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Ideal cardiovascular health, biomarkers, and coronary artery disease in persons with HIV

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Objective: To investigate relationships between Life's Simple 7 (LS7), an assessment of cardiovascular health (CVH), and coronary plaque among people with HIV (PWH).

Design: Cross-sectional.

Methods: Coronary computed tomography angiography, immune/inflammatory biomarkers, and characterization of LS7 were collected among a subset of ART-treated PWH enrolled in REPRIEVE, a primary prevention trial. Analyses adjusted for cardiovascular disease risk (ASCVD score).

Results: Median age of the 735 participants was 51(±6) years, 16% female, and median (Q1–Q3) CVD risk was 4.5% (2.6–6.9). Forty percent had poor (≤2 ideal components), 51% had intermediate (three or four ideal components), and only 9% had ideal CVH (≥5). Coronary plaque was present in 357 (49%); 167 (23%) had one or more vulnerable plaque features, 293 (40%) had noncalcified plaque, and 242 (35%) had a coronary artery calcium score >0. All three phenotypes were increasingly more prevalent with poorer CVH and these relationships remained after adjusting for ASCVD risk. Poor CVH was associated with higher high-sensitivity C-reactive protein, oxidized low-density cholesterol, and interleukin-6. The relationship of LS7 to plaque remained after adjusting for these biomarkers.

Conclusions: Among PWH, poor CVH as measured by LS7 was associated with coronary plaque presence, vulnerable features, and calcification. LS7 was also associated with selected biomarkers; adjustment for these and ASCVD score reduced but did not eliminate LS7's association with plaque, suggesting the possibility of additional protective mechanisms against atherogenesis and plaque remodeling. Clinical use of

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LS7 and further exploration of its relationships with coronary artery disease may enhance efforts to reduce cardiovascular morbidity and mortality in PWH.

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Graphical abstract, http://links.lww.com/QAD/C694

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Introduction

Although cardiovascular disease (CVD) risk is most commonly assessed by the presence of specific risk factors which portend a worse prognosis, an alternative approach is the assessment of cardiovascular health (CVH). This is most often accomplished using the American Heart Association's (AHA) Life's Simple 7 (LS7) score, which emphasizes behavioral factors and includes blood pressure, total cholesterol, fasting glucose, body mass index (BMI), diet, physical activity, and smoking [1]. More ideal (higher) LS7 scores have been associated with reductions in all-cause and cardiovascular death, nonfatal MI, and incident CVD [2–6]. Further, better CVH has been linked to less preclinical atherosclerosis using carotid intima-media thickness (CIMT) and coronary calcium score in the general population [7–13].

In addition to being associated with better outcomes and less preclinical atherosclerosis, ideal CVH, as measured by LS7, has been associated with lower levels of markers of inflammation, coagulation, and target-organ damage [8,14]. In one study, CVH remained independently and significantly associated with a lower risk for CVD events even after adjustment for biomarkers and subclinical disease measures, suggesting additional unquantified benefits of CVH [8,15].

People with HIV (PWH) have an elevated risk of coronary artery disease (CAD) and CV events not fully explained by traditional risk factors [16–19]. In part, this risk has been explained by immune activation and is associated with elevated inflammatory indices [20]. However, we have recently shown that ideal CVH, as measured by LS7, is rare among PWH in the United States, regardless of ASCVD risk measured by the Pooled Cohort Equations (PCE) [21]. PWH also have a substantial prevalence of coronary computed tomography angiography (CTA)-determined adverse coronary phenotypes beyond that expected for risk factors [22]. Further, the presence and characteristics of plaque were related to higher levels of interleukin (IL)-6 and lipoprotein-associated phospholipase A2 (LpPLA2) independently of traditional risk indices, suggesting that coronary atherosclerosis in PWH is mediated, at least in part, by inflammatory pathways.

Given relatively poor CVH and higher risk of CAD, we hypothesized that, independent of age and sex, there would be a relationship between lower LS7 and higher prevalence of coronary atherosclerosis phenotypes in PWH. Further, we hypothesized that lower LS7 would be related to adverse biomarker levels, but that inflammatory pathways and traditional risk would only partially explain the contribution of poor CVH to CAD. To explore these hypotheses we analyzed baseline 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 [23].

Methods

People with HIV, aged 40–75 years, without known CVD and receiving stable ART, not receiving statin therapy, and with low-to-moderate 10-year traditional cardiovascular risk using the 2013 American College of Cardiology/AHA PCE [24] were enrolled in the REPRIEVE trial, as previously described [23,25]. The present cohort derives from the mechanistic substudy of REPRIEVE, which was performed at 31 US REPRIEVE sites, with additional exclusion criteria being contraindications to CTA. Enrollment occurred from May 2015 to February 2018 [25]. The coordinating centers and sites obtained institutional review board and other applicable regulatory entity approvals. All participants provided informed consent.

Clinical data and Life's Simple 7 assessment

Data on demographic parameters, medical history, lifestyle behaviors, and HIV-specific parameters were collected as part of REPRIEVE, as previously described [21,23]. Natal sex, race, and ethnicity were self-reported. Diet and physical activity assessments were conducted using the Rapid Eating and Activity Assessment for Patients Questionnaire [26]. Fasting lipids were obtained

at study entry and tested at a Quest Diagnostic lab (Baltimore, Maryland, USA).

