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Reliability and Utility Of CACS = 0 To Exclude Coronary Plaque In Diverse Global Cohorts

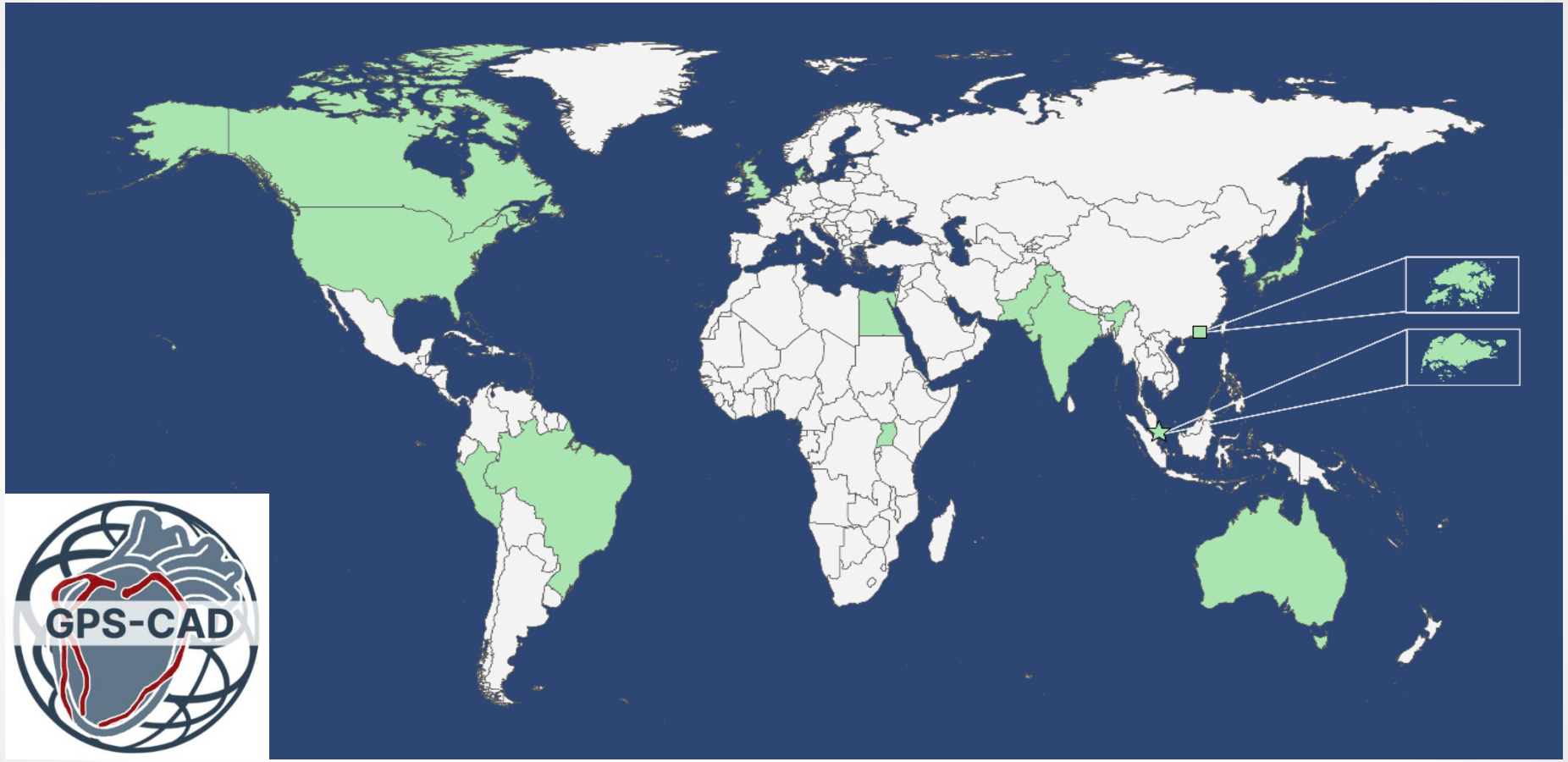
Lohendran (Logen) Baskaran,
National Heart Centre Singapore
Pamela S. Douglas,
Duke University
on behalf of GPS-CAD Investigators

AMERICAN COLLEGE of CARDIOLOGY

ACC, 28 March 2026

A report from the

GPS CAD: Global Probability Study of Coronary Artery Disease



Overall Aim: To collect real-world data on the global patterns and predictors of early-phase atherosclerotic coronary artery disease

Background – Race, Ethnicity + Country

- ‘Ancestry’ and ‘environment’ (social/cultural/geography) are well accepted, important determinants of health, including atherosclerotic coronary artery disease (ACAD). Yet, there is no clear consensus on how to quantify these concepts.
- GPS-CAD previously created an **amalgamated variable of [Race, Ethnicity + Country]** as a **surrogate** to estimate the influence of ancestry and environment in ACAD**.**

