



Impact of Variance in Cohort Phenotype Definitions on Real-World Research: An Assessment of ASCVD Definitions on Real-World Data

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So What?

Different ASCVD definitions produce dramatically different study cohorts — across 5 replicated definitions: total number of distinct codes varied 202-637, and patient counts ranged dramatically with only 31-37% shared across all cohorts. Researchers should publish complete code lists and use data-driven computable operational definition (CODEf) selection.

BACKGROUND

Context

In real-world research (RWR), complex clinical concepts like Atherosclerotic Cardiovascular Disease (ASCVD) are defined by combining multiple composite medical conditions into cohort phenotypes. Consistent conceptual and computable operational definitions (CODEfs) are essential for meaningful, reproducible results.

The Gap / Problem

Prior work (see companion poster MSR49) identified significant variability in ASCVD conceptual and operational definitions. However, the direct impact on actual patient cohorts in real-world data (RWD) had not been quantified.

HEOR / RWE Relevance

FDA Guidance (2023) states: "small differences in the choice of operational definition ... may have a large impact on study results." This study provides empirical evidence quantifying that impact, demonstrating that definition choice directly shapes study cohorts.

OBJECTIVES

Primary Objective

To assess the impact of definition variability on cohort phenotypes by replicating published ASCVD definitions in two real-world data sources and comparing the resulting patient cohorts.

Secondary Objectives

- Quantify overlap of patient coverage across replicated ASCVD cohort definitions
- Identify significant differences that impact study outcomes
- Demonstrate the relationship between code count and cohort size

REFERENCES

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METHODS

Study Design & Data Source

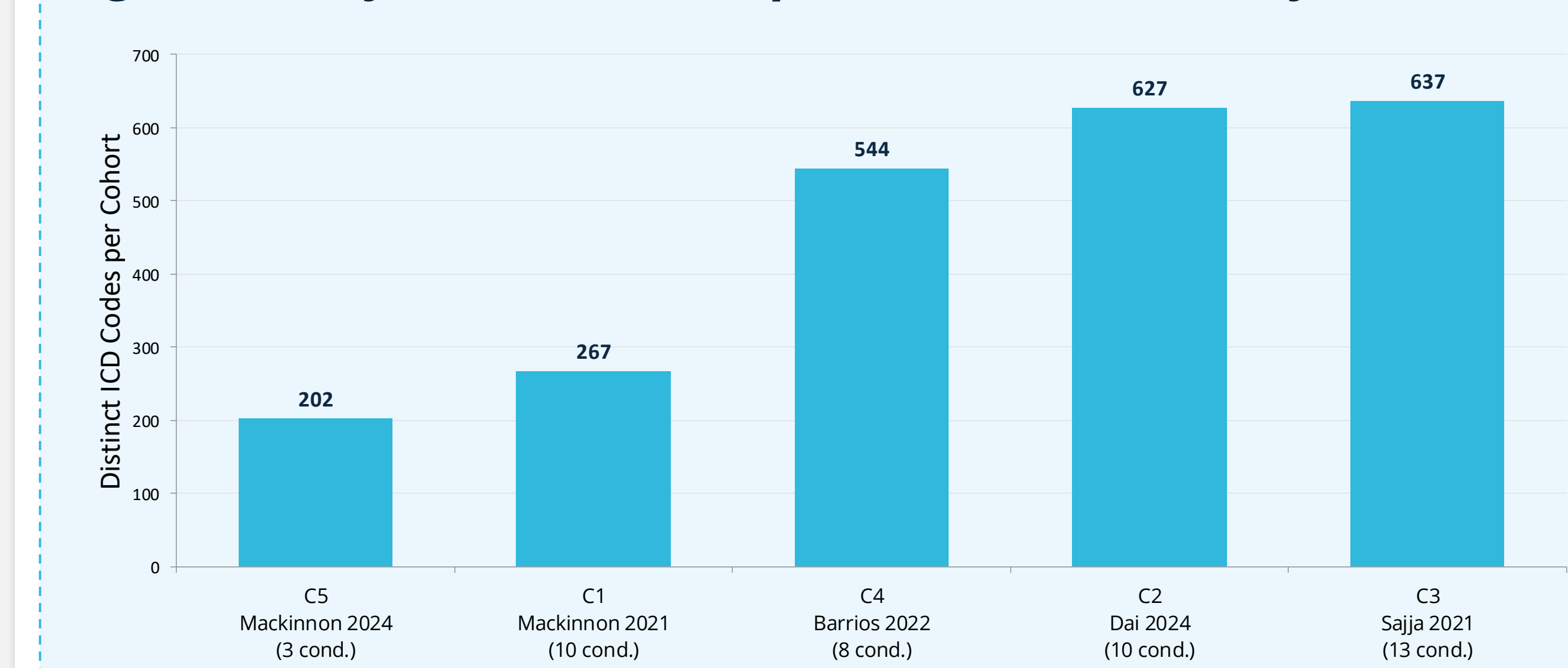
In this cross-sectional cohort replication study, six published ASCVD cohort definitions, with ICD-10-CM / ICD-10-CA / ICD-9-CM code lists, were identified from a targeted literature review. All six were replicated in PurpleLab® CLEAR Claims (US national claims) and MIMIC-IV (EHR from 28 hospitals).

