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Exercise Mediates the Association Between Positive Affect and 5-Year Mortality in Patients With Ischemic Heart Disease

Madelein T. Hoogwegt, MSc; Henneke Versteeg, PhD; Tina B. Hansen, MSc; Lau C. Thygesen, PhD; Susanne S. Pedersen, PhD; Ann-Dorthe Zwisler, MD, PhD

Background—Positive affect has been associated with better prognosis in patients with ischemic heart disease, but the underlying mechanisms remain unclear. We examined whether positive affect predicted time to first cardiac-related hospitalization and all-cause mortality, and whether exercise mediated this relationship in patients with established ischemic heart disease.

Methods and Results—The sample comprised 607 patients with ischemic heart disease from Holbæk Hospital, Denmark. In 2005, patients completed the Global Mood Scale (GMS) to assess positive affect and a purpose-designed question on exercise. Data on mortality and hospitalization were collected from Danish national registers for the period 2006–2010. Adjusted Cox and logistic regression were used to analyze the mediation model. Because no significant association between positive affect and cardiac-related hospitalization was found, we constructed no mediation model for hospitalization. Importantly, patients with high positive affect had a significantly reduced risk of all-cause mortality (hazard ratio, 0.58; 95% confidence interval, 0.37–0.92; unadjusted analysis) and were more likely to exercise (odds ratio, 1.99; 95% confidence interval, 1.44–2.76; unadjusted analysis; odds ratio, 1.48; 95% confidence interval, 1.03–2.13; adjusted analysis). When controlling for positive affect and other relevant variables, patients engaged in exercise were less likely to die during follow-up (hazard ratio, 0.50; 95% confidence interval, 0.31–0.80; \( P = 0.004 \)). Importantly, exercise acted as a mediator in the relationship between positive affect and mortality.

Conclusions—Patients with higher levels of positive affect were more likely to exercise and had a lower risk of dying during 5-year follow-up, with exercise mediating the relationship between positive affect and mortality. Interventions aimed at increasing both positive affect and exercise may have better results with respect to patients’ prognosis and psychological well-being than interventions focusing on 1 of these factors alone. (Circ Cardiovasc Qual Outcomes. 2013;6:559-566.)

Key Words: exercise • myocardial ischemia • mediation • positive affect
WHAT IS KNOWN

- Positive affect has been associated with better prognosis in patients with ischemic heart disease, but the underlying mechanisms remain unclear.

WHAT THE STUDY ADDS

- Identification of exercise as a possible mediating mechanism explaining the relationship between positive affect and prognosis, independent of demographic and clinical characteristics.
- Recommendations for effective combined physical and psychological treatment strategies in clinical practice.

Cardiac-related hospitalization and all-cause mortality, and (2) exercise mediated the relationship between positive affect and hospitalization and mortality in patients treated for IHD in an outpatient setting.

Methods

Patient Sample and Study Design

Patients (n=938) treated for IHD in an ambulatory setting at Holbæk Hospital, Denmark, comprised the current study sample. All patients participated in the cross-sectional survey of the international health-related quality of life questionnaire (HeartQoL) project, primarily designed to develop and validate a new core health-related quality of life questionnaire for patients with IHD. The patient sample has been described previously. In short, patients with documented angina (Canadian Cardiovascular Society functional classes II, III, or IV), myocardial infarction, and ischemic heart failure (New York Heart Association functional classes II, III, and IV), ≥18 years of age with sufficient understanding of the Danish language to complete the self-administered battery of health-related quality of life instruments were eligible for inclusion. Patients were identified in local databases, after which medical records were screened according to the inclusion and exclusion criteria by trained nurses. Because psychiatric patient files are not accessible as part of the medical record in Denmark, patients were only excluded if they were diagnosed with severe or acute psychiatric illness known by the responsible cardiologist. Because use of psychotropic medication is not uncommon in patients with medical illness but does not necessarily indicate severe psychiatric illness and inability to complete a psychological questionnaire, only patients suffering from a serious psychiatric disorder and current substance abusers were excluded from participation.

