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Sleep duration and sleep disturbances partly explain the association between depressive symptoms and cardiovascular mortality: The Whitehall II cohort study

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Abstract

Depressive symptoms are associated with an increased risk of death but most of this association remains unexplained. Our aim was to explore the contribution of sleep duration and disturbances to the association between depressive symptoms, all-cause and cardiovascular disease mortality. A total of 5813 (4220 men and 1593 women) aged 50 to 74 at baseline, participants of the British Whitehall II prospective cohort study, were included. Depressive symptoms, sleep duration and disturbances were assessed in 2003-2004. Mortality was ascertained through linkage to the national mortality register until August 2012; mean follow-up of 8.8 years. Depressive symptoms were associated with an increased risk of mortality from all-causes (HR= 1.51; 95% CI, 1.16-1.97) and cardiovascular diseases (HR=1.63; 95% CI, 1.01-2.64) after adjustment for sociodemographic characteristics. Further adjustment for sleep duration and disturbances reduced the association between depressive symptoms and cardiovascular mortality by 21% (HR=1.53 95% CI, 0.91-2.57). Sleep seems to have a role, as a mediator or confounder, in explaining the association between depressive symptoms and cardiovascular mortality. These findings need replication in larger studies with longer follow-up.

Keywords

Sleep disturbances; sleep duration; depression; mortality; epidemiology

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Author contributorship

HN designed the study. MADS and HN managed the literature searches. MADS undertook the Statistical analysis and wrote the first draft of the manuscript with HN. All authors contributed to the interpretation of the results and have approved the final manuscript.

INTRODUCTION

There is consistent evidence for an increased risk of mortality, particularly cardiovascular deaths, among persons with depressive symptoms.(Ariyo et al., 2000, Nicholson et al., 2006, Nabi et al., 2010, Lefevre et al., 2012) In parallel, an increasing number of studies have also found sleep duration and sleep disturbances to be associated with mortality risk (Cappuccio et al., 2010, Rod et al., 2011, Ferrie et al., 2007). What is more, depression and sleep are associated with each other in a bidirectional fashion (Mezick et al., 2011, Breslau et al., 1996). However, we are aware of no previous study that has examined the role of sleep in the association between depression and mortality. Accordingly, we explored the contribution of sleep duration and disturbances to the association between depressive symptoms, all-cause and cardiovascular mortality.

METHODS

Participants

The Whitehall II study, established in 1985, is a longitudinal study based on 10,308 civil servants (6,895 men and 3,413 women)(Marmot and Brunner, 2005). Baseline examination (phase 1) took place between 1985 and 1988 and involved a clinical examination and a self-administered questionnaire. Subsequent data collection phases have alternated between a questionnaire (even-numbered phases), and questionnaire plus clinical examination (odd-numbered phases). University College London Medical School Committee on the Ethics of Human Research approved the protocol and informed consent was gained from all participants.

Measures

Depressive symptoms assessed at phase 7(2003–2004) used the Center for Epidemiologic Studies Depression Scale (CES-D, Cronbach's alpha = 0.83) for the first time in the Whitehall II study. Scores ≥ 16 from a total possible score of 60 were used to distinguish depressed from non-depressed participants (Radloff, 1977).

Sleep duration was assessed at phase 7 by asking participants "how many hours of sleep do you have on an average week night?" Responses choices were: 5 hours or less, 6 hours, 7 hours, 8 hours, and 9 hours or more. Those reporting ≤5 hours per night were assigned to the "short sleep duration" category and those reporting ≥6 hours per night to the "long or normal sleep duration" category (the reference group)(Gallicchio and Kalesan, 2009, Groeger et al., 2004).

