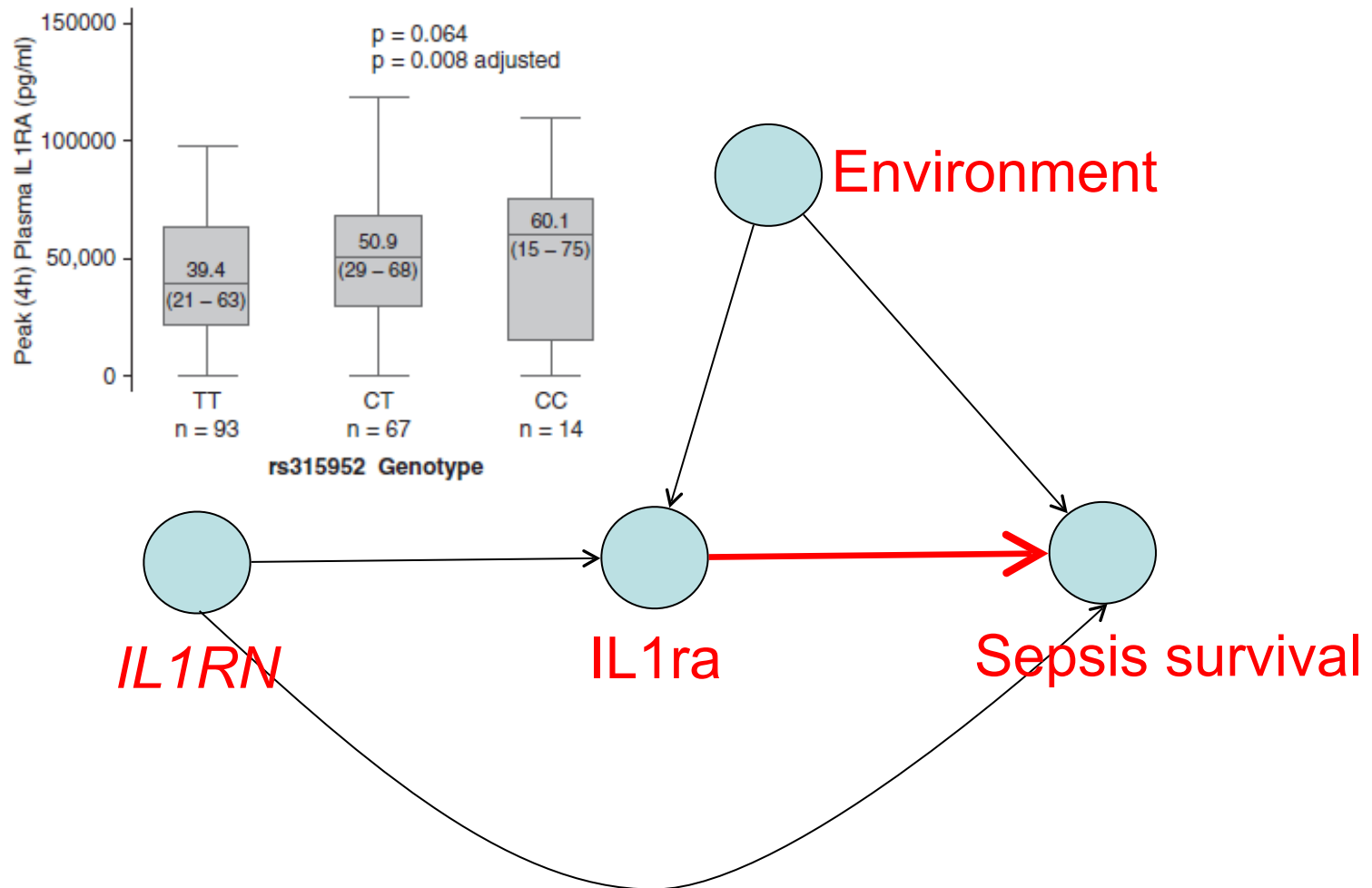


Number at risk

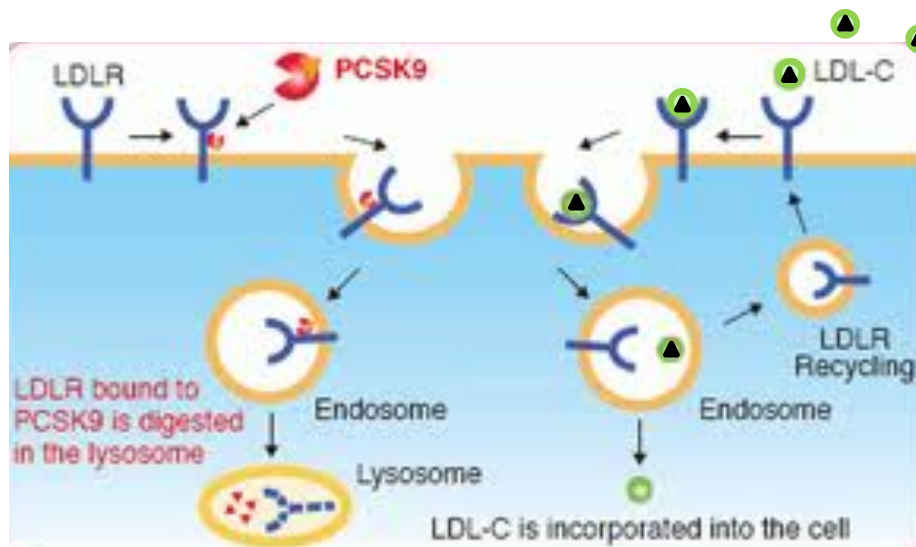
TT:	263	177	155	148	143	0
CT:	217	157	139	133	132	0
CC:	46	38	34	34	32	0

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

