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Plasma Citrate and Succinate Are Associated With Neurocognitive Impairment in Older People With HIV

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Background. Neurocognitive impairment (NCI) is associated with monocyte activation in people with HIV (PWH). Activated monocytes increase glycolysis, reduce oxidative phosphorylation, and accumulate citrate and succinate, tricarboxylic acid (TCA) cycle metabolites that promote inflammation—this metabolic shift may contribute to NCI and slowed gait speed in PWH.

Methods. Plasma citrate and succinate were assayed by liquid chromatography–mass spectrometry from 957 participants upon entry to a multicenter, prospective cohort of older PWH. Logistic, linear, and mixed-effects linear regression models were used to examine associations between entry/baseline TCA cycle metabolites and cross-sectional and longitudinal NCI, neuropsychological test scores (NPZ-4), and gait speed.

Results: Median age was 51 (range 40–78) years. Each 1 standard deviation (SD) citrate increment was associated with 1.18 higher odds of prevalent NCI at baseline ($P = .03$), 0.07 SD lower time-updated NPZ-4 score ($P = .01$), and 0.02 m/s slower time-updated gait speed ($P < .0001$). Age accentuated these effects. In the oldest age-quartile, higher citrate was associated with 1.64 higher odds of prevalent NCI, 0.17 SD lower NPZ-4, and 0.04 m/s slower gait speed ($P \leq .01$ for each). Similar associations were apparent with succinate in the oldest age-quintile, but not with gait speed. In participants without NCI at entry, higher citrate predicted a faster rate of neurocognitive decline.

Conclusions. Higher plasma citrate and succinate are associated with worse cross-sectional and longitudinal measures of neurocognitive function and gait speed that are age-dependent, supporting the importance of altered bioenergetic metabolism in the pathogenesis of NCI in older PWH.

Keywords. citrate; succinate; tricarboxylic acid cycle; neurocognitive impairment; human immunodeficiency virus.

INTRODUCTION

Neurocognitive impairment (NCI) is common among people with HIV (PWH) despite virally suppressive antiretroviral therapy (ART) [1, 2]. HIV infects perivascular macrophages, microglia, and astrocytes, but not neurons [3, 4]. Associations between NCI and biomarkers of inflammation, including those associated with macrophage activation, support important contributions by ongoing neuroinflammation to this disorder [4–8].

Upon activation by lipopolysaccharide (LPS) and other stimuli, macrophages and microglia substantially increase glycolysis and reduce oxidative phosphorylation, a process similar to that described in cancer cells as the Warburg effect [9, 10]. This metabolic shift results in an accumulation of some tricarboxylic acid (TCA) cycle metabolites, including citrate and succinate. Actively transported from mitochondria to cytosol, these metabolites may directly promote disease by inducing reactive oxygen species (ROS) formation, while also engaging pro-inflammatory pathways [11].

In metabolomic analyses, higher citrate and succinate concentrations in cerebrospinal fluid (CSF) were previously associated

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Nonstandard Abbreviations: ACTG, AIDS Clinical Trials Group; ALLRT, ACTG Longitudinal Linked Randomized Trials; aOR, adjusted odds ratio; ART, antiretroviral therapy; CSF, cerebrospinal fluid; GLUT-1, glucose transporter; HAILO, HIV Infection Aging and Immune Function Long-Term Observational Study; HIF1-a, hypoxia inducible factor; IQR, interquartile range; LC-MS/MS, liquid chromatography mass spectrometry; LPS, lipopolysaccharide; MACS, Multicenter AIDS Cohort Study; NCI, neurocognitive impairment; PWH, people with HIV; ROC, receiver operating characteristic; ROS, reactive oxygen species; SUCNR-1, succinate receptor; TCA, tricarboxylic acid.

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with NCI in PWH [12, 13]. Based on these observations, we hypothesized that a metabolic shift akin to the Warburg effect may contribute to NCI in PWH. To test this hypothesis, we explored associations between fasting plasma citrate and succinate concentrations with cross-sectional and longitudinal measures of NCI in the multicenter AIDS Clinical Trials Group (ACTG) A5322 study (the HIV Infection, Aging, and Immune Function Long-Term Observational study; HAILO). Because gait speed closely correlates with neurocognitive function, and slower gait speed may precede cognitive decline [14–16], we also examined associations between these TCA cycle metabolites and gait speed.

METHODS

Study Participants

HAILO is a prospective observational study of 1035 PWH who received their initial ART through a randomized ACTG treatment trial. Participants who were first followed in the ACTG Longitudinal Linked Randomized Trials (ALLRT) study and who were 40 years and older when their participation in ALLRT ended in October 2013 were eligible to enroll in HAILO [17, 18]. Participants included in this analysis had neuropsychological testing and stored plasma available from HAILO entry (n = 957).

