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Title: Insomnia and Risk of Myocardial Infarction Among People Living with HIV

Running Head: Insomnia and Myocardial Infarction

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Abstract

Background: Insomnia is common among people living with HIV (PLWH) and may be associated with increased risk of myocardial infarction (MI). This study examines the association of insomnia with MI risk by MI type among PLWH.

Setting: Longitudinal, multisite cohort study of adult PLWH in care at five Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) sites in the US.

Methods: Clinical data and patient-reported measures and outcomes (PROs) from PLWH in CNICS between 2005-2018 were utilized in this study. Insomnia, measured at baseline, was defined as having difficulty falling or staying asleep with bothersome symptoms. CNICS centrally adjudicates MIs using expert reviewers, with distinction between type 1 (T1MI) and type 2 MIs (T2MI). Associations between insomnia and first incident MI by MI type were measured using separate Cox proportional hazard models adjusted for age, sex, race/ethnicity, HIV viral suppression, CD4 count, traditional cardiovascular disease (CVD) risk factors (hypertension, dyslipidemia, poor kidney function, smoking), and stimulant use.

Results: Among 12,436 PLWH, 48% reported insomnia. Over an average of 3.8 years of follow-up, 153 T1MIs and 105 T2MIs were identified; approximately half of T2MIs were attributed to sepsis or stimulant use. After adjustment for demographic characteristics, CVD risk factors, and stimulant

use, the hazard ratios for T1MI and T2MI among PLWH reporting insomnia were 1.04 (95%CI:0.75-1.45) and 1.57 (95%CI:1.05-2.36), respectively. **Conclusions:** PLWH reporting insomnia are at an increased risk of T2MI, but not T1MI, compared to PLWH without insomnia, highlighting the importance of distinguishing MI types among PLWH.

Keywords: HIV; insomnia; myocardial infarction; type 1 myocardial infarction; type 2 myocardial infarction

Introduction

People living with HIV (PLWH) have a much higher rate of cardiovascular disease (CVD), including myocardial infarction (MI), than the general population.[1,2] MIs are classified into types based on mechanism according to the Universal Definition of MI.[3] Type 1 myocardial infarctions (T1MIs) occur from atherothrombotic coronary plaque rupture. Type 2 myocardial infarctions (T2MIs) occur secondary to oxygen supply-demand mismatch such as in cocaine-induced vasospasm or sepsis/bacteremia. T2MIs make up a much larger proportion of MIs among PLWH (~49%) compared to the general population (<2-26%).[4]

PLWH also have a higher prevalence of insomnia and other sleep disturbances (~50-70%)[5,6] compared to the general population (~10%),[7] particularly PLWH with psychological morbidities or cognitive impairment.[8,9] The incidence of insomnia correlates with increasing duration and/or stage of HIV infection.[10,11] Insomnia is a reported risk factor for CVD, including MI, in the general population.[12,13] The mechanisms underlying this association are not fully understood, but include sympathetic nervous system activation and elevated levels of cortisol and proinflammatory cytokines.[12,14–16]

Questions remain regarding the relationship between insomnia and MI among PLWH, particularly given the differences in MI types among PLWH compared with the general population.[4] An association between insomnia and CVD among PLWH was reported by one study of ~3,100 Veterans with HIV, but was based on a composite outcome including MI, stroke, and others,

rather than centrally adjudicated MIs distinguished by MI type and included virtually no women with HIV.[17] Differentiating between T1MIs and T2MIs is important because their treatment and prevention methods differ, as do risk factors, patient demographics, and clinical characteristics.[18] Therefore, we conducted this study to examine the relationship between insomnia and both T1MI and T2MI risk among PLWH to better understand the mechanisms and risk factors for MIs among PLWH.

