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Sleep Disturbance in Women Prior to Myocardial Infarction

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Abstract

OBJECTIVE—To describe the prevalence and correlates of sleep disturbances among women who retrospectively reported sleep disturbance prior to their myocardial infarction (MI).

BACKGROUND—MI is frequently unrecognized in women because they may have only vague symptoms, such as sleep disturbance. Describing correlates of sleep disturbance prior to MI may assist in recognizing women at risk for coronary heart disease.

METHODS—Secondary analysis of dataset derived from 15 sites.

RESULTS—Of 1270 women experiencing initial MI, 632 reported new onset of or worsening sleep disturbance before MI. Prevalence was similar across racial groups. Women reporting prodromal sleep disturbance were more likely to be older, heavier, and report cognitive changes (aOR= 1.47), new or increasing anxiety (aOR= 2.21), and unusual fatigue (aOR= 2.16).

CONCLUSIONS—Subjective report of sleep disturbance preceding MI appear to be prevalent in women of all races and may be an important warning sign for MI in women.

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Keywords

cardiovascular disease; cognitive disorders; sleep disturbance; menopause; women

Introduction

Although cardiovascular disease has been thought to occur primarily in men, a substantial number of women have coronary heart disease (CHD), a type of cardiovascular disease. In fact, the prevalence of CHD is 7.5 million in women and of these, 3.1 million have experienced a myocardial infarction (MI).¹ When women experience MI, they have worse outcomes than men, more disability, and are more likely to experience repeat MI within a year, and death.^{1,2} A contributing factor to these worse outcomes includes pre-hospital delays in seeking treatment.³ For example, in one study, when asked to describe events prior to their MIs, 30% of women reported that within 1 hour of symptom onset they recognized their symptoms as cardiac and sought medical assistance. However, 70% delayed seeking treatment from 1 to more than 5 days, thereby limiting treatment options.⁴

One reason for delays, less aggressive treatment, and poorer outcomes may be that women's symptoms of MI are often vague and do not fit the classic pattern of crushing chest pain. Indeed, when women describe their symptoms of MI, chest pain is not the most frequently mentioned.^{5,6} Because women's symptoms of MI are not typical, they and their healthcare providers may not recognize the symptom(s) as cardiac. However, identifying early warning symptoms that occur prior to the acute MI and are amenable to treatment may prevent or delay progression to MI and limit the costly effects of this devastating disease in women.

New onset sleep disturbance is one of the vague symptoms described by women prior to MI.⁵⁻⁹ However, although studies from our group and other investigators have identified sleep disturbance as a prodromal symptom, they did not identify the characteristics of women, other than race, who were most likely to experience sleep disturbance. Complex prodromal symptoms often include sleep disturbance, severe, unusual fatigue and shortness of breath.⁷ For example, when McSweeney and colleagues focused on the symptoms women believed were early warning symptoms of their MI, they found that unusual fatigue (70.7%), sleep disturbance (47.8%), and changes in cognition (23.9%) were the most frequently reported prodromal symptoms.⁶ The unusual fatigue was described as unexplained, often interfering with ability to conduct activities of dialing living, such as making a bed.⁶

Further, because both long and short sleep are independently associated with an increased risk of coronary events, sleep disturbance may be a previously underappreciated risk factor for MI in women and a potentially important warning of impending MI.¹⁰ Therefore, the purpose of this study was to describe the relationships among sleep disturbance, CHD prodromal symptoms, and cognitive impairment in a unique cohort of women, defined by an index event (first time MI). This design differs from many other population-based studies that have linked short sleep duration and/or sleep disturbance to adverse outcomes in women, such as the Study of Osteoporotic Fracture,¹¹ the Study of Women's Health Across the Nation,¹² or the Nurses' Health Study¹³ because formation of the current cohort was based entirely on the existence of an index event, i.e., a previously documented and verified myocardial infarct.⁶

