

## Integrating Inflammation into Cardiovascular Disease Risk Prediction

Namita Nedumala, BS<sup>1</sup>; Hongtian Wang, MA<sup>3</sup>; Oscar Fawcett, BS<sup>2</sup>; Christopher McKennan, PhD<sup>2</sup>; Floyd Thoma, PhD<sup>3</sup>; Jianhui Zhu, PhD<sup>3</sup>; Suresh Mulukutla, MD<sup>3</sup>; Zachary Rhinehart, MD<sup>3</sup>; Martha Gulati, MD<sup>4</sup>; Anum Saeed, MD<sup>3</sup>  
Lake Erie College of Osteopathic Medicine, Greensburg, PA<sup>1</sup>. Department of Statistics, University of Pittsburgh, Pittsburgh, PA<sup>2</sup>. University of Pittsburgh Medical Center, Pittsburgh, PA<sup>3</sup>. Division of Cardiology, Houston Methodist DeBakey Heart & Vascular Center, Houston, TX<sup>4</sup>.

### BACKGROUND

- Inflammation plays a central role in atherosclerotic cardiovascular disease (ASCVD)
- High sensitivity C-reactive protein (hsCRP) is associated with ASCVD risk and is recognized as a risk enhancer
- The 2023 AHA PREVENT equations estimate ASCVD risk but **do not include inflammatory biomarkers**.
- The incremental predictive value of CRP beyond PREVENT variables remains unclear.

### OBJECTIVE

- To evaluate whether inflammatory markers (hsCRP/CRP) improve ASCVD risk prediction beyond the PREVENT equations

### METHODS

- Retrospective cohort study using two independent populations without baseline ASCVD
- Outcome: Incident ASCVD events
- Analysis: Cause-specific Cox models and model discrimination (AUC, ΔC) with bootstrap validation
- Subgroup analyses by baseline risk category, age, and sex

	Cohort 1	Cohort 2
<b>Data Source</b>	UPMC primary prevention registry (EHR-based)	NIH All of Us Research Program (EHR-derived)
<b>Biomarker</b>	CRP	hsCRP
<b>Sample Size</b>	4,027	1,170
<b>Mean age (years)</b>	59.9	61.0
<b>Female (%)</b>	55.8%	71.2%
<b>White race (%)</b>	87.7%	51.5%
<b>Diabetes (%)</b>	19.3%	28.4%

Table 1. Baseline Characteristics of Study Cohorts

### RESULTS

#### Cohort 1 (UPMC)

- CRP associated with:
  - ASCVD (HR 1.06, 95% CI 1.04–1.08)
  - All-cause mortality (HR 1.19, 95% CI 1.14–1.24)
- Minimal improvement in risk prediction metrics:
  - 5-year risk: 0.609 → 0.618 (ΔC = 0.010)
  - 10-year risk: 0.598 → 0.603 (ΔC = 0.005)

