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Cardiovascular Risk and Health Among People With Human Immunodeficiency Virus (HIV) Eligible for Primary Prevention: Insights From the REPRIEVE Trial

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Background. In addition to traditional cardiovascular (CV) risk factors, antiretroviral therapy, lifestyle, and human immunodeficiency virus (HIV)-related factors may contribute to future CV events in persons with HIV (PWH).

Methods. Among participants in the global REPRIEVE randomized trial, we characterized demographics and HIV characteristics relative to ACC/AHA pooled cohort equations (PCE) for atherosclerotic CV disease predicted risk and CV health evaluated by Life's Simple 7 (LS7; includes smoking, diet, physical activity, body mass index, blood pressure, total cholesterol, and glucose).

Results. Among 7382 REPRIEVE participants (31% women, 45% Black), the median PCE risk score was 4.5% (lower and upper quartiles Q1, Q3: 2.2, 7.2); 29% had a PCE score <2.5%, and 9% scored above 10%. PCE score was related closely to known CV risk factors and modestly (<1% difference in risk score) to immune function and HIV parameters. The median LS7 score was 9 (Q1, Q3: 7, 10) of a possible 14. Only 24 participants (0.3%) had 7/7 ideal components, and 36% had ≤2 ideal components; 90% had <5 ideal components. The distribution of LS7 did not vary by age or natal sex, although ideal health was more common in low sociodemographic index countries and among Asians. Poor dietary and physical activity patterns on LS7 were seen across all PCE scores, including the lowest risk categories.

Conclusions. Poor CV health by LS7 was common among REPRIEVE participants, regardless of PCE. This suggests a critical and independent role for lifestyle interventions in conjunction with conventional treatment to improve CV outcomes in PWH.

Clinical Trials Registration: NCT02344290.

Keywords. atherosclerotic cardiovascular disease; cardiac prevention; cardiovascular health; cardiovascular risk; lifestyle modifications.

Persons with human immunodeficiency virus (HIV, PWH) are at increased risk for major adverse cardiovascular (CV) events, including myocardial infarction, heart failure, stroke, pulmonary hypertension, and sudden cardiac death [1-4], even after controlling for known risk factors. The associations between HIV and CV events are multifactorial and include inflammation and immune function changes related to chronic infection as well as metabolic dysregulation associated with HIV [2, 3, 5]. Furthermore, HIV is associated with adverse social determinants of health, with attendant increases in CV risk [6, 7]. Finally, both uncontrolled viremia and antiretroviral therapy (ART) can adversely affect CV risk factors and may increase CV risk [8].

As survival with HIV has improved, the relative impact of cardiovascular disease (CVD) has increased [6]. As a result, CVD is an important, potentially modifiable cause of morbidity and mortality [9] and an important challenge [10]. Although HIV is recognized in current guidelines [11] as a "risk enhancer" using the American College of Cardiology/American Heart Association Pooled Cohort Equations (PCE), optimal strategies for primary prevention in PWH remain unknown.

In addition to traditional risk factors and scores, the American Heart Association recommends evaluating Life's Simple 7 (LS7) as a novel, comprehensive measure of CV health,

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both to characterize populations and to guide interventions [12]. LS7 was conceived as more actionable given its inclusion of 4 health behaviors—smoking, diet, physical activity, and body mass index (BMI)—and 3 health factors—blood pressure, total cholesterol, and glucose—with defined goals for improvement. Furthermore, LS7 is closely associated with CV outcomes in multiple cohorts [13]. However, to our knowledge, it has not been applied in a population of PWH.

The Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) is the largest long-term randomized trial to assess statin therapy as a primary CVD prevention strategy among PWH [14]. Using baseline data from trial participants enrolled across 5 continents, we sought to describe CVD risk factor distributions, examine associations between CVD risk and HIV characteristics, and characterize CV health among middle-aged PWH without known CVD.

METHODS

Trial Design and Study Participants

REPRIEVE (NCT02344290) enrolled 7770 participants in a prospective, double-blind, placebo-controlled, multicenter, phase III efficacy study comparing pitavastatin calcium 4 mg daily versus placebo among PWH on ART [14]. The trial enrolled at >100 sites in 12 countries between March 2015 and July 2019. Primary entry criteria included PWH ≥40 and ≤75 years of age, on stable combination ART for at least 6 months, with a CD4 + T-cell count >100 cells/mm^3 and low-to-intermediate 10-year atherosclerotic cardiovascular disease (ASCVD) risk of <15%, in combination with low-density lipoprotein (LDL) cholesterol level as previously described [15]. During the course of the study, the ASCVD eligibility criterion was modified to ensure adequate numbers across the desired spectrum of low to intermediate traditional risk [14]. Key exclusion criteria throughout enrollment included known CV disease, diabetes with LDL cholesterol ≥70 mg/dL, impaired renal function, decompensated cirrhosis, active cancer, and ongoing statin use. Details are available in the REPRIEVE rationale and design article [14].

At trial entry, detailed information on medical history and lifestyle behaviors was ascertained. Diet and physical activity assessments were conducted using the Rapid Eating and Activity Assessment for Patients Questionnaire [16]. In addition to lipids tested locally that were used to determine trial eligibility, fasting lipids were obtained at study entry and tested at a Quest Diagnostic lab (Baltimore, Maryland, USA). Further information on ascertainment methods of key data elements and their presentation is provided in the Supplementary materials.

The coordinating centers and sites obtained institutional review board and other applicable regulatory entity approvals. All participants provided informed consent.

CV Risk and Health Scores

PCE were used to predict 10-year CV risk [15]. Because the PCE risk score used to determine study eligibility may have been obtained with nonfasting lipids, we recalculated the score using centrally tested fasting lipids from study entry, and other inputs as recorded into the study database. The recalculated PCE score showed good agreement with site scores used for study eligibility (not shown).

CV health was evaluated with LS7 metrics adapted from Lloyd-Jones et al [12] with modifications for scoring diet, physical activity, and smoking (Supplementary Tables 1 and 2). Each individual component of LS7 was categorized as ideal, intermediate, and poor. A total of 5–7 ideal components out of 7 was considered ideal, 3–4 intermediate, and ≤2 poor overall CV health, according to prognostically validated cut points. An ordinal overall score was calculated as the sum of the 7 individual components as either poor (0 points), intermediate (1 point), or ideal (2 points), yielding a scale from 0 (worst) to 14 (best).

Further details on PCE and LS7 and their adaptation in REPRIEVE are provided in the Supplementary materials.

