REPRIEVE

Program for the Community
Thursday June 17th
11AM EDT

NIH National Heart, Lung, and Blood Institute

NIH National Institute of Allergy and Infectious Diseases

ACTG AIDS CLINICAL TRIALS GROUP

Kowa

GILEAD

ViiV Healthcare

Agenda

Time	Topic	Presenter
11:00 – 11:05AM	Welcome on Behalf of the REPRIEVE Team	Turner Overton, MD
11:05 – 11:10AM	REPRIEVE Trial Updates	Steve Grinspoon, MD Michael Lu, MD, MPH
11:10 – 11:15AM	Cardiovascular Risk and Health Assessments among PWH Eligible for Primary Prevention: Insights from the REPRIEVE Trial	Steve Grinspoon, MD
11:15 – 11:20AM	Coronary Artery Disease, Traditional Risk and Inflammation Among PWH in REPRIEVE	Michael Lu, MD, MPH
11:20 – 11:25AM	Diet Quality by Global Burden of Disease Region in PWH in the REPRIEVE Trial	Katie Fitch, MSN
11:25 – 11:35AM	Assessment of Obesity and Metabolic Profile by Integrase Inhibitor Use in REPRIEVE	Emma Kileel, MPH
11:35 – 11:50AM	Questions	Team

News from the Data Coordinating Center!

- Principal Investigator transition—Michael Lu, MD, MPH is the new Co-PI of the DCC.
  - Dr. Lu, has served as Co-Chair of the REPRIEVE Mechanistic Substudy (A5333s) since 2014 has now assumed the role of DCC Co-PI. Dr. Lu is replacing Dr. Udo Hoffmann.
  - Dr. Lu is a cardiovascular radiologist and Co-Director of the Massachusetts General Hospital Cardiovascular Imaging Research Center (CIRC).
  - He leads the REPRIEVE Cardiac CT core laboratory as well as several other studies involving cardiac CT and HIV.
  - Outside of work, Dr. Lu's twin school-age children keep him very busy!

What We Have Accomplished So Far

- REPRIEVE is fully enrolled! The population is:
  - diverse
  - representative of adults living with HIV worldwide
- Participant retention rates have been maintained!
  - Even during the pandemic
- We have published key data from baseline and are sharing our findings with the community.
  - Go to: https://www.reprievetrial.org/learnmore/reprieve-publications/
- We are collecting critical data on COVID-19 symptoms and experiences, biomarkers, and post COVID experience as well
- Mechanistic Substudy (A5333s) completed 2 year follow up visits!
  - Baseline data will be shared in a few minutes
- We continue to collect data on major adverse cardiovascular events—like heart attacks and strokes—moving toward the finish line…
- The Data Safety and Monitoring Board (DSMB) has not had any safety concerns to date.

Data and Safety Monitoring Board Meeting (DSMB)

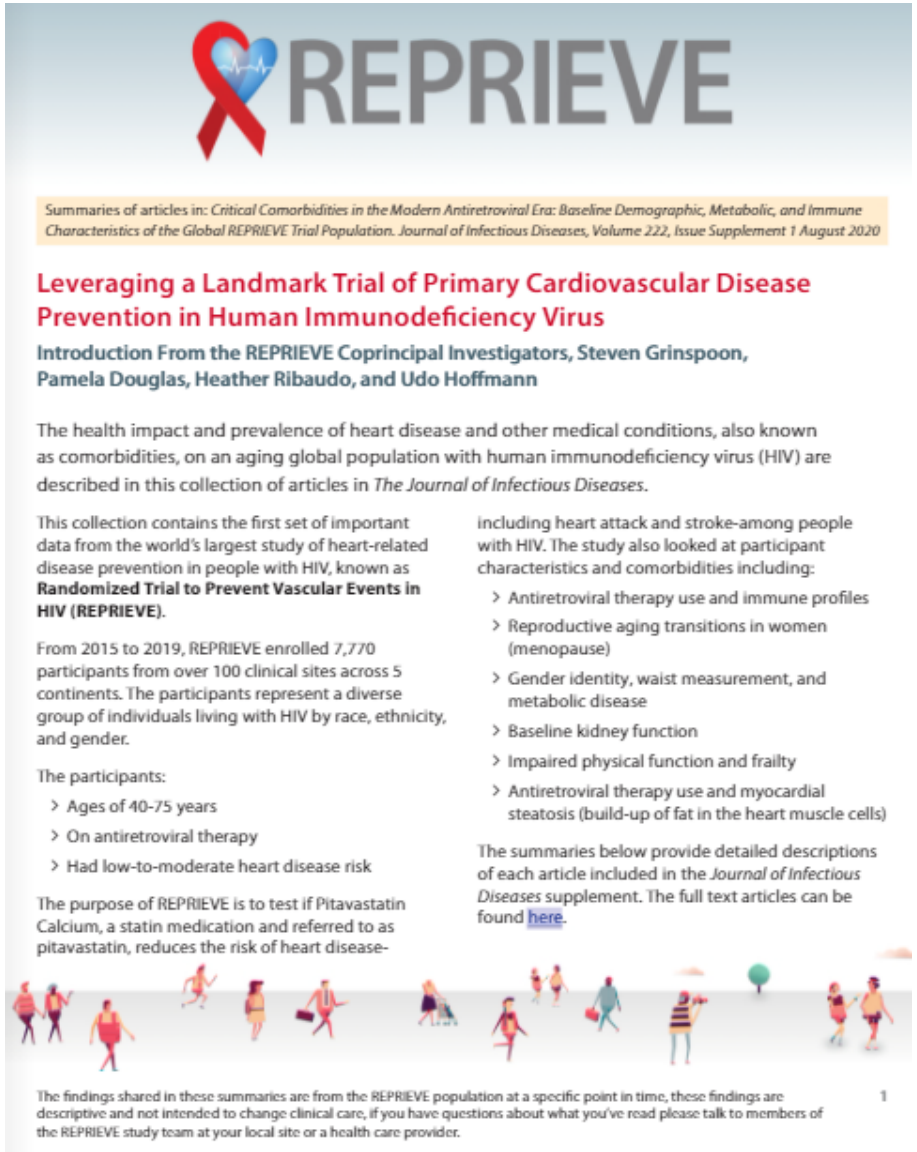
- We are excited to announce that the ***14th*** DSMB meeting will take place on September 21, 2021
- Why is this meeting important?
  - The DSMB will continue to look at safety and will begin its initial look at effects of the study treatment (pitavastatin) on heart disease.
  - All data that participants have contributed and that sites have collected thus far will be looked at by the DSMB.
    - ***Thank you all*** for helping REPRIEVE reach this important milestone!!!
  - If you are part of a REPRIEVE site team joining us today, please don't forget to pay attention to the DSMB timeline
    - *The next deadline is Friday, July 9th →all data for visits through June 25th are to be entered into OpenClinica.*

Did you know, ensuring REPRIEVE data is available is one of our top priorities?

- So far we have published 11 articles with broad authorship
- 2 articles will be published soon
- 8 abstracts have been presented at conferences such as:
  - Conference on Retroviruses and Opportunistic Infections (CROI)
  - International AIDS Society (IAS)
  - Association of Nurses in AIDS Care (ANAC)
  - International Association of Clinical Research Nurses (IACRN)

To stay up to date with our publications, visit our website at:

https://www.reprievetrial.org/learnmore/reprieve-publications/



REPRIEVE

Summaries of articles in: *Critical Comorbidities in the Modern Antiretroviral Era: Baseline Demographic, Metabolic, and Immune Characteristics of the Global REPRIEVE Trial Population. Journal of Infectious Diseases, Volume 222, Issue Supplement 1 August 2020*

Leveraging a Landmark Trial of Primary Cardiovascular Disease Prevention in Human Immunodeficiency Virus

Introduction From the REPRIEVE Coprincipal Investigators, Steven Grinspoon, Pamela Douglas, Heather Ribaudo, and Udo Hoffmann

The health impact and prevalence of heart disease and other medical conditions, also known as comorbidities, on an aging global population with human immunodeficiency virus (HIV) are described in this collection of articles in *The Journal of Infectious Diseases*.

This collection contains the first set of important data from the world's largest study of heart-related disease prevention in people with HIV, known as **Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE)**.

From 2015 to 2019, REPRIEVE enrolled 7,770 participants from over 100 clinical sites across 5 continents. The participants represent a diverse group of individuals living with HIV by race, ethnicity, and gender.

The participants:

- Ages of 40-75 years
- On antiretroviral therapy
- Had low-to-moderate heart disease risk

The purpose of REPRIEVE is to test if Pitavastatin Calcium, a statin medication and referred to as pitavastatin, reduces the risk of heart disease-including heart attack and stroke-among people with HIV. The study also looked at participant characteristics and comorbidities including:

- Antiretroviral therapy use and immune profiles
- Reproductive aging transitions in women (menopause)
- Gender identity, waist measurement, and metabolic disease
- Baseline kidney function
- Impaired physical function and frailty
- Antiretroviral therapy use and myocardial steatosis (build-up of fat in the heart muscle cells)

The summaries below provide detailed descriptions of each article included in the *Journal of Infectious Diseases* supplement. The full text articles can be found here.

The findings shared in these summaries are from the REPRIEVE population at a specific point in time, these findings are descriptive and not intended to change clinical care, if you have questions about what you've read please talk to members of the REPRIEVE study team at your local site or a health care provider.

1

We also have short summaries of many of our publications on the REPRIEVE website!

Cardiovascular Risk and Health Assessments among PLWH Eligible for Primary Prevention: Insights from the REPRIEVE Trial

Steve Grinspoon, MD
on behalf of the CV risk writing team

Accepted for publication in Clinical Infectious Diseases!

Background

- PWH are at 1.5 to 2 times the risk for heart disease, beyond traditional risk factors (like high cholesterol, high blood pressure etc.)
- As PWH live longer, co-morbidities like heart disease are becoming more prevalent
- Unique factors including inflammation/immune activation, uncontrolled viremia, ART, metabolic dysregulation, social determinants of health, may be contributing to additional risk in the setting of HIV
- Understanding these unique factors is essential so that we can better modify risks
- **AIM:** To assess heart disease risk and heart health in PLWH and determine their interrelationships

