

# Genetically Predicted CD40 Levels Have Differential Effects on Early and Late Onset Ischemic Stroke Subtypes

Kevin Nguyen<sup>1</sup>, Huichun Xu<sup>1</sup>, Brady Gaynor<sup>1</sup>, John W Cole<sup>2</sup>, Michael Chong<sup>3</sup>, Steven J Kittner<sup>2</sup>, and Braxton D Mitchell<sup>1</sup>,

on behalf of ISGC, SiGN, and the EOSC Departments of Medicine<sup>1</sup> and Neurology<sup>2</sup>, University of Maryland School of Medicine, Baltimore, MD, USA; McMaster University, Hamilton, Ontario, Canada<sup>3</sup>

## Objective

To estimate the causal effects of circulating inflammatory biomarkers on early and late onset ischemic stroke (IS; EOS age 18-59 years; LOS age > 60 years) and assess effect heterogeneity.

## Introduction

- Chronic Inflammation is an underappreciated contributor to IS stroke risk.
- Inflammation's role in IS is complex
  - Elevated chronic inflammation is also a symptom of other stroke risk factors (diabetes, hypertension, obesity, etc.)
  - Is associated with response to brain injury.
- Goals: Use Mendelian Randomization to assess the causal effects of inflammation, represented by genetically predicted levels of inflammatory biomarkers, upon IS risk.
- We hypothesize that genetic proxies for inflammation have differing causal relationships with IS, depending on the etiology and age of stroke onset.

## References

- Chen L, Peters JE, Prins B, et al. Systematic Mendelian randomization using the human plasma proteome to discover potential therapeutic targets for stroke. *Nat Commun.* 2022;13(1):6143.
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- Ferro D, Loffredo L, Polimeni L, et al. Soluble CD40 ligand predicts ischemic stroke and myocardial infarction in patients with nonvalvular atrial fibrillation. *Arterioscler Thromb Vasc Biol.* 2007
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## Methods

### Exposure

- Biomarkers**  
20 circulating inflammation-related biomarkers identified from literature as being associated with stroke
- Instrumental Variable (IVs) sourced from large-scale, EUR-based GWAS summary statistics**
- Selection of IVs:**
  - P value Thresholding:  $P \leq 5 \times 10^{-8}$
  - Clumping: kb = 10,000,  $r^2 \leq 0.1$
  - F statistics > 10

### Outcome

Individual-level data of SiGN and EOSC Stratified by EUR-ancestry and toast subtypes

Subtypes	Late Onset Sample Size	Early Onset Sample Size
Allstroke	9272	6728
toastCE	2579	825
toastLAA	1681	821
toastOTHER	63	627
toastSAO	1627	885
toastUNDETER	2058	1747
Controls	25124	33764

