

# Health-related quality of life among people with HIV at low-to-moderate risk for atherosclerotic cardiovascular disease in the REPRIEVE Trial

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**Background:** There is limited evidence concerning the relationship between cardio-metabolic characteristics and health-related quality of life (HRQoL), and potential effects of statin therapy among people with HIV (PWH).

**Methods:** The Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) enrolled PWH aged 40–75 years on antiretroviral therapy (ART) with low-to-moderate ASCVD risk. Coronary computed tomography angiography assessed coronary plaque among a subset of participants in the REPRIEVE Mechanistic Substudy at baseline and 24 months. The Short Form-36-Item Health Survey Version 2 was collected at baseline, and physical (PCS) and mental (MCS) component summary scores were determined. We explored the relationship of PCS and MCS with cardiometabolic characteristics, coronary atherosclerosis, and assessed change in score by treatment group (pitavastatin vs. placebo).

**Results:** Of 733 participants, median age was 51 years, 84% were male, 34% were Black non-Hispanic, and median years diagnosed with HIV was 15. At baseline, for participants randomized to pitavastatin vs. placebo the median PCS was 54.5 (Q1, Q3: 46.9, 57.7) vs. 54.1 (47.5, 58.0), and the median MCS was 52.9 (44.1, 57.6) vs. 52.8 (44.0, 57.9). In fully adjusted analyses, older age, Black non-Hispanic race/ethnicity,

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ART regimen class, elevated BMI, and cigarette smoking were associated with lower PCS. No clear trends were apparent with MCS. Between baseline and month 24, declines in PCS and MCS were minimal with no apparent difference by treatment group.

**Conclusions:** Among this cohort of ART-treated PWH, baseline cardiometabolic risk factors were associated with worse self-reported physical HRQoL, with no apparent effect of statin therapy.

**Trial Registration:** REPRIEVE; NCT02344290; <https://clinicaltrials.gov/study/NCT02344290>

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## Introduction

Life expectancy of people with HIV (PWH) is approaching that of the general population [1,2]. This is due in part to advances in the treatment and care of PWH, such as earlier initiation of antiretroviral therapy (ART), advances in ART, and policies focused on increasing engagement in care [3]. While increased life expectancy and aging are successes in the trajectory of HIV, a recent focus has been on improving the quality of life and well being of PWH across the life span [4,5].

Understanding the health outcomes that individuals report holds significance in research, clinical practice, and health planning [6,7]. One notable patient-reported health outcome is health-related quality of life (HRQoL). HRQoL, a multidimensional construct, delves into how health impacts an individual's well being and functioning across essential domains encompassing physical and mental aspects. Patient-reported HRQoL can complement traditional health outcomes by providing an individual's perspective about their health status. Notably, studies consistently reveal that PWH exhibit significantly lower HRQoL compared to the general population despite advancements in HIV treatment and care [8,9]. Assessing HRQoL among individuals with chronic conditions like HIV allows for evaluating the effectiveness of specific medications and interventions, as well as exploring the influences of HIV and its associated comorbidities on HRQoL.

As PWH live longer, age-associated comorbidities are increasingly prevalent and may lead to disability and limitations at an earlier age [10], both of which may reduce quality of life. Among these comorbidities is cardiovascular disease (CVD), and it has been predicted that by 2030, 78% of PWH will have CVD [11]. Having metabolic disease, characterized by a cluster of traditional CVD risk factors such as abdominal obesity, impaired glucose, elevated triglyceride levels, reduced high-density

lipoprotein levels, and hypertension, is highly associated with increased risk of CVD, which may lead to physical and mental impairment [12,13]. The correlation between HRQoL and cardiometabolic disease is not yet fully elucidated. Few studies to date have evaluated the impact of cardiovascular characteristics on HRQoL among PWH [14,15].

To explore these questions, we analyzed data from the Mechanistic Substudy of the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE; NCT02344290), a randomized trial assessing statin therapy as a primary CVD prevention strategy among PWH [16]. The present study examined self-reported HRQoL and factors associated with physical and mental HRQoL domains in a population of PWH at low-to-moderate risk for atherosclerotic CVD (ASCVD). We further sought to evaluate whether the physical and mental domains of HRQoL were associated with cardiometabolic risk factors and the change in each domain over time by treatment group (pitavastatin vs. placebo), hypothesizing that subclinical atherosclerosis would be associated with worse HRQoL.

## Methods

### Trial design and study population

The REPRIEVE trial enrolled PWH, aged 40–75 years, on stable ART, and with low-to-moderate traditional ASCVD risk measured by the 2013 ACC/AHA Pooled Cohort Equations, as previously described [17–19]. The present analysis of the REPRIEVE Mechanistic Substudy includes participants who underwent coronary CT angiography (CTA) at baseline and completed the Short Form–36-Item Health Survey Version 2 (SF-36v2) questionnaire at baseline and month 24. Thirty-one U.S. REPRIEVE sites participated in the Mechanistic Substudy and enrolled participants without contraindications to CTA between

May 2015 and February 2018 [16,20,21]. The design and primary results of the Mechanistic Substudy have been previously described [16,21]. Mass General Brigham and local site institutional review board approvals were obtained for the Mechanistic Substudy. All participants provided written informed consent.

