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Psychosocial predictors of long-term mortality among women with suspected myocardial ischemia: the NHLBI-sponsored Women's Ischemia Syndrome Evaluation

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Abstract

This paper evaluated long-term associations between psychosocial factors and premature mortality among women with suspected coronary artery disease (CAD). We tracked total mortality events over a median 9.3 years in a cohort of 517 women [baseline mean age = 58.3 (11.4) years]. Baseline evaluations included coronary angiography, psychosocial testing, and CAD risk factors. Measures included the Spielberger Trait Anxiety Scale, Beck Depression Inventory, self-rated health, and Social Network Index. Cox regression analysis was used to assess relationships. Covariates included age, CAD risk factors, and CAD severity. BDI scores (HR 1.09, 95 % CI 1.02–1.15), STAI scores (HR .86, 95 % CI .78–.93), and very good self-rated health (relative to the poor self-rated health group; HR .33, 95 % CI .12–.96) each independently predicted time to

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Compliance with Ethical Standards

Conflict of interest: Thomas Rutledge, Tanya S. Kenkre, Diane V. Thompson, Vera A. Bittner, Kerry Whittaker, Jo-Ann Eastwood, Wafia Eteiba, Carol E. Cornell, David S. Krantz, Carl J. Pepine, B. Delia Johnson, Eileen M. Handberg and C. Noel Bairey Merz declare that they have no conflict of interest.

Human and animal rights and Informed consent: All procedures followed were in accordance with ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

mortality outcomes in the combined model. SNI scores (HR .91, 95 % CI .81–1.06) and other self-rated health categories (i.e., fair, good, and excellent categories) were not significant mortality predictors after adjusting for other psychosocial factors. These results reinforce and extend prior psychosocial research in CAD populations.

Keywords

Coronary artery disease; Prospective; Psychological; Stress; Women

Introduction

Among patients with coronary artery disease (CAD), psychosocial factors are consistent predictors of premature morbidity and mortality (Everson-Rose & Lewis, 2005; Rosengren et al., 2004). Depression is arguably the most empirically validated of these factors. Reviews of mostly short and medium terms follow-up periods suggest that the presence of depression by self-report questionnaires or diagnostic interviews is associated with significantly higher rates of adverse events in patients with CAD (Barth, Schumacher, & Herrmann-Lingen, 2004; Burg et al., 2013; Van Melle et al., 2004). Other well-established but less studied psychosocial predictors of cardiovascular events in CAD populations include anxiety (Tully, Cosh, & Baune, 2013; Watkins et al., 2013), social networks (a measure of the size and diversity of a person's social circle; Cohen et al., 1997; Uchino et al., 2013), and self-rated health (a single item rating of overall health; Ernsten et al., 2011; Idler & Benyamini, 1999). Observational studies such as the Women's Health Initiative (WHI; Smoller et al., 2009), Nurses' Health Study (NHS; Whang et al., 2009), and Women's Ischemia Syndrome Evaluation (WISE; Handberg et al., 2013) have also demonstrated the importance of psychosocial factors for understanding the health of women. Psychosocial factors may influence the development and/or progression of CAD through multiple pathophysiological mechanisms (Steptoe & Kivimäki, 2013; Wei et al., 2014); this has spurred a growing field of interventional research on potential benefits of treating psychosocial factors in patients with CAD (Dickens et al., 2013; Rozanski, 2014; Reid, Ski, & Thomp, 2013).

This report describes new long-term results from the WISE in which we followed a cohort of women with suspected myocardial ischemia to track total mortality events over a median 9.3 year interval and included an extensive battery of psychosocial, CAD risk factor, and coronary angiography assessments as predictors. Only a small fraction of prior research linking psychosocial factors such as depression symptoms to mortality examines relationships beyond a few years (e.g., Barth et al., 2004; Van Melle et al., 2004) and long-term relationships between psychosocial factors and mortality may not mirror shorter-term relationships because demographic (e.g., age) and biomedical factors exert an increasing influence as the age of the sample and length of follow-up extends. The study builds upon previous WISE reports (e.g., Eastwood et al., 2013; Rutledge et al., 2014; Whittaker et al., 2012) in two ways: (1) The extended follow-up period in the current study (median 9.3 years here versus a maximum median of 5.9 years in prior WISE reports); (2) The prediction of mortality using a combination of established psychosocial measures known to predict

shorter-term mortality and CAD outcomes (depression and anxiety symptoms, social network size, and self-rated health).