GPS-CAD previously found that:

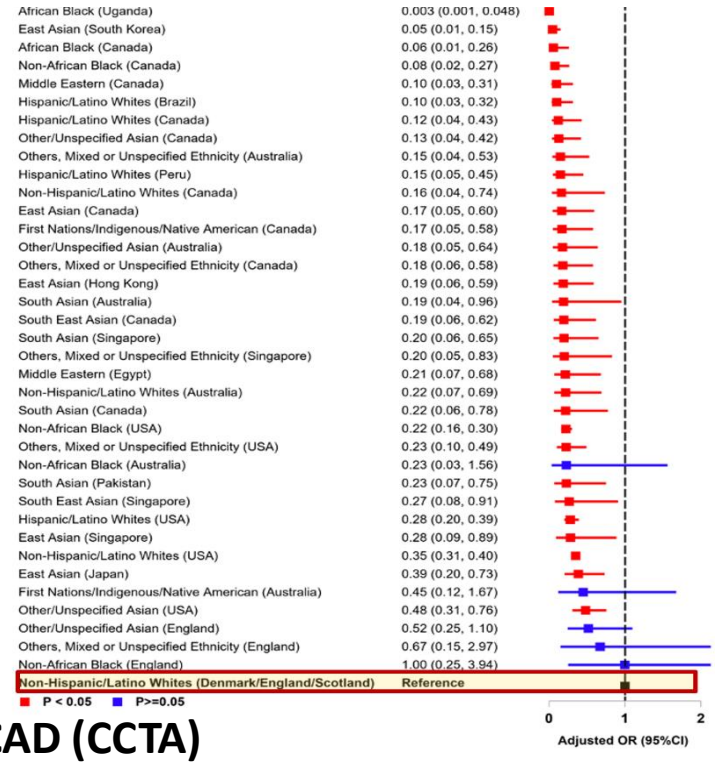
1. [Race/Ethnicity + Country] are **independent** and **important** determinants of ACAD presence and severity, beyond most traditional risk factors

2. [Race/Ethnicity + Country] is associated with varying prevalences of CAC +, plaque + and obstructive plaque (shown) phenotypes

1.

Variable	AUC Rank	AIC Rank
Age	1	1
Race/Ethnicity + Country	2	2
Sex	3	3
HTN	4	4
Study Design	5	5
Hyperlipidemia	6	6
DM	7	7
Symptom	8	8
Smoking Status	9	9
Family History	10	10
BMI	11	11

2.



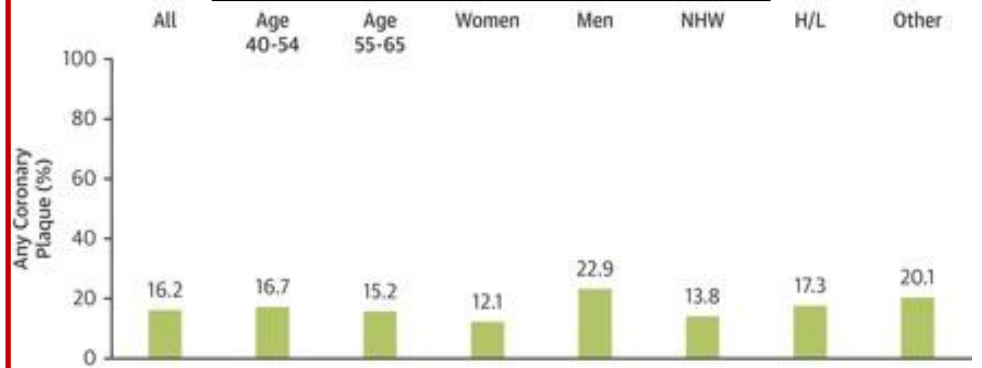
Obstructive CAD (CCTA)

Baskaran et al. Late-breaking presentation, ESC, 2024.

