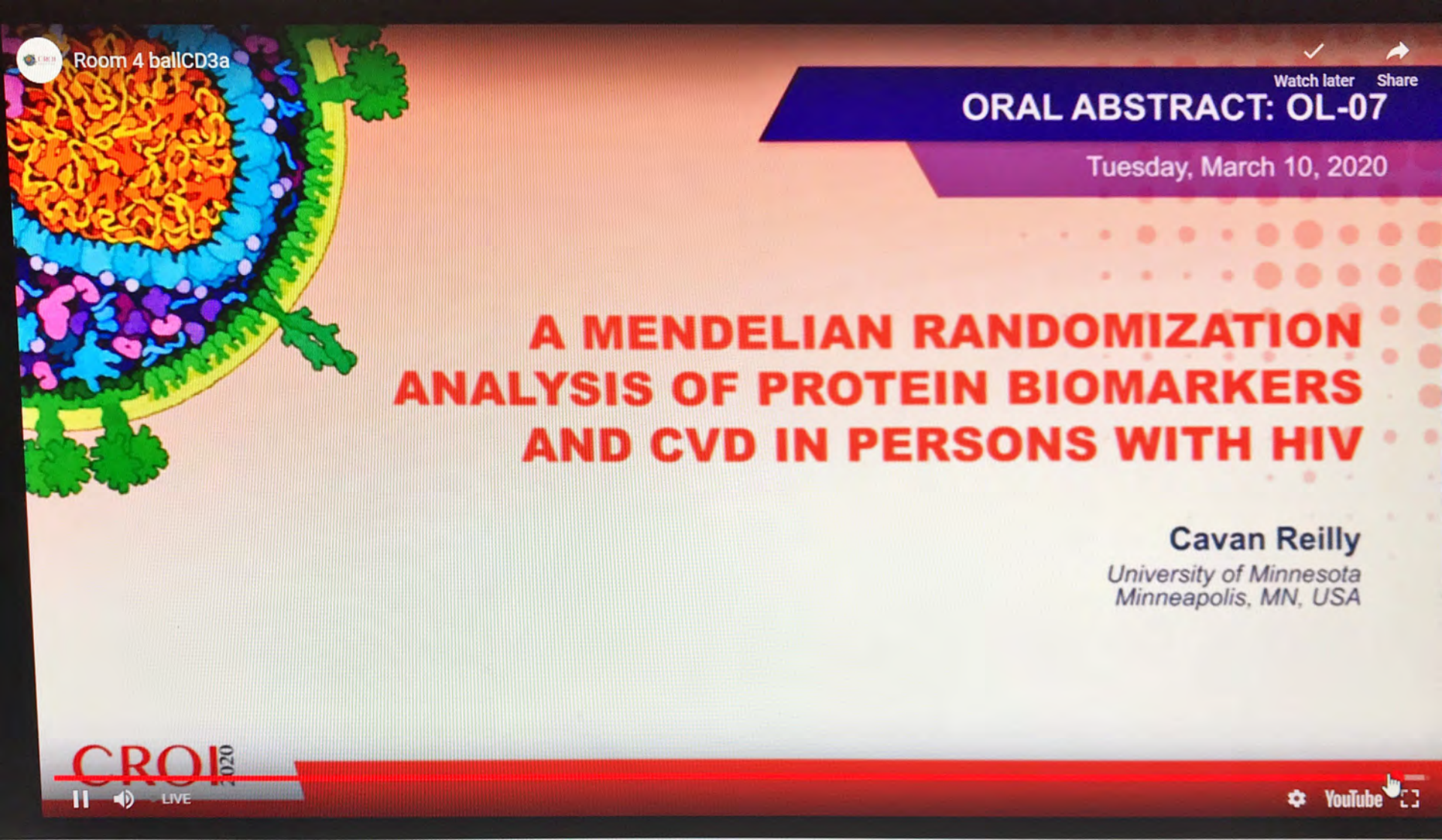
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ORAL ABSTRACT: OL-07
Tuesday, March 10, 2020
A MENDELIAN RANDOMIZATION ANALYSIS OF PROTEIN BIOMARKERS AND CVD IN PERSONS WITH HIV
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LIVE
YouTube

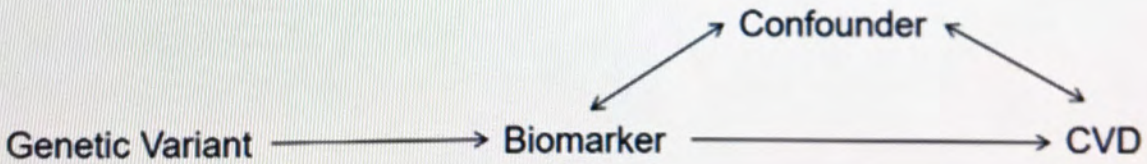
HIV and Cardiovascular disease

- According to recent meta-analyses, PLWH are about twice as likely to develop CVD compared to those without HIV.
- While the sources of increased risk are not well understood, a variety of reasons have been proposed, including:
  - Increased exposure to traditional risk factors
  - Inflammation and immune activation
  - ART
  - Endothelial disfunction, cardiac fibrosis, platelet abnormalities, viral coinfections, cardiac steatosis,…
- Many biomarkers for CVD have been studied in the general population, but the causal nature of these is difficult to assess.
- Contemporary methods of causal inference that are widely used in the epidemiological literature may help identify therapeutic targets.

Mendelian randomization (MR)

Mendelian randomization is a statistical method that can be used to identify a causal link between a biomarker and an outcome by identification of a genetic variant that is

1. Related to the biomarker
2. Related to the outcome
3. Unrelated to confounders that obscure the relationship between the biomarker and the outcome.