LS7 CVH metrics were adapted from Lloyd-Jones *et al.* [1] with modifications for scoring diet, physical activity, and smoking, as previously described (Table 1, Supplemental Digital Content, http://links.lww.com/QAD/C693) [21]. Each individual component of LS7 was categorized as ideal, intermediate, and poor. A total of 5–7 ideal components out of seven was considered ideal overall CVH, 3–4 intermediate and two or less poor, according to prognostically validated cut points [2–5]. In addition, an ordinal overall score was calculated as the sum of the seven individual components as either poor (0 points), intermediate (1 point), or ideal (2 points), yielding a scale from 0 (worst) to 14 (best). Since a large proportion of participants in our dataset were classified in the intermediate CVH category (3–4 ideal components), an exploratory analysis used a second four-level classification according to the overall score: 0–6, 7–8, 9–10, 11-14.

Coronary computed tomography angiography acquisition and analysis

Coronary CTA was performed at enrollment on at least 64 slice CT scanners according to standardized protocols consistent with Society of Cardiovascular CT guidelines [27], with robust quality-control measures for data acquisition and clinical safety review, as previously described [22]. Coronary artery calcium (CAC) score was quantified on noncontrast, ECG-gated CT using a modified Agatston method [28]. Contrast-enhanced CTAs were centrally reviewed for the presence of atherosclerotic plaque, stenosis, and comprehensive CT Leaman score, which includes the degree of stenosis, coronary dominance, plaque location, and composition [29]. We also assessed the presence of vulnerable plaque features, including positive remodeling (remodeling index, >1.1), CT attenuation less than 30 Hounsfield units, and napkin-ring sign (low central attenuation with ring-like peripheral high attenuation) [30]. Interobserver variability was established in a subset of 20 CTAs analyzed by all readers, with good agreement for coronary plaque presence (Cohen $\kappa = 0.89$). All analyses were performed on a dedicated workstation (Aquarius iNtuition, TeraRecon).

Biomarker data

$CD4^+$ T-cell count and HIV viral load were obtained from clinical care. Prespecified inflammatory and immune activation biomarkers representing potentially statin-modifiable pathways, including monocyte chemoattractant protein-1 (MCP-1), interleukin-6 (IL-6), soluble CD14 (sCD14), sCD163, LpPLA2, D-dimer, and oxidized low-density lipoprotein (oxLDL) were obtained from fasting samples and measured centrally from plasma using enzyme-linked immunosorbent assay kits at Temple University (Philadelphia, Pennsylvania, USA). High-sensitivity C-reactive protein (hsCRP) assays were performed at Quest Diagnostics. Assay limits and variability have been previously published [22,31].

Statistical analysis

Continuous variables are presented as means with SDs or medians with first and third quartiles (Q1, Q3). Categorical variables are presented with percentages calculated out of those with data. Comparisons across LS7 groups were performed with the use of Cochran–Armitage trend tests (binary outcomes) and linear-by-linear association tests (ordinal outcomes). Log binomial regression models assessed the association of CVH with CAD. Relative risks (interpreted as prevalence in this cross-sectional analysis) were estimated against intermediate CVH as reference. A linear trend in the prevalence across LS7 groups was assessed with CVH modeled as a numeric variable (0, 1 ,2). The primary outcome was presence of plaque as an overall index of CAD. Secondary outcomes were vulnerable plaque features including noncalcified plaque (NCP) and CAC. Results are presented unadjusted, adjusted for sex and age (primary hypothesis), and adjusted for ASCVD score. The latter adjustment was made to assess our hypothesis that traditional risk would only partially explain the contribution of poor CVH to CAD. The association of CVH and biomarkers used linear regression. Biomarkers were analyzed on the $\log_2$ scale with effects back transformed and presented as geometric mean ratios relative to intermediate CVH as reference.

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

Results

Demographic and clinical parameters

Data necessary for calculation of LS7 and a diagnostic coronary CTA that permitted assessment of presence, extent, and composition of coronary atherosclerosis were available in 735 participants, defining the study cohort. Baseline demographic characteristics are shown in Table 1. The cohort had a mean (SD) age of 51 (6) years and included 120 (16%) female participants. Approximately half of the participants identified as White non-Hispanic [280 (38%)], 178 participants (24%) identified as Hispanic (regardless of race), 250 participants identified as Black non-Hispanic (34%), and 9 participants identified as Asian (1%).

Participants had a low estimated ASCVD risk [median (Q1–Q3) PCE risk score, 4.5% (2.6–6.9%)]. The median LDL-C level was 107 (87–126) mg/dl reflecting the inclusion criteria of REPRIEVE to enroll a primary prevention cohort. All participants were receiving ART with good virologic control. Nearly 60% (426) had been receiving ART for more than 10 years (Table 1). The mechanistic substudy population was generally representative of participants enrolled in REPRIEVE [22].

Table 1. Demographic characteristics by Life's Simple 7 category based on number of ideal components.

Characteristic		Total ($N = 735$)	Poor [0–2] ($N = 296$)	Intermediate [3–4] ($N = 373$)	Ideal [5+] ($N = 66$)
Overall					
All participants		735	296 (40%)	373 (51%)	66 (9%)
Demographics					
Age (years)	Mean (SD)	50.8 (5.8)	51.0 (5.6)	50.7 (5.8)	50.8 (6.7)
Natal sex	Female	120 (16%)	58 (20%)	54 (14%)	8 (12%)
Race/ethnicity	White non-Hispanic	280 (38%)	101 (34%)	149 (40%)	30 (45%)
	Black non-Hispanic	250 (34%)	112 (38%)	121 (32%)	17 (26%)
	Hispanic (regardless of race)	178 (24%)	75 (25%)	87 (23%)	16 (24%)
	Asian, Pacific Islander	9 (1%)	3 (1%)	5 (1%)	1 (2%)
	American Indian, Alaskan Native	3 (<0.5%)	1 (<0.5%)	1 (<0.5%)	1 (2%)
	Subject does not know	7 (1%)	2 (1%)	4 (1%)	1 (2%)
	More than one race	8 (1%)	2 (1%)	6 (2%)	0 (0%)
ASCVD risk score					
ASCVD risk score (%)	Median (Q1–Q3)	4.5 (2.6–6.9)	5.3 (3.5–7.7)	4.1 (2.4–6.3)	2.9 (1.6–5.0)
	0–<2.5	170 (23%)	47 (16%)	94 (25%)	29 (44%)
	2.5–<5	239 (33%)	87 (29%)	132 (35%)	20 (30%)
	5+	326 (44%)	162 (55%)	147 (39%)	17 (26%)
Smoking status	Current	178 (24%)	88 (30%)	86 (23%)	4 (6%)
	Former	229 (31%)	125 (42%)	95 (25%)	9 (14%)
	Never	328 (45%)	83 (28%)	192 (51%)	53 (80%)
Use of antihypertensive medication		154 (21%)	85 (29%)	65 (17%)	4 (6%)
Systolic BP of those not on antihypertensive medication	Median (Q1–Q3)	121 (112–130)	126 (120–133)	119 (110–128)	112 (108–118)
Total cholesterol (mg/dl)	Median (Q1–Q3)	184 (161–206)	195 (170–218)	179 (157–200)	174 (150–191)
HDL-C (mg/dl)	Median (Q1–Q3)	48 (39–61)	49 (40–64)	48 (39–59)	48 (39–55)
LDL calculated (mg/dl)	Median (Q1–Q3)	107 (87–126)	114 (93–133)	103 (83–123)	101 (85–115)
Triglycerides (mg/dl)	Median (Q1–Q3)	111 (78–168)	130 (89–197)	103 (72–153)	104 (74–136)
LS7 ideal cardiovascular health					
Number of ideal LS7 components	0	17 (2%)	17 (6%)	0 (0%)	0 (0%)
	1	87 (12%)	87 (29%)	0 (0%)	0 (0%)
	2	192 (26%)	192 (65%)	0 (0%)	0 (0%)
	3	243 (33%)	0 (0%)	243 (65%)	0 (0%)
	4	130 (18%)	0 (0%)	130 (35%)	0 (0%)
	5	55 (7%)	0 (0%)	0 (0%)	55 (83%)
	6	10 (1%)	0 (0%)	0 (0%)	10 (15%)
	7	1 (<0.5%)	0 (0%)	0 (0%)	1 (2%)
LS7: Overall score	Median (Q1–Q3)	8 (7–10)	7 (6–8)	9 (8–10)	12 (12–12)
	10–90%	6-11	5–8	8-11	11-13
LS7: Blood pressure	Ideal	207 (28%)	21 (7%)	141 (38%)	45 (68%)
	Intermediate	423 (58%)	205 (69%)	198 (53%)	20 (30%)
	Poor	105 (14%)	70 (24%)	34 (9%)	1 (2%)
LS7: Total cholesterol	Ideal	470 (64%)	130 (44%)	282 (76%)	58 (88%)
	Intermediate	210 (29%)	125 (42%)	77 (21%)	8 (12%)
	Poor	55 (7%)	41 (14%)	14 (4%)	0 (0%)
LS7: Glucose	Ideal	583 (79%)	180 (61%)	339 (91%)	64 (97%)
	Intermediate	136 (19%)	104 (35%)	30 (8%)	2 (3%)
	Poor	16 (2%)	12 (4%)	4 (1%)	0 (0%)
LS7: BMI	Ideal	245 (33%)	34 (11%)	161 (43%)	50 (76%)
	Intermediate	299 (41%)	149 (50%)	137 (37%)	13 (20%)
	Poor	191 (26%)	113 (38%)	75 (20%)	3 (5%)
LS7: Diet	Ideal	140 (19%)	16 (5%)	85 (23%)	39 (59%)

Table 1 (*continued*)