- Slightly greater improvement observed in low-risk and female subgroups

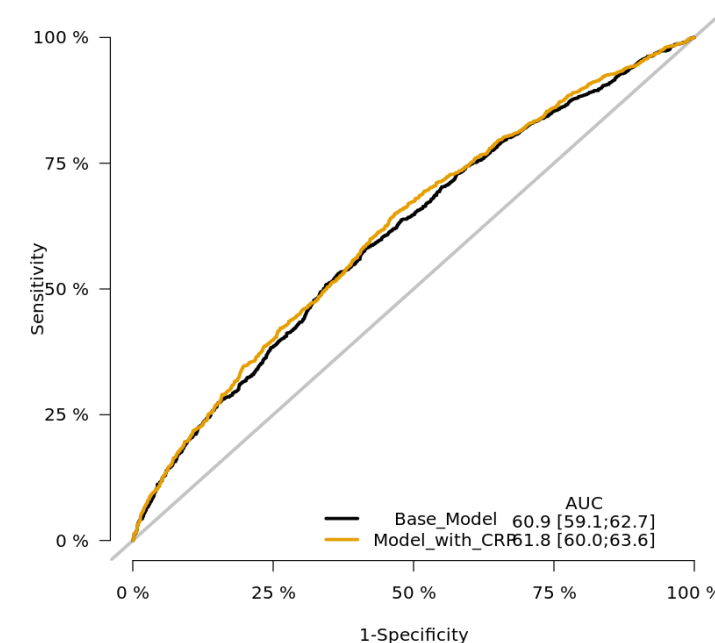


Figure 1. 5-year ASCVD Risk Prediction Metrics Cohort 1

#### Cohort 2 (All of Us)

- No significant association between hsCRP and ASCVD (HR 1.06, 95% CI 0.97–1.16; p = 0.216)
- No improvement in risk prediction performance across age groups (ΔC ≈ 0 or negative)

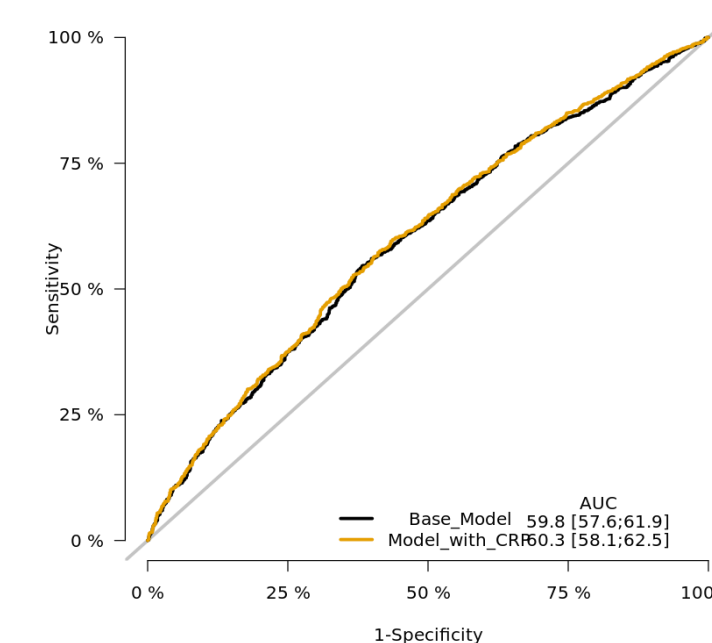


Figure 2. 10-year ASCVD Risk Prediction Metrics Cohort 1

	Cohort 1	Cohort 2
<b>Association</b>	Yes	No
<b>ΔC (Model Improvement)</b>	0.005–0.010	~0

Table 2. Summary of Findings

### KEY FINDINGS

- CRP was associated with ASCVD and all-cause mortality in Cohort 1
- No significant association was observed in Cohort 2
- Addition of CRP/hsCRP resulted in **minimal or no improvement in risk prediction performance** (ΔC ≤ 0.01)

### INTERPRETATION

- Observed associations did not translate into meaningful improvement in risk prediction beyond PREVENT variables
- Findings suggest substantial overlap between CRP and established clinical risk factors
- Findings were not consistent across cohorts, supporting limited generalizability

### CLINICAL IMPLICATIONS

- Findings do not support routine inclusion of CRP in population-level risk prediction models
- CRP may remain useful as a risk-enhancing factor in select patients

### LIMITATIONS

- Observational EHR-based design with potential residual confounding
- Single time-point CRP/hsCRP measurement may not reflect chronic inflammation
- Differences between cohorts (clinical vs national dataset) may affect generalizability
- Subgroup analyses were exploratory

### KEY REFERENCES

- Khan SS, Matsushita K, Sang Y, et al. Development and validation of the American Heart Association's PREVENT equations. *Circulation*. 2023;149:430–449.
- Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease. *Circulation*. 2019;140(11):e596–e646.
- Ridker PM, Danielson E, Fonseca FAH, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein (JUPITER). *N Engl J Med*. 2008;359(21):2195–2207.

### ACKNOWLEDGEMENTS

This research used data from the All of Us Research Program (NIH). We thank the UPMC data teams and research collaborators for their support.