# Mendelian Randomization



# Example mechanism of action

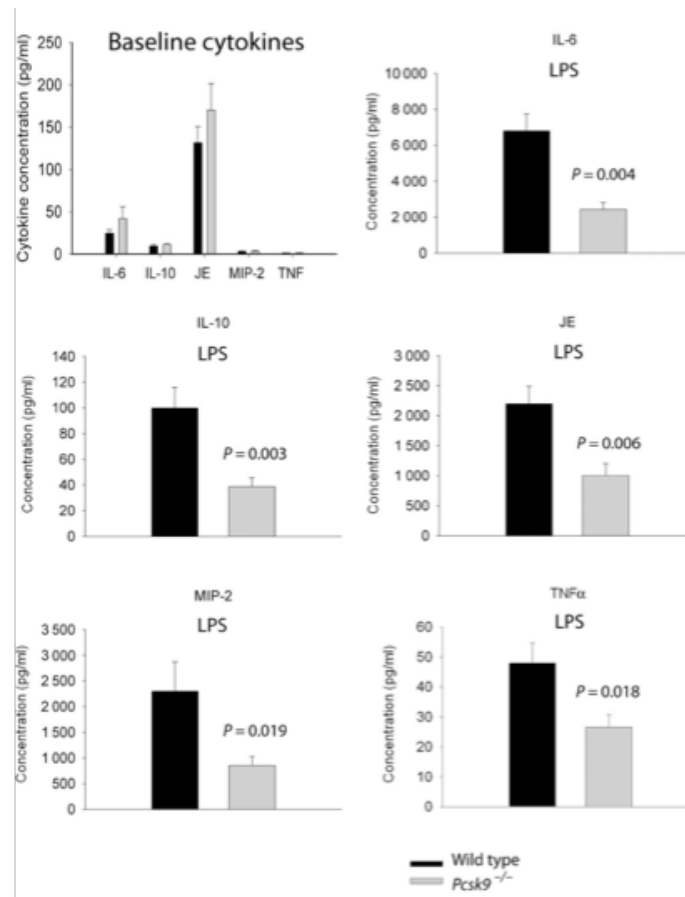


- ▲ Lipopolysaccharide (LPS) Gram - endotoxin
- ▲ Lipoteichoic acid (LTA) Gram +

Could PCSK9 inhibition increase pathogen lipid clearance?

