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Insomnia symptoms and acute coronary syndrome-induced posttraumatic stress symptoms: a comprehensive analysis of cross-sectional and prospective associations

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Abstract: Background: Acute coronary syndrome (ACS) induces clinically significant posttraumatic stress symptoms (PTSS) in 12% of patients. Subjective sleep problems are a risk factor for the development of PTSS, but this is underexplored in patients with ACS. Purpose: To examine the association of insomnia symptoms with ACS-induced PTSS. Methods: In this longitudinal study with 154 patients (all white, 84.4% male, mean age 58.7 years) with a verified ACS, insomnia symptoms were interviewer assessed at hospital admission and at 3 months, using the Jenkins Sleep Scale (JSS)-4. ACS-induced PTSS were assessed with the Clinician-Administered Posttraumatic Stress Disorder Scale 3 months after hospital admission. In multivariable linear models, insomnia symptoms were regressed on PTSS, adjusting for demographics, clinical variables, health behaviors, and psychological data, including cognitive depressive symptoms. Results: Greater insomnia symptoms at admission ($\beta = .165$, $p = .034$), greater increase in insomnia symptoms from admission to 3 months ($\beta = .233$, $p = .008$), and greater insomnia symptoms at 3 months ($\beta = .239$, $p = .002$) were independently associated with more severe total PTSS at 3 months. Concerning the individual PTSS clusters, both insomnia symptoms at admission ($\beta = .214$, $p = .007$) and at 3 months ($\beta = .213$, $p = .012$) were independently associated with reexperiencing symptoms. Removing sleep items from PTSS scores and excluding patients on antidepressants in two sensitivity analyses did not substantially change the results. Conclusions: Insomnia symptoms could play an important role in the development and severity of ACS-induced PTSS. This relationship seems not simply explained by the fact that sleeping difficulties are inherent to the phenotype of posttraumatic stress disorder. Clinical trial information: NCT01781247.

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**Insomnia symptoms and acute coronary syndrome-induced posttraumatic stress
symptoms: A comprehensive analysis of cross-sectional and prospective associations**

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ABSTRACT

Background: Acute coronary syndrome (ACS) induces clinically significant posttraumatic stress symptoms (PTSS) in 12% of patients. Subjective sleep problems are a risk factor for the development of PTSS, but this is underexplored in patients with ACS.

Purpose: To examine the association of insomnia symptoms with ACS-induced PTSS.

Methods: In this longitudinal study with 154 patients (all white, 84.4% male, mean age 58.7 years) with a verified ACS, insomnia symptoms were interviewer-assessed at hospital admission and at 3 months, using the Jenkins Sleep Scale (JSS)-4. ACS-induced PTSS were assessed with the Clinician-Administered Posttraumatic Stress Disorder Scale 3 months after hospital admission. In multivariable linear models, insomnia symptoms were regressed on PTSS, adjusting for demographics, clinical variables, health behaviors and psychological data, including cognitive depressive symptoms.

Results: Greater insomnia symptoms at admission ($\beta=.165$, $p=.034$), greater increase in insomnia symptoms from admission to 3 months ($\beta=.233$, $p=.008$), and greater insomnia symptoms at 3 months ($\beta=.239$, $p=.002$) were independently associated with more severe total PTSS at 3 months. Concerning the individual PTSS clusters, both insomnia symptoms at admission ($\beta=.214$, $p=.007$) and at 3 months ($\beta=.213$, $p=.012$) were independently associated with re-experiencing symptoms. Removing sleep items from PTSS scores and excluding patients on antidepressants in two sensitivity analyses did not substantially change the results.

Conclusions: Insomnia symptoms could play an important role in the development and severity of ACS-induced PTSS. This relationship seems not simply explained by the fact that sleeping difficulties are inherent to the phenotype of posttraumatic stress disorder.

ClinicalTrials.gov # NCT01781247.

Keywords: Cardiovascular disease; insomnia; myocardial infarction; psychological stress; risk factor; sleep disturbances

INTRODUCTION

Research over the last quarter century has convincingly shown that cardiac diseases can induce posttraumatic stress symptoms (PTSS) which, if they occur with sufficient intensity and frequency, can fulfil the criteria for a psychiatric diagnosis of posttraumatic stress disorder (PTSD) [1]. Both PTSS and PTSD may develop in individuals who have been exposed to a traumatic or stressful event involving experiences of threatened death or injury [2]. In patients with acute coronary syndromes (ACS), including myocardial infarction (MI), the prevalence of clinically significant levels of PTSS and PTSD is 12% and 4%, respectively [3]. Typical PTSS may include re-experiencing aspects of ACS in intrusive images and nightmares, avoidance of activities and places that remind of ACS, feeling distant from other people and hyperarousal, evidenced for example by hypervigilance and sleeping difficulties [4]. A recent systematic review of 120 studies revealed numerous sociodemographic, clinical and psychological risk factors for PTSS due to cardiac diseases [1]. For ACS, these include younger age [5], female sex [6], high medical comorbidity [7], high distress during ACS [5], history of depression [8] and depressive symptoms at hospital admission [9].

Sleep disturbances in the form of recurring posttraumatic anxiety dreams, due to dysfunctional rapid eye movement sleep, have long been considered a hallmark of PTSD [10]. Given that there is now ample evidence for a role of sleep disturbances in PTSD, both in medical and non-medical patients [11,12], there is a surprising lack of research on sleep problems as a risk factor for cardiac disease-induced PTSS [1]. In the only study of its kind to date, examining patients 3 months after ACS, there was a cross-sectional association between poor self-reported sleep and self-reported PTSS [13]. Importantly, this association was

statistically independent of demographics, health behaviors, comorbidity and psychological factors, including depressive symptoms as an obvious potential confounding variable [13].