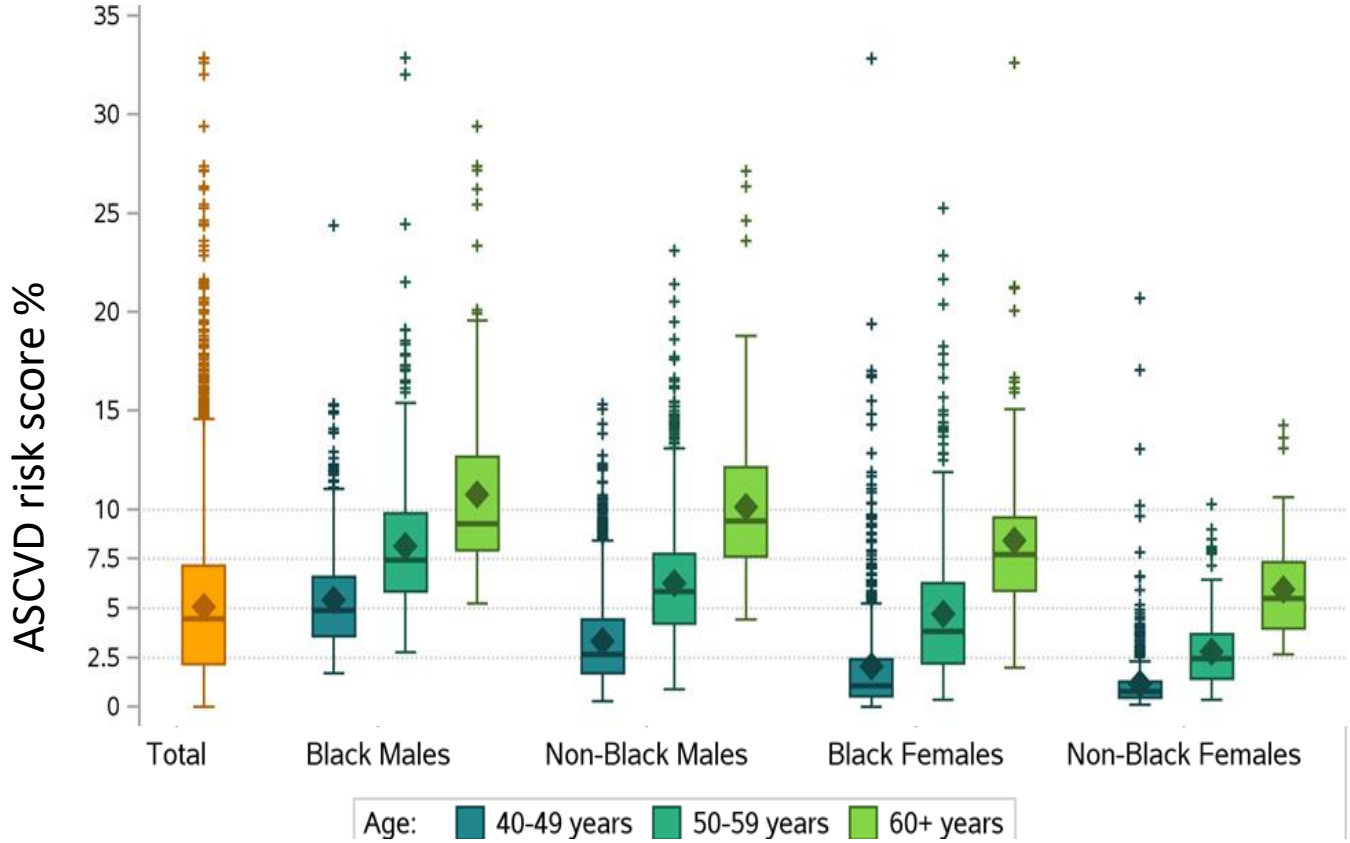
What We Did

- 7382 of the 7770 REPRIEVE participants were included in this analysis
- In our analysis we looked at entry fasting cholesterol levels, heart disease risk, medications, and lifestyle behaviors, including diet and physical activity assessments using REAP (Rapid Eating and Activity Assessment for Patients Questionnaire)
- A 10-year heart disease risk prediction score was calculated at entry→ this score is referred to as the *10-year ASCVD risk score*.
  - Age, sex at birth, race, blood pressure, cholesterol levels and history of diabetes and treatment for high blood pressure are used to calculate the score
- We then characterized lifetime heart health using the American Heart Association's **Life's Simple 7**, referred to as LS7.
  - 4 health behaviors: smoking, diet, exercise, and obesity
  - 3 health factors: blood pressure, total cholesterol, and glucose
  - Each behavior or factor was rated as poor, moderate or ideal and scored 0, 1 or 2
  - Possible scores range 0-14

Want to check your Life's Simple 7?
Go to: https://www.heart.org/en/healthy-living/healthy-lifestyle/my-life-check--lifes-simple-7

Results: Heart Disease Risk

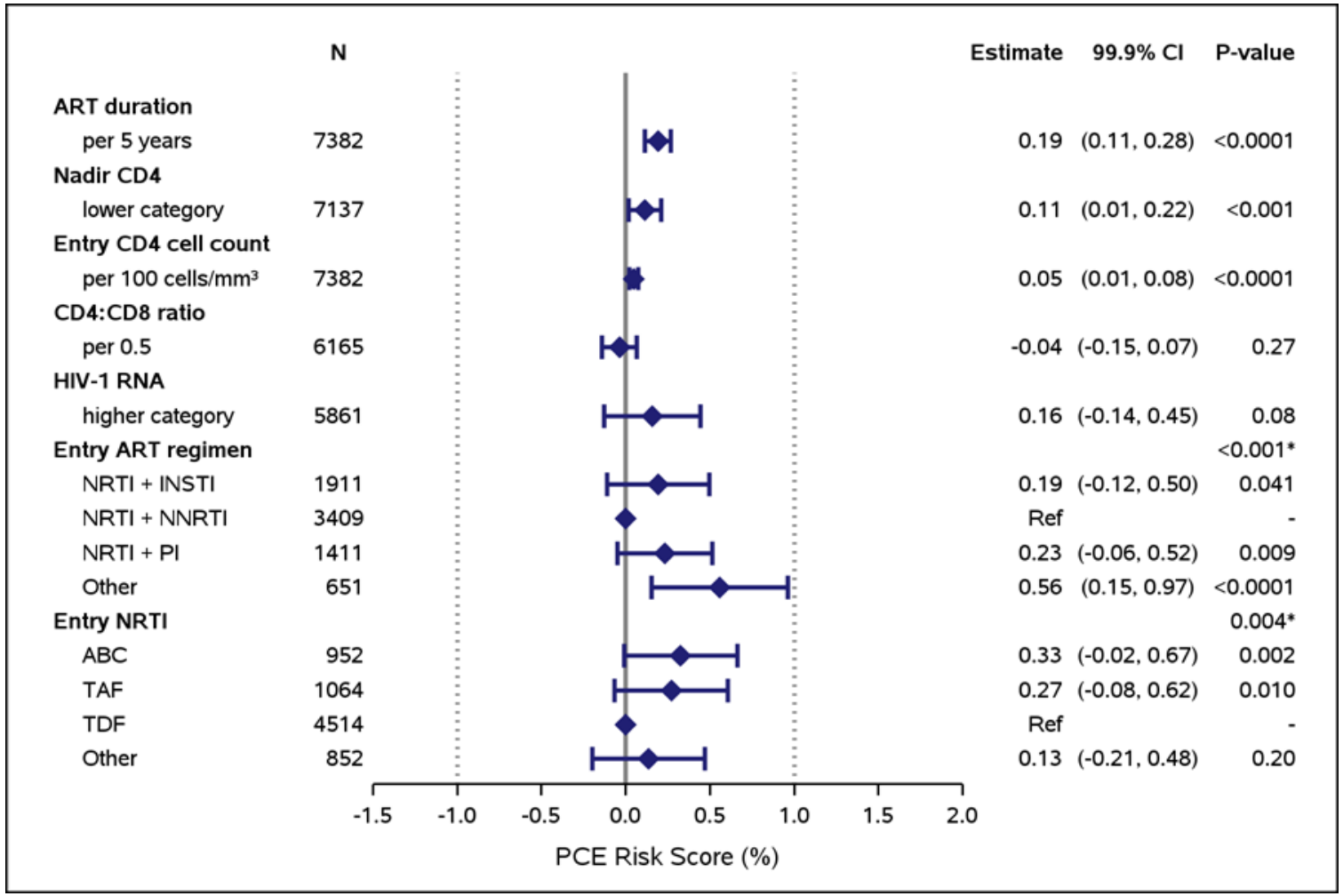
- Median ASCVD risk score: 4.5% (Q1, Q3: 2.2, 7.2)
- Heart disease risk factor increases with age
- Other factors also increased from lowest to highest ASCVD risk score category
  - Depression 25 →35%
  - Metabolic syndrome 18→41%
  - Waist circumference 90→95cm



REPRIEVE

Results: Heart Disease Risk, HIV Characteristics & ART

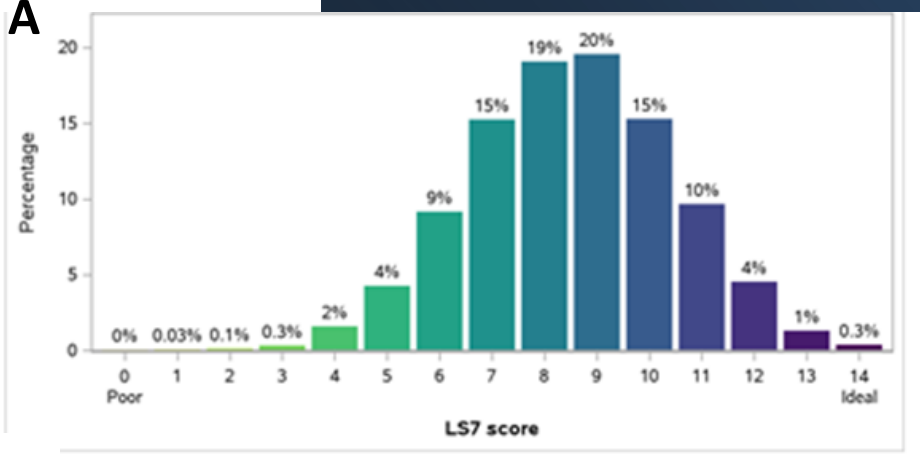
- Higher ASCVD was only modestly associated with HIV and ART characteristics. Most significant associations with:
  - Longer ART duration
  - Lower nadir CD4
- ***All effect sizes were very small***
  - Upper bound of 99.9% CI→ <1% diff

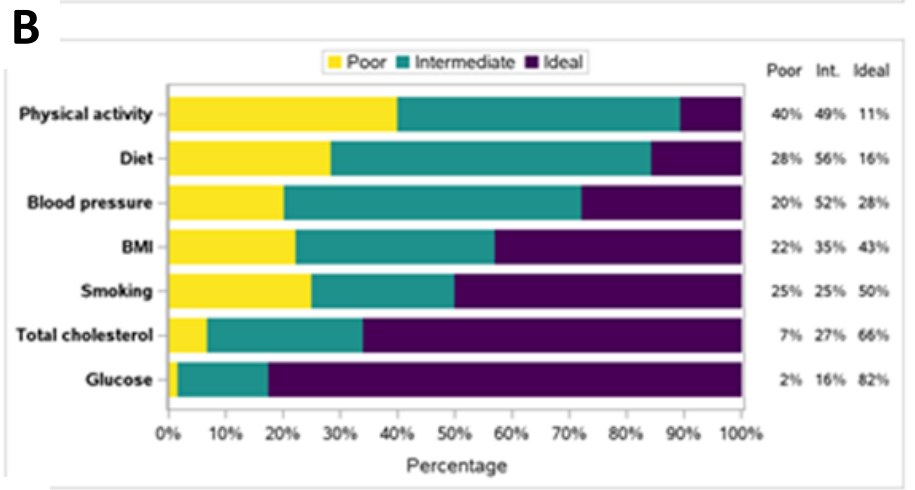


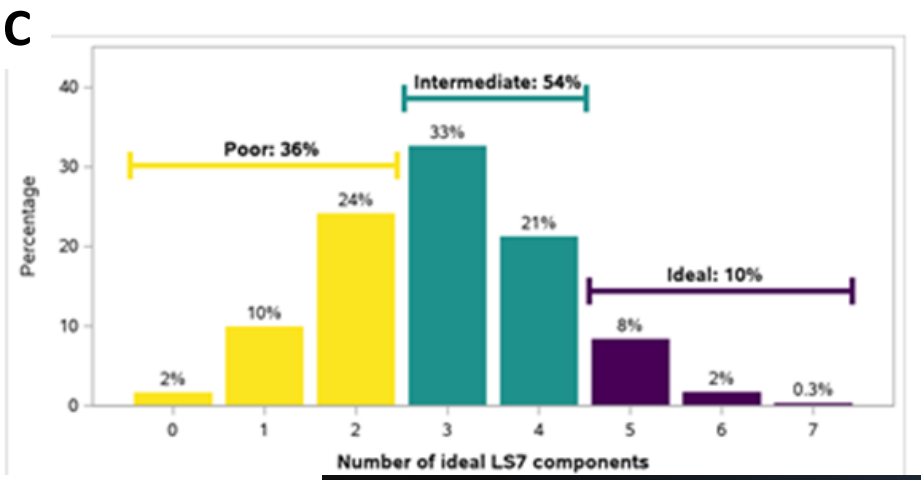
REPRIEVE

Results: Life's Simple 7 (LS7)

