

Social Integration and Mortality in Patients With Coronary Heart Disease: Findings From the Heart and Soul Study

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Objective: To determine why lower social integration predicts higher mortality in patients with coronary heart disease (CHD). **Methods:** The association between social integration and mortality was examined prospectively in 1019 outpatients with stable CHD from the Heart and Soul Study. Baseline social integration was assessed with the Berkman Social Network Index. Cox proportional hazards models were used to determine the extent to which demographic and disease-relevant confounders and potential biological, behavioral, and psychological mediators explained the association between social integration and mortality. **Results:** During a mean (standard deviation) follow-up period of 6.7 (2.3) years, the age-adjusted annual rate of mortality was 6.3% among socially isolated patients and 4.1% among nonisolated patients (age-adjusted hazard ratio [HR] = 1.61, 95% confidence interval [CI] = 1.26–2.05, $p < .001$). After adjustment for demographic and disease-relevant confounders, socially isolated patients had a 50% greater risk of death than did nonisolated patients (HR = 1.50, 95% CI = 1.07–2.10). Separate adjustment for potential biological (HR = 1.53, CI = 1.05–2.25) and psychological mediators (HR = 1.52, CI = 1.08–2.14) did not significantly attenuate this association, whereas adjustment for potential behavioral mediators did (HR = 1.30, CI = 0.91–1.86). C-reactive protein and hemoglobin A1c were identified as important biological and omega-3 fatty acids, smoking, and medication adherence as important behavioral potential mediators, with smoking making the largest contribution. **Conclusions:** In this sample of outpatients with baseline stable CHD, the association between social integration and mortality was largely explained by health-related behavioral pathways, particularly smoking. **Key words:** coronary artery disease, epidemiology, social integration, mortality, observational study, survival analysis.

ACE inhibitors = angiotensin-converting enzyme inhibitors; **ARB** = angiotensin II receptor blocker; **CHD** = coronary heart disease; **CI** = confidence interval; **CRP** = C-reactive protein; **CV** = cardiovascular; **HbA1c** = glycated hemoglobin; **HDL** = high-density lipoprotein; **HR** = hazard ratio; **SI** = social integration; **SNI** = Social Network Index; **WBC** = white blood cell count.

INTRODUCTION

Lack of social integration (SI) is a robust predictor of morbidity and mortality (1). SI, that is, participation in a broad range of social relationships (2), also referred to as structural social support (3,4), is quantified based on indicators of marital status, number of social relationships (network size), frequency of contact, and membership in community groups. It has been demonstrated that people with lower SI die earlier than do those with higher SI, both in community (1) and higher-risk samples, such as patients with coronary heart disease (CHD) (4,5).

Although the link between low SI and increased risk of all-cause mortality has been repeatedly shown, the mechanisms that explain this association are not well understood. SI may affect mortality through biological, behavioral, and psychological pathways (3). For example, low SI is associated with poor biological outcomes that are known risk factors for mortality, including perturbed endocrine and autonomic nervous system function, as demonstrated by elevated catecholamine levels (6), elevated chronic low-grade inflammation (7), and increased occurrence of systemic diseases (8–10). Low SI is also associated with behaviors that increase mortality risk: increased likelihood of smoking (11), physical inactivity (12), and medication nonadherence (13). Low SI is further known to

lead to negative psychological states, such as anxiety or depression (14,15) that, in turn, may influence health either through biological processes or adverse health behaviors (16). Because few studies have used adjusted statistical models to account for confounders and potential mediators (3), the specific mechanisms that link SI and mortality remain unclear.

In a prospective cohort study of 1024 patients with stable CHD, we sought to determine whether demographic and disease-relevant confounders and potential biological, behavioral, and psychological mediators explain the association between SI and mortality.

METHODS

Participants

We evaluated patients from the Heart and Soul Study, a prospective cohort study of psychosocial factors and health outcomes in patients with stable CHD. Details of the study have been described previously (17). Between September 2000 and December 2002, 1024 patients with stable CHD were recruited from 12 outpatient clinics in northern California. One patient did not complete the SI questionnaire and 4 were lost due to follow-up, leaving 1019 patients. The appropriate institutional review boards approved the study protocol. All patients provided written informed consent.

Procedure

Patients completed a baseline examination that included medical history, health and psychiatric interviews, questionnaires, blood samples, echocardiogram, exercise treadmill test, and 24-hour urine collection. Annual telephone follow-up interviews with patients or their proxies were conducted to monitor survival. For any reported death, two independent blinded adjudicators reviewed medical records, death certificates, and coroner's reports. In case of disagreement, a third blinded adjudicator reviewed the event and determined the outcome.

Measures

Predictor Variable: SI

The Berkman Social Network Index (SNI) (18) is a validated self-report questionnaire that assesses a person's degree of SI by marital status, sociability (number of close friends and relatives and frequency of contact), church membership, and nonreligious group memberships. The index gives more weight to intimate contacts than church and group memberships and classifies individuals into low, medium, medium-high, and high levels of SI (19).

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Outcome Variable: All-Cause Mortality

Death over a maximum follow-up period of 10 years was determined by death certificates and coroner's report.

Candidate Confounding Variables

Theoretically relevant confounders, including demographic patient characteristics, comorbid conditions, cardiac disease severity and risk factors, and medication use, were measured at baseline. Sex, race, education, and income were determined by self-report. Weight, height, and waist and hip circumferences were measured for calculating body mass index (in kg/m²) and waist-to-hip ratio. Medical history was determined by self-report. Fasting serum samples were obtained to measure serum creatinine. Left ventricular ejection fraction was obtained from echocardiography using an Acuson Sequoia Ultrasound System (Mountain View, CA) with a 3.5-MHz transducer. The presence of inducible cardiac ischemia was determined through exercise treadmill testing with stress echocardiography (20). Systolic and diastolic blood pressures were measured in a supine position after 5 minutes of rest. To determine medication use, patients were instructed to bring their medication bottles to the study appointment. Study personnel recorded all current medications, except nutritional supplements.