Methods

This study was conducted among adult PLWH receiving HIV care at five of the eight Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) sites between 2005-2018 (Johns Hopkins University; University of Alabama at Birmingham; University of California at San Diego; University of North Carolina at Chapel Hill; and University of Washington). CNICS, a longitudinal, multisite clinical cohort of PLWH, collects comprehensive clinical data from electronic medical records and other institutional data sources for both outpatient and inpatient visits including demographic characteristics, clinical codes, laboratory data, and patient-reported measures and outcomes (PROs).[19]

Insomnia

CNICS participants complete an ~10 minute clinical assessment of PROs using touch-screen tablets every ~6 months at the start of routine care appointments.[20] The assessment includes the HIV Symptom Index, which

measures sleep disturbance, including difficulty falling or staying asleep.[21–23] For this analysis, insomnia was measured at initial PRO assessment (baseline) and was defined as having difficulty falling or staying asleep with symptoms that are bothersome (“no symptom” or “symptom does not bother me” vs. “symptom bothers me a little”, “symptom bothers me”, or “symptom bothers me a lot”).

Myocardial Infarctions

CNICS has an established approach for high-quality MI adjudication,[24] with MIs categorized by type based on the categories in the Universal Myocardial Infarction definition.[25] Potential MIs are identified using a comprehensive set of MI diagnostic and procedure codes and elevated cardiac biomarker values, and deidentified packets of the primary data including ECGs, provider notes, etc. are centrally adjudicated by two expert physicians (more if discrepancies occur). While the Universal MI classification has five types, we focus on type 1 and 2 MIs as they are the vast majority of MIs in CNICS.

Covariates

Covariates of interest were measured at baseline and included demographic factors (age, sex, race/ethnicity), HIV markers (viral suppression and CD4 count), traditional CVD risk factors (hypertension, dyslipidemia, poor kidney function, and smoking), stimulant use (cocaine/crack and/or methamphetamines), and depressive symptoms. Viral suppression was defined as a viral load (VL) ≤400, hypertension as a

diagnosis plus medication, dyslipidemia as a lipid abnormality that required statin treatment, and poor kidney function as an eGFR<30. Substance use and smoking (via modified ASSIST[26]), as well as depressive symptoms (via PHQ-9[27]), were collected from PROs.[26]

Statistical Analysis

The associations between insomnia and incident MI by MI type were evaluated using Cox proportional hazards regression analyses. We examined T1MI and T2MI separately and evaluated four iterations of model adjustment, each one building upon the last. First, we examined the association between insomnia and MI adjusting for demographic variables only (age, sex, race/ethnicity). Second, we additionally adjusted for traditional CVD risk factors (hypertension, dyslipidemia, poor kidney function, and smoking). Third, we added adjustment for viral suppression and CD4 count. Fourth, we added adjustment for stimulant use (cocaine/crack and/or methamphetamines). This adjustment scheme was used to understand how unmeasured or residual confounding may have affected our results. Lastly, we conducted sensitivity analyses including different parameterizations of depressive symptoms as an additional adjustment factor; we excluded depression from our main models out of concern that it is a mediator rather than a confounder. The relationship between insomnia and depression is complex and not fully understood[28,29], so we felt a sensitivity analysis was appropriate.

Participants were censored at (1) the time of their first MI, (2) the time of last activity in CNICS, (3) time of death, or (4) date of administrative censoring, whichever came first. The timescale for the models was time since initial PRO assessment. Written informed consent was obtained from all participants. All analyses were conducted in Stata version 15 (StataCorp, College Station, TX).

Results

Overall, 12,436 PLWH were eligible for inclusion in analyses. The mean age was 43 years, 16% were female, and insomnia was common: 57% reported any difficulty falling or staying asleep, while 48% reported bothersome symptoms. Overall, 258 incident MIs occurred over an average of 3.8 years (IQR: 1.8-7.3) of follow-up (153 T1MIs and 105 T2MIs). The prevalence of insomnia among PLWH with type 1 and 2 MIs was 50% and 59%, respectively (Table 1).