Neurocognitive Impairment and Gait Speed

Neurocognitive performance was assessed using normalized, demographic-adjusted scores (as z-scores) from performance on Trail Making A (speed of information processing), Trail Making B (executive functioning), Hopkins Verbal Learning (verbal learning and memory), and the Wechsler Adult Intelligence Scale-Revised Digit Symbol tests (speed of information processing) [19, 20]. Neurocognitive impairment was defined by at least 1 z-score ≥ 2 standard deviations (SD) below the mean, or at least 2 z-scores ≥ 1 SD below the mean. Individual test scores were also averaged into a single score (NPZ-4). Gait speed was calculated for each participant from the average of 2 measurements. Participants were instructed to walk 4 meters at usual pace from a standing start. Neurocognitive performance and gait speed were assessed by study staff upon entry into HAILO and every 48 weeks during follow-up.

Tricarboxylic Acid Cycle Metabolite Assays

Succinate and citrate concentrations were assayed from frozen (4 ˚C) plasma samples (EDTA) that were collected at study entry. Metabolites were separated on a Kinetex-C18 column, measured by liquid chromatography mass spectrometry (LC-MS/MS), and calibrated using a linear standard curve for each metabolite (0.1–160 μg/mL). Metabolite data was processed and quantified using the MassHunter qualitative and quantitative analysis software (version 8.0; Agilent Technologies, CA). The Supplementary Appendix provides additional details on study methods.

Statistical Analysis

Entry continuous and categorical variables were defined by measurements that were obtained at HAILO entry and compared according to NCI status at the entry visit using the Kruskal-Wallis and chi-square tests, respectively. Associations between selected entry variables with each metabolite were evaluated by Spearman correlation analyses and Wilcoxon rank sum tests for continuous and categorical variables, respectively. To minimize collinearity, metabolite concentrations were transformed as standardized *z* scores by subtracting the sample value from the study population's mean value and then dividing by the standard deviation.

Separate multivariable logistic regression models were used to examine associations between NCI that was present at the entry visit (or prevalent NCI) and each metabolite. Variables that were included in all models as possible confounders were age, sex, self-reported race/ethnicity (as white but not Hispanic, black but not Hispanic, or Hispanic regardless of race), education status (≤ 12 years vs > 12 years), ART duration, CD4+ cell counts and plasma HIV viral loads (< 200 vs ≥ 200 and < 1000 vs ≥ 1000 copies/mL). These models also explored interactions by age with each metabolite. The significant interactions by age were further evaluated in analyses that were stratified within age-quartiles and using increasingly older age thresholds (oldest 20th and 10th percentiles). Receiver operating characteristic (ROC) curves for each metabolite were estimated from univariable logistic regression models of prevalent NCI; area under the curve estimates are presented overall and by oldest 25th and 10th percentiles.

Associations between metabolite concentrations at entry with time-updated average (NPZ-4) neuropsychological test scores, individual component test scores, and average gait speed were examined by repeated measures analyses using mixed-effects linear models which were adjusted for confounders as in the above models; CD4+ cell counts and HIV viral loads were time-updated. Here, time-updated means the value of the variable is allowed to change at each successive visit. These models assumed an successive autoregressive covariance structure. Because of significant interactions with age, stratified analyses limited to participants in the oldest age-quartile and using increasingly older age thresholds (upper 20th and 10th percentiles by age) were performed for NPZ-4, individual component test scores (upper 20th percentile by age), and gait speed. Additionally, associations between entry metabolite concentrations with NPZ-4 change over time (slope) were evaluated utilizing similar mixed-effect linear models as described above; however, only those without NCI at entry were included. These models included entry NPZ-4, study week-by-TCA cycle metabolite interaction (slope) and all covariates as described above.

All analyses used SAS, version 9.4 (Carey, North Carolina). Statistical significance was defined by $P < .05$, except for interaction terms where statistical significance was defined by $P < .10$.

Ethics Statement

The Institutional Review Board at each study site approved the HAILO protocol. All participants provided written informed consent.

RESULTS

Entry Demographics and HIV-Related Factors

For this analysis, 957 participants were included. The median (interquartile range; IQR) age was 51 (46, 56) years, 81% were men and 74% were current or former smokers. The median duration of ART at entry was 7.7 (4.4, 11.9) years and 91% had HIV-1 RNA < 50 copies/mL at entry. Median entry and nadir CD4+ cell counts were 616 (447, 821) cells/mm^3 and 192 (59, 301) cells/mm^3, respectively. The median (IQR) follow-up duration was 192 (144, 192) weeks encompassing 4166 person years. Participants with NCI at entry were significantly more likely to be female, Hispanic regardless of race, have ≤ 12 years of education, and have shorter ART duration (Table 1).

