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Insomnia as an Independent Predictor of Incident Cardiovascular Disease in HIV: Data from the Veterans Aging Cohort Study

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Abstract

Background: Insomnia is associated with increased cardiovascular disease (CVD) risk in the general population and is highly prevalent in people with HIV. The CVD risk conferred by insomnia in the HIV population is unknown.

Methods: Using the Veterans Aging Cohort Study-Survey Cohort, insomnia symptoms were measured and dummy coded with the item, "Difficulty falling or staying asleep?" (5-point scale from no difficulty to bothers a lot). Incident CVD event ICD-9 codes (acute myocardial infarction, stroke, or coronary artery revascularization) were identified with VA and Medicare administrative data and VA fee-for-service data. Those with baseline CVD were excluded.

Results: HIV-infected (*N*=3,108) veterans had a median follow-up time of 10.8 years, during which 267 CVD events occurred. Compared to HIV-infected veterans with no difficulty falling or staying asleep, HIV-infected veterans bothered a lot by insomnia symptoms had an increased risk of incident CVD after adjusting for demographics (*HR*=1.64, 95%*CI*=1.16-2.31, *p*=.005), CVD risk factors (*HR*=1.62, 95%*CI*=1.14-2.30, *p*=.007), additional potential confounders (hepatitis C infection, renal disease, anemia, alcohol use, cocaine use; *HR*=1.70, 95%*CI*=1.19-2.43, *p*=.003), and HIV-specific factors (HIV-1 RNA, $CD4^+$ T-cell count, ART; *HR*=1.66,

95%*CI*=1.16-2.37, *p*=.005). Additional adjustment for non-benzodiazepine sleep medication (*HR*=1.62, 95%*CI*=1.13-2.32, *p*=.009) did not attenuate the association; however, it fell short of significance at $p < .01$ after adjustment for depressive symptoms (*HR*=1.51, 95%*CI*=0.98-2.32, *p*=.060) or antidepressant medication (*HR*=1.51, 95%*CI*=1.04-2.19, *p*=.031).

Conclusion: Highly bothersome insomnia symptoms were significantly associated with incident CVD in HIV-infected veterans, suggesting that insomnia may be a novel, modifiable risk factor for CVD in HIV.

Key Words: HIV, cardiovascular disease, insomnia, sleep disturbance, Veterans, VACS, prospective study

Introduction

Antiretroviral therapy (ART) has transformed human immunodeficiency virus (HIV) into a chronic, manageable condition. However, the decrease in AIDS-related mortality has been accompanied by an increase in the prevalence of non-communicable chronic diseases, including cardiovascular disease (CVD). In fact, CVD is a leading cause of death among HIV-infected adults.[1-3] A 2012 meta-analysis reported a 1.6-2.0 times greater risk of CVD in HIV-infected versus uninfected adults.[4] A portion of the elevated HIV-CVD risk has been attributed to the HIV virus,[5-7] ART treatment,[4,8,9] and both traditional[10] and non-traditional (e.g., renal disease and hepatitis C)[11,12] CVD risk factors. Even so, excess CVD risk is still observed among HIV-infected adults after controlling for HIV viral load, ART use, and CVD risk factors[13] and is observed in those with optimal CVD risk profiles.[14] Other factors thought to contribute to the excess CVD risk in HIV include altered immune, coagulation, and endothelial function.[15] While these biological mechanisms improve with ART, markers of these factors do not fully normalize among virologically-suppressed HIV-infected adults.[16-22] Thus, there is a need to identify novel,

modifiable risk factors for HIV-CVD with the potential to improve these dysregulated mechanisms.