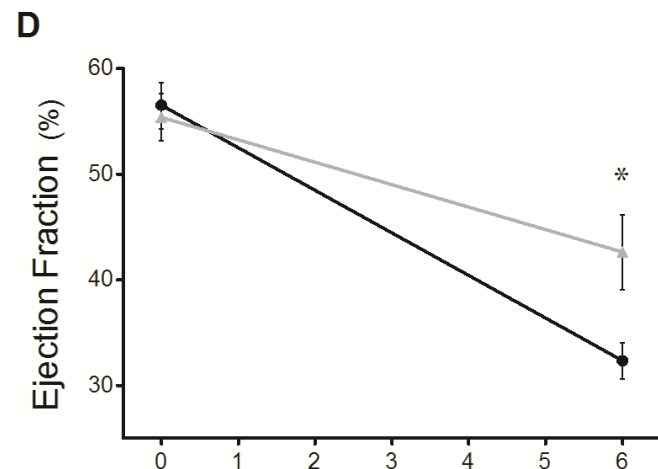
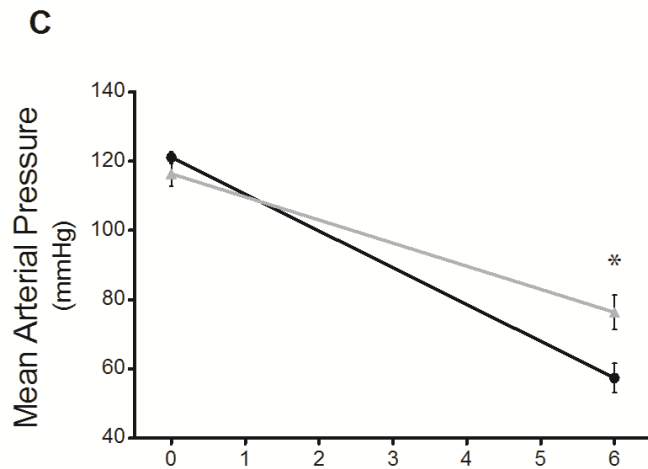
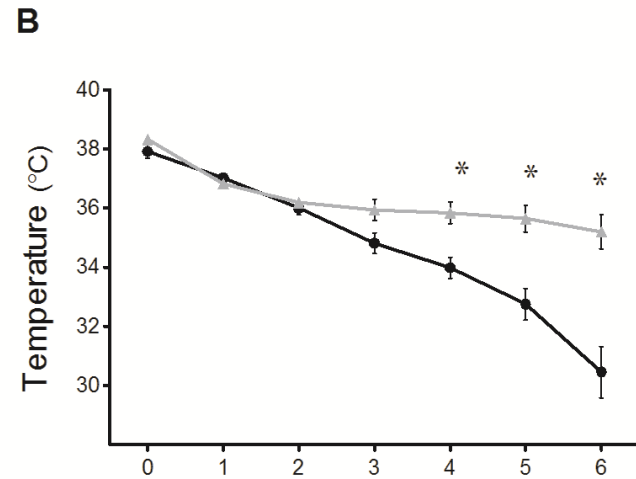
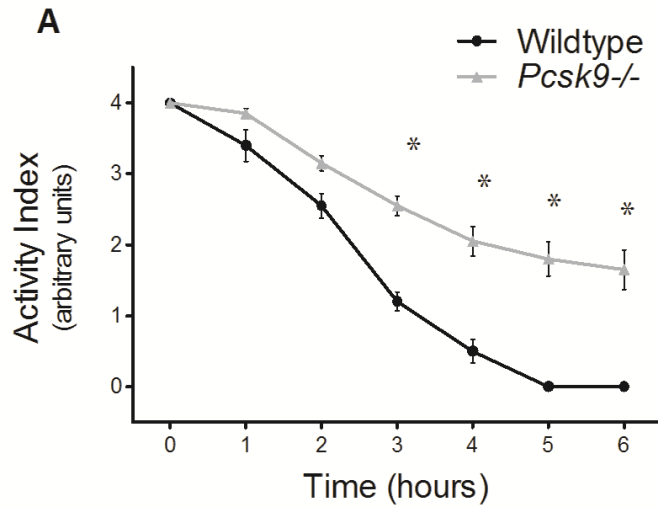
# *Pcsk9* knockout mice