Potential Biological Mediators

Stress-related, inflammatory, glycemic, and cholesteric biomarkers were measured at baseline. Cortisol, epinephrine, and norepinephrine excretion were measured based on 24-hour urine samples (21). Cortisol was analyzed using either a radioimmunoassay or high-performance liquid chromatography/tandem mass spectrometry. Epinephrine and norepinephrine were measured using gas chromatography/mass spectrometry at the Associated Regional and University Pathologists, Inc (Salt Lake City, UT). High-sensitivity C-reactive protein (CRP), glycated hemoglobin (HbA1c), white blood cell count (WBC), low- and high-density lipoprotein (HDL) cholesterol, and triglycerides were measured in fasting venous blood samples. High-sensitivity CRP was measured using either the Roche (Indianapolis, IN) Integra assay or the Beckman (Galway, Ireland) Extended Range assay (22).

Potential Behavioral Mediators

Relevant behavioral variables including diet, alcohol use, subjective sleep quality, medication adherence, and physical activity were estimated from self-report items at baseline, except omega-3 fatty acid level (an indicator of dietary intake), which was quantified as blood levels of docosahexaenoic acid and eicosapentaenoic acid measured by capillary gas chromatography as the percentage composition of total fatty acid methyl esters in the red blood cell membranes.

Alcohol use was assessed with the Alcohol Use Disorders Identification Test, a validated three-item screening questionnaire that evaluates alcohol use frequency and quantity (23). Regular alcohol use was defined as a score of at least 4 (range, 0–12), which indicates a positive screen for alcohol dependence. Smoking was assessed by self-report questionnaire.

Subjective sleep quality was assessed with the overall sleep quality item from the Pittsburgh Sleep Quality Index (24). Poor sleep quality was defined as "fairly bad" or below.

Medication adherence was assessed using the question, "In the past month, how often did you take your medications as the doctor prescribed?" Responses included the following: "all of the time (100%)," "nearly all of the time (~90%)," "most of the time (~75%)," "about half of the time (~50%)," and "less than half of the time (<50%)." Medication nonadherence was defined as "most of the time (~75%)" or less (25).

Physical activity was assessed by the question, "Which of the following statements best describes how physically active you have been during the last month, that is, done activities such as 15 to 20 minutes of brisk walking, swimming, general conditioning, or recreational sports?" and responses included the following: "not at all active (0 times per month)," "a little active (1–2 times per month)," "fairly active (3–4 times per month)," "quite active (1–2 times per week)," "very active (3–4 times per week)," and "extremely active (≥5 times per week)." Responses were categorized into low (not or a little active), medium (fairly or quite active), and high (very or extremely active) physical activity. Single response

self-report items have been shown to be a reliable, valid, and accurate method of assessing physical activity (26).

Potential Psychological Mediators

Anxiety and depression were measured at baseline. Levels of anxiety were assessed using the anxiety subscale of the Hospital Anxiety and Depression scale, which has been validated in psychiatric, primary care, and general population samples (27,28). Questions from this seven-item scale are scored on a scale from 0 to 3. Scores range from 0 to 21, with higher scores indicating greater anxiety.

We assessed depressive symptoms using the nine-item Patient Health Questionnaire, a self-report instrument that measures the frequency of experiencing each symptom corresponding to the nine criteria for depression listed in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (29).

Statistical Analysis

Preliminary analyses indicated a detrimental effect of patients with low levels of SI, that is, socially isolated, on mortality but no differentiation between patients with medium, medium-high, and high levels of SI, that is, nonisolated. Because it has been suggested that the relationship between SI and morbidity and mortality may be according to a threshold rather than linear (30,31), we used a dichotomization of socially isolated versus nonisolated patient groups for our main analyses. Shapiro-Wilk normality tests revealed that CRP and omega-3 fatty acids had a nonnormal distribution; both variables were log transformed before analyses.

Baseline characteristics were compared between socially isolated and nonisolated patients using χ^2 tests for categorical and *t* tests for continuous variables.

We used Cox proportional hazards models to a) identify demographic and disease-relevant predictors of mortality and b) evaluate the association between SI and all-cause mortality by sequentially controlling for age and blocks of demographic and disease-relevant confounders and potential biological, behavioral, and psychological mediators using change in effect sizes ($|\beta_{\text{Model1}} - \beta_{\text{Modelk}}|/\beta_{\text{Model1}}$) derived from nested models. Following guidelines for recommended number of events per variable (32), we first reduced the variable set by retaining the theoretically more important one of two strongly correlated variables (33). In addition, we compared results from complex models with those from which weaker predictors had been excluded (32). Variables were retained in reduced models for $|z| > 1.28$ (equivalent to $p \leq .20$) (34). We tested the proportional hazards assumption of models using weighted residuals (35). Variables that did not meet this assumption were stratified. In each model, we tested for interactions between SI and covariates and, if significant, calculated models on stratified subsamples. Analyses were performed using R (36).

RESULTS

A total of 1019 patients were followed up for an average (standard deviation) of 6.7 (2.3) years. According to SNI scoring, 24% of patients had low, 40% had medium, 16% had medium-high, and 20% had high levels of SI. Patients with the lowest levels of SI were less likely to be married (15.9%) than patients with medium SI (22.7%; $\chi^2(1) = 3.90, p = .048$), were more likely to have no relatives (29.6%) or friends (16.2%), and reported having less than one social contact per month (16.2%) compared with patients with medium SI (no relatives: 13.4%, no friends: 7.1%, frequency: 5.4%; all $\chi^2(4) > 36.22, p < .001$) and more likely to report no church or group memberships (all 100%) compared with patients with medium SI (58.3%–91.9%; all $\chi^2(1) > 18.81, p < .001$).

Compared with nonisolated patients (subsuming medium, medium-high, and high levels of SI), socially isolated patients (those with low levels of SI) were younger, were less likely to have completed higher education, and had lower income levels (Table 1). They were more likely to have comorbidities,