### Assessment of health-related quality of life

The primary outcomes of this analysis were the HRQoL physical (PCS) and mental (MCS) component scores derived from participant responses to the SF-36v2 at baseline. SF-36v2 is constructed to measure functional health and well being from the participant's perspective using 36 multiple-choice questions. The SF-36v2 measures four domains in physical health (physical functioning, role limitation—physical, bodily pain, general health), and four in mental health (role limitation—emotional, vitality, mental health, and social functioning) to yield an eight-scale profile of functional health and well being. These eight scales are then aggregated into two psychometrically-based physical and mental health component scores, PCS and MCS. Mean imputation was used for each of the eight scales to address missing data of individual scale questions. A complete SF-36v2 questionnaire was required to calculate PCS and MCS. Possible scores for each component range from 0 to 100, with higher scores representing better health status. The PCS and MCS were chosen as the primary outcomes because they have lower inherent variability than the individual scales.

### Coronary computed tomography angiography acquisition and assessment of coronary artery disease (CAD)

Coronary CTA and plaque assessments were performed at baseline and month 24, as previously described [16,20,21]. The primary risk factors in this analysis were the presence (plaque vs. no plaque) and extent [coronary artery calcium (CAC) score, segment involvement score, percentage maximum stenosis] of subclinical atherosclerosis. CAC score was quantified on noncontrast, ECG-gated CT using a modified Agatston method (CAC categories of 0; 1–100; >100) [22]. Segment involvement score was calculated as previously described (0; 1; 2; 3+), and percentage maximum stenosis (0%; 1–49%; ≥50%) was assessed using the standard 18-segment coronary model [20]. Coronary CTA was acquired locally at baseline. Reading of images was performed centrally by the Imaging Core of the REPRIEVE Data Coordinating Center, and site training for CTA image acquisition and quality control measures were implemented as previously described [21].

### Duke activity status instrument

The Duke Activity Status Instrument (DASI) was administered at the baseline visit. This instrument estimates functional capacity from an individual's self-reported ability to complete activities of variable intensity

[23]. The maximum DASI score is 58.2, with higher scores indicating better functional status.

### Statistical analysis

The primary outcomes of this analysis were HRQoL PCS and MCS. Per the SF-36v2 score manual [24], all outcomes are standardized to 1998 population norms with a mean of 50 and standard deviation of 10. The PCS and MCS outcomes were primarily analyzed on their continuous scale. However, when needed for descriptive analyses, a binary outcome  $\leq 45 / > 45$  was used. A lower threshold of  $\leq 45 / > 45$ , was chosen a priori to better define a group with physical or mental deficits compared to the population norms.

Per the SF-36v2 manual, internal validity was evaluated before proceeding with statistical analyses. Baseline demographics, HIV-1 RNA, cardiometabolic characteristics, and CAD markers were individually assessed for their association with PCS and MCS using linear regression models. For characteristics that were significantly associated with PCS or MCS, individual linear regression models were repeated with additional adjustment for age, sex, and race/ethnicity. Lastly, we performed three permutations of models adjusted for cardiovascular risk with adjustment for ASCVD risk score, the individual components of the ASCVD risk score, and the components of the risk score and CAC score.

In longitudinal analyses, we summarized PCS and MCS at baseline and month 24 overall and by randomized treatment group. We also estimated the change from baseline in PCS and MCS with baseline-adjusted regression estimates via linear models additionally adjusted for treatment group. Lastly, we visually assessed the distributions of PCS and MCS at baseline, month 24, and change from baseline by age, sex-at-birth, race, and ethnicity.

Supplemental analyses were performed relating PCS to MCS and assessing distributions of each across risk factors. Lastly, we compared demographics in participants with concordant and discordant PCS and MCS scores.

Inference was guided by clinically meaningful effect sizes and a two-sided 5% false-positive error rate without adjustment for multiple comparisons. Statistical analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, North Carolina, USA).

## Results

### Baseline demographics

A total of 804 participants were randomized in the REPRIEVE Mechanistic Substudy [20]. Of those, 733 participants who underwent baseline coronary CTA and

completed the SF-36v2 were included in this analysis (CONSORT Diagram/Supplemental Figure 1, Supplemental Digital Content, <http://links.lww.com/QAD/D716>). Among these participants, median age was 51 years, 84% were male, 34% were Black non-Hispanic, 24% were Hispanic (regardless of race), and median duration of HIV was 15 years (Table 1). Demographic characteristics of the Mechanistic Substudy population were generally similar to the REPRIEVE population enrolled in the United States [20].

### Baseline factors associated with physical component summary and mental component summary

At baseline among participants randomized to pitavastatin vs. placebo, the median PCS was 54.5 (Q1, Q3: 46.9, 57.7) vs. 54.1 (47.5, 58.0), and the median MCS was 52.9 (44.1, 57.6) vs. 52.8 (44.0, 57.9) (Table 2).