Methods

Study Design

This descriptive study analyzed a dataset assembled from two studies that used the McSweeney Acute and Prodromal Myocardial Infarction Symptom Survey (MAPMISS) to evaluate women's prodromal and acute symptoms of MI.⁸ We differentiated a prodromal symptom from a risk factor preceding the event: a risk factor was defined as a stable, trait-like moderator, while a prodromal symptom was defined as one increasing in frequency or intensity prior to the event, with diminution of the symptom following the event.⁸ The MAPMISS was administered to subjects by telephone. Prior to and during administration of the prodromal symptom section of the MAPMISS, women were reminded of the definition of prodromal symptoms, i.e. new onset or increase in intensity and/or frequency of a symptom(s) prior to the MI and then a return to previous levels after the MI.⁸ The reminders assisted in capturing new and worsening symptoms.

Setting and Subjects

Data were collected from 15 sites in eight states from 1999 to 2005. Sites were primarily in the Southern region and included both rural and urban settings. Subjects were a nonprobability sample of women diagnosed with confirmed MI (ICD-9 codes 410.0 to 410.9). In addition to having a documented first-time MI, all women in the original studies were aged 21 years or older, cognitively intact, English or Spanish speaking, self-identifying as black, Hispanic or white and with telephone access.

To determine cognition, each woman also completed the Short Orientation-Memory-Concentration (SOMC) Test, a six-item scale used to screen for changes in cognition.¹⁴ An advantage of the SOMC is that it is relatively culturally unbiased and it has been validated against neuropathology.¹⁵ Scores on the six-item test were positively correlated with plaque counts (an indication of impaired cognition) obtained from the cerebral cortex of 38 subjects at autopsy ($r = 0.60$, $p < 0.001$). Scores on the SOMC range from 0 to 28 with zero indicating no impairment.¹⁵ Optimum sensitivity and specificity, i.e., 88% and 94%, are achieved with a 10/11 cut point, giving an 11% false positive rate.¹⁶ However, because cut points as high as 22 may indicate cognitive impairment,¹⁵ this study used a cut point of 16 to balance adequate sensitivity and specificity with optimal study enrollment. Davous, Lamour, Debrand and Prondot¹⁶ reported that a cutoff score of 16 had 100% specificity and 70% sensitivity for detecting dementia, supporting the selection of this cut-off point.

We analyzed data both for the entire study sample ($N = 1270$) and also for those who were postmenopausal at the time of their MI ($n = 1169$) to minimize the confounding of prodromal sleep disturbance and sleep disturbance related to menopause. In the original studies, approval was secured from the committee for protection of human subjects at each site; eligible women were contacted by telephone, gave consent, and were screened. We obtained additional human subjects approval for this analysis of de-identified data.

Data Source

The MAPMISS contains questions on the frequency and severity of prodromal and acute symptoms of MI, delays in seeking treatment, general health, comorbidities and risk factors, medications, demographics, work history, household characteristics, family history, education, and socioeconomic status.⁶ In the current analysis, we focused on sleep disturbance and changes in cognition (thinking and remembering) as prodromal symptoms, i.e., symptoms which became more frequent and/or severe prior to the MI and resolved afterwards.¹⁷ (Variables measured are listed in Table 1). The MAPMISS has high content validity and acceptable test-retest reliability. When 90 women were retested 7 to 14 days

after an initial MAPMISS survey, the average kappa of prodromal symptoms was 0.49. The kappa for the prodromal sleep disturbance question was higher, at 0.57 but it was slightly lower for change in cognition, kappa = 0.42. The mean prodromal score at time 1 was 23.80 (SD = 24.24); the mean score at time 2 was 26.79 (SD = 30.52) with a Pearson correlation, $r = 0.72$; $p < 0.01$ indicating measurement stability.¹⁷

The presence of sleep disturbance was measured as a dichotomized variable. Sleep disturbance severity was measured with a scale constructed from subject responses to a MAPMISS item on presence, intensity, and frequency. A sleep disturbance severity score was calculated by multiplying reported intensity (mild, medium, severe) by seven levels of frequency (from less than monthly to daily). The range of scores for the constructed scale was 0 to 21, with 21 indicating severe daily sleep disturbance.