Methods

Participants

Women (18 + years old) undergoing a clinically indicated coronary angiogram (completed at baseline only) for suspected myocardial ischemia were recruited for the WISE from four sites (University of Alabama at Birmingham; University of Florida, Gainesville; University of Pittsburgh; and Allegheny General Hospital, Pittsburgh; Merz et al., 1999). The purpose of the WISE was to improve the understanding and diagnosis of ischemic heart disease in women. The protocol has been described elsewhere (Merz et al., 1999). Briefly, exclusion criteria included major comorbidity compromising follow-up, recent myocardial infarction or revascularization procedure, significant valvular or congenital heart disease, and language barrier. All participants provided written informed consent, and all sites obtained Institutional Review Board approval.

The WISE Angiographic Core Laboratory (Rhode Island Hospital, Providence, RI) performed quantitative and qualitative analyses of coronary angiograms, masked to all other subject data (Sharaf et al., 2013). Luminal diameter was measured at all stenoses and at nearby reference segments using an electronic cine projector-based “cross-hair” technique (Vanguard Instrument Corporation, Melville, NY). Each participant received a continuous CAD severity score based on angiogram results and a modified Gensini score (hereafter referred to as a CAD severity score). This severity score was developed with points assigned according to the category of severity of the stenosis (0–19, 20–49, 50–69, 70–89, 90–98, 99–100) adjusting for partial and complete collaterals. Scores were further adjusted according to lesion location, with more proximal lesions receiving a higher weighting factor (Sharaf et al., 2013). CAD severity scores were logarithmically transformed to normalize the distribution.

Clinical events

We completed a National Death Index (NDI) search to determine mortality status for participants at the final follow-up date. The NDI is a centralized database of death records established by the National Center for Health Statistics and available to approved researchers. For study purposes, we matched participants to NDI records using Social Security numbers to confirm mortality status and mortality dates.

Modifiable risk factors

Major CVD risk factors assessed at baseline included history of smoking, hypertension, dyslipidemia, and diabetes. We defined hypertension, dyslipidemia, and diabetes status for this report dichotomously based upon participant’s report of a history of diagnosis or treatment for these conditions. Participants reported their smoking history as never smokers, previous smokers, or current smokers.

Psychosocial measures

Women completed a battery of psychosocial measures at study baseline, with the current sample reflecting participants with complete scores on each of the psychosocial measures ($N = 517$). The measures included: (1) Beck Depression Inventory (BDI), a 21-item measure of depressive symptom severity validated with CAD samples (Beck, 1978); (2) Spielberger Trait Anxiety Scale [10-item subscale; STAI (Spielberger, Gorsuch, & Lushene, 1970)]; (3) Self-rated health, a single item measure assessing participant's global rating of their health including categories of poor, fair, good, very good, and excellent [SRH (Jylha, 2009)]; (4) Social Network Index [SNI (Cohen et al., 1997)], a 12-item measure of social network size including relationships domains such as friends, coworkers, marital status, close family and children, and participation in volunteer or organizational activities.

Statistical analyses

We completed descriptive and bivariate statistical comparisons using means, standard deviations, correlations, and t tests. We used Cox regression methods to evaluate prospective relationships between the four psychosocial measures and time to mortality outcomes over the median 9.3 year follow-up interval, with hazard ratios representing the increase in mortality per point on the BDI, STAI, and SNI questionnaires. Based on a sample size of 517, a two sided alpha level of .05, and a minimum effect size of a 25 % change in mortality risk in association with the psychosocial measures, statistical power levels $>.90$. We combined current and former smokers from the smoking history question, using the never smokers as the reference category for this variable. For the self-rated health regression model, we used the "Poor" category as the reference group in the analyses. In our primary predictor analyses, we computed a combined Cox regression model including demographic variables, CAD covariates and CAD severity scores, and all four of the psychosocial questionnaire measures. All statistical analyses were completed using SPSS software, version 17.0 (SPSS Inc., Chicago, IL, USA), with statistical significance declared at $p < .05$.

