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The Impact of Angina and Cardiac History on Health Related Quality of Life and Depression in Coronary Heart Disease Patients

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Abstract

Objective—To prospectively examine the contribution of angina and cardiac history to health-related quality of life (HRQoL) and depression in cardiac patients, over 6 months post-hospitalization.

Methods—Participants were myocardial infarction (MI), percutaneous coronary intervention (PCI), or coronary artery bypass grafting surgery (CABG) out-patients under the age of 70. One hundred and seventy one patients consented to participate, with 121 patients retained 6 months later (71% response rate). The impact of the patient's cardiac history and the presence of angina on physical, social and emotional HRQoL and depression was examined.

Results—At baseline, cardiac history was not significantly related to any of the dimensions of HRQoL or depression. At 6-months follow-up, cardiac history significantly predicted a higher level of depression, and angina was predictive of a significantly worse emotional, physical, and social HRQoL and a higher level of depression.

Discussion—The presence of a cardiac history is associated with depression 6 months post-cardiac event, and angina is associated with both an adverse HRQoL and higher levels of depression. As past research has demonstrated depression is a risk factor for mortality in patients

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with established heart disease, it is important both from a clinical and a research perspective to address these issues.

Keywords

angina; cardiac history; coronary heart disease; depression; quality of life

Introduction

The profile of diseases contributing most heavily to death, illness, and disability among western/developed countries has changed dramatically during the last century. Today, chronic diseases — such as cardiovascular disease (primarily heart disease and stroke), — are among the most prevalent, costly, and preventable of all health problems. The prolonged course of illness and disability from chronic disease results in extended pain and suffering, and decreased quality of life for millions of people around the world. Coronary Heart Disease (CHD) is the primary cause of premature death in the western world. Due to such a high prevalence and incidence, CHD has taken a high priority in health research. 2

As many people live with chronic CHD, health related quality of life (HRQoL) has become an increasingly important outcome measure after hospital admission for a myocardial infarction (MI) or invasive procedures. HRQoL is considered an important outcome measure of medical technology and disease control by patients, clinicians, and society alike.³ Although there is no internationally agreed definition of HRQoL, there is a consensus that it is a multifaceted construct with physiological, psychological, emotional, and social components.⁴

Although previous research has focused on HRQoL after a cardiac event, to our knowledge, very little research has evaluated the impact of cardiac history on multidimensional HRQoL and depression. To date, it is unclear whether patients whom have suffered a previous event recover differently from patients whom have not suffered this fate with respect to a multifaceted construct of quality of life in cardiac patients.

Angina remains the most common initial manifestation of coronary heart disease. There are still many misconceptions about the continuing importance of angina which results from the success of revascularization and recent clinical trials. Not all patients who have angina access medical care or receive a diagnosis. More importantly, not all angina patients are able to undergo revascularization which has been shown to reduce symptoms of chest pain and discomfort. Much of the previous literature has focused on the admission of patients with acute coronary syndrome, as this is reasonably well defined, but this is not the case for stable angina. Although incident angina may be considered as too soft an endpoint by epidemiologists, it does not dismiss the fact that these patients do suffer adverse affects in the form of decreased quality of life. Pocock et al. [7] found that the patients' grade of angina had a marked relationship with every aspect of perceived health status. Patients with angina had a worse HRQoL than angina-free patients. Bengtsson et al. [8] found that anginal grade was negatively related to HRQoL. Significant differences were found between patients with and without angina in physical capacity and self-reported general health, where angina grade was negatively related to QoL. As previous literature has described that patients with

angina have an increased risk of mortality ^{5,9} and lower health related-quality of life levels, ^{7,8,10} additional research is warranted to further investigate health outcomes of patients with angina.

Although angina patients indicate that their HRQoL is affected in many cases, depression is also strongly correlated with the presence of angina within a CHD population. ¹¹ Treatment of depression has been shown to reduce chest discomfort, ischemia, and utilization of medical care. ⁷

Previous studies have demonstrated repeatedly that depression is significantly related to morbidity and mortality after cardiac events. ^{12–18} Therefore it is important, both from a clinical and a research perspective to assess depression after a patient has experienced a cardiac event.

The present study examines the impact of angina and cardiac history on physical, social, emotional HRQoL and depression in CHD patients. Moreover, this study attempts to show that patients with angina and a cardiac history may not be recovering at an acceptable rate by 6-months post-hospitalization. More specifically, this study attempts to assess (1) if the fact that patients have had a previous cardiac event (either MI, PCI, or CABG) is associated with an adverse HRQoL and higher depression, both at baseline and at follow-up, and; (2) if the presence of angina pectoris is associated with a poorer HRQoL and higher levels of depression at follow-up.