Change in cognition was measured with a similarly constructed scale based on responses to a MAPMISS item on changes in thinking or remembering. A score of 21 indicated severe daily problems in thinking or remembering. Covariates were measured as binary variables and were derived from MAPMISS items on comorbidities, risk factors, and medications; we included demographic characteristics as well (see Table 1). Medications included in the model were those prescribed prior to MI and included anti-hypertensives, diuretics, and psychotropic medications.

Statistical Methods

Preliminary analyses focused on descriptive statistics to characterize the sample and determine the prevalence of sleep disturbance. The prevalence of cardiovascular risk factors by ethnic group was examined using Chi square test, followed by Bonferroni adjusted post-hoc comparisons to identified racial groups that differed significantly. Linear models were used to examine the correlates of sleep disturbance severity and to compare sleep disturbance severity in different racial groups, adjusting for covariates. Unconditional logistic regression was used to estimate odds ratios at a 95% confidence interval for the associations between the presence of sleep disturbance and other prodromal symptoms, comorbidities, risk factors, and medications. The most parsimonious logistic regression models were selected using the best subset method while retaining race, age, BMI and educational level.¹⁸

Results

The average age of the women in the MAPMISS database was 64.79 (± 12.9); (range: 24–97). They were racially diverse (43% black, 15% Hispanic, and 42% white). The great majority (84.7%) were over the age of 50. Many had less than a high school education (44.4%), 29.5% had a high school education, and 26.1% college or higher. The mean body mass index (BMI) of subjects was 29.8 (± 7.0) and the median BMI was 28.3.

The majority of subjects had multiple cardiac risk factors: high cholesterol (64.3%), hypertension (78.3%), family history of cardiovascular disease (92.0%), exposure to secondhand smoke (62.4%), and no exercise for 6 months before the MI (55.4%). Table 2 on cardiovascular risk factors by ethnic group shows that certain racial groups were more likely to have particular risk factors (e.g., high diabetes prevalence among black and Hispanic women, greater family history of CVD among white women, and less smoke exposure among Hispanic women).

Because women in the original study were asked to identify only new symptoms or a worsening of existing symptoms prior to the MI, the sleep disturbance reported by the women was either new or had increased in intensity and or frequency. McSweeney and

colleagues⁸ found that women in all ethnic groups reported sleep disturbance, but they did not examine the characteristics of women who reported this symptom.

This secondary analysis confirmed that some degree of prodromal sleep disturbance was common in all ethnic groups (50.2% overall; 52.1% black; 50.5% Hispanic; and 48.2% white), and differences in prevalence between ethnic groups were not significant after adjusting for comorbidities, age, education, and BMI. However, the 638 women reporting prodromal sleep disturbances were significantly older ($p < 0.03$) and heavier ($p < 0.001$) than other women (Table 3). Their mean sleep disturbance severity score was 11.21 (SD = 6.89). Black women and Hispanic women had similar sleep disturbance severity scores (10.93 and 10.94, respectively), and the sleep disturbance score for white women was slightly, although not significantly, higher (11.6). There was no significant difference in sleep disturbance scores for women over 50 years of age and those under age 50; however, obese women (BMI > 30) had higher sleep disturbance scores than non-obese women ($p = 0.0127$).