Based on study findings in non-cardiac populations, sleep - as a modifiable behavior - could be an important target for both the prevention and treatment of ACS-induced PTSS. In traumatically injured patients, impairment in sleep onset, maintenance, early waking, disturbance and distress caused by sleep problems immediately prior to trauma predicted PTSD at 3 months [14]. In injured survivors of a motor vehicle accident, early self-reported insomnia predicted PTSD at one year [15], and medical-surgical intensive care unit survivors showed an association between poor self-reported sleep quality and higher level of PTSS half a year after hospital discharge [16]. In earthquake survivors, sleep disturbances predicted the development and persistence of PTSD [17], whereas sleep-related interventions in patients with PTSD may reduce insomnia symptoms, nightmares and PTSS severity [18,19].

To our knowledge, population-based and clinical studies have not systematically investigated whether sleep problems predict symptom clusters of PTSD differently. However, first experimental studies suggest this could be the case. For instance, individuals who were allowed to sleep after watching a trauma film developed fewer intrusions than those not allowed to sleep [20]. In another study, insomnia symptoms prior to a trauma film predicted intrusion and hyperarousal symptoms, although not avoidance symptoms, at one week [21]. Moreover, sleep quality was poorer, and sleep efficiency was lower, in women with PTSD and prominent hyperarousal symptoms compared to their counterparts with few hyperarousal symptoms [22]. Taken together, based on this literature, it could be hypothesized that insomnia symptoms are particularly predictive for re-experiencing and hyperarousal symptoms, but less so for avoidance symptoms. Furthermore, the effects of sleep disturbances on PTSS may not be explained simply by the fact that sleeping difficulties are embedded in the PTSD phenotype [11,12]. For instance, in combat veterans, baseline

insomnia remained to be a predictor of greater PTSS severity over six months even when removing insomnia and nightmare items from the PTSD-Checklist score [23].

In patients admitted for acute coronary intervention, we investigated the cross-sectional and longitudinal relationship between insomnia symptoms and ACS-induced PTSS severity, adjusting for potentially confounding variables. We hypothesized that 1) greater insomnia symptoms at hospital admission, 2) a greater increase in insomnia symptoms from admission to 3-month follow-up, and 3) greater insomnia symptoms at 3 months would be associated with greater PTSS at 3 months. In two sensitivity analyses, we examined whether removal of sleep symptoms from PTSS scores and excluding patients taking antidepressants that may affect sleep would alter the relationship between insomnia symptoms and PTSS.

METHODS

Participants

The data for the present study were obtained from 154 patients who participated in the Myocardial Infarction-Stress Prevention Intervention (MI-SPRINT) randomized controlled trial on the effects of early psychological counseling on the development of ACS-induced PTSS. The trial protocol was approved by the ethics committee of the State of Bern, Switzerland, and registered under ClinicalTrials.gov (NCT01781247) [24]. All participants provided written informed consent. To be included, patients had to be at least 18 years old with verified acute ST segment elevation MI (STEMI) or non-STEMI, stable circulatory conditions and high peritraumatic distress during MI. The latter was defined by a score of at least 5 for pain intensity plus at least 5 for fear of dying and/or feelings of helplessness on numeric rating scales from 0-10. Patients were excluded when they had emergency coronary artery bypass grafting, severe comorbid diseases, limited orientation, cognitive impairment, current severe depression (per the cardiologist's medical history), suicidal ideations in the

prior two weeks, or when they participated in another randomized controlled trial. Patients with insufficient knowledge of German were also excluded, as both the counseling sessions and the survey were conducted in either Swiss German or standard German, depending on the patient's specific language skills.

Procedures

The recruitment of patients in the MI-SPRINT trial has been detailed elsewhere [25]. In brief, of 1,758 consecutive patients with acute STEMI or non-STEMI, referred for acute coronary care intervention to the Cardiology Department, Bern University Hospital, Switzerland, 710 were approached by study staff. Of these, 444 (62.5%) agreed to in-person screening, 190 were eligible for one of two counseling sessions, and 154 completed the 3-month follow-up; their data were used for the present study. The primary aim of the trial was to prevent the development of interviewer-rated ACS-induced PTSS severity, at 3 months through trauma-focused counseling compared to stress-focused counseling (active control) [24]. Both sessions lasted 45 minutes and were performed at the bedside in the coronary care unit within 48 hours after the patients had reached stable circulatory conditions. For the present study, we made no distinction between patients in the trauma-focused and stress counseling group, as there was neither an intervention effect on the primary outcome of the trial, interviewer-rated severity of PTSS at 3 months [25], nor was the intervention significantly associated with sleep problems reported here.

Research assistants who were doctoral students in psychology and medicine performed counseling and obtained measures at admission from patient files, through a structured medical history and a clinical interview for insomnia symptoms. All Research assistants were trained and supervised by senior clinical psychotherapists with degrees in psychology, psychiatry or internal medicine. All baseline assessments were made before the

intervention except if the sequence had to be changed due to medical or hospital organizational reasons. Patients were invited for a follow-up examination at 3 months during which research assistants conducted an interview to assess insomnia symptoms and PTSS.