Associations Between Tricarboxylic Acid Cycle Metabolites and Demographics

Overall, the mean entry fasting plasma citrate and succinate concentrations were 10.08 (range, 0.98–39.91 μg/mL) and 0.92 (0.01–7.43 μg/mL), respectively, and these were positively correlated with each other ($\rho = 0.15$, $P < .0001$). Higher citrate concentrations correlated with older age ($\rho = 0.09$; $P = .006$), and female sex ($P = .01$), but not race. Succinate concentrations were not correlated with age, sex or race.

Associations Between Tricarboxylic Acid Cycle Metabolites and Prevalent Neurocognitive Impairment

Participants with NCI at entry (prevalent NCI) had higher plasma citrate than those without NCI (mean ± SD citrate: 10.5 ± 4.19 μg/mL vs 9.90 ± 3.65 μg/mL; $P = .06$). Overall, the adjusted odds for NCI were 1.18 (95% CI 1.02–1.37; $P = .03$) times higher for each 1 SD increase in citrate concentration, with the association driven by the effect in the oldest age-quartile (citrate-by-age interaction term $P = .03$) (Supplementary Table 1). In the oldest age-quartile (≥56 years old), the adjusted odds ratio (aOR) for NCI was highest at 1.64 (95% CI 1.21, 2.24; $P = .002$) (Figure 1).

Participants with prevalent NCI also had higher plasma succinate than those without NCI at entry (mean succinate: 0.97 ± 0.82 μg/mL vs 0.89 ± 0.77 μg/mL; $P = .03$); however, the association did not remain after adjusting for clinically relevant covariates (aOR 1.09; 95% CI 0.94, 1.26; $P = .25$). Although the interaction with age was not statistically significant (succinate-by-age interaction term $P = .93$), in assessing the effect in those in the oldest 20th (≥ 58 years old) and 10th (≥ 62 years old) percentiles for age, the association between higher plasma succinate and NCI was apparent even with adjustment (Figure 1).

Table 1. Entry Demographics, HIV-Related Factors, TCA Cycle Metabolites, and Gait Speed by Neurocognitive Impairment Status at Entry

	NCI absent n = 692	NCI present n = 265	*P*
Age, years	51 (46, 56)	51 (46, 57)	.34
Male	574 (83%)	197 (74%)	.003
Race/Ethnicity			<.0001
White, not Hispanic	362 (53%)	112 (43%)	
Black, not Hispanic	224 (32%)	62 (23%)	
Hispanic regardless of race	106 (15%)	91 (34%)	
Education ≤12 years, n (%)	233 (34%)	129 (49%)	<.0001
Viral load < 50 copies/mL	634 (92%)	238 (90%)	.63
CD4+ cell count, cells/mm^3	616 (450, 820)	617 (431, 829)	.74
Nadir CD4+ cell count, cells/mm^3	189 (63, 294)	215 (44, 323)	.41
ART duration, years	7.8 (4.5, 11.5)	7.1 (4.1, 11.5)	.007
Smoking history			.46
Current	279 (41%)	102 (39%)	
Past	228 (34%)	83 (32%)	
Never	170 (25%)	76 (29%)	
Citrate, μg/mL			
Median	9.77 (7.57, 11.79)	10.09 (7.92, 12.50)	.06
Mean	9.90 (+/– 3.65)	10.54 (+/– 4.19)	
Succinate, μg/mL			
Median	0.69 (0.48, 1.02)	0.79 (0.51, 1.11)	.02
Mean	0.89 (+/– 0.77)	0.97 (+/– 0.82)	
Gait speed, seconds			
Median	3.75 (3.25, 4.26)	4.13 (3.53, 5.01)	<.0001
Mean	3.87 (+/– 0.93)	4.43 (+/– 1.27)	

Categorical variables are presented as frequency (column percent), continuous variables as median values (interquartile range) or where indicated, as mean values (+/– standard deviation).