In November and December 2005, patients completed a battery of self-reported questionnaires. A reminder was sent to patients if the questionnaire was not returned within 4 weeks. Questionnaire data were linked to data from the national Danish registers by using the unique personal identification number (CPR number) assigned to all persons living permanently in Denmark. Data extraction and processing were accomplished according to the Act on Processing of personal data (Act No. 10 of 31 May 2000 with amendments: http://datatilsynet.dk/english) to follow the rules and regulations stated in the Danish law. The study was approved by the review committee of the Holbæk Hospital, Denmark.

Measures

Sociodemographic and Clinical Variables

Several Danish national registers were used to extract information on demographic and clinical characteristics. The Civil Registration System was used to obtain information on gender, age, marital status, and vital status. Information on highest completed education was extracted from the Population’s Education Register, and the Register-based Labor Force Statistics was used to look up information on occupational status. To ensure that medical conditions that may impact on the relationship between positive affect and mortality was recognized, information on clinical history up to 10 years before baseline (January 1996–November 2005) was collected from the National Patient Register. This information included the diagnoses and hospital surgeries of myocardial infarction, angina, heart failure, arrhythmias, cardiac arrest, percutaneous coronary intervention, coronary artery bypass grafting surgery, peripheral arterial disease, cerebrovascular disease, hypertension, hypercholesterolemia, renal failure, diabetes mellitus, and chronic obstructive pulmonary disease. Information on medication use in 2005, including cardiac (ie, β-blockers, statins, diuretics, calcium antagonists, angiotensin-converting enzyme inhibitors, angiotensin-II antagonists, antithrombotics, and digoxin) and psychotropic (ie, antidepressants, anxiolytics, and hypnotics) medications, was collected from the Danish National Prescription Registry, which contains all dispensed prescriptions in Denmark. Furthermore, the questionnaire contained information on health behaviors, including physical exercise, smoking (yes/no), and body mass index.

Mortality and Hospitalization

Information on survival status and cause of death between January 2006 and December 2010 was collected from the Danish Register of Causes of Death. In the present study, all-cause mortality was used as an end point. The National Patient Register was used to extract information on hospitalization for cardiac diagnoses focusing only on inpatient hospital visits. Hospitalizations were categorized according to the International Classification of Diseases (ICD-10) codes: I20 for angina, I21-I22 for myocardial infarction, I23-I25 for IHD, and I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.150, and P29.0 for heart failure. The first hospitalization for cardiac reasons during follow-up was used as an end point.

Exercise

Information on exercise during leisure time was obtained via a purpose-designed question with 4 possible response options as follows: (1) no exercise; (2) 1 to 2 times a week exercise; (3) 3 to 5 times a week exercise; and (4) ≥5 times a week exercise. For analytic purposes and according to the American Heart Association/American College of Cardiology guidelines, these 4 categories were reduced to a dichotomous variable with no exercise (original category 1) versus moderate to intensive exercise (original categories 2, 3, and 4).

Positive and Negative Affect

The Global Mood Scale, used to assess positive and negative affect in this study, was originally developed in cardiac patients. The 2-dimensional questionnaire consists of 20 items, including 10 positive affect items (ie, relaxed, self-confident) and 10 negative affect items (ie, helpless, insecure). Items are rated on a 5-point Likert scale from 0 (not at all) to 4 (extremely), with a score range of 0 to 40. The Global Mood Scale is a psychometrically sound instrument with respect to its internal consistency (Cronbach’s α=0.94 for positive affect and 0.93 for negative affect) and test-retest reliability (r=0.57) that has been validated in Danish cardiac patients and has been shown to be responsive to treatment-related changes after cardiac rehabilitation. In our study, a median split was used to identify patients with high- versus low positive and negative affect.