After adjustment for demographic characteristics, the association between insomnia and T1MI was null (Hazard Ratio (HR)=1.12, 95% Confidence Interval (CI):0.81-1.53), while insomnia was associated with a 81% increased hazard of T2MI (95%CI:1.22-2.68) (Figure 1, Supplemental Table 1). After additional adjustment for potential confounders, including CVD risk factors, HIV markers, and stimulant use, the association between insomnia and T1MI did not meaningfully change (HR=1.04, 95%CI:0.75-1.45)

and the association with T2MI was slightly attenuated (HR=1.57, 95%CI:1.05-2.36); stimulant use contributed minimally to this attenuation.

Including “insomnia symptom present, does not bother me” in the definition of insomnia slightly attenuated the association between insomnia and T2MIs, and increased the HRs for T1MIs (Supplemental Table 2). Results remained similar for both T1MI and T2MI after adjustment for depressive symptoms, both including and excluding sleep-related items, (T1MI HR range: 0.84-0.93; T2MI range: 1.36-1.44) (Supplemental Table 3).

Compared to PLWH with no MI or with a T1MI, PLWH who experienced a T2MI had lower CD4 counts and less viral suppression, consistent with poorer control over their HIV (Table 1). Overall, the causes of T2MIs were heterogeneous, but approximately half were attributed to either sepsis (35%) or cocaine/other illicit drug use (10%) (Supplemental Figure 1).

Discussion

This is the first study to examine the association of insomnia with MI by MI type in PLWH. We demonstrated that PLWH who reported insomnia were at an increased risk of T2MI, but not T1MI. Since insomnia is an established risk factor for MIs[12,30,31] and is a reported CVD risk factor in HIV-infected veterans,[17] these findings give important insight into this relationship and may guide future prevention and treatment strategies for CVD in PLWH.

The relationship between insomnia and T2MI’s, but not T1MI’s, was not hypothesized. Understanding the mechanisms contributing to this

relationship is complicated by the heterogenous causes of T2MI's; the most common cause of T2MI in our cohort, sepsis/bacteremia, only comprised 35% of all T2MI's. To the best of our knowledge, no studies, even of the general population, have previously investigated the relationship of insomnia and MI by MI type related, despite insomnia being a commonly cited risk factor for cardiovascular disease.[12,13]

Consistent with past estimates, approximately half of PLWH in the CNICS cohort reported insomnia.[5,6] The reason insomnia is so highly prevalent in PLWH is not well understood, but proposed mechanisms include psychiatric morbidities[32,33] and central nervous system (CNS) damage from the cumulative neurotoxic effects of inflammation and neurotoxins produced by HIV.[10,11] This correlates with cumulative VL being more strongly associated with T2MIs compared to T1MIs in PLWH,[34] despite the incidence of T1MIs in PLWH also increasing with higher VL and lower CD4 counts.[2] However, after adjusting for baseline VL and CD4 count, the relationship between insomnia and MI was only slightly attenuated, suggesting poor HIV control is not solely responsible for this relationship. Although some antiretroviral therapy (ART) side effects include insomnia (particularly efavirenz), these symptoms tend to improve.[35,36]

The role of depression in the association between insomnia and T2MI is complicated and not fully understood; adjusting for depressive symptoms may be inappropriate as it could be a mediatior of the relationship between insomnia and T2MI, as depression has a complex and potentially bidirectional

relationship with insomnia.[28,29] After adjustment for depressive symptoms in sensitivity analyses, the relationship between insomnia and T2MI was alightly attenuated, with sleep-related items having the greatest impact on the point estimate. However, although the relationship between insomnia and T2MI became non-signifigant after adjustment, the point estimate was only slightly attenudated after accounting for depressive symptoms (HR:1.58→1.40); this indicates that after accrual of more events (i.e. greater power), the relationship between insomnia and T2MI would likely remain stasitically significant after PHQ-9 adjustment. Further longitudinal studies are needed to elucidate the mechanisms between depressive symptoms and both insomnia and MI by MI type.