Table 4 shows the odds ratios and corresponding 95% confidence intervals (CI) for the most parsimonious logistic regression model of the associations between other prodromal symptoms such as anxiety and headaches, co-morbid conditions, risk factors, and medications and the presence of sleep disturbance. The model also included race, age, BMI, and educational level as covariates. Among the 1270 women, eight variables were retained in the final model as significantly associated with increased risk of sleep disturbance. Anxiety and unusual fatigue were the two strongest predictors, followed by leg pain and change in thinking and remembering. Back pain, arm pain and headaches were also significantly associated with increased sleep disturbance, independent of the other factors. Since sleep disturbance may be related to menopause, we also conducted analyses of those women who were post-menopausal ($n = 1169$); results were similar to those for the entire sample (Table 5). Because the strong association of changes in thinking and remembering with sleep disturbance was unexpected, we examined this further in a logistic regression model that included only race, age, BMI, and educational level as covariates. We found that women reporting severe changes in cognition were nearly three times as likely to report sleep disturbances as women reporting no change or only mild change in thinking and remembering (adjusted OR= 2.69; 95% CI: 1.73, 4.16 for entire cohort, and adjusted OR=2.85; 95% CI: 1.77, 4.58 for post-menopausal women only).

Discussion

This study expands on previous research on prodromal symptoms of MI in women.^{5,7,8,19} Our analysis found that subjective report of sleep disturbance preceding MI was highly prevalent in women of all races. Both pre and post-menopausal women frequently complained of sleep disturbance prior to an MI. In addition to known risk factors - anxiety, fatigue and pain, changes in thinking and remembering were strongly associated with prodromal sleep disturbance. Taken together, our findings suggest that when women with cardiovascular risk factors (such as increased BMI) report sleep disturbance accompanied by changes in thinking and remembering, anxiety, fatigue and pain, sleep disturbance may be an important warning symptom of impending MI.

Since over 50% of women in all ethnic groups reported prodromal sleep disturbance, this needs to be examined in greater depth. Sleep disturbance is a complex problem and the general question in the MAPMISS did not identify the type of disturbance or the characteristics of the disturbance, for example difficulty falling asleep, frequent arousals, duration of sleep, etc. Nevertheless, despite the limitations of a single question related to

sleep, our study provides valuable information about the characteristics of the women who were most likely to report experiencing incremental sleep disturbance prior to their MI.

Although relationships and causal pathways between MI and sleep disturbance are unclear, our findings are consistent with a growing body of evidence that suggests association of sleep disturbance with cardiovascular disease in women. It is well known that MI and sleep disturbance share many risk factors, such as inflammation.^{20–22} Additionally, observational studies of both men and women have shown inconsistent associations between short sleep, long sleep, sleep disruption, and cardiovascular status.^{23–25} One large ($N = 10,308$) prospective study found that short sleep (< 6 hours) and sleep disturbance were both associated with increased risk of cardiovascular disease in women as well as men (relative risk: 1.55, 95% confidence interval: 1.33–1.81).²⁴ However, another epidemiological study ($N = 6896$) of incident MI reported an adjusted hazard ratio of MI among women who slept 5 hours compared to women who slept 8 hours per night of 2.98 (95% CI, 1.48–6.03) but could not find an association in men.⁹ Also, the Whitehall II Study ($n = 4642$) found cross-sectional relationships between elevated interleukin-6 and high sensitivity C-reactive protein and short sleep durations in women, but not men.²⁶

In women, one of the most frequently reported prodromal symptoms of MI is unusual fatigue^{5,7,8,19,27} and prodromal sleep disturbance could be associated with this reported fatigue. This supposition is supported by Lindgren et al. who found that prodromal symptoms occurred in three clusters: (1) Classic Acute Coronary Syndrome (severe ischemic pain; 22%); (2) Weary (severe fatigue, sleep disturbance, and shortness of breath; 29%); and (3) Diffuse Symptoms (mild symptoms; 49%).⁷ Typically, sleep disturbances are associated with reports of excessive daytime sleepiness (the overwhelming need to sleep and inability to stay awake) or hypersomnia (sleeping unintentionally or at inappropriate times).²⁸ However, because the word “fatigue” does not have a standard definition, it is possible that persons feeling sleepy, tired, and/or weak could choose to use the word “fatigue.” The fatigue described by the women in MAPMISS was overwhelming and it interfered with their activities of daily living. In fact, some women reported being so tired that they could not make a bed without resting between making sides of the bed.^{4,6} One woman said, “Thinking back, I was tired more so than usual. I’d get home from work in the afternoon, and I wouldn’t do anything...I’d fall asleep for half an hour.”⁵ Although this description of fatigue may indicate something distinct from excessive daytime sleepiness or hypersomnia, future research should probe with questions about sleep, tiredness, and weakness to illuminate the relationships with MI.