Background – Utility of CAC

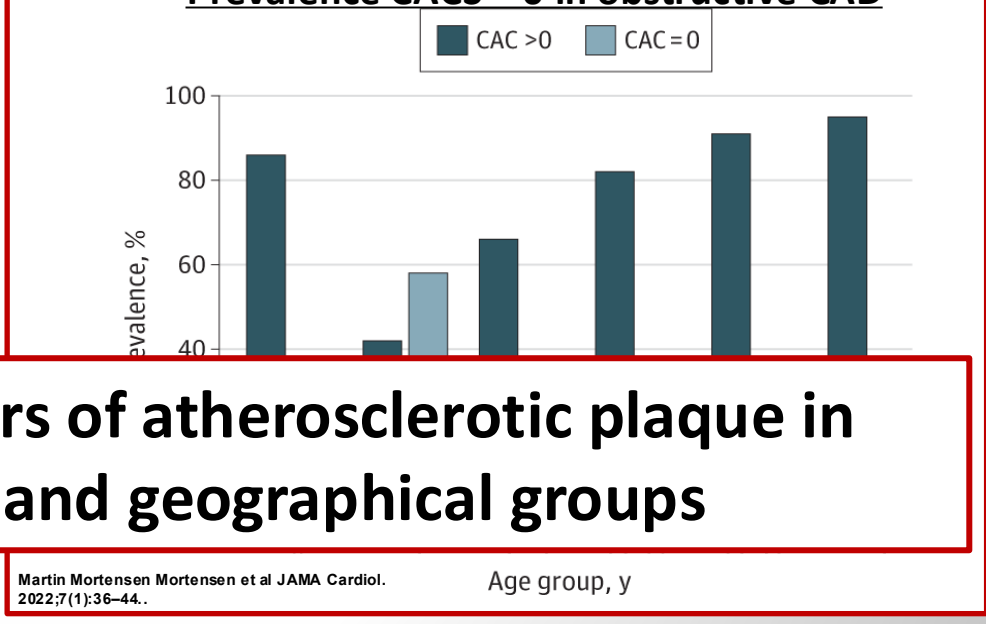
- Coronary artery calcification (CAC) is often used to screen for ACAD.
- However, ACAD may be present in 10-20% even with CACS = 0, due to non-calcified plaque.
- This is especially true in younger or more diverse race/ethnicity groups.
- There is insufficient knowledge regarding the presence of plaque in CACS = 0 in these diverse groups on a global level.

Prevalence of ACAD in CACS = 0



Khurram Nasir et al. *J Am Coll Cardiol Img* 2022; 15:1604-1618.

Prevalence CACS = 0 in obstructive CAD



Martin Mortensen Mortensen et al JAMA Cardiol. 2022;7(1):36–44..

Specific Aim: To assess the presence and predictors of atherosclerotic plaque in those with CACS = 0 in diverse racial, ethnic and geographical groups

Gulati et al. ACC Guidelines, JACC 2021. Vrints et al. ESC Guidelines, EHJ 2024.Winther et al, JACC 2022. Villines et al, JACC 2011. Mortensen et al, JAMA Cardiol 2022 ; Nasir et al, JACC: Cardiovascular Imaging 2022. Budoff et al, Circulation 2017. Manubolu et al, Atherosclerosis 2025.

Methods - Data set creation and phenotype definition

- The GPS-CAD real-world CT database encompassing **32,690 people in 15 countries** (22 populations) with simultaneous CCTA + CAC assessment performed to rule out ACAD
- **Endpoints for CAC study**
  1. **Coronary artery calcium score (CACS)**
  2. **Any plaque (CCTA)**
- Definitions of phenotypes based on test results were as follows:

Scan finding	CCTA plaque negative	CCTA plaque positive
CACS = 0 (negative)	True negative	False negative
CACS > 0 (positive)	False positive	True positive

- Statistical analysis
  - Co-variate relative importance determined by higher AUC
  - Multivariable models adjusted for: age, sex, body mass index, symptom, diabetes, hypertension, dyslipidemia, smoking, family history and originating study design (registry/trial/clinical)

Results (N=32,690; 15 countries; 22 populations)

Demographics and Risk Factors	
Age, yrs	59 (11)
Sex, Female	45%
Symptomatic	73%
Hypertension	49%
Dyslipidaemia	45%
Diabetes	16%
Family History	30%
Smoking History	14%
Race/Ethnicity	
Non-Hispanic/Latino White	39%
Hispanic/Latino White	29%
Black	5%
Asian	20%
Middle Eastern	4%
First Nation, Indigenous, Native American, Aboriginal, Pacific Islander, or Torres Strait Islander	1%
Others, Mixed, or Unspecified Ethnicity	2%
CT Endpoints	
CACS > 0	55%
Any plaque (CCTA)	60%
CAD (≥ 50% stenosis) (CCTA)	18%

Scan finding	CCTA –	CCTA +
CAC -	38.2% (12,525)	7.0% (2,282)
CAC +	1.4% (477)	53.1% (17,406)

Finding 1: [Race/Ethnicity + Country] is the strongest predictor of scan findings, including both False Negative and True Positive CAC, beyond all traditional risk factors.