Among those with a PCS  $\leq 45$ , the population skewed slightly older and featured a higher proportion of participants with female natal sex and Black non-Hispanic race/ethnicity (Table 1). Additionally, this subgroup exhibited a higher prevalence of individuals living with HIV for  $>10$  years, antiretroviral therapy (ART) duration  $>10$  years, and a lower prevalence of current use of an NRTI + NNRTI regimen. In terms of cardiometabolic characteristics, this subgroup displayed a higher prevalence of overweight/obesity, ASCVD risk scores  $>5\%$ , current smoking, hypertension, coronary plaque, CAC score  $>100$ , and elevated segment involvement score.

There were fewer notable distinctions for the MCS domain (Table 1). Among participants with MCS  $\leq 45$ , a larger proportion had a lower CD4:CD8 ratio ( $<0.5$ ) and eGFR of  $<90$ , and a smaller proportion had current use of an NRTI + NNRTI regimen. With respect to cardiometabolic characteristics, there was a higher prevalence of current smoking, coronary plaque, and elevated segment involvement score.

Distribution of PCS and MCS across risk factors is shown (Supplemental Figure 8, Supplemental Digital Content, <http://links.lww.com/QAD/D716>). Risk factors are further compared in those with simultaneous PCS and MCS  $<45$  ( $n=73$ ), PCS and MCS  $>45$  ( $n=453$ ) and discordant values [PCS  $\leq 45$ , MCS  $>45$  ( $n=81$ ) and PCS  $>45$ , MCS  $<45$  ( $n=126$ )] (Supplemental Table 2, Supplemental Digital Content, <http://links.lww.com/QAD/D716>). Participants with low MCS only appeared to be younger, fewer demonstrated BMI  $\geq 30$  mg/kg<sup>2</sup>, and more demonstrated low ASCVD risk scores (0 to  $<2.5\%$ ). More participants with low PCS only were Black Non-Hispanic, had a longer duration of HIV  $\geq 10$  years, and had been on ART  $\geq 10$  years. Slightly more participants with both low PCS and low MCS had CD4 count 500+ (cells/mm<sup>3</sup>). Slightly more participants with both high PCS and high MCS were on NRTI +

NNRTI. Most other factors have similar distributions (Supplemental Table 2, Supplemental Digital Content, <http://links.lww.com/QAD/D716>).

### Factors associated with physical component summary

In single variable analyses exploring associations between baseline factors and PCS (Supplemental Figure 2, Supplemental Digital Content, <http://links.lww.com/QAD/D716>), factors associated with lower PCS included older age ( $\geq 55$  years), female sex, Black non-Hispanic race, higher BMI ( $\geq 30$  mg/kg<sup>2</sup>), higher ASCVD risk ( $\geq 5\%$ ), current and former smoking, hypertension, longer time living with HIV ( $\geq 10$  years), and longer time on ART ( $\geq 10$  years). PCS differed across ART regimen classes, with higher scores among participants taking NRTI+NNRTI and the lowest among those on other NRTI-containing regimens.

These associations were similar in models adjusted for age, sex, and race. Significant associations remained for ART regimen class, BMI, ASCVD risk ( $\geq 5\%$ ), and current and former smoking. Longer duration of ART use appeared to be associated with lower PCS, but the overall test for differences across ART duration was not statistically significant ( $P=0.09$ ) (Supplemental Figure 3, Supplemental Digital Content, <http://links.lww.com/QAD/D716>).

Single variable analyses exploring associations between CAD markers and PCS revealed that higher CAC score ( $>100$ ) was associated with lower PCS (Supplemental Figure 4, Supplemental Digital Content, <http://links.lww.com/QAD/D716>). This association remained significant after adjustment for age, sex, and race. Although not statistically significant, there were trends suggesting that the presence of plaque (vs. no plaque), higher percentage of maximum stenosis and elevated segment involvement score were associated with lower PCS.

### Comprehensive multivariable modeling for factors associated with physical component summary

Fully adjusted models included factors which were significantly associated with PCS in the single variable analyses (Fig. 1). Age, race/ethnicity, ART regimen class, BMI, and smoking remained significant after inclusion of other covariates. The effects of female sex, duration of ART use, ASCVD risk score, hypertension, and CAC score on PCS were attenuated and not statistically significant in fully adjusted analyses.

### Factors associated with mental component summary

In single variable analyses for associations between baseline factors, CAD markers, and MCS, the trends seen for PCS were less notable for MCS (Supplemental Figure 5, Supplemental Digital Content, <http://links.lww.com/QAD/D716>). We found that only lower CD4:CD8 ratio was associated with a lower MCS ( $P=0.049$ ). Use of INSTI or NRTI-sparing regimens appeared to be associated with a lower MCS, but the overall test for

Table 1. Baseline demographics by PCS and MCS  $\leq 45$  /  $>45$ .

