Genetic insights into IL-6 signaling

Dipender Gill

CHARGE Mendelian Randomization Workshop

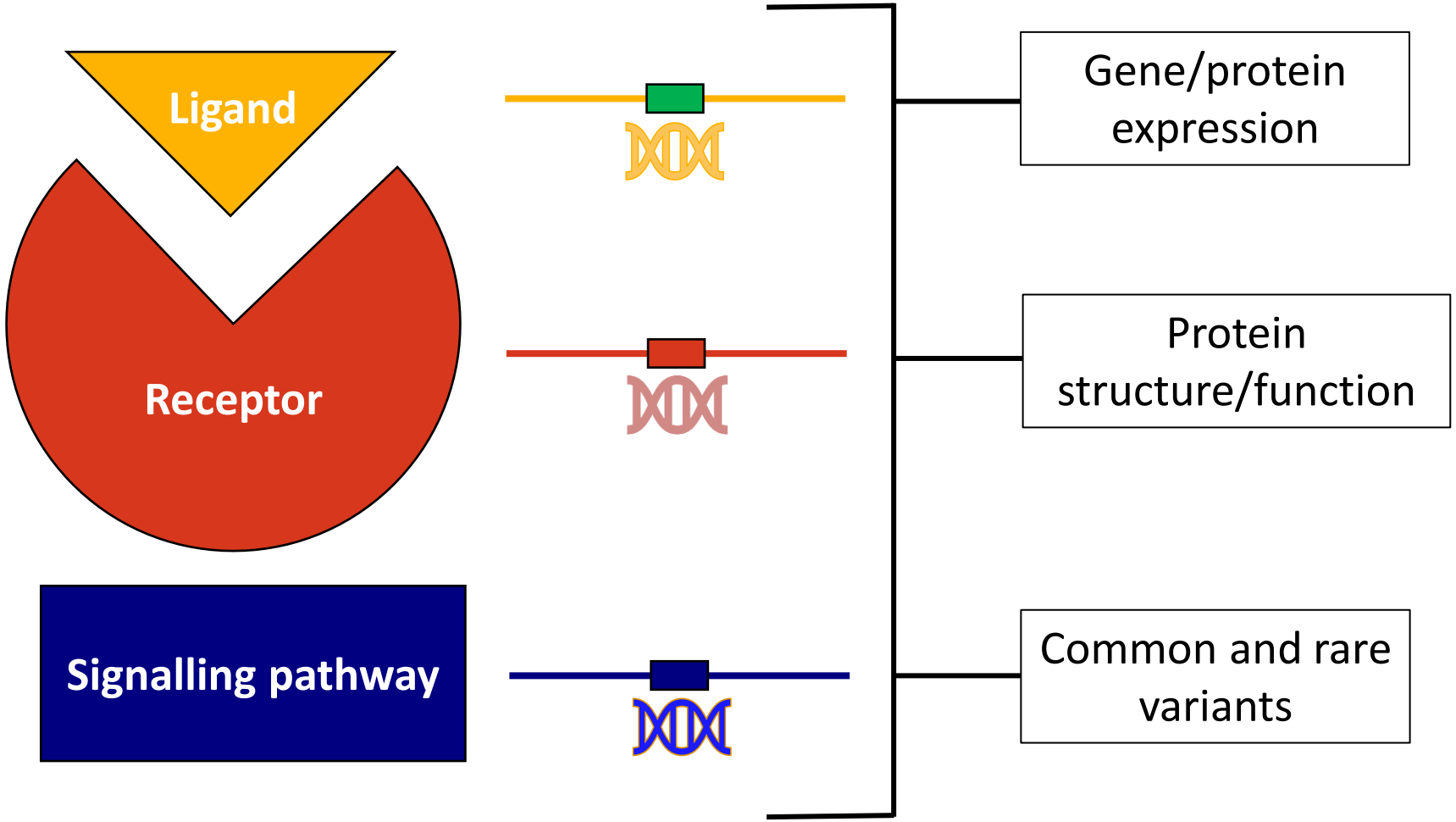
9 May 2023

Agenda

- Instrument selection and validation
- Genetic insights into cardiovascular disease
- Genetic insights into adverse effects and repurposing opportunities
- Questions and discussion

Instrument selection and validation

Genetic variants to proxy drug target perturbation identified through relational to functionally relevant traits



The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis

*The Interleukin-6 Receptor Mendelian Randomisation Analysis (IL6R MR) Consortium**

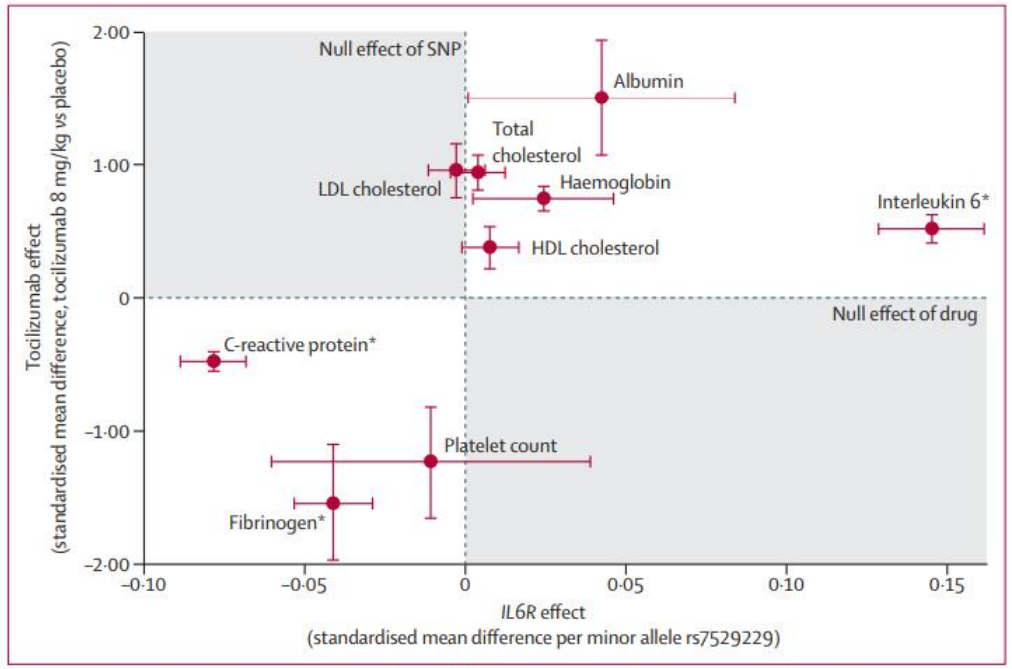


Figure 2: **Associations of the minor allele of the *IL6R* SNP rs7529229 and tocilizumab (8 mg/kg) versus placebo with commonly reported biomarkers**

Concordance between the drug and genetic variants is shown. Effects are presented as standardised mean difference apart from $\log_e$ transformed variables (shown by *), for which rs7529229 effects represent the mean difference on the log scale. Estimates for soluble interleukin-6 receptor were not plotted since their substantially greater magnitude would disrupt the scale of the graph: standardised mean differences were 0·75 (95% CI 0·59–0·91) ng/mL per minor allele for rs7529229, and 93·67 (95% CI 90·27–97·06) ng/mL for tocilizumab 8 mg/kg versus placebo. SNP=single nucleotide polymorphism.