↑ LPS clearance, ↓ inflammation

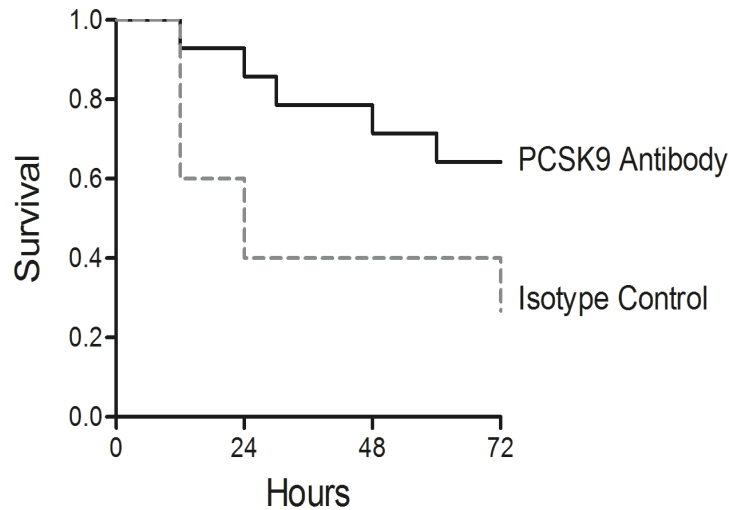




# *Pcsk9* knockout mice ↓ physiologic response

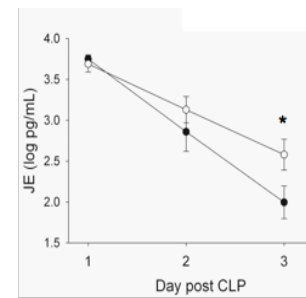
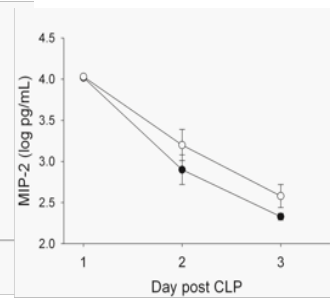
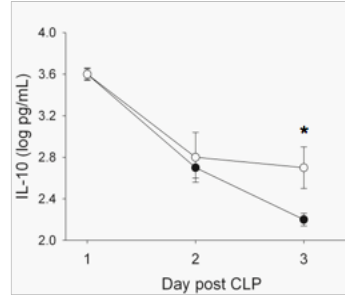
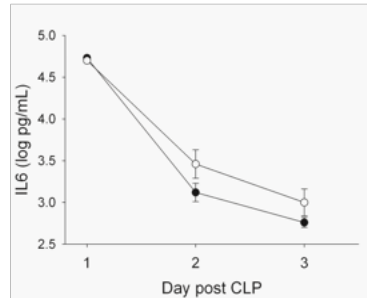
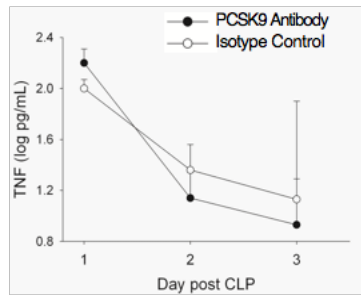