SOCIAL INTEGRATION AND MORTALITY IN CHD

TABLE 1. Baseline Characteristics of 1019 Patients With Coronary Heart Disease by Social Network Index

| Variable | Social Network Index | | <i>p</i> ^a |
|--|-----------------------------|---------------------------|-----------------------|
| | Socially Isolated (SNI = 1) | Nonisolated (SNI ≥ 2) | |
| Demographic characteristics | | | |
| Age, M (SD), y ^(241,778) | 63.4 (10.7) | 68.0 (10.7) | <.001 |
| Male sex ^(241,778) | 198 (82%) | 638 (82%) | >.99 |
| White ^(241,777) | 153 (63%) | 459 (59%) | .25 |
| Body mass index, M (SD), kg/m ² ^(240,778) | 28.4 (5.8) | 28.4 (5.2) | .98 |
| Waist-to-hip ratio, M (SD) ^(230,751) | 0.96 (0.08) | 0.96 (0.08) | .43 |
| Education^(241,776) | | | |
| <High school | 41 (17%) | 90 (12%) | <.001 |
| High school | 61 (25%) | 120 (15%) | |
| >High school | 139 (58%) | 566 (73%) | |
| Income^(211,650), US\$ | | | |
| <20,000 | 160 (76%) | 335 (52%) | <.001 |
| 20,000–50,000 | 27 (13%) | 151 (23%) | |
| >50,000 | 24 (11%) | 164 (25%) | |
| Comorbid conditions | | | |
| Hypertension ^(241,776) | 170 (71%) | 551 (71%) | .95 |
| Myocardial infarction ^(240,773) | 123 (51%) | 422 (55%) | .41 |
| Stroke ^(241,775) | 32 (13%) | 116 (15%) | .59 |
| Revascularization ^(241,776) | 130 (54%) | 471 (61%) | .074 |
| Heart Failure ^(240,774) | 41 (17%) | 138 (18%) | .87 |
| Diabetes mellitus ^(241,776) | 78 (32%) | 187 (24%) | .014 |
| Chronic obstructive pulmonary disease ^(241,776) | 49 (20%) | 114 (15%) | .047 |
| Serum creatinine, M (SD), mg/dl ^(241,777) | 1.12 (0.65) | 1.16 (0.68) | .41 |
| Cardiac disease severity and risk factors | | | |
| Left ventricular ejection fraction, M (SD), % ^(232,760) | 62 (10) | 62 (10) | .65 |
| Inducible ischemia ^{(211,721)*} | 51 (24%) | 177 (25%) | .98 |
| Systolic blood pressure, M (SD), mm Hg ^(236,773) | 135.0 (20.1) | 132.4 (21.1) | .097 |
| Diastolic blood pressure, M (SD), mm Hg ^(236,773) | 76.6 (12.3) | 74.0 (10.9) | .002 |
| Medication use | | | |
| β-Blocker ^(241,778) | 140 (58%) | 450 (58%) | >.99 |
| ACE inhibitors/ARB ^(241,778) | 118 (49%) | 406 (52%) | .42 |
| Statin ^(241,778) | 140 (58%) | 515 (66%) | .027 |
| Aspirin ^(241,778) | 184 (76%) | 606 (78%) | .68 |
| Potential biological mediators | | | |
| Urine cortisol, M (SD), μg/d ^(209,674) | 38.5 (38.6) | 38.5 (25.9) | .99 |
| Urine epinephrine, M (SD), μg/d ^(224,737) | 4.34 (3.34) | 4.63 (5.69) | .47 |
| Urine norepinephrine, M (SD), μg/d ^(224,737) | 53.8 (26.1) | 50.9 (26.8) | .15 |
| Log C-reactive protein, M (SD), mg/l ^(234,746) | 0.95 (1.26) | 0.64 (1.32) | .001 |
| White blood cell count, M (SD), per HPF ^(240,777) | 7.0 (2.3) | 6.4 (1.8) | <.001 |
| Hemoglobin A1c, M (SD), % ^(240,771) | 5.9 (1.1) | 6.0 (1.2) | .44 |
| Low-density lipoprotein, M (SD), mg/dl ^{(227,762)**} | 106.2 (32.4) | 103.7 (34.1) | .33 |
| High-density lipoprotein, M (SD), mg/dl ^(240,777) | 44.3 (14.4) | 46.3 (14.0) | .051 |
| Triglycerides, M (SD), mg/dl ^(240,777) | 162.7 (172.5) | 133.7 (109.1) | .002 |
| Potential behavioral mediators | | | |
| Log omega-3 fatty acids (% DHA + EPA), M (SD) ^(234,748) | 0.036 (0.02) ^b | 0.042 (0.02) ^b | <.001 |
| Alcohol use (AUDIT-C score), M (SD) ^(240,772) | 2.6 (2.7) | 2.1 (2.3) | .005 |
| Smoking^(241,777) | | | |
| Never | 52 (22%) | 263 (34%) | <.001 |
| Past | 107 (44%) | 397 (51%) | |
| Current | 82 (34%) | 117 (15%) | |
| Poor sleep quality ^(241,777) | 89 (37%) | 195 (25%) | <.001 |

(Continued on next page)

TABLE 1. (Continued)

| Variable | Social Network Index | | <i>p</i> ^a |
|--|-----------------------------|-----------------------|-----------------------|
| | Socially Isolated (SNI = 1) | Nonisolated (SNI ≥ 2) | |
| Medication nonadherence ^(237,773) | 25 (11%) | 58 (8%) | .17 |
| Self-reported physical activity ^(240,776) | | | |
| Low | 117 (49%) | 254 (33%) | <.001 |
| Medium | 66 (28%) | 244 (31%) | |
| High | 57 (24%) | 278 (36%) | |
| Potential psychological mediators | | | |
| HADS anxiety score, M (SD) ^(241,776) | 6.73 (4.47) | 5.04 (3.66) | <.001 |
| Depression by PHQ score, M (SD) ^(241,778) | 7.37 (6.23) | 4.52 (5.03) | <.001 |

SNI = Social Network Index; M = mean; SD = standard deviation; ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; HPF = high-power field; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AUDIT = Alcohol Use Disorders Identification Test; HADS = Hospital Anxiety and Depression Scale; PHQ = Patient Health Questionnaire.

Superscript numbers after variable names indicate group sizes. Missing data points were more frequent for socially isolated than nonisolated patients.

* $\chi^2(1) = 5.54, p < .05$, ** $\chi^2(1) = 7.80, p < .01$.

^a Baseline characteristics were compared using χ^2 tests for categorical variables and *t* tests for continuous variables using two-tailed tests.

^b Log omega-3 fatty acids correspond to 3.7% and 4.3% of total fatty acid methyl esters for socially isolated and nonisolated.

particularly diabetes mellitus and chronic obstructive pulmonary disease, and elevated cardiac disease risk, as indicated by higher diastolic blood pressure, and were less likely to use statins. With respect to biological risk factors, socially isolated versus nonisolated patients had higher levels of log CRP, WBC, and triglycerides and had lower levels of HDL. Differences in behavioral risk factors indicated that socially isolated versus nonisolated patients had lower log omega-3 fatty acid levels and were more likely to use alcohol and smoke and be less physically active and sleep poorly. Socially isolated patients also showed more psychological risk factors than did nonisolated patients, including a higher number of symptoms of anxiety and depression.