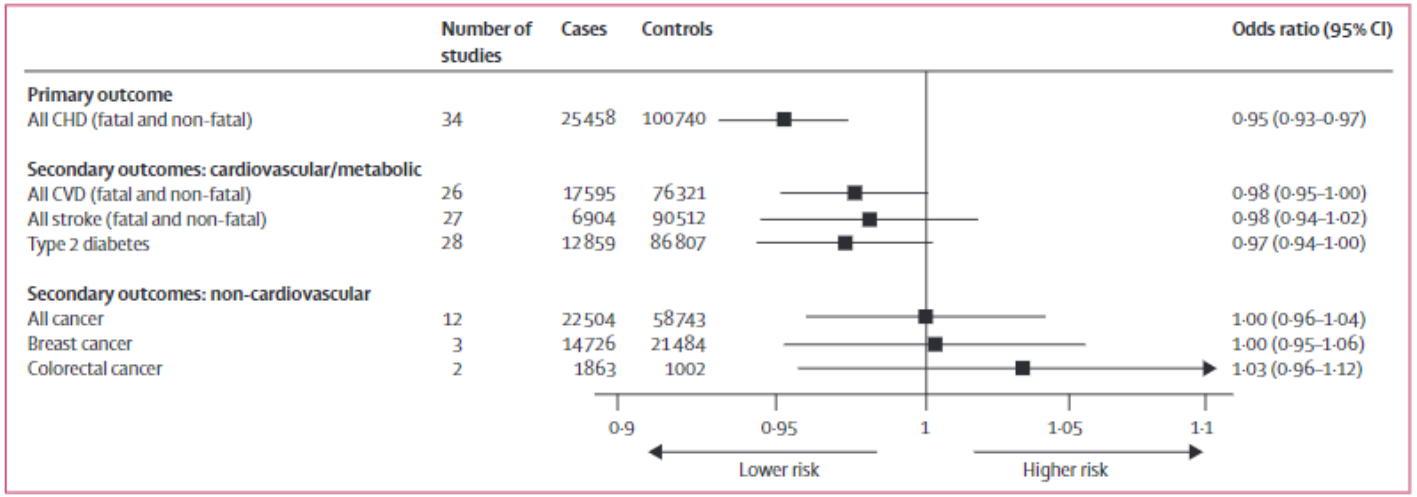


Figure 4: **Association of *IL6R* rs7529229 with secondary and safety endpoints**

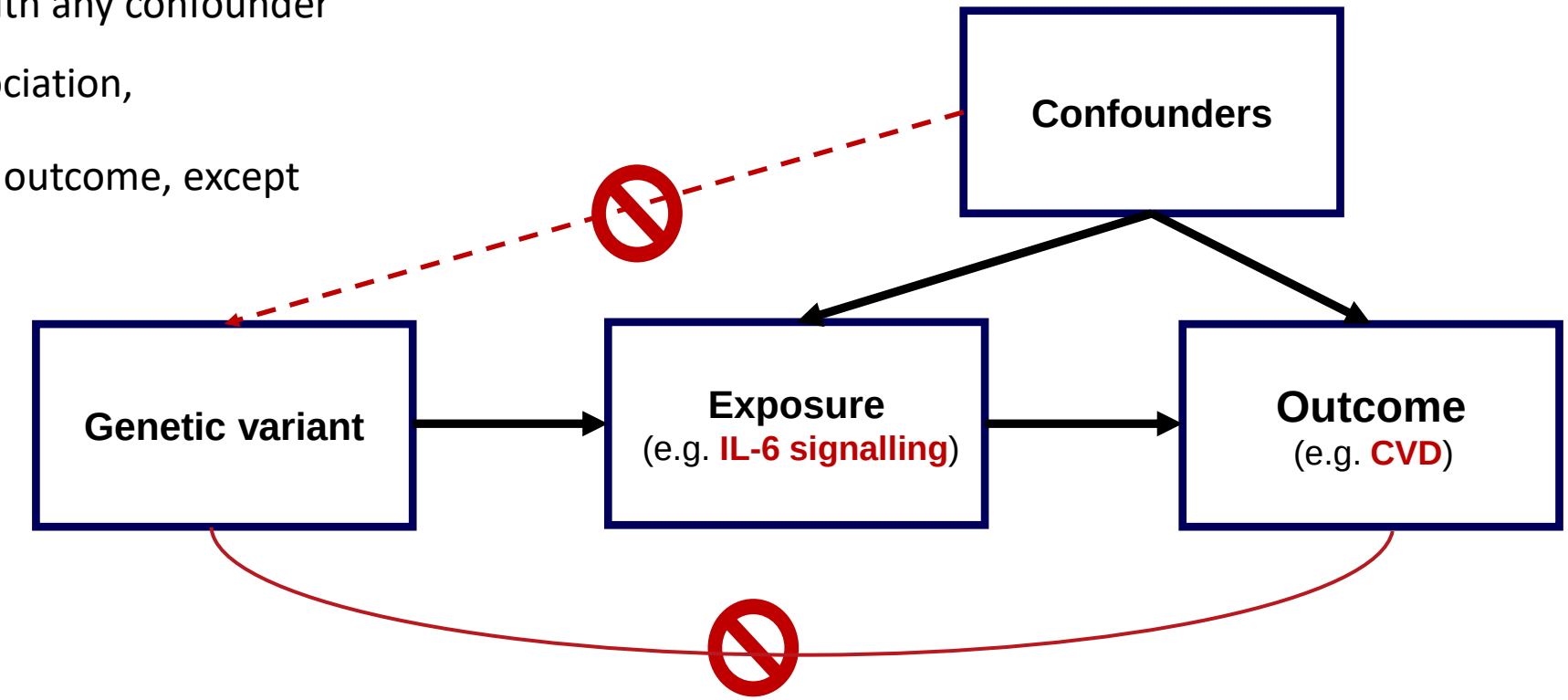
Summary per-allele odds ratio for cardiovascular and non-cardiovascular endpoints for the *IL6R* rs7529229 variant. Individual study odds ratios were based on a per-allele model in the present collaborative analysis and genome-wide association studies and pooled with fixed effects meta-analysis. CHD=coronary heart disease. CVD=cardiovascular disease.

Lancet. 2012 Mar 31;379(9822):1214-24.