Characteristic		Total ($N = 735$)	Poor [0–2] ($N = 296$)	Intermediate [3–4] ($N = 373$)	Ideal [5+] ($N = 66$)
	Intermediate	400 (54%)	186 (63%)	194 (52%)	20 (30%)
	Poor	195 (27%)	94 (32%)	94 (25%)	7 (11%)
LS7: Physical activity	Ideal	89 (12%)	7 (2%)	49 (13%)	33 (50%)
	Intermediate	387 (53%)	162 (55%)	197 (53%)	28 (42%)
	Poor	259 (35%)	127 (43%)	127 (34%)	5 (8%)
LS7: Smoking	Ideal	328 (45%)	83 (28%)	192 (51%)	53 (80%)
	Intermediate	229 (31%)	125 (42%)	95 (25%)	9 (14%)
	Poor	178 (24%)	88 (30%)	86 (23%)	4 (6%)
HIV-related health status					
Duration of HIV (years)	<5	65 (9%)	22 (7%)	34 (9%)	9 (14%)
	5–10	163 (22%)	58 (20%)	97 (26%)	8 (12%)
	>10	507 (69%)	216 (73%)	242 (65%)	49 (74%)
Nadir $CD4^+$ cell count (cells/μl)	<50	158 (21%)	65 (22%)	79 (21%)	14 (21%)
	50–199	212 (29%)	93 (31%)	105 (28%)	14 (21%)
	200–349	199 (27%)	73 (25%)	103 (28%)	23 (35%)
	350+	144 (20%)	58 (20%)	73 (20%)	13 (20%)
	Unknown	22 (3%)	7 (2%)	13 (3%)	2 (3%)
HIV-1 RNA (copies/ml)	<LLQ	641 (88%)	257 (88%)	329 (89%)	55 (85%)
	LLQ–< 400	69 (10%)	31 (11%)	31 (8%)	7 (11%)
	400+	16 (2%)	4 (1%)	9 (2%)	3 (5%)
CD4 count (cells/μl)	<350	108 (15%)	39 (13%)	52 (14%)	17 (26%)
	350–499	145 (20%)	53 (18%)	83 (22%)	9 (14%)
	500+	482 (66%)	204 (69%)	238 (64%)	40 (61%)
Total ART use (years)	<5	116 (16%)	40 (14%)	65 (17%)	11 (17%)
	5–10	193 (26%)	74 (25%)	104 (28%)	15 (23%)
	10+	426 (58%)	182 (61%)	204 (55%)	40 (61%)
ART regimen (by class)	NRTI + INSTI	325 (44%)	133 (45%)	165 (44%)	27 (41%)
	NRTI + NNRTI	193 (26%)	83 (28%)	93 (25%)	17 (26%)
	NRTI + PI	125 (17%)	39 (13%)	76 (20%)	10 (15%)
	NRTI-sparing	22 (3%)	12 (4%)	9 (2%)	1 (2%)
	Other NRTI-containing	70 (10%)	29 (10%)	30 (8%)	11 (17%)

All statistics are calculated out of participants with data collected. Twenty participants are missing the Lifestyle CV risk [no. ideal comp.] at the time of analysis and are excluded. Screening lipids were tested locally using various assays and are not necessarily fasting. ART, antiretroviral therapy; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; INSTI, integrase-strand transfer inhibitor; LS7, Life's Simple 7; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor. Created by: /home/reprieve/A5333S/final/bsl_ls7Plaque/programs/tables_figures/working/t_manu_baseline.sas on May 13, 2022.

Clinical characteristics and Life's Simple 7

The cohort's median LS7 score (out of an ideal score of 14) was 8 (7–10) (Table 1, Figure 1, Supplemental Digital Content, http://links.lww.com/QAD/C693). Sixty-six (9%) had ideal CVH (≥5/7 ideal components) including one participant with 7 out of 7 ideal components, 10 (1%) with 6 out of 7, and 55 (7%) with 5 out of 7 ideal components. Forty percent (296) met ideal targets in two or more components, considered poor CVH. Table 1 shows distribution of demographics and select characteristics by CVH group. Distributions of age, natal sex and race did not vary across CVH groups. Better CVH was associated with lower ASCVD risk score as well as a lower prevalence or levels of ASCVD components related to LS7, including hypertension, diabetes, total and LDL cholesterol, and smoking. HIV-related parameters were similar across LS7 groups (Table 1).

Coronary artery disease characteristics and Life's Simple 7

Nearly half the participants [357 (49%)] had evidence of plaque on coronary CTA, which was increasingly more prevalent with poorer CVH (from 39% among ideal to 56% among poor CVH; $P < 0.001$; Table 2). Non-calcified plaque was present in 293 participants (40%) and also related to LS7 score (poor vs ideal: 45 vs. 32%; $P = 0.02$). Nearly one-quarter of participants [167 (23%)] had at least one vulnerable plaque feature; this was more than twice as prevalent among those with poor CVH than ideal (27% vs. 11%; $P = 0.005$). A CAC score greater than 0 was detected in 242 of 700 participants (35%), and was more common in those with poor CVH (poor vs. ideal: 40 vs. 32%; $P = 0.006$). Presence, composition, and distribution of plaque, extent of CAC, vulnerable plaque features, and Leaman score, were all higher in those with fewer ideal LS7 components (Table 2, Figure 2, Supplemental Digital Content, http://links.lww.com/QAD/C693).