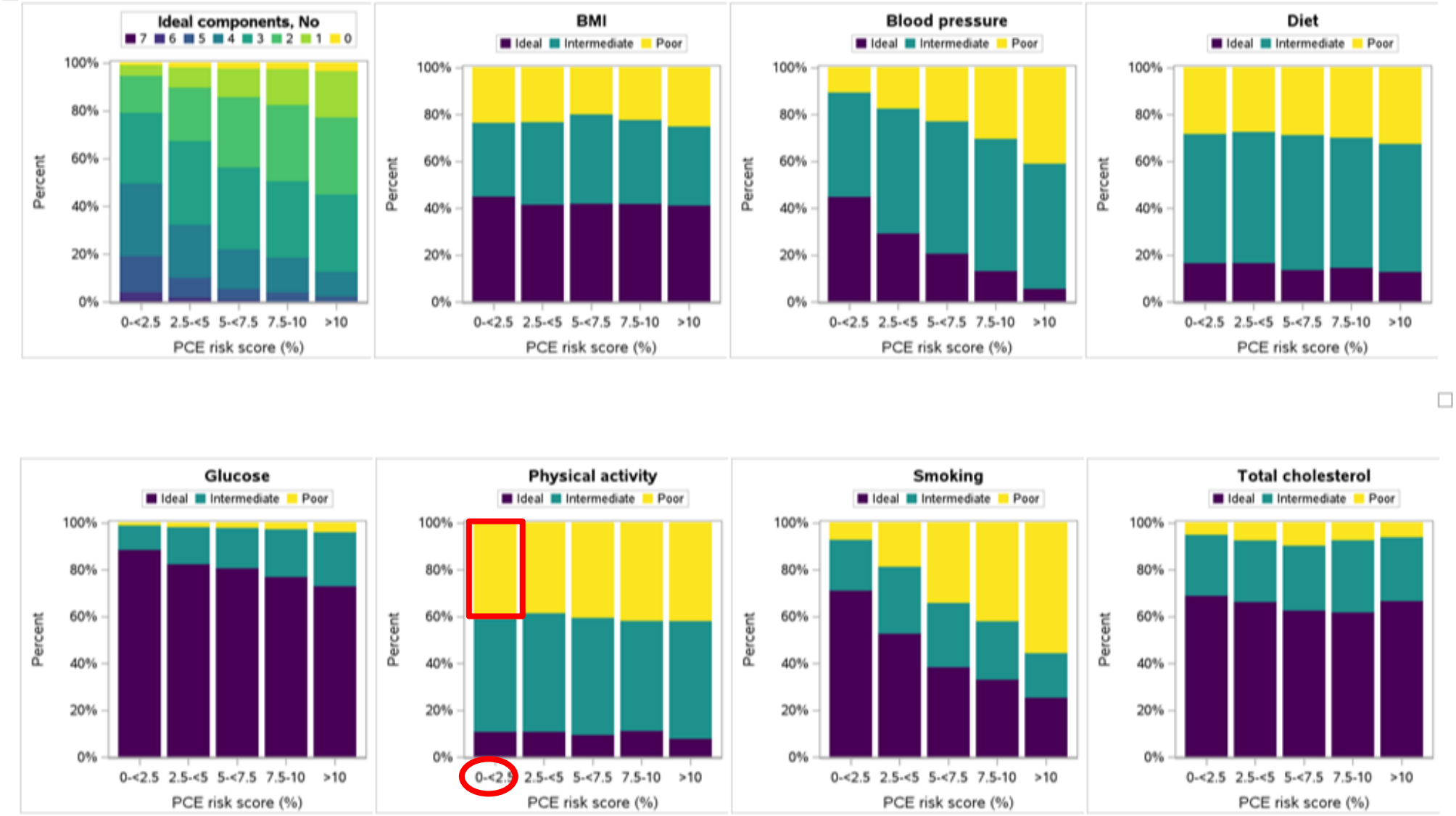
- Median LS7 score was 9 (range 0-14) **(Figure A)**
- Lifestyle components were most likely to be categorized as "poor" included:
  - Physical activity, diet, smoking, body mass index and blood pressure **(Figure B)**
- Only 10% of participants had 'ideal' heart health **(Figure C)**







Results: Unhealthy lifestyle behaviors seen even among participant's low traditional risk



Summary and Conclusions

- Among 7382 REPRIEVE trial participants, heart disease risk and heart health assessments showed:
  - 10-year heart disease risk was aligned with demographics and traditional risk factors and was weakly related to HIV characteristics or specific ART use
  - Ideal heart health was rare, with a high burden of adverse behaviors, including poor diet, high BMI and low physical activity.
  - Adverse lifestyle behaviors were common even in the lowest heart disease risk groups.
- In the future, REPRIEVE will assess how well the ASCVD risk score and lifestyle-based behavior assessment algorithms predict incident CVD over time in PLWH and will help to determine the optimal risk/health stratification system in this population.

Coronary Artery Disease, Traditional Risk and Inflammation Among PLWH in REPRIEVE

Michael Lu, MD, MPH
on behalf of the CAD writing team

In Press

Data were presented at CROI 2021

Background and Study Objective

Introduction

- Heart disease is increased among PLWH, in young asymptomatic individuals, with lower traditional heart disease risk factors.
- The Mechanistic Substudy (A5333s) is designed to assess effects of this strategy on plaque and key inflammatory and immune biomarkers.

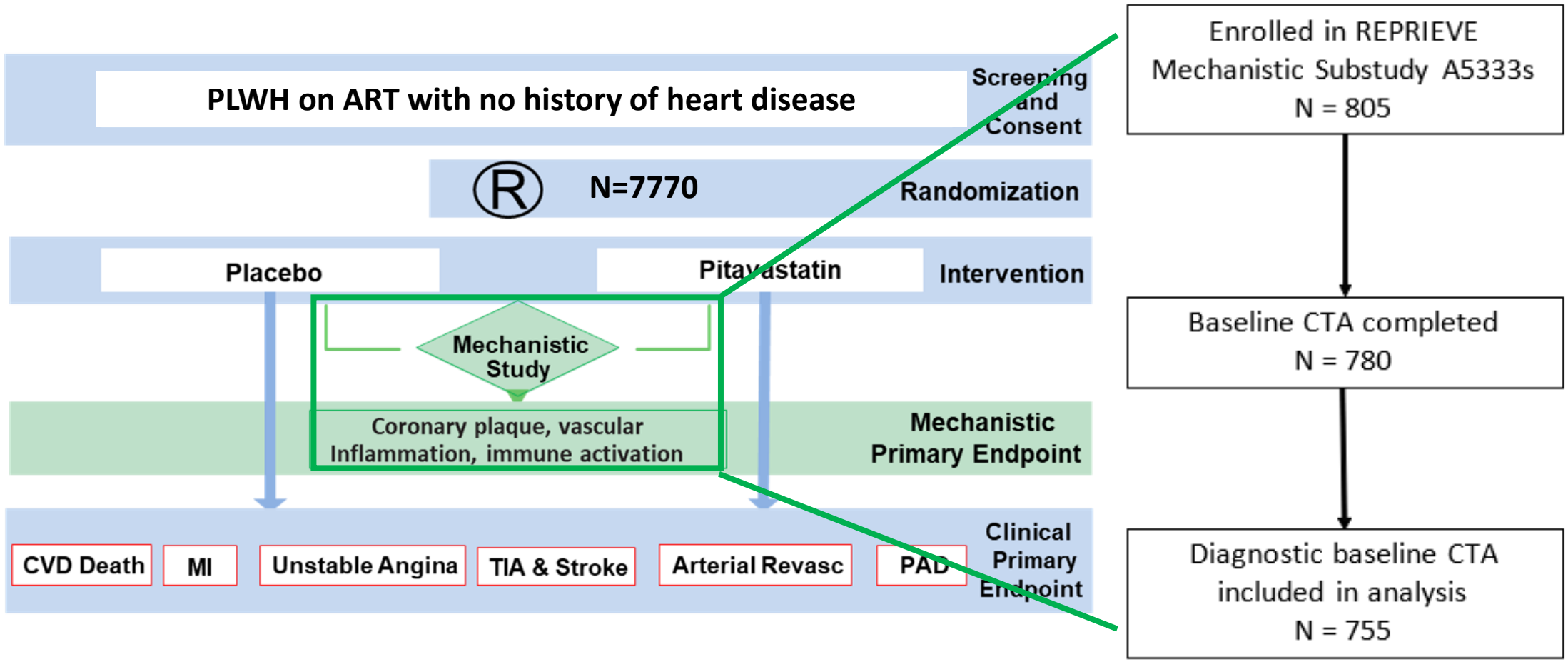
Study Objective

- Compare coronary plaque features: presence of plaque, significant stenosis (narrowing), coronary artery calcium (CAC), and vulnerable plaque across heart disease risk strata (ASCVD risk score).
- Compare key biomarkers by coronary plaque characteristics in univariate and multivariate modelling
  - Immune activation: sCD14, sCD163, MCP-1, IL-6,
  - Inflammation: Lp-PLA2, oxLDL, hsCRP

Hypothesis

- Coronary plaque will be prevalent among PLWH with low traditional risk and relate strongly to key immune and inflammatory biomarkers, suggesting the importance of these pathways in plaque development and as targets for prevention strategies.

Methods



Grinspoon, AHJ 2019

Participants

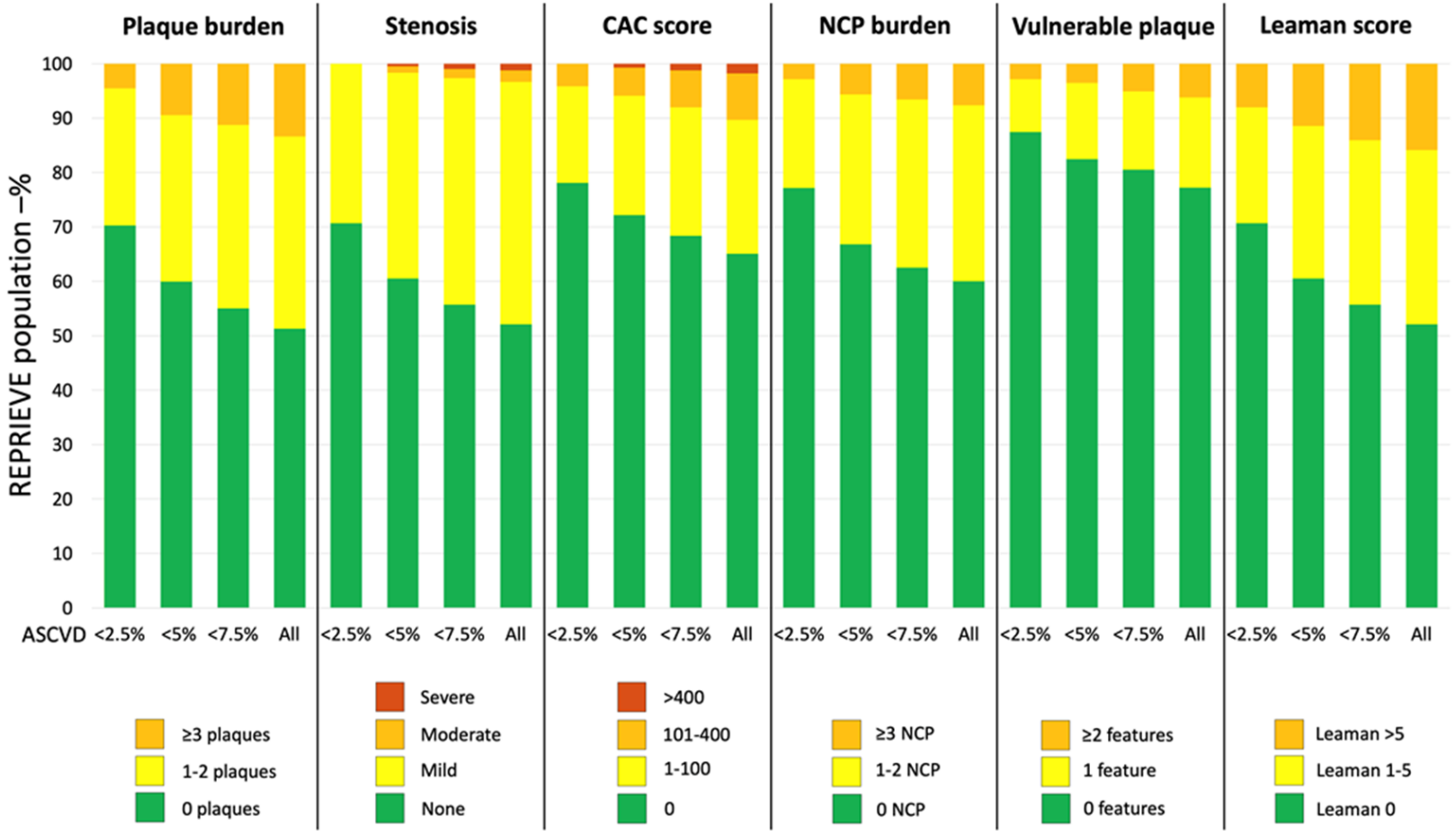
Characteristic –n (%), mean±SD, or median[25%–75%]	Substudy participants with CT results (N=755)
Demographics and behavioral	
Age –years	51±6
Women	124 (16)
Non White	349 (46)
Hispanic or Latino	182 (24)
Cardiovascular and metabolic	
ASCVD risk score –%	4.5 [2.6–6.8]
0–2.5	175 (23)
2.5–5	247 (33)
5–10	286 (38)
>10	47 (6)