Three hundred forty-seven deaths occurred in 6869 person-years of follow-up. Overall, the age-adjusted annual rate of mortality was 6.3% (91 deaths) among socially isolated patients and 4.1% (256 deaths) in nonisolated patients.

We found strong correlations between systolic blood pressure and diastolic blood pressure ($r = 0.64, t(1007) = 26.21, p < .001$), diabetes mellitus and HbA1c ($r = 0.63, t(1007) = 26.00, p < .001$), and depression and anxiety ($r = 0.64, t(1015) = 26.37, p < .001$). Systolic blood pressure, HbA1c, and depression were retained for subsequent analyses.

Table 2 summarizes the results of Cox proportional hazards models of demographic and disease-relevant predictors of mortality. Because income and statin use did not meet the proportionality of hazards assumption, these were entered as stratified variables. Model 1 identified age, ethnicity, body mass index, income, left ventricular ejection fraction, inducible ischemia, chronic obstructive pulmonary disease, and use of statins and diuretics as predicting mortality in the present sample. These were confirmed in Model 2.

Tables 3 and 4 report results from Cox proportional hazards models for predicting mortality by SI, controlling for age, candidate confounders, and potential mediators. When entering SI as the original four-group variable, age-adjusted hazard ra-

tios [HRs] did not differ among groups of medium, medium-high, and high SI (in reference to high SI; HR = 0.90, 95% confidence interval [CI] = 0.63–1.29, $p = .57$, for medium-high SI; HR = 1.09, CI = 0.82–1.45, for medium SI; HR = 1.65, CI = 1.21–2.25, for low SI). Compared with nonisolated patients, socially isolated ones had a 61% greater mortality risk (Model 1, see Fig. 1). Adjustment for strong demographic and disease-relevant predictors of mortality (Model 2) and potential biological (Model 3a) or psychological mediators (Model 5) had only small effects on the β coefficient. Urine norepinephrine, CRP, and HbA1c were retained in the reduced model with potential biological mediators, of which CRP and HbA1c continued to be significant predictors of mortality (each individually reducing the β coefficient by at least 25%, Model 3b). Adjustment for potential behavioral mediators reduced the β coefficient by 49.0% and rendered the association nonsignificant (Model 4a). Omega-3 fatty acids, smoking, and medication adherence were retained and were significant predictors of mortality in the reduced model (each individually reducing the β coefficient by at least 25%, with smoking effecting the largest reduction by 38.0%, Model 4b). Adjustment for all potential biological, behavioral, and psychological mediators reduced the β coefficient by 41.6% and rendered the association nonsignificant (Model 6a). Urine norepinephrine, CRP, HbA1c, omega-3 fatty acids, smoking, and medication adherence were retained in the reduced model, of which CRP, HbA1c, smoking, and medication adherence were significant predictors of mortality (Model 6b, see Fig. 1).

There was a significant interaction of past (HR = 2.72, CI = 1.22–6.08) and current smoking (HR = 2.47, CI = 1.03–5.90) with SI in the age-adjusted model, of past (HR = 2.67, CI = 0.93–7.70) but not current smoking (HR = 2.50, CI = 0.93–7.70) in the age- and confounder-adjusted model, and of past (HR = 3.23, CI = 1.02–10.30) and current smoking (HR = 3.21, CI = 0.92–11.14) in the age-, confounder-, and mediator-adjusted model. Stratification for smoking status

SOCIAL INTEGRATION AND MORTALITY IN CHD

TABLE 2. Potentially Confounding Demographic and Disease-Relevant Predictors of Mortality

| | Model 1 | | | Model 2 | | |
|---|-------------|------------------|-------------|-------------|------------------|-------------|
| | HR | 95% CI | <i>p</i> | HR | 95% CI | <i>p</i> |
| Demographic characteristics | | | | | | |
| Age | 1.04 | 1.02–1.05 | <.001 | 1.04 | 1.02–1.05 | <.001 |
| Male sex | 1.61 | 0.88–2.96 | .12 | 1.59 | 0.99–2.55 | .054 |
| White | 1.42 | 1.02–1.97 | .037 | 1.40 | 1.03–1.90 | .030 |
| Body mass index | 0.97 | 0.93–1.01 | .099 | 0.98 | 0.95–1.01 | .20 |
| Waist-to-hip ratio | 3.32 | 0.25–44.11 | .36 | | | |
| Education (high school) | 1.17 | 0.71–1.94 | .53 | | | |
| Education (>high school) | 0.82 | 0.53–1.27 | .38 | | | |
| Income (US\$20,000–US\$50,000) | — | — | — | — | — | — |
| Income (>US\$50,000) | — | — | — | — | — | — |
| Cardiac disease severity and risk factors | | | | | | |
| Left ventricular ejection fraction | 0.98 | 0.97–1.00 | .015 | 0.98 | 0.97–0.99 | .005 |
| Inducible ischemia | 1.89 | 1.37–2.60 | <.001 | 2.00 | 1.48–2.69 | <.001 |
| Systolic blood pressure | 1.00 | 0.99–1.01 | .69 | | | |
| Comorbid conditions | | | | | | |
| Hypertension | 0.98 | 0.68–1.41 | .90 | | | |
| Myocardial infarction | 1.23 | 0.89–1.70 | .20 | 1.22 | 0.91–1.65 | .19 |
| Stroke | 1.40 | 0.96–2.05 | .080 | 1.34 | 0.94–1.92 | .11 |
| Revascularization | 0.92 | 0.66–1.27 | .61 | | | |
| Heart Failure | 1.09 | 0.73–1.63 | .67 | | | |
| Chronic obstructive pulmonary disease | 1.47 | 1.00–2.15 | .050 | 1.56 | 1.10–2.21 | .012 |
| Serum creatinine | 1.41 | 1.20–1.66 | <.001 | 1.42 | 1.21–1.66 | <.001 |
| Medication use | | | | | | |
| β-Blocker | 0.88 | 0.64–1.21 | .43 | | | |
| ACE inhibitors/ARB | 1.06 | 0.77–1.46 | .73 | | | |
| Statin | — | — | — | — | — | — |
| Aspirin | 0.98 | 0.68–1.42 | .93 | | | |
| Diuretic | 1.41 | 1.01–1.97 | .044 | 1.48 | 1.10–1.99 | .010 |

Model 1 = potentially confounding predictors of mortality; Model 2 = Model 1 excluding weaker predictors; — = entered as stratified variable. HR = hazard ratio; CI = confidence interval; ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker. Values set in bold meet the $p \leq .05$ criterion.

showed the association between SI and mortality in past and current smokers (HR = 1.75, CI = 1.34–2.30), but it was absent in those who never smoked (HR = 0.85, CI = 0.44–1.65).