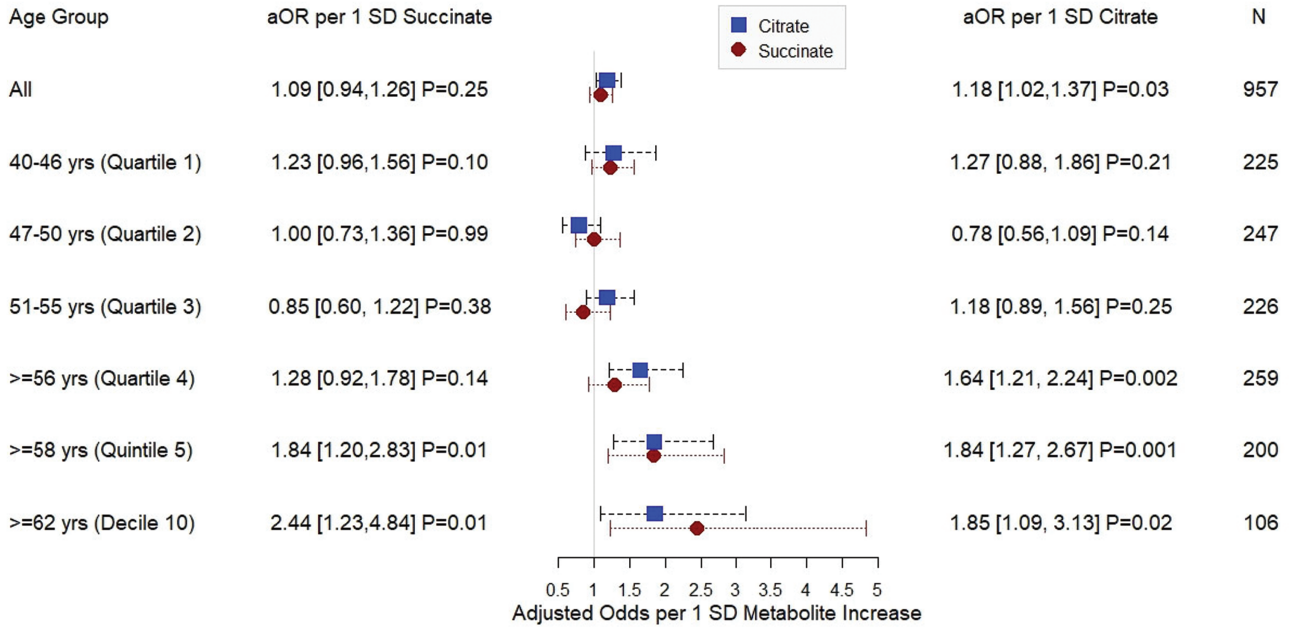

Figure 1. Association between prevalent NCI at entry and 1 SD increase in the plasma citrate and succinate concentration overall, by age-quartiles, and for oldest 20th and 10th percentiles. Symbols represent adjusted odds ratios for NCI per 1 SD increase in TCA cycle metabolite concentration in adjusted logistic regression models of prevalent NCI at entry; error bars represent 95% confidence intervals. Models adjusted for age, sex, race, education status, antiretroviral therapy duration, CD4+ cell count, and plasma viral load. Abbreviations: aOR, adjusted odds ratio; NCI, neurocognitive impairment; SD, standard deviation; TCA, tricarboxylic acid.

Associations Between Tricarboxylic Acid Cycle Metabolites and Neuropsychological Test Scores and Components

Entry plasma citrate concentrations were independently associated with entry and time-updated NPZ-4 scores, and this effect was dependent on age (citrate-by-age interaction $P = .01$ for each) (Supplementary Table 2A and 2B). Overall, each 1 SD citrate increase was associated with a 0.07 SD lower NPZ-4 score in adjusted models (ρ = −0.07; 95% CI −0.13, −0.02; $P = .01$) (Figure 2). The association was more pronounced in the oldest age-quartile where each 1 SD citrate increase was associated with a 0.17 SD lower NPZ-4 score in adjusted models (ρ = −0.17; 95% CI −0.25, −0.09; $P < .0001$; Figure 2).

Furthermore, higher entry plasma citrate concentrations were independently associated with the time-updated individual components of the NPZ-4 score (Supplementary Table 2C). The associations were significant in the overall population, but were stronger among participants within the oldest age-quintile (chosen because both TCA cycle metabolites were associated with NPZ-4 score in this subgroup; see Figure 2). In participants ≥ 58 years old (upper 20th percentile for age), higher citrate concentrations were also associated with lower scores on the following tests: Trail Making A (ρ = −0.19; 95% CI −0.30, −0.08; $P = .001$), Trail Making B (ρ = −0.18; 95% CI −0.29, −0.06; $P < .01$), Wechsler Adult Intelligence Scale-Revised Digit-Symbol Test (ρ = −0.20; 95% CI −0.32, −0.08; $p = 0.001$), and Hopkins Verbal Learning Test scores (ρ = −0.15; 95% CI −0.29, −0.01; $P = .04$) (Supplementary Table 2C).