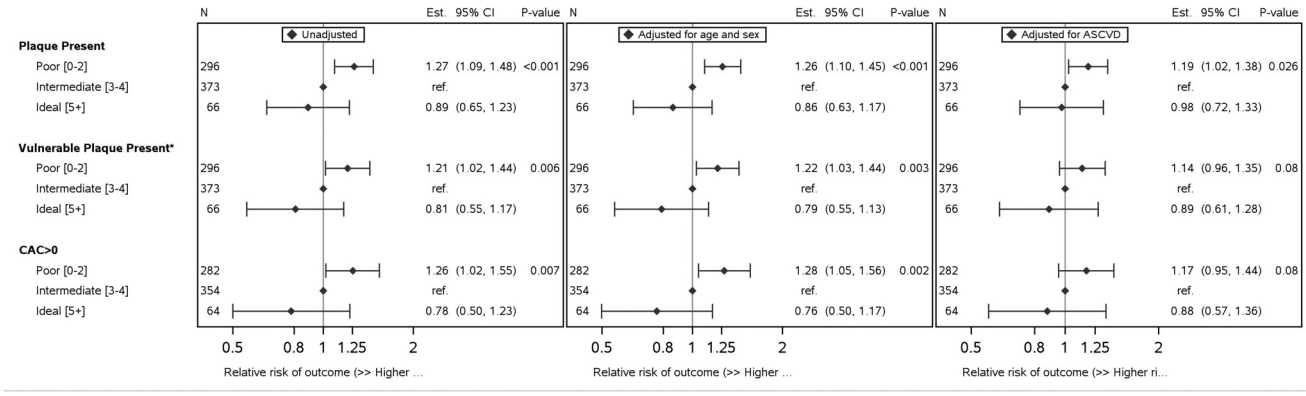
In unadjusted analyses, plaque, vulnerable plaque, and CAC >0 all showed higher prevalence with poorer CVH (fewer ideal LS7 components; Fig. 1). Adjustment for natal sex and age did not alter these relationships. Although adjustment for ASCVD attenuated the associations, the association with plaque and CVH remained statistically significant, and increasing trends were still apparent for vulnerable plaque and CAC, although no longer statistically significant.

As an exploratory analysis, we evaluated CTA outcomes in relation to the overall LS7 score (Table 2, Supplemental Digital Content, http://links.lww.com/QAD/C693). Any plaque presence and vulnerable plaque remained related to LS7, whereas CAC >0 did not (results not shown). However, adjustment for ASCVD risk almost completely controlled for LS7, suggesting that the overall score more closely reflects the ASCVD risk score than the number of ideal components.

Table 2. Coronary CTA plaque outcomes by Life's Simple 7 categories.

		All participants				
		Total ($N = 735$)	Poor [0–2] ($N = 296$)	Intermediate [3–4] ($N = 373$)	Ideal [5+] ($N = 66$)	*P*-value
Participants with plaque present[a]	Yes	357 (49%)	166 (56%)	165 (44%)	26 (39%)	0.0007
Noncalcified plaque[a]	Yes	293 (40%)	132 (45%)	140 (38%)	21 (32%)	0.02
Plaque with vulnerable features[a]	Yes	167 (23%)	80 (27%)	80 (21%)	7 (11%)	0.005
Low attenuation plaque	Yes	44 (6%)	24 (8%)	18 (5%)	2 (3%)	-
Napkin ring sign	Yes	21 (3%)	12 (4%)	8 (2%)	1 (2%)	-
Positive remodeling	Yes	161 (22%)	74 (25%)	80 (21%)	7 (11%)	-
Plaque with noncalcified portion or plaque with vulnerable features	Yes	309 (42%)	141 (48%)	147 (39%)	21 (32%)	0.006
calcium score (Agatston)[a]	>0	242 (35%)	113 (40%)	113 (32%)	16 (25%)	0.006
	# missing	*35*	*14*	*19*	*2*	-
Among those with CAC > 0[b]	1–100	170 (70%)	76 (67%)	85 (75%)	9 (56%)	0.96
	101–400	59 (24%)	31 (27%)	22 (19%)	6 (38%)	-
	>400	13 (5%)	6 (5%)	6 (5%)	1 (6%)	-
Leaman score category[b]	0	378 (52%)	130 (45%)	208 (57%)	40 (61%)	0.02
	>0–5	231 (32%)	109 (38%)	109 (30%)	13 (20%)	–
	>5	114 (16%)	51 (18%)	50 (14%)	13 (20%)	–
Leaman score	*# missing*	*12*	*6*	*6*		–

[a]Cochran–Armitage trend test.
[b]Linear-by-linear association test.
Created by: /home/reprieve/A5333S/final/bsl_ls7Plaque/programs/tables_figures/working/t_manu_plaque.sas on May 16, 2022.