Measures

Insomnia symptoms

Sleep problems in terms of insomnia symptoms were assessed with the 4-item Jenkins Sleep Scale (JSS-4) at admission and at 3-month follow-up. The items ask about the frequency of difficulties initiating sleep, nighttime awakenings, difficulties maintaining sleep, and non-restorative sleep in the past month [26]. The response format for each item is “0” (not at all), “1” (1-3 days), “2” (4-7 days), “3” (8-14 days), “4” (15-21 days) or “5” (22-31 days), yielding a sleep problem total score of 0-5 (mean value of the 4 items). Cronbach’s α was 0.64 at admission (3 patients missed data) and 0.71 at 3 months indicating moderate ($\alpha \geq 0.61$) and good ($\alpha \geq 0.71$) internal consistency, respectively [27].

Cronbach’s α values in our study were lower than in some population-based studies (0.84 in [28]; 0.90 in [29]) and clinical samples of patients with cancer (0.84 in [30]) or rheumatoid arthritis (0.80 in [31]), but somewhat higher than in another population-based study with elderly individuals (0.60 in [32]) or clinical samples of patients with fibromyalgia (0.70 in [33]) or cardiac valve surgery (0.63 in [26]).

Posttraumatic stress symptoms

At 3 months after admission, ACS-induced PTSS were assessed with the German version of the Clinician-Administered PTSD Scale (CAPS) [34]. With reference to the previous month, trained research staff rated the frequency and intensity of each of the 17 PTSS between 0 (“never”) and 4 (“almost always”). The questions for individual PTSS were

modified to ask about acute MI as the potentially traumatizing event. Severity scores are 0-136 for total PTSS, 0-40 for re-experiencing (5 items), 0-56 for avoidance/numbing (7 items) and 0-40 for hyperarousal (5 items) symptoms. A CAPS total severity score of 20 and higher has been proposed as an indication of clinically significant PTSS: <19 = few PTSS, 20-39=mild PTSS, 40-59 = moderate PTSS, 60-79 = severe PTSS, >80 = extreme PTSS [35]. Cronbach's α was 0.79 for the CAPS total scale (0.79 without insomnia/nightmare items), 0.68 for the re-experiencing scale (0.64 without nightmare item), 0.66 for the avoidance/numbing scale and 0.44 for the hyperarousal scale (0.48 without insomnia item). Thus, internal consistency was good for the CAPS total scale, moderate for the re-experiencing and avoidance/numbing scale, but not satisfactory ($\alpha \leq 0.55$) for the hyperarousal scale [27]. Therefore, we decided not to use the hyperarousal scale, both with and without the insomnia item, for the analyses with the individual PTSS clusters.

In general, Cronbach's α values are typically in the 0.80-0.90 range for the three PTSS clusters and for all 17 PTSS, but values below 0.80 have also been reported for individual clusters [35]. For instance, in a sample of patients with war-related trauma and psychiatric outpatients, Cronbach's α was 0.63 for re-experiencing, 0.78 for avoidance/numbing and 0.79 for hyperarousal [36]. In a study on accident survivors, using the German version of the CAPS as in our study, Cronbach's α was 0.88-0.92 for the severity score of all 17 items and 0.73-0.88 for each of the three symptom clusters [34].

Covariates

Demographic factors: Demographic variables included age, gender and education. Education was defined as high (university graduation, including applied sciences; high school graduation/matura), medium (apprenticeship or vocational school) or low (lower than apprenticeship or vocational school) educational level [37].

Clinical variables: We calculated the Global Registry of Acute Coronary Events (GRACE) score as an index of MI severity and cumulative risk of death or recurrent ACS for six months after hospital discharge [38], and the Charlson comorbidity index, categorized by low, medium or high 10-year mortality risk [39]. To obtain information on sleep apnea, patients were asked “Have you ever been diagnosed with sleep apnea? (yes/no)”

Health behaviors: Patients were categorized in current, former or never smokers. The average frequency of physical activity per week “that makes you sweat” was categorized as none, 1-2x or 3-7x. Alcohol consumption was categorized as none, moderate or heavy (>21 standard drinks/week for men, >14 for women). The body mass index (BMI) was calculated based on self-disclosed weight and height (kg/m²).

Psychological data: For information on lifetime depression, patients were asked, “Have you ever had a depression in your life? (yes/no)”. Peritraumatic distress during MI (range 3.33-10) was calculated by dividing the sum of the numeric ratings for pain, fear of dying and helplessness by three [40]. We assessed the severity of depressive symptoms at admission and at 3 months with the 13-item self-rated cognitive/affective subscale of the Beck Depression Inventory [41] to limit study burden on the patient and to prevent a bias of mood ratings with medical disease symptoms. The scale yields a total score of 0-39 and comprises no sleep item. Cronbach’s α was 0.72 at admission (26 patients missed data) and 0.82 at follow-up (10 patients missed data), indicating good internal consistency for the scale. Use of antidepressant medications was also noted.

Data analysis

Data were analyzed with SPSS 26.0 for Windows (SPSS Inc., Chicago, IL) and significance level of $p \leq 0.05$ (two-sided). We used multiple imputation ($k=5$) to replace missing values for index MI, education, antidepressants, smoking ($n=1$); height, physical

activity (n=2); insomnia symptoms at admission, lifetime depression history (n=3); sleep apnea history (n=4); BDI score at follow-up (n=10); GRACE score (n=12); and BDI score at admission (n=26). There were no significant differences (all p-values >.27) in insomnia symptoms both at admission and at follow up and in all CAPS scores between participants with complete data (n=114) and those with incomplete data (n=40). To approximate a more normal distribution, CAPS and GRACE scores were square root transformed, and BMI values and BDI scores were log10 transformed before analysis. Changes over time in insomnia symptoms (JSS-4 score) and in depressive symptoms (BDI score) were calculated as change scores by subtracting admission scores from follow-up scores.