Entry plasma succinate concentrations were not independently associated with entry or time-updated NPZ-4 scores in all participants (Figure 2). However, among the oldest age quintile, each 1 SD succinate increase was associated with lower NPZ-4 score (ρ = −0.16; 95% CI −0.28, −0.03; $P = .02$), as well as with lower Trail Making A (ρ = −0.18; 95% CI −0.34, −0.03; $P = .02$), and Trail Making B (ρ = −0.18; 95% CI −0.34, −0.02; $P = .02$) test scores, and there was some evidence of an association with lower Wechsler Adult Intelligence Scale-Revised Digit-Symbol Test scores (ρ = −0.15; 95% CI −0.33, 0.03; $P = .11$) and Hopkins Verbal Learning Test scores (ρ = −0.11; 95% CI −0.26, 0.03; $P = .12$) (Supplementary Table 2C).

Associations Between Tricarboxylic Acid Cycle Metabolites and Change in NPZ-4 Score Over Time (Figure 3)

The NPZ-4 slope for all participants did not differ from zero (slope = 0.002 SD per year; 95% CI −0.009, 0.014; $P = .70$). When examining associations between TCA metabolites and NPZ-4 slope, higher entry citrate concentrations, but not succinate, predicted a more rapid decline in a stratified analysis among participants without prevalent impairment (citrate-by-slope interaction: −0.016 SD per year; 95% CI −0.032, −0.0003, $P = .046$ per each 1 SD citrate increment; Supplementary Table 2D). Neither metabolite was associated with NPZ-4 slope in participants with prevalent impairment.

Associations Between Tricarboxylic Acid Cycle Metabolites with Entry/Baseline and Time-Updated Gait Speed

Higher entry plasma citrate concentrations were associated with slower 4-meter gait speed by repeated measures models (Supplementary Table 3A) and the effect was modified by

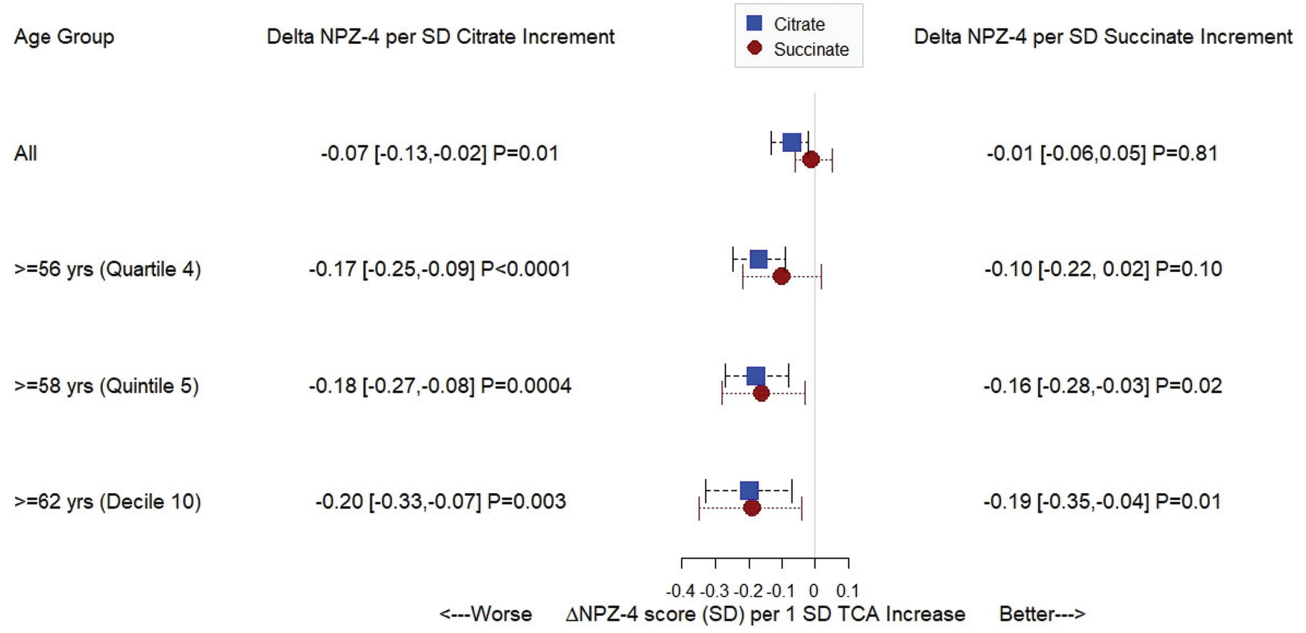

Figure 2. Association between time-updated NPZ-4 scores and 1 SD increase in plasma citrate and succinate concentrations overall, and for oldest 25th, 20th, and 10th percentiles. Symbols represent change in NPZ-4 score per 1 SD increase in entry TCA cycle metabolites in adjusted mixed effects linear models for time-updated NPZ-4 scores; error bars represent 95% confidence interval. Models adjusted for age, sex, race, education status, antiretroviral therapy duration, and time-updated CD4+ cell counts, plasma viral loads and study week. Abbreviation: SD, standard deviation; TCA, tricarboxylic acid.

age (P = .08 for citrate-by-age interaction; Figure 4). Each 1 SD citrate concentration increase was associated with a −0.02 m/s (95% CI −0.04, −0.01; P < .0001) slower gait-speed in all participants, compared to −0.04 and −0.05 m/s slower speeds among participants in the oldest age quartile and decile, respectively ($P \leq .01$ for each). Succinate concentrations were not associated with gait speed (Supplementary Table 3A).