Sleep disturbances were assessed at phase 7 using the 4-item Jenkins Scale (Jenkins et al., 1988). This scale includes 4 questions on "having trouble falling asleep", "waking up several times per night," "having trouble staying asleep," "waking up after the usual amount of sleep feeling tired and worn out" (i.e., waking without feeling refreshed); all items have a 6-point response scale (1 = never; 2 = 1–3 days; 3 = 4–7 days; 4 = 8–14 days; 5 = 15–21 days; 6 = 22–31 days). In the absence of defined cut-off score for the Jenkins scale, we categorized participants into two groups: No sleep disturbances (any sleep problem ≤14 days and no hypnotics use during the last month, the reference group). Those who reported experiencing any of the four items ≥15 days or reported the use of hypnotics were considered to have sleep disturbances.

Mortality—Mortality follow-up was available through the National Health Services Central Registry until August 2012. Death certificates were coded using the 10_{th} revision of the International Classification of Disease (ICD). All-cause mortality and death from

cardiovascular diseases (CVD; ICD-10 codes I20-I25 and I60-I67) were the outcomes of interest.

Covariates—Sociodemographic measures included age, sex, ethnicity, marital status and occupational grade assessed by British civil service grade of employment taken from the phase 7 questionnaire. Behavioural risk factors were assessed using responses to the phase 7 questionnaire: smoking status (none, former or current), recommended physical activity (yes or no), high alcohol consumption (yes or no). The following biological CVD risk factors at phase 7 clinical examination were considered: hypertension (systolic/diastolic blood pressure ≥140/90 mmHg or antihypertensive medication), body mass index (BMI <20, 20-24.9, 25-29.9, or ≥30 kg/m^2) and diabetes (yes or no).

Statistical analyses

We examined the associations of depressive symptoms with mortality outcomes using serially adjusted Cox regression models. The contribution of sleep to these associations was assessed by including the two sleep variables into the Cox regression model separately and simultaneously and calculating the percentage of reduction in the hazard ratios. We combined men and women in the analyses ($p > 0.05$ for interaction with sex) and verified that the assumptions for proportional hazards were not violated (all $p > 0.05$).

RESULTS

A total 5813 participants (4220 men and 1593 women) aged 50 to 74 had complete data on the variables of interest in 2002-04 (the baseline of the present study) and were included in the analysis. Of these participants, 14.6% were above our cut-point for depression, 8.0% were considered “short sleepers” and 31.0% as with “sleep disturbances”. As expected the depressive symptoms score and sleep scores were correlated, with coefficients of −0.22 for sleep duration and 0.27-0.50 for sleep quality items.

During a mean follow-up of 8.8 years, 338 deaths from all causes occurred, including 98 deaths from cardiovascular diseases. There was some evidence suggesting an association between “short sleep” duration (fully adjusted HR=1.41; 95% 0.75-2.68) and “sleep disturbances” (Fully adjusted HR=1.26; 95% 0.83-1.90) and cardiovascular mortality, although the evidence was weak, probably due to lack of power. For all-cause mortality, HRs varied between 0.99 and 1.14 and there was no evidence of an association (data not shown).

Table 1 shows the associations between depressive symptoms and mortality and the contribution of sleep to these associations. After adjustment for sociodemographic variables, depressive symptoms were associated with an increased risk of all-cause mortality (HR= 1.57; CI 95%, 1.19-2.06). Additional adjustment for sleep variables did not materially changed the magnitude and the significance of this association.

Depressive symptoms were associated with increased cardiovascular mortality (HR=1.67; 95% CI, 1.02-2.75) in model adjusted for sociodemographic variables. Additional adjustment for sleep variables reduced the magnitude of the association by 21% (HR=1.53; 95% CI, 0.91-2.57) and rendered it statistically non-significant.

DISCUSSION

We sought to examine the role of sleep in explaining the association of depressive symptoms with all-cause and cardiovascular mortality. We found that depressive symptoms predicted both mortality outcomes even after adjustment for sociodemographic

characteristics. However, the association between depressive symptoms and cardiovascular mortality was reduced and no longer significant after additional adjustment for sleep duration and disturbances.