Statistical Analysis

CVD risk prediction by PCE was described using summary statistics and risk categories (<2.5%, 2.5% to <5%, 5% to <7.5%, 7.5% to 10%, >10%), overall and within strata defined by unmodifiable PCE components: sex, race (Black, non-Black), and age (40–49 years, 50–59 years, ≥60 years). The contributions of modifiable PCE components (total cholesterol, high-density lipoprotein [HDL] cholesterol, systolic blood pressure, hypertension treatment, smoking, and diabetes) were examined by PCE risk score categories overall and stratified by sex, race, and age.

PCE risk score distributions in relation to HIV characteristics were examined graphically using box plots. Furthermore, linear regression models were used to estimate the effect size, adjusted for sex, race, age, and enrollment period (before and after enrollment closed to participants with lowest CVD risk). Evaluation of ART types was also adjusted by sociodemographic index (SDI) (high including US, Canada, and Europe vs middle/low) to account for regional differences in ART use known from previous analyses [17].

CV health by LS7 was summarized descriptively overall, by factors of interest, and in relation to PCE risk category overall and stratified by sex, race, and age.

Given the large sample size and high power to detect minimal effect sizes, formal statistical inference was guided by very low significance level (alpha = 0.001) and clinically meaningful estimated effect sizes (1% shift in PCE risk score). All analyses were conducted using SAS software, Version 9.4 (TS1M5, SAS/STAT 14.3, SAS Institute Inc., Cary, North Carolina, USA) on a Linux operating environment.

RESULTS

Population

Among the 7770 REPRIEVE participants, PCE risk score was calculated using centrally determined fasting lipids in 7382

Table 1. Demographics, Risk Factors, and Human Immunodeficiency Virus (HIV) Characteristics by Pooled Cohort Equations (PCE) Risk Score

Characteristic[a]	PCE Risk Score (%)					
	Total (N = 7382)	0–<2.5 (N = 2113, 29%)	2.5–<5 (N = 1956, 26%)	5–<7.5 (N = 1676, 23%)	7.5–10 (N = 954, 13%)	>10 (N = 683, 9%)
Demographics						
Sociodemographic index						
High	3 986 (54%)	840 (40%)	1075 (55%)	1010 (60%)	618 (65%)	443 (65%)
Middle	2 663 (36%)	1087 (51%)	677 (35%)	477 (28%)	239 (25%)	183 (27%)
Low	733 (10%)	186 (9%)	204 (10%)	189 (11%)	97 (10%)	57 (8%)
Age, y	50 (45, 55)	45 (42, 48)	49 (46, 53)	53 (48, 56)	55 (51, 59)	57 (53, 61)
Min, Max	40, 74	40, 61	40, 66	40, 69	40, 72	40, 74
Natal sex						
Male	5066 (69%)	779 (37%)	1467 (75%)	1418 (85%)	816 (86%)	586 (86%)
Female	2316 (31%)	1334 (63%)	489 (25%)	258 (15%)	138 (14%)	97 (14%)
Race						
Black	3294 (45%)	755 (36%)	825 (42%)	821 (49%)	485 (51%)	408 (60%)
White	2614 (35%)	654 (31%)	762 (39%)	618 (37%)	367 (38%)	213 (31%)
Asian	923 (13%)	519 (25%)	205 (10%)	129 (8%)	43 (5%)	27 (4%)
Other	551 (7%)	185 (9%)	164 (8%)	108 (6%)	59 (6%)	35 (5%)
Cardiovascular risk factors						
Smoking status						
Current	1852 (25%)	147 (7%)	361 (18%)	568 (34%)	398 (42%)	378 (55%)
Former	1845 (25%)	458 (22%)	559 (29%)	460 (27%)	238 (25%)	130 (19%)
Never	3685 (50%)	1508 (71%)	1036 (53%)	648 (39%)	318 (33%)	175 (26%)
Family history of premature CVD						
Yes	1385 (19%)	357 (17%)	380 (19%)	308 (18%)	198 (21%)	142 (21%)
No	5763 (78%)	1710 (81%)	1514 (77%)	1326 (79%)	704 (74%)	509 (75%)
Unknown	230 (3%)	44 (2%)	61 (3%)	42 (3%)	51 (5%)	32 (5%)
Hypertension	2624 (36%)	401 (19%)	596 (30%)	671 (40%)	499 (52%)	457 (67%)
History of diabetes	63 (1%)	2 (<0.5%)	10 (1%)	10 (1%)	10 (1%)	31 (5%)
BMI, kg/m^2	25.9 (22.9, 29.5)	25.6 (22.5, 29.6)	26.0 (23.0, 29.6)	25.9 (23.1, 29.1)	26.0 (23.2, 29.4)	26.2 (22.9, 29.9)
Waist circumference, cm	92 (84, 101)	90 (82, 99)	92 (85, 101)	93 (85, 101)	94 (86, 103)	95 (86, 103)
Metabolic syndrome	2046 (28%)	382 (18%)	556 (29%)	502 (30%)	331 (35%)	275 (41%)
History of depression treatment	2149 (29%)	518 (25%)	573 (29%)	513 (31%)	309 (32%)	236 (35%)
Entry lipids						
Triglycerides, mg/dL	112 (80, 166)	98 (72, 141)	116 (83, 171)	120 (83, 179)	123 (85, 177)	127 (88, 199)
Total cholesterol, mg/dL	183 (160, 208)	180 (157, 204)	182 (159, 208)	185 (161, 212)	188 (164, 213)	182 (159, 206)
LDL-C, mg/dL	106 (86, 128)	103 (85, 123)	106 (86, 128)	108 (88, 131)	112 (90, 132)	105 (86, 125)
HDL-C, mg/dL	47 (39, 59)	51 (42, 63)	47 (39, 57)	46 (39, 57)	45 (37, 57)	44 (36, 53)
Cardiovascular medications						
Ever been on a statin	475 (6%)	111 (5%)	124 (6%)	108 (6%)	81 (8%)	51 (7%)
Current use of antihypertensive medication	1470 (20%)	179 (8%)	300 (15%)	346 (21%)	319 (33%)	326 (48%)
Current use of antiplatelet therapy	272 (4%)	27 (1%)	61 (3%)	88 (5%)	54 (6%)	42 (6%)