	PCS		MCS	
	$\leq 45$	$>45$	$\leq 45$	$>45$
Age (years)				
n	154	579	733	534
Mean (SD)	52.5 (5.97)	50.5 (5.74)	50.9 (5.84)	51.0 (5.84)
Median (Q1, Q3)	52.0 (48.0, 57.0)	50.0 (46.0, 54.0)	51.0 (47.0, 55.0)	51.0 (47.0, 55.0)
Min, Max	40, 71	40, 71	40, 71	40, 71
40-44	12 (8%)	91 (16%)	103 (14%)	71 (13%)
45-49	40 (26%)	166 (29%)	206 (28%)	155 (29%)
50-54	45 (29%)	186 (32%)	231 (32%)	168 (31%)
55+	57 (37%)	136 (23%)	193 (26%)	140 (26%)
Female	33 (21%)	86 (15%)	119 (16%)	88 (16%)
Male	121 (79%)	493 (85%)	614 (84%)	446 (84%)
Race/Ethnicity				
White Non-Hispanic	42 (27%)	242 (42%)	284 (39%)	208 (39%)
Black Non-Hispanic	74 (48%)	173 (30%)	247 (34%)	177 (33%)
Hispanic (Regardless of Race)	34 (22%)	140 (24%)	174 (24%)	128 (24%)
Other	4 (3%)	24 (4%)	28 (4%)	21 (4%)
Chronic active HBV	2 (1%)	16 (3%)	18 (2%)	14 (3%)
Chronic active HCV	9 (6%)	12 (2%)	21 (3%)	13 (2%)
Time since HIV diagnosis (years)				
Median (Q1, Q3)	18.0 (12.0, 24.0)	14.0 (9.00, 21.0)	15.0 (9.00, 22.0)	15.0 (9.00, 21.0)
Min, Max	1, 36	0, 35	0, 36	0, 35
Duration of HIV (years)				
<5	11 (7%)	56 (10%)	67 (9%)	51 (10%)
5-10	25 (16%)	138 (24%)	163 (22%)	112 (21%)
>10	118 (77%)	385 (66%)	503 (69%)	371 (69%)
HIV-1 RNA (copies/ml)				
<LLQ	134 (88%)	504 (88%)	638 (88%)	468 (89%)
LLQ <- 400	16 (11%)	53 (9%)	69 (10%)	48 (9%)
400+	2 (1%)	14 (2%)	16 (2%)	12 (2%)
Quantifiable HIV-1 RNA (copies/ml)				
n	18	67	85	60
Median (Q1, Q3)	51.0 (37.0, 98.0)	60.0 (36.0, 199)	57.0 (37.0, 167)	57.0 (34.5, 160)
Min, Max	20, 866	20, 242580	20, 242580	20, 134013
CD4+ cell count (cells/mm <sup>3</sup> )				
Median (Q1, Q3)	598 (465, 800)	599 (424, 765)	599 (428, 772)	600 (425, 752)
Min, Max	143, 1674	110, 1772	116, 1714	110, 1772
<350	20 (13%)	90 (16%)	110 (15%)	80 (15%)
350-499	30 (19%)	116 (20%)	146 (20%)	111 (21%)
500+	104 (68%)	373 (64%)	477 (65%)	343 (64%)
Nadir CD4 (cells/mm <sup>3</sup> )				
<50	38 (25%)	121 (21%)	159 (22%)	120 (22%)
50-199	49 (32%)	162 (28%)	211 (29%)	151 (28%)
200-349	38 (25%)	159 (27%)	197 (27%)	144 (27%)
350+	26 (17%)	117 (20%)	143 (20%)	101 (19%)
Unknown	3 (2%)	20 (3%)	23 (3%)	18 (3%)
CD4:CD8 ratio				
Median (Q1, Q3)	0.858 (0.558, 1.37)	0.856 (0.551, 1.19)	0.858 (0.551, 1.21)	0.871 (0.562, 1.21)
Min, Max	0.153, 4.59	0.097, 4.41	0.097, 4.59	0.097, 4.41
# missing	13	49	62	47
<0.5	29 (21%)	107 (20%)	136 (20%)	87 (18%)
0.5-<1	54 (38%)	219 (41%)	273 (41%)	207 (43%)
1+	58 (41%)	204 (38%)	262 (39%)	193 (40%)
Total ART use (years)				
Median (Q1, Q3)	13.0 (7.40, 19.0)	10.6 (6.10, 16.0)	11.0 (6.30, 16.6)	11.7 (6.50, 16.5)
Min, Max	0.70, 30.00	0.50, 33.00	0.50, 33.00	0.50, 30.00
<5	21 (14%)	92 (16%)	113 (15%)	81 (15%)
5-10	31 (20%)	160 (28%)	191 (26%)	134 (25%)
10+	102 (66%)	327 (56%)	429 (59%)	319 (60%)
ART regimen class				
NRTI + INSTI	71 (46%)	253 (44%)	324 (44%)	229 (43%)
NRTI + NNRTI	28 (18%)	163 (28%)	191 (26%)	149 (28%)
NRTI + PI	30 (19%)	92 (16%)	122 (17%)	84 (16%)
NRTI-sparing	6 (4%)	17 (3%)	23 (3%)	17 (3%)