Figure 1: Literature Review → Cohort Definition Selection



RESULTS

Figure 2: # of Distinct Codes per ASCVD Cohort Definition



Computable Operational Definitions (CODEfs™)

Study elements — exposures, outcomes, and covariates — were defined using Navidence CODEfs™: rigorous, data source-agnostic algorithms that ensure precision and reproducibility across RWR.

RESULTS

5 ASCVD Cohort Definitions | 14.7K, 19.2M Qualifying Patients per Data Source | 31-37% Patients Common Across All Cohorts

Figure 3: Included Conditions by ASCVD Cohort Definition

Condition	C1	C2	C3	C4	C5	Count
Peripheral Artery Disease (PAD)	✓	✓	✓	✓	✓	5/5
Ischemic Stroke	✓	✓	✓	✓	✓	5/5
Myocardial Infarction (MI)	✓	✓	✓	✓	✓	5/5
Stable Angina	✓	✓	✓	✓		4/5
Unstable Angina	✓	✓	✓	✓		4/5
Abdominal Aortic Aneurysm	✓	✓	✓	✓		4/5
Descending Thoracic Aneurysm	✓	✓	✓	✓		4/5
Transient Ischemic Attack (TIA)	✓		✓	✓		3/5
Coronary Revascularization	✓	✓	✓			3/5
Other Arterial Revascularization	✓	✓	✓			3/5
Acute Coronary Syndrome (ACS)		✓	✓			2/5
Coronary Artery Disease (CAD)			✓			1/5
Cerebrovascular Disease			✓			1/5