Table 1. Continued

Characteristic[a]	Total (N = 7382)	PCE Risk Score (%) 0–<2.5 (N = 2113, 29%)	2.5–<5 (N = 1956, 26%)	5–<7.5 (N = 1676, 23%)	7.5–10 (N = 954, 13%)	>10 (N = 683, 9%)
Current use of non-statin lipid-lowering therapy	159 (2%)	34 (2%)	51 (3%)	41 (2%)	23 (2%)	10 (1%)
HIV characteristics						
Nadir CD4 count, cells/mm^3						
<50	1342 (18%)	319 (15%)	361 (18%)	338 (20%)	193 (20%)	131 (19%)
50–199	2219 (30%)	639 (30%)	575 (29%)	513 (31%)	267 (28%)	225 (33%)
200–349	1960 (27%)	611 (29%)	518 (26%)	434 (26%)	245 (26%)	152 (22%)
≥350	1616 (22%)	494 (23%)	454 (23%)	326 (19%)	204 (21%)	138 (20%)
Unknown	245 (3%)	50 (2%)	48 (2%)	65 (4%)	45 (5%)	37 (5%)
History of AIDS-defining diagnosis	1724 (23%)	504 (24%)	430 (22%)	417 (25%)	225 (24%)	148 (22%)
CD4 count, cells/mm^3	626 (453, 832)	646 (480, 840)	629 (465, 839)	616 (428, 814)	597 (435, 823)	623 (434, 842)
CD4:CD8 ratio	0.83 (0.57, 1.16)	0.88 (0.64, 1.22)	0.83 (0.56, 1.17)	0.80 (0.52, 1.13)	0.78 (0.52, 1.09)	0.75 (0.50, 1.05)
HIV-1 RNA, copies/mL						
<LLQ	5140 (88%)	1448 (89%)	1365 (87%)	1160 (87%)	688 (87%)	479 (86%)
LLQ–< 400	593 (10%)	144 (9%)	158 (10%)	136 (10%)	88 (11%)	67 (12%)
≥400	128 (2%)	27 (2%)	39 (2%)	36 (3%)	15 (2%)	11 (2%)
Antiretroviral treatment						
Total ART use, y	10 (5, 15)	9 (5, 13)	9 (5, 15)	10 (6, 16)	11 (6, 16)	12 (7, 18)
Entry ART regimen duration, y	2.3 (0.8, 5.1)	2.5 (0.8, 5.1)	2.4 (0.8, 5.3)	2.3 (0.8, 5.3)	2.1 (0.8, 4.9)	1.9 (0.8, 4.3)
Entry ART regimen class						
NRTI + NNRTI	3409 (46%)	1197 (57%)	896 (46%)	683 (41%)	363 (38%)	270 (40%)
NRTI + INSTI	1911 (26%)	394 (19%)	524 (27%)	468 (28%)	314 (33%)	211 (31%)
NRTI + PI	1411 (19%)	412 (19%)	370 (19%)	338 (20%)	170 (18%)	121 (18%)
NRTI-sparing	195 (3%)	34 (2%)	55 (3%)	55 (3%)	32 (3%)	19 (3%)
Other NRTI-containing	456 (6%)	76 (4%)	111 (6%)	132 (8%)	75 (8%)	62 (9%)
Entry NRTI[b]						
ABC	952 (13%)	177 (8%)	237 (12%)	258 (15%)	157 (16%)	123 (18%)
TDF	4514 (61%)	1562 (74%)	1211 (62%)	940 (56%)	474 (50%)	327 (48%)
TAF	1064 (14%)	155 (7%)	271 (14%)	287 (17%)	198 (21%)	153 (22%)
Other	852 (12%)	219 (10%)	237 (12%)	191 (11%)	125 (13%)	80 (12%)

Data shown are n (%) for categorical measures, median with lower and upper quartiles (Q1, Q3) for continuous measures. For age, minimum (min) and maximum (max) are also shown. All statistics are calculated out of participants with data collected. Missing data include family history of premature CVD (n = 4); BMI (n = 4); waist circumference (n = 97); metabolic syndrome (n = 34); LDL-C (n = 46); CD4:CD8 ratio (n = 1217); HIV-1 RNA (n = 1521); total ART use (n = 2); entry ART regimen duration (n = 1).

Abbreviations: ABC, abacavir; ART, antiretroviral therapy; BMI, body mass index; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; INSTI, integrase strand transfer inhibitor; LDL-C, low-density lipoprotein cholesterol; LLQ, lower limit of quantification; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

[a]Refer to Supplementary materials for definitions of characteristics and ascertainment of associated data elements.

[b]Entry NRTI is defined as any ABC use including use with TDF (n = 63) or TAF (n = 6), TDF without ABC, TAF without ABC, and Other.

participants, with a median age of 50 years (lower and upper quartiles Q1, Q3: 45, 55; minimum, maximum: 40, 74); 69% were natal males, and 45% Black, 35% White, and 13% Asian (Table 1). The 388 participants excluded from the analysis (380 due to no fasting lipids [69% of those due to participant not fasting] and 8 due to missing smoking status) included a higher proportion of participants from countries with low SDI (56% vs 10% among those included in the analysis) and non-Blacks (81% vs 55%); distributions of sex and age were similar (data not shown).

Risk Factors

CV risk factors were common, with 50% being current or former smokers, 19% having a family history of premature CVD, 36% being hypertensive, a median BMI of 25.9 kg/m^2, and 29% having a history of treatment for depression (Table 1). Trial entry criteria limited enrollment of people with diabetes to those with very low LDL cholesterol [14]. The overall median PCE risk score was 4.5% (Q1, Q3: 2.2, 7.2), with the proportion of participants decreasing from 29% in the lowest PCE risk category (<2.5%) to 9% in the highest category (>10%); 78% had a PCE risk score <7.5%. As expected, the prevalence of factors used to compute the PCE score increased across increasing PCE risk categories, including age, sex, smoking, diabetes, race, and elevated blood pressure. There were limited increases in LDL cholesterol across PCE risk categories, as expected based on trial entry criteria.

Risk factors not included in the PCE scoring algorithm, including depression, metabolic syndrome, and waist circumference, were more prevalent in the higher PCE risk categories. For example, across PCE risk categories, median waist circumference increased by 5 cm, metabolic syndrome prevalence increased from 18% to 41%, and the proportion of participants from high SDI countries increased from 40% to 65% (Table 1).

Relative Contribution of Risk Score Components

PCE risk score distributions stratified by unmodifiable PCE components (sex, race, and age) are shown in Figure 1. The distributions of modifiable PCE components across risk score categories suggested a strong contribution of hypertension treatment and blood pressure across all subgroups, greatest among Blacks (Supplementary Figure 1*A*). Likewise, the percentage of smokers also increased with increasing risk score categories with more smokers in the younger age groups (data not shown). In contrast, trends in the distributions of total cholesterol and HDL cholesterol were less clear, perhaps due to constraining eligibility criteria (Supplementary Figure 1*B*), although greater contributions of total cholesterol and HDL cholesterol were seen among nonsmokers (data not shown).