DISCUSSION

In this prospective cohort study of 1019 outpatients with stable CHD, we found that low SI was associated with a 61% greater mortality risk. Whereas adjustment for demographic and disease-relevant confounders and potential biological or psychological mediators did not significantly attenuate this association, adjustment for potential behavioral mediators did, as did combined adjustment for potential biological and behavioral mediators. A combination of biological (CRP, HbA1c) and behavioral factors (omega-3 fatty acids, smoking, medication adherence) seemed to be important in explaining the association between SI and mortality. Behavioral factors, particularly smoking, made the largest contribution.

Our finding of a 61% increased mortality risk in low SI is comparable to previous studies that, according to a recent meta-

analysis, suggest on average a 41% increased relative risk (CI = 1.17–1.70) of low SI on all-cause mortality (3). Our results suggested a critical level of SI, above which no further effect was apparent. The low SI group had an increased mortality risk, but there was little or no difference between groups of medium, medium-high, and high SI. Although other studies present support of a more graded effect of SI on mortality (37), threshold effects have been observed in general population (18,38,39) and CHD patient samples (40). It may indicate that a minimum number—between one and three—and diversity of contacts needs to be surpassed for protective health effects to materialize (31).

Potential Biological Mediators

A number of biological factors are known to play an important role in the etiology and progression of CHD. Our findings expand upon prior work by examining a comprehensive set of biological variables and testing whether one or more of these might explain the link between low SI and mortality.

TABLE 3. Prediction of Mortality by Social Integration as Quantified by Social Network Index in Models Adjusted for Age, Confounders, and Potential Mediators, Models 1 to 3

| | Model 1 | | | Model 2 ($\Delta\beta = 31.6\%$) | | | Model 3a ($\Delta\beta = 24.3\%$) | | | Model 3b ($\Delta\beta = 28.5\%$) | | |
|---|---------|-----------|-----------------|------------------------------------|-----------|-----------------|-------------------------------------|-----------|-----------------|-------------------------------------|-----------|-----------------|
| | HR | 95% CI | <i>p</i> | HR | 95% CI | <i>p</i> | HR | 95% CI | <i>p</i> | HR | 95% CI | <i>p</i> |
| SNI (dichotomous) | 1.61 | 1.26–2.05 | <.001 | 1.50 | 1.07–2.10 | .017 | 1.53 | 1.05–2.25 | .029 | 1.43 | 1.00–2.05 | .047 |
| Demographic characteristics | | | | | | | | | | | | |
| Age | 1.05 | 1.04–1.06 | <.001 | 1.04 | 1.02–1.06 | <.001 | 1.04 | 1.02–1.06 | <.001 | 1.05 | 1.03–1.07 | <.001 |
| Male sex | | | | 1.59 | 0.99–2.56 | .055 | 2.02 | 1.07–3.82 | .030 | 2.31 | 1.31–4.06 | .004 |
| White | | | | 1.32 | 0.97–1.80 | .075 | 1.42 | 0.96–2.09 | .076 | 1.35 | 0.96–1.92 | .088 |
| Body mass index | | | | 0.98 | 0.95–1.01 | .28 | | | | | | |
| Income (US\$20,000–US\$50,000) | | | | — | — | — | — | — | — | — | — | — |
| Income (>US\$50,000) | | | | — | — | — | — | — | — | — | — | — |
| Cardiac disease severity and risk factors | | | | | | | | | | | | |
| Left ventricular ejection fraction | | | | 0.98 | 0.96–0.99 | .002 | 0.98 | 0.96–0.99 | .010 | 0.98 | 0.96–0.99 | .003 |
| Inducible ischemia | | | | 1.95 | 1.45–2.63 | <.001 | 1.60 | 1.13–2.27 | .008 | 1.85 | 1.35–2.53 | <.001 |
| Comorbid conditions | | | | | | | | | | | | |
| Myocardial infarction | | | | 1.22 | 0.90–1.65 | .19 | 1.18 | 0.84–1.67 | .34 | | | |
| Stroke | | | | 1.34 | 0.94–1.92 | .11 | 1.61 | 1.06–2.44 | .027 | 1.37 | 0.93–2.01 | .11 |
| Chronic obstructive pulmonary disease | | | | 1.50 | 1.06–2.13 | .023 | 1.42 | 0.94–2.17 | .098 | 1.56 | 1.06–2.30 | .025 |
| Serum creatinine | | | | 1.40 | 1.20–1.63 | <.001 | 1.38 | 0.89–2.16 | .15 | 1.32 | 0.93–1.85 | .12 |
| Medication use | | | | | | | | | | | | |
| Statin | | | | — | — | — | — | — | — | — | — | — |
| Diuretic | | | | 1.48 | 1.10–2.00 | .010 | 1.31 | 0.92–1.87 | .14 | 1.33 | 0.95–1.85 | .097 |
| Potential biological mediators | | | | | | | | | | | | |
| Urine epinephrine | | | | | | | 0.98 | 0.94–1.02 | .37 | | | |
| Urine cortisol | | | | | | | 1.00 | 0.99–1.01 | .92 | | | |
| Urine norepinephrine | | | | | | | 1.01 | 1.00–1.01 | .088 | 1.00 | 1.00–1.01 | .53 |
| Log C-reactive protein | | | | | | | 1.16 | 1.01–1.33 | .041 | 1.20 | 1.06–1.35 | .004 |
| White blood cell count | | | | | | | 1.01 | 0.92–1.10 | .87 | | | |
| Hemoglobin A1c | | | | | | | 1.11 | 0.96–1.29 | .16 | 1.14 | 1.01–1.29 | .029 |
| Low-density lipoprotein | | | | | | | 1.00 | 0.99–1.01 | .94 | | | |
| High-density lipoprotein | | | | | | | 1.00 | 0.99–1.02 | .66 | | | |
| Triglycerides | | | | | | | 1.00 | 1.00–1.00 | .66 | | | |
| Potential behavioral mediators | | | | | | | | | | | | |
| Log omega-3 fatty acids (% DHA + EPA) | | | | | | | | | | | | |
| Alcohol use (AUDIT-C score) | | | | | | | | | | | | |
| Smoking (past) | | | | | | | | | | | | |
| Smoking (current) | | | | | | | | | | | | |
| Poor sleep quality | | | | | | | | | | | | |
| Medication nonadherence | | | | | | | | | | | | |
| Self-reported physical activity (medium) | | | | | | | | | | | | |
| Self-reported physical activity (high) | | | | | | | | | | | | |
| Potential psychological mediators | | | | | | | | | | | | |
| Depression by PHQ score | | | | | | | | | | | | |