The Mendelian randomization paradigm

The fundamental conditions for a genetic variant to satisfy to be an instrumental variable:

1. the variant is associated with the exposure,
2. the variant is not associated with any confounder of the exposure–outcome association,
3. the variant does not affect the outcome, except via the exposure.

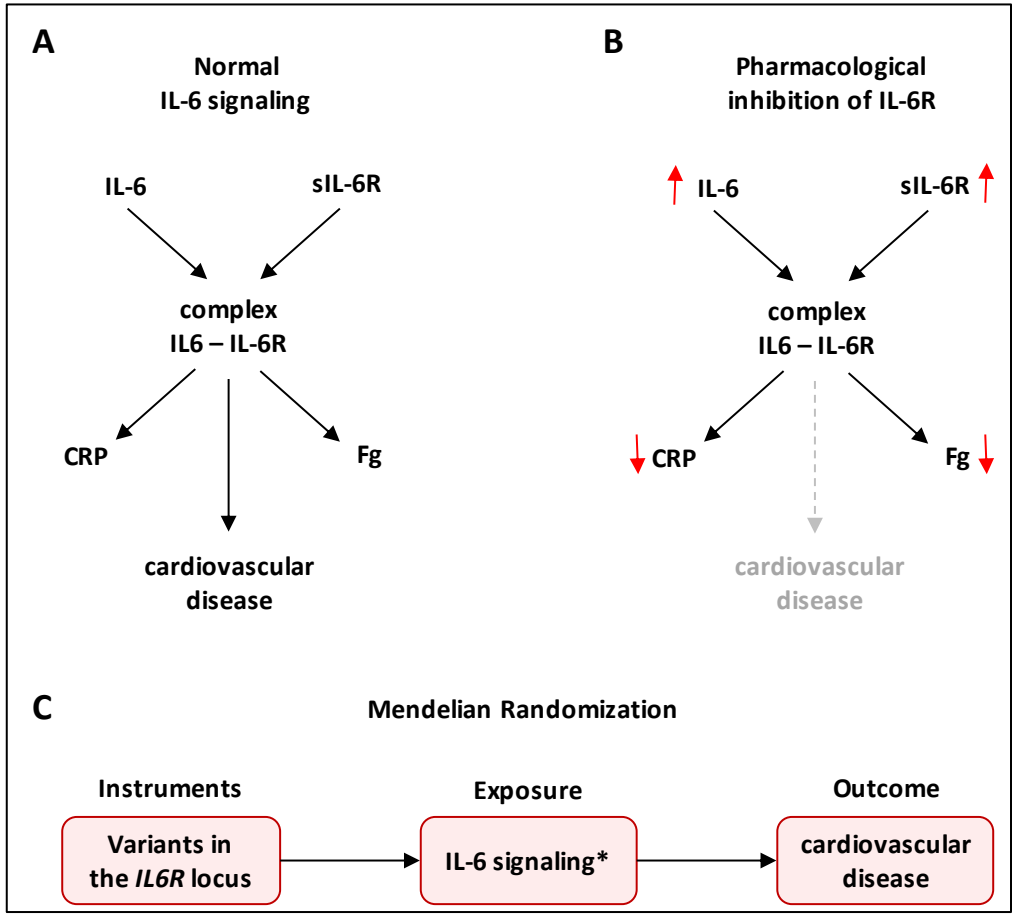


Genetic insights into cardiovascular disease

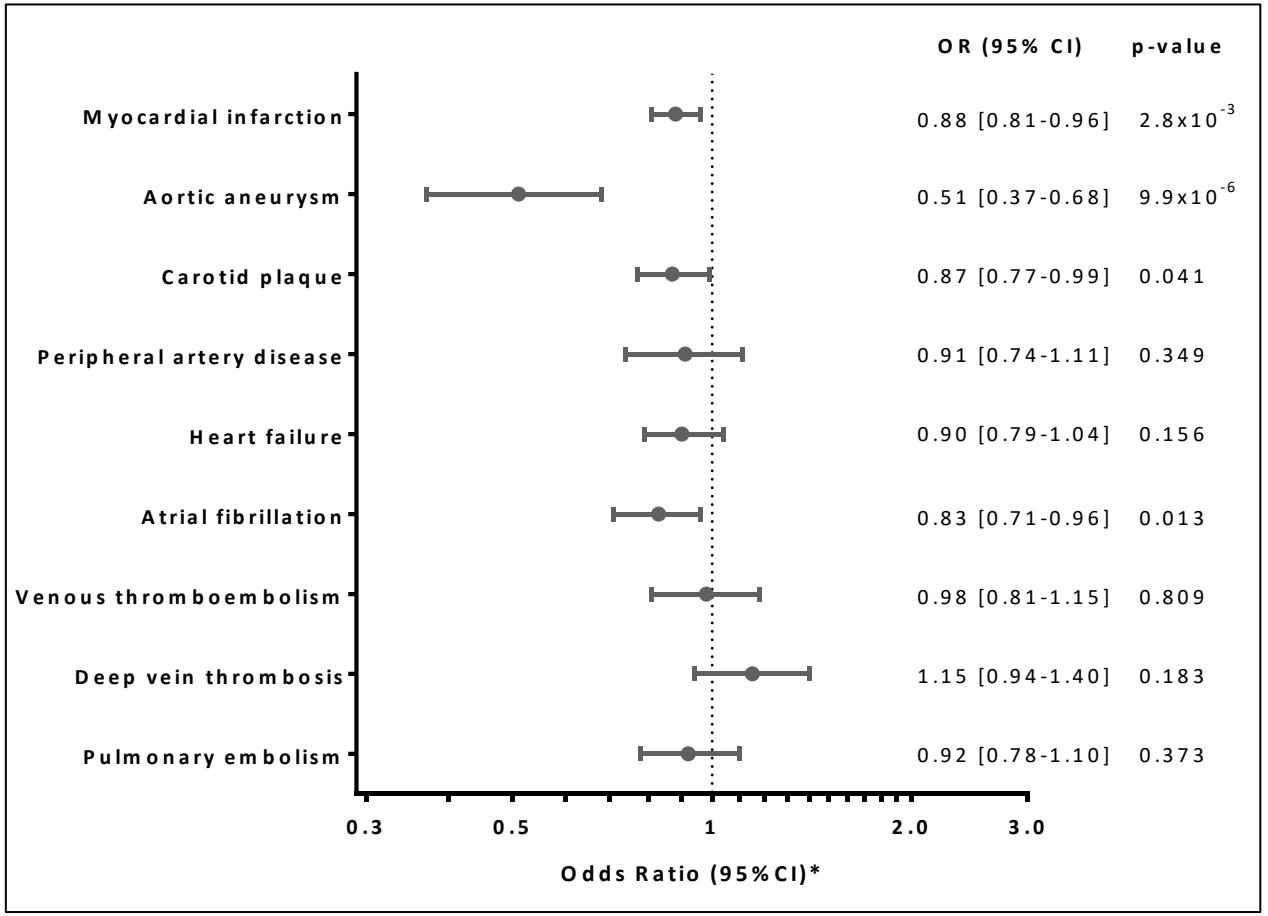
Interleukin-6 Signaling Effects on Ischemic Stroke and Other Cardiovascular Outcomes

Marios K. Georgakis, Rainer Malik, Dipender Gill, Nora Franceschini, Cathie L. M. Sudlow, Martin Dichgans

Interleukin-6 signalling



Cardiovascular outcomes

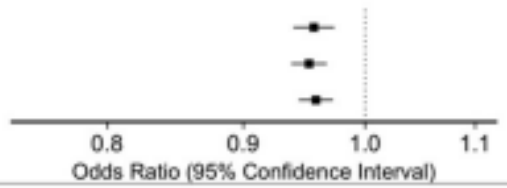


A Missense Variant in the IL-6 Receptor and Protection From Peripheral Artery Disease

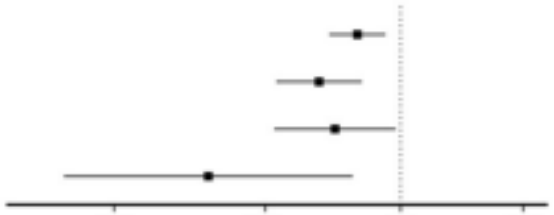
Meet the First Author, see p 894

Michael G. Levin, Derek Klarin, Marios K. Georgakis, Julie Lynch, Katherine P. Liao, Benjamin F. Voight, Christopher J. O'Donnell, Kyong-Mi Chang, Themistocles L. Assimes, Philip S. Tsao, Scott M. Damrauer, and on behalf of the VA Million Veteran Program

Exposure	Outcome	Study	Cases	Controls	OR	95% CI	P
IL6R Asp358Ala	PAD	MVP	35042	247115	0.96	[0.94, 0.97]	9×10^{-7}
IL6R Asp358Ala	PAD	MVP/BBJ/FNG	45733	662516	0.95	[0.94, 0.97]	5×10^{-10}
IL6R Asp358Ala	CAD	MVP	77241	139284	0.96	[0.94, 0.97]	1×10^{-6}



Exposure	Outcome	Cases	Controls	OR	95% CI	P
IL6R Asp358Ala	Non-specific	21059	247115	0.97	[0.95, 0.99]	0.003
IL6R Asp358Ala	Claudication	8646	247115	0.94	[0.91, 0.97]	2×10^{-4}
IL6R Asp358Ala	CLTI	4185	247115	0.95	[0.91, 1]	0.03
IL6R Asp358Ala	Amputation	786	247115	0.86	[0.77, 0.96]	0.009



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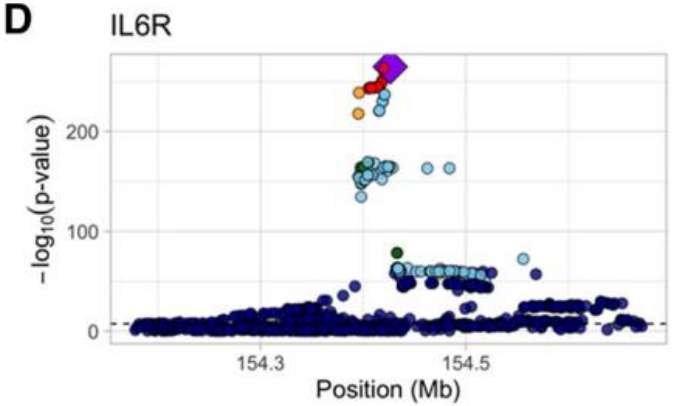
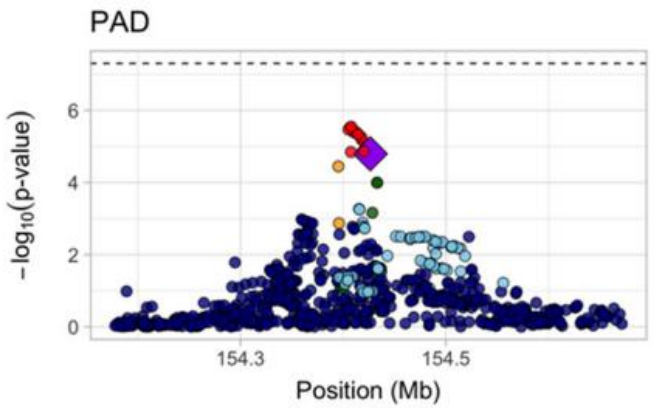




European Heart Journal (2013) **34**, 3707–3716
doi:10.1093/eurheartj/ehs354

CLINICAL RESEARCH
Vascular disease

Interleukin-6 receptor pathways in abdominal aortic aneurysm

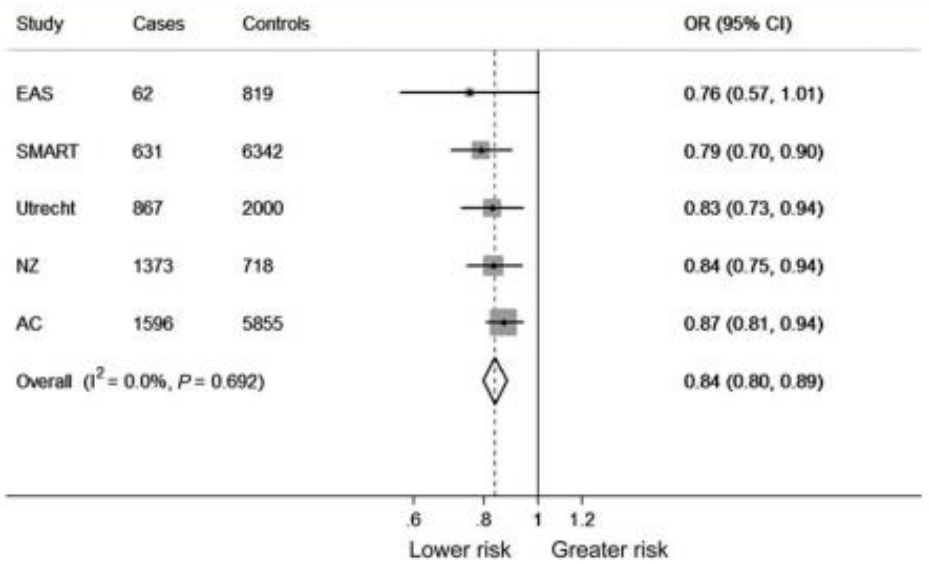
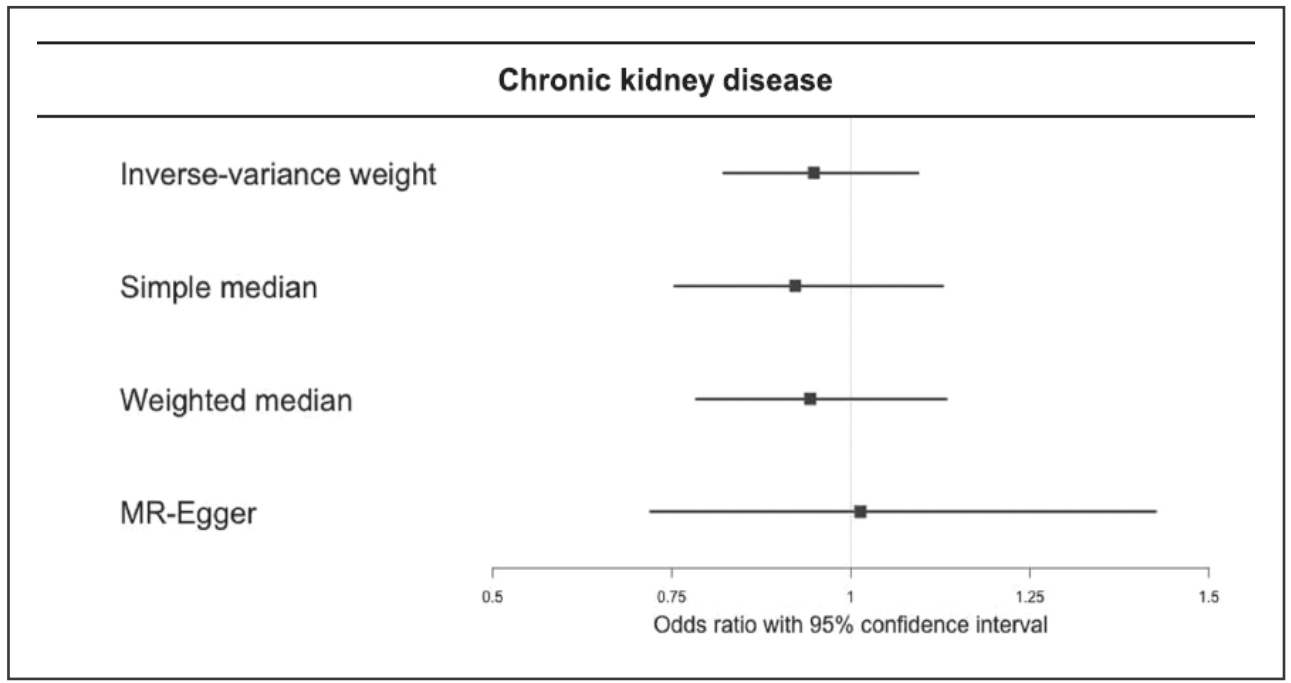


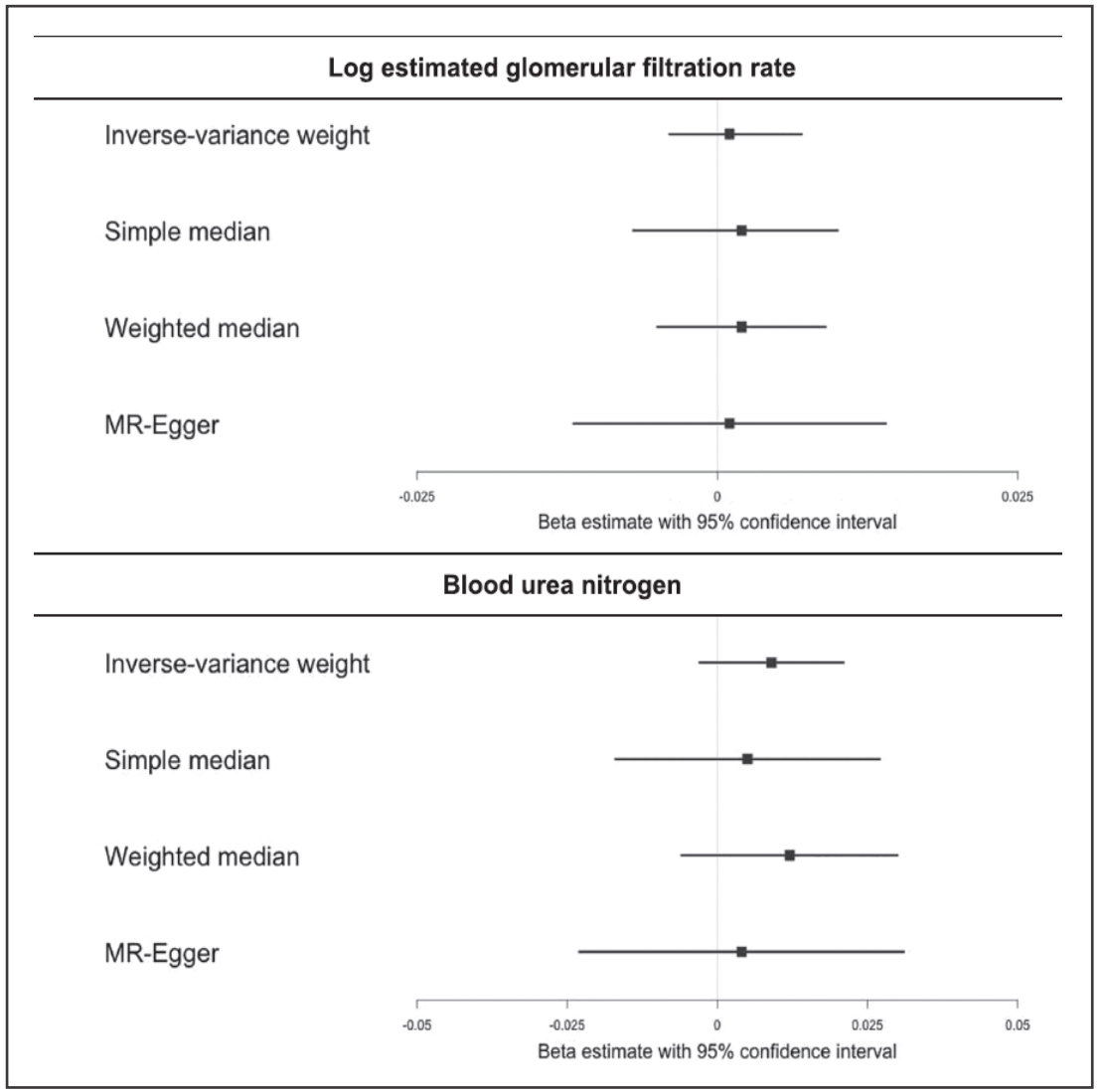
Figure 2 Association between rs7529229 and abdominal aortic aneurysms following fixed-effect meta-analysis of four case–control studies (4524 cases/15 710 controls). Per allele odds ratio = 0.84 (95% CI: 0.80–0.89, $I^2 = 0$, $P = 2.7 \times 10^{-11}$).