HIV-related Characteristics and PCE

Median duration of ART use was 10 years (Q1, Q3: 5, 15), and 88% had viral suppression with a median CD4 count of

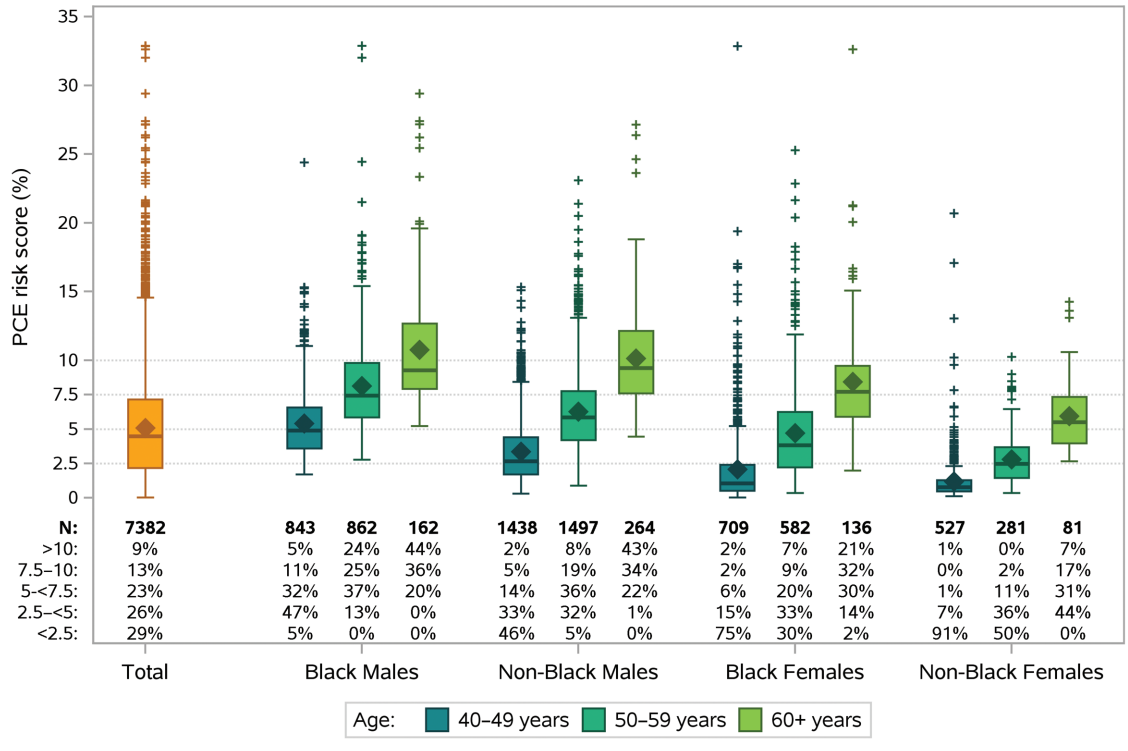

Figure 1. Distribution of PCE risk score by natal sex, race, and age. Distribution of PCE risk score as a continuous measure (box plots) and according to risk categories (axis table). Abbreviation: PCE, pooled cohort equations.

626 cells/mm^3 (Table 1). ART regimens are shown in Table 1. Comparison of HIV characteristics by PCE risk category showed some trends in ART duration and clinical immunologic parameters. For example, lower nadir CD4 was associated with increased PCE risk score but was attenuated when stratified by sex, race, and age (Supplementary Figure 2). In models adjusted for sex, race, age, and enrollment period, longer ART duration, entry ART regimen, lower nadir CD4, and higher entry CD4 were each associated with higher PCE risk score ($P < .001$), but all effect sizes were small (upper bound of 99.9% confidence interval [CI] was <1% difference in score; Figure 2).

Life's Simple 7

The population median LS7 score (out of an ideal score of 14) was 9 (Q1, Q3: 7, 10; Figure 3). Ten percent had overall ideal CV health (≥5/7 ideal components) including 24 participants (0.3%) with 7/7 ideal components, 2% with 6 out of 7, and 8% with 5 out of 7 ideal components. Table 2 shows distribution of overall CV health by demographics and select characteristics. Thirty-six percent (34% of women; 37% of men) met ideal targets in ≤2 components, considered poor CV health. LS7 distributions were similar by sex, age, most HIV characteristics, and ART use. Asians and those in low SDI regions had a higher proportion with overall ideal CV health, largely driven by lower BMI and less smoking (Supplementary Figure 3). Note that the majority of Asians were enrolled from low and middle SDI countries.

When assessed in relation to PCE CV risk, LS7 scores for smoking, blood pressure, and glucose all worsened with increasing PCE risk, as expected given their inclusion as PCE components. As a result, the number of components meeting ideal targets and LS7 score also tracked with PCE (Figure 4, Table 3). In contrast, diet quality, physical activity, total cholesterol, and BMI did not show clinically significant variation with increasing PCE overall, although trends with BMI were more apparent when stratified by sex, race, and age (Supplementary Figure 4). Importantly, the lifestyle-modifiable components of poor dietary and physical activity patterns and BMI were common even among those with low PCE score. Indeed across the entire cohort, only 111 participants (2%) had ideal lifestyle components (3/3 ideal health behaviors), 11% had 2 out of 3, and 87% (91% of women; 86% of men) had either 1 out of 3 ideal health behaviors (43%) or none (44%).

DISCUSSION

Among 7382 participants in the global REPRIEVE trial, CV risk measured by the PCE risk score tracked with demographics and