SNI = Social Network Index; HR = hazard ratio; CI = confidence interval; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AUDIT = Alcohol Use Disorders Identification Test; PHQ = Patient Health Questionnaire.

Model 1 = age-adjusted model. Model 2 = Model 1 + demographic and disease-relevant confounders. Model 3a = Model 2 + biological variables. Model 3b = Model 3a excluding weaker predictors.

Values set in bold meet the $p \leq .05$ criterion.

We found that patients with low SI had higher inflammatory activity, as indicated by higher levels of CRP and WBC, and a less favorable lipoprotein profile consisting of higher levels of

triglycerides and lower levels of HDL cholesterol. Accordingly, prior research documents higher levels of CRP, WBC, and triglycerides, and lower cholesterol in patients with lower SI (8–10).

SOCIAL INTEGRATION AND MORTALITY IN CHD

TABLE 4. Prediction of Mortality by Social Integration as Quantified by Social Network Index in Models Adjusted for Age, Confounders, and Potential Mediators, Models 4 to 6

| | Model 4a (Δβ = 49.0%) | | Model 4b (Δβ = 38.3%) | | Model 5 (Δβ = 29.0%) | | Model 6a (Δβ = 41.6%) | | Model 6b (Δβ = 43.6%) | | | | | | |
|---|--------------------------|-----------|--------------------------|------|-------------------------|-------------|--------------------------|-----------|--------------------------|------|-----------|-------------|------|-----------|-------------|
| | HR | 95% CI | p | HR | 95% CI | p | HR | 95% CI | p | HR | 95% CI | | | | |
| SNI (dichotomous) | 1.30 | 0.91–1.86 | .15 | 1.38 | 0.98–1.96 | 0.066 | 1.52 | 1.08–2.14 | .016 | 1.36 | 0.91–2.04 | .13 | 1.33 | 0.92–1.91 | .12 |
| Demographic characteristics | | | | | | | | | | | | | | | |
| Age | 1.05 | 1.04–1.07 | <.001 | 1.05 | 1.04–1.07 | <.001 | 1.04 | 1.03–1.06 | <.001 | 1.05 | 1.03–1.07 | <.001 | 1.06 | 1.04–1.08 | <.001 |
| Male sex | 1.43 | 0.88–2.34 | .15 | 1.38 | 0.87–2.19 | .18 | 1.60 | 0.99–2.57 | .053 | 1.67 | 0.87–3.21 | .12 | 1.91 | 1.09–3.34 | .024 |
| White | 1.29 | 0.93–1.79 | .12 | 1.33 | 0.96–1.83 | .082 | 1.30 | 0.96–1.77 | .091 | 1.58 | 1.05–2.38 | .028 | 1.49 | 1.05–2.12 | .027 |
| Body mass index | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| Income (US\$20,000-US\$50,000) | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| Income (>US\$50,000) | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| Cardiac disease severity and risk factors | | | | | | | | | | | | | | | |
| Left ventricular ejection fraction | 0.98 | 0.97–1.00 | .010 | 0.98 | 0.97–0.99 | .006 | 0.98 | 0.96–0.99 | .002 | 0.98 | 0.96–1.00 | .034 | 0.98 | 0.96–0.99 | .005 |
| Inducible ischemia | 1.90 | 1.38–2.61 | <.001 | 1.99 | 1.46–2.71 | <.001 | 1.95 | 1.45–2.64 | <.001 | 1.60 | 1.11–2.29 | .011 | 1.89 | 1.38–2.60 | <.001 |
| Comorbid conditions | | | | | | | | | | | | | | | |
| Myocardial infarction | 1.19 | 0.86–1.63 | .29 | 1.49 | 1.03–2.17 | .036 | 1.46 | 1.02–2.10 | .040 | 1.24 | 0.92–1.67 | .16 | 1.13 | 0.79–1.61 | .50 |
| Stroke | 1.49 | 1.03–2.17 | .036 | 1.46 | 1.02–2.10 | .040 | 1.34 | 0.93–1.91 | .11 | 1.79 | 1.17–2.74 | .007 | 1.41 | 0.96–2.07 | .078 |
| Chronic obstructive pulmonary disease | 1.25 | 0.86–1.84 | .25 | 1.25 | 0.86–1.84 | .25 | 1.51 | 1.06–2.14 | .022 | 1.26 | 0.811.96 | .31 | 1.26 | 0.811.96 | .31 |
| Serum creatinine | 1.59 | 1.28–1.97 | <.001 | 1.63 | 1.35–1.97 | <.001 | 1.42 | 1.21–1.66 | <.001 | 1.56 | 0.98–2.46 | .058 | 1.39 | 0.99–1.95 | .059 |
| Medication use | | | | | | | | | | | | | | | |
| Statin | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| Diuretic | 1.50 | 1.10–2.06 | .011 | 1.52 | 1.12–2.06 | .007 | 1.44 | 1.07–1.94 | .016 | 1.42 | 0.98–2.06 | .064 | 1.43 | 1.02–2.00 | .038 |
| Potential biological mediators | | | | | | | | | | | | | | | |
| Urine epinephrine | 0.98 | 0.94–1.02 | .34 | 1.00 | 0.99–1.01 | .97 | 1.01 | 1.00–1.02 | .055 | 1.00 | 1.00–1.01 | .535 | 1.00 | 1.00–1.01 | .535 |
| Urine cortisol | 1.00 | 0.99–1.01 | .97 | 1.01 | 1.00–1.02 | .055 | 1.13 | 0.97–1.31 | .11 | 1.18 | 1.04–1.33 | .009 | 1.18 | 1.04–1.33 | .009 |
| Urine norepinephrine | 1.01 | 1.00–1.02 | .055 | 1.01 | 1.00–1.02 | .055 | 1.00 | 0.91–1.10 | .97 | 1.14 | 0.98–1.32 | .093 | 1.14 | 1.01–1.29 | .037 |
| Log C-reactive protein | 1.13 | 0.97–1.31 | .11 | 1.00 | 0.99–1.01 | .93 | 1.00 | 0.99–1.01 | .97 | 1.00 | 0.99–1.01 | .97 | 1.00 | 0.99–1.01 | .97 |
| White blood cell count | 1.00 | 0.91–1.10 | .97 | 1.00 | 1.00–1.00 | .41 | 1.00 | 1.00–1.00 | .41 | 1.00 | 1.00–1.00 | .41 | 1.00 | 1.00–1.00 | .41 |
| Hemoglobin A1c | 1.14 | 0.98–1.32 | .093 | 1.00 | 0.99–1.01 | .93 | 1.00 | 0.99–1.01 | .97 | 1.00 | 0.99–1.01 | .97 | 1.00 | 0.99–1.01 | .97 |
| Low-density lipoprotein | 1.00 | 0.99–1.01 | .93 | 1.00 | 0.99–1.01 | .97 | 1.00 | 0.99–1.01 | .97 | 1.00 | 0.99–1.01 | .97 | 1.00 | 0.99–1.01 | .97 |
| High-density lipoprotein | 1.00 | 0.99–1.01 | .97 | 1.00 | 0.99–1.01 | .97 | 1.00 | 0.99–1.01 | .97 | 1.00 | 0.99–1.01 | .97 | 1.00 | 0.99–1.01 | .97 |
| Triglycerides | 1.00 | 1.00–1.00 | .41 | 1.00 | 1.00–1.00 | .41 | 1.00 | 1.00–1.00 | .41 | 1.00 | 1.00–1.00 | .41 | 1.00 | 1.00–1.00 | .41 |
| Potential behavioral mediators | | | | | | | | | | | | | | | |
| Log omega-3 fatty acids (% DHA + EPA) | 0.70 | 0.49–1.01 | .055 | 0.71 | 0.50–1.01 | .057 | 0.68 | 0.45–1.03 | .069 | 0.81 | 0.56–1.16 | .25 | 0.81 | 0.56–1.16 | .25 |
| Alcohol use (AUDIT-C score) | 1.03 | 0.97–1.09 | .39 | 1.03 | 0.96–1.11 | .38 | 1.03 | 0.96–1.11 | .38 | 1.03 | 0.96–1.11 | .38 | 1.03 | 0.96–1.11 | .38 |
| Smoking (past) | 1.25 | 0.86–1.81 | .25 | 1.31 | 0.91–1.88 | .15 | 1.16 | 0.76–1.76 | .49 | 1.34 | 0.91–1.96 | .13 | 1.34 | 0.91–1.96 | .13 |
| Smoking (current) | 1.84 | 1.13–3.01 | .014 | 2.00 | 1.25–3.20 | .004 | 1.95 | 1.13–3.37 | .017 | 1.99 | 1.21–3.29 | .007 | 1.99 | 1.21–3.29 | .007 |
| Poor sleep quality | 1.04 | 0.74–1.45 | .83 | 1.04 | 0.74–1.45 | .83 | 1.10 | 0.73–1.66 | .64 | 1.10 | 0.73–1.66 | .64 | 1.10 | 0.73–1.66 | .64 |

