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RUNNING HEAD: Insomnia, Depressive Symptoms, and Mortality

18

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Abstract

Objectives: Insomnia and depressive symptoms are commonly reported by adults and have independently been found to be associated with mortality, though contrasting findings are reported. Given the high comorbidity and interrelatedness between these symptoms, we tested whether insomnia symptoms explain risk of death independent of depressive symptoms. We examined insomnia symptoms and depressive symptoms, in addition to other health and demographic covariates, as predictors of all-cause mortality.

Methods: The sample included 15,418 adults aged 51 and older drawn from a nationally representative, population-based study of adults in the United States, the Health and Retirement Study (HRS). Cox survival models were used to analyze time to death between the 2002 and 2014 study waves (5 waves). Controlling for health and demographic covariates, in three separate models depressive symptoms and insomnia symptoms were independently and then together considered as risk factors for all-cause mortality (drawn from the National Death Index).

Results: After adjustment for covariates, insomnia symptoms (HR=1.10, CI:1.07-1.13) and depressive symptoms (HR=1.14, CI:1.12-1.16) each were associated with a greater hazard of death. When considered together, however, depressive symptoms fully accounted for the association between insomnia symptoms and mortality.

Conclusion: Though their effects are small relative to health and demographic characteristics, both insomnia symptoms and depressive symptoms were associated with a greater hazard of death. Yet depressive symptoms accounted for the insomnia association when both were considered in the model. Screening for depression and providing validated treatments may reduce mortality risk in older adults with depressive symptoms.

Key words: death, sleep disturbance, depressed mood

Key points: This study adds to the literature by showing that insomnia is associated with all-cause mortality, but this association is explained by depressive symptoms.

The Association of Insomnia and Depressive Symptoms with All-Cause Mortality among Middle-Aged and Older Adults

Introduction

Sleep disturbances and other depressive symptoms are frequently reported by older adults, and both are associated with adverse mental and physical health outcomes (1-3). Accumulating evidence also indicates that insomnia and depression are each associated with mortality, though inconsistent results have been found, and methodologies are mixed (4-7). Further, insomnia and depression are commonly comorbid and associated with poor health behaviors which can consequently impair an individual's ability to adaptively cope and respond to their illness (8-10). Therefore, it is important to understand whether insomnia and depressive

symptoms may be associated with mortality both independently and in conjunction. This is particularly critical given the existence of validated treatments for both conditions that may positively influence mortality outcomes. The current study considers whether insomnia symptoms are associated with greater risk of mortality controlling for depressive symptoms in a nationally representative sample of adults aged 51 and older from the Health and Retirement Study (HRS) (11).

Putative Associations among Aging, Depression and Insomnia

Though depression is less prevalent among older adults than younger age groups, subsyndromal symptoms are common, and prognosis is often poor (12, 13). For example, in a longitudinal study of depressed older adults, three-fourths of the sample had a fluctuating or severe chronic course of symptoms, with only 23% achieving remission (14). Further, recent studies suggest that older adults still stigmatize mental illness and mental health treatment, and thus may be undertreated leading to worse outcomes (Conner et al, 2010). On the other hand, while approximately half of older adults report sleep complaints, studies show that most changes in sleep patterns occur by age 60, with only a slight decrease in quality of sleep thereafter (15-17). It may be that factors such as chronic illness and functional status impact sleep more than aging alone as a putative mechanism. However, considering depressive and insomnia symptoms as risk factors for mortality among older adults in particular is of importance.

Depression, Insomnia, and Mortality

Major Depressive Disorder (MDD) and depressive symptoms have been associated with premature risk of death and mortality (18, 19). Over a 12-year follow-up of community dwelling older adults, men with depression, for example, had a 1.9 times higher death rate than men without depression (20). One explanation for this finding may be the high suicide completion rate among depressed men, and in particular non-Hispanic White men (21). However, prior research has also identified depression as a risk for other causes of mortality such as heart disease (22). Similarly, symptoms of insomnia have been associated with higher odds of mortality and premature risk of death, though the effect size is more modest than that associated with depression (4, 19). In a community-based sample of middle aged adults in Norway followed for 13-15 years, models adjusting for demographic characteristics, lifestyle behaviors, mental health and health variables found insomnia to be associated with a 3-fold increase in mortality. When models were run with a continuous measure of insomnia symptoms, for each increasing score value (from zero to 16), the mortality rate increased by 10% (6). Likewise, another study found that insomnia was a strong predictor of nursing home placement and death for men, however only marginally so for women (5). Yet nonsignificant associations have also been identified (23).