Genetic insights into adverse effects and repurposing opportunities

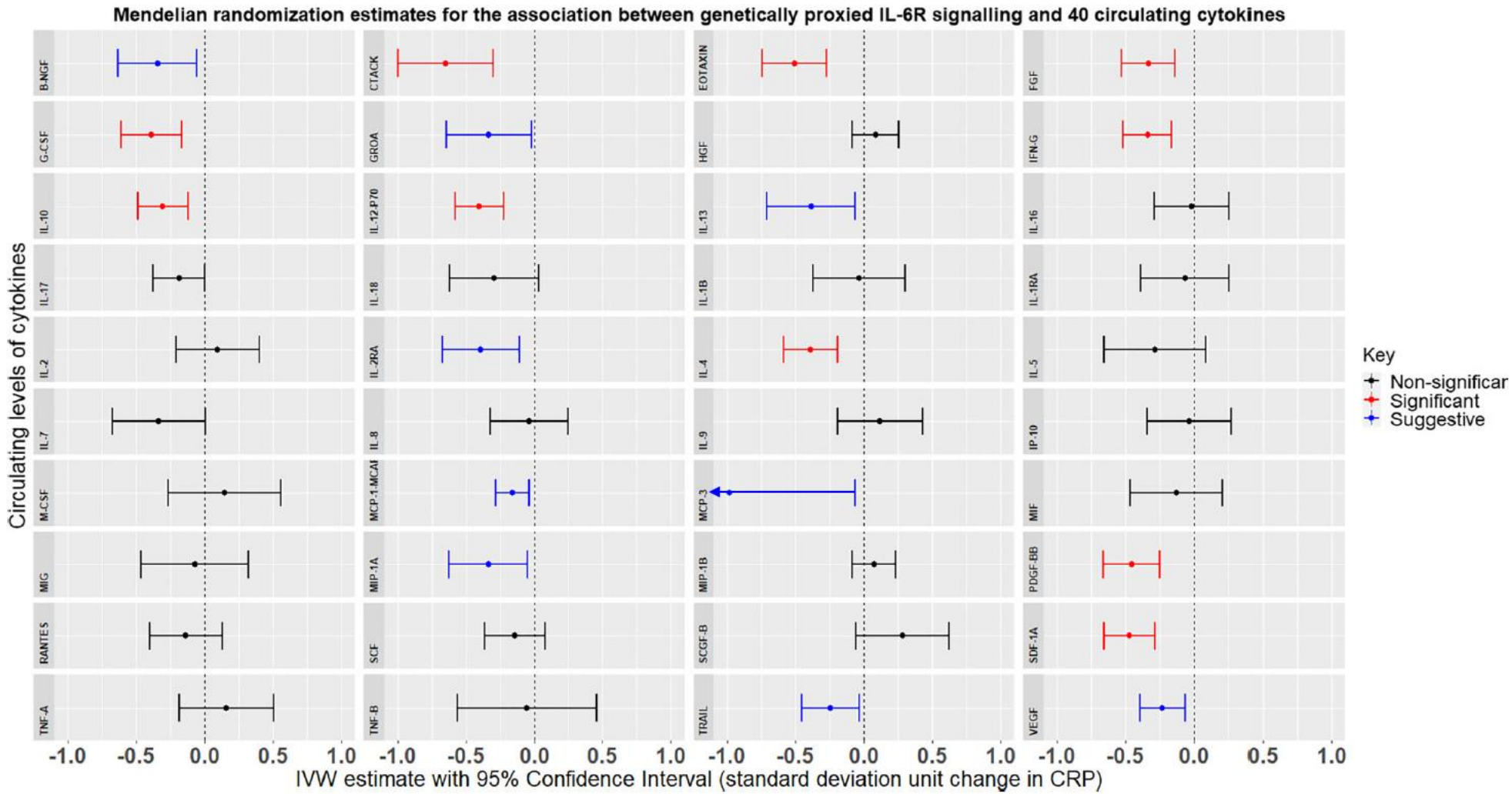
Inhibition of interleukin 6 signalling and renal function: A Mendelian randomization study



Effects of genetically proxied IL-6 signal inhibition on renal function



Leveraging genetic data to investigate the effects of interleukin-6 receptor signalling on levels of 40 circulating cytokines