# PCSK9 antibody: ↑ CLP survival



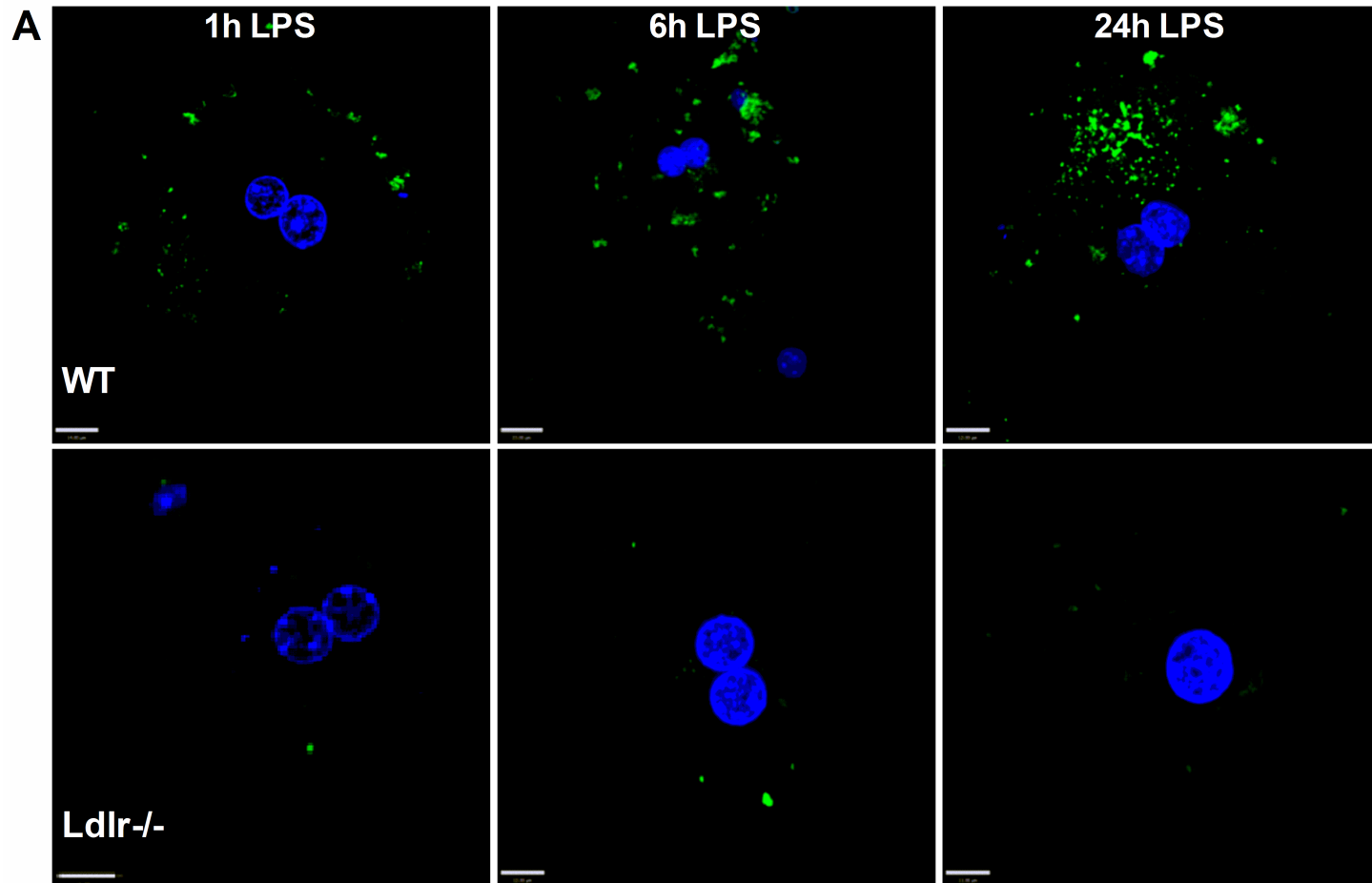
Number at Risk:

PCSK9 Antibody	14	13	11	10
Isotype Control	15	9	6	6



TNF $\alpha$  ( $p=0.027$ ), IL-6 ( $p=0.051$ ), IL-10 ( $p=0.068$ ), JE ( $p=0.0085$ ) and MIP-2 ( $p=0.040$ )

# LPS uptake by hepatocytes



# Example link to other datasets

File Edit View History Bookmarks Tools Help

Human hg38 chr7:22,725,884-22,732,002 X +

genome.ucsc.edu/cgi-bin/hgTracks?db=hg38&lastVirtModeType=default&... Search

Most Visited Information Manage...

Genomes Genome Browser Tools Mirrors Downloads My Data View Help About Us

## UCSC Genome Browser on Human Dec. 2013 (GRCh38/hg38) Assembly

move <<< << < > >> >>> zoom in 1.5x 3x 10x base zoom out 1.5x 3x 10x 100x

chr7:22,725,884-22,732,002 6,119 bp enter position, gene symbol, HGVS or search terms go

chr7 (p15.3)

Scale chr7: 2 kb hg38  
Chromosome Band  
Gap  
STS Markers  
GENCODE v24 Comprehensive Transcript Set (only Basic displayed by default)  
RefSeq Curated  
Genscan Genes  
OMIM Alleles  
Human mRNAs from GenBank  
Spliced ESTs  
Gene Expression in 53 tissues from GTEx RNA-seq of 8555 samples (576 donors)  
Layered H3K27ac  
DNase Clusters  
Cons 100 Verts  
Rhesus Mouse Dog Elephant Chicken X\_tropicalia Zebrafish Lamprey  
Common SNPs (159)  
RepeatMasker

Click on a feature for details. Click or drag in the base position track to zoom in. Click side bars for track options. Drag side bars or labels up or down to reorder tracks. Drag tracks left or right to new position. Press "?" for keyboard shortcuts.

move start < 2.0 > move end < 2.0 >

track search default tracks default order hide all add custom tracks track hubs configure multi-region reverse resize refresh

collapse all expand all

Mapping and Sequencing refresh

Base Position Alt Map... Assembly Centromeres Chromosome Band Clone Ends

full hide hide hide dense hide

# 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

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Jim Russell

U Penn co-investigators

Muredach Reilly  
Nuala Meyer  
Jason Christie  
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VASST Investigators

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