Statistical Analyses

Baseline characteristics between study participants and patients excluded from analyses, and between patients with high versus low positive affect were compared with the χ² test (Fisher exact test when appropriate) for nominal variables and Student independent samples t test for continuous variables. To test our hypothesis that patients with high positive affect have a lower risk of hospitalization and mortality, and that this relationship is mediated by exercise, we first checked the assumptions of the mediation model according
to Baron and Kenny: (1) positive affect had to be associated with hospitalization and mortality, (2) positive affect had to be associated with the hypothesized mediator exercise, and (3) exercise had to be related to hospitalization and mortality, adjusting for positive affect. Assumptions (1) and (3) were assessed using Cox regression. Prior to Cox regression analyses, the proportional hazards assumption was checked by inspection of the log-minus-log plots for each dichotomous variable in the model and by inspection of partial residual plots for continuous variables. Cumulative survival curves for positive affect (ie, high versus low positive affect) were constructed using the Kaplan–Meier method and log-rank test to compare the proportion of cumulative survival stratified by group. Assumption (2) was tested using logistic regression. Afterward, several demographic and clinical covariates were added to the model. A priori we decided to adjust for age, sex, body mass index, use of psychotropic medication, and presence of negative affect because positive and negative affect can be experienced at the same time. In addition, a comorbidity index (the Tu index) was constructed according to the Ontario acute myocardial infarction prediction rules which was also added as a covariate to the model. The advantage of this specific index is that it is adapted to the risk profile of patients with a cardiac condition. We included all in- and outpatient contacts for heart failure, cardiogenic shock, arrhythmia, pulmonary edema, malignancy, diabetes mellitus with complications, cerebrovascular disease, acute or chronic renal failure, and chronic obstructive pulmonary disease in the period 1995–2005 for the construction of the index. The Tu index was included as a continuous variable in the adjusted model. Data were analyzed using PASW Statistics 19 statistical software (PASW IBM Corp, Armonk, NY). All tests were 2-tailed, and a P value <0.05 was used to indicate statistical significance.

Results
Participants Versus Nonparticipants
From the 938 eligible patients treated for IHD, 662 filled out the questionnaires (response rate, 70.6%). For 55 of these patients, data on the Global Mood Scale (n=45) or exercise (n=10) were missing. These patients were, therefore, also considered as nonparticipants and excluded from statistical analyses, leaving 607 patients for analyses (ie, study participants). We compared participants and nonparticipants on baseline characteristics. Nonparticipants were significantly more likely to live alone (P<0.001); have a low-educational level (P<0.001); be unemployed (P=0.010); have a history of heart failure (P<0.001), arrhythmia (P=0.030), and cerebrovascular disease (P<0.001); and use diuretics (P=0.004) and antidepressants (P=0.022). Finally, patients who did not complete the questionnaire were significantly more likely to die during the 5 years of follow-up (P<0.001).

Baseline Characteristics
Baseline sociodemographic and clinical characteristics of the total patient sample and stratified by the presence of high versus low positive affect are displayed in Table 1. The mean age was 65.5±10.7 years, and 75.5% of the patients were men. Of all patients, 278 (46.0%) were not regularly exercising, whereas 328 (54.0%) reported to be involved in moderate to intensive exercise. Patients with high positive affect were more likely to be men (P=0.002), higher educated (P<0.001), and employed (P=0.004). No differences between patients with high versus low positive affect were found with respect to clinical risk factors, except for patients with high positive affect being less likely to have diabetes mellitus (P=0.039) and chronic obstructive pulmonary disease (P<0.001). On medication use, patients with high positive affect were less likely to be prescribed diuretics (P=0.006) and to use psychotropic medications (P<0.001 for antidepressants and anxiolytics; P=0.001 for hypnotics).

Events During the 5-Year Follow-Up Period
In total, 80 patients (13.2%) died during follow-up (mean follow-up period, 4.7±0.9 years; range, 0.2–5.0 years). Three patients were lost to follow-up because of migration and were censored at the date of migration. Twenty-nine patients died because of cardiovascular disease, 14 patients died of cancer, 6 patients died because of respiratory disease, 2 patients died because of diabetes mellitus, 1 patient died of renal failure, 1 patient committed suicide, 7 patients died because of other causes, and 23 patients died of unknown causes.