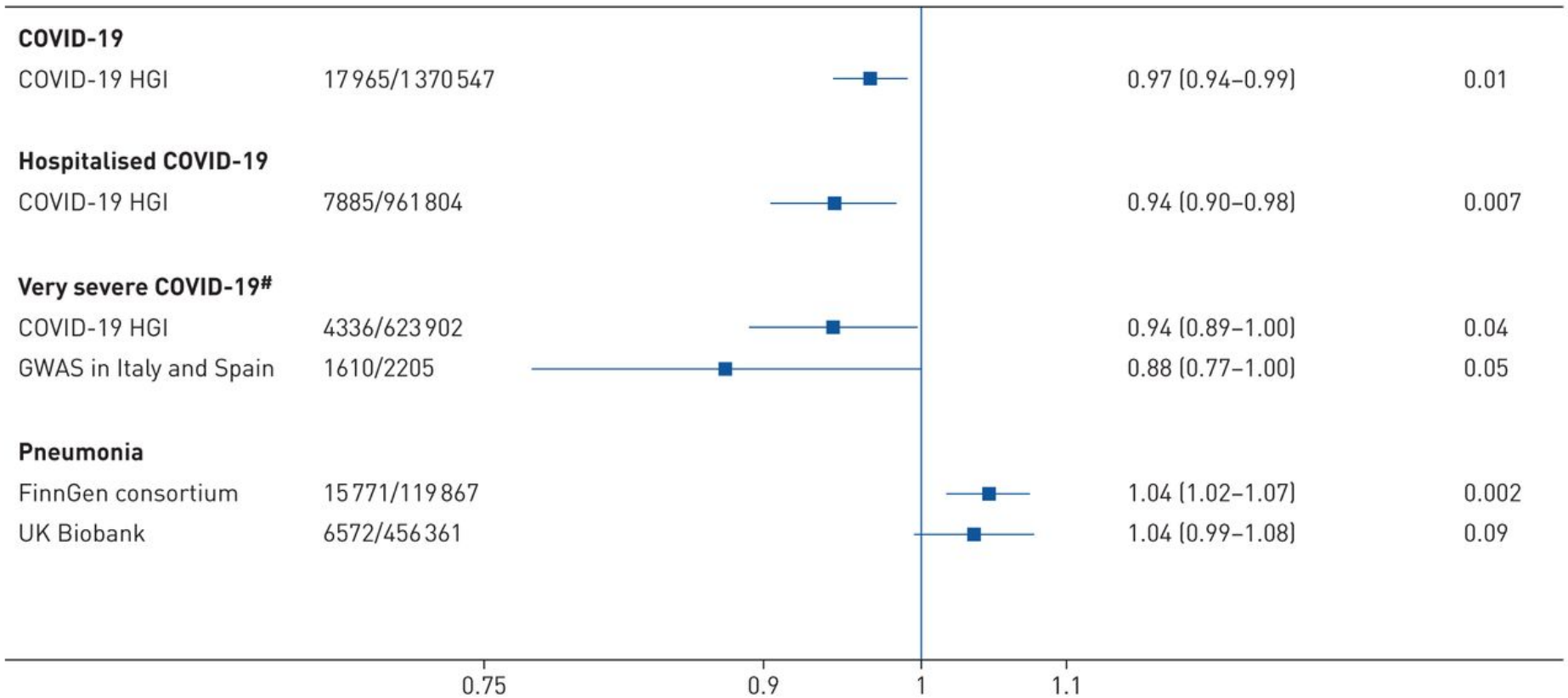


Genetically proxied interleukin-6 receptor inhibition: opposing associations with COVID-19 and pneumonia

Susanna C. Larsson, Stephen Burgess, Dipender Gill

European Respiratory Journal 2021 57: 2003545; **DOI:** 10.1183/13993003.03545-2020

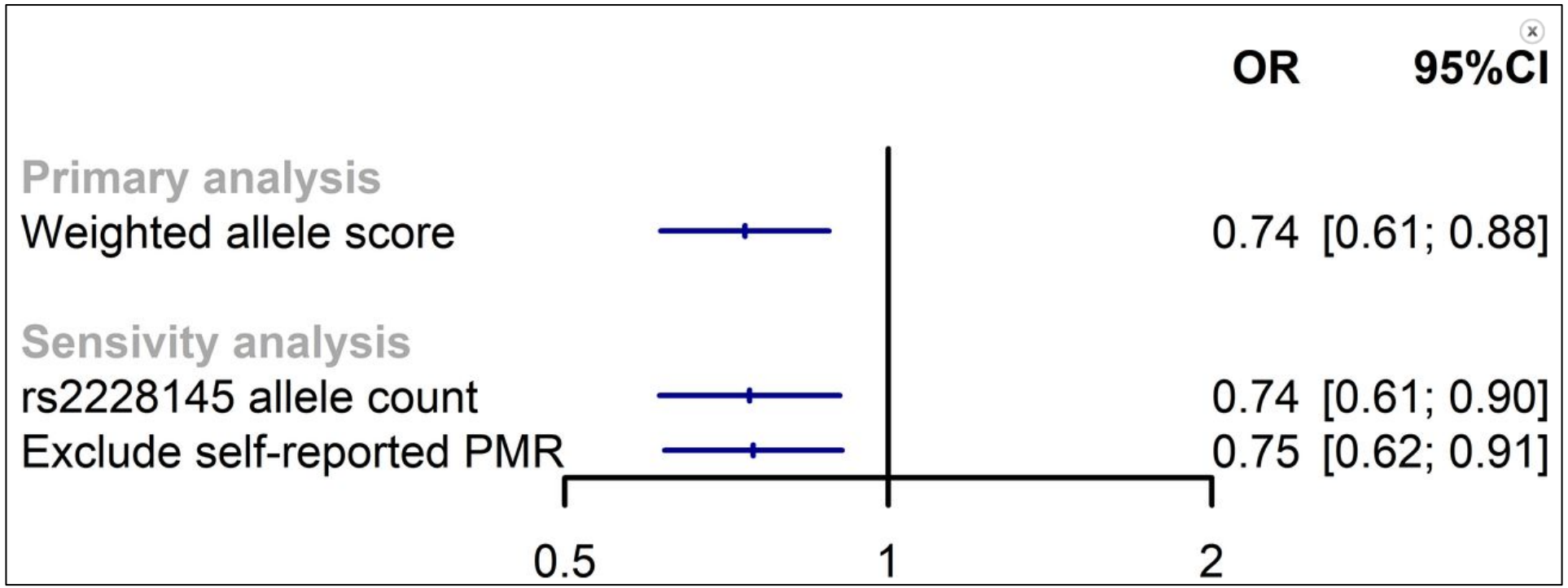
Outcome	Cases/controls	OR (95% CI)	p-value
COVID-19			
COVID-19 HGI	17 965/1 370 547	0.97 (0.94–0.99)	0.01
Hospitalised COVID-19			
COVID-19 HGI	7885/961 804	0.94 (0.90–0.98)	0.007
Very severe COVID-19#			
COVID-19 HGI	4336/623 902	0.94 (0.89–1.00)	0.04
GWAS in Italy and Spain	1610/2205	0.88 (0.77–1.00)	0.05
Pneumonia			
FinnGen consortium	15 771/119 867	1.04 (1.02–1.07)	0.002
UK Biobank	6572/456 361	1.04 (0.99–1.08)	0.09



Ann Rheum Dis. 2022 Jun 14;annrheumdis-2022-222578. doi: 10.1136/annrheumdis-2022-222578. Online ahead of print.