Table 1 (continued)

	PCS		Total	MCS	
	≤45	>45		≤45	>45
BMI (kg/m <sup>2</sup> )	Other NRTI-containing				
n	19 (12%)	54 (9%)	73 (10%)	18 (9%)	55 (10%)
Median (Q1, Q3)	154	579	733	199	534
Min, Max	28.4 (24.7, 31.4)	26.7 (24.1, 29.6)	27.0 (24.3, 30.1)	27.1 (24.3, 29.8)	26.9 (24.3, 30.3)
# missing	0	0	0	0	0
<25	41 (27%)	203 (35%)	244 (33%)	67 (34%)	177 (33%)
25–29.9	57 (37%)	244 (42%)	301 (41%)	84 (42%)	217 (41%)
30+	56 (36%)	132 (23%)	188 (26%)	48 (24%)	140 (26%)
ASCVD risk score (%)	23 (15%)	146 (25%)	169 (23%)	44 (22%)	125 (23%)
0–<2.5	38 (25%)	198 (34%)	236 (32%)	60 (30%)	176 (33%)
2.5–<5	93 (60%)	235 (41%)	328 (45%)	95 (48%)	233 (44%)
5+	47 (31%)	129 (22%)	176 (24%)	59 (30%)	117 (22%)
Smoking status	50 (32%)	179 (31%)	229 (31%)	62 (31%)	167 (31%)
Current	57 (37%)	271 (47%)	328 (45%)	78 (39%)	250 (47%)
Former	64 (42%)	171 (30%)	235 (32%)	64 (32%)	171 (32%)
Never	122 (114, 130)	122 (114, 132)	122 (114, 131)	120 (112, 129)	122 (114, 132)
Hypertension	85.0, 156	86.0, 164	85.0, 164	85.0, 160	92.0, 164
Systolic blood pressure (mmHg)	0	0	0	0	0
eGFR by CKD-EPI	69 (45%)	266 (46%)	335 (46%)	79 (40%)	256 (48%)
90+	85 (55%)	313 (54%)	398 (54%)	120 (60%)	278 (52%)
<90	186 (38.2)	185 (33.7)	185 (34.7)	185 (35.9)	185 (34.3)
Total cholesterol (mg/dl)	187 (160, 209)	184 (163, 206)	185 (162, 207)	180 (159, 207)	185 (164, 207)
HDL-C (mg/dl)	103, 298	92.0, 288	92.0, 298	103, 280	92.0, 298
LDL-C, calculated (mg/dl) (from CRF)	52.1 (17.4)	51.6 (17.1)	51.6 (17.1)	52.0 (18.9)	51.4 (16.4)
LDL-C, calculated (mg/dl)	51.0 (40.0, 62.0)	48.0 (39.3, 60.3)	49.0 (40.0, 61.0)	49.0 (39.0, 62.0)	48.6 (40.0, 60.0)
Triglycerides (mg/dl)	14.0, 134	18.0, 146	14.0, 146	14.0, 146	18.0, 143
Fasting glucose (mg/dl)	106 (30.7)	107 (27.4)	107 (28.1)	107 (28.4)	107 (28.0)
Plaque Present	102 (86.0, 127)	110 (89.6, 126)	108 (89.0, 127)	103 (89.0, 127)	110 (88.0, 127)
Calcium score – all groups	31.0, 183	14.7, 184	14.7, 184	31.0, 184	14.7, 183
Segment involvement score	138 (74.4)	134 (77.2)	134 (76.6)	134 (75.7)	134 (77.0)
Plaque Present	116 (83.0, 176)	111 (77.0, 166)	112 (79.0, 168)	112 (80.0, 164)	112 (78.0, 171)
Calcium score – all groups	37.0, 422	20.0, 488	20.0, 488	26.0, 422	20.0, 488
Segment involvement score	94.0 (14.6)	93.0 (12.1)	93.2 (12.7)	92.7 (12.3)	93.4 (12.8)
Plaque Present	92.0 (85.0, 99.0)	92.0 (85.0, 98.0)	92.0 (85.0, 98.0)	91.0 (85.0, 99.0)	92.0 (86.0, 98.0)
Calcium score – all groups	58.0, 162	67.0, 178	58.0, 178	67.0, 147	58.0, 178
Segment involvement score	0	8	8	3	5
Plaque Present	73 (47%)	300 (52%)	373 (51%)	96 (48%)	277 (52%)
Calcium score – all groups	81 (53%)	279 (48%)	360 (49%)	103 (52%)	257 (48%)
Segment involvement score	88 (61%)	363 (66%)	451 (65%)	119 (64%)	332 (65%)
Plaque Present	35 (24%)	140 (25%)	175 (25%)	48 (26%)	127 (25%)
Calcium score – all groups	22 (15%)	50 (9%)	72 (10%)	20 (11%)	52 (10%)
Segment involvement score	73 (48%)	300 (53%)	373 (52%)	96 (49%)	277 (53%)
Plaque Present	35 (23%)	143 (25%)	178 (25%)	51 (26%)	127 (24%)
Calcium score – all groups	19 (13%)	61 (11%)	80 (11%)	19 (10%)	61 (12%)
Segment involvement score	24 (16%)	66 (12%)	90 (12%)	31 (16%)	59 (11%)

Summary statistics of participant demographics, comorbidities, and CAD markers are presented overall and by PCS and MCS scores ≤45/>45.