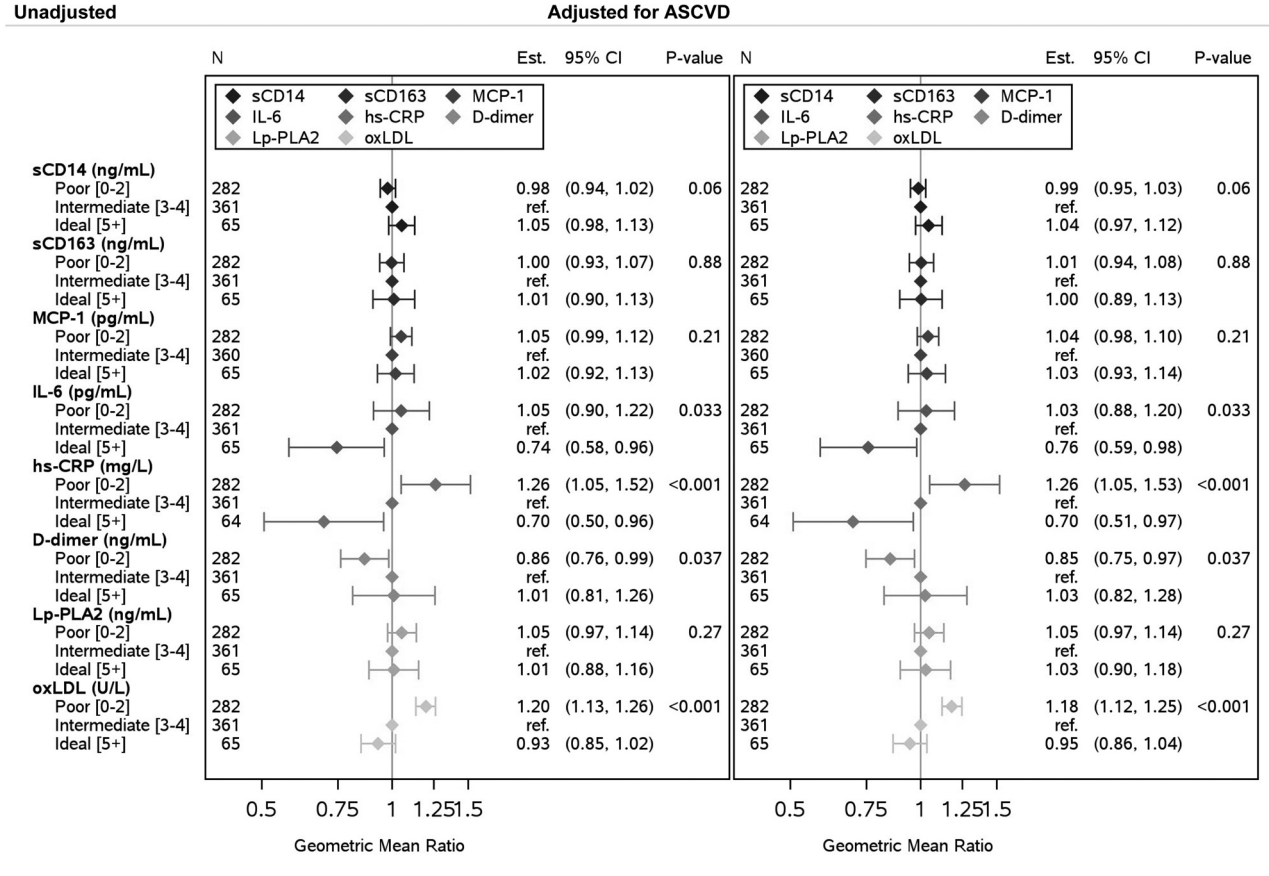


**Plaque with Noncalcified Portion or Plaque with Vulnerable Features*
The p-value gives tests for a linear trend in the log-odds ratio.
Created by: /home/reprieve/A5333S/final/bsl_ls7Plaque/programs/tables_figures/working/f_manu_ls7_analyses.sas on May 16, 2022

Fig. 1. Regression modeling for presence of plaque, vulnerable plaque and coronary calcium based on Life's Simple 7 categories.

Biomarkers, Life's Simple 7 and atherosclerosis

Better CVH, as measured by more ideal LS7 components, was associated with lower levels of IL-6, hs-CRP, and oxLDL and higher D-dimer, but not soluble CD163, MCP-1 or LpPLA-2 (Fig. 2, Table 3, Supplemental Digital Content, http://links.lww.com/QAD/C693) These findings persisted after adjustment for age and sex, and for ASCVD score. Since IL-6, hsCRP, and oxLDL have each been previously shown to relate to coronary plaque phenotypes in this population [22], we



Created by: /home/reprieve/A5333S/final/bsl_ls7Plaque/programs/tables_figures/working/f_manu_linear_analyses_biomrkr.sas on May 13, 2022

Fig. 2. Biomarker distributions by Life's Simple 7 categories.