Mendelian randomization

- One tests for an association between the genetic variant (as a proxy for the biomarker) and the outcome.
- Due to independent assortment of chromosomes during gametogenesis and recombination, genetic variants will be independent of potential confounders.
  - For example, someone having a particular nucleotide at some location in his genome will generally not help me predict if that person smokes.
  - But if having this particular nucleotide is associated with a biomarker level, then associations between CVD and having that nucleotide tell you about the association between the biomarker and CVD independent of smoking.
- A critical assumption for this technique is that there is not an association between the genetic variant and potential confounders.

Study Design

- We identified 500 participants from INSIGHT trials who experienced a clinical event (composite outcome of AIDS, serious non-AIDS including CVD, and death) and individually matched them (1:2) with study-specific controls who did not.
  - Mean follow-up of 6 years.

	ESPRIT	FIRST	SMART	START	TOTAL
Cases	262	42	52	144	500
CVD cases	77	8	16	30	131
Controls	517	84	104	288	993

- Stored plasma from study entry was used to measure protein levels using 5 panels made by OLINK (panels: CVD2, CVD3, immune response, cardiometabolic and inflammation).
- Genotypic data from a genome-wide Affymetrix array was available for all.

Participant characteristics

Trait	Cases	Controls
Age	44 (37, 53)	44 (36, 51)
Sex (Male)	422 (84%)	823 (83%)
Black	101 (20%)	183 (18%)
Diabetes at baseline	34 (7%)	48 (5%)
Hypertension at baseline	83 (17%)	116 (12%)

- The matching created balance across the groups for age, sex and race.
- There were higher baseline levels of diabetes and hypertension among the cases.

Sequential testing approach

- The following sequential approach was used to conduct MR tests:
  1. Test for associations between proteins and CVD, and exclude proteins that aren't associated from further analysis
  2. Test for associations between proteins and genetic variants and exclude proteins that aren't associated with any variants from further analysis
     - Only genetic variants within 5Kb of the protein coding region of the corresponding gene were tested to reduce likelihood of inclusion of pleiotropic variants
  3. Test for causal effects of the remaining proteins on CVD using MR analysis methods.
- This approach controls the overall error rate across all MR tests at 5% (like a Bonferroni correction).

Results

459 proteins

↓

389 proteins with sufficiently high-quality data

↓

89 proteins associated with CVD

↓

38 proteins associated with at least 1 SNP in corresponding gene

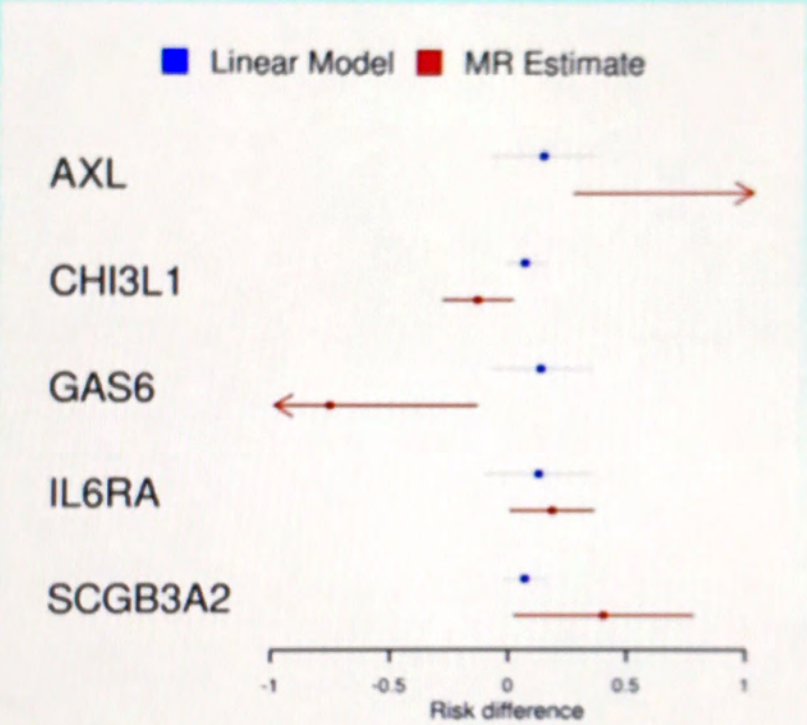
↓

AXL, CHI3L1, GAS6, IL1RL2, IL6RA, SCGB3A2

↓

IL1RL2 excluded due to it being a "weak instrument"

Absolute risk differences



insight

Interpretation based on current literature

- AXL: involved in inflammatory responses and progression of CVD
- CHI3L1: mediates inflammation and fibrosis
- GAS6: ligand of AXL, involved in a variety of diseases and thought to be a marker for adverse conditions
  - Appears to lower risk of CVD here
- IL6RA: previously established causal role in the development of coronary heart disease in the general population
  - Operates via promotion of inflammation
- SCGB3A2: anti-inflammatory and anti-fibrotic properties

Conclusions

- Methods for screening large numbers of potential biomarkers for causal effects that control the Type I error rate for MR tests are possible.
- Application of these methods demonstrated potential causal effects of 5 proteins on CVD outcomes among a global population of PLWH.
- These proteins warrant further study as interventional targets for candidate treatments to reduce CVD risk among PLWH.
  - Some of these have interventions in various stages of clinical development (CHI3L1 and IL6RA).
  - The identified proteins have been described as having a role in tissue fibrosis and inflammation.