We used Pearson correlation analysis to estimate the univariable relationship between two variables and independent samples t-test to determine group differences in variables. Repeated measures analysis of variance and covariance were used to estimate the significance of changes in insomnia and depressive symptoms from admission to 3-month follow-up. We ran multivariable regression analyses to test whether insomnia symptoms at admission (Model 1), change over time in insomnia symptoms (Model 2) and insomnia symptoms at follow-up (Model 3), were associated with total PTSS (i.e., CAPS total severity score) at 3 months, adjusting for covariates. Covariates were selected a priori based on the literature on risk factors of ACS-induced PTSS [1] and/or their potential interference with good sleep. However, the number of covariates was limited to guard Models 1-3 against overfitting. Specifically, all models were adjusted for age, sex, education (demographics), GRACE score, Charlson comorbidity index, history of sleep apnea (clinical variables), alcohol consumption, physical activity, BMI (health behaviors), peritraumatic distress, lifetime depression history, and antidepressant use (psychological data). Additional adjustment was made in Model 1 for depressive symptoms at admission and in Model 3 for depressive symptoms at follow-up. In

Model 2, additional adjustment was made for insomnia symptoms at admission, depressive symptoms at admission and change over time in depressive symptoms.

When insomnia symptoms showed a significant association with total PTSS, we conducted post hoc analyses to identify any significant association of insomnia symptoms with re-experiencing and avoidance/numbing symptoms; no post hoc analyses were conducted for hyperarousal symptoms because the hyperarousal scale showed low reliability (see above). We did not adjust p-values for multiple comparisons because of the pre-established hierarchy of outcomes. We performed two sensitivity analyses. In the first one, we removed insomnia and nightmare items from PTSS scores to test the influence of sleeping difficulties inherent to the PTSD phenotype on the link between insomnia symptoms and PTSS. In the second one, we excluded patients with current antidepressant use, as antidepressants may affect sleep. There was no indication of influential outliers or concern for multicollinearity in the set of predictor variables. Because this was a secondary analysis of data of an RCT, there was no pre-planned power analysis on insomnia outcomes.

RESULTS

Patient characteristics

Table 1 shows the characteristics of the 154 patients with ACS who underwent the CAPS interview 3 months after hospital admission. The study participants, all of white ethnicity, were predominantly male, of medium-to-high educational level and had rather low comorbidity. The median GRACE score indicated a mortality risk of 5% (IQR 2-8). In terms of health behaviors, patients were on average overweight and most often in the category of current smokers, moderate alcohol consumers and those with low physical activity.

Depressive symptoms at admission and at follow-up were at low level and correlated with each other ($r=.48$, $p<.001$). Only few patients ($n=11$) took antidepressants. Three out of

10 patients confirmed a lifetime depression history; these reported a higher median depressive symptom score than patients without lifetime depression, both at admission (3.9, IQR 1.3-6.4 vs. 2, IQR 0-4; $p<.001$) and at follow-up (2, IQR 1-5.4 vs. 1.5, IQR 0-3; $p<.001$). Insomnia symptoms at admission correlated with insomnia symptoms at follow-up ($r=.33$, $p<.001$). At follow-up, 28 (18.2%) patients had clinically significant PTSS (CAPS total score >20). Of these, 24 (15.6%) had mild PTSS and 4 (2.6%) had moderate PTSS.

Regarding differences by sex in insomnia symptoms and PTSS, women had significantly greater mean (SD) insomnia symptoms at follow-up than men (2.11 (1.19) vs. 1.10 (1.18); $p<.001$). In contrast, there were no significant differences by sex (women vs. men) in insomnia symptoms at admission (1.88 (1.17) vs. 1.41 (1.20); $p>.08$), median total PTSS (10, IQR 8-15.75 vs. 6.5, IQR 2-15; $p>.08$), re-experiencing (2, IQR 0-3.75 vs. 1.5, IQR 0-3.25; $p=.73$), avoidance/numbing (2, IQR 0.5-4.75 vs. 2, IQR 0-4; $p=.39$) and hyperarousal (6, IQR 4-8 vs. 4, IQR 2-7; $p>.05$) symptoms.

Changes in insomnia and depressive symptoms from admission to follow-up

Repeated measures analysis of variance showed a significant decrease over time in both insomnia symptoms (partial $\eta^2=.026$, $p=.043$) and depressive symptoms (partial $\eta^2=.037$, $p=.019$) from admission to follow-up. The change over time in insomnia symptoms was no longer significant in repeated measures analyses of covariance with adjustment for age, sex, education, GRACE score, Charlson comorbidity index, sleep apnea history, alcohol consumption, physical activity, BMI, peritraumatic distress, lifetime depression, antidepressant use and depressive symptoms at admission ($p=.49$). Likewise, the change over time in depressive symptoms was no longer significant with adjustment for age, sex, education, GRACE score, Charlson comorbidity index, sleep apnea history, alcohol

consumption, physical activity, BMI, peritraumatic distress, lifetime depression, antidepressant use and insomnia symptoms at admission ($p=.49$).