Positive Affect, Exercise, and Mortality
According to the log-minus-log and partial residual plots, the proportional hazards assumption was met for each variable in the model. The number of all-cause deaths during follow-up was 30 (9.9%) in patients with high positive affect and 50 (16.5%) in patients with low-positive affect, with the cumulative hazard functions differing significantly between patients with high versus low positive affect (log-rank χ²=5.59; P=0.018; Figure 1). In unadjusted Cox regression analysis, high positive affect was significantly associated with a reduced risk of mortality (hazard ratio [HR], 0.58; 95% confidence interval [CI], 0.37–0.92; P=0.020). The associated risk reduction was 42%, thus supporting the first assumption of the mediation model.

The second assumption of the model was tested with logistic regression analysis. Positive affect was significantly associated with exercise in both unadjusted (odds ratio, 1.99; 95% CI, 1.44–2.76; P<0.001) and adjusted (odds ratio, 1.48; 95% CI, 1.03–2.13; P=0.036) analyses, with patients reporting high levels of positive affect being more likely to be physically active.

Cox regression analysis showed that patients engaging in exercise were less likely to die during follow-up both unadjusted (HR, 0.39; 95% CI, 0.24–0.62; P<0.001) and adjusted (HR, 0.41; 95% CI, 0.26–0.66; P<0.001) for positive affect, confirming the third assumption of the mediation model. When examining whether the relationship between positive affect and mortality was mediated by exercise, the relationship between positive affect and mortality became marginally significant (HR, 0.65; 95% CI, 0.43–1.07; P=0.09) once exercise was included in the model, indicating mediation. In the final, further adjusted model, controlling for sex, age, body mass index, Tu comorbidity index, negative affect, and the use of psychotropic medication, exercise remained a significant independent predictor of mortality (HR, 0.50; 95% CI, 0.31–0.80; P=0.004; Table 2; Figure 2).

Repeating the results with a continuous measure of positive affect yielded similar results with respect to the association between positive affect and mortality (HR, 0.97; 95% CI, 0.95–0.998; P=0.033), results of the association between exercise and mortality remained similar, and comparable results were found for the adjusted mediation model (positive affect: HR, 1.01; 95% CI, 0.98–1.04; P=0.62; exercise: HR, 0.51; 95% CI, 0.32–0.83; P=0.007).
Positive Affect, Exercise, and Hospitalizations
The incidence of hospitalization for myocardial infarction, angina, heart failure, and IHD was 145 (47.7%) for patients with high positive affect and 167 (55.1%) for patients with low positive affect. We found no significant association between positive affect and cardiac-related hospitalization (log-rank $\chi^2=3.37$; HR, 0.81; 95% CI, 0.65–1.02; $P=0.07$) in unadjusted analysis. Because the first assumption of the model was not supported, a mediation model for positive affect and exercise in relation to hospitalization was not pursued further.

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics for the Total Study Population Stratified by Positive Affect*</th>
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<tbody>
<tr>
<td>Total, n=607</td>
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<tr>
<td>Sociodemographics</td>
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<tr>
<td>Age (mean±SD)</td>
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<tr>
<td>Men</td>
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<tr>
<td>Living alone†</td>
</tr>
<tr>
<td>Low education‡</td>
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<tr>
<td>Currently employed§</td>
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<tr>
<td>Clinical factors</td>
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<tr>
<td>Myocardial infarction</td>
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<td>Angina</td>
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<td>Heart failure</td>
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<td>Arrhythmias</td>
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<td>Cardiac arrest</td>
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<td>Previous PCI</td>
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<td>Previous CABG</td>
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<td>PAD</td>
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<td>Cerebrovascular disease</td>
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<td>Hypertension</td>
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<td>Renal failure</td>
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<td>Diabetes mellitus</td>
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<td>COPD</td>
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<td>Smoking¶</td>
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<tr>
<td>BMI (mean±SD)#</td>
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<tr>
<td>Medication</td>
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<tr>
<td>β-blockers</td>
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<td>Statins</td>
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<td>Diuretics</td>
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<td>Calcium antagonists</td>
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<tr>
<td>ACE inhibitors</td>
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<tr>
<td>Angiotensin-II antagonists</td>
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<td>Antiarrhythmics**</td>
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<td>Digoxin</td>
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<td>Psychotropic medication</td>
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<td>Antidepressants</td>
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<td>Anxiolytics</td>
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<td>Hypnotics</td>
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</table>

ACE indicates angiotensin-converting enzyme; BMI, body mass index (kg/m²); CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; GMS, global mood scale; n, number; PAD, peripheral arterial disease; and PCI, percutaneous coronary intervention.

