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Relationship of Exercise, Sleep, and Inflammation Markers in People Living With HIV

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HEALTH Study: Statistical Analysis Plan

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Primary Contact: <Publication Lead>



Primary Investigators:

Kristine Erlandson, MD at the University of Colorado Anschutz School of Medicine
Allison Webel, RN, PhD at the University of Washington

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Created by:

Christine Horvat Davey

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Contact Information

1. Christine Horvat Davey, cmh166@case.edu, Assistant Professor, Case Western Reserve University, Frances Payne Bolton School of Nursing

Version History

Version	Changes Made	Date Finalized
1	Original Version	

1. Study Rationale/Background

K23 Sleep Sub Study:

Up to 75% of PWH experience sleep deficiencies including poor sleep quality, insomnia, and daytime sleepiness. Poor sleep quality leads to poor outcomes, including limited mobility, decrease in performance of daily activities, and increased mortality. Systemic inflammation markers such as IL-10, IL-13, IFN- γ , and TNF- α are associated with sleep disturbance in PWH, while CRP, TNF- α , IL-1 β , IL-6, and IL-13 are associated with impaired sleep quality in other chronically ill populations. Less physical activity is also associated with increased inflammation. The collective or interacting impact of low levels of physical activity and

inflammation on poor sleep quality may be stronger than either independent factor; therefore, it is vital to examine the potentially causal pathway between physical activity, sleep, and inflammation to help mitigate poor sleep quality.

Regular exercise is known to improve sleep quality and reduce inflammation across populations. Continuous moderate-intensity exercise (CME) and high-intensity resistance exercise improves sleep quality in older adults. HIIT is safe and has higher efficacy in improving health outcomes compared to CME in those with chronic illness (i.e., coronary artery disease, diabetes), yet little is known about the effects of HIIT on sleep in people living with HIV.

2. Study Objectives

a. Overview

The purpose of this K23 study is to conduct a pilot study to compare the effectiveness of two exercise interventions, HIIT and CME, on sleep quality in older PWH (≥ 50 years). We will also examine the underlying inflammatory mechanism of sleep in older PWH.

b. Primary Hypothesis and Objective

- a. Objective: Compare the effectiveness of HIIT and CME exercise interventions on sleep in older PWH.
- b. Primary Hypothesis: PWH who are randomized to the HIIT exercise intervention will experience greater improvement in sleep (duration and quality) compared to CME.

Approach: In a pilot study ($n=50$), we will establish the effect of 16 weeks of HIIT and CME on change in sleep quality of PWH through self-report surveys and objectively measured actigraphy at baseline and after exercise interventions (Week 16) within each intervention and between the two exercise interventions (Week 16).

c. Secondary Hypothesis 1 and Objective

- a. Objective: Quantify the longitudinal association between inflammation markers and sleep quality (self-report surveys) in older PWH at baseline, between (Week 8), and after 16 weeks of HIIT and CME.
- b. Primary Hypothesis: PWH who experience poor sleep quality and the CME intervention will have increased inflammation markers compared to older PWH who experience better sleep quality and the HIIT intervention.

Approach: We will quantify the inflammation markers (primary inflammation markers, IL-6, IL-10, IL-13, IFN- γ , CRP, TNF- α and exploratory inflammation markers, IL-1 β , IL-2, IL-4, IL-8, IL-12p70) through multiplex assays pre-exercise intervention (baseline), at Week 8, and at completion, Week 16 in the overall study population and by intervention group.

d. Secondary Hypothesis 2 and Objective

e. Exploratory Objectives

- a. Compare the change in sleep quality of PWH through self-report surveys and objectively measured actigraphy at baseline and after exercise interventions (Week 16) within each intervention and between the two exercise interventions (Week 16) between sites (UW and UCD), sex, and age.

3. Study Population

a. Inclusion criteria-

Enrollment in the HEALTH-HIV study with medical clearance by SIU HIV clinician and the following additional criteria: (1) confirmed HIV infection; (2) sedentary lifestyle, defined as self-reported physical activity that breaks a sweat <3 days/week, with no regular resistance exercise for 3 months prior to the study; (3) on a current, modern ART regimen; (4) documented HIV-1 RNA <200 copies/mL in the past 12 months; (5) willing to engage in a supervised exercise program 3 times/week for 16 weeks; (6) women must be post-menopausal due to potential confounding effects based on the skeletal muscle evaluation in the parent HEALTH-HIV study; (7) *poor sleep quality based on self-report survey (Pittsburgh Sleep Quality Index, total score >5)*; (8) Aged ≥ 50 years; and (9) English speaking.

b. Exclusion criteria

HEALTH Clinical Trial criteria

c. Anticipated sample size

N= 50

4. Timeline

a. Deadlines

N/A

b. Anticipated timeline

- a. SAP draft for review: 03/10/2024

5. Statistical Analysis Plan

Table 4.1: Analysis Variable Definitions

Analysis	Variables	Variable Type	Time points
Outcome			
Primary	Sleep quality (actigraphy): Sleep duration Sleep efficiency Wake after sleep onset (WASO) Sleep fragmentation index	Continuous	Baseline and week 16.
	Sleep quality (self-report): PSQI	Ordinal Ordinal	Baseline and week 16.
Primary Exposure(s)			
	HIIT CME		
Other Covariates			
	Age Sex at birth BMI		
Secondary	inflammation markers (primary inflammation markers, IL-6, IL-10, IL-13, IFN- γ , CRP, TNF- α and exploratory inflammation markers, IL-1 β , IL-2, IL-4, IL-8, IL-12p70)	Continuous	Baseline, week 8 and 16.
Primary Exposure(s)			
	HIIT CME Sleep quality Actigraphy Self-report		
Other Covariates			
	Age Sex at birth BMI		

a. Primary Analysis:

a. Analysis overview

- i. Linear, logistic and mixed effects regression models will be utilized with adjustment for baseline values, potential confounders and precision efficiency variables. Analyses will be conducted in SPSS (26) and R.

b. Figures/Tables

- i. Table 1. Demographic and Participant Characteristics

- ii. Table 2. Differences in objective and subjective sleep at baseline and 16-week intervention and between intervention arms (HIIT and CME).

b. Secondary Analysis:

- a. Analysis overview
 - i. Linear, logistic and mixed effects regression models will be utilized with adjustment for baseline values, potential confounders and precision efficiency variables. Analyses will be conducted in SPSS (26) and R.
- b. Figures/Tables
 - i. Table 3. Quantify the longitudinal association between inflammation markers and sleep quality at baseline, week 8 and week 16 and between intervention arms (HIIT and CME).

6. Report Details (Figures, Tables, Text)

In addition to the previously described analyses, the following elements will be detailed in the final analysis report.

- a. Participant inclusion details (CONSORT)
- b. Baseline characteristics for Table 1
 - a. Demographics: Age, sex assigned at birth/gender, race/ethnicity, HIV characteristics (years with HIV, VL)
 - b. Laboratory values at baseline:
- c. Descriptive Summary of Outcome Measures
 - a. Primary
 - b. Secondary
- d. Statistical methods section