General population research provides three lines of evidence suggesting that insomnia may be a novel risk factor for HIV-CVD. First, insomnia is an independent risk factor for CVD in the general population. Meta-analytic findings show that adults with elevated insomnia symptoms have an increased risk for CVD (risk ratio [*RR*] = 1.45),[23] including coronary heart disease (*RR* = 1.28), myocardial infarction (*RR* = 1.41), stroke (*RR* = 1.55), and CVD-related mortality (*RR* = 1.33), after adjustment for traditional CVD risk factors.[24] In addition, a meta-analysis examining individual insomnia symptoms found that difficulty initiating sleep, difficulty maintaining sleep, and non-restorative sleep were associated with increased CVD risk (*RR*s = 1.27, 1.11, and 1.18, respectively).[25] Moreover, recent evidence suggests that the atherogenic effects of insomnia are independent from that of sleep apnea.[26,27]

Second, intriguing evidence suggests that insomnia may be a causal risk factor for CVD in the general population. The largest randomized control trial (RCT) of behavioral interventions for insomnia by Irwin et al.[28] found that older adults with insomnia treated with cognitive behavioral therapy for insomnia (CBT-I), versus an educational sleep seminar, had a significantly reduced risk (odds ratio = 0.26) of elevated C-reactive protein (CRP; 3.0 mg/L), an inflammatory marker predictive of incident CVD.[29] The authors concluded that CBT-I is a viable option for modifying an inflammatory marker of CVD risk.

Third, insomnia may be a novel driver of putative biological mechanisms underlying HIV-CVD. In addition, insomnia has been associated with altered immune function,[30] systemic inflammation,[31] and altered coagulation.[32-38]

Despite the extensive literature supporting an insomnia-CVD association in the general population and the high insomnia/sleep disturbance prevalence among HIV-infected adults,[39,40] to our knowledge, no study has examined whether indicators of insomnia predict incident CVD in HIV-infected adults. Thus, the study purpose was to test whether insomnia symptoms independently predict incident CVD events among HIV-infected veterans.

Methods

Study Design and Setting

We utilized the HIV-infected sample from the Veterans Aging Cohort Study (VACS)-Survey Cohort – a prospectively enrolled observational longitudinal survey cohort of HIV-infected veterans and 1:1 matched uninfected veterans on age, sex, race/ethnicity, and clinical site.[41] The VACS-Survey Cohort undergoes continuous enrollment, beginning in June of 2002. We defined the baseline period as -ever to +6 months of the enrollment date. All participants were followed until the occurrence of a CVD event, death, or the last date of our follow-up period (December 25, 2014). From the total HIV-infected sample of the VACS-Survey Cohort (N = 3,714), we excluded: (1) veterans with pre-existing CVD *International Classification of Diseases, Ninth Revision* [ICD-9] codes for acute myocardial infarction [AMI], unstable angina, cardiovascular revascularization, stroke or transient ischemic attack, peripheral vascular disease, or heart failure in the VA, Medicare, and Medicaid administrative data or VA fee-for-service data during our baseline period (n = 523); (2) veterans missing insomnia symptoms data (n = 40); (3) veterans missing more than two items on the Patient Health Questionnaire-9 (PHQ-9; n = 40); and (4) veterans with coding errors (i.e., negative follow-up time; n = 3). Our final sample consisted of 3,108 HIV-infected veterans.

Measures and Procedures

Baseline insomnia symptoms. Insomnia symptoms were assessed at enrollment by the insomnia symptom item of the VACS HIV Symptom Index – a 20-item, self-report questionnaire assessing the frequency and bother of common symptoms in HIV-infected adults exposed to multidrug ART and protease inhibitors.[42] Participants were asked to indicate what response best described their experience of each symptom over the past four weeks using the following options: 0 = "I do not have this symptom" or "I have this symptom and…" 1 = "it doesn't bother me," 2 = "it bothers me a little," 3 = "it bothers me," 4 = "it bothers me a lot." We used responses to the insomnia item – "Difficulty falling or staying asleep?" – to create a 5-level insomnia symptoms variable. From this variable, four dummy coded variables were created with the "No Difficulty Falling or Staying Asleep" group as the reference category. Although our insomnia symptoms measure is a single-item, one-time assessment, data from the VACS-Survey Cohort suggests that this measure is moderately stable over time and thus likely captures participants' long-term exposure to insomnia symptoms. Specifically, when correlating responses to this item across VACS-Survey Cohort follow-ups occurring between 2002-2011, we observed medium positive correlations (r_s range: 0.44-0.60; all ps < .001) between adjacent follow-ups.