(Continued on next page)

TABLE 4. (Continued)

| | Model 4a ($\Delta\beta = 49.0\%$) | | | Model 4b ($\Delta\beta = 38.3\%$) | | | Model 5 ($\Delta\beta = 29.0\%$) | | | Model 6a ($\Delta\beta = 41.6\%$) | | | Model 6b ($\Delta\beta = 43.6\%$) | | |
|--|--|-----------|-----|--|-----------|-------------|---------------------------------------|-----------|-----|--|-----------|-------------|--|--------|---|
| | HR | 95% CI | p | HR | 95% CI | p | HR | 95% CI | p | HR | 95% CI | p | HR | 95% CI | p |
| Medication nonadherence | 1.63 | 0.91–2.91 | .10 | 1.83 | 1.05–3.19 | .033 | 1.64 | 0.80–3.37 | .18 | 1.92 | 1.07–3.43 | .028 | | | |
| Self-reported physical activity (medium) | 0.92 | 0.65–1.31 | .64 | | | | 1.08 | 0.71–1.64 | .71 | | | | | | |
| Self-reported physical activity (high) | 0.89 | 0.60–1.30 | .54 | | | | 1.06 | 0.68–1.65 | .80 | | | | | | |
| Potential psychological mediators | | | | | | | | | | | | | | | |
| Depression by PHQ score | | | | | | | 1.00 | 0.97–1.03 | .93 | 1.00 | 0.96–1.03 | .79 | | | |

SNI = Social Network Index; HR = hazard ratio; CI = confidence interval; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AUDIT = Alcohol Use Disorders Identification Test; PHQ = Patient Health Questionnaire.
 Model 4a = Model 2 + behavioral variables; Model 4b = Model 4a excluding weaker predictors; Model 5 = Model 2 + psychological variables; Model 6a = Model 2 + biological, behavioral, and psychological variables.
 Values set in bold meet the $p \geq .05$ criterion.

The association between SI and mortality was partially explained by CRP and HbA1c—markers of systemic inflammation and blood glucose concentration. Previous research documents associations between SI and increased levels of CRP (7) as well as between higher levels of CRP and mortality (41). Similarly, higher levels of SI have been associated with lower levels of HbA1c (42), and higher HbA1c has been associated with increased mortality (43). Our finding extends previous research by demonstrating that CRP and HbA1c contribute to explaining the relation between SI and mortality.

Potential Behavioral Mediators

In addition to biological variables, poor health behaviors can lead to cardiovascular events. We considered a comprehensive set of behavioral variables to further elucidate the association between SI and mortality. Our results showed that SI groups differed in omega-3 fatty acids, alcohol use, smoking, sleep quality, and physical activity, with the low SI group showing less favorable outcomes on each of these indicators. This is consistent with prior research that documents lower dietary fish intake, higher alcohol use, increased smoking rate, poorer sleep quality, and higher likelihood of physical inactivity in low SI (7,12,44,45).