HIV-related health at REPRIEVE entry	
Entry CD4 count –cells/mm^3	
<350	112 (15)
350–499	148 (20)
≥500	495 (66)
Entry HIV-1 RNA	
<LLQ	658 (88)
LLQ<400	71 (10)
LLQ>400	16 (2)
Entry ART regimen (by class)	
NRTI + INSTI	335 (44)
NRTI + NNRTI	196 (26)
NRTI + PI	127 (17)
NRTI-sparing	22 (3)
Other NRTI-containing	75 (10)

LLQ = lower limit of quantitation

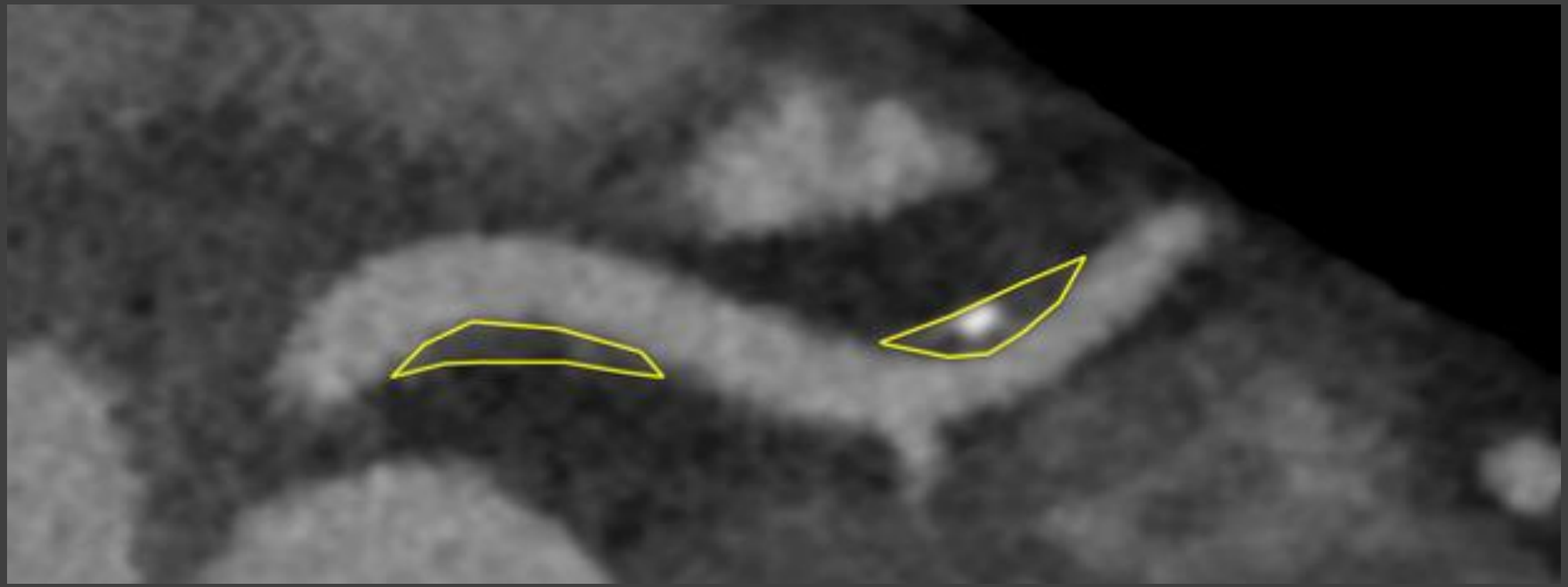
Results

Plaque increases with ASCVD risk, even among those in the low-risk range



- Overall
  - 49% with plaque
  - 35% CAC>0
  - 23% vulnerable plaque

- ASCVD Risk <2.5%
  - 30% with plaque
  - 22% CAC>0
  - 13% vulnerable plaque



REPRESENTATIVE CORONARY CT ANGIOGRAPHY (CTA)

46-year-old male with HIV with 10-year ASCVD risk of 6.6%. Baseline CTA with predominantly noncalcified plaques in the left anterior descending coronary artery (yellow outline).

RESULTS

- Key biomarkers were increased in those with plaque and remained significant in relationship to plaque, controlling for ASCVD risk score and HIV factors
- Relationship most robust for LpPLA2

	Multivariate Model 3***		
	aOR	95%CI	p-value
Biomarker#			
MCP-1	1.10	1.00 - 1.21	0.047
IL-6	1.06	1.01 - 1.11	0.025
LpPLA2	1.18	1.09 - 1.26	<0.001
oxLDL	1.07	0.97 - 1.18	0.176
ASCVD risk	1.16	1.10 - 1.22	<0.001
Total ART Use duration (years)			
<5	Base		
5-10	0.84	0.51 - 1.37	0.478
>10	1.03	0.65 - 1.62	0.904
CD4			
<350	Base		
350-499	0.83	0.49 - 1.42	0.504
≥500	0.97	0.60 - 1.57	0.906
Nadir CD4			
<50	Base		
50-199	0.62	0.40 - 0.96	0.033
200-349	0.72	0.45 - 1.14	0.160
≥350	0.69	0.40 - 1.16	0.163
Unknown	0.54	0.21 - 1.40	0.204

–n/N (%), mean±SD, or median [25%–75%]	Any Plaque (PL)		
	No PL N=387 (51.3%)	PL present N=368 (48.7%)	p-value
Inflammation & Immune Activation Biomarkers			
Insulin –uIU/mL	6.7 [4.4–11.7]	6.8 [4.7–11.8]	0.292
sCD14 –ng/mL	1838 [1549–2188]	1786 [1468–2176]	0.178
sCD163 –ng/mL	839 [615–1107]	842 [628–1087]	0.668
MCP-1 –pg/mL	180 [139–229]	194 [155–252]	<0.001
IL-6 –pg/mL	1.45 [0.96–2.60]	1.71 [1.05–3.04]	0.008
LpPLA2 –ng/mL	120 [85–157]	136 [103–177]	<0.001
oxLDL –mU/L	50.4 [40.4–64.2]	56.6 [45.0–73.3]	<0.001
hsCRP categories			0.172
Lower risk <1.0	121/380 (31.8)	98/362 (27.1)	
Average risk 1.0–3.0	155/380 (40.8)	146/362 (40.3)	
Higher risk 3.1–10.0	80/380 (21.1)	81/362 (22.4)	
Highest risk >10.0	24/380 (6.3)	37/362 (10.2)	

Summary

- Coronary artery plaque (49%), CAC (35%) and vulnerable plaque (23%) are prevalent among PLWH with low-to-moderate traditional heart disease risk.
  - Severe stenosis is rare.

- Markers of innate immune activation and inflammation were significantly higher among those with coronary plaque. These markers, were significantly associated with plaque characteristics, controlling for traditional heart disease risk and HIV indices.

Conclusion

- PLWH, eligible for primary heart disease prevention, with low ASCVD risk scores, have a unique plaque phenotype with increased overall plaque, which relates strongly and independently to markers of innate immune activation and arterial inflammation.

- REPRIEVE will test the effects of statin therapy to reduce plaque and inflammatory indices in this population.

Diet Quality by Global Burden of Disease Region in PLWH in the REPRIEVE Trial

Katie Fitch, MSN

on behalf of the diet quality writing team

Data were presented at CROI 2021

Background

- People living with HIV (PLWH) experience aging-associated comorbidities, including cardiovascular disease (CVD), at rates higher than the general population.

- Optimizing modifiable factors, such as diet, may delay onset or improve aging-associated comorbidities.

Study Objective

- To explore diet quality across a global cohort of PLWH and its association with demographics, clinical characteristics and risk factors.

Methods

- Cross-sectional analysis, 7736 participants who completed the Rapid Eating Assessment for Participants (REAP) questionnaire at entry.
- An overall REAP Score was generated.
- ***Higher REAP score represents more optimal diet quality.***
- Findings were summarized by Global Burden of Disease (GBD) super-region.
- Adjusted linear regression analyses were performed to examine differences in diet by key covariates..

REAP sample question			
***In an average week how often do you*, add butter, margarine or oil to bread, potatoes, rice or vegetables at the table?**	**Usually/often (0)**	**Sometimes (1)**	**Rarely/Never (2)**

Demographic and Clinical Characteristics

		Global Burden of Disease (GBD) Super Region				
Characteristic[1]	**Total (N=7736)**	**High Income (N=4065)**	**Latin America & Caribbean (N=1421)**	**S. East/ East Asia (N=590)**	**South Asia (N=504)**	**sub-Saharan Africa (N=1156)**
Age (years)	50 (45-55)	51 (46-55)	50 (45-55)	47 (44-52)	47 (44-52)	49 (44-54)
Natal sex female, n (%)	31%	21%	28%	56%	26%	58%
Race, n (%)						
Black or African American	43%	41%	38%	0%	0%	100%
White	35%	53%	38%	0%	0%	0%
Asian	15%	1%	0%	100%	100%	0%
Other	7%	5%	24%	0%	0%	0%
Alcohol use (Rarely/Never), n (%)	75%	73%	76%	73%	95%	73%
ASCVD risk score (%)	5 (2-7)	5 (3-8)	4 (3-7)	2 (1-4)	3 (1-5)	4 (1-7)
BMI (kg/m^2)	25.8 (22.7-29.4)	26.8 (23.9-30.6)	25.8 (23.3-28.6)	22.7 (20.5-25.0)	22.9 (20.2-25.9)	24.7 (21.2-29.6)
Total ART use >10 years, n (%)	48%	56%	33%	70%	31%	36%
CD4 count >500 cells/mm^3 n (%)	68%	67%	72%	72%	62%	64%

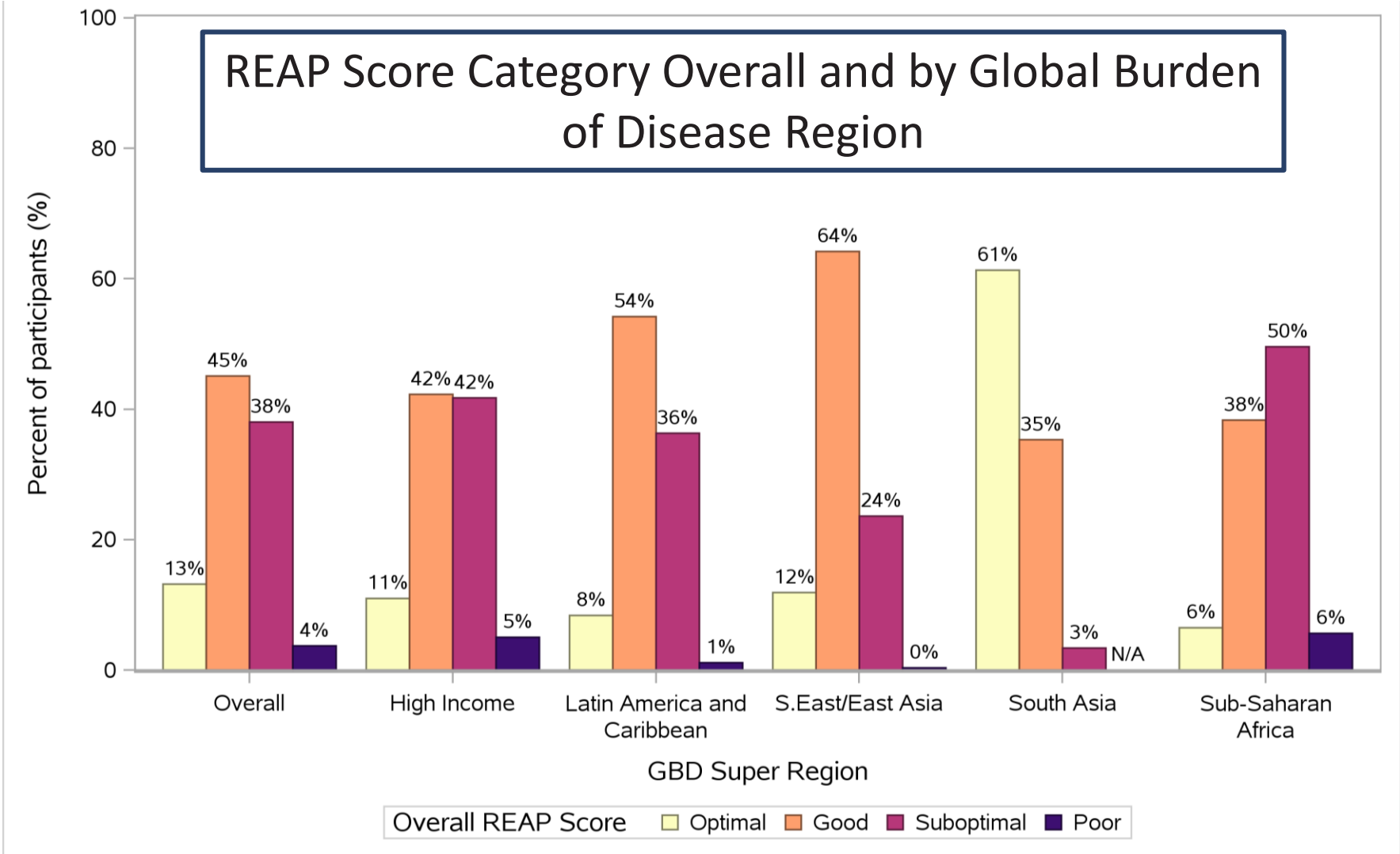
[1]Data are presented as median (interquartile range) unless otherwise specified