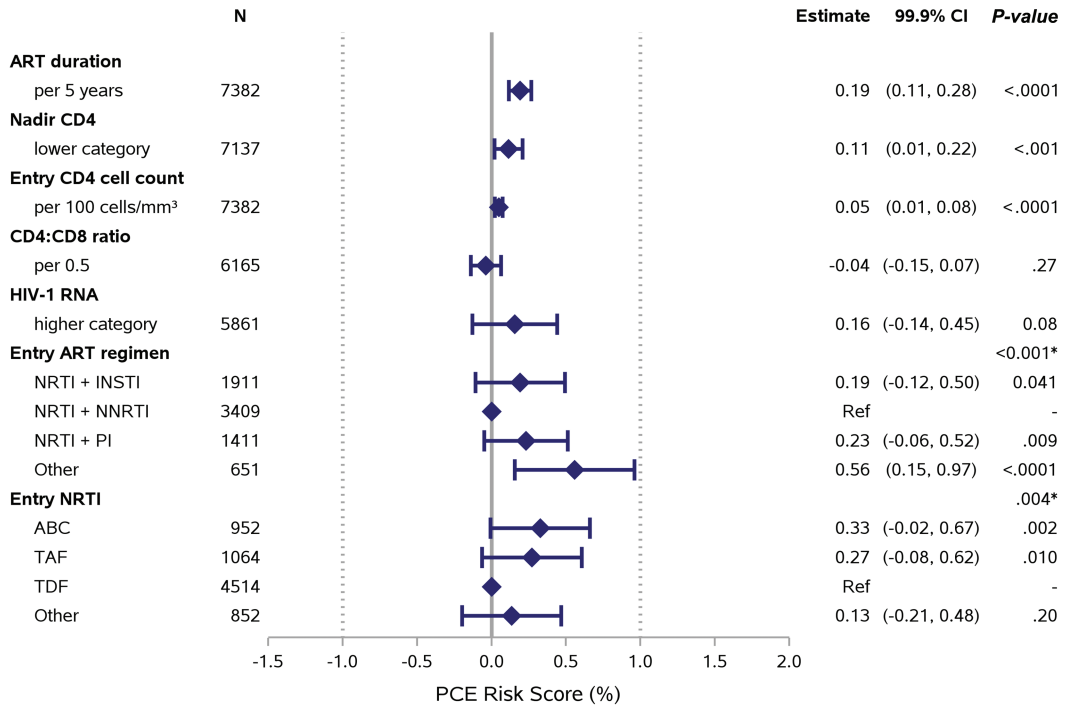

Figure 2. Associations between HIV characteristics and PCE risk score. Each factor of interest was evaluated in a separate linear regression model, adjusted for natal sex, race, age, and enrollment period. The models for ART regimen and NRTI also adjusted for sociodemographic index. Nadir CD4 categories (<50, 50–199, 200–349, ≥350 cells/mm^3) and HIV-1 RNA categories (<LLQ, LLQ –<400, ≥400 copies/mL) were treated as linear terms. Reference lines are shown at 0% (no effect) and at shift of 1% (minimum clinically meaningful effect). Other ART regimen includes other NRTI-containing and NRTI-sparing regimens. Other NRTI includes no NRTI. *Type 3 *P*-values for any difference between groups. Abbreviations: ABC, abacavir; ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; HIV-1, human immunodeficiency virus type 1; INSTI, integrase strand transfer inhibitor; LLQ, lower limit of quantification; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PCE, pooled cohort equations; PI, protease inhibitor; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

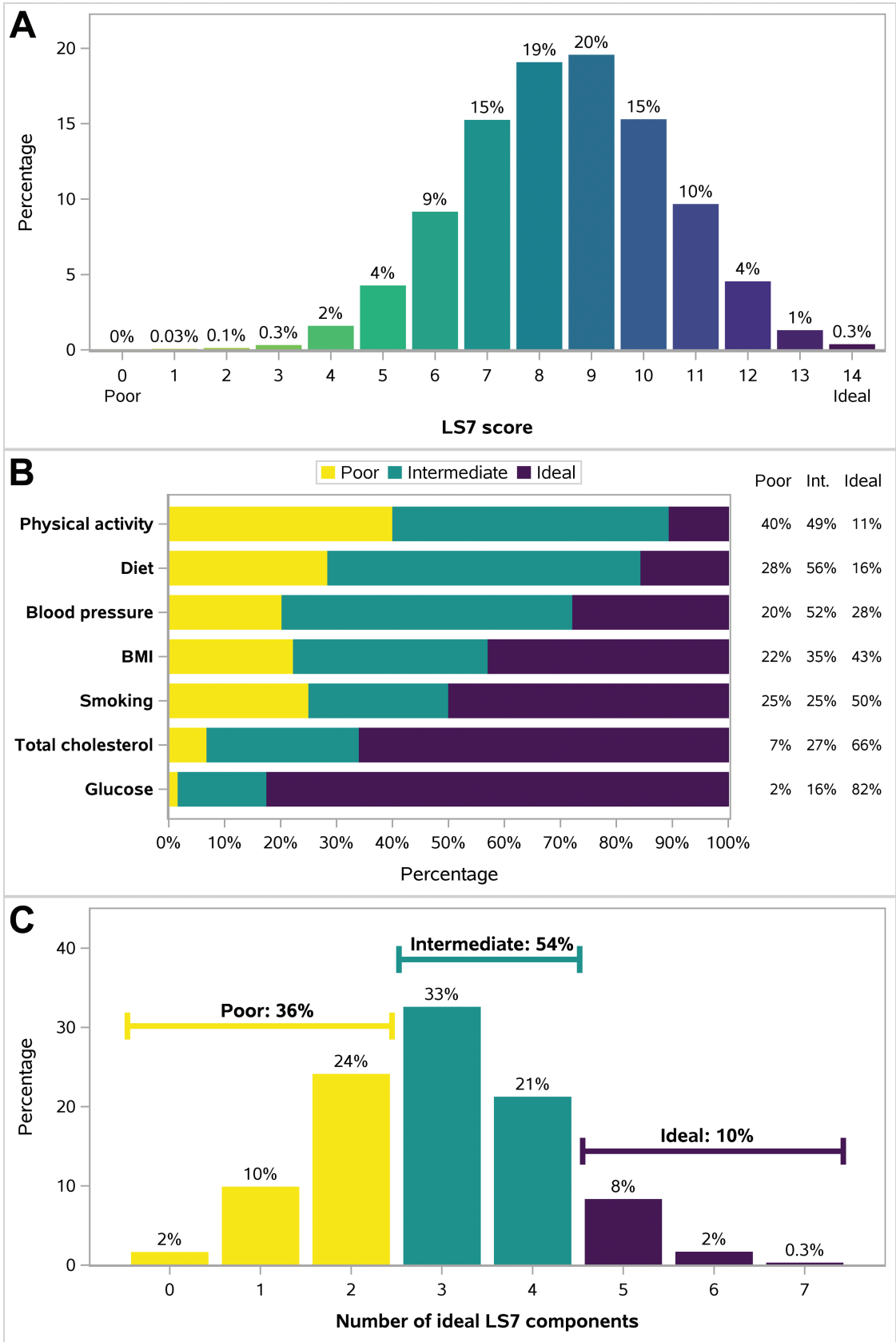

Figure 3. Distribution of LS7. *A*, Overall LS7 score. *B*, Individual LS7 components. *C*, Overall ideal CV health categories based on number of components meeting ideal targets. Number of participants = 7382. Percentages are calculated out of participants with data collected. Missing data include: number of ideal LS7 components and LS7 score (n = 89); BMI (n = 4); physical activity (n = 25); diet (n = 18); glucose (n = 53). Abbreviations: BMI, body mass index; CV, cardiovascular; Int, intermediate; LS7, Life's Simple 7.