Univariable correlations with insomnia symptoms

The zero-order correlations between patient characteristics and insomnia symptoms at admission and at follow-up are displayed in Electronic Supplementary Table 1. There were significant correlations between greater insomnia symptoms at admission and greater peritraumatic distress ($r=.18$, $p=.030$), lifetime depression ($r=.18$, $p=.023$) and more severe total PTSS ($r=.24$, $p=.003$), re-experiencing ($r=.27$, $p=.001$) and avoidance/numbing ($r=.19$, $p=.018$) symptoms. Greater insomnia symptoms at follow-up were also significantly correlated with greater peritraumatic distress ($r=.26$, $p=.001$), lifetime depression ($r=.27$, $p=.001$) and more severe total PTSS ($r=.43$, $p<.001$), re-experiencing ($r=.34$, $p<.001$) and avoidance/numbing ($r=.32$, $p<.001$) symptoms. Greater insomnia symptoms at follow-up showed additional significant correlations with female sex ($r=.30$, $p<.001$) and with greater depressive symptoms at admission ($r=.26$, $p=.001$) and at follow-up ($r=.29$, $p<.001$).

Multivariable associations between insomnia symptoms and PTSS at follow-up

Insomnia symptoms at admission and PTSS at follow-up

The fully adjusted Model 1 in Table 2a shows that patients who reported greater insomnia symptoms at hospital admission had more severe total PTSS (standardized $\beta=.165$, $p=.034$) and, in post hoc analyses, re-experiencing symptoms ($\beta=.214$, $p=.007$) at follow-up. In addition, younger age was predictive of more severe total PTSS ($\beta=-.225$, $p=.031$) and re-experiencing symptoms ($\beta=-.230$, $p=.029$), and higher education was predictive for lower re-experiencing symptoms ($\beta=-.204$, $p=.008$). Greater peritraumatic distress was predictive for more severe total PTSS ($\beta=.170$, $p=.031$) and re-experiencing symptoms ($\beta=.182$, $p=.024$).

Greater depressive symptoms at admission were predictive for more severe total PTSS ($\beta=-.314$, $p<.001$), re-experiencing symptoms ($\beta=.192$, $p=.017$) and avoidance/numbing symptoms ($\beta=.363$, $p<.001$) at follow-up.

Change over time in insomnia symptoms and PTSS at follow-up

The fully adjusted Model 2 in Table 2b shows a significant association between a greater increase in insomnia symptoms from admission to follow-up and more severe total PTSS at follow-up ($\beta=.233$, $p=.008$). In particular, these relationships were independent of admission scores for both insomnia symptoms and depressive symptoms and the change over time in depressive symptoms. Regarding the latter variable, a greater increase in depressive symptoms from admission to follow-up was also associated with more severe total PTSS ($\beta=.382$, $p<.001$) and, additionally, with more severe re-experiencing ($\beta=.215$, $p=.016$) and avoidance/numbing ($\beta=.428$, $p<.001$) symptoms at follow-up.

As in Model 1, higher education was predictive for lower re-experiencing symptoms ($\beta=-.178$, $p=.018$) and greater peritraumatic distress was predictive for more severe total PTSS ($\beta=.149$, $p=.036$) and re-experiencing symptoms ($\beta=.163$, $p=.040$). Also, insomnia symptoms at admission remained to be an independent predictor for more severe total PTSS ($\beta=.301$, $p=.001$) and re-experiencing symptoms ($\beta=.327$, $p=.001$) at follow-up. Likewise, greater depressive symptoms at admission remained predictive for more severe total PTSS ($\beta=.487$, $p<.001$), re-experiencing ($\beta=.283$, $p=.002$) and avoidance/numbing ($\beta=.574$, $p<.001$) symptoms at follow-up.

Insomnia symptoms at follow-up and PTSS at follow-up

The fully adjusted Model 3 in Table 2c shows that greater insomnia symptoms at follow-up were significantly associated with more severe total PTSS ($\beta=.239$, $p=0.002$) and

re-experiencing symptoms ($\beta=.213$, $p=.012$) at follow-up. Greater depressive symptoms at follow-up were also associated with more severe total PTSS ($\beta=.425$, $p<.001$), re-experiencing ($\beta=.244$, $p=.002$) and avoidance/numbing ($\beta=.488$, $p<.001$) symptoms at follow-up.

As in Models 1 and 2, higher education was predictive for lower re-experiencing symptoms ($\beta=-.174$, $p=.023$) and greater peritraumatic distress was predictive for more severe total PTSS ($\beta=.181$, $p=.010$) and re-experiencing symptoms ($\beta=.196$, $p=.012$). Unlike in Models 1 and 2, greater peritraumatic distress was also predictive for more severe avoidance symptoms at follow-up ($\beta=.156$, $p=.033$).

Sensitivity analyses

Insomnia symptoms and PTSS deprived of sleep items

For the first sensitivity analysis (Electronic Supplementary Table 2), we subtracted scores of item 5 “Recurrent and distressing dreams of MI” and item 13 “Difficulty falling or staying asleep” from the CAPS total scores (both these items) and re-experiencing score (item 5). Greater insomnia symptoms at admission ($\beta=.159$, $p=.042$) remained significantly and independently associated with more severe total PTSS at follow-up. Moreover, greater insomnia symptoms at admission ($\beta=.226$, $p=.006$), greater increase in insomnia symptoms from baseline to follow-up ($\beta=.191$, $p=0.050$) and greater insomnia symptoms at follow-up ($\beta=.219$, $p=.010$) all showed significant associations with more severe re-experiencing symptoms at follow-up (Supplementary Table 2).