ART, antiretroviral therapy; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; INSTI, integrase strand transfer inhibitor; LDL-C, low-density lipoprotein cholesterol; MCS, mental component score; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PCS, physical component score; PI, protease inhibitor.

**Table 2. PCS and MCS descriptive summaries at baseline and month 24 by randomized treatment arm.**

Health-related QOL measure		Pitavastatin			Placebo		
		Baseline	Month 24	Change from baseline	Baseline	Month 24	Change from baseline
Physical component summary (PCS) measure	<i>n</i>	364	331	331	369	336	336
	Median (Q1, Q3)	54.5 (46.9, 57.7)	53.0 (45.4, 57.3)	-0.616 (-4.46, 2.51)	54.1 (47.5, 58.0)	52.8 (45.7, 57.3)	-0.665 (-4.49, 2.86)
	P10, P90	39.6, 59.4	37.4, 59.2	-11.7, 7.92	39.0, 60.1	37.7, 59.5	-10.1, 8.05
	# missing	38	71	71	33	66	66
	Estimated change in PCS with adjustment for baseline score			-0.22 (-1.01, 0.57)			-0.14 (-0.70, 0.42)
Mental component summary (MCS) measure	<i>n</i>	364	331	331	369	336	336
	Median (Q1, Q3)	52.9 (44.1, 57.6)	52.2 (41.1, 57.4)	-0.498 (-5.75, 4.09)	52.8 (44.0, 57.9)	53.5 (44.3, 58.2)	0.122 (-3.43, 4.50)
	P10, P90	32.5, 60.8	32.1, 61.5	-12.6, 10.7	34.8, 60.9	33.3, 61.6	-11.3, 12.4
	# missing	38	71	71	33	66	66
	Estimated change in MCS with adjustment for baseline score			-0.90 (-1.93, 0.12)			-0.42 (-1.14, 0.30)

Summary statistics of PCS and MCS scores at baseline and month 24 as well as the change in score from baseline to Month 24 are presented by randomized treatment arm. The change in PCS and MCS from baseline is estimated using baseline score and treatment group-adjusted linear regression models. Models are not adjusted for any additional baseline risk factors. The mean changes from baseline are estimated for a participant with the PCS/MCS scores of 50.

MCS, mental component score; P10, 10<sup>th</sup> percentile; P90, 90<sup>th</sup> percentile; PCS, physical component score; QOL, quality of life.

differences across regimen classes was not statistically significant ( $P=0.08$ ). There were no notable findings in analyses of MCS adjusted for age, sex, and race/ethnicity (Supplemental Figure 6, Supplemental Digital Content, <http://links.lww.com/QAD/D716>).

Single variable analyses for associations between CAD markers and MCS revealed neither strong nor statistically significant associations with PCS (Supplemental Figure 7, <http://links.lww.com/QAD/D716>).

#### *Comprehensive multivariable modeling for factors associated with mental component summary*

As no factors emerged as significant predictors of MCS, we were unable to perform comprehensive multivariable modeling for factors associated with MCS.

#### **Associations between Duke Activity Status Instrument and physical component summary and mental component summary**

In Spearman correlations, a strong association was apparent between DASI score and PCS ( $r=0.48$ ;  $P<0.0001$ ) (Supplemental Table 1, <http://links.lww.com/QAD/D716>). A modest association was seen between DASI score and MCS ( $r=0.24$ ;  $P<0.0001$ ).

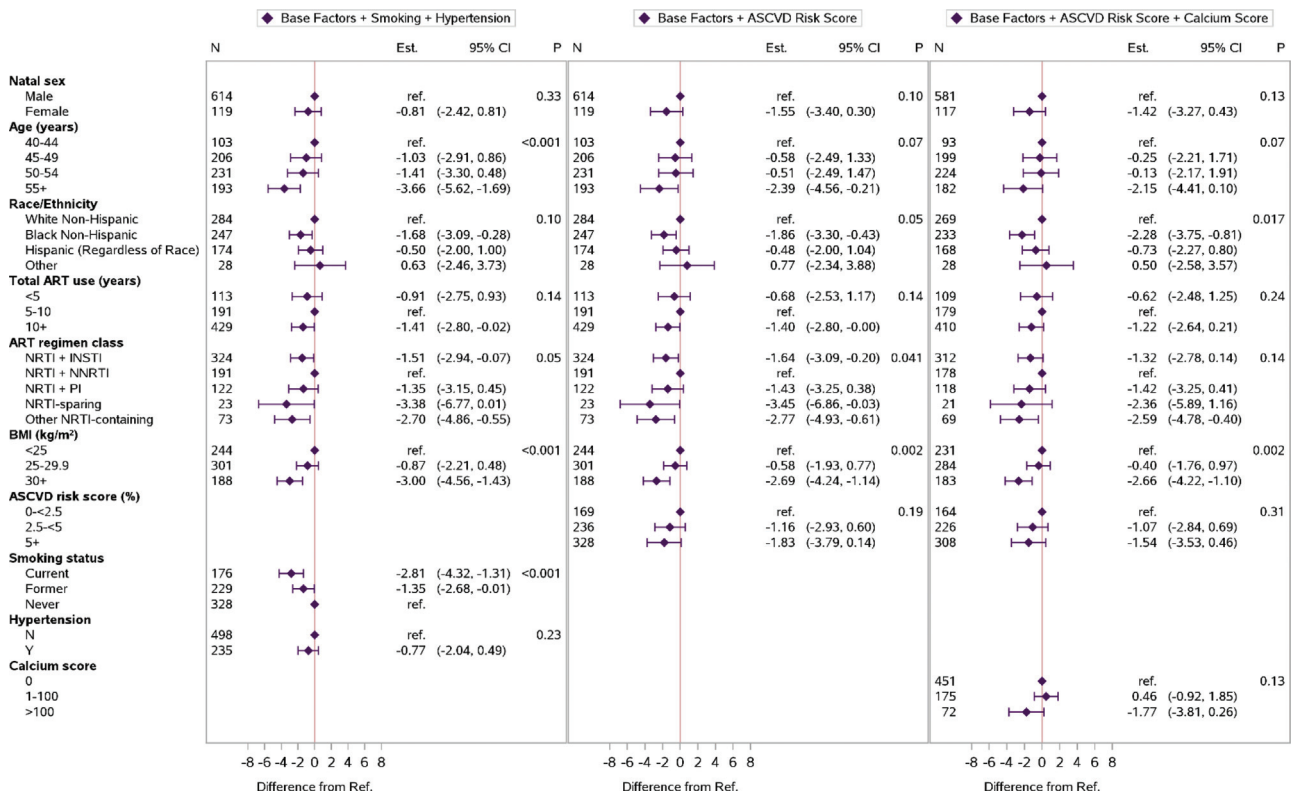
#### **Statin effects on physical component summary and mental component summary**

Analyses of changes in PCS and MCS from baseline to month 24 by treatment arm did not reveal any adverse or

favorable effects of pitavastatin. The estimated mean change in PCS was  $-0.22$  (95% CI:  $-1.01, 0.57$ ) points among participants randomized to pitavastatin and  $-0.14$  ( $-0.70, 0.42$ ) points among those randomized to placebo. The estimated mean changes in MCS were  $-0.90$  (95% CI:  $-1.93, 0.12$ ) points and  $-0.42$  ( $-1.14, 0.30$ ) points for pitavastatin and placebo, respectively (Table 2). There were no apparent effects of age, sex, race, or ethnicity on change in PCS or MCS.

## **Discussion**

In a well characterized cohort of PWH from the REPRIEVE Mechanistic Substudy, encompassing a group of 733 participants with low-to-moderate ASCVD risk, we explored cardiometabolic characteristics associated with physical and mental HRQoL domains assessed by the SF-36v2 questionnaire. Our findings showed that the factors most strongly associated with worse physical HRQoL were older age, Black non-Hispanic race, elevated BMI, and current/former cigarette smoking. These associations are consistent in well-established findings in the general population [25–28], and our study now demonstrates comparable associations between established risk factors and PCS among PWH, while also considering HIV specific factors like immune function that have been understudied in relation to HRQoL. Our study findings did not show strong associations between



**Fig. 1. Comprehensive linear regression models for association of baseline demographics and characteristics with PCS.** Risk factor estimates and 95% confidence intervals are from single multivariable linear regression models of PCS scores including all presented risk factors. ART, antiretroviral therapy; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PCS, physical component score; PI, protease inhibitor.

coronary artery disease factors and physical HRQoL, in fully adjusted models. Parallel analyses evaluating factors associated with mental HRQoL did not reveal any substantial associations. Notably, these findings reinforce the overall safety profile of statins and highlight areas of focus to preserve quality of life among the aging population of PWH.

Our study found that Black or African American race, but not sex at birth, was associated with lower physical HRQoL scores. The former finding aligns with prior studies showing that non-White race is associated with worse physical HRQoL [29,30] and prior work from REPRIEVE showing that Black race was associated with greater physical impairment [31,32]. Our finding that sex at birth was not associated with physical or mental HRQoL differs from prior studies, which have suggested that women are more likely to have poor HRQoL and worse physical function as compared to men [31,33–35]. Future studies are needed to identify and address factors contributing to disparities in HRQoL among PWH.