Table 2. Life's Simple 7 (LS7) by Demographics, Risk Factors and Human Immunodeficiency Virus (HIV) Characteristics

Characteristic[b]		Total (N = 7293)	Overall Cardiovascular Health by LS7[a]		
			Poor (N = 2607, 36%)	Intermediate (N = 3930, 54%)	Ideal (N = 756, 10%)
Demographics					
Sociodemographic index	High	3910	1727 (44%)	1889 (48%)	294 (8%)
	Middle	2652	776 (29%)	1588 (60%)	288 (11%)
	Low	731	104 (14%)	453 (62%)	174 (24%)
Age, y	40–49	3481	1079 (31%)	1967 (57%)	435 (12%)
	50–59	3177	1294 (41%)	1627 (51%)	256 (8%)
	≥60	635	234 (37%)	336 (53%)	65 (10%)
Natal sex	Male	5002	1838 (37%)	2665 (53%)	499 (10%)
	Female	2291	769 (34%)	1265 (55%)	257 (11%)
Race	Black	3256	1162 (36%)	1831 (56%)	263 (8%)
	White	2575	1056 (41%)	1278 (50%)	241 (9%)
	Asian	921	163 (18%)	546 (59%)	212 (23%)
	Other	541	226 (42%)	275 (51%)	40 (7%)
Cardiovascular risk factors					
Family history of premature CVD	Yes	1362	577 (42%)	680 (50%)	105 (8%)
	No	5700	1927 (34%)	3143 (55%)	630 (11%)
	Unknown	227	103 (45%)	103 (45%)	21 (9%)
History of depression treatment	Yes	2107	941 (45%)	1017 (48%)	149 (7%)
	No	5184	1665 (32%)	2912 (56%)	607 (12%)
Alcohol use	Rarely/Never	5421	1842 (34%)	2941 (54%)	638 (12%)
	Sometimes	1479	597 (40%)	782 (53%)	100 (7%)
	Usually/Often	393	168 (43%)	207 (53%)	18 (5%)
Substance use	Current	138	58 (42%)	68 (49%)	12 (9%)
	Former	2171	1021 (47%)	1023 (47%)	127 (6%)
	Never	4983	1528 (31%)	2838 (57%)	617 (12%)
HIV characteristics					
Nadir CD4 count (cells/mm^3)	<50	1325	489 (37%)	711 (54%)	125 (9%)
	50–199	2198	746 (34%)	1210 (55%)	242 (11%)
	200–349	1937	675 (35%)	1046 (54%)	216 (11%)
	≥350	1593	599 (38%)	836 (52%)	158 (10%)
	Unknown	240	98 (41%)	127 (53%)	15 (6%)
History of AIDS-defining diagnosis	Yes	1707	595 (35%)	904 (53%)	208 (12%)
	No	5586	2012 (36%)	3026 (54%)	548 (10%)
CD4 count (cells/mm^3)	<350	962	319 (33%)	519 (54%)	124 (13%)
	350–499	1350	440 (33%)	765 (57%)	145 (11%)
	≥500	4981	1848 (37%)	2646 (53%)	487 (10%)
CD4:CD8 ratio	<0.5	1194	417 (35%)	665 (56%)	112 (9%)
	0.5–<1	2720	901 (33%)	1522 (56%)	297 (11%)
	≥1	2177	795 (37%)	1143 (53%)	239 (11%)

Table 2. Continued

Characteristic[b]		Total (N = 7293)	Overall Cardiovascular Health by LS7[a]		
			Poor (N = 2607, 36%)	Intermediate (N = 3930, 54%)	Ideal (N = 756, 10%)
HIV-1 RNA (copies/mL)	<LLQ	5075	1971 (39%)	2643 (52%)	461 (9%)
	LLQ–< 400	583	254 (44%)	287 (49%)	42 (7%)
	≥400	127	42 (33%)	74 (58%)	11 (9%)
Antiretroviral treatment					
Total ART use, y	<5	1582	539 (34%)	884 (56%)	159 (10%)
	5–10	2132	754 (35%)	1156 (54%)	222 (10%)
	≥10	3577	1312 (37%)	1890 (53%)	375 (10%)
Entry ART regimen class	NRTI + NNRTI	3385	1032 (30%)	1926 (57%)	427 (13%)
	NRTI + INSTI	1872	827 (44%)	911 (49%)	134 (7%)
	NRTI + PI	1394	461 (33%)	790 (57%)	143 (10%)
	NRTI-sparing	192	88 (46%)	88 (46%)	16 (8%)
	Other NRTI-containing	450	199 (44%)	215 (48%)	36 (8%)
Entry NRTI[c]	ABC	937	414 (44%)	457 (49%)	66 (7%)
	TDF	4468	1398 (31%)	2559 (57%)	511 (11%)
	TAF	1040	522 (50%)	455 (44%)	63 (6%)
	Other	848	273 (32%)	459 (54%)	116 (14%)

Data shown are n (%).

Abbreviations: ABC, abacavir; ART, antiretroviral therapy; BMI, body mass index; CVD, cardiovascular disease; INSTI, integrase strand transfer inhibitor; LLQ, lower limit of quantification; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SDI, sociodemographic index; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

[a]Overall cardiovascular health defined by the number of ideal LS7 components: poor (0–2 ideal components), intermediate (3–4), and ideal (5–7).

[b]Refer to the Supplementary materials for definitions of characteristics and ascertainment of associated data elements.

[c]Entry NRTI is defined as any ABC use including use with TDF (n = 63) or TAF (n = 6), TDF without ABC, TAF without ABC and Other.