*Results are presented as n (%) unless otherwise indicated.
†1 missing (0.2%).
‡Less than secondary school.
§4 missing (0.7%).
║Including both ventricular and atrial arrhythmias.
¶5 missing (0.8%).
#15 missing (2.5%).
**Class I and III antiarrhythmics.
Again, we also examined the results with a continuous measure of positive affect. There was a significant association between positive affect and hospitalization in unadjusted analysis (HR, 0.98; 95% CI, 0.97–0.99; \( P = 0.004 \)), and we also found a significant association between exercise and hospitalization (with patients performing exercise being less likely to be hospitalized for cardiac diagnoses when compared with patients not performing exercise: odds ratio, 0.76; 95% CI, 0.61–0.95). However, there was no mediating effect of exercise because neither the association between positive affect and hospitalization (HR, 0.998; 95% CI, 0.98–1.01; \( P = 0.79 \)) nor the relationship between exercise and hospitalization (HR, 0.90; 95% CI, 0.72–1.14; \( P = 0.39 \)) was significant in the mediation model.

**Discussion**

The associations among positive affect and mortality, positive affect and exercise, and exercise and mortality have frequently been investigated separately, but the mediating effect of exercise on the relationship between positive affect and mortality in 1 model remains understudied. We found that high levels of positive affect were associated with a 42% risk reduction in all-cause mortality during a 5-year follow-up period in patients with established IHD, whereas no relationship was found with cardiac-related hospitalizations. When adding exercise to the model, with exercise being significantly associated with mortality, the relationship between positive affect and mortality became marginally significant. These results indicate that exercise might act as a mediator in this relationship, independent of demographic and clinical risk factors.

Our finding that high levels of positive affect reduce the risk of mortality has been confirmed by previous studies in both the general\(^{35,36} \) and cardiovascular\(^{14,16,17,37} \) populations. However, no study has been specifically focusing on the effect of positive affect on long-term mortality in patients with IHD. The association between positive affect and exercise merits more attention as well because a paucity of studies has considered this relationship. Available research shows a positive association between positive affect and exercise,\(^{18,38,39} \) which is confirmed by the present results. Only 1 similar study assessing the mediating role of exercise in the relationship between positive affect and mortality has been performed so far, yielding similar results.\(^{40} \) Our study confirms this knowledge by the use of highly reliable data on clinical history, hospitalization, and mortality from the national Danish registers.

However, because positive affect and exercise were both measured at baseline, the design of this study does not permit to draw conclusions about the direction of causality. In the literature, evidence exists for both directions. Netz et al\(^{41} \)
concluded in their meta-analysis that engaging in exercise leads to improved psychological well-being. In a randomized controlled trial, positive affect increased in patients who engaged in walking and yoga activities during follow-up when compared with patients who were not physically active.52 The opposite direction has also been studied. In 2132 sedentary adults, those with a more positive outlook on life were more likely to exercise during 6 months of follow-up than adults who did not feel positive.18 To our knowledge, the only study that investigated the effect of positive affect on exercise in cardiac patients was a randomized controlled trial in postpercutaneous coronary intervention patients.19 In this study, positive affect induction led to increased exercise and energy expenditure during 12 months of follow-up, and patients with higher positive affect were capable of maintaining their physically active lifestyle during the entire follow-up period. Importantly, the intervention was particularly effective in patients with a high-comorbidity burden. These and other results suggest that patients with higher levels of positive affect might possess more adequate coping strategies, and higher levels of self-regulation, by which health-behavior change, including being physically active, can occur and be maintained.20,21 Drawing conclusions about the direction of the relationship is yet premature, but the most likely conclusion regarding this interrelationship would be that it is bidirectional.40