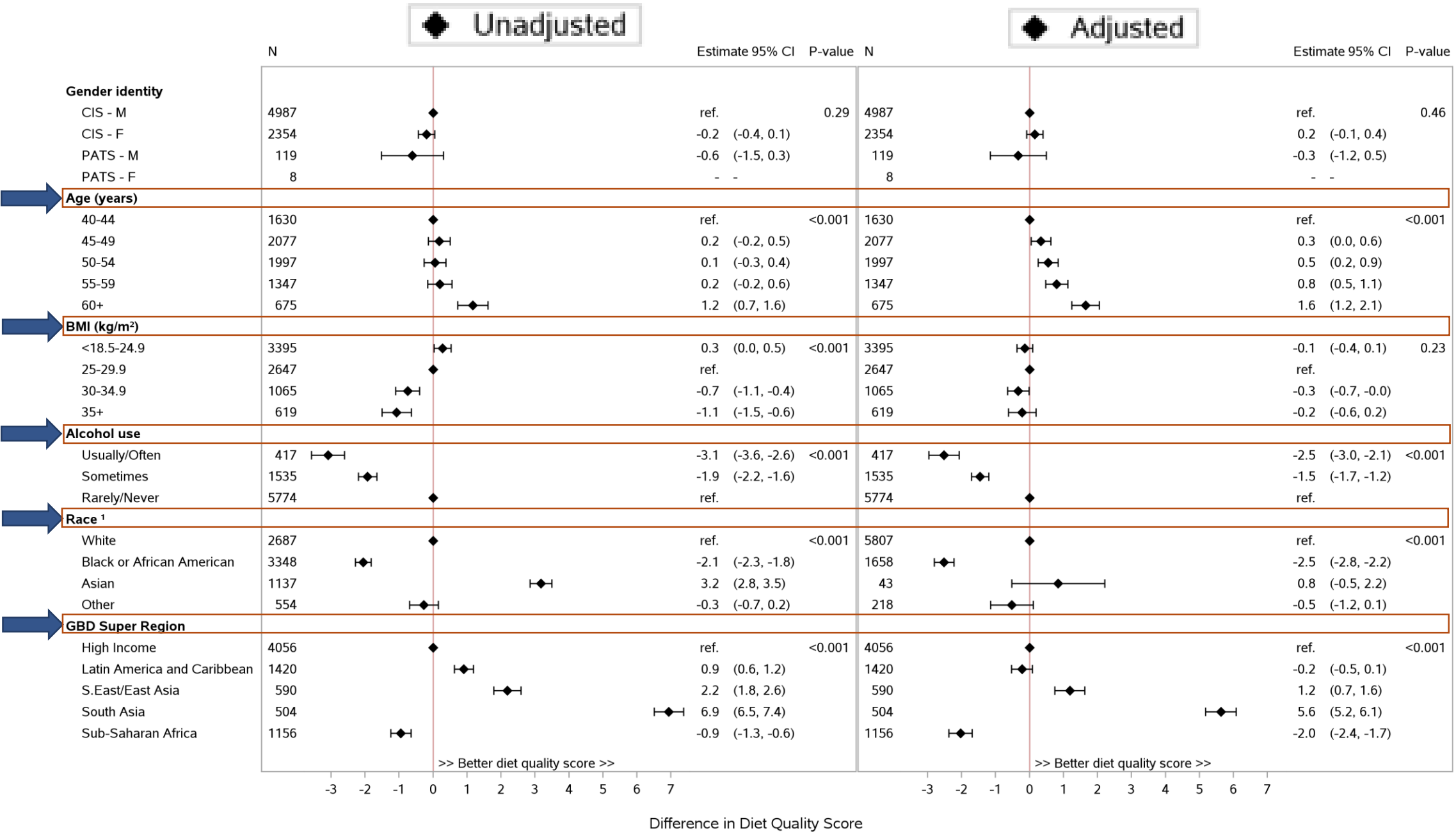
Abbreviations: ASCVD, atherosclerotic cardiovascular disease score; BMI, body mass index; ART, antiretroviral therapy

REAP Score Overall and by Global Burden of Disease Region

Characteristic[1]	Total (N=7736)	High Income (N=4065)	Latin America & Caribbean (N=1421)	S. East/ East Asia (N=590)	South Asia (N=504)	sub-Saharan Africa (N=1156)
Overall REAP Score[2] (max score: 30)	**17 (13-20)**	16 (12-20)	17 (14-20)	18 (16-21)	**23 (21-25)**	**15 (12-18)**

[1]Data are presented as median (IQR) unless otherwise specified, [2]Higher REAP score and component score (saturated fat, fiber, sodium) indicates more optimal diet
Abbreviations: REAP, Rapid Eating Assessment for Participants





In the adjusted analysis, race effect estimated within High income region only due to limited racial variability in other regions; the GBD region effects thus reflect differences compared to white race within the High income region

Main Findings

- Among PLWH eligible for primary heart disease prevention, diet was suboptimal or poor for 42% of REPRIEVE participants at study entry.

- Substantial variations in diet quality were reported by GBD region.

- Important factors associated with poor diet quality:
  - age less than 60 years (may reflect selection bias related to entry criteria)
  - more frequent alcohol use
  - race
  - GBD super-region

Conclusions

- Poor diet is an important, common modifiable risk factor which may be optimized to reduce cardiovascular risk among PLWH.

- Specific subgroups of PLWH such as by region, race or lifestyle behavior (alcohol use) may be at higher risk for poor diet. Further exploration is needed.

- In longitudinal analyses we will explore relationship of diet to major adverse cardiovascular events and differentiate findings by GBD region.

Assessment of Obesity and Cardiometabolic Status by Integrase Inhibitor Use in REPRIEVE: A Propensity Weighted Analysis of a Multinational Primary Cardiovascular Prevention Cohort of People with HIV

Emma Kileel, MPH
On behalf of the INSTI writing team

Data were presented at CROI 2021

Background

What do we know?

- INSTI-based regimens are highly effective in suppressing the HIV virus and are now first line therapy in most countries.
- Many recent studies have demonstrated weight gain within the first 6-12 months after initiation of an INSTI based regimen.

What don’t we know?

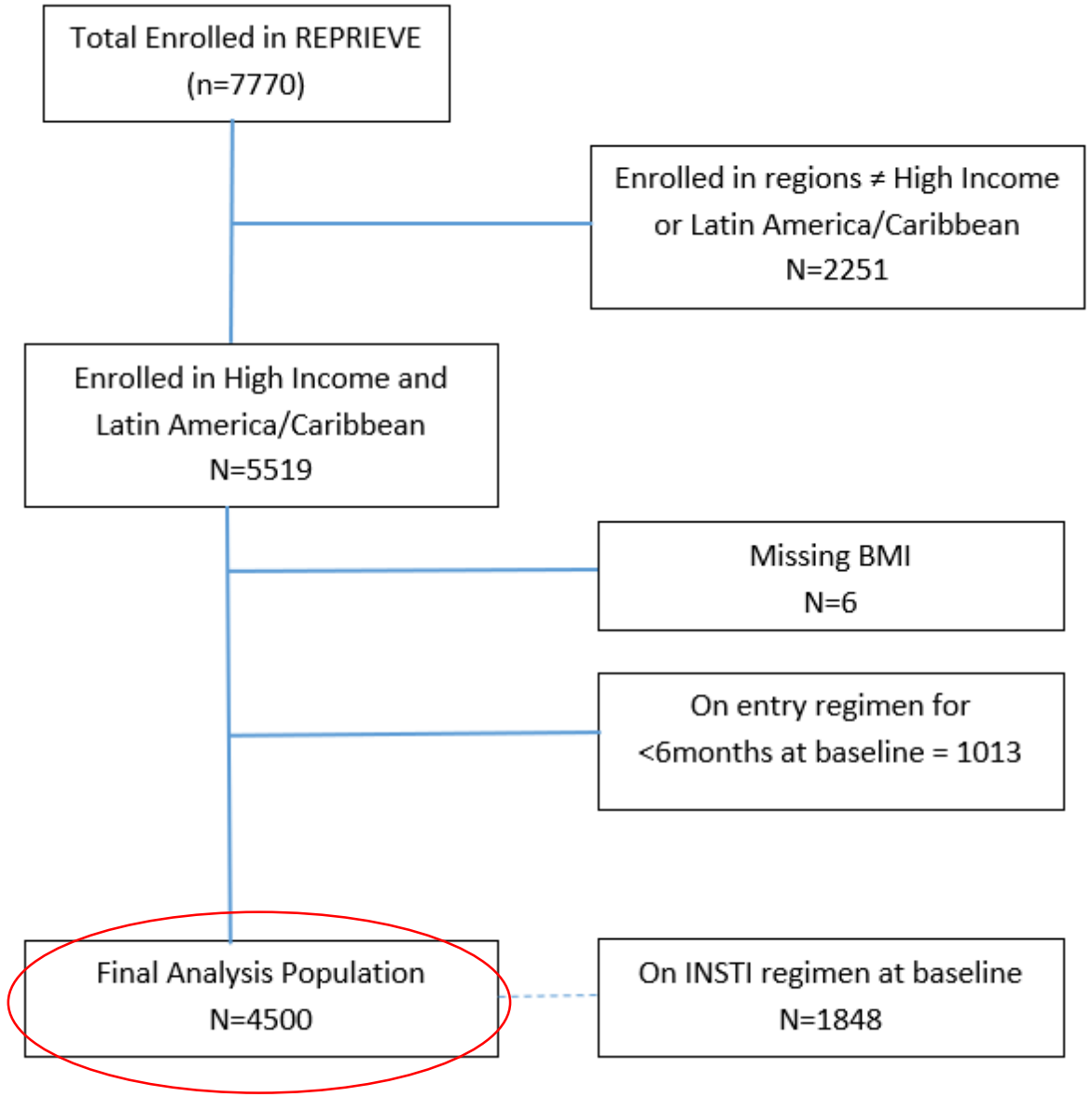
- Are there any adverse cardio and metabolic health effects of this weight gain? I.e., increased risk of metabolic syndrome or heart disease?
- Are certain groups of people more at risk for weight gain or adverse cardiometabolic health outcomes?