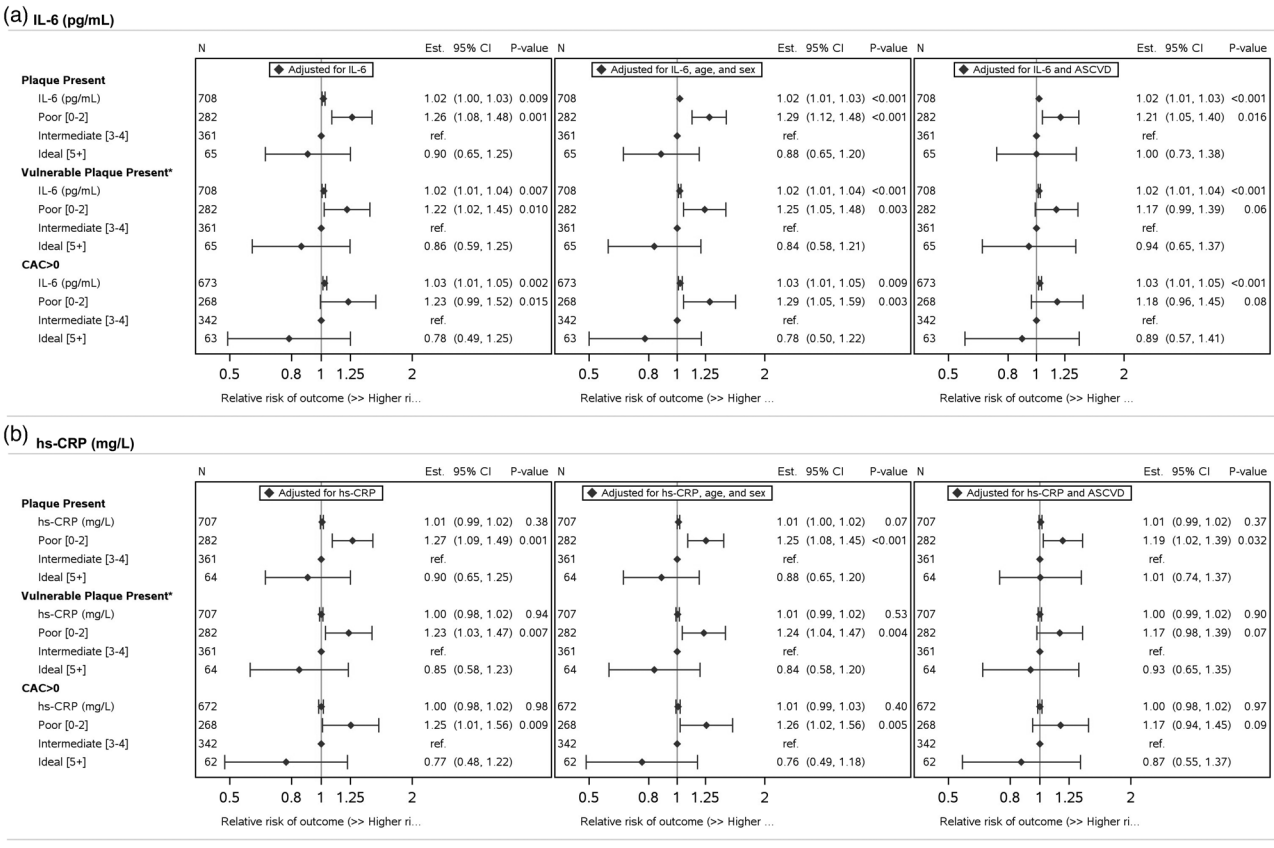


Fig. 3. Regression modeling of individual biomarkers for presence of plaque, vulnerable plaque and coronary calcium based on number of Life's Simple 7 ideal components.

assessed the interplay between biomarkers, plaque, and CVH by adding IL-6, hs-CRP, and oxLDL to the models assessing the relationships between LS7 and coronary phenotype. In each case the results were similar to the analyses unadjusted for biomarkers (Fig. 1) suggesting that effects of LS7 on atherosclerosis are unrelated to these biomarkers (Fig. 3a–c).

Discussion

People with HIV have both an unexplained excess risk of CVD and poor CVH. Among the 735 PWH in the REPRIEVE trial substudy, an established measure of CVH (LS7), was associated with coronary plaque presence, vulnerable features, and calcification. Further, while LS7 was also associated with select biomarkers implicated in CVD pathways, the effects on plaque remained after adjustment for both traditional risk factors and immune pathways. A better understanding of the underlying mechanisms linking CVH and atherosclerosis may inform ongoing efforts to reduce CV morbidity and mortality in PWH.

Cardiovascular disease risk is usually estimated as risk of incident events using traditional risk factors; an alternative, complementary assessment of CVH is closely related to the converse, improved CV outcomes. The robustness of this relationship is underscored by a recent meta-analysis of nine prospective cohort studies involving 193 126 participants, which found higher LS7 (better CVH) to be inversely related to all-cause death, CV death, stroke, and incident CVD (hazard ratios 0.22–0.54) [2]. Another recent meta-analysis of 210 443 adults showed a 'dose-dependent' effect with improvement in just one or two LS7 metrics conferring protection from incident CV events: using those with poor CVH as the reference, the HR fell from 0.53 for those who have 3–4 ideal metrics compared to 0.28 for those with 5–7 [3]. Similar relationships have been demonstrated in smaller studies using additional outcomes (peripheral arterial disease, heart failure, aortic stenosis, and atrial fibrillation) [32,33]. Our data extend prior studies associating poor CVH with elevated inflammatory markers [8,14] by demonstrating these relationships in PWH and showing that increased inflammation may be a characteristic of poor CVH.