Results

Among a total of 936 women enrolled in WISE between 1996 and 1999, 517 had complete questionnaire data on the STAI, BDI, SNI, and self-rated health measures (questionnaires were phased in during the start of the WISE study, resulting in the first several hundred participants enrolled in the first year not completing these measures). Table 1 provides a summary of participants according to their status on demographic, psychosocial, CAD risk factors, and CAD severity scores. CAD risk factors were common in the sample, including high rates of diabetes (24.9 %), dyslipidemia (50.6 %), hypertension (58.9 %), and smoking history (52.9 %). We performed group comparisons of age, CAD risk factors and CAD severity between the subsamples with psychosocial data and the full WISE sample without evidence of statistically significant differences. There were 85 (16.7 %) mortality events in the WISE sample over follow-up.

In the WISE sample, 45.3 % scored ≥ 10 on the BDI during their baseline visit. Scores on the psychosocial measures were significantly correlated. BDI scores overlapped highly with STAI scores ($r = .69$, $p < .001$), moderately with self-rated health status ($r = -.41$, $p < .001$)

and modestly with SNI scores ($r = -.20, p < .001$). Better self-rated health was also inversely correlated with STAI scores ($-.30, p < .001$) and smaller SNI scores ($r = -.30, p < .001$).

Psychosocial factors and mortality

In the combined regression model—using time to mortality events as the dependent variable—we simultaneously included age, CAD covariates, CAD severity scores, and all four of the psychosocial measures as predictors. The complete model is shown in Table 2. In this combined model, covariates including smoking history (HR 1.7, 95 % CI 1.1–2.8) and CAD severity scores (HR 1.8, 95 % CI 1.1–3.0) were significant predictors of time to mortality outcomes. Among the psychosocial measures, BDI scores (HR 1.09, 95 % CI 1.02–1.15), STAI scores (HR .86, 95 % CI .78 to .93), and very good (relative to the poor self-rated health group) self-rated health (HR .33, 95 % CI .12 to .96) were each associated with mortality outcomes independent of covariates and other psychosocial measures. SNI scores (HR .91, 95 % CI .81–1.06) and other self-rated health categories (i.e., fair, good, and excellent categories) were not significant predictors.

Discussion

These new data described psychosocial predictors of longer-term mortality outcomes in the WISE cohort. Specifically, the current data document evidence of statistical relationships between social network size, self-rated health, trait anxiety symptoms, and depressive symptoms with mortality over a median 9.3 year interval. In the combined Cox regression model including all covariates and psychosocial measures, anxiety (inversely) and depression symptoms and self-rated health were each significant predictors of time to mortality among women in WISE. Overall, these results are consistent with the larger literature based on comparatively shorter term outcomes in demonstrating the value of psychosocial factors in predicting objective health event risk while reinforcing future efforts to examine these factors as potentially overlapping constructs rather than as independent markers of distress.

Over shorter follow-up intervals, previous WISE psychosocial publications employed psychosocial measures in the prediction of combined mortality and CVD events (Eastwood et al., 2013; Rutledge et al., 2014; Whittaker et al., 2012). For example, BDI scores, antidepressant use, and a history of depression treatment were each adversely related to mortality and CVD events (heart failure, myocardial infarction, and stroke) in previous WISE research (Rutledge et al., 2006; Vaccarino et al., 2008, 2007), and both anxiety and depression symptoms were linked to higher rates of CVD risk factors and increased healthcare costs (Rutledge et al., 2013, 2009). This is the first psychosocial WISE report to focus exclusively on total mortality events as the extended follow-up period provided sufficient statistical power to focus exclusively on this most important endpoint. Prior psychosocial reports from WISE included mortality and CVD events over time points not exceeding a median 5.9 years, versus the median 9.3 year follow-up interval in the current report. It is also important to note that the current report now includes deaths reported from the NDI search, a methodological improvement compared to previous WISE publications wherein some participants had previously been “censored” because they were lost to follow-

up. Thus, this paper represents the highest quality mortality information in relation to psychosocial factors available from the WISE.