Multivariable associations excluding patients with antidepressant use

For the second sensitivity analysis (Electronic Supplementary Table 3), we excluded the 11 patients with current use of antidepressants at hospital admission. In the subsample of

143 study participants without antidepressant use, greater insomnia symptoms at admission were no longer predictive for total PTSS at follow-up but remained predictive for more severe re-experiencing symptoms ($\beta=.213$, $p=.011$) as in the total sample (see Table 2a). A greater increase in insomnia symptoms from baseline to follow-up was significantly predictive for more severe total PTSS ($\beta=.256$, $p=.007$) and, unlike in the total sample (see Table 2b), also for more severe re-experiencing symptoms ($\beta=.230$, $p=.029$). As in the total sample (see Table 2c), greater insomnia symptoms at follow-up were significantly associated with more severe total PTSS ($\beta=.248$, $p=.002$) and re-experiencing symptoms ($\beta=.243$, $p=.007$).

DISCUSSION

This study yielded several novel results. First of all, we found that patients who indicated more sleep problems in the form of insomnia symptoms at the time of their hospital admission had developed more total ACS-induced PTSS after 3 months. Because this association was prospective, we can interpret that insomnia symptoms in the month preceding an ACS are a risk factor for ACS-induced PTSS, which has not yet been described in cardiac populations [1]. Admission insomnia symptoms were as significantly predictive for total PTSS, as were younger age, perceived distress during ACS, and depressive symptoms, all risk factors for ACS-induced PTSS already known [3,5,9]. It should be considered that patients with greater peritraumatic distress could have overestimated sleep problems in their retrospective assessment during the acute medical situation. The same may be true for those with poorer sleep, as insomnia patients tend to misperceive their sleep quality relative to objective sleep measures [42]. Nonetheless, this should not discount the importance of ACS patients' perceived insomnia symptoms regarding an increased risk of developing PTSS.

Our results on the effects of dynamics in insomnia symptoms over time on the development of ACS-induced PTSS are also novel. We found that patients who indicated an increase in insomnia symptoms from admission to follow-up had also more severe ACS-induced total PTSS at follow-up. A regression to the mean effect is an unlikely explanation for this observation, as this analysis was adjusted for admission insomnia symptoms. Again, younger age, greater peritraumatic distress and depressive symptoms emerged as significant covariates of this association. Notably, an increase in depressive symptoms over time was also independently associated with more severe total PTSS at follow-up.

Confirming a previous study in which ACS-induced self-rated PTSS were assessed at 1 month [13], we found a positive cross-sectional association between insomnia symptoms at 3 months and severity of total PTSS. The sample sizes were comparable in the two studies and we had deliberately selected a very similar set of covariates. The earlier study applied the Pittsburgh Sleep Quality Index (PSQI), which allows a more differentiated sleep assessment than the shorter JSS-4, overwhelmingly asking questions about insomnia symptoms, we used in our study for reasons of practicability in an acute medical environment. However, instead of self-rated questionnaires, as applied in the previous study [13], we used a clinical interview to assess insomnia symptoms and ACS-induced PTSS with relatively greater confidence. Studies on the role of sleep in cardiac disease-induced PTSS do not exist for patients who do not have coronary heart disease [1]. Such investigations are warranted, as the prevalence of clinically relevant PTSS in survivors of a cardiac arrest [43], patients who underwent cardiac surgery [44] or cardioverter defibrillator implantation [45] is at least as high as in ACS patients [3]. In our study, 18.2% of patients had clinically significant, i.e., at least mild ACS-induced PTSS, which concurs with the prevalence estimate of 12% (95% CI 9-16) of a previous meta-analysis [3].

Post hoc analyses revealed that insomnia symptoms were predominantly associated with ACS-induced symptoms of re-experiencing but not with avoidance/numbing symptoms. An apparent explanation for this could be that sleeping difficulties are part of the re-experiencing symptom cluster of PTSD. However, when removing the item “Recurrent and distressing dreams of myocardial infarction” from the re-experiencing symptom cluster, re-experiencing symptoms became significant in all three models. In agreement, experimental evidence suggests that poor sleep following trauma exposure could contribute to the development of intrusive re-experiencing [20]. When we also removed the item “Difficulty falling and staying asleep”, which is equivalent wording to items 1 and 3 of the JSS-4, from the hyperarousal symptom cluster, significance remained for the association between admission insomnia symptoms and total PTSS as well. Therefore, the results of our sensitivity analysis lend credence to the view that the associations between sleep problems and ACS-induced PTSS seem not simply explained by the fact that sleeping difficulties are embedded in the PTSD phenotype [11,12]. However, findings may vary depending on the sleep dimensions studied and the cross-sectional or longitudinal designs applied. The link may not be causal, but insomnia symptoms share genetic etiology with PTSD [46], further supporting the notion that disturbed sleep is more a core feature than a secondary symptom of PTSD [47]. Moreover, we found little evidence that the association between insomnia symptoms and PTSS could be substantially explained by the use of antidepressants.

Depending on the model, only between 2.3% and 4.2% of the unique variance of PTSS was significantly explained by insomnia symptoms, but the effect sizes were by and large similar to those for the other significant covariates in the regression models. Therefore, the findings from our study may have clinical implications. The literature on effective elements of early behavioral interventions to prevent PTSS induced by life-threatening medical events, including cardiac diseases, is still scarce [48]. Future trials could test whether

targeting sleep problems in cardiac rehabilitation through cognitive behavioral therapy for insomnia adapted to patients with cardiovascular disease [49] will prevent PTSS. In patients with overt ACS-induced PTSS, cognitive therapies could improve sleep and reduce PTSS, as shown for non-cardiac populations with PTSD [19]. Clinical importance could reach beyond symptom relief as both ACS-induced PTSS [3] and insomnia symptoms may increase the risk of recurrent cardiac events and mortality [50].