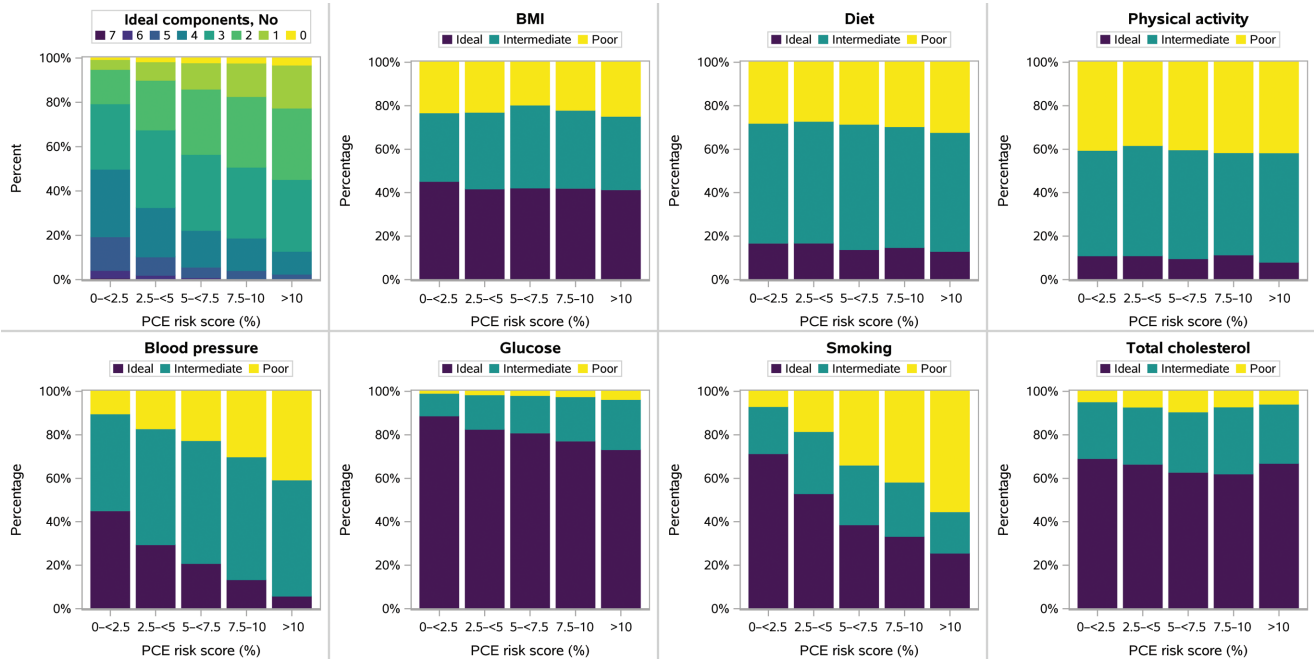

Figure 4. Life's Simple 7 by PCE risk score. Abbreviations: BMI, body mass index; PCE, pooled cohort equations.

risk factors. HIV-related factors and immune function parameters were less strongly associated, but in a direction suggesting importance of immune dysfunction. The vast majority (90%) of this global population with low to moderate CVD risk demonstrated poor to intermediate health using a standardized assessment of CV health. Several components, including BMI, physical activity, and diet, did not relate to the PCE risk score, suggesting the critical need to assess and address these poor health characteristics to improve overall CVD outcomes in this population.

As expected, higher PCE score tracked well with its input components including age, sex, race, smoking, and systolic blood pressure [15]. Relationships with diabetes and especially hyperlipidemia were limited by trial entry requirements. Known risk factors not included in the PCE inputs also tracked with increasing scores, including family history of premature CVD, depression, and the metabolic abnormalities of obesity, metabolic syndrome, and waist circumference.

Several HIV parameters were modestly related to PCE risk score. However, the higher PCE risk among those with longer ART duration is potentially due to long-term adverse effects of HIV infection or various ART regimens on metabolic pathways [18], including lipids [19]. PCE risk also tended to be higher among those with entry NRTI-containing regimens that included ABC or TAF. A relationship between ABC and increased myocardial infarction rates has been found in some studies [20], possibly related to effects on platelet and endothelial function [21], but not in other studies [22]. In contrast, TAF was associated with higher PCE, possibly due to enrollment timing, as well as direct effects on lipids levels relative to TDF, or preferential use in higher risk groups [23]. Notably, neither integrase strand transfer inhibitor use nor BMI was associated with PCE risk. In this cross-sectional study, it is impossible to assess complex relationships between various ART regimens and CV risk, lipids and inflammation, or outcomes.

Lower nadir CD4 was associated with increased PCE risk score, suggesting that degree of initial immune dysfunction relates to traditional longer-term risk indices. These findings are consistent with current theories, supported by associations between coronary plaque and arterial inflammation in HIV [24, 25], that increased inflammation and immune activation may contribute to excess CVD risk in PWH [24–26]. The degree and directionality of these effects extends our knowledge of the potential biological impact of immunological dysfunction on risk in PWH and suggests that immunological effects may be reflected in the components of the PCE score, despite its lack of any HIV-specific elements. Future REPRIEVE analyses will compare more nuanced mechanistic measures of immune function [27] to PCE risk, providing further insights as to whether immunologic factors drive events through risk pathways not assessed in traditional scoring algorithms.

In contrast to scores predicting risk for future CV events, LS7 assesses CV health. It is inversely and closely related to CV outcomes in diverse populations even after adjustment for age, race, and sex and other characteristics, as shown in a meta-analysis of nine prospective cohort studies involving 12 878 participants [13]. The LS7 metrics include only potentially modifiable components, some of which overlap with PCE (health factors:

Table 3. Life's Simple 7 (LS7) by Pooled Cohort Equations (PCE) Risk Score

Characteristic	Total (N = 7382)	PCE Risk Score (%)				
		0–<2.5 (N = 2113)	2.5–<5 (N = 1956)	5–<7.5 (N = 1676)	7.5–10 (N = 954)	>10 (N = 683)
LS7 overall						
Number of ideal LS7 components						
0	122 (2%)	13 (1%)	32 (2%)	35 (2%)	21 (2%)	21 (3%)
1	723 (10%)	94 (4%)	161 (8%)	196 (12%)	142 (15%)	130 (19%)
2	1762 (24%)	326 (16%)	433 (22%)	487 (29%)	300 (32%)	216 (32%)
3	2379 (33%)	619 (29%)	676 (35%)	566 (34%)	301 (32%)	217 (32%)
4	1551 (21%)	640 (30%)	430 (22%)	274 (17%)	138 (15%)	69 (10%)
5	609 (8%)	319 (15%)	160 (8%)	78 (5%)	36 (4%)	16 (2%)
6	123 (2%)	72 (3%)	32 (2%)	16 (1%)	3 (<1%)	0 (0%)
7	24 (<1%)	16 (1%)	7 (<1%)	0 (0%)	0 (0%)	1 (<1%)
LS7 score[a]						
Min-Max	1–14	3–14	1–14	1–13	2–13	3–14
Median (Q1, Q3)	9 (7, 10)	9 (8, 11)	9 (7, 10)	8 (7, 9)	8 (7, 9)	7 (6, 9)
10th, 90th percentiles	6–11	7–12	6–11	6–10	6–10	5–9
LS7 components						
LS7: Smoking						
Ideal (2)	3685 (50%)	1508 (71%)	1036 (53%)	648 (39%)	318 (33%)	175 (26%)
Intermediate (1)	1845 (25%)	458 (22%)	559 (29%)	460 (27%)	238 (25%)	130 (19%)
Poor (0)	1852 (25%)	147 (7%)	361 (18%)	568 (34%)	398 (42%)	378 (55%)
LS7: BMI						
Ideal	3163 (43%)	956 (45%)	817 (42%)	707 (42%)	401 (42%)	282 (41%)
Intermediate	2567 (35%)	666 (32%)	690 (35%)	639 (38%)	342 (36%)	230 (34%)
Poor	1648 (22%)	491 (23%)	449 (23%)	329 (20%)	210 (22%)	169 (25%)
LS7: Physical activity						
Ideal	773 (11%)	232 (11%)	215 (11%)	162 (10%)	109 (11%)	55 (8%)
Intermediate	3635 (49%)	1022 (49%)	987 (51%)	836 (50%)	448 (47%)	342 (50%)
Poor	2949 (40%)	853 (40%)	745 (38%)	672 (40%)	396 (42%)	283 (42%)
LS7: Diet						
Ideal	1146 (16%)	355 (17%)	329 (17%)	232 (14%)	141 (15%)	89 (13%)
Intermediate	4121 (56%)	1163 (55%)	1093 (56%)	964 (58%)	528 (56%)	373 (55%)
Poor	2097 (28%)	591 (28%)	529 (27%)	476 (28%)	281 (30%)	220 (32%)
LS7: Total cholesterol						
Ideal	4864 (66%)	1461 (69%)	1301 (67%)	1053 (63%)	592 (62%)	457 (67%)
Intermediate	2010 (27%)	551 (26%)	514 (26%)	465 (28%)	294 (31%)	186 (27%)
Poor	508 (7%)	101 (5%)	141 (7%)	158 (9%)	68 (7%)	40 (6%)
LS7: Blood pressure						
Ideal	2048 (28%)	953 (45%)	577 (29%)	350 (21%)	128 (13%)	40 (6%)
Intermediate	3836 (52%)	942 (45%)	1043 (53%)	947 (57%)	539 (56%)	365 (53%)
Poor	1498 (20%)	218 (10%)	336 (17%)	379 (23%)	287 (30%)	278 (41%)

Table 3. Continued

Characteristic	Total (N = 7382)	PCE Risk Score (%) 0–<2.5 (N = 2113)	2.5–<5 (N = 1956)	5–<7.5 (N = 1676)	7.5–10 (N = 954)	>10 (N = 683)
LS7: Glucose						
Ideal	6040 (82%)	1869 (89%)	1602 (83%)	1343 (81%)	731 (77%)	495 (73%)
Intermediate	1162 (16%)	219 (10%)	308 (16%)	286 (17%)	193 (20%)	156 (23%)
Poor	127 (2%)	18 (1%)	30 (2%)	31 (2%)	23 (2%)	25 (4%)

Data shown are *n* (%) for categorical measures, median with lower and upper quartiles (Q1, Q3), 10th and 90th percentiles, minimum (min) and maximum (max) for continuous measures. All statistics are calculated out of participants with data collected. Missing data include number of ideal LS7 components and LS7 score (n = 89) due to no BMI (n = 4), Physical activity (n = 25), Diet (n = 18) or Glucose (n = 53).

Abbreviation: BMI, body mass index.

[a]Overall score was calculated as the sum of the 7 individual components as shown in the smoking component in the table yielding a scale from 0 (worst cardiovascular health) to 14 (best cardiovascular health).

blood pressure, total cholesterol, smoking), whereas others do not (lifestyle or health behaviors: diet, physical activity, BMI, glucose). To our knowledge, this is the first application of LS7 to a large PWH cohort. Overall, only 10% of individuals had ≥5 of 7 categories meeting criteria for ideal CV health, compared with nearly 17% in the 2011–12 National Health and Nutrition Examination Survey assessment, and over a third had poor CV health (≤2 of categories meeting ideal) [28]. Other cohorts show similar poor CV health, including Atherosclerosis Risk in Communities (ARIC), which showed that just 0.1% had all 7 categories meeting ideal criteria [29]. Of note, compared to the ARIC cohort, higher proportions of REPRIEVE participants had ideal status for BMI, diet, cholesterol, and glucose, but fewer met ideal criteria for smoking, physical activity, and blood pressure.

As expected, those characteristics common to LS7 and PCE showed progressive worsening with increasing risk category; however, the others did not. Thus, LS7 complements the PCE risk score for overall assessments of CV status and underscores its possible utility as a tool for guiding CV health improvement. Specifically, even among those with lowest PCE risk, there were many participants with poor diet, elevated BMI, and low physical activity. It is likely that CV health is poorer among the higher CVD risk PWH population not included in this trial. Our findings are congruent with previous data in a small cohort study showing PWH to be substantially more sedentary than demographically matched HIV-negative controls, although differences in healthy diet were not significant [30]. Ongoing research in this area is expected to shed more light on these modifiable components of CV health [31].

Although this study has considerable strengths, including use of a large sample size and global multiracial populations, it also has limitations in representing the overall population of PWH. Trial inclusion and exclusion criteria were related to risk scores, lipids, and other relevant factors which may have shaped some of the distributions. The study was not a randomized trial of ART, and thus our purpose was not to compare CVD risk/health between ART treatment groups but to examine whether such factors are associated with traditional risk/health algorithms. Ultimately, the ongoing REPRIEVE trial will examine CV risk and health estimates in relation to incident major adverse CV events.

CONCLUSION

Among 7382 REPRIEVE trial participants, the 10-year PCE-predicted CV risk score tracked well with demographics and other CV risk factors but was related less strongly to HIV characteristics or specific ART use. Ideal CV health was rare regardless of PCE risk score. Moreover, the PCE risk score did not capture common unhealthy behaviors, including poor diet, high BMI, and low physical activity. Our findings strongly suggest that key

health behaviors should be assessed, in addition to standard risk, to better understand CV health in PWH. Furthermore, lifestyle interventions may be indicated regardless of CV risk estimate and/or conventional treatment. Ultimately, it will be important to assess how well the PCE and lifestyle-based behavior assessment algorithms can predict CVD risk over time in REPRIEVE and to determine the optimal risk/health stratification system in this population.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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