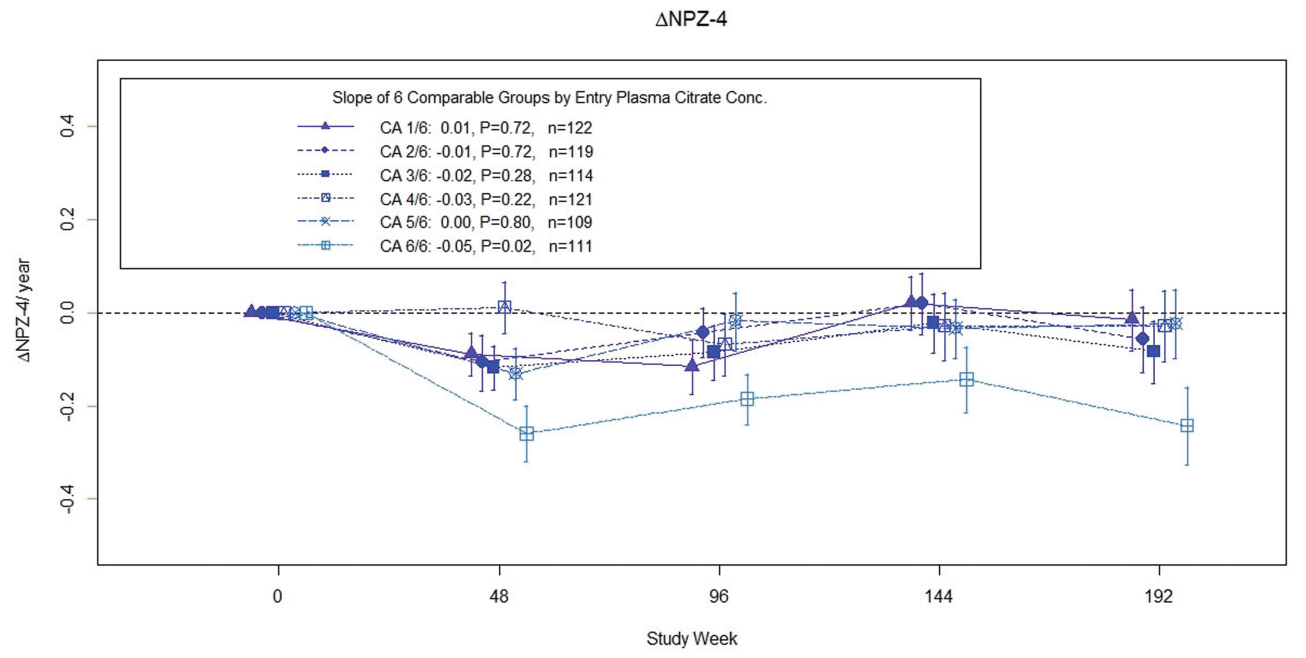

Figure 3. Change in NPZ-4 over time by entry plasma citrate concentrations in participants without NCI at entry. Symbols represent median NPZ-4 scores at each timepoint for participants grouped by entry plasma citrate concentration from lowest to highest. Error bars represent upper and lower 15th percentiles. The figure inset shows NPZ-4 slope over time for each of the 6 groups. Abbreviations: CA, citrate; NCI, neurocognitive impairment.