Incident cardiovascular disease events. CVD events were identified using VA and Medicare administrative data and VA fee-for-service data. We defined an incident CVD event as first occurrence of at least one inpatient ICD-9 code for AMI or stroke or one inpatient ICD-9 Clinical Modification (ICD-9-CM) code or Current Procedural Terminology (CPT) code for coronary artery revascularization (i.e., percutaneous coronary intervention or coronary artery bypass graft).

Baseline covariates. Five groups of covariates were included, all of which were determined either using self-report questionnaire data collected at baseline or using routine clinical care data in the electronic medical record abstracted for the encounter closest to the participant's enrollment date during the baseline period (i.e., -ever to +6 months of enrollment date). The specific ICD-9, ICD-9-CM, and CPT codes utilized in variable definitions are presented in Table 5, Supplemental Digital Content 2, http://links.lww.com/QAI/B279. First, demographic factors were age, sex (0=male, 1=female), and race/ethnicity (0=White, Hispanic, Other, 1=African American).

Second, cardiovascular risk factors were hypertension, diabetes, body mass index (BMI), smoking, total cholesterol, and statin use. Blood pressure was defined as the average of the last three outpatient clinical measurements collected during routine clinical care closest to the enrollment date during the baseline period.[43,44] Hypertension was categorized as no hypertension (blood pressure <140/90 mmHg and no antihypertensive medication [reference category]), controlled hypertension (<140/90 mmHg with antihypertensive medication), or uncontrolled hypertension (≥140/90 mmHg). Diabetes (yes/no) was identified by a previously validated metric incorporating glucose measurements, diabetes medication use, and/or at least one inpatient or two outpatient ICD-9 codes for diabetes.[45,46] BMI (kg/m^2) was defined by one outpatient clinical measurement collected during routine clinical care closest to the enrollment date during the baseline period and modeled as a continuous variable. Smoking (never [reference category], former, and current smoker) was assessed by self-report at enrollment. Total cholesterol was defined by one outpatient clinical measurement collected during routine clinical care closest to the enrollment date during the baseline period and modeled as a continuous variable. Baseline

statin use (yes/no) was defined as a filled prescription receipt for a 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor at time of enrollment.

Third, additional potential confounders were hepatitis C infection, renal disease, anemia, alcohol use, and cocaine use. Hepatitis C infection (yes/no) was identified by a positive hepatitis C virus antibody test or at least one inpatient or two outpatient ICD-9 codes for hepatitis C infection.[47] Renal disease was defined by estimated glomerular filtration rate (eGFR),[48] and anemia was defined using a hemoglobin; both were based on a measurement collected during routine clinical care closest to the enrollment date during the baseline period and were modeled as a continuous variables. Alcohol use was assessed by the Alcohol Use Disorders Identification Test (AUDIT-C) at baseline and alcohol abuse/dependence ICD-9 codes during the baseline period and dichotomized as no current use or non-hazardous use versus hazardous use (AUDIT-C $\geq$ 4) or alcohol abuse/dependence disorder. Cocaine use was assessed by self-report at baseline and cocaine use disorder ICD-9 codes during the baseline period and dichotomized as never tried or no use in past 12 months versus use in the past 12 months or cocaine abuse/dependence disorder.

Fourth, HIV-specific factors were HIV-1 RNA viral load, $CD4^+$ T-cell count, and ART regimen. HIV-1 RNA viral load and $CD4^+$ T-cell count were defined by outpatient clinical measurements collected during routine clinical care closest to the enrollment date during the baseline period and modeled as continuous variables. Baseline ART regimen (yes/no) was defined by a filled prescription receipt for any ART (-180 days to +7 days of enrollment date).

Finally, insomnia-related variables were non-benzodiazepine sleep medication use, depressive symptoms, and antidepressant medication use. Non-benzodiazepine sleep medication use (yes/no) was defined by a filled prescription receipt closest to baseline (-ever to +180 days of

enrollment date) for the following medications: zolpidem, zaleplon, eszopiclone, and indiplon. Depressive symptoms were assessed by the PHQ-9 at baseline. Antidepressant medication use was defined by a filled prescription receipt for an antidepressant medication closest to baseline (-ever to +180 days of enrollment date). We computed three dichotomous variables (yes/no) based on the antidepressant medication type – serotonin reuptake inhibitor (SSRI), tricyclic antidepressant (TCA), and miscellaneous other antidepressant.