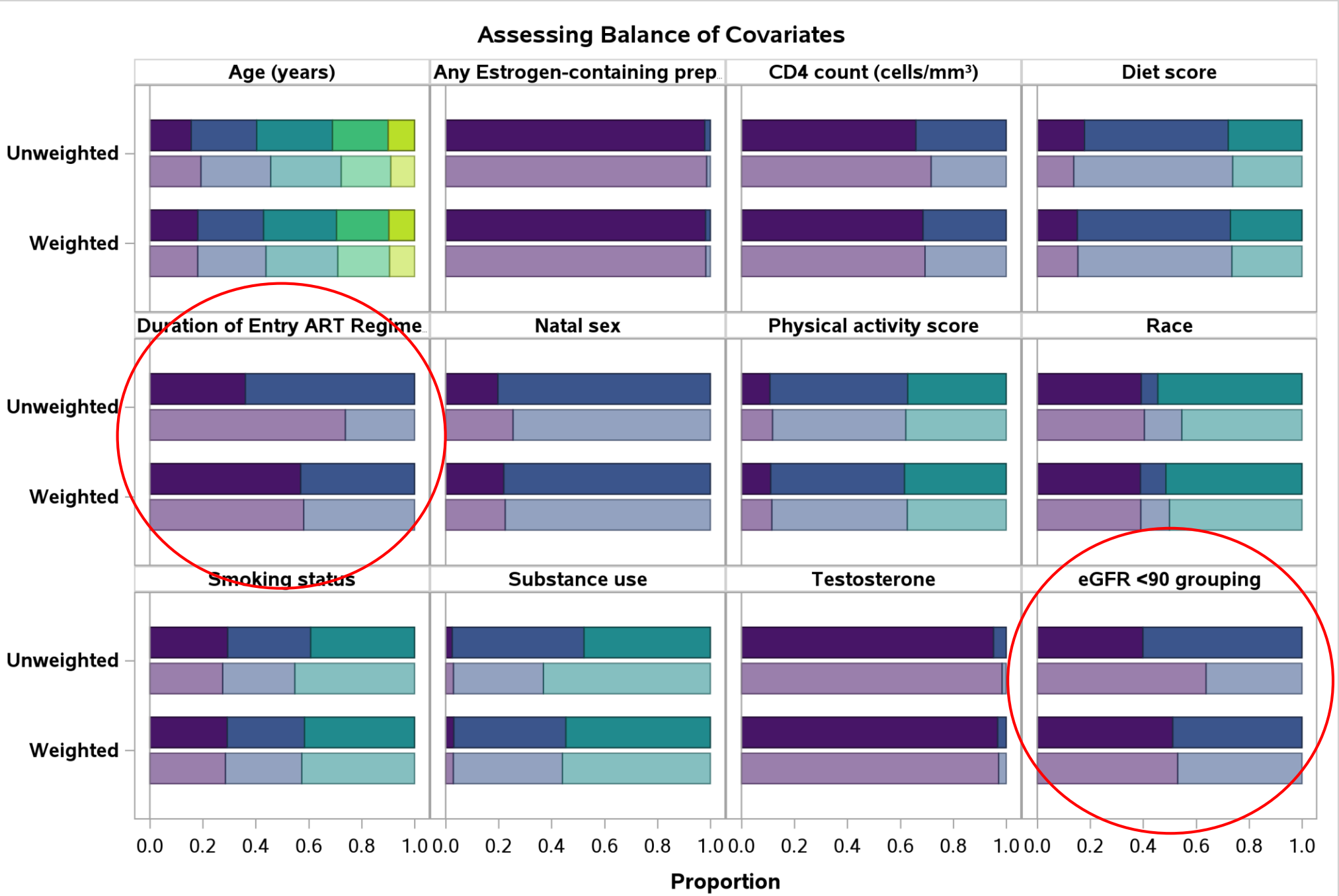
Objectives

1. Evaluate the effects of INSTI-based ART regimens vs non-INSTI based ART regimens on weight – specifically **BMI and Waist Circumference** – and associated clinically relevant cardiometabolic health outcomes at REPRIEVE entry, including:
    - **Fasting glucose (blood sugar), LDL-C (*bad* cholesterol), metabolic syndrome, and hypertension (high blood pressure)**
2. Evaluate effects of specific INSTI-based regimens (DTG vs EVG vs other (where other is a combination of RAL and BIC)) on weight and cardiometabolic health outcomes at entry

Methods

- This analysis used a subset of the 7770 REPRIEVE participants.
- We evaluated at **differences** in BMI (kg/m2), waist circumference, (cm), blood sugar(mg/dL), and cholesterol (mg/dL) between INSTI users and non INSTI users.
- We evaluated the **odds** (risk) of obesity, metabolic syndrome, and ↑ blood pressure between INSTI users vs non INSTI users.
- To control for confounding, we used a method called **inverse-probability-treatment-weighting**





Treated (INSTI=Y) group is shown with solid shading; Untreated (INSTI=N) shown with muted shading

Baseline Characteristics

	Overall (n=4500)	INSTI users at entry (n=1848)	Non-INSTI users at entry (n=2652)
Age (years)	51 (46, 55)	51 (47, 56)	50 (46, 55)
Female sex	1040 (23%)	365 (20%)	675 (25%)
BMI (kg/m2)	27.5 (±5.7)	28.2 (±6.1)	26.9 (±5.3)
Waist Circumference (cm)	95.5 (±13.8)	97.7 (±14.8)	94 (±12.8)
Fasting Glucose [blood sugar] (mg/dL)	93.0 (±14)	93..1 (±14.1)	93.0 (±14)
Fasting LDL-C [cholesterol] (mg/dL)	108 (±31)	108 (±30)	108 (±31)
Metabolic Syndrome (yes)	28%	27%	29%
Hypertension [↑ blood pressure] (yes)	37%	39%	36%
Duration of entry ART regimen (years)	4 (±3)	2 (±2)	5 (±4)
CD4 count <500 (cells/mm3)	31%	34%	28%

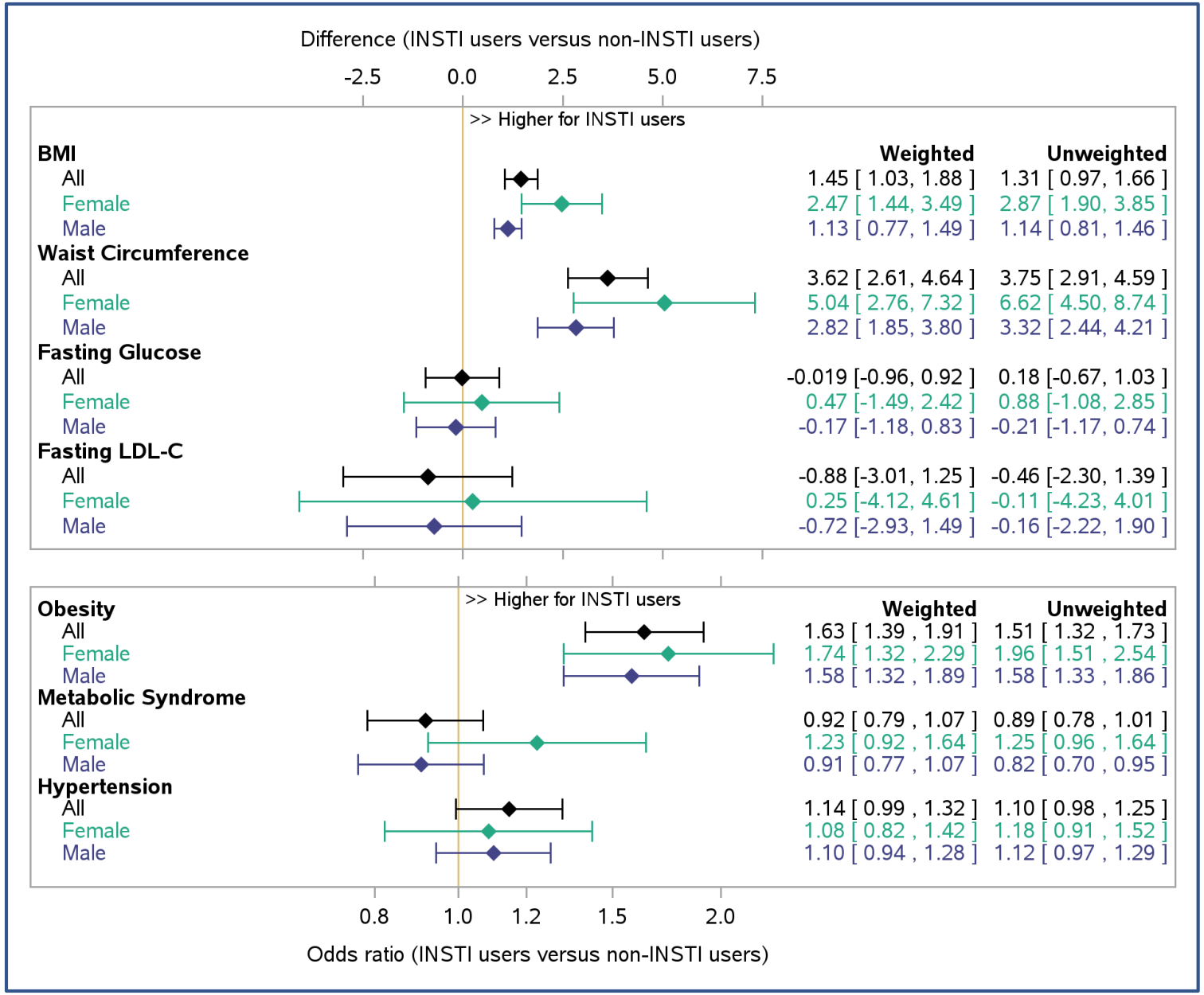
Age is presented as median (Q1, Q3). All other continuous variables, including BMI, WC, fasting Glucose, LDL-C, and duration of entry regimen are presented as mean (+/- sd).

Baseline Regimen Details

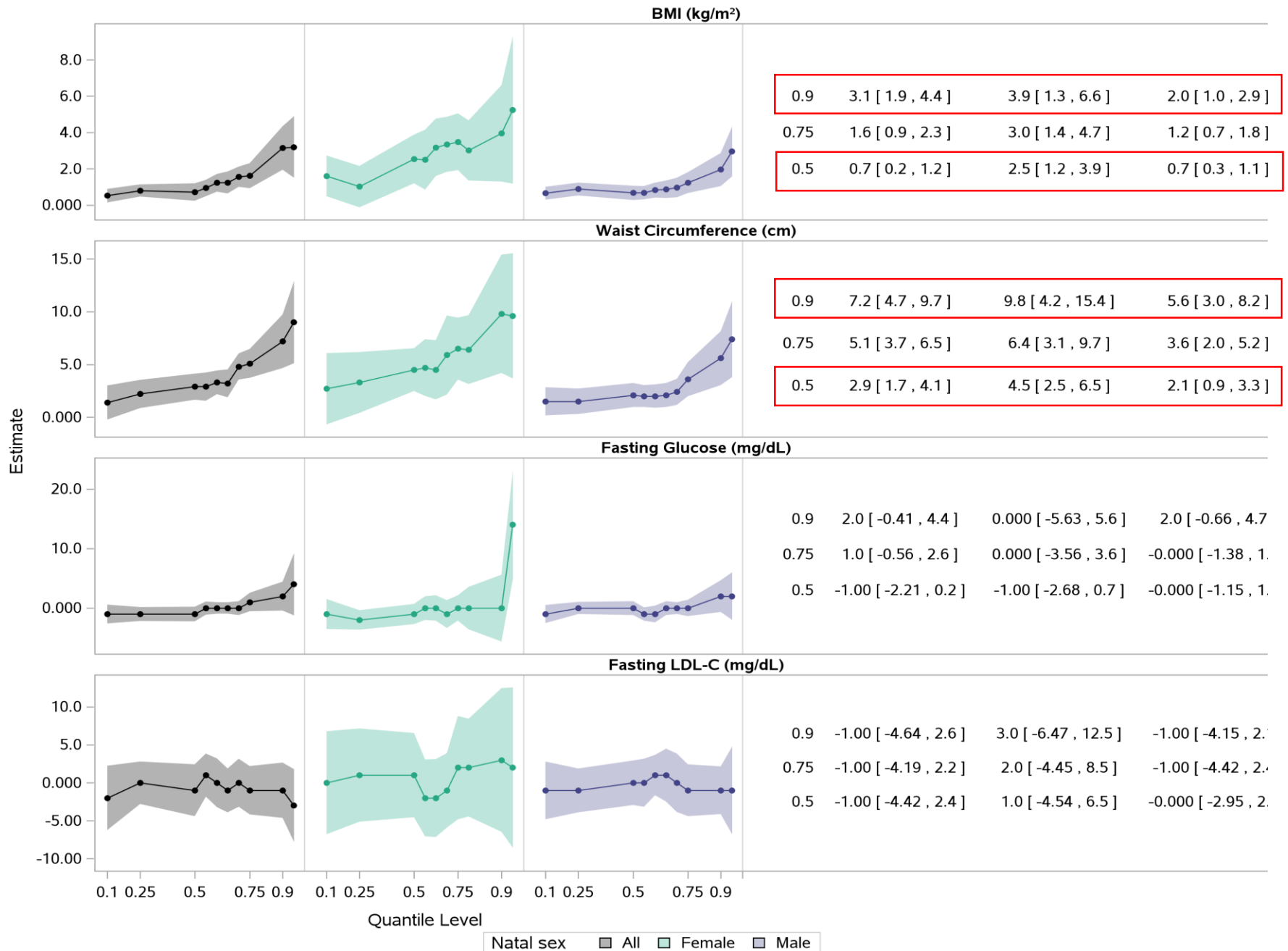
Regimen Details		Among Analysis Population			Among Participants on INSTI at Entry		
		Total (N=4500)	Non-INSTI entry ART (N=2652)	INSTI entry ART (N=1848)	Entry INSTI = DTG (N=882)	Entry INSTI = EVG (N=643)	Entry INSTI = RAL/BIC (N=323)
ART regimen (by class)	NRTI + NNRTI	1,638 (36%)	1,638 (62%)	0 (0%)			
	NRTI + INSTI	1,437 (32%)	0 (0%)	1,437 (78%)	689 (78%)	592 (92%)	156 (48%)
	NRTI + PI	930 (21%)	930 (35%)	0 (0%)			
	NRTI-sparing	146 (3%)	25 (1%)	121 (7%)	69 (8%)	0 (0%)	52 (16%)
	Other NRTI-containing	349 (8%)	59 (2%)	290 (16%)	124 (14%)	51 (8%)	115 (36%)
Entry NRTI	TDF	2,574 (59%)	1,891 (72%)	683 (40%)	200 (25%)	293 (46%)	190 (70%)
	ABC	678 (16%)	208 (8%)	470 (27%)	448 (55%)	0 (0%)	22 (8%)
	TAF	668 (15%)	182 (7%)	486 (28%)	107 (13%)	350 (54%)	29 (11%)
	ZDV	261 (6%)	255 (10%)	6 (0%)	3 (0%)	0 (0%)	3 (1%)
	Other NRTI	173 (4%)	91 (3%)	82 (5%)	55 (7%)	0 (0%)	27 (10%)
Entry NNRTI	EFV	1,271 (70%)	1,261 (75%)	10 (8%)	0 (0%)	0 (0%)	10 (15%)
	RPV	337 (19%)	291 (17%)	46 (37%)	43 (72%)	0 (0%)	3 (5%)
	NVP	103 (6%)	103 (6%)	0 (0%)			
	ETR	97 (5%)	28 (2%)	69 (55%)	17 (28%)	0 (0%)	52 (80%)
Entry PI	DRV	655 (50%)	377 (38%)	278 (84%)	130 (88%)	44 (86%)	104 (79%)
	ATV	529 (40%)	493 (50%)	36 (11%)	13 (9%)	7 (14%)	16 (12%)
	LPV	112 (8%)	99 (10%)	13 (4%)	3 (2%)	0 (0%)	10 (8%)
	Other PI	27 (2%)	23 (2%)	4 (1%)	2 (1%)	0 (0%)	2 (2%)