A key strength of this study is the central adjudication protocol of MIs by type in CNICS.[2] Additionally, the CNICS cohort represents a wide range of HIV disease in a large, ethnically and geographically diverse, gender-representative population of PLWH. Our study also has several limitations. Since T2MIs do not have a distinct diagnostic code and the definition of T2MI is not fully consolidated (i.e. T2MI diagnosis relies on clinical judgment), incomplete ascertainment of T2MIs is possible, although we minimize this with multiple ascertainment approaches beyond diagnoses (e.g. cardiac biomarkers).[37] Additionally, only a single item was used to assess insomnia and we do not have data on obstructive sleep apnea. Lastly, residual confounding, from either unmeasured or crudely measured confounders, is a possibility in all observational research. While we cannot eliminate the

possibility of residual confounding, the inclusion of important potential confounders only modestly attenuated the association between insomnia and T2MI (HR:1.81→1.57) and the association remained signifgant.

Further studies are warranted to identify the insomnia-induced mechanisms of T2MI risk in PLWH and whether it is a direct effect or an association through other factors contributing to the high rate of T2MIs in PLWH, timing of insomnia impacts, and whether, given the heterogenous nature of T2MIs, insomnia is a risk factor for all or specific T2MIs. Additionally, the relationship between insomnia and other potentially related factors, such as depression and ART, needs to be be futher elucidated.

This study demonstrates that baseline insomnia, which is highly prevalent (~50-70%)[5,6] in PLWH, is associated with an increased risk of T2MI, but not T1MI. T2MIs are markedly increased in PLWH relative to the general population (~50% vs <2-26%), however underlying reasons for this are not fully understood. Screening for insomnia in PLWH may help to identify individuals with increased risk of T2MI. These findings underscore the importance of distinguishing the mechanisms and risk factors for MI types, especially in PLWH who are at a considerably increased risk of T2MI.

Supplemental Digital Content

Supplemental Digital Content 1-3 (Tables).docx

Supplemental Digital Content 2 (Figure).docx,pdf

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BRL drafted the manuscript and BMW conducted all analyses. JACD contributed to the methodological approach and analysis and RMN contributed to methodological approach, data preparation, and analysis. BMW, HMC, JACD contributed to conception and design of the work. MJB, WMC, RDM, MJF, GAB, MJM, JJE, MSS, MMK, and HMC contributed to data collection. BRL, RMN, JACD, SAR, SHR, MJB, WMC, RDM, MJF, GAB, MJM, JJE, MSS, MMK, HMC, and BMW contributed to interpretation of data and critically revising the manuscript for important intellectual content. All authors have contributed substantively to the study design, data acquisition, or analysis. All authors have contributed to the drafting of the manuscript or reviewed it and have approved the content for submission.

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Data Statement

Statistical code is available upon request to rmnance@uw.edu. Data from CNICS may be shared with investigators with an approved concept proposal. Instructions for data access and concept proposal forms may be found at: https://www.uab.edu/cnics/submit-proposal.