Statistical Analysis

To examine the association between baseline insomnia symptoms and incident CVD events among HIV-infected veterans, first, we constructed Kaplan-Meier event-free survival curves to illustrate the time from enrollment to first CVD event for each of the five levels of our insomnia symptoms variable. Second, we constructed Cox proportional hazard regression models to estimate the hazard ratio (*HR*) and 95% confidence intervals (CI) for each level of the insomnia symptoms variable (reference category: "No Difficulty Falling or Staying Asleep"), given our interest in the most clinically relevant insomnia symptoms group ("Bothers a Lot") and the novelty of our research question in the HIV population. We also performed a likelihood ratio test of two Cox models (one with the insomnia symptoms variable and the other without) to present the overall significance of the insomnia symptoms variable.

Five Cox proportional hazard regression models were constructed to hierarchically add the main covariates to create Model 4, our primary model, as follows: Model 0 – unadjusted (insomnia symptoms dummy coded variables alone predicting incident CVD); Model 1 – Model 0 + demographics (age, sex, and race/ethnicity); Model 2 – Model 1 + CVD risk factors (hypertension, diabetes, BMI, smoking, total cholesterol, and statin use); Model 3 – Model 2 + additional potential confounders (hepatitis C infection, renal disease, anemia, alcohol use, and

cocaine use); and Model 4 – Model 3 + HIV-specific factors (HIV-1 RNA level, $CD4^+$ T-cell count, and ART regimen).

An additional four exploratory Cox proportional hazard regression models were constructed to examine the potential influence of insomnia-related variables. The first three Cox models hierarchically and individually added insomnia-related variables to Model 4 to examine the influence of each variable on Model 4. Three versions of Model 5 were constructed as follows: Model 5a – Model 4 + non-benzodiazepine sleep medication use; Model 5b – Model 4 + PHQ-9 total score; and Model 5c – Model 4 + SSRI use, TCA use, and miscellaneous other antidepressant use. The fourth Cox model included all of the covariates in one model as follows: Model 6 – Model 4 + non-benzodiazepine sleep medication use, PHQ-9 total score, SSRI use, TCA use, and miscellaneous other antidepressant use.

We also conducted four exploratory sensitivity analyses. First, to examine the influence of adjusting for ART medications associated with insomnia or disruption of the metabolism of insomnia medications on our primary model,[49,50] we re-ran two separate Model 4's. The first replaced the ART regimen variable with an efavirenz use variable (yes: n = 787; no: n = 2,321) and the second replaced the ART regiment variable with a protease inhibitor use variable (yes: n = 1,457; no: n = 1,651). Second, to examine the influence of omitting item 3 of the PHQ-9 ("Trouble falling or staying asleep, or sleeping too much") on models including depression, we removed the item from the PHQ-9 total score calculation and re-ran Model 5b and Model 6.

Multiple imputations using chained equations with five separate imputed datasets were generated based on predictive mean matching using the Hmisc library of R programming language. Cox survival models were fitted in each imputed dataset and then combined to obtain pooled *HR*s and standard errors. All analyses were performed using R software (version 3.3.3;

www.r-project.org). To account for inflation in type 1 error associated with multiple tests, we considered $p < .01$ as statistically significant.

Results

Participant Characteristics

Participant characteristics are shown in Table 1. The median age was 49 years. Most participants were men (97%), and two-thirds were African American (66%). The distribution of participants and incident CVD events across insomnia symptom categories are displayed in Table 2. At enrollment, the majority of HIV-infected veterans endorsed some level of insomnia symptoms (59%). During a median follow-up time of 10.8 years (1^{st} quartile: 6.7, 3^{rd} quartile: 11.8), 267 incident CVD (8.6%) events occurred.

Baseline Insomnia Symptoms and Incident CVD Events

Figure 1 presents Kaplan-Meier survival curves illustrating the time to first CVD event for each of the five insomnia symptom categories. For HIV-infected veterans, the "Bothers a Lot" survival curve consistently separates from those for the other four categories around the sixth year of follow-up. Though visually supporting a difference in time to CVD event between "Bothers a Lot" and the other four categories, this is not reflected in the omnibus test of the survival curves (log-rank $\chi^2 = 5.2$, $df = 4$, $p = .267$).

The five Cox models constructed to hierarchically create our primary Model 4 examining the association between baseline insomnia symptoms and incident CVD events revealed that the test of overall significance across the four insomnia symptoms dummy coded variables was not significant in Models 0-4 (p-value range: .069-.304; Table 3). These omnibus null results were driven by the lack of associations between incident CVD events and the dummy coded variables

comparing the “Doesn’t Bother,” “Bothers a Little,” and “Bothers” groups to the “No difficulty Falling or Staying Asleep” group in Model 0-4 (*p*-value range: .305-.971). In contrast, the dummy coded variable comparing the “Bothers a Lot” group to the “No difficulty Falling or Staying Asleep” group fell just short of significant in Model 0 ($p = .034$) and was significantly associated with incident CVD in Models 1-4 (*HR* range: 1.45-1.70; *p*-value range: .003-.007). To illustrate, our primary Model 4 results indicate that HIV-infected veterans bothered a lot by difficulty falling or staying asleep had a 66% greater risk of incident CVD events than HIV-infected veterans without these symptoms, independent of demographics, CVD risk factors, additional potential confounders, and HIV-specific factors.

The four additional exploratory Cox models constructed to hierarchically examine the potential influence of insomnia-related variables revealed similar results to Models 0-4 for the overall significance across the four insomnia symptoms dummy coded variables in Models 5a-5c and Model 6 (*p*-value range: .147-.591; Table 3) and the dummy coded variables comparing the “Doesn’t Bother,” “Bothers a Little,” and “Bothers” groups to the “No difficulty Falling or Staying Asleep” group in Model 5a-5a and Model 6 (*p*-value range: .360-.933). Similar to Model 4, the dummy coded variable comparing the “Bothers a Lot” group to the “No difficulty Falling or Staying Asleep” group remained significantly associated with incident CVD after including non-benzodiazepine sleep medication use in Model 5a (62% greater risk; $p = .009$). However, the “Bothers a Lot” and “No difficulty Falling or Staying Asleep” group comparison fell short of significance after including PHQ-9 total score in Model 5b (51% greater risk; $p = .060$), antidepressant medication use in Model 5c (51% greater risk; $p = .031$), or all three insomnia-related variables in Model 6 (42% greater risk, $p = .115$).

Results of the four exploratory sensitivity analyses are presented in Table 4, Supplemental Digital Content 1, http://links.lww.com/QAI/B279. Our first and second sensitivity analyses, in which ART regimen was replaced with either efavirenz use or protease inhibitor use in Model 4, yielded nearly identical results (Bothers a Lot *HR* in Model 4 with efavirenz use = 1.68, 95%*CI*: 1.17-2.39, $p = .005$; Bothers a Lot *HR* in Model 4 with protease inhibitor use = 1.67, 95%*CI*: 1.17-2.39, $p = .004$) to our original Model 4. Our third and fourth sensitivity analyses, in which the sleep disturbance item was omitted from the PHQ-9 total score calculation in Models 5b and 6, also produced nearly identical results (Bothers a Lot *HR* in Model 5b = 1.53, 95%*CI*: 1.02-2.32, $p = .042$; Bothers a Lot *HR* in Model 6 = 1.43, 95%*CI*: 0.94-2.17, $p = .093$) to our original Models 5b and 6. These findings indicate that (a) adjusting for ART medications with recognized effects on insomnia or insomnia medications and (b) removing the sleep disturbance item from the depressive symptoms measure had a negligible influence on the relationships of interest.

Discussion

In this large prospective cohort study utilizing the VACS-Survey Cohort data, we found that insomnia symptoms were associated with incident CVD among HIV-infected veterans. After adjustment for demographics, CVD risk factors, additional potential confounders (hepatitis C infection, renal disease, anemia, alcohol use, and cocaine use), and HIV-specific factors (HIV-1 RNA level, $CD4^+$ T cell count, and ART regimen), HIV-infected veterans bothered a lot by difficulty falling or staying asleep exhibited a 66% greater risk of an incident CVD event than HIV-infected veterans without these symptoms. This association persisted after individually adjusting for non-benzodiazepine sleep medication use (62% greater risk). However, while the hazard ratios were similar in magnitude (*HR*s = 1.51), the association between highly

bothersome insomnia symptoms and incident CVD fell short of significance after individually adjusting for depressive symptoms or antidepressant medication use. We did not observe associations between the other insomnia symptoms category comparisons ("Doesn't Bother," "Bothers a Little," and "Bothers" versus "No Difficulty Falling or Staying Asleep") and incident CVD events. Taken together, the present results suggest that highly bothersome insomnia symptoms may be an independent predictor of incident CVD events among HIV-infected adults, although the overlap with depression and its treatment needs further investigation.

To our knowledge, this is the first examination of the insomnia-CVD relationship in people with HIV. We observed a threshold effect, with only the highest level of insomnia symptoms exhibiting an elevated CVD risk. The leading potential explanation for this finding is that (a) the "Bothers a Lot" group may have the highest rate of insomnia disorder and that (b) it is insomnia disorder, but not subclinical insomnia symptoms, that is related to elevated CVD risk. Future studies are needed to evaluate this possibility.

The biological plausibility of the insomnia-CVD relationship in the HIV population has preliminary support. Insomnia symptoms have been associated with inflammation-related single nucleotide polymorphisms[51,52] and elevated circulating levels of interleukin-6 and CRP,[53] both of which are implicated in atherosclerosis among HIV-infected adults.[54] Additional support for the insomnia-CVD relationship can be drawn from the general population literature, as three meta-analyses have linked insomnia symptoms with future CVD.[23-25] In addition, general population evidence supports associations between insomnia symptoms and biological mechanisms underlying CVD development, including systemic inflammation,[31] altered coagulation,[32-38] and endothelial dysfunction.[55-57]

There are study limitations that warrant consideration. First, our insomnia symptoms assessment was obtained only at baseline and relied on a single item. While the VACS HIV Symptom Index's[42] insomnia item does assess difficulty initiating or maintaining sleep and bothersomeness, it misses other insomnia symptoms (e.g., early morning awakening and functional impairment), and it does not measure frequency or duration. These content validity issues could lead to misclassification (e.g., coding a veteran with insomnia symptoms as not having them), which could contribute to effect size underestimation. That said, the majority of general population studies have used single-item insomnia assessments (most often assessing difficulty falling asleep) and have observed positive associations with CVD-related outcomes.[24] In addition, the insomnia symptoms item does not capture chronicity of insomnia. Future research should examine the potential influence of insomnia duration or chronic versus acute insomnia on incident CVD risk. Second, because we utilized a veteran sample comprised of mostly men, it is unclear whether our results extend to HIV-infected women. Third, due to the timeframe of this study, we could not assess for newer ART therapies linked to insomnia – namely, rilpivirine and dolutegravir. Fourth, due to the absence of a strong assessment, we were unable to adjust our models for sleep apnea – a sleep disorder with an estimated prevalence of 2.9% among veterans[58] and an established independent risk factor for incident CVD.[59] Fifth, we were unable to include posttraumatic stress disorder (PTSD) as a potential confounder. Some of the symptoms of PTSD have strong conceptual and measurement overlap with the insomnia symptoms of interest here (i.e., nightmares and difficulty sleeping due to alterations in arousal and reactivity)[60] and the available PTSD assessments do not allow for the separation of insomnia and PTSD symptoms. Future research should examine include comprehensive measures of

insomnia and PTSD symptoms in order to tease apart the potential influence of these overlapping factors on incident CVD.

In summary, we provide intriguing evidence that highly bothersome insomnia symptoms may be an independent predictor of incident CVD events among HIV-infected adults. Future prospective studies with comprehensive insomnia assessments utilizing non-veteran samples are needed to fully characterize the insomnia-CVD relationship and to identify its underlying mechanisms in the HIV population. Ultimately, such research could lead to the identification of a novel, modifiable risk factor for HIV-CVD and could inform the development of new primary prevention programs that include insomnia interventions to prevent CVD in people with HIV.