Examining the mechanisms that may explain the relationship between positive affect and mortality is important because these mechanisms could provide us with information on targets for future intervention. Exercise is used in cardiac rehabilitation settings to improve patients’ functional status and prognosis.43 However, many patients do not achieve and maintain a desirable level of exercise even when they participate in a cardiac rehabilitation program.34,45 Identification of the factors that determine whether a patient will engage in exercise training is, therefore, very important. Among others, being women, having a low-educational level, having a high-comorbidity burden, depression, and having a low physical activity level before the onset of disease have been shown to be predictive of a poor exercise pattern in cardiac patients.46-47 Besides these demographic and clinical factors, patients’ personality traits, including positive affect, may also determine the extent to which patients are physically active. Interventions aimed at elevating patients’ exercise levels may be much more effective when the underlying mechanism is modified as well. Focusing on increasing positive affect could, thus, increase the likelihood of the accomplishment and maintenance of a healthy exercise pattern.

The results of this study should be interpreted with the following limitations in mind. First, the nonparticipants of this study were more likely to have a higher risk profile, both in terms of sociodemographic and clinical risk factors. We had no information on positive affect and exercise of the nonparticipants in this study, but given that these patients tended to be sicker and more likely to use antidepressants, they may have had lower positive affect and exercise scores than those who did respond to the questionnaire. Nevertheless, this implies that the associations found in this study are likely to be underestimated and that the direction of the results would not be different had these patients been included. Second, because information on cause of death was missing for a subset of patients (n=23), we used all-cause mortality as the primary end point and were not able to differentiate between cardiac- and noncardiac-related causes of death. Furthermore, because of the limited number of events, we did not include symptoms of depression and anxiety as additional covariates in our analyses. However, as the negative affect component shared across different negative emotions has been shown to independently predict disease pathology in cardiac patients,48 we decided to include a broad measure of negative affect instead of the more narrow representations of negative affect, such as anxiety and depression. In addition, the sample mainly consisted of patients from European origin. As such, the results are not necessarily generalizable to patients of other races. Finally, we did not have information on patients’ exercise intensity and type of exercise. These aspects should be incorporated in future research because they may impact on the relationship between positive affect and exercise, and exercise and prognosis.

An important strength of the study is the use of registers to collect data on demographic and clinical characteristics, hospitalizations, and mortality. This enables us to provide reliable information with respect to the demographic and clinical risk profiles of the patients. In addition, we used a validated self-report scale of positive affect that was developed in cardiac patients. Although some studies advocate the use of interviews to measure affect, scores on self-report scales have shown to be highly correlated with interviewer-based levels.49 Third, we adjusted for important potential demographic and clinical confounders in the mediation model, including negative affect, because positive and negative affect are independent constructs.13 Finally, the prospective study design with a relatively long follow-up duration also comprises a strength of the study.

In conclusion, we found that patients with higher levels of positive affect were more likely to exercise and were at lower risk of dying during 5 years of follow-up, with exercise mediating the relationship between positive affect and mortality, independent of demographic and clinical risk factors.
factors. Because positive affect is related to exercise, interventions aimed at positive affect induction in combination with exercise promotion may induce better outcomes for patients, both in terms of increasing the likelihood of the accomplishment and maintenance of a healthy exercise pattern and in terms of better psychological functioning, than interventions focusing on the promotion of exercise alone. Future studies should focus on the development of such interventions tailored to the specific needs of patients with IHD.

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Disclosures
Dr Pedersen has received moderate consultancy and speaker’s fees from St. Jude Medical, Sanofi-Aventis, Medtronic, and Cameron Health BV in the past and is currently serving as a consultant for Boston Scientific. Dr Zwisler has received speaker’s fees from Pfizer, MSD, and Astra Zeneca. The other authors report no conflicts.

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13. Hoogwegt et al. Positive Affect, Exercise, and Mortality in IHD 565