False Negative CAC		
Rank	**Variables**	**AUC**
1	**Race/Ethnicity + Country**	**0.64**
2	Sex	0.57
3	Age	0.56
4	Study Design	0.54
5	Diabetes	0.54
6	Dyslipidemia	0.54
7	Hypertension	0.53
8	Body Mass Index	0.53
9	Smoking History	0.51
10	Family History of CAD	0.50

True Positive CAC		
Rank	**Variables**	**AUC**
1	**Race/Ethnicity + Country**	**0.84**
2	Age	0.62
3	Hypertension	0.56
4	Study Design	0.54
5	Sex	0.54
6	Diabetes	0.52
7	Smoking History	0.51
8	Symptom	0.51
9	Family History of CAD	0.51
10	Dyslipidemia	0.50

Finding 2a: The absolute prevalence and likelihood of Concordant/ Discordant CAC and CCTA results varies significantly by <u>country</u>

True Positive:
21% (Uganda) to 63% (USA)

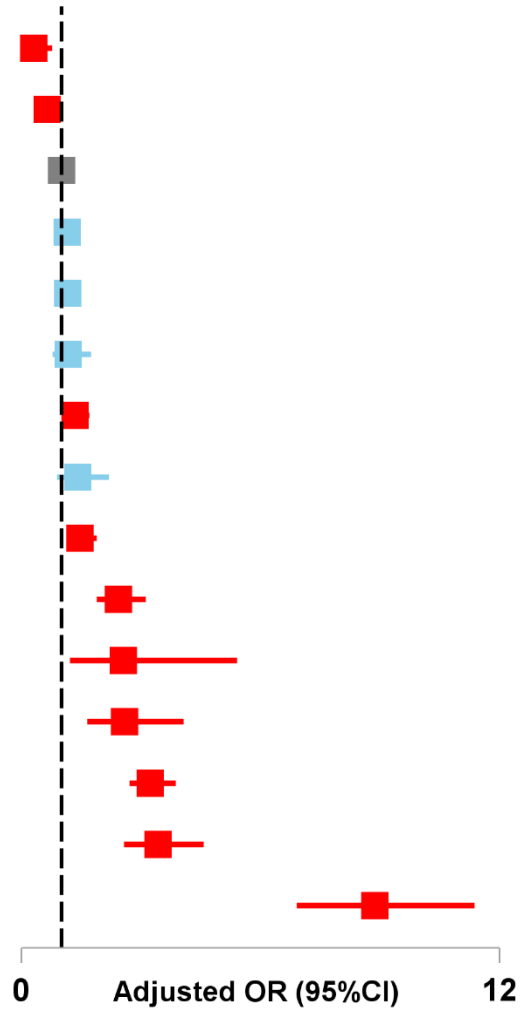
True Negative:
31% (USA) to 76% (Uganda)

False Negative:
2% (Uganda) to 28% (Egypt)

Finding 2b: Country is an *independent predictor* of the likelihood of a False Negative CAC scan

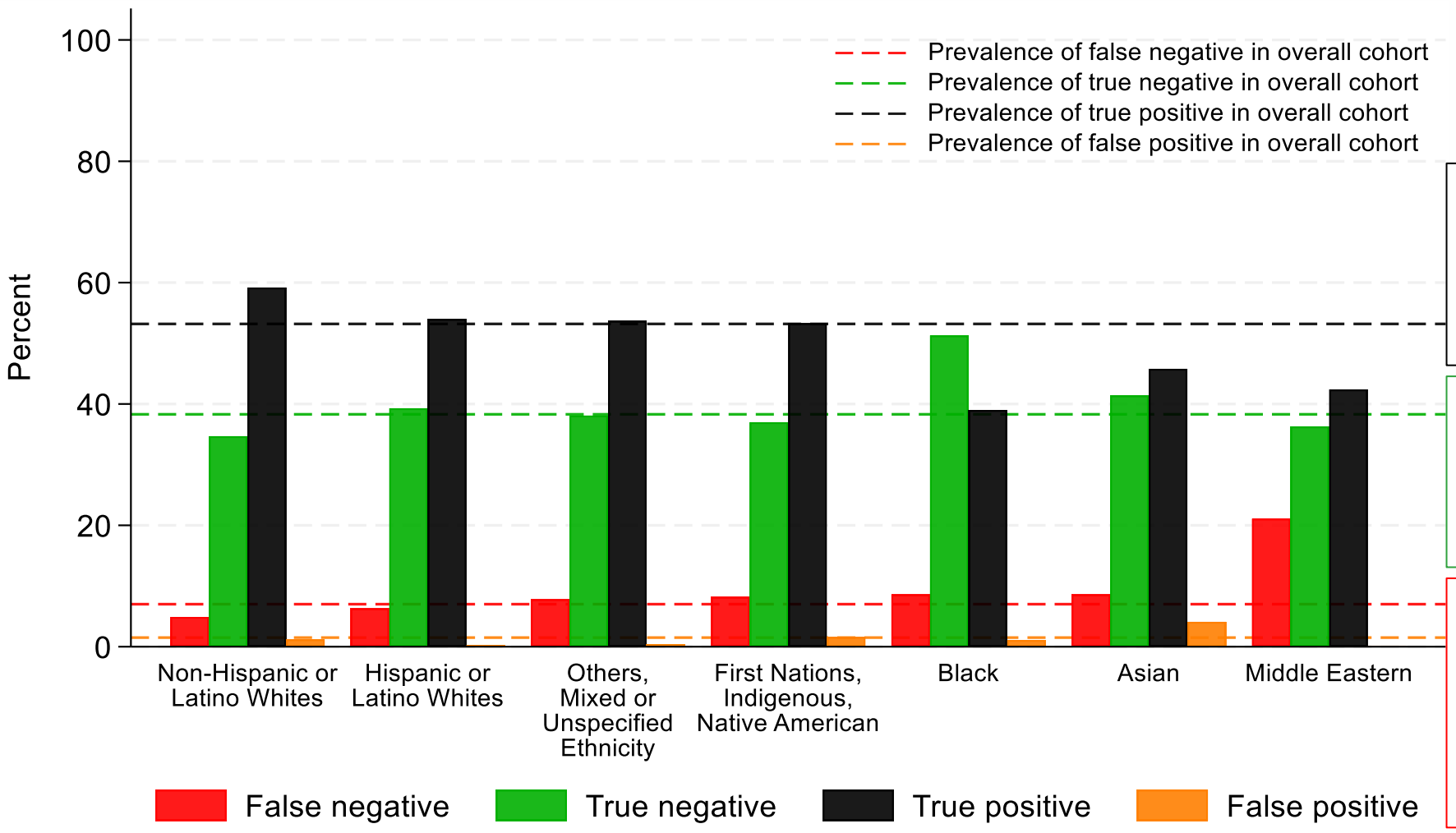
	Adjusted OR (95%CI)	NPV
Uganda	0.30 (0.12, 0.77)	0.855
Denmark	0.65 (0.53, 0.79)	0.910
USA	Reference	0.980
Scotland	1.14 (0.90, 1.44)	0.827
Brazil	1.16 (0.98, 1.38)	0.875
Hong Kong	1.17 (0.78, 1.75)	0.862
Australia	1.34 (1.05, 1.70)	0.864
South Korea	1.40 (0.90, 2.20)	0.907
Singapore	1.46 (1.13, 1.89)	0.841
India	2.42 (1.88, 3.12)	0.803
Japan	2.56 (1.21, 5.41)	0.869
Pakistan	2.59 (1.64, 4.07)	0.752
Canada	3.23 (2.70, 3.87)	0.717
Peru	3.43 (2.57, 4.58)	0.713
Egypt	8.86 (6.91, 11.37)	0.530

aOR 1.3x - 8.9x
vs USA reference



*covariates: age, sex, body mass index, symptom, diabetes, hypertension, dyslipidemia, smoking, family history, originating study design

Finding 3: The absolute prevalence of False Negative CAC scan results varies significantly by race/ethnicity



True Positive:
39% (Black) to 59% (Non-Hispanic/Latino Whites)

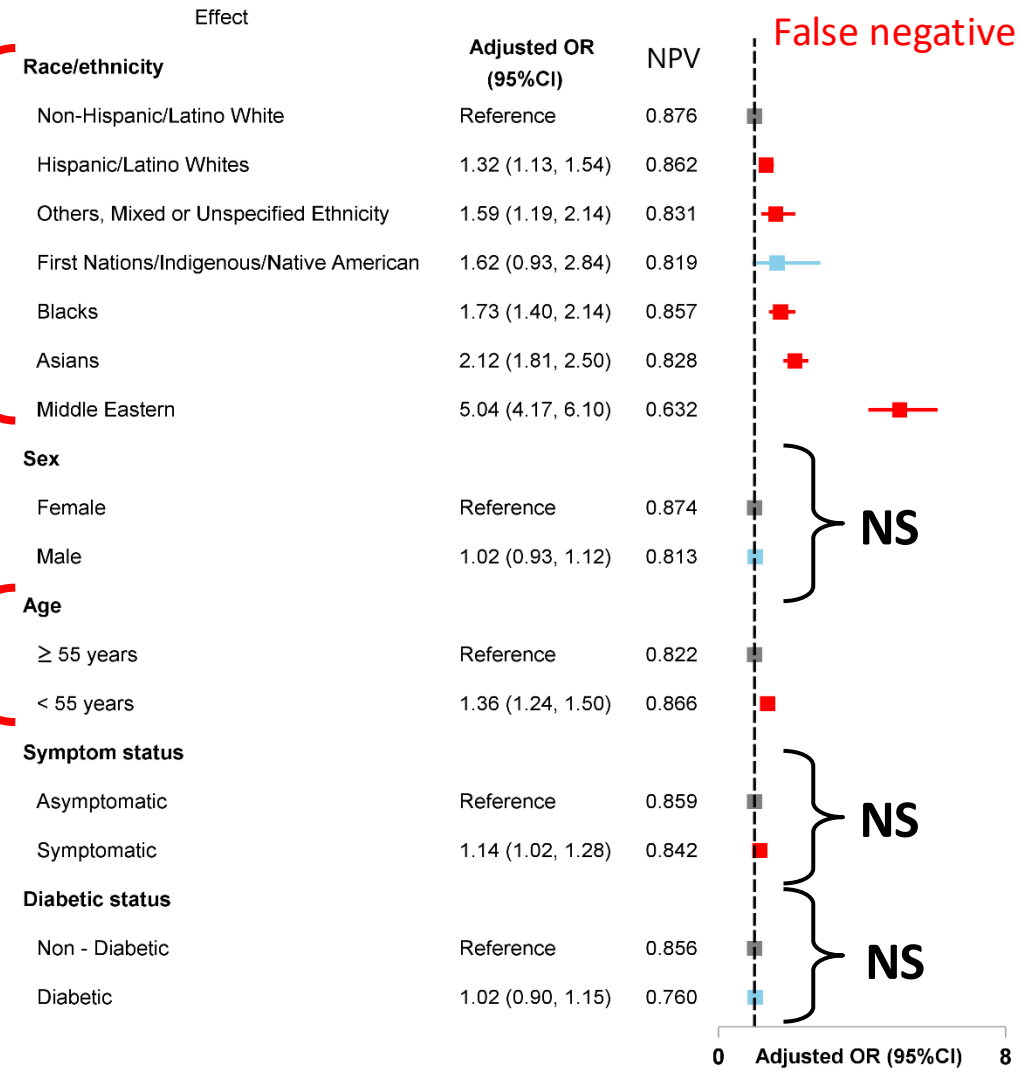
True Negative:
36% (Middle Eastern) to 51% (Black)

False Negative:
6% (Hispanic/Latino Whites) to 21% (Middle Eastern)

Finding 4: Race/ethnicity and age are *independent predictors* of the likelihood of a False Negative CAC scan

aOR 1.3x – 5.0x
vs Non-Hispanic/Latino White reference

aOR 1.4x
vs ≧55yrs



No independent differences in FN rates observed based on sex, symptom or diabetic status

Summary - 1

GPS-CAD created a large, global data base of 32,690 subjects across 22 diverse groups from 15 countries with simultaneous CAC and CCTA scans

We have previously shown that **[Race/Ethnicity + Country],** reflecting differences in ancestry, environment and other determinants, was an independent and important determinant of ACAD presence and severity

In the current analysis, we examined the utility of CAC to rule out, or to confirm, the presence of atherosclerotic coronary artery disease (ACAD), finding that:

1. [Race/Ethnicity + Country] is THE most important determinant of **False Negative (CAC-/CCTA+)** and **True Positive (CAC+/CCTA+)** ACAD phenotypes, beyond all traditional risk factors.

Summary - 2

2. False Negative findings (CAC-/CCTA+) varied widely by many factors.

3. However, only **country, race/ethnicity** and **age** were *independent predictors* of **False Negative** findings with:

Country: aORs 0.3x to 8.9x
Race/ethnicity: aORs 1.3x to 5.0x
Age: aOR 1.4x for <55 yrs

4. No independent differences were found based on **sex**, **symptoms** or **diabetes**.

Clinical impact: In patients with suspected ACAD, decision-making regarding the use of CAC or CCTA, and interpretation of CACS = 0 findings should consider race/ethnicity, country and age.

Simultaneous publication

ARTICLE IN PRESS

JACC Asia

ORIGINAL RESEARCH

Design and Rationale of GPS-CAD

Global Pretest Probability Study of Coronary Artery Disease

Lohendran Baskaran, MBBS,[a,b,c] Jeremy John Selva, BSc (Hons),[a] Anand Viren Ivan Mantri, BEng,[c] Pamela S. Douglas, MD,[d] GPS-CAD Investigators[a]

ABSTRACT

BACKGROUND Atherosclerotic coronary artery disease (ACAD) is a prevalent condition causing a significant number of deaths worldwide. Even though Asian and other non-Western regions are the main drivers of future increase, there are insufficient data on ACAD patterns in those regions. Pretest probability (PTP) tools developed to evaluate patients with stable chest pain for coronary artery disease were largely developed in predominantly White Western populations, limiting their application on a global scale.

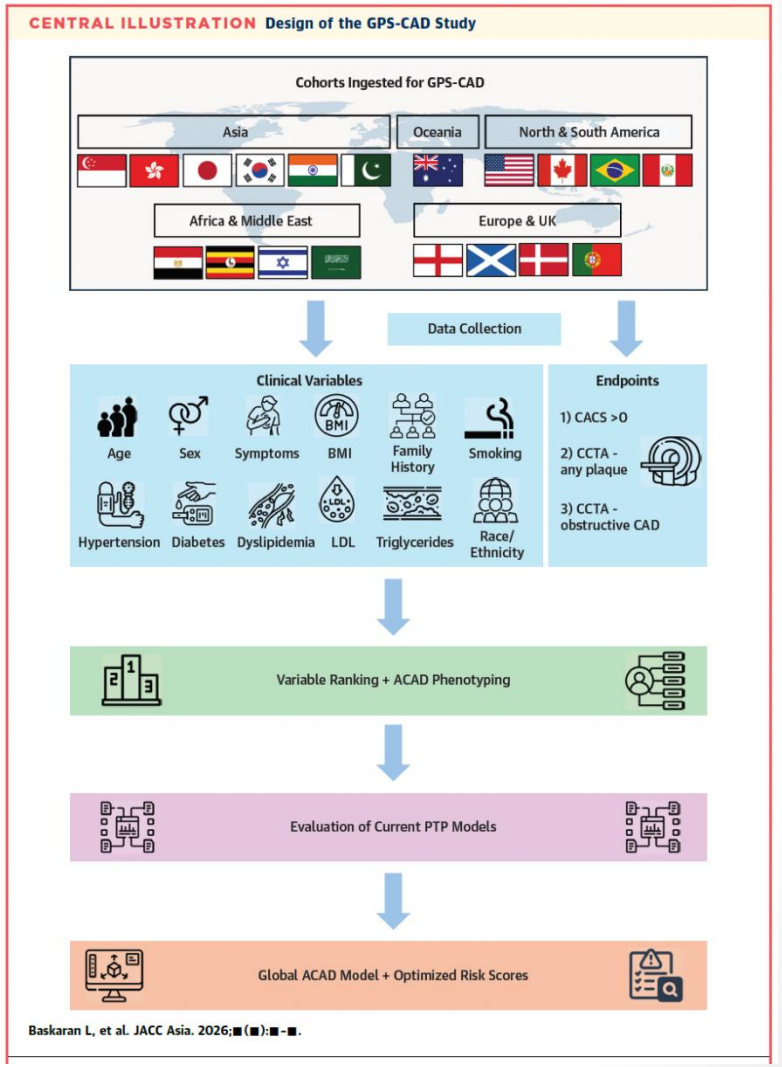
OBJECTIVES The aims of the Global Pretest Probability Study of Coronary Artery Disease (GPS-CAD) are to define the importance of ancestry, race, ethnicity and environment on ACAD patterns across diverse populations, evaluate current PTP tools and potentially create new algorithm(s) that are more aligned with a diverse global population.

METHODS GPS-CAD is a multicenter retrospective cross-sectional observational study of individuals referred for computed tomography owing to suspected ACAD. The target enrolment is 100,000 participants across 6 continents. Data on demographics, cardiovascular risk factors, race, ethnicity and medications will be collected. The primary endpoints of ACAD are defined as: 1) coronary artery calcium score >0; 2) any coronary plaque (>0% stenosis); or 3) obstructive CAD (≥50% stenosis).

RESULTS Data from more than 60,000 participants have been ingested thus far across 17 countries, with a mean age of 56.43 years and 41.55% female.

CONCLUSIONS By understanding the varying influence of factors and phenotypes of ACAD across diverse groups, GPS-CAD will facilitate the development of locally contextualized strategies to tackle this dominant and growing healthcare burden. (Global Pretest Probability Study of Coronary Artery Disease [GPS-CAD; NCT05722145])

(JACC Asia. 2026;■:■-■)



Organization Structure & Appreciation

Executive Committee

PI:	Lohendran Baskaran	Chair:	Pamela S. Douglas

Members	
Bon-Kwon Koo	Matthew J. Budoff
David E. Newby	Ming-Yen Ng
Jonathon A. Leipsic	Simon Winther
Leslee J. Shaw	

National Heart Centre Singapore (NHCS)

Leadership
Yeo Khung Keong
Terrance Chua Siang Jin
Derek J. Hausenloy
David S. Sim
Zhong Liang

Data operations
Jeremy J. Selva (CVS.AI)
Statistics
Fei Gao (NHCS)
Yilin Jiang (NHCS)
Rehena Sultana (Duke-NUS)

Regulatory
Florence Ng Swee Phyaw (RADO)
Project management
Jen-Yin Goh (CVS.AI)

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Working Groups

Protocol	
Chair	Simon Winther
Co-chair	Rodrigo J. Cerci
Members	Michelle C. Williams
	Ming-Yen Ng
	Zoe Nicholas