As previously shown [21], the vast majority (90%) of the REPRIEVE cohort demonstrated poor to intermediate health using LS7 [6,9,34,35]. Based on our previous analyses, several LS7 components, including BMI,

physical activity, and diet, were not strongly related to traditional ASCVD risk or to HIV-related parameters including antiretroviral medications in our cohort. Given the known strong relationships between LS7 and CV events, this finding suggests an independent contribution of poor CVH to atherosclerosis, which we sought to explore in the present study. Further, given the known contribution of inflammation to excess CVD risk in PWH and its association with coronary plaque [20,22], we also explored relationships between LS7, coronary plaque, and inflammatory biomarkers, hypothesizing that CVH might have independent effects on atherosclerosis beyond known relationships with traditional risk and immune function.

Although this excess risk is very well established, information regarding subclinical coronary atherosclerosis is limited and suggests an excess of CAC and noncalcified and vulnerable plaque [22,36–38]. In prior analyses of the current cohort, we found associations with ASCVD risk estimates and presence of plaque, number of involved segments, noncalcified and vulnerable plaque as well as stenosis [22]. In the present study we found an association between LS7 and plaque presence, vulnerable plaque and CAC that remained after adjusting for age and sex, and ASCVD risk score. These findings are congruent with others noting associations between LS7 and calcium score [10,11] and CIMT [7–9,11–13]. However, these authors generally corrected only for age and sex and not the full range of risk factors captured in the ASCVD risk score, and did not provide detailed phenotyping of coronary plaque. Thus, our findings significantly extend previous work by establishing that, despite some similarities in LS7 and ACSVD components, LS7 with its broader focus on CVH, provides additional information beyond traditional ASCVD risk scoring with respect to plaque development in PWH.

Numerous studies have noted altered immune activation and inflammatory indices in PWH; the excess in CV events has been attributed to this alternative mechanistic pathway independent of traditional risk factors [20,39]. As with the relationships noted between CVH and events and atherosclerosis, two studies in the general population have also found relationships between poor CVH and a variety of biomarkers including higher PAI-1, aldosterone, hs-CRP, D-dimer, fibrinogen, homocysteine, GDF-15, hs-troponin T, IL-6 and GlycA, and lower levels of NT-proBNP [8,14]. Our data replicate these findings demonstrating higher levels of hs-CRP, oxLDL and IL-6 in those with poor CVH, even after adjusting for ASCVD risk. Importantly, we also uniquely assessed the impact of these plaque-associated biomarkers on the relationship between LS7 and plaque and found minimal impact, suggesting the relationship between CVH and plaque is not only independent of traditional risk factors but also remains after considering inflammation—and suggesting that other factors may be in play [15]. Only one other study has explored a relationship between subclinical disease measures and LS7, which was muted but not eliminated by the addition of biomarkers (rose from HR 0.77 (0.70–0.86) to HR 0.87 (0.78–0.97)) [8]. Notably, while authors controlled for age and sex, they did not adjust for ASCVD risk score, and therefore did not eliminate the influence of traditional risk factors. While risk score adjustment alone cannot remove all the influence of risk factors, the retained significance of CVH highlights the unique value of the LS7 categories. A second critical difference from prior work is our use of detailed coronary artery plaque parameters, a preferred phenotype over other subclinical measures. Our findings therefore add significantly to the understanding of the 'CVH phenotype', and indicate the need for a new line of inquiry related to the mechanisms by which poor CVH may affect coronary atherosclerosis independently of traditional risk factors and immune function.

Strengths and limitations

Among this study's considerable strengths are the meticulous and simultaneous delineation of three different biologic pathways contributing to atherosclerosis (traditional risk factors, inflammatory biomarkers, and CVH behaviors) within a large, lower risk, primary prevention cohort, for whom lifestyle risk reduction is particularly germane. However, our population does not represent PWH with increased risk or known disease, in whom the relationship with CVH may differ. Ultimately, the ongoing REPRIEVE trial and its mechanistic substudy will prospectively examine the contributions of poor CVH, traditional risk, atherosclerosis phenotypes, and biomarkers to incident major adverse CV events.

Implications

Although LS7 was derived as an implementation tool to aid lifestyle modification, a large body of evidence shows its robust relationship to outcomes. Our data build on this relationship to identify a strong independent association between CVH and atherosclerosis, beyond that of traditional risk and inflammatory markers, indicating that the biology of CVH merits investigation in its own right. While our findings are hypothesis-generating and require further investigation, they strongly underscore current recommendations for a healthy lifestyle to prevent CVD. Importantly, since all LS7 components are modifiable, it is especially useful in prevention strategies.

Conclusion

The excess cardiovascular morbidity and mortality among PWH is not fully explained. We found that poor CVH as measured by LS7 was associated with coronary plaque presence, vulnerable features, and calcification, and also associated with adverse biomarker levels. Since the effects on plaque remained after adjustment for ASCVD risk score and inflammatory biomarkers, CV heath behaviors may protect against atherogenesis and adverse plaque modeling through additional pathways. Ongoing efforts

to reduce CV morbidity and mortality in PWH may be strengthened by attention to modifying CVH and a better understanding of the mechanisms underlying the relationship between CVH and CAD.

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Conflicts of interest

None.

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