Insomnia and depression have a number of risk factors, physiological pathways, and behavioral mechanisms in common that may make the two conditions in combination particularly critical for mortality risk (e.g. poor health behaviors, smoking, physical inactivity, obesity, HPA axis dysregulation, increased autonomic nervous system activity, inflammation) (8,

9, 24). However, it is unclear whether poor sleep and depression have independent effects on all-cause mortality, or whether similar pathways of risk are leading to their association with mortality.

In sum, prior research suggests a moderate association between both insomnia and depression with mortality, though inconsistent results have been found, often with mortality effects only among men. Further, most studies have been conducted in community or clinical samples, and additional work is needed in a nationally representative older adult sample. This study advances the literature in several ways: by considering insomnia and depressive symptoms as single predictors and in conjunction, examining associations among men and women, and using data from the HRS, a nationally representative sample of adults which utilizes the gold standard of mortality indices- the National Death Index. Insomnia is among the diagnostic criteria for a major depressive episode as well as a common comorbid condition, yet it is unknown whether it carries risk for mortality over and above depressive symptoms. The current study aimed to examine insomnia symptoms and depressive symptoms as risk factors of all-cause mortality in adults, and to see whether insomnia symptoms remained a significant risk factor with the inclusion of depressive symptoms.

Methods

Sample

Data were drawn from the HRS, a biennial longitudinal survey of a nationally representative sample of the United States (U.S.) population over the age of 50 begun in 1992.

HRS public release data and RAND HRS data were utilized. Sampling for the study utilized a multi-stage area probability design with clustering and geographic stratification. Black and Hispanic households were oversampled at approximately twice the rate of whites. Sample weights were analytically applied to account for differential probability of selection into the study and differential non-response. HRS is funded by the National Institute on Aging (NIA U01AG0097) and housed at the Institute for Social Research at the University of Michigan (UM). Written informed consent was collected from all participants, and the study protocol was approved by the UM Institutional Review Board. Given the availability of a measure of insomnia symptoms, we used data from the 2002, 2004, 2006, 2010, and 2014 waves (12 years of follow-up). The analytic sample was 15,419 individuals aged 51 and over with 149,860 person years of follow-up analyzed.

Measures

Outcome. Mortality was determined through an HRS respondent-level linkage to the National Death Index (NDI). The NDI is a centralized, national database of death record information including dates of death, the state in which the death occurred, and cause of death. Time to death (in months) was calculated from the respondent's 2002 interview date to the NDI date of death.

Predictors.

Insomnia symptoms. Insomnia symptoms were measured with four items representing the key symptoms of insomnia namely difficulty initiating sleep, difficulty maintaining sleep, early

morning awakening, and nonrestorative sleep adapted from the Brief Insomnia Questionnaire (BIQ) (25). Respondents were asked how often they have trouble with "falling asleep," "waking up during the night," "waking up too early and not being able to fall asleep again" and "you feel really rested when you wake up in the morning?" Response categories were "most of the time," "sometimes," and "rarely or never." To assess the greatest severity of insomnia, we defined a symptom as positive if a participant endorsed having it "most of the time" for the first three items and "rarely or never" for the fourth item. We then created a symptom index ranging from 0 to 4 for the number of insomnia symptoms.

Depressive symptoms. A modified 8-item version of the Center for Epidemiologic Studies Depression Scale (CES-D) was used to assess depressive symptoms (26). Respondents reported the extent to which in the previous week, they felt: depressed, everything was an effort, sleep was restless, that he or she could not get going, lonely, that he or she enjoyed life, sad, and happy. These are coded dichotomously by RAND in order to address differences in response categories over waves. To minimize operational confounding of this predictor with our outcome, we removed the item about restless sleep. Following others, we reverse-coded the positive items and summed the remaining 7 items for a count of recent depressive symptoms ranging from 0 to 7 (27).

Covariates. We controlled for demographic and health characteristics known to be associated with mortality including participant age, gender, race (categorized as white, black and other), years of education, and history of smoking. Multi-morbidity during the study (the mean

of seven possible chronic medical conditions across study waves, including high blood pressure, diabetes, cancer, lung disease, heart disease, stroke, and arthritis) was controlled in a sensitivity analysis. Other than chronic medical conditions, all demographic characteristics were taken from the current study baseline wave (2002).