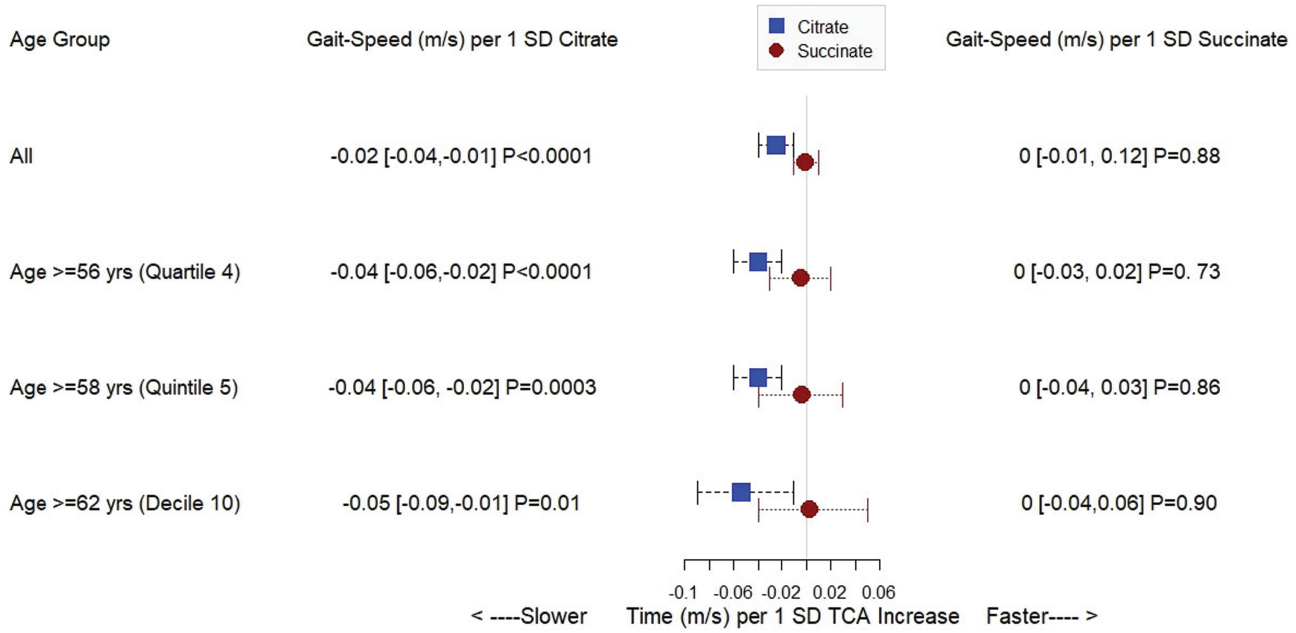

Figure 4. Association between time-updated gait speed and 1 SD increase in plasma citrate concentrations overall, and for oldest 25th, 20th, and 10th percentiles. Symbols represent effect on gait-speed (as m/s) for each 1 SD increase of entry TCA cycle metabolites in adjusted mixed effects linear models for time-updated gait speed; error bars represent 95% confidence interval. Models adjusted for age, sex, race, ART-duration, and time-updated CD4+ count, plasma viral load, and study week. Abbreviations: ART, antiretroviral therapy; SD, standard deviation; TCA, tricarboxylic acid.

Receiver Operating Characteristic (ROC) Curves for Prevalent NCI

Despite robust associations among older participants, the diagnostic discrimination for NCI by these TCA metabolites was poor by ROC analysis (area under the curve for the oldest age quartile was 0.59 and 0.55 for citrate and succinate, respectively) (Supplementary Figure 1).

DISCUSSION

In this multicenter, prospective longitudinal cohort of PWH, we observed novel associations between fasting metabolites of glycolysis in plasma and aging-related clinical outcomes, neurocognitive function, and gait speed. Higher fasting plasma citrate concentrations were associated with prevalent NCI, lower neuropsychological test scores, and slower gait speeds. These associations were age-dependent, mainly evident in persons aged 56 years and older (the oldest age-quartile of participants). Further, in participants without NCI at entry, higher citrate concentrations predicted NPZ-4 decline over time. Last, higher succinate concentrations were associated with prevalent NCI and lower neuropsychological test scores among persons aged 58 years and older (the oldest age-quintile of participants).

To meet anabolic needs, rapidly proliferating cancer cells dramatically increase aerobic glucose metabolism, upregulating and diverting glycolytic pathways toward involving purine, amino acid, and fatty acid synthesis pathways [21, 22]. First described by Warburg, this metabolic reprogramming is accompanied by an accumulation of some TCA cycle metabolites [23]. Macrophages and microglia undergo a similar metabolic shift upon activation by LPS and other pro-inflammatory stimuli, with upregulation of glycolysis and increased cell surface expression of the glucose transporter-1 (GLUT-1), down regulation of oxidative phosphorylation and accumulation of citrate and succinate, among other metabolites [10, 11, 24].