Materials and Methods

Study population

The subject population were patients under the age of 70 (M = 53.98, SD = 8.39), recruited after having been admitted to either one of two hospitals or one of two cardiac rehabilitation centers in the Netherlands after an MI, PCI or CABG. All patients were recruited about 45-days post-cardiac event.

Two hundred patients were initially approached by their cardiologist for participation in the study. Of these, 171 patients (143 males; 86%) agreed to participate. Seventy-seven patients were admitted for an MI (45%), 61 (36%) for a PCI, and 33 (19%) for a CABG. Patients were not approached for participation if they were unable to give informed consent, unable to understand the Dutch language and if they suffered from a serious organic non-cardiac disease.

The patients who participated at the first measurement were sent a follow-up questionnaire (which was identical to the baseline questionnaire) 6 months later. The response rate at follow-up was 71% (N = 121). The sample characteristics at baseline and follow-up are reported in Table 1. No significant differences were found on any of the sociodemographic and medical variables between the participants for whom baseline and follow-up data were available, and for those participants that dropped out prior to follow-up.

Data Collection

This was a prospective study that examined participants' perceptions of their physical, social, emotional HRQoL and psychological well-being. The self-report survey consisted of questions that examined sociodemographic characteristics, HRQoL and depression at 45 days (baseline) and 6 months (follow-up) after the date of admittance. ¹⁹ More specifically, the instrument used to measure HRQoL was the Dutch MacNew Questionnaire (MacNew). ²⁰ This self-report measure consists of 26 items related to 3 domains of HRQoL, emotional, social, and physical HRQoL. Each item is rated on a 7-point Likert scale, where '1' indicates poor HRQoL and '7' indicates good HRQoL. The Dutch MacNew was demonstrated to have adequate reliability and validity, and the internal consistency was fair to (very) good (ranging between .78 and .95). ²⁰ The 90-Item Symptom Checklist (SCL-90R) was used to assess depression. ^{21–23} The depression subscale consists of 16 items. A higher score indicates a higher level of depression. The SCL-90R depression subscale has shown good reliability and validity. ^{21,22}

In the baseline survey, patients were asked to report if they had experienced a previous cardiac event prior to their current admission. Angina pectoris status was also obtained by patient self-report.

Statistics

All statistical analyses were performed with SPSS release 12.0. Data were cleaned and screened to evaluate statistical assumptions. Descriptive examination of the variables was performed using chi-square and Analysis of Variance (ANOVA) as appropriate. Multiple linear regression analyses were used to examine predictors of HRQoL and depression. The regression analyses adjusted for demographic characteristics (age and gender), and reason for admittance (MI, PCI, CABG) as these variables showed significance in the initial descriptives analysis. All predictors were entered into the model using the forced entry method. All statistical tests were two-tailed. P < 0.05 was used for all tests to indicate statistical significance.

Results

Impact of cardiac history on health-related quality of life and depression at baseline

Multiple linear regression analyses revealed that at baseline the presence or absence of a previous cardiac event (cardiac history) was not significantly related to any of the dimensions of HRQoL or depression (see Table 2).

Gender was shown to be significant on all of the HRQoL subscales as well as the depression measure, where women had significantly worse HRQOL and a higher depression level compared to men. It is also noteworthy to mention that patients with a cardiac history have slightly lower baseline MacNew HRQoL scores and a slightly higher depression mean score on the SCL-90 (see Table 3).

Health-related quality of life and depression 6 months post-cardiac event

Impact of Cardiac History—Multiple linear regression analyses showed that a cardiac history was not predictive of a worse HRQoL at follow-up. Gender was significant on the social HRQoL subscale (women had lower mean scores compared to men) and the CABG variable was also significant at follow-up on the emotional HRQoL subscale (CABG patients indicated a better emotional HRQoL) (see Table 4). It is noteworthy to mention that patients with a cardiac history did indicate lower follow-up mean scores on the MacNew HRQoL questionnaire (see Table 3).

Moreover, the follow-up analysis showed that cardiac history was significantly predictive of higher depression levels (p = .042) (Table 4). The effect size is 0.2, which is considered a small effect according to Cohen's standard.