GWAS of stroke and subtypes, using PC1-10 and Sex as covariates

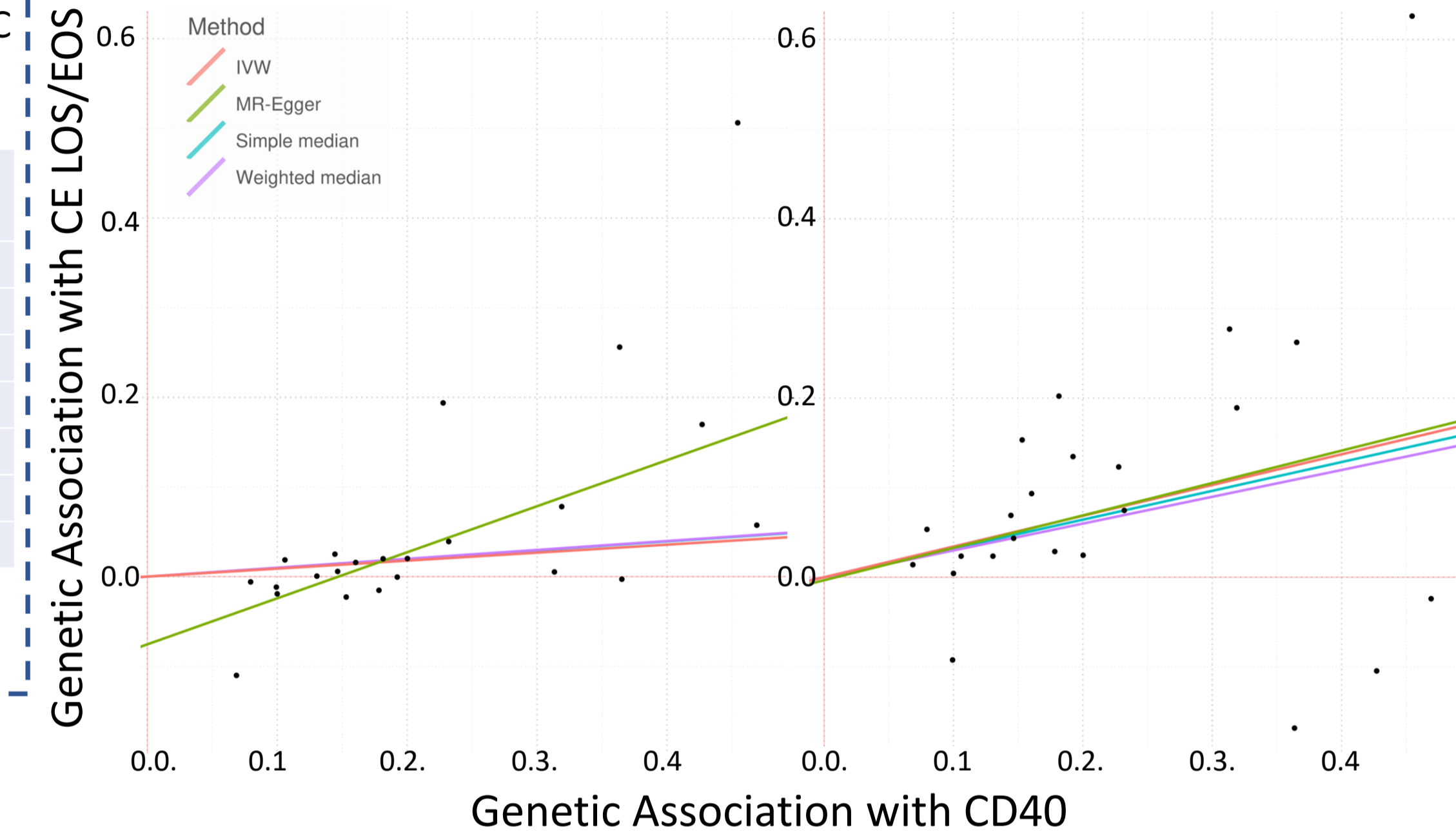
### Data Harmonization

### Two Sample MR Analysis

- Outlier Detection and Removal**
  - Cook's Distance filtering: 4/#SNPs
  - MR-PRESSO
- Selection of In Common SNPs Within the EOS and LOS Analysis**
- Two Sample MR Analysis**
  - IVW
  - MR-Egger
  - Simple Median
  - Weighted Median
- Assessment of Estimates**
  - Comparison of EOS and LOS causal estimate using Wald's Test

## Results Cont.

MR Scatterplots Plots Illustrating Differential Effects of CD40 on CE for LOS and EOS



## Discussion

- Causal estimates assessment from MR analyses indicate that increased genetically predicted levels of CD40 is protective for stroke except for cardioembolic EOS. These finds are in line with and expands upon previous MR analyses.
- Chen et al.<sup>1</sup> looked mainly at older stroke, finding an inverse/protective causal effect for all IS, LAA, and SAO but an insignificant trend towards increased risk of CE.
- The reasons for the differing effects by stroke subtype are unknown but could be attributed to CD40's various roles in signaling.<sup>2,3,4</sup>
- Limitations: Statistical Power may be weakened due to limited sample size and European-stratified analyses.

## Results

### MR Associations of CD40 With Early and Late-onset Stroke Risk

Subtype	SNPs	P-value	OR	L95	U95
allstroke	24	1.43E-01	0.96	0.90	1.01
allstroke	24	7.32E-05	0.90	0.85	0.95
toastCE	23	5.66E-05	1.37	1.17	1.59
toastCE	23	5.21E-01	1.04	0.93	1.15
toastLAA	22	1.47E-05	0.72	0.62	0.84
toastLAA	22	4.54E-04	0.80	0.71	0.91
toastOTHER	22	5.61E-05	0.72	0.62	0.85
toastOTHER	22	6.79E-01	0.90	0.54	1.50
toastSAO	23	1.23E-01	0.89	0.77	1.03
toastSAO	23	2.57E-02	0.86	0.76	0.98
toastUNDETER	22	6.21E-01	0.97	0.88	1.08
toastUNDETER	22	1.42E-03	0.84	0.75	0.93

Wald's Test: \* P < 0.05

Bonferroni adjusted P-value < 0.05/(20\*6) = 4.16x10<sup>-4</sup>

Odds Ratio

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