The relationships observed in the separate covariate adjusted models between self-rated health with total mortality are consistent with the existing research linking smaller social networks and poorer self-rated health to a higher risk of adverse health outcomes (e.g., Idler & Benyamini, 1999). The durability over time of both of self-rated health as a predictor of mortality is remarkable, dating back at least to the Human Population Laboratory survey of Alameda County residents in 1965, where self-rated health predicted premature mortality risk in the cohort (Berkman & Syme, 1979; Kaplan & Camacho, 1983). The mechanisms accounting for the relationship between self-rated health and outcomes such as premature mortality are speculated to involve emotional and behavioral components, but remain unproven (Jylha, 2009).

Our results are also consistent with the results from a 2015 report focused on cardiac catheterization characteristics among more than 3000 female armed forces Veterans (as opposed to the civilian WISE sample; Davis et al., 2015). Similar to the WISE results reported here, female Veterans obtaining cardiac catheterization in the latter study showed low rates of obstructive CAD but relatively high rates of psychiatric comorbidities such as depression and anxiety (e.g., 55.3 and 20.1 % of the women in the latter sample met criteria for depression and posttraumatic stress disorder based on medical chart review). In the WISE sample, >45 % reported elevated depressive symptoms (≥ 10 on the BDI) and over 20 % (Rutledge et al., 2013) reported clinical anxiety as indicated by anxiolytic medication. The results from both studies suggest that depression and anxiety conditions are common in this clinical population and may play an important role in the clinical presentation dynamics of women undergoing coronary angiogram testing.

The implications of these results should be understood in the context of both past and present WISE findings. WISE publications consistently demonstrate the importance of anxiety and depressive symptoms in forecasting women's health behaviors and subsequent healthcare utilization and risk of health outcomes over follow-up periods now approaching 10 years. Psychosocial measures such as those studied here overlapped substantially in WISE and in many previous studies, leading some researchers to employ statistical methods such as factor analysis to synthesize data across measures into a smaller number of factors for health predictions (e.g., Whittaker et al., 2012). The inverse relationship between anxiety and mortality differs from the often positive relationship between these variables observed in general population studies (e.g., Tully et al., 2013) but is consistent with previous WISE papers and reflects the distinct characteristics of the WISE cohort. Unlike general population studies, women in WISE were recruited based upon suspected cardiac symptoms but had low rates of obstructive CAD, suggesting that anxiety may have contributed to the symptoms reported by many women or their motivation to participate in a study investigating suspected myocardial ischemia. In addition to mortality events, higher anxiety was also inversely correlated with the presence of CAD on angiogram testing (Rutledge et al., 2013). Because CAD severity was strongly and positively associated with premature mortality but negatively associated with anxiety, the relationship between anxiety and premature mortality was also not surprisingly negative. However, this should not be interpreted that anxiety was

“protective” for mortality; only that anxiety was likely a primary factor that led many of the WISE women to be enrolled through its effects on cardiac symptom presentation.

Limitations

Psychosocial measures were a secondary design feature in the WISE, resulting in a delayed introduction of most of the psychosocial instruments into the baseline evaluation. The result was that about a third of the total WISE sample did not complete some of the psychosocial measures and, therefore, leave us unable to generalize the reported results to all WISE participants. Similarly, the psychosocial measures in WISE primarily included questionnaires assessing symptom severity and should not be interpreted as evidence of psychiatric disorders drawn from structured diagnostic interviews. It is possible that psychiatric disorders captured using gold standard interviews may have revealed stronger relationships with the mortality outcomes. In the WISE protocol, women completed the psychosocial measures only at baseline, a factor of perhaps particular importance in the current WISE report due to the elongated period of follow-up (a median 4.4 years of additional follow-up relative to prior WISE papers) over which we investigated events. The reliability and validity of psychosocial stress measures probably decreases with the passage of time, raising the possibility that, for example, the different pattern of associations that we observed between the psychosocial measures reported here and total mortality events relative to previous WISE papers was at least partly a result of diminishing psychometric qualities from the instability of self-reported symptoms over time.