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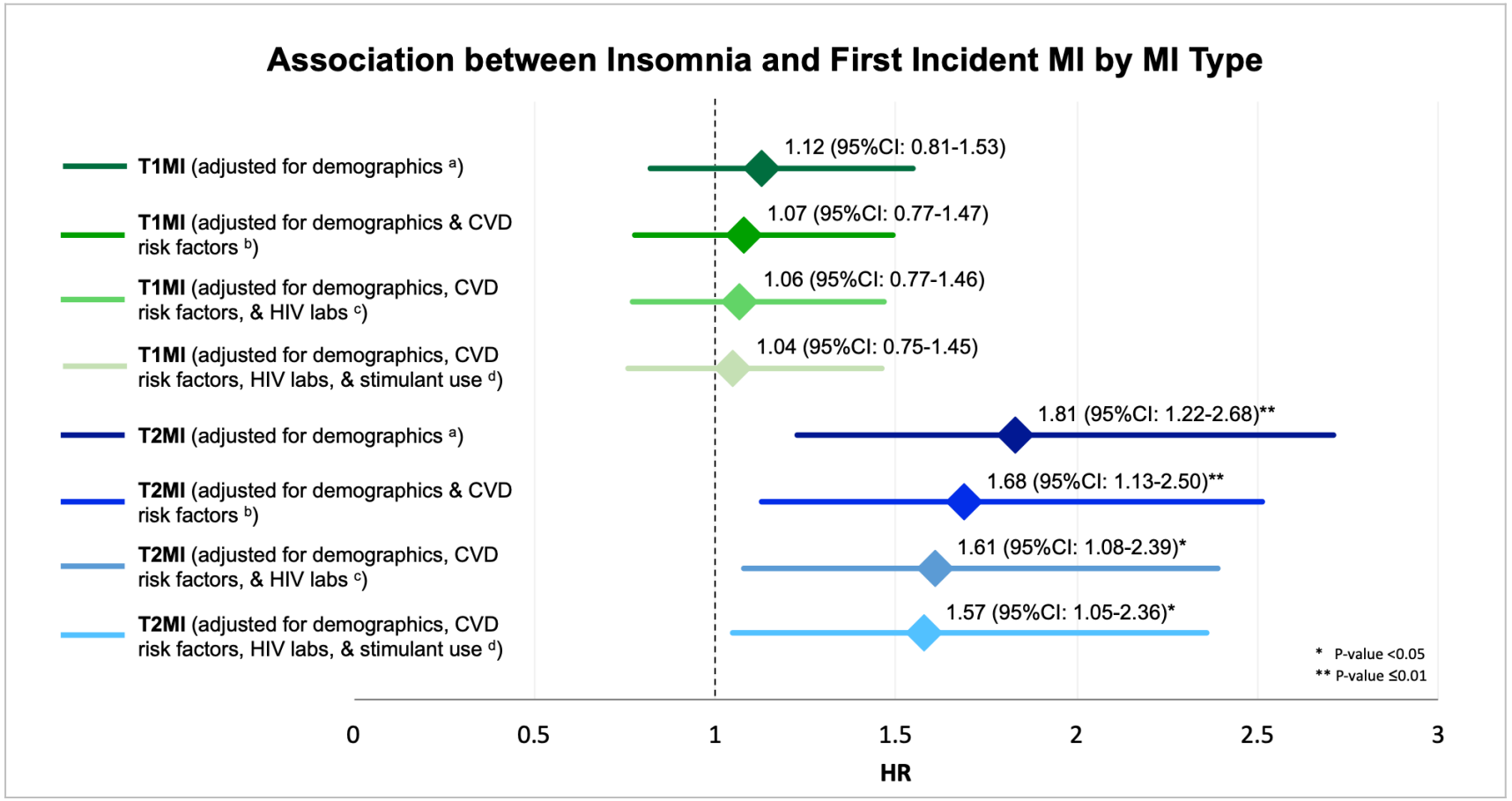
Table 1. Demographic and clinical characteristics, by myocardial infarction status and overall, among people with HIV from five CNICS sites across the US (N=12,436).

N (%) or Mean (SD)	No MI	T1MI	T2MI	Overall
N	12,178 (97.9%)	153 (1.2%)	105 (0.8%)	12,436
Age	43 (11)	51 (8)	49 (11)	43 (11)
Female	1,906 (16)	13 (9)	23 (22)	1,942 (16)
Race/Ethnicity				
White	5,682 (47)	84 (55)	45 (43)	5,811 (47)
Black	3,835 (31)	39 (25)	49 (47)	3,923 (32)
Hispanic	1,996 (16)	24 (16)	9 (9)	2,029 (16)
Other/unknown	665 (5)	6 (4)	2 (2)	673 (5)