There were some limitations to our analysis. First, retrospective report of sleep disturbance is subject to recall bias. Future studies would benefit from both objective and prospective measurements of sleep instead of relying on subjective retrospective reports. Second, we were unable to determine the presence of specific sleep disorders, such as obstructive sleep apnea (OSA) or restless legs syndrome, which might be present prior to MI and confer cardiovascular risk. For example, our findings that older age and higher BMI were associated with prodromal sleep disturbance are consistent with the possibility that OSA plays a role in this symptom. OSA is known to be highly prevalent in midlife women,²⁹ but we did not have objective measures of OSA available in this study. Third, our use of a single MAPMISS item to assess sleep disturbance could not begin to capture the complex dimensions of insomnia that might be collected with a more thoroughly validated instrument, such as the Pittsburgh Sleep Quality Inventory.³⁰ Fourth, changes in thinking and remembering, a key variable associated with sleep disturbance, was based on participants’ reports rather than objective, norm-based neuropsychological tests. Fifth, other physiologic markers known to be associated with short or disturbed sleep (e.g., markers of

inflammation)³¹ were not available in MAPMISS though these could help to explain the association between poor sleep and daytime fatigue.

Despite these limitations, this cohort of over 1250 women who experienced a documented index event (hospitalization for MI) were able to retrospectively describe their prodromal sleep symptoms. Understanding whether and when women's complaints of sleep disturbance indicate an impending MI could improve healthcare providers' ability to quickly refer women for definitive intervention. An expert Institute of Medicine panel has suggested that future studies should focus on causal pathways that take sex into consideration.³² Our data suggest that future studies should consider sleep patterns in women.

Implications for Practice and Research

Because poor sleep is linked with compromised cardiovascular health,^{23,33,34} as both a relatively stable risk factor and as a transitory prodromal symptom of MI, it is essential to improve clinicians' skills in assessing disturbed sleep in women at risk for a MI. Description of correlates of prodromal sleep disturbance can provide a foundation for developing clinical practice guidelines to assist primary care providers and female patients in their decisions regarding appropriate health care.³⁵ Further research is needed to determine what specific types and levels of sleep disturbance are most highly correlated with CHD.

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Abbreviation List

CHD	Coronary heart disease
MI	Myocardial Infarction
MAPMISS	The McSweeney Acute and Prodromal Myocardial Infarction Symptom Survey

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Table 1

Data Source for Analyses

Variable	Data Source	MAPMISS text:
		Please tell me what other general symptoms you had. For each symptom ask: How severe was it? How often did it occur?
Sleep Disturbance	Item 4a (Sleep Disturbance)	Sleep disturbance? (0=No, 1=Mild, 2=Medium, 3=Severe). How often did it occur? (1= Less than monthly, 7 = daily).
Covariates	Item 4b (Change in Cognition)	Problems thinking or remembering? (0=No, 1=Mild, 2=Medium, 3=Severe) How often did it occur? (1=less than monthly - 7=daily).
	Items 5 – 11 (Comobidities)	Chest pain due to heart problems (angina)? Congestive heart failure? Chronic obstructive pulmonary disease? Depression or other emotional troubles? Chronic heart burn, stomach problems (GERD)? Chronic back pain? Chronic Joint problems?
	Items 14 – 23 (CHD Risk Factors)	Age 50 or older? Hypertension? Diabetes? Body Mass Index > 29? High cholesterol? Smoker? Second hand smoke exposure? Personal history of coronary heart disease? Family history of coronary heart disease? No exercise?
	Item 26 (Medications Prescribed prior to MI)	Drugs to lower blood pressure (Antihypertensives)? Water pills (Diuretics) Nerve pills (Psychotropic drugs)?
Descriptive Variables	Items 27 – 29 (Demographics)	Race Age Education