Data Analysis

We used Cox proportional hazards models in SAS 9.4 to examine the association between depressive symptoms and insomnia symptoms with all-cause mortality over 12 years, modelling time to death from the baseline wave in 2002. The HRS analytic weight was applied to all models, and we accounted for the clustering and stratification of the complex sample design. Respondents who were still alive at our last study wave (2014) and those lost to follow-up were censored at their last available interview. We estimated four models starting with demographic and health characteristics alone predicting mortality (Model 1), adding insomnia symptoms alone (Model 2), adding depressive symptoms alone (Model 3), and finally a model with all controls and both depressive and insomnia symptoms (Model 4). Also given the possibility that chronic diseases may be on a causal pathway linking depression and insomnia with death, we added chronic medical conditions as a control to Model 4 in a sensitivity analysis. Hazard ratios as well as 95% confidence intervals are reported.

Results

Sample characteristics are described in Table 1. By 12 year follow-up, 27% of the sample had died. In this population-based sample of older adults, reports of insomnia symptoms and

depressive symptoms were consistent with the general population with participants reporting less than one insomnia symptom on average (*M*=0.6, *SE*=0.01; 38% reported at least 1 symptom with 6.5% endorsing 3 or 4) and just over one depressive symptom on average (*M*=1.2, *SE*=0.02; 48% reported at least 1 symptom with 12% reporting 4 or more). Examining demographic covariates of mortality in Model 1, for each additional year of age respondents had a 10% increased risk (HR=1.10, p<.001), females had a 20% decreased risk (HR=0.80, p<.001), and for each additional year of educational attainment, respondents hada 4% decreased risk of death during the 12 year follow-up (HR=0.96, p<.001). Individuals with a history of smoking had a 58% greater hazard of death (HR=1.58, p<.001). Full results for Models 1 through 4 may be found in Table 2.

Controlling for the demographic and health characteristics in Model 2, each additional insomnia symptom was associated with a 10% greater hazard of death (HR=1.10, p<.001). Likewise in Model 3, each additional depressive symptom was associated with a 14% greater hazard of death (HR=1.14, p<.001). However, in Model 4 where both insomnia and depressive symptoms were included in the model, insomnia symptoms were no longer significantly associated with a greater hazard of mortality suggesting that this association is explained by depressive symptoms. In a sensitivity analysis, Model 4 results were consistent even with chronic medical conditions controlled in the model. Finally, in a post-hoc test with Model 4 run separately by gender, the findings were the same for both men and women as in the combined model.

Discussion

Rates of depressive and insomnia symptoms were similar to those found in other community-based samples of middle aged and older adults, with 38% of our sample reporting one or more of four insomnia symptoms (America Insomnia Survey reporting 43% with at least 1 of 4 symptoms) and 12% reporting symptoms of depression above the derived clinical cut-point (25, 27). Though small in effect relative to demographic characteristics and smoking history, both depressive and insomnia symptoms were independently associated with an increased hazard of death with each insomnia symptom increasing the hazard by 10% and each depressive symptom by 14%. The hazard associated with insomnia was similar to a community-based study in Norway which also found a 10% increase for each increasing score value on a continuous insomnia scale (6). This finding remained, however, after adjusting for depressive symptoms in contrast with our finding. In the current study, upon including both depressive and insomnia symptoms in the model, depressive symptoms accounted for the effect of insomnia symptoms, maintaining significance and reducing the insomnia hazard ratio to approximately one. Depression and insomnia, though separate disorders, are highly interrelated with as many as 90% of individuals with depression reporting disturbed sleep (10). Though insomnia can of course occur independently from depression, comorbidity is high, and our findings suggest that depression may be the key risk factor for all-cause mortality, with insomnia's effect perhaps reflected as a component of depression. In a post-hoc test, we did consider our final model separately by gender, and found the same result for men and women, with depressive symptoms

being a significant predictor of all-cause mortality and insomnia symptoms not maintaining significance. This is in contrast with some prior work which only found insomnia and depressive symptoms associated with risk of death among men (5, 20).

There are several reasons why depression may be related to mortality independent of sleep. First, depression is highly related with risk for chronic illness and complications with illness that put one at increased risk for mortality. For example, depression has been associated with cardiac, cancer, and COPD morbidity, exacerbations, and mortality (22, 28-30). Additionally, though a less common cause of death, both insomnia and depression have been associated with an increased risk of suicide, with death by suicide particularly common among depressed, non-Hispanic White men (31-33). An additional reason depression may be associated with mortality is through associated negative health behaviors such as reduced physical inactivity. Whooley, de Jonge, Vittinghoff and et al. (8) found that smoking, medication nonadherence, and in particular inactivity explained the association between depression and cardiac events. Though insomnia is a key symptom of depression and shares several physiological pathways, our study shows that depression accounted for the association of insomnia and mortality. Given the high comorbidity between the two sets of symptoms, it may also be that insomnia symptoms are related to mortality due to coexisting depressive symptoms. Future studies on sleep and mortality should thus account for the role of depression.