CD4 count (cells/mm^3)	540 (306)	492 (313)	395 (293)	538 (306)
Hypertension	2,630 (22)	81 (53)	45 (43)	2,756 (22)
VL <400 (copies/ml)	9,829 (81)	117 (76)	72 (69)	10,018 (81)
Dyslipidemia	1,916 (16)	64 (42)	32 (30)	2,012 (16)
eGFR <30 (mL/min/ 1.73 m^2)	108 (1)	9 (6)	12 (11)	129 (1)
Current smoking	4,457 (37)	76 (50)	49 (47)	4,582 (37)
Insomnia – difficulty falling or staying asleep				
I do not have symptom	5,306 (44)	61 (40)	35 (33)	5,402 (43)
I have symptoms but it does not bother me	1,084 (9)	17 (11)	7 (7)	1,108 (9)
I have symptoms and it bothers me a little	2,286 (19)	27 (18)	24 (23)	2,337 (19)
I have symptoms and it bothers me	1,645 (14)	21 (14)	22 (21)	1,668 (14)
I have symptoms and it bothers me a lot	1,857 (15)	27 (18)	17 (15)	1,901 (15)

Abbreviations: CNICS; Centers for AIDS Research Network of Integrated Clinical Systems; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; T1MI, type 1 myocardial infarction; T2MI, type 2 myocardial infarction; VL, viral load.

Figure 1. Association between insomnia and first incident myocardial infarction by myocardial infarction type among people with HIV.



Abbreviations: CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; T1MI, type 1 myocardial infarction; T2MI, type 2 myocardial infarction.

[a] Cox model adjusted for age, sex, race/ethnicity.

[b] Cox model adjusted for age, sex, race/ethnicity, traditional CVD risk factors (hypertension, dyslipidemia, poor kidney function, and smoking).

[c] Cox model adjusted for age, sex, race/ethnicity, traditional CVD risk factors (hypertension, dyslipidemia, poor kidney function, and smoking), viral suppression (VL≤400), CD4 count.

[d] Cox model adjusted for age, sex, race/ethnicity, traditional CVD risk factors (hypertension, dyslipidemia, poor kidney function, and smoking), viral suppression (VL≤400), CD4 count, stimulant use (cocaine/crack and/or methamphetamines).

Supplemental Table 1. Association between insomnia and incident myocardial infarction by myocardial infarction type – models adjusted individually for demographics and strong potential confounders including baseline viral suppression, traditional CVD risk factors and stimulant use.

Type 1 MI	HR	95% CI	P-value
Insomnia [a]	1.12	0.81-1.53	0.504
Insomnia [b]	1.07	0.77-1.47	0.687
Insomnia [c]	1.06	0.77-1.46	0.717
Insomnia [d]	1.04	0.75-1.45	0.799
Type 2 MI	**HR**	**95% CI**	**P-value**
Insomnia [a]	1.81	1.22-2.68	0.003
Insomnia [b]	1.68	1.13-2.50	0.010
Insomnia [c]	1.61	1.08-2.39	0.020
Insomnia [d]	1.57	1.05-2.36	0.028

Abbreviations: CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.
[a] Cox model adjusted for age, sex, and race/ethnicity.
[b] Cox model adjusted for age, sex, race/ethnicity, and traditional CVD risk factors (hypertension, dyslipidemia, poor kidney function, and smoking).
[c] Cox model adjusted for age, sex, race/ethnicity, traditional CVD risk factors (hypertension, dyslipidemia, poor kidney function, and smoking), and baseline viral suppression (VL≤400) and CD4 count.
[d] Cox model adjusted for age, sex, race/ethnicity, traditional CVD risk factors (hypertension, dyslipidemia, poor kidney function, and smoking), baseline viral suppression (VL≤400) and CD4 count, and stimulant use (cocaine/crack and/or methamphetamines).

Supplemental Table 2. Association between insomnia and incident myocardial infarction by myocardial infarction type with “symptom, does not bother” included in the insomnia group – models adjusted individually for demographics and strong potential confounders including baseline viral suppression, traditional CVD risk factors and stimulant use.