So, why are high levels of citrate and succinate clinically important, and how might they contribute to the impairments we found? Citrate is the first metabolic intermediate of the TCA cycle and is actively transported to the cytosol by the mitochondrial citrate–malate exchanger, a process that is induced by inflammation [25]. In the cytosol, citrate is oxidized to acetyl-CoA and oxaloacetate, fueling fatty acid and lipid biosynthesis [26] while also driving nitric oxide (NO) production and ROS formation. These ROS stabilize hypoxia inducible factor (HIF1-α), a major immune regulator, which promotes interleukin-1β and GLUT-1 gene expression [9, 23, 27, 28]. As with citrate, succinate is actively transported to the cytosol. Succinate is oxidized by succinate dehydrogenase, the only enzyme that directly links the TCA cycle to the electron transport chain (complex II) [29]. Consequently, succinate accumulates with reduced complex II activity [30]. In the cytosol, succinate also stabilizes HIF-1α [31] and engages succinate receptor (SUCNR-1), a

G-protein-coupled receptor localized within the kidneys, brain, and heart [32]. Activated SUCNR-1 induces glucose metabolism, angiogenesis, prostaglandin E2, and renin synthesis, while also enhancing the release of proinflammatory cytokines via the nuclear factor-kappa beta (NF-κB) pathway [31, 32].

Our findings are relevant to understanding the pathogenesis of NCI specifically in the context of aging with HIV infection, even despite the poor diagnostic discrimination of these TCA cycle metabolites by ROC analysis. The local and systemic effects of these TCA cycle metabolites which accumulate in the presence of inflammatory mediators and mitochondrial dysfunction lend biologic plausibility to the association of macrophage–monocyte and microglia activation with NCI. This is particularly relevant among PWH, in whom the migration of activated monocytes across the blood brain barrier may be critical in the development of HIV-associated NCI, and where damage to the tight epithelial barrier of the gastrointestinal tract allows microbial products, such as LPS, to enter the systemic circulation, contributing to a generalized state of immune dysregulation [33–36].

Further, these results extend previous studies identifying the importance of increased glycolysis and possibly mitochondrial dysfunction in the pathogenesis of NCI in HIV. In the Central Nervous System HIV Anti-Retroviral Therapy Effects Research (CHARTER) study, higher CSF concentrations of the TCA cycle metabolite citrate was prognostic, in recursive partitioning models, of worsening neurocognitive status [13]. Additionally, higher CSF citrate concentrations were associated with worse global, executive function, and motor ability domains in cross-sectional analyses [13]. In another cross-sectional study, metabolomic profiling of CSF identified higher succinate concentrations as associated with NCI in PWH on ART [12]. Importantly, the findings from our study were most evident in PWH over the age of 55. While the reason behind this observation is not clear, it is consistent with findings from the Multicenter AIDS Cohort Study (MACS), a long-term prospective cohort study of HIV infection in men who have sex with men in the United States, which identified lower performance on all 5 neurocognitive domains with older age, with a greater-than-expected effect of age on episodic memory and motor function in individuals with late-stage HIV disease [37]. Perhaps the observed interactions with age result from enhanced vulnerability among older persons to common detrimental metabolic effects on both neurocognitive and physical function in PWH, or there could be a threshold effect due to mitochondrial dysfunction. Interestingly, however, the association between citrate and gait speed suggest that this process may begin earlier in life as slowing gait speed may predict future NCI [14–16].

Strengths of this study include repeated assessments of neurocognitive function using validated tests, corresponding to more extensive neuropsychological testing in PWH [20]. Nevertheless, we have noted a few limitations. Because we only studied PWH, we do not know whether these associations are specific to HIV-associated NCI. While altered gut integrity and resultant microbial translocation are known to be important drivers of chronic immune activation among PWH potentially promoting the Warburg effect, it is possible that similar changes in succinate and citrate metabolism occur with aging in the general population. Also, we do not know whether the observed associations with citrate and succinate reflect changes in mitochondrial function and glycolysis, or changes in other cellular pathways that include these metabolites. Although we were not able to correlate findings with specific inflammatory or oxidative stress pathways, additional studies are planned to assess these potential links more fully. Finally, our study had limited power to detect all potential clinically meaningful interactions including possible interactions with race/ethnicity; such effects which will be important to assess in future analyses.

In conclusion, we have shown that fasting plasma TCA cycle metabolites are associated with cross-sectional and longitudinal measures of neurocognitive function and gait speed in PWH in an age-dependent manner. These associations support the importance of altered bioenergetic metabolism in the pathogenesis of NCI, and imply differential mechanisms by age. Further, it is possible that these TCA cycle metabolites are potential targets for future NCI therapeutics.

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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Potential conflicts of interest. C. O. H. has served as consultant for Gilead Sciences and Theratechnologies, and received research funding from Gilead Sciences. R. B. has served as consultant for ViiV Healthcare and Merck & Co, and has received research funding from ViiV Healthcare. K. M. E. has served as consultant for ViiV and Gilead Sciences and has received research funding from Gilead Sciences. A. L. serves on the advisory board of Merck, and chairs the Gilead HIV Research Scholars Program. F. J. P. has received honoraria from Gilead Sciences, Janssen, ViiV and Merck. R. K. has received research funding from Gilead Sciences. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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