Our finding is consistent with the notion that sleep in part mediates the association between depressive symptoms and cardiovascular mortality. However, given that depressive symptoms and sleep variables were measured concurrently, we cannot exclude the possibility that sleep may confound (rather than mediate) the observed association with cardiovascular mortality. For instance, sleep problems may independently influence the onset of depressive symptoms (Mezick et al., 2011) and increase mortality risk, supporting their role as a confounding factor.

We found sleep to play a more important role in the association between depressive symptoms and cardiovascular mortality than in the association with all-cause mortality. This finding is biologically plausible because sleep problems have been found to be associated with major CVD risk factors, including obesity, hypertension, diabetes, and inflammation(Tasali and Ip, 2008, Spiegel et al., 2005, Williams et al., 2007).

To our knowledge, this is the first study to explore the role of sleep in explaining the association between depressive symptoms and mortality. We were able to adjust for a wide range of factors which can potentially confound the associations of interest. The present findings should be interpreted in light of some limitations. First, our study is based on government employees and is not representative of the general population, limiting the generalizability of these findings. Second, we examined depressive symptoms rather than clinical depression. Thus, the relationship between depression and mortality may have been underestimated. Moreover, sleep duration and sleep disturbances were self-reported. Reporting bias and measurement errors due to how sleep duration was recorded (responses were recorded as whole numbers of hours) may have biased the contribution of sleep to the relationship between depression and cardiovascular mortality. Third, the mean follow-up period was 8.8 years which explains the low number of deaths, particularly CVD deaths. Larger studies with longer follow-up and with repeated measures of depressive symptoms and sleep are needed to test the role of sleep.

Despite these limitations, the results represent a unique contribution to the literature. These results suggest that sleep may partially explain the association between depressive symptoms and cardiovascular mortality. Although sleep may also act as a confounder, these findings underscore the importance of considering sleep in studies aimed at examining increased cardiovascular mortality in depressive individuals. If the mediating role of sleep is confirmed, the implication is that preventive efforts for persons with depression should take into account aspects related to the quality of their sleep.

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Table1

Role of sleep in the association between depressive symptoms and all-cause and cardiovascular mortality

Adjusted for:	Depressive symptoms	N events/N total	HR [IC 95%]	% reduction
All-cause mortality				
None	No	270/4965	1	-
	Yes	68/848	1.51 (1.16-1.97)**	
Sociodemographics[a]	No	270/4965	1	-
	Yes	68/848	1.57 (1.19-2.06)**	
Sociodemographics[a] + biobehavioural risk factors[b]	No	270/4965	1	
	Yes	68/848	1.39 (1.05-1.83)*	−32
Sociodemographics + sleep duration	No	270/4965	1	
	Yes	68/848	1.57 (1.19-2.07)**	0
Sociodemographics + sleep disturbances	No	270/4965	1	
	Yes	68/848	1.53 (1.15-2.02)**	−7
Sociodemographics + sleep duration and disturbances	No	270/4965	1	
	Yes	68/848	1.54 (1.16-2.04)**	−5
Cardiovascular mortality				
None	No	77/4963[c]	1	-
	Yes	21/848	1.63 (1.01-2.64)*	
Sociodemographics[a]	No	77/4963	1	-
	Yes	21/848	1.67 (1.02-2.75)*	
Sociodemographics[a] + biobehavioural risk factors[b]	No	77/4963	1	
	Yes	21/848	1.45 (0.87-2.40)	−33
Sociodemographics + sleep duration	No	77/4963	1	
	Yes	21/848	1.61 (0.97-2.67)	−8
Sociodemographics + sleep disturbances	No	77/4963	1	
	Yes	21/848	1.57 (0.94-2.62)	−17
Sociodemographics + sleep duration and disturbances	No	77/4963	1	
	Yes	21/848	1.53 (0.91-2.57)	−21

[a] Adjusted for sex, age, ethnicity, marital status and occupational grade

[b] Adjusted for smoking, alcohol intake, body mass index, physical activity, hypertension and diabetes

[c] Two participants with unknown cause of death have been excluded from these analyses.

* $p<0.05$

** $p<0.01$