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Figure Legend

Figure 1. Kaplan-Meier survival curves illustrating the time to first incident CVD event over a median follow-up of 10.8 years for HIV-infected Veterans (N = 3,108; log-rank χ^2 = 5.2, df = 4, p = .267).

CVD = cardiovascular disease; HIV = human immunodeficiency virus

Table 1
Baseline Characteristics of HIV-Infected VACS-Survey Cohort Participants (*N* = 3,108)

Age, years	49.0 [43.3, 54.6]
Sex, % Male	3,018 (97.1)
Race/ethnicity, % African American	2,059 (66.2)
Hypertension[a]	
None	1,376 (44.3)
Controlled	1,033 (33.2)
Uncontrolled	699 (22.5)
Diabetes	390 (12.5)
BMI, kg/m^2	25.2 [22.6, 28.1]
Smoking[a]	
Current	1,619 (52.3)
Former	727 (23.5)
Never	749 (24.2)
Total Cholesterol[a], mg/dL	173 [148, 203]
Statin Use	468 (15.1)
Hepatitis C Infection	1,064 (34.3)
eGFR[a], $mL/min/1.73m^2$	97.0 [82.6, 113.3]
Hemoglobin[a], g/dL	13.9 [12.8, 15.0]
Alcohol Use[a]	
No current use or non-hazardous use	1,905 (61.5)
Hazardous use or abuse/dependence	1,192 (38.5)
Cocaine Use[a]	
Never tried or no past-year use	2,430 (77.5)
Past-year use or abuse/dependence	678 (22.5)
Non-benzodiazepine Sleep Medication	203 (6.5)
PHQ-9 Total Score[a]	4 [1, 9]
Antidepressant Medication	
SSRI	1,037 (33.4)
TCA	621 (20.0)
Miscellaneous	1,010 (32.5)
HIV-1 RNA[a], copies/mL	400.0 [75.0, 14667.7]
$CD4^+$ T Cell Count[a]	370.0 [218.0, 552.0]
ART regimen	2,490 (80.1)

Note. Continuous variables are presented as median [first quartile, third quartile]. Dichotomous/categorical variables are presented as *n* (%). VACS = Veterans Aging Cohort Study; HIV = human immunodeficiency virus; BMI = body mass index; eGFR = estimated glomerular filtration rate; PHQ-9 = Patient Health Questionnaire-9; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; ART = antiretroviral therapy.
[a]The following variables include fewer than 3,108 participants because of missing data (n, % missing): BMI (11, 0.4%), smoking (13, 0.4%), total cholesterol (154, 5%), eGFR (5, 0.2%), hemoglobin (4, 0.1%), alcohol use (11, 0.4%), cocaine use (94, 3%), HIV-1 RNA (14, 0.5%), and CD4+ cell count (12, 0.4%).

Table 2
HIV-Infected VACS-Survey Cohort Participants and Incident CVD Events across Baseline Insomnia Symptom Categories

Baseline Insomnia Symptoms	Total Cases		Incident CVD Cases	
	n	**%**	***n***	**%**
N = 3,108	---	---	267	8.6
No Difficulty Falling or Staying Asleep	1,270	40.9	103	8.1
Doesn't Bother	285	9.2	24	8.4
Bothers a Little	643	20.7	52	8.1
Bothers	465	15.0	40	8.6
Bothers a Lot	445	14.3	48	10.8

Note. VACS-SC = Veterans Aging Cohort Study; CVD = cardiovascular disease; HIV = human immunodeficiency virus.

Table 3
Cox Proportional Hazards Regression Models Examining the Association Between Baseline Insomnia Symptom and Incident CVD Events in the HIV-Infected VACS-Survey Cohort Participants (N = 3,108)