The assessment of insomnia symptoms and PTSS with an interview, the longitudinal design with the measurement of insomnia symptoms at two time points, allowing a dynamic perspective, and extensive adjustment for potentially confounding variables were strengths of our study. Due to the study design and sample composition, our study also has notable limitations which must be considered for the interpretation and potential clinical implications of the results. In particular, we recognize that the potential overall impact of our findings on medical care is limited for at least two reasons. First, our study participants were a somewhat unrepresentative group, as they were intentionally selected based on a high level of peritraumatic distress during MI, assuming they would be at risk of developing clinically significant PTSS. Therefore, an intervention to reduce ACS-induced PTSS through a sleep intervention concerns only a minority of patients with ACS. Second, our study participants received a psychosocial intervention beyond usual ACS care in the context of an RCT. Although the two active interventions showed no difference in their effect on both clinician-rated PTSS and insomnia symptoms, their effects on the associations between insomnia symptoms and PTSS may still differ from those of usual care.

The findings have limited generalizability to women, as only 15.6% of our study participants were female. It is well known that women are more susceptible to both insomnia [51] and PTSD [52] than men. Women show also more severe PTSS than men with low or moderate levels of potentially traumatizing event types [53]. In our sample, women had

higher absolute levels of insomnia symptoms and PTSS than men, although limited statistical power likely prevented several of these differences from becoming statistically significant. Moreover, women had about double the severity of insomnia symptoms compared to the general German population, whereas men were closer to population norms [29]. Therefore, it is possible that a more balanced ratio of men and women could have yielded stronger associations between insomnia symptoms and PTSS. We did not measure sleep objectively and sleep apnea history was based on self-report. The JSS-4 is less comprehensive regarding different sleep components than the PSQI, so unfortunately we had no measure available for self-reported short sleep, which has been shown to predict recurrent cardiac events and mortality in patients with ACS [54]. The survey item to assess lifetime depression did not ask for a doctor or health professional diagnosis of depression. The range of scores on the CAPS was rather low; nevertheless, one in six patients had clinically significant PTSS. Some of Cronbach's α values were at the lower end of the acceptable range and the reliability of the hyperarousal scale was unsatisfactory. It is unclear if findings were the same when DSM-5 criteria for PTSD would be applied.

To sum up, the results of our study are consistent with a growing literature indicating the importance of sleep quality in the development of a number of psychological and medical problems. Our findings particularly contribute to a better understanding of the temporal associations between sleep problems, exposure to a traumatic cardiac event and development of PTSS. Sleep problems could be a risk factor for the development and severity of ACS-induced PTSS. Behavioral intervention trials are warranted to test whether improvement of sleep problems in patients with ACS can prevent and reduce PTSS.

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Table 1. Admission and follow-up characteristics of the 154 study participants

Variables	Admission	Follow-up
Ethnicity, white, n (%)	154 (100)	
Age (years), mean (SD)	58.7 (10.9)	
Male sex, n (%)	130 (84.4)	
Educational level, n (%)		
High, medium, low	30 (19.5), 113 (73.4), 11 (7.1)	
Peritraumatic distress, mean (SD)	6.18 (1.35)	
ST-elevation MI, n (%)	111 (72.1)	
GRACE score, median (IQR)	104 (86-120)	
Charlson comorbidity index, n (%)		
Low, medium, high	88 (57.2), 39 (25.3), 27 (17.5)	
Sleep apnea history (yes), n (%)	18 (11.7)	
Smoking, n (%)		
Never, former, current	45 (29.2), 42 (27.3), 67 (43.5)	
Alcohol consumption, n (%)		
None, moderate, heavy	26 (16.9), 120 (77.9), 8 (5.2)	
Physical activity, n (%)		
None, 1-2x/week, 3-7x/week	68 (44.2), 45 (29.2), 41 (26.6)	
Body mass index, kg/m ² , median (IQR)	27.1 (24.8-30.3)	
Lifetime depression history (yes), n (%)	46 (29.9)	
Antidepressant use (yes), n (%)	11 (7.1)	
BDI cognitive score, median (IQR)	2.06 (0.74-4.56)	2.00 (0-3.13)
JSS-4 scores, mean (SD)	1.49 (1.21)	1.26 (1.24)
CAPS scores, median (IQR)		
Total symptom severity		8 (3-15)
Re-experiencing symptoms		2 (0-3.25)
Avoidance / numbing symptoms		2 (0-4)
Hyperarousal symptoms		4 (2-7.25)

BDI, Beck Depression Inventory; CAPS, Clinician-Administered Post-Traumatic Disorder Scale; IQR, inter-quartile range; JSS, Jenkins Sleep Scale; SD, standard deviation

Table 2a. Multivariable linear associations between insomnia symptoms at admission and PTSS at follow-up