Results

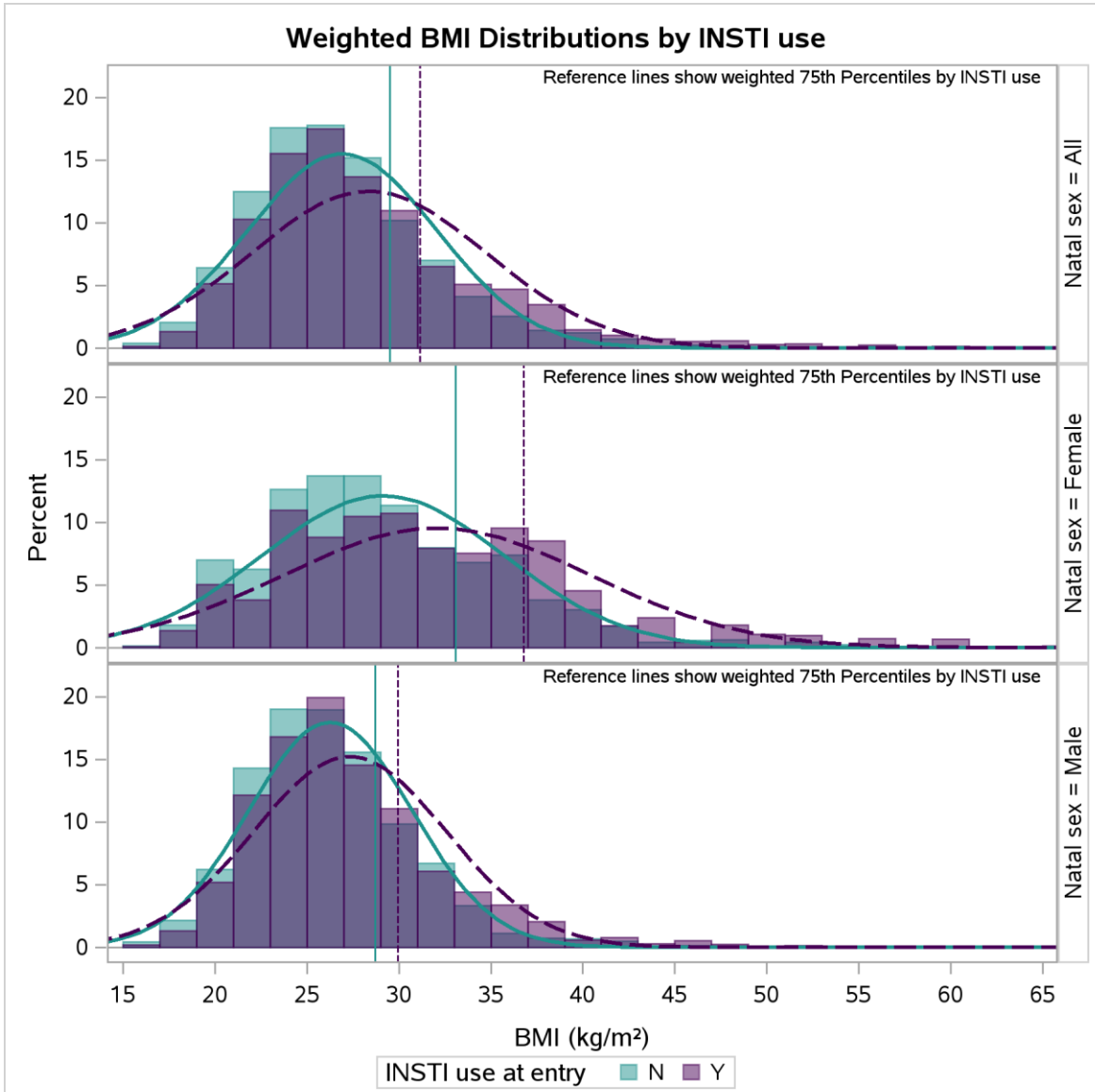
- Higher mean WC of 3.6cm associated with INSTI based regimens vs non
- 63% higher odds of obesity associated with INSTI based regimens vs non
- Bigger differences among females
- No differences in blood sugar or cholesterol levels
- No increased risk of metabolic syndrome or ↑ blood pressure

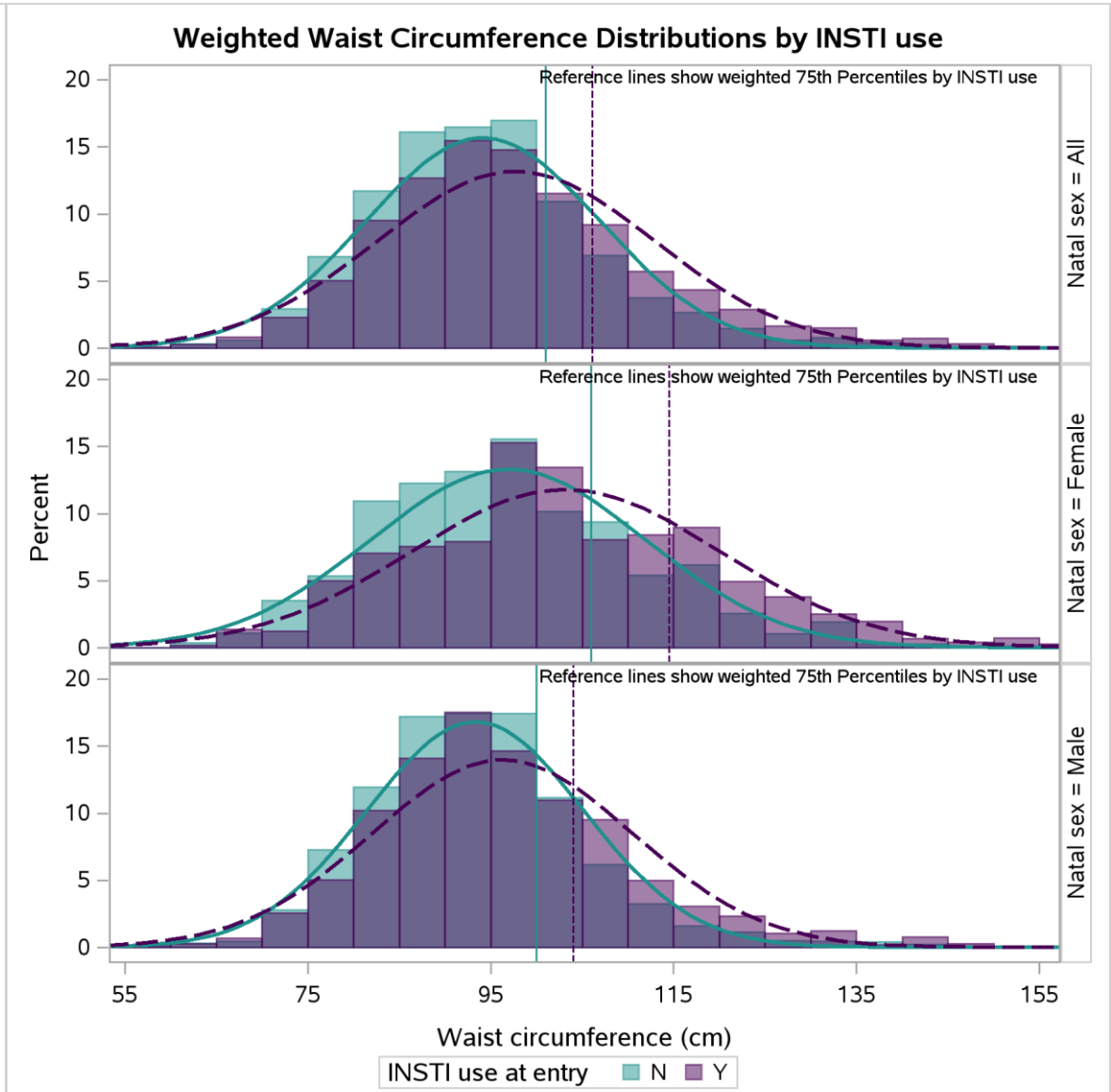


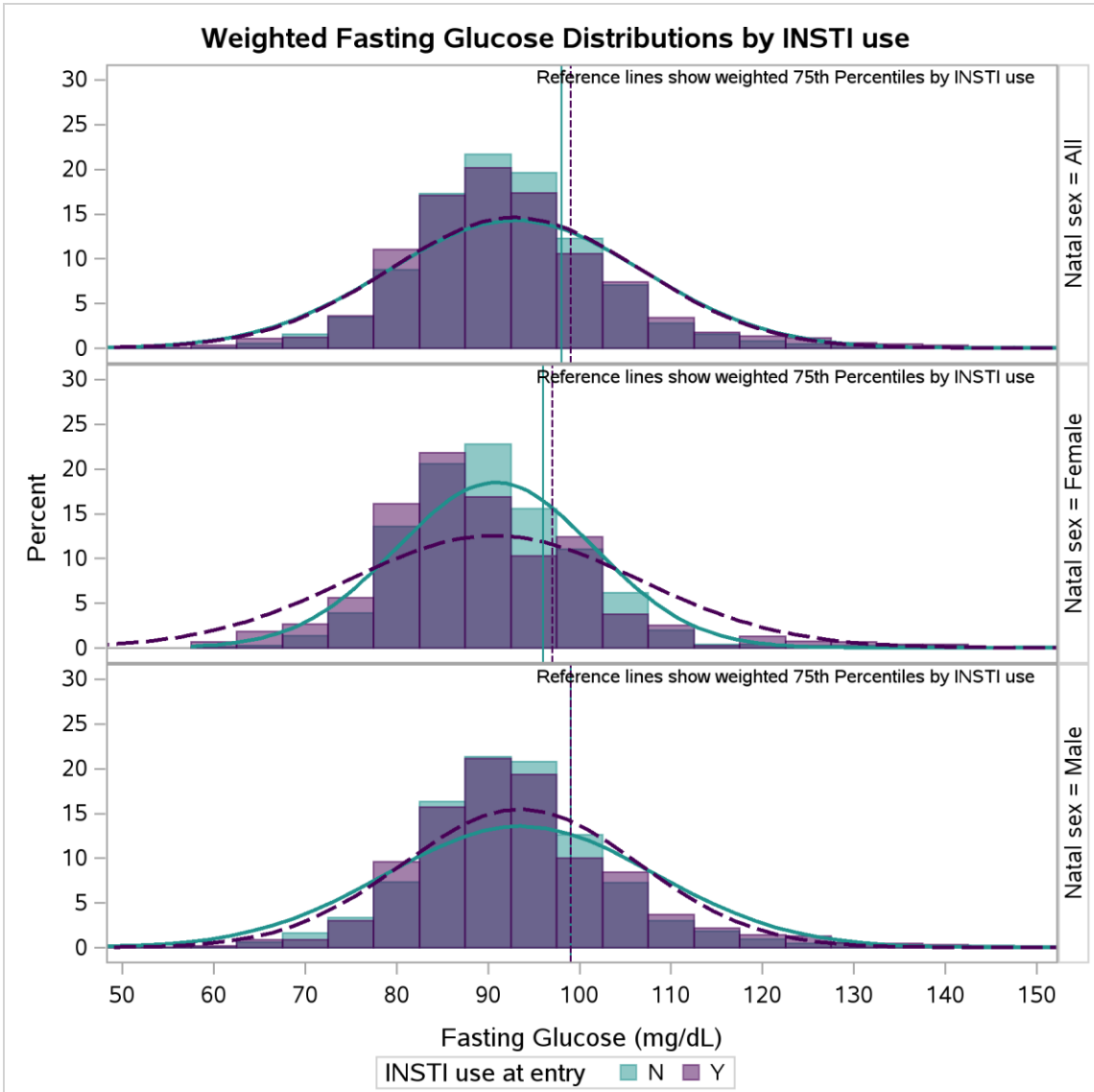
Estimated Parameter Difference (INSTI users vs Non-INSTI users) by Quantile