Model	*HR* (95% *CI*)	*p*-value
Model 0: Unadjusted		.304
No Difficulty Falling or Staying Asleep	1.00	---
Doesn't Bother	1.01 (0.65, 1.58)	.951
Bothers a Little	1.01 (0.72, 1.41)	.962
Bothers	1.14 (0.79, 1.65)	.470
Bothers a Lot	1.45 (1.03, 2.04)	.034
Model 1: Demographics		.099
No Difficulty Falling or Staying Asleep	1.00	---
Doesn't Bother	1.05 (0.67-1.63)	.844
Bothers a Little	1.08 (0.77-1.51)	.650
Bothers	1.21 (0.84-1.75)	.305
Bothers a Lot	1.64* (1.16-2.31)	.005
Model 2: CVD Risk Factors		.114
No Difficulty Falling or Staying Asleep	1.00	---
Doesn't Bother	1.01 (0.65-1.58)	.971
Bothers a Little	1.05 (0.75-1.47)	.778
Bothers	1.15 (0.79-1.66)	.465
Bothers a Lot	1.62* (1.14-2.30)	.007
Model 3: Additional Potential Confounders		.069
No Difficulty Falling or Staying Asleep	1.00	---
Doesn't Bother	1.03 (0.66-1.62)	.883
Bothers a Little	1.07 (0.76-1.49)	.704
Bothers	1.21 (0.83-1.76)	.315
Bothers a Lot	1.70* (1.19-2.43)	.003
Model 4: HIV-Specific Factors		.104
No Difficulty Falling or Staying Asleep	1.00	---
Doesn't Bother	1.06 (0.68-1.67)	.787
Bothers a Little	1.08 (0.77-1.51)	.667
Bothers	1.21 (0.83-1.76)	.321
Bothers a Lot	1.66* (1.16-2.37)	.005
Model 5a: Non-Benzodiazepine Sleep Medication Use		.147
No Difficulty Falling or Staying Asleep	1.00	---
Doesn't Bother	1.06 (0.68-1.66)	.795
Bothers a Little	1.07 (0.76-1.50)	.699
Bothers	1.19 (0.82-1.74)	.360
Bothers a Lot	1.62* (1.13-2.32)	.009
Model 5b: PHQ-9 Total Score		.443
No Difficulty Falling or Staying Asleep	1.00	---
Doesn't Bother	1.04 (0.66-1.64)	.856
Bothers a Little	1.05 (0.74-1.48)	.791

Bothers	1.14 (0.76-1.71)	.516
Bothers a Lot	1.51 (0.98-2.32)	.060
Model 5c: Antidepressant Medication Use		.309
No Difficulty Falling or Staying Asleep	1.00	---
Doesn't Bother	1.06 (0.68-1.66)	.797
Bothers a Little	1.03 (0.73-1.45)	.856
Bothers	1.12 (0.76-1.65)	.552
Bothers a Lot	1.51 (1.04-2.19)	.031
Model 6: All Covariates		.591
No Difficulty Falling or Staying Asleep	1.00	---
Doesn't Bother	1.05 (0.67-1.64)	.846
Bothers a Little	1.01 (0.72-1.43)	.933
Bothers	1.09 (0.72-1.63)	.694
Bothers a Lot	1.42 (0.92-2.19)	.115

Note. The *p*-value for the test of overall significance across the four insomnia symptoms dummy coded variables is displayed in respective model row. CVD = cardiovascular disease; VACS-SC = Veterans Aging Cohort Study; HIV = human immunodeficiency virus; HR = hazard ratio; CI = confidence interval; PHQ-9: Patient Health Questionnaire-9; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.
Model 0: Unadjusted (insomnia symptoms dummy coded variables alone predicting incident CVD)
Model 1: Demographics (age, sex, race/ethnicity)
Model 2: CVD Risk Factors (Model 1 + hypertension, diabetes, BMI, smoking, total cholesterol, statin use)
Model 3: Additional Potential Confounders (Model 2 + hepatitis C infection, renal disease, anemia, alcohol use, cocaine use)
Model 4: HIV-Specific Factors (Model 3 + HIV-1 RNA level, $CD4^+$ T-cell count, ART regimen)
Model 5a: Non-Benzodiazepine Sleep Medication Use (Model 4 + non-benzodiazepine sleep medication use)
Model 5b: PHQ-9 Total Score (Model 4 + PHQ-9 total score)
Model 5c: Antidepressant Medication Use (Model 4 + SSRI use, TCA use, and miscellaneous/other antidepressant use)
Model 6: All Covariates (Model 4 + non-benzodiazepine sleep medication use, PHQ-9 total score, SSRI use, TCA use, and miscellaneous other antidepressant use)
*$p < .01$

Figure 1