The association between SI and mortality was largely explained by omega-3 fatty acids, smoking, and medication adherence, but omega-3 fatty acids lost its predictive power in the model with potential biological and behavioral mediators. High omega-3 fatty acids intake has been shown to reduce inflammation (46). Accordingly, we found a negative relation between omega-3 fatty acids and CRP in our sample ($r = -0.19$, $t(976) = -6.06$, $p < .001$). This suggests attenuation of the role of the behavioral predictor when entering the biological predictor, as both may index the contribution of inflammation on mortality.

Previous research has documented associations of low SI with higher smoking rates (11) and lower medication adherence (13), but not with lower levels of omega-3 fatty acids. Associations are also known to exist between these poor health behaviors and CHD mortality, with increased consumption of fish and omega-3 fatty acids (47) as well as medication adherence (25,48) reducing mortality risk and cigarette smoking increasing it (49). Our findings extend previous research by demonstrating that omega-3 fatty acids, medication adherence, and particularly smoking contribute to explaining the relation between SI and mortality in CHD patients. This finding supports the idea that low SI is associated with increased mortality because of poor health behaviors.

Smoking also moderated the association between SI and mortality. Consistent with previous investigations (11), past and current smokers (26.9%) were more likely than nonsmokers (16.5%) to be socially isolated ($\chi^2(1) = 12.40$, $p < .001$). Whereas socially isolated past or current smokers had a 75% increased mortality risk, nonsmokers were buffered from the effects of low SI on mortality.

Potential Psychological Mediators

Low SI can also exacerbate negative psychological states. We found increased anxiety and depressive symptoms in the

SOCIAL INTEGRATION AND MORTALITY IN CHD

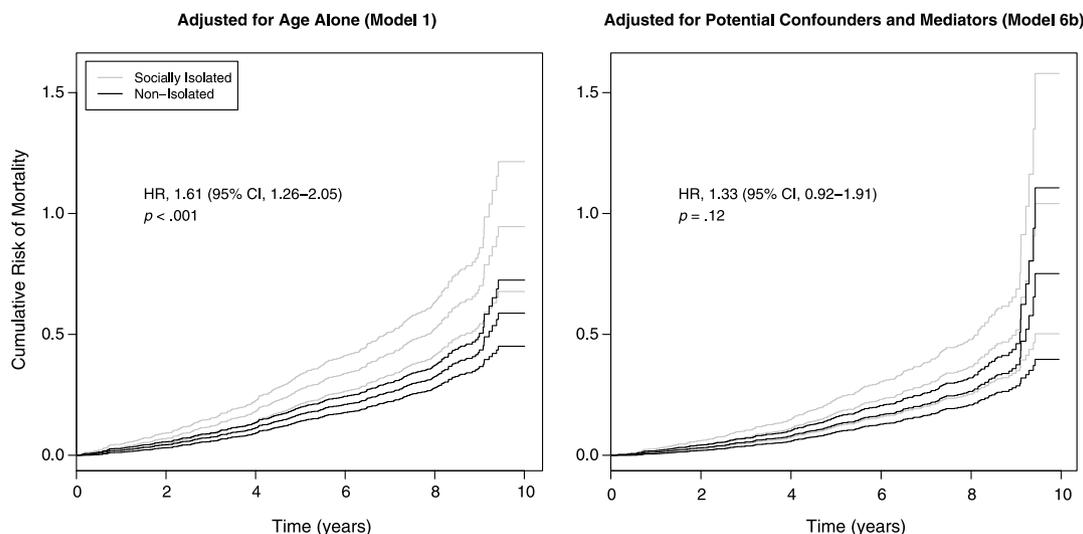


Figure 1. Cumulative risk of mortality. Data are stratified by social integration (socially isolated versus nonisolated) before and after adjustment for candidate confounders and potential mediators. Ninety percent CIs are indicated. CI = confidence interval; HR = hazard ratio.

low SI group. Low SI has been shown to be associated with high levels of anxiety and depression (14,15). However, depression did not contribute to explaining the relation between SI and mortality in our sample after controlling for confounding demographic and disease-related variables.

Limitations

Several limitations should be considered. First, the study population was predominately older men with preexisting stable CHD. Our findings may not generalize to women, younger healthy populations, populations with recent CV events, or other disease contexts. Because of missing data for some of the laboratory variables, only a subset of patients could be included in our analysis. However, frequency of missing data did not differ systematically between SI groups.

Second, this study focused on SI as the structural aspect of social relationships. It is unknown whether our findings generalize to other dimensions of social relationships, such as social support (30). Use of the Berkman SNI and a restricted sample size may have influenced the structure of findings, such as the threshold effect of SI on mortality.

Third, results, particularly for urinary catecholamines, may be limited by compliance with the urine collection procedure and self-reported medication use. Behavioral variables sleep quality, medication adherence, and physical activity were estimated from single-item self-reports. Reporting biases in health behaviors (50) may limit generalizability of results. Absence of detailed dietary information does not allow conclusion regarding intake of omega-3 fatty acids through dietary consumption or supplementation.

Fourth, only baseline status of SI was considered. Although the SNI has a strong test-retest reliability over multiple years (19), our analyses cannot address whether SI changed during the analysis period. Similarly, because covariates were measured at baseline, we could not account for possible changes in these variables. The large number of variables entered into the model

raises the issue of overfitting, although simulations suggest that the number of variables was still in the acceptable range (32).

Finally, although our cross-sectional data support the conclusion that health-related behavioral pathways explained the association between low SI and higher mortality, we cannot infer causality. Influences may be bidirectional, with low SI leading to poor health and vice versa (51). Clarifying the specific causal direction through mediation analyses is an important topic for future research to allow a better understanding of the underlying mechanisms and for designing more targeted interventions.

CONCLUSIONS

This study showed that low SI is associated with higher all-cause mortality in patients with stable CHD. Our findings suggest that much of this association is attributable to health-related behavioral pathways, particularly smoking. These findings suggest that special attention should be placed on encouraging healthy behaviors in patients with low SI. Identification of CHD patients with low SI by screening measures might be of use. Future studies should explore the extent by which behavioral interventions may improve survival in CHD patients of low SI.

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