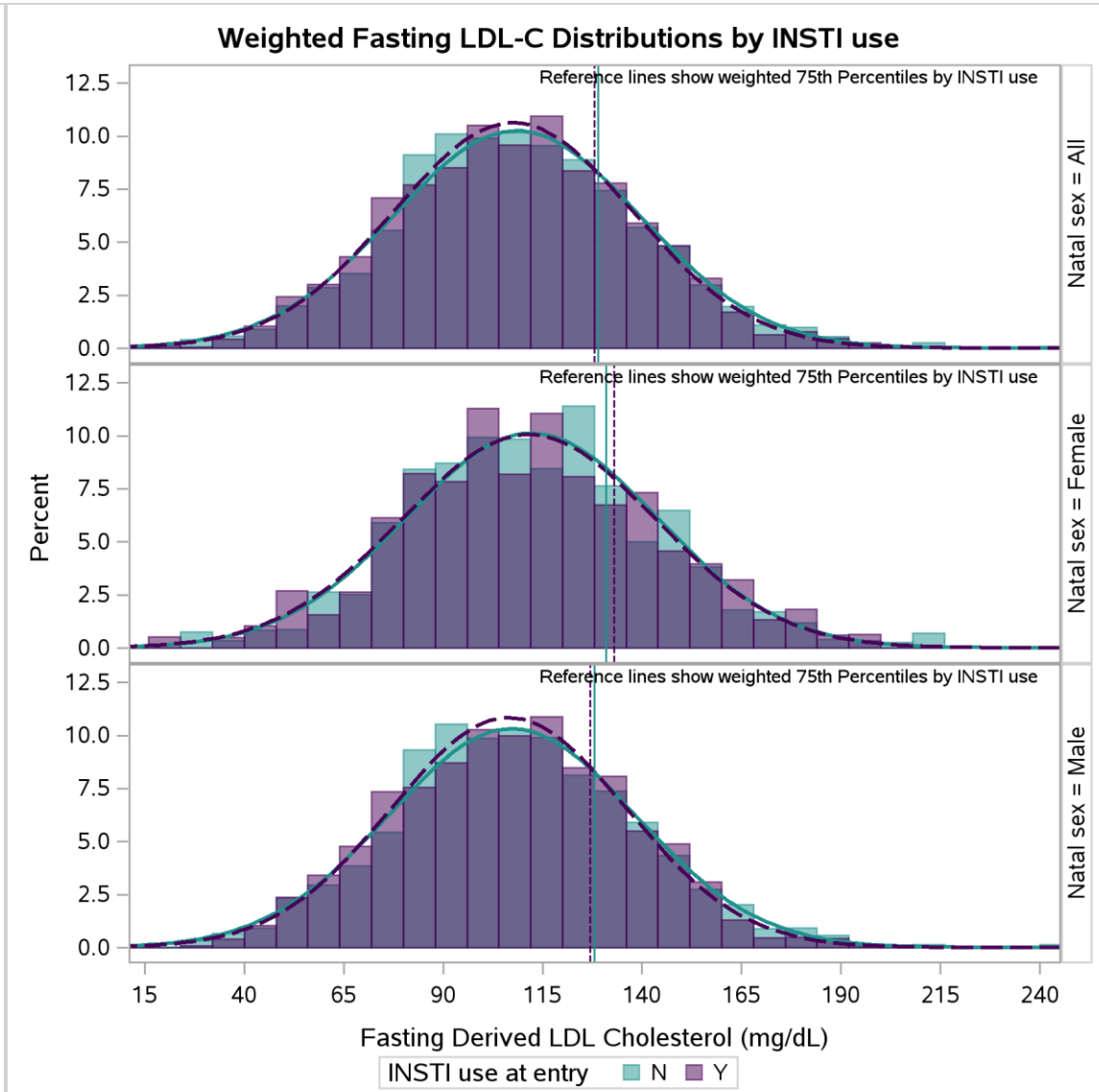


Quantile	All	Female	Male
BMI (kg/m²)			
0.9	3.1 [1.9 , 4.4]	3.9 [1.3 , 6.6]	2.0 [1.0 , 2.9]
0.75	1.6 [0.9 , 2.3]	3.0 [1.4 , 4.7]	1.2 [0.7 , 1.8]
0.5	0.7 [0.2 , 1.2]	2.5 [1.2 , 3.9]	0.7 [0.3 , 1.1]
Waist Circumference (cm)			
0.9	7.2 [4.7 , 9.7]	9.8 [4.2 , 15.4]	5.6 [3.0 , 8.2]
0.75	5.1 [3.7 , 6.5]	6.4 [3.1 , 9.7]	3.6 [2.0 , 5.2]
0.5	2.9 [1.7 , 4.1]	4.5 [2.5 , 6.5]	2.1 [0.9 , 3.3]
Fasting Glucose (mg/dL)			
0.9	2.0 [-0.41 , 4.4]	0.000 [-5.63 , 5.6]	2.0 [-0.66 , 4.7
0.75	1.0 [-0.56 , 2.6]	0.000 [-3.56 , 3.6]	-0.000 [-1.38 , 1.
0.5	-1.00 [-2.21 , 0.2]	-1.00 [-2.68 , 0.7]	-0.000 [-1.15 , 1.
Fasting LDL-C (mg/dL)			
0.9	-1.00 [-4.64 , 2.6]	3.0 [-6.47 , 12.5]	-1.00 [-4.15 , 2.
0.75	-1.00 [-4.19 , 2.2]	2.0 [-4.45 , 8.5]	-1.00 [-4.42 , 2.
0.5	-1.00 [-4.42 , 2.4]	1.0 [-4.54 , 6.5]	-0.000 [-2.95 , 2.


Weighted BMI Distributions by INSTI use
Reference lines show weighted 75th Percentiles by INSTI use
Natal sex = All
Natal sex = Female
Natal sex = Male
Percent
BMI (kg/m²)
INSTI use at entry N Y


Weighted Waist Circumference Distributions by INSTI use
Reference lines show weighted 75th Percentiles by INSTI use
Natal sex = All
Natal sex = Female
Natal sex = Male
Percent
Waist circumference (cm)
INSTI use at entry N Y


Weighted Fasting Glucose Distributions by INSTI use
Reference lines show weighted 75th Percentiles by INSTI use
Natal sex = All
Natal sex = Female
Natal sex = Male
Percent
0
5
10
15
20
25
30
50
60
70
80
90
100
110
120
130
140
150
Fasting Glucose (mg/dL)
INSTI use at entry
N
Y


Weighted Fasting LDL-C Distributions by INSTI use
Reference lines show weighted 75th Percentiles by INSTI use
Natal sex = All
Natal sex = Female
Natal sex = Male
Percent
0.0
2.5
5.0
7.5
10.0
12.5
15
40
65
90
115
140
165
190
215
240
Fasting Derived LDL Cholesterol (mg/dL)
INSTI use at entry
N
Y

Evaluating the effects of specific INSTIs

- Biggest differences in BMI and waist circumference among participants who were on an EVG-containing regimen
- Overall, no differences in blood sugar or cholesterol

Outcome	Overall (n=4500)	
	Difference (INSTI users vs non- INSTI users) [Weighted Estimate (95% CI)]	P-value
BMI (kg/m^2)		
EVG vs No INSTI	1.6 (1.1, 2.2)	<0.0001
DTG vs No INSTI	1.2 (0.7, 1.7)	<0.0001
RAL/BIC vs No INSTI	0.9 (0.1, 1.6)	0.03
Waist Circumference (cm)		
EVG vs No INSTI	4.1 (2.7 5.5)	<0.0001
DTG vs No INSTI	3.5 (2.3, 4.8)	<0.0001
RAL/BIC vs No INSTI	2.7 (0.8, 4.6)	0.005
Fasting Glucose [blood sugar] (mg/dL)		
EVG vs No INSTI	-0.4 (-1.7, 0.9)	0.58
DTG vs No INSTI	0.9 (-0.4, 2.2)	0.17
RAL/BIC vs No INSTI	-0.9 (-2.6, 0.8)	0.30
Fasting LDL-C (mg/dL)		
EVG vs No INSTI	2.0 (-0.9, 4.9)	0.17
DTG vs No INSTI	-1.5 (-4.1, 1.2)	0.27
RAL/BIC vs No INSTI	-3.6 (-7.7, 0.4)	0.08

TAF Sensitivity Analyses

Sensitivity Analysis 1: TAF vs no TAF **among INSTI users only**	
Outcome	**Difference [Estimate (95% CI)]**
BMI (kg/m^2)	1.0 (0.3, 1.8)
Waist circumference (cm)	2.6 (0.9, 4.3)
Blood sugar (mg/dL)	0.5 (-1.1, 2.1)
Cholesterol (mg/dL)	8.9 (5.3, 12.5)
	Odds Ratio [OR (95% CI)]
Obesity	1.4 (1.1, 1.7)
Metabolic Syndrome	1.1 (0.9, 1.5)
↑ Blood Pressure	1.0 (0.8, 1.3)

Sensitivity Analysis 2: INSTI use vs no INSTI use **excluding TAF users**		
Outcome	**Including TAF users**	**Excluding TAF users**
	Difference [Estimate (95% CI)]	
BMI (kg/m^2)	1.5 (1.0, 1.9)	1.4 (0.9, 1.9)
Waist circumference (cm)	3.6 (2.6, 4.6)	3.4 (2.2, 4.5)
Blood sugar (mg/dL)	-0.02 (-1.0, 0.9)	-0.01 (-1.0, 1.0)
Cholesterol (mg/dL)	-0.9 (-3.0, 1.3)	-1.6 (-4.0, 0.7)
	Odds Ratio [OR (95% CI)]	
Obesity	1.6 (1.4, 1.9)	1.6 (1.3, 1.9)
Metabolic Syndrome	0.9 (0.8, 1.1)	0.9 (0.8, 1.1)
↑ Blood Pressure	1.1 (1.0, 1.3)	1.2 (1.0, 1.4)

Summary

- INSTI-based regimens were associated with higher BMI, WC, and higher odds of obesity, but not with higher blood sugar, cholesterol, metabolic syndrome, or blood pressure.
- Biggest differences in BMI and WC among females and among participants in the 90th centile of BMI and WC
- Biggest differences in BMI and WC among participants on EVG-containing regimens
- Both INSTI and TAF use are associated with higher BMI and WC, *and* that the INSTI effects on weight occur independent of TAF use

These results provide a degree of reassurance that, in general, higher weights associated with INSTI use are not associated with increased cardiometabolic risk but highlight subgroups for whom such changes may be concerning

REPRIEVE

Participants & Study Teams

Sponsors

NIH National Heart, Lung, and Blood Institute

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Questions?

Thank you so much for joining us today!