Figure 4: Patient Count % across ASCVD Cohort Definitions Replicated in RWD

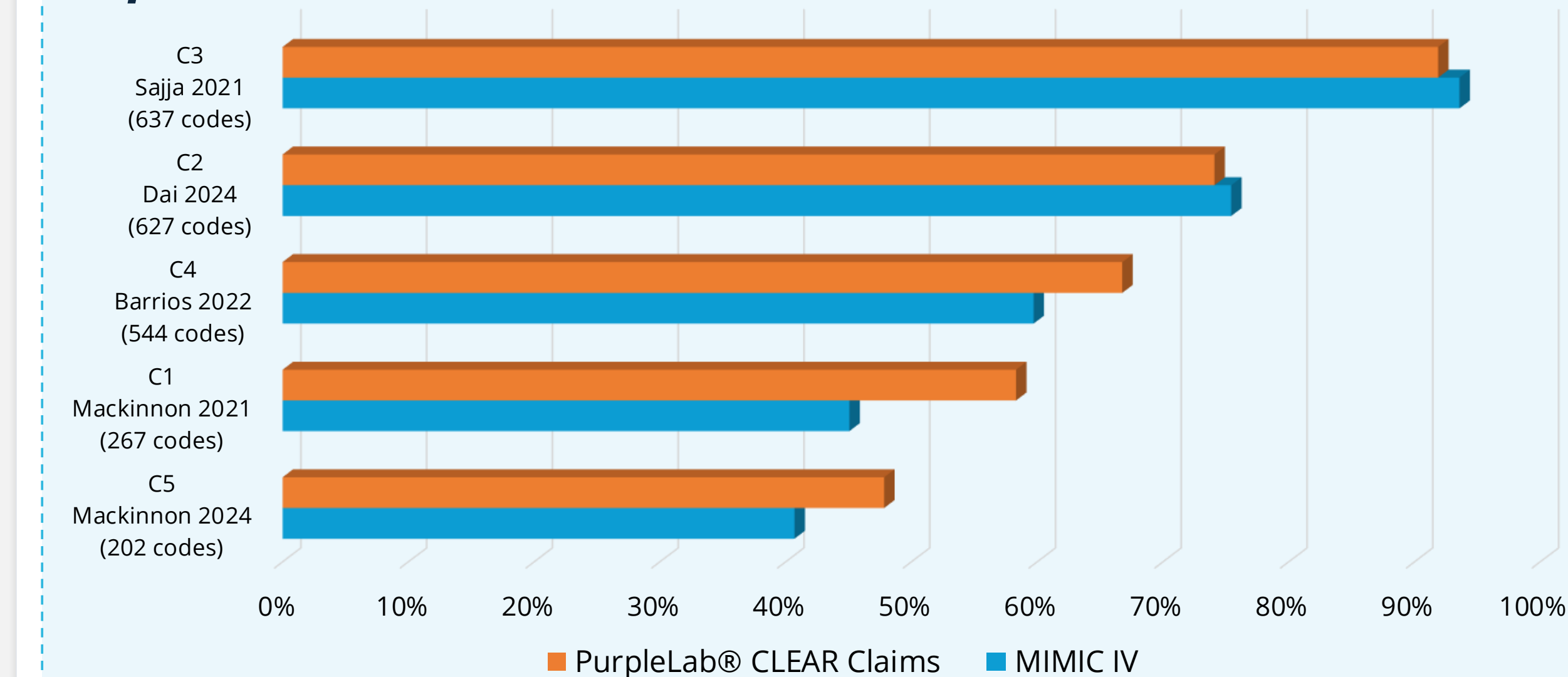


Figure 5: Top 7 Patient Overlaps across ASCVD Cohort Definitions Replicated in RWD

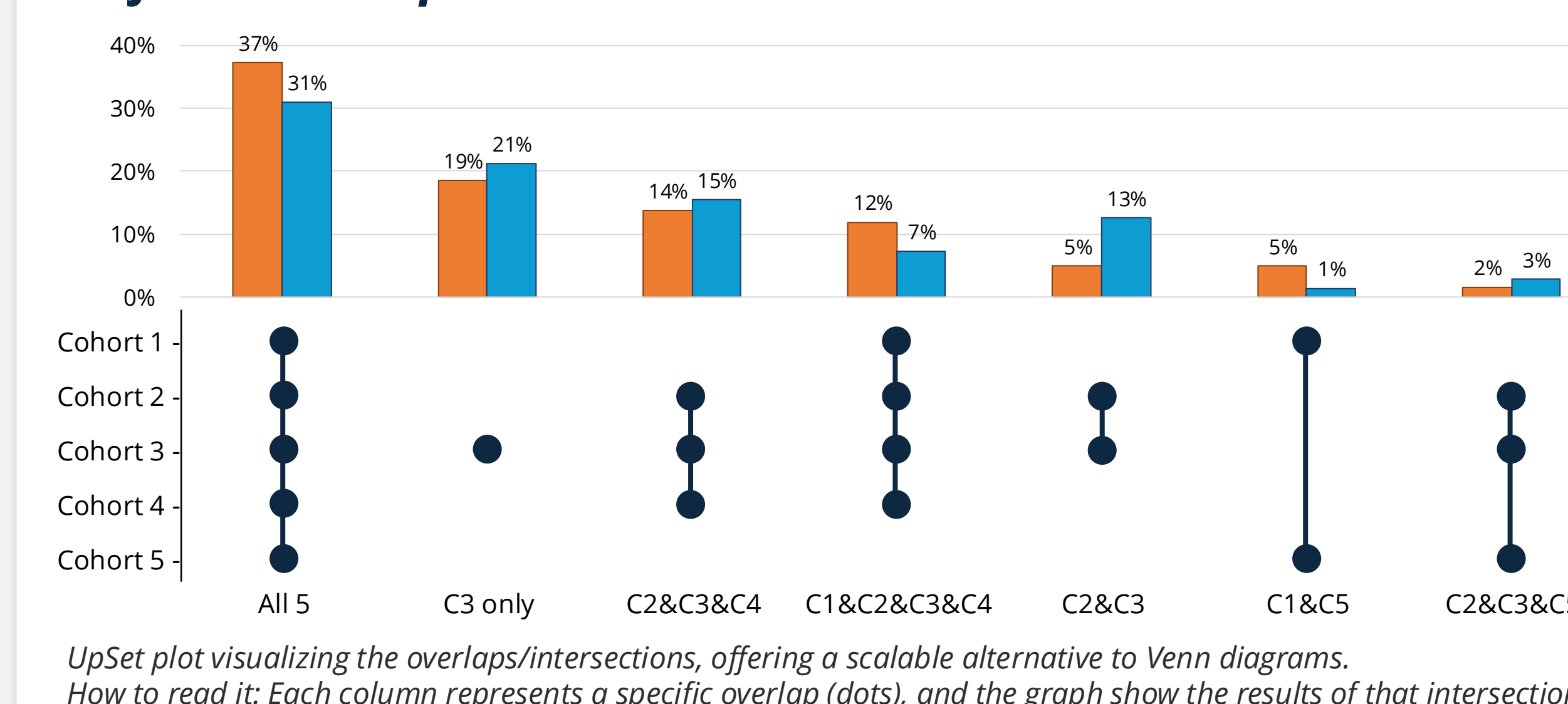
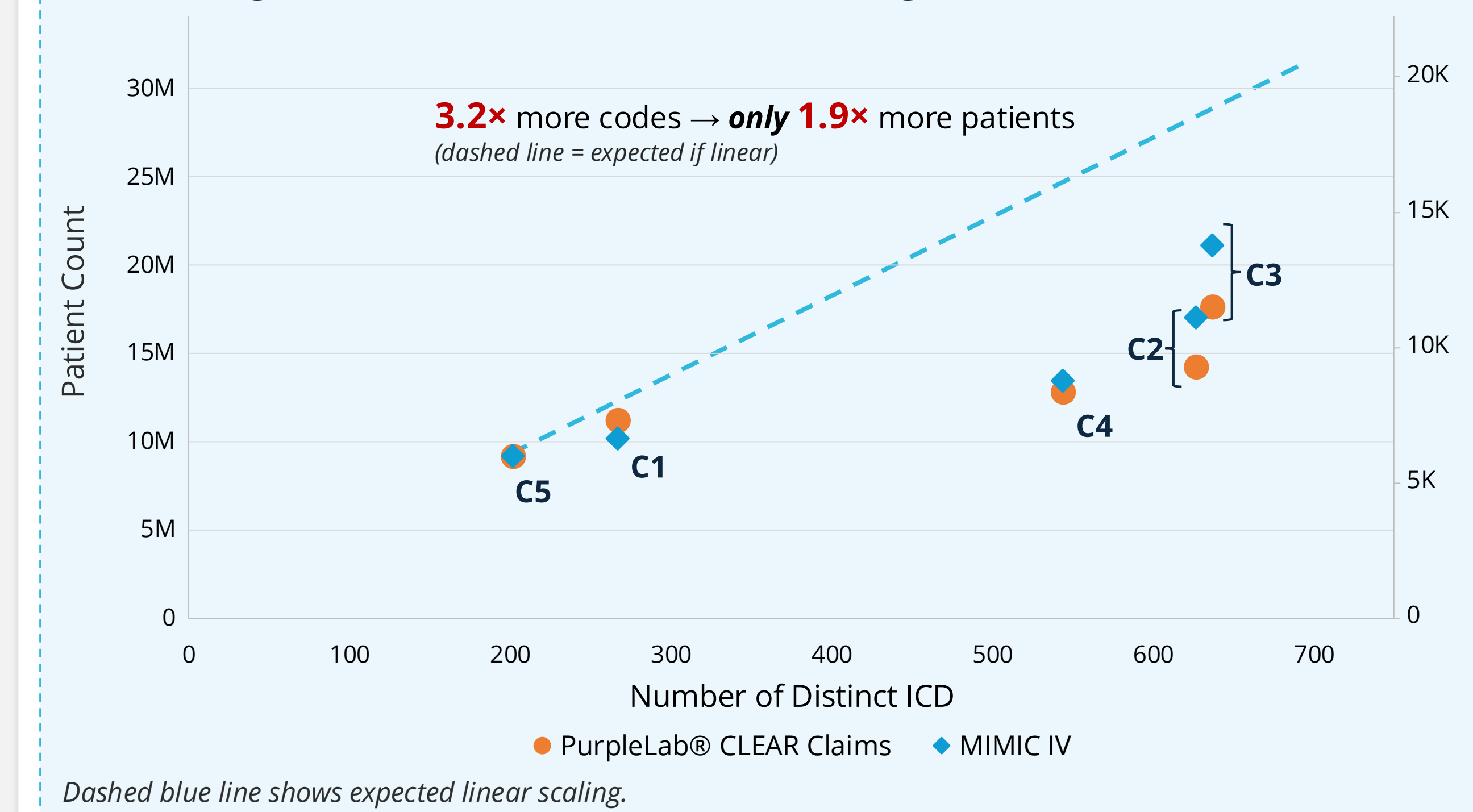


Figure 6: # of Distinct Codes per ASCVD Cohort Definition vs. Resulting Patient Counts: Diminishing Returns



CONCLUSIONS

Key Findings

- Six published ASCVD definitions used 202-637 distinct codes covering 3-13 conditions — variance compounds.
- Despite >3x more codes, the largest cohort had <2x patients — impact is driven by which codes, not how many.
- Only 31-37% of patients were shared across all 5 definitions, demonstrating that cohorts are not interchangeable.
- Data-driven CODEf selection is essential for research cohorts given the significant impact on health outcomes and endpoints.

Clinical Research Implications

- Researchers, regulators, and payers **expect** published, complete CODEfs and code lists for all RWR studies.
- While study needs ultimately determine final decisions, definition selection should be **informed by data** with transparent reporting to enable proper cross-study comparison.
- Publishing complete definitions supports the FDA's call for rigor in operational definitions for RWE-based regulatory decision-making.

LIMITATIONS

Patient overlap analysis based on PurpleLab® CLEAR Claims and MIMIC-IV; results may vary across other data sources.

Cross-cohort patient characteristic comparisons planned as next step.