Analyses	
Co-chairs	Krishna K. Patel
	Borek Foldyna
Members	Rodrigo J. Cerci
	Seokhun Yang
	Simon Winther

Publications	
Chair	Jonathon A. Leipsic
Co-chair	Neha J. Pagidipati
Members	Marcio S. Bittencourt
	Matthew J. Budoff
	Ming-Yen Ng
	Mouaz H. Al-Mallah

GPS-CAD Sites and Contributors

Region	Country	Cohort or Institution Name	Contributors
Africa	Uganda	Epidemiology of Coronary Atherosclerosis among People Living with HIV in Uganda: A Cross-Sectional Study	Mark J. Siedner, Stephen Asiimwe, Brian Ghoshhajra, Samson Okello, Chris Longenecker, Geoffrey Erem, Rita Nassanga, Moses Acan, Ntobeko Ntusi, Alexander Tsai, Susanne Hoeppner
	Uganda	**U**gandan S**T**udy of H**I**V effects on the **M**yocardium and **A**therosclerosis (mUTIMA)	Chris T. Longenecker Cissy Kityo Geoffrey Erem
Asia	Hong Kong	The University of Hong Kong	Ming-Yen Ng Yueyi Xu
	India	All India Institute of Medical Sciences	Satyavir Yadav Ganesan Karthikeyan
	India	Kovai Medical Center and Hospital	Arunachalam Pudhiavan Sandeep S. Hedgire
	Japan	Toho University Omori Medical Center	Rine Nakanishi
	Korea	Seoul National University College of Medicine	Bon-Kwon Koo Seokhun Yang Su-Yeon Choi
	Pakistan	Aga Khan University	Fateh Ali Tipoo Zainab Samad
	Singapore	National Heart Centre Singapore	Lohendran Baskaran
Europe	Denmark	**Dan**ish study of **N**on-**I**nvasive testing in **C**oronary **A**rtery **D**isease (Dan-NICAD) 1, 2 & 3	Simon Winther Laust D. Rasmussen
	England	**F**ractional Fl**O**w **RE**serve Derived From Computed Tomography **C**oronary **A**ngiography in the Assessment and Management of **ST**able Chest Pain (FORECAST)	Nick Curzen Zoe Nicholas Mohamed Kira
	Portugal	Hospital de Santa Cruz, Centro Hospitalar de Lisboa Ocidental	Pedro M. Lopes António Ferreira Pedro Freitas Maria Rita Lima
	Scotland	**S**cottish **CO**mputed **T**omography of the **HEART** (SCOT-HEART)	David E. Newby Michelle C. Williams

Region	Country	Cohort or Institution Name	Contributors
Middle East	Egypt	Aswan Heart Centre	Mahmoud Shaaban Wesam Elmozy Mohamed Abdelfattah Rehab Elnagar
	Egypt	Misr Radiology Center	Sara W. Tantawy Ahmed Samir Basant M. Raief Sheif N. A. Hegazy
	Israel	Edith Wolfson Medical Center	Ronen Rubinshtein Aby Orbach Udi Nussinovitch
	Saudi Arabia	King Abdulaziz Medical City-Riyadh	Ahmed Aljizeeri
North America	Canada	University of Ottawa Heart Institute	Benjamin J. W. Chow Yeung Yam
	USA	Allina Health Minneapolis Heart Institute	Victor Y. Cheng Michael D. Miedema Larissa Stanberry
	USA	Cedars-Sinai Medical Center	Daniel Berman Heidi Gransar Rebekah Park
	USA	**PRO**spective **M**ulticenter **I**maging **S**tudy for **E**valuation of Chest Pain (PROMISE)	Pamela S. Douglas Neha Pagidipati Borek Foldyna Thomas Mayrhofer Michael T. Lu
	USA	UCLA Medical Centre	Matthew J. Budoff
Oceania	Australia	MonashHeart	Brian Ko Abdul Rahman Ihdayhid
	Australia	Royal Perth Hospital	Jonathan Spiro Adil Rajwani
South America	Brazil	Diagnósticos da América S.A.	Fernanda Erthal Flávia Paiva Lopes
	Brazil	Quanta Diagnóstico por Imagem	Rodrigo J. Cerci
	Peru	University of Cincinnati College of Medicine and Clínica Internacional (USA-Peru collaboration)	Moises A. Huaman Sara E. Ramirez-Flores Laura V. Medina-Rodriguez

SingHealth DukeNUS ACADEMIC MEDICAL CENTRE

National Heart Centre Singapore

CVS·AI Cardiovascular Systems Imaging and Artificial Intelligence

Funders and collaborators welcome

Email us: gps.cad@nhcs.com.sg

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gps.cad@nhcs.com.sg

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