A number of empirically validated treatments for depression and insomnia exist which may be helpful in reducing mortality risk. For example, the American College of Physicians

endorsed Cognitive Behavioral Therapy as the gold standard for initial treatment of insomnia. Pharmacotherapy with antidepressants is the most common treatment for older adults with depression and is effective when used at adequate doses for a prescribed length of time (34). Similarly, chronic use of over-the-counter sleep medications is common among older adults (more than 1/3 of adults aged 65 and over report using them more than 15 days a month) despite anticholinergic side-effects and warnings against these medications as listed in the Beers Criteria (35). However, prior work has found that only about 20-30% of years lived with disability from depression can be avoided using these treatments (36, 37). While effective pharmacological and non-pharmacological treatments exist, research should be extending beyond a model of depression treatment, and utilize knowledge of risk and protective factors to develop preventive interventions. Such interventions may not only decrease incidence of new disorder and reduce mortality risk as well. Future work might also consider whether those with depressive and/or insomnia symptoms who were also adhering to pharmacological treatment were at reduced mortality risk relative to those not receiving treatment.

Limitations. Our findings generalize to a nationally representative sample of older adults but are not reflective of a clinical population with diagnosed depression and/or insomnia. Our measures of symptomatology are condensed scales assessing cardinal symptoms of depression and insomnia which carry both convergent and face validity, but results may differ from the full-length, validated forms of these measures or clinical diagnostic scales. Additionally considering the overlay of conditions such as sleep apnea with self-reported insomnia symptoms may be

important for future inquiry given the known association of sleep apnea and other mortality risk factors such as obesity and cardiovascular disease (38, 39). Finally, we were unable to consider history of these conditions but only the presence of symptomatology at the study baseline wave. Respondents may therefore have experienced an episode prior to or following the 2002 measurement wave.

These limitations notwithstanding, this study extends the literatures on the mortality risks associated with insomnia and depression by using data from a large nationally representative sample of older adults in the United States to consider the independent and additive risk of both. It appears that insomnia symptoms are only associated with mortality risk when the variance explained by depression is unaccounted for. Though small in effect relative to other risk factors for all-cause mortality such as smoking history, gender, and multi-morbidity, depressive symptoms significantly increase the hazard of death. While depression rates are low among older adults, it is the most common mental disorder among this population, and a number of empirically validated treatments exist which may improve individuals' quality of life and ultimately reduce risk for mortality (12).

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Table 1. Sample Characteristics

Sample Characteristics	M(SE) or %
Age	67.5(0.2)
Female	58.1%
Race	
Caucasian American	87.7%
African American	9.0%
Other	3.3%
Years of education	12.6(0.1)
History of smoking	59.0%
Chronic medical conditions (mean across waves; range= 0-8)	2.3(0.02)
Depressive symptoms (range= 0-7)	1.2(0.02)
Insomnia symptoms (range = 0-4)	0.6(0.01)
Percent died during 12 years of follow-up	26.0%

Notes. n=15,419

Table 2. Hazard Model of Insomnia and Depressive Symptoms as Predictors of All-Cause Mortality

	Model 1		Model 2		Model 3		Model 4	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Age	1.10***	(1.10-1.11)	1.10***	(1.10-1.11)	1.10***	(1.10-1.11)	1.10***	(1.10-1.11)
Female	0.80***	(0.75-0.86)	0.79***	(0.74-0.84)	0.76***	(0.70-0.81)	0.75***	(0.70-0.81)
Black	1.12	(0.98-1.27)	1.12	(0.98-1.27)	1.07	(0.95-1.22)	1.07	(0.95-1.21)
Other	0.93	(0.76-1.14)	0.94	(0.77-1.15)	0.83	(0.66-1.04)	0.83	(0.67-1.05)
Education	0.96***	(0.95-0.97)	0.96***	(0.95-0.97)	0.98***	(0.96-0.99)	0.97***	(0.96-0.99)
Smoking History	1.58***	(1.47-1.69)	1.57***	(1.46-1.67)	1.55***	(1.44-1.66)	1.55***	(1.45-1.66)
Insomnia symptoms	--	--	1.10***	(1.07-1.13)	--	--	1.04	(1.00-1.07)
Depressive Symptoms	--	--	--	--	1.14***	(1.12-1.16)	1.13***	(1.11-1.15)

Notes. $p<.05$*, $p<.01$**, $p<.001$***; n=15,419