Type 1 MI	HR	95% CI	P-value
Insomnia [a]	1.22	0.88-1.68	0.240
Insomnia [b]	1.18	0.85-1.64	0.318
Insomnia [c]	1.17	0.84-1.62	0.357
Insomnia [d]	1.16	0.83-1.63	0.374
Type 2 MI	**HR**	**95% CI**	**P-value**
Insomnia [a]	1.69	1.12-2.55	0.012
Insomnia [b]	1.60	1.06-2.42	0.024
Insomnia [c]	1.52	1.01-2.29	0.046
Insomnia [d]	1.50	0.99-2.28	0.057

Abbreviations: CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.
[a] Cox model adjusted for age, sex, and race/ethnicity.
[b] Cox model adjusted for age, sex, race/ethnicity, and traditional CVD risk factors (hypertension, dyslipidemia, poor kidney function, and smoking).
[c] Cox model adjusted for age, sex, race/ethnicity, traditional CVD risk factors (hypertension, dyslipidemia, poor kidney function, and smoking), and baseline viral suppression (VL≤400) and CD4 count.
[d] Cox model adjusted for age, sex, race/ethnicity, traditional CVD risk factors (hypertension, dyslipidemia, poor kidney function, and smoking), baseline viral suppression (VL≤400) and CD4 count, and stimulant use (cocaine/crack and/or methamphetamines).

Supplemental Table 3. Association between insomnia and incident myocardial infarction by myocardial infarction type – models adjusted individually for demographics and strong potential confounders including baseline viral suppression, traditional CVD risk factors, stimulant use, and depressive symptoms.

Type 1 MI	Depression Parameterization	HR	95% CI	P-value
Insomnia [a]	Not included	1.04	0.75-1.45	0.799
Insomnia [b]	PHQ-9 score	0.89	0.61-1.30	0.540
Insomnia [c]	PHQ-7 score (without sleep-related items)	0.93	0.65-1.34	0.697
Insomnia [d]	PHQ-2 score (sleep-related items only)	0.84	0.57-1.25	0.390
Insomnia [e]	IRT latent trait scores - PHQ-9	0.87	0.60-1.27	0.481
Type 2 MI	**Depression Parameterization**	**HR**	**95% CI**	**P-value**
Insomnia [a]	Not included	1.57	1.05-2.36	0.028
Insomnia [b]	PHQ-9 score	1.40	0.89-2.20	0.147
Insomnia [c]	PHQ-7 score (without sleep-related items)	1.44	0.93-2.23	0.101
Insomnia [d]	PHQ-2 score (sleep-related items only)	1.36	0.85-2.20	0.202
Insomnia [e]	IRT latent trait scores - PHQ-9	1.44	0.91-2.27	0.119

Abbreviations: CI, confidence interval; HR, hazard ratio; IRT, item response theory; MI, myocardial infarction.

[a] Cox model adjusted for age, sex, race/ethnicity, traditional CVD risk factors (hypertension, dyslipidemia, poor kidney function, and smoking), baseline viral suppression (VL≤400) and CD4 count, and stimulant use (cocaine/crack and/or methamphetamines).

[b] Cox model adjusted for age, sex, race/ethnicity, traditional CVD risk factors (hypertension, dyslipidemia, poor kidney function, and smoking), baseline viral suppression (VL≤400) and CD4 count, stimulant use (cocaine/crack and/or methamphetamines), and PHQ-9 score.

[c] Cox model adjusted for age, sex, race/ethnicity, traditional CVD risk factors (hypertension, dyslipidemia, poor kidney function, and smoking), baseline viral suppression (VL≤400) and CD4 count, stimulant use (cocaine/crack and/or methamphetamines), and PHQ-7 score (without the sleep-related items – questions 3 & 4).

[d] Cox model adjusted for age, sex, race/ethnicity, traditional CVD risk factors (hypertension, dyslipidemia, poor kidney function, and smoking), baseline viral suppression (VL≤400) and CD4 count, stimulant use (cocaine/crack and/or methamphetamines), and PHQ-2 score (sleep-related items only – questions 3 & 4).

[e] Cox model adjusted for age, sex, race/ethnicity, traditional CVD risk factors (hypertension, dyslipidemia, poor kidney function, and smoking), baseline viral suppression (VL≤400) and CD4 count, stimulant use (cocaine/crack and/or methamphetamines), and item response theory (IRT) latent trait scores for depression including the PHQ-9.

Supplemental Figure 1. Identified causes of type 2 myocardial infarctions (N=105).