The study analyses show that having an elevated BMI >30 kg/m<sup>2</sup> was associated with a lower PCS score and remained statistically significant in adjusted analyses. A BMI >30 kg/m<sup>2</sup> is classified as obesity, and rates of obesity

continue to rise worldwide, contributing to cardiovascular, metabolic, and musculoskeletal conditions [36]. Two previous systematic reviews of the general population identified a relationship between higher BMI and PCS, where increased BMI was associated with lower PCS [37,38]. In contrast, MCS was only reduced in individuals with a BMI >40 kg/m<sup>2</sup>[37]. One review also highlighted the relationship between weight loss and improved HRQoL through bariatric surgery, a nontraditional method of weight loss [37]. In a cross-sectional study conducted by Martin *et al.*, PWH, as compared to people without HIV, were less likely to meet the regular physical activity WHO-recommended guidelines, and those who reported higher physical activity were shown to have higher quality of life scores [9]. Additionally, the association of comorbidity (additional coexisting conditions beyond HIV) was strongly correlated to lower PCS [9]. Given the association between obesity and lower QoL and PCS observed in this study, along with its correlation with various health conditions, it is essential to focus on reducing obesity rates in PWH.

Cigarette smoking was strongly associated with worse physical HRQoL, consistent with existing findings that smoking is linked to adverse health outcomes and highlights the importance of continued efforts in smoking

cessation. The negative health effects of smoking are well established [39,40]. Epidemiologic studies have shown that PWH have higher rates of cigarette smoking compared to the general population [41,42], and among PWH, QoL is worse among those who smoke compared to those who do not [43,44]. Quitting smoking has been shown to improve QoL in the general population [45]. This finding is reinforced by our study, which showed that former cigarette use had a smaller negative effect on physical HRQoL compared to current use. However, rates of smoking cessation among PWH are low [46] despite estimates suggesting that two-thirds of PWH who smoke were planning to quit and had made past attempts to quit. Studies of factors influencing smoking cessation found that PWH who currently smoke have a lower perceived health risk for continued smoking compared to those who had stopped smoking, and greater emotional distress and substance use were notable barriers to smoking cessation [47]. Additionally, in the general population, while low physical QoL was a motivator to quit smoking among individuals without depressed mood, in individuals with depressed mood, low physical QoL was a barrier to quitting smoking [48]. These studies emphasize the need for holistic efforts to address known barriers to smoking cessation to preserve QoL in this aging population.

In longitudinal analyses, statin therapy did not have a notable effect on HRQoL. PCS and MCS were not substantially different when analyzed by treatment group, and scores changed minimally over two years of follow-up [49]. Some studies have reported adverse effects of statins on muscle function and cognition [50,51], our study showed there no significant negative association between statin use with physical or mental quality of life. This finding is reassuring with respect to recent clinical guidelines changes regarding the use of statins in the HIV population [52–54]. This is an important safety finding and supports the use of statins for the primary prevention of MACE in this low-to-moderate ASCVD risk population without concern of detrimental effects on physical or mental quality of life. Previous studies from REPRIEVE further support the safety of statin use in this population, finding that statin therapy did not negatively affect neurocognitive function [55], physical function [56], or noncardiovascular events [57], including AIDS-defining events, cancers, renal and liver disease. In addition, adverse events and safety findings, such as muscle aches and myalgias, were uncommon in REPRIEVE [18,19]. Taken together, these findings underscore the safety profile of statins in PWH for primary CVD prevention without significant adverse events or impairment in quality of life.

The major strengths of this study include the large cohort of PWH, prospectively enrolled from various sites across the US, and well characterized for cardiometabolic and CAD characteristics. Our longitudinal findings are further

strengthened by the randomized-controlled study design and blinded statin assignment. There are a few limitations to note. First, the REPRIEVE trial population was recruited for low-to-moderate ASCVD risk and the substudy population was limited to the US. Therefore, our study results may not be generalizable to the broader, global population of PWH with different risk profiles. The baseline analysis of factors associated with PCS and MCS is cross-sectional in nature, comparing the PCS and MCS with various factors collected at baseline. This limits our ability to determine causality between the risk factors and HRQoL. However, we were able to assess changes in PCS and MCS over 2 years to assess trends in relation to statin randomization, and we did not observe differences in change in score by statin randomization, age, sex, race, or ethnicity. Measures of HRQoL may also differ in other regions. Despite these limitations, our findings do highlight important factors that may be deleterious to preservation of HRQoL in PWH across the lifespan, particularly among those living in the US. Future longer longitudinal studies may help to determine whether statins have potential effects on HRQoL, possibly through improvement in CVD health.

Among PWH in the REPRIEVE Mechanistic Substudy with low-to-moderate ASCVD risk, utilizing the SF-36v2 instrument, we found that older age, Black non-Hispanic race, higher BMI, and smoking were associated with worse physical HRQoL. Notably, our analysis showed no strong association between cardiometabolic factors and physical HRQoL in adjusted models. For mental HRQoL, no significant associations were found in this cohort. Moreover, statin use did not have a negative effect on quality of life in the study population. These findings highlight the importance of addressing modifiable risk factors in PWH to sustain, preserve, and enhance quality of life across the lifespan.

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### Conflicts of interest

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