Model 1	CAPS symptoms		
Variables entered (one block)	Total PTSS	Re-experiencing	Avoidance/numbing
Age	-.034 (.016)*	-.026 (.012)*	-.005 (.013)
Female sex	.301 (.349)	-.077 (.268)	.104 (.269)
Education	-.333 (.247)	-.501 (.190)**	-.308 (.192)
GRACE score	.079 (.139)	.100 (.105)	.017 (.114)
Charlson score	.115 (.166)	.002 (.127)	.212 (.128)
Sleep apnea history	.165 (.435)	-.081 (.325)	.190 (.347)
Alcohol consumption	-.296 (.229)	.108 (.176)	-.166 (.177)
Physical activity	.273 (.156)	.234 (.120)	.019 (.121)
Body mass index	-1.797 (1.878)	.151 (1.444)	-1.651 (1.453)
Peritraumatic distress	.207 (.096)*	.166 (.074)*	.113 (.074)
Lifetime depression	.143 (.287)	.020 (.221)	-.147 (.223)
Antidepressant use	-.346 (.497)	.119 (.381)	-.581 (.383)
Depressive symptoms (AD)	1.529 (.397)***	.701 (.295)*	1.325 (.306)***
Insomnia symptoms (AD)	.225 (.106)*	.219 (.081)**	.109 (.083)
Model statistics			
Total R2	.282	.243	.242
Change in R2 after adding insomnia symptoms (AD)	.023	.039	.010

Values are unstandardized coefficients B (s.e.); *P≤0.05, **P≤0.010, ***P≤0.001.

AD, admission; CAPS, Clinician-Administered Post-Traumatic Stress Disorder Scale;

GRACE, Global Registry of Acute Coronary Events; PTSS, posttraumatic stress symptoms

Table 2b. Multivariable linear associations between changes over time in insomnia symptoms and PTSS at follow-up

Model 2	CAPS symptoms		
Variables entered (one block)	Total PTSS	Re-experiencing	Avoidance/numbing
Age	-.025 (.014)	-.022 (.012)	<.001 (.011)
Female sex	.026 (.320)	-.227 (.266)	-.032 (.250)
Education	-.210 (.222)	-.437 (.185)*	-.241 (.174)
GRACE score	.059 (.122)	.091 (.102)	.001 (.100)
Charlson score	.024 (.150)	-.038 (.124)	.137 (.118)
Sleep apnea history	.195 (.385)	-.080 (.316)	.248 (.308)
Alcohol consumption	-.282 (.204)	.113 (.170)	-.153 (.159)
Physical activity	.234 (.139)	.214 (.116)	<.001 (.109)
Body mass index	-1.897 (1.699)	.211 (1.410)	-2.022 (1.339)
Peritraumatic distress	.182 (.087)*	.148 (.072)*	.112 (.068)
Lifetime depression	-.043 (.260)	-.076 (.216)	-.254 (.203)
Antidepressant use	-.239 (.442)	.172 (.368)	-.512 (.346)
Depressive symptoms (AD)	2.368 (.423)***	1.032 (.339)**	2.095 (.322)***
Depressive symptoms (FU-AD)	1.826 (.485)***	.771 (.321)*	1.535 (.292)***
Insomnia symptoms (AD)	.411 (.124)**	.334 (.103)**	.162 (.097)
Insomnia symptoms (FU-AD)	.274 (.103)**	.164 (.068)	.094 (.081)
Model statistics			
Total R2	.437	.305	.389
Change in R2 after adding insomnia symptoms (FU-AD)	.029	.019	.006

Values are unstandardized coefficients B (s.e.); *P≤0.05, **P≤0.010, ***P≤0.001.

CAPS, Clinician-Administered Post-Traumatic Stress Disorder Scale; FU-AD, change score in depressive and insomnia symptoms from admission (AD) to follow-up (FU); GRACE, Global Registry of Acute Coronary Events; PTSS, posttraumatic stress symptoms

Table 2c. Multivariable linear associations between insomnia symptoms at follow-up and PTSS at follow-up

Model 3	CAPS symptoms		
Variables entered (one block)	Total PTSS	Re-experiencing	Avoidance/numbing
Age	-.023 (.014)	-.019 (.012)	.002 (.011)
Female sex	-.005 (.322)	-.243 (.268)	-.063 (.252)
Education	-.197 (.223)	-.428 (.188)*	-.228 (.175)
GRACE score	.048 (.124)	.090 (.104)	-.012 (.101)
Charlson score	.031 (.151)	-.025 (.125)	.138 (.119)
Sleep apnea history	.304 (.380)	.031 (.317)	.321 (.302)
Alcohol consumption	-.209 (.203)	.174 (.169)	-.094 (.158)
Physical activity	.233 (.139)	.210 (.117)	.001 (.109)
Body mass index	-2.196 (1.701)	-.050 (1.419)	-2.249 (1.341)
Peritraumatic distress	.220 (.085)**	.179 (.071)*	.142 (.067)*
Lifetime depression	.059 (.256)	-.006 (.213)	-.163 (.201)
Antidepressant use	-.218 (.444)	.176 (.372)	-.486 (.348)
Depressive symptoms (FU)	2.060 (.355)***	.887 (.289)**	1.774 (.267)***
Insomnia symptoms (FU)	.317 (.101)**	.212 (.084)*	.119 (.079)
Model statistics			
Total R2	.419	.279	.242
Change in R2 after adding insomnia symptoms (AD)	.042	.032	.010

Values are unstandardized coefficients B (s.e.); *P≤0.05, **P≤0.010, ***P≤0.001.

CAPS, Clinician-Administered Post-Traumatic Stress Disorder Scale; FU, follow-up;

GRACE, Global Registry of Acute Coronary Events; PTSS, posttraumatic stress symptoms