Table 2

Distribution of Cardiovascular Risk Factors among 1270 Women

	Black n = 545 (43%)	Hispanic n = 186 (15%)	White n = 539 (42%)	p- values
	n (%)	n (%)	n (%)	
Age > 50	438 (80.4) ^a	156 (83.9) ^{a,b}	481 (89.2) ^b	0.0003
BMI > 29	327 (60.0) ^a	70 (37.6) ^b	216 (40.1) ^b	<0.0001
Hypertension	471 (86.4) ^a	135 (72.6) ^b	389 (72.2) ^b	<0.0001
Diabetes	286 (52.5) ^a	87 (46.8) ^a	174 (32.3) ^b	<0.0001
High Cholesterol	357 (65.5) ^a	135 (72.6) ^a	325 (60.3) ^b	0.0080
Personal History of CHD	335 (61.5) ^a	132 (71.0) ^a	320 (59.4) ^b	0.0184
Family History of CHD	494 (90.6) ^a	158 (84.9) ^a	516 (95.7) ^b	<0.0001
Smoker	154 (28.3) ^a	19 (10.2) ^b	161 (29.9) ^a	<0.0001
Second-hand Smoke Exposure	345 (63.3) ^a	85 (45.7) ^b	363 (67.3) ^a	<0.0001
No Exercise	331 (60.7) ^a	78 (41.9) ^b	295 (54.7) ^a	<0.0001

Superscripts that differ indicate significant post hoc differences (Bonferroni adjusted $p < 0.05$)

Table 3

Proportions of Study Population With Sleep Disturbance by Race, Age and BMI

	No (n =632)	Yes (n =638)	<i>p</i> -value
Race			
White	51.76% (279)	48.24% (260)	reference
Black	47.89% (261)	52.11% (284)	0.2023
Hispanic	49.46% (92)	50.54% (94)	0.5884
Age			
< 50	42.56% (83)	57.44% (112)	reference
50	51.07% (549)	48.93% (526)	0.0288
Body Mass Index (BMI)			
29	54.34% (357)	45.66% (300)	reference
>29	44.86% (275)	55.14% (338)	0.0007

Table 4

Most Parsimonious Logistic Regression Model Evaluating the Association between Sleep Disturbance and all other Prodromal Symptoms, Co-morbid Conditions, Risk Factors, and Medications among 1270 women

	Odds Ratio (95% CI)*	p-value
Anxious	2.21 (1.71, 2.84)	<0.0001
Unusual fatigue	2.16 (1.62, 2.89)	<0.0001
Leg pain	2.10 (1.29, 3.43)	0.0030
Arms ache	1.56 (1.14, 2.12)	0.0054
Change in thinking and remembering	1.47 (1.12, 1.94)	0.0056
Back pain	1.35 (1.03, 1.78)	0.0318
Headaches	1.54 (1.03, 2.29)	0.0338
Gastroesophageal Reflux Disease (GERD)	1.29 (1.00, 1.67)	0.0480

* Race, age, BMI and educational level were also retained in the final model

Table 5

Most Parsimonious Logistic Regression Model Evaluating the Association between Sleep Disturbance and all other Prodromal Symptoms, co-morbid Conditions, Risk Factors, and Medications among 1169 post-menopausal women

Symptom	Odds Ratio (95% CI)*	p-value
Anxious	2.18 (1.67, 2.84)	<0.0001
Unusual fatigue	2.41 (1.77, 3.27)	<0.0001
Leg pain	2.45 (1.44, 4.18)	0.0010
Change in Cognition	1.51 (1.13, 2.01)	0.0057
Arms ache	1.57 (1.13, 2.17)	0.0067
Back pain	1.39 (1.05, 1.85)	0.0228
Headaches	1.55 (1.01, 2.37)	0.0451

* Race, age, BMI and educational level were also retained in the final model