We also recommend caution comparing psychosocialmortality relationships in the WISE cohort to similar findings from other prospective studies. WISE enrollment criteria limit our ability to make generalizations to men or even to similarly aged women with different CAD risk profiles. WISE participants were recruited in tertiary care centers for evaluation of suspected myocardial ischemia. The clinical characteristics of the WISE sample were intended to resemble as closely as possible women undergoing routine coronary assessments. However, these same characteristics set the WISE sample apart from asymptomatic women or from samples of women with established CAD (women in WISE had symptoms of ischemia but were found to have low rates of CAD on angiogram testing).

Summary

This paper described relationships between multiple established psychosocial predictors of health outcomes—including measures of anxiety and depression symptoms, self-rated health, and social network size—and total mortality outcomes in a sample of women experiencing symptoms consistent with myocardial ischemia followed for a median 9.3 years of follow-up. In a combined model including multiple established psychosocial predictors of cardiac outcomes, anxiety and depressive symptoms and self-rated health independently predicted time to mortality events after adjusting for CAD severity and demographic and CAD covariates. Our results are the first to describe relationships between psychosocial status and total mortality in the WISE cohort, and extends follow-up period by 60 % (5.9–9.3 median years of follow-up) compared to previous WISE publications reporting on psychosocial measures. The results offer further evidence supporting the role of

psychosocial factors in the long-term health of women and suggest that these measures may have independent and overlapping values as predictors. These findings may benefit future research by highlighting psychosocial factors most relevant to women in cardiology settings.

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Table 1

Demographic, CAD risk factors, and psychosocial factors among WISE participants Characteristic WISE sample (N = 517)

Characteristic	WISE sample (N = 517)
Age, M (SD)	58.3 (11.4)
Race (%)	
African American	17.4
Non-Hispanic white	81.1
Other	1.4
High school graduate or above (%)	78.6
Current/former/Never smoker (%)	20.2/33.0/46.8
History of hypertension (%)	58.9
History of diabetes (%)	24.9
History of dyslipidemia (%)	50.6
CAD severity score [Mean (SD)]	13.3 (12.8)
Beck depression inventory [mean (SD)]	10.4 (8.2)
Use of antidepressants (%)	18.2
History of depression treatment (%)	42.2
Spielberger trait anxiety inventory [mean (SD)]	19.0 (5.8)
Social Network Index [mean (SD)]	6.5 (1.8)
Self-rated health, n (%)	
Poor	97 (10.5)
Fair	269 (29.1)
Good	328 (35.5)
Very good	177 (19.1)
Excellent	54 (5.8)

M mean, *SD* standard deviation, *CAD* coronary artery disease

Table 2

Cox regression results summarizing prospective relationships between anxiety and depression symptom measures with total mortality over 9.3 years in the WISE sample (N = 517)

Psychosocial factor	Hazard ratio	95 % confidence interval
Age	1.03	.99–1.1
CAD severity	1.8	1.1–3.0
Diabetes history	1.4	.70–3.0
Dyslipidemia history	.97	.44–2.1
Hypertension history	1.8	.74–4.1
Smoking history	1.7	1.1–2.8
BDI	1.09	1.02–1.15
STAI	.86	.78–.93
SNI	.85	.67–1.1
Self-rated health ^a excellent	.34	.10–1.2
Self-rated health very good	.33	.12–.96
Self-rated health good	.27	.10–1.1
Self-rated health fair	.43	.16–1.1

BDI beck depression inventory, *STAI* Spielberger trait anxiety scale, *SNI* social network index

^aThe Poor Self-rated health group served as the reference category