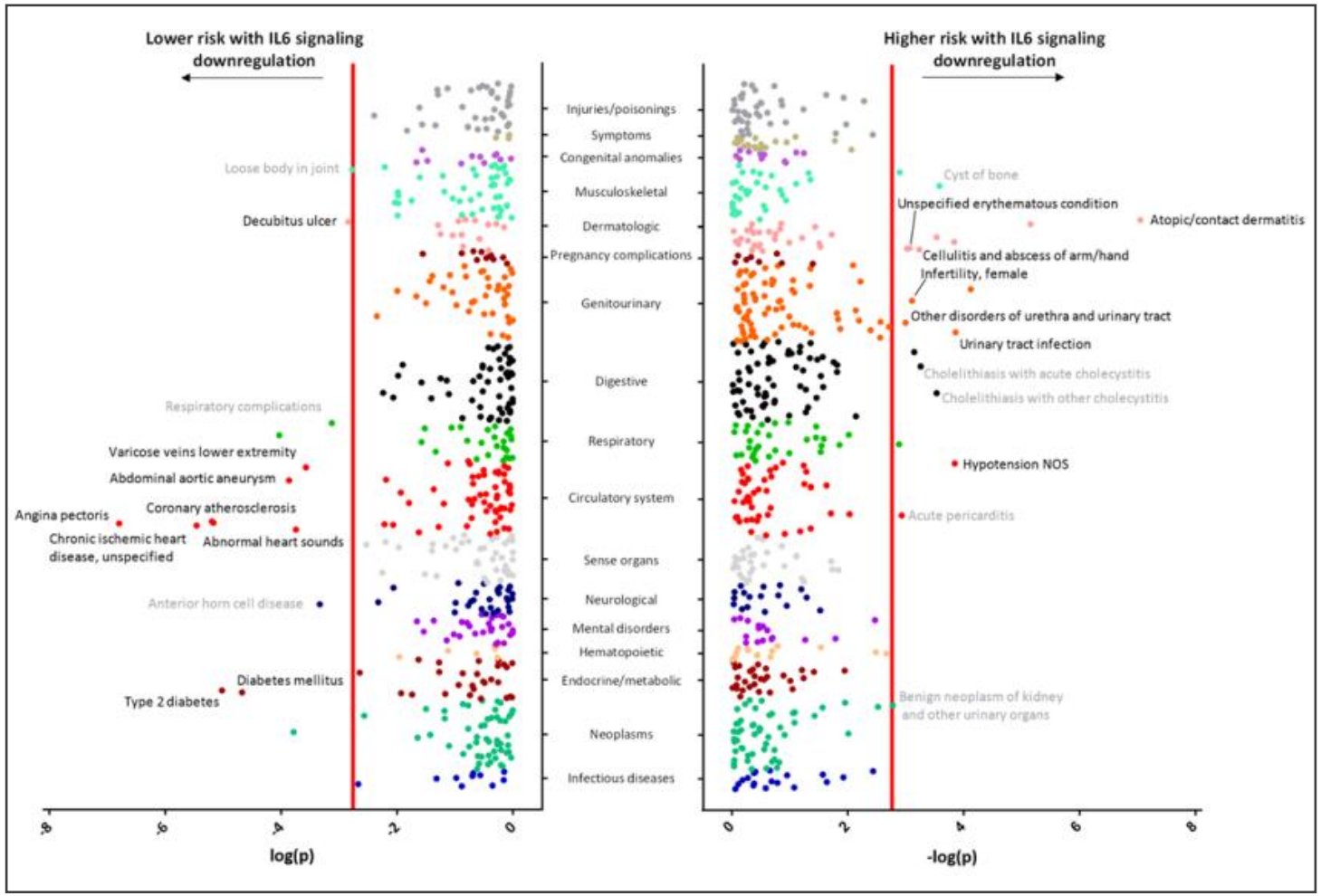
Genetically proxied IL-6 receptor inhibition and risk of polymyalgia rheumatica

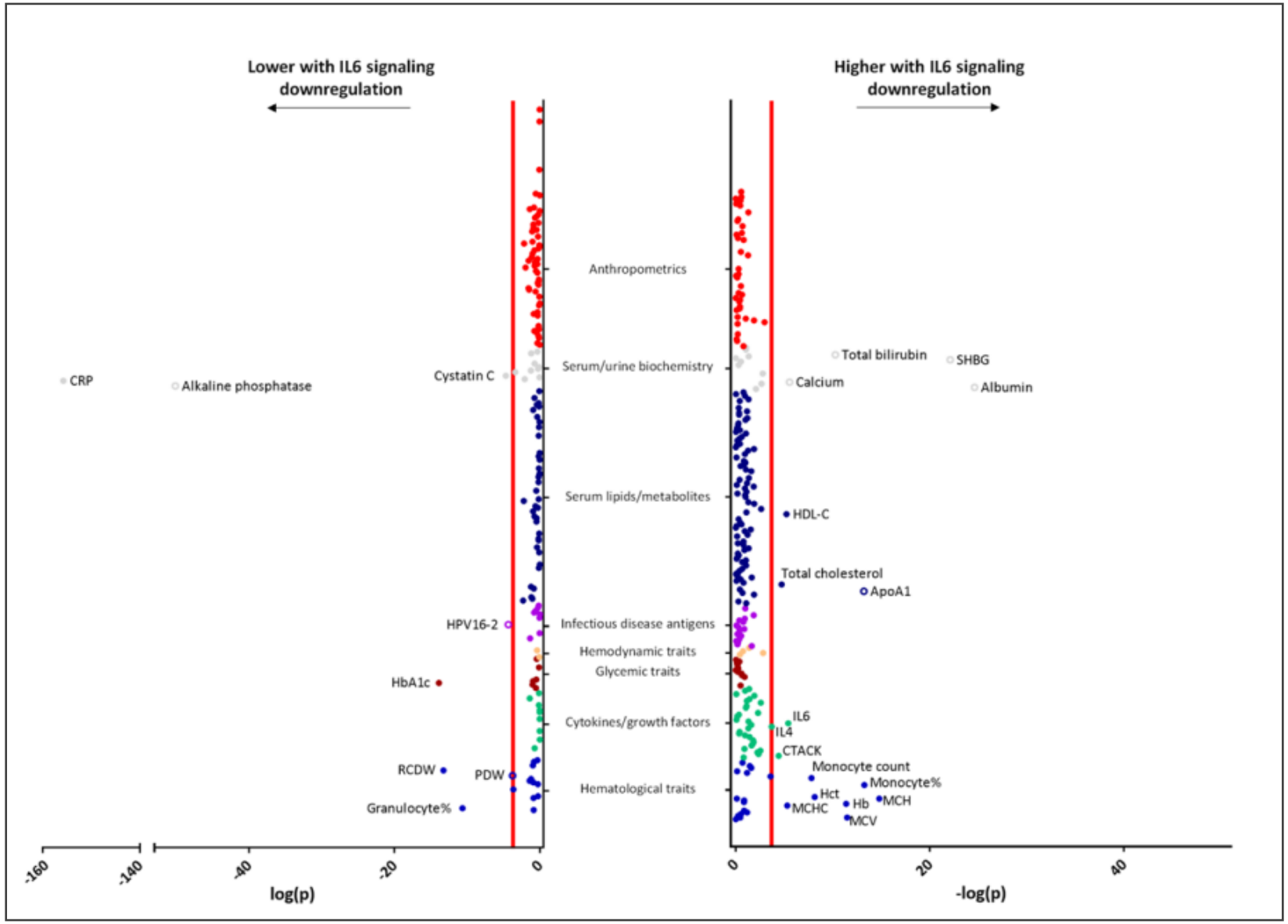
Sizheng Steven Zhao [1], Dipender Gill [2 3 4]



Genetically Downregulated Interleukin-6 Signaling Is Associated With a Favorable Cardiometabolic Profile

A Phenome-Wide Association Study




Lower with IL6 signaling downregulation
Higher with IL6 signaling downregulation
Anthropometrics
Serum/urine biochemistry
Serum lipids/metabolites
Infectious disease antigens
Hemodynamic traits
Glycemic traits
Cytokines/growth factors
Hematological traits
CRP
Alkaline phosphatase
Cystatin C
HPV16-2
HbA1c
RCDW
PDW
Granulocyte%
Total bilirubin
SHBG
Calcium
Albumin
HDL-C
Total cholesterol
ApoA1
IL6
IL4
CTACK
Monocyte count
Monocyte%
Hct
MCH
MCHC
Hb
MCV
-160
-140
-40
-20
0
log(p)
0
20
40
-log(p)

Questions and comments?