The results suggest that there may be two different basic recovery trajectories based on whether a patient has or has not experienced a prior cardiac event. The results may indicate that patients with a cardiac history are recovering differently than patients with no previous cardiac event (specifically with regard to depression). Figure 1 depicts the different pathways of recovery for depression.

Angina Pectoris—The angina variable was coded into two groups. The first group consisted of patients that had angina at follow-up. The second group did not have angina at the 6-month measurement.

Descriptive analyses showed that at follow-up, only 2% of bypass patients reported angina, whereas 20% of PCI and 27% of MI patients reported that they were experiencing angina at the second measurement (data not shown).

The linear regression analyses showed that angina at follow-up was predictive of a significantly worse emotional (p = .006), physical (p = .001), and social (p = .042) HRQoL, and a higher depression level on the SCL-90 (p = .041) (See Table 4).

Additional analyses, controlling for HRQoL and depression subscale scores at baseline, revealed that, whereas the impact of angina on overall emotional, physical, and social HRQoL and depression at follow-up remained significant, the impact of cardiac history on depression no longer was (data not shown).

Discussion

Summary of Main Findings

The main objective of the present study was to examine whether a cardiac history (presence versus absence of previous cardiac events), and the presence of angina six months after hospital admittance for an MI, PCI, or CABG have a significant impact on physical, social and emotional HRQoL and depression in a CHD population.

Very little research has been conducted on the impact of cardiac history on multidimensional HRQoL and depression in patients with heart disease. The findings of the present study showed that both at baseline and at follow-up there were no significant differences on

emotional, physical and social HRQoL between patients with and without a cardiac history. With respect to depression, significant differences were found at 6 months follow-up on this dimension. The depression scores of patients with a cardiac history seem to remain stable over the 6-month follow-up period, whereas the level of depression in patients without a cardiac history decreases over time (Figure 1).

It is noteworthy to mention that although a significant difference with respect to cardiac history was only found for depression, patients with a cardiac history also had a lower overall HRQoL mean scores compared to patients that had never experienced a cardiac event (linear regression however failed to find significance).

At the six-month follow-up, patients with angina reported significantly worse HRQoL and higher depression levels.

Clinical relevance of working towards improving HRQoL in patients after multiple events - and not just accepting it

The findings suggest that, from a psychological point of view, patients with and without previous cardiac events, may be functioning at similar levels at baseline, but differently at follow-up. Perhaps after experiencing a cardiac event, both groups might be feeling a moment of optimism, thinking that a cardiac procedure and/or lifestyle change will improve their life and life chances. However, as time continues, the fact that symptoms and stresses do not fade easily, might have a bigger impact on patients who have experienced a prior cardiac event.

Existing literature shows that after a cardiac event, patients are confronted with a number of challenges, ranging from the management of chest pain, to coping with imposed lifestyle changes, and an uncertain future. The stress of these challenges results in a significant number of individuals experiencing considerable psychological and life difficulties which interfere with their daily functioning. ²⁴ Those patients who had already experienced all the life adjustments and stresses the first time around, only to have another cardiac episode, would most likely experience all the above in an even more intensive manner, particularly a fear of an uncertain future.

The findings in the present study indicate a clinical relevance with respect to patients whom have experienced a repeat cardiac event. As patients with a cardiac history are reporting higher depression levels, it seems critical to identify these patients when developing treatment programs. Identification and targeting of patients with a cardiac history in cardiac rehabilitation (CR) or home-based programs may be important in reducing depression, stress and worry in everyday life. Targeting these patients may help to improve daily functioning and decrease morbidity and mortality rates.

With respect to angina, the results of the present study indicate that patients who continue to experience angina symptoms six months after their cardiac event, report significantly worse emotional, physical and social quality of life, and a significantly higher level of depression than patients without angina. At follow-up only 2% of bypass patients reported angina; however, 20% and 27% of PCI and MI patients reported angina respectively.

With respect to angina, the results of the present study indicate that patients who continue to experience angina symptoms six months after their cardiac event, report significantly worse emotional, physical and social quality of life, and a significantly higher level of depression than patients without angina. At follow-up only 2% of bypass patients reported angina; however, 20% and 27% of PCI and MI patients reported angina respectively. As patients with still existing angina at follow-up are relatively in the MI and PCI groups, this may been an indication of still existing myocardial ischemia resulting from incomplete revascularization or the inability of the patient to be amenable with PCI or CABG after an MI. Not all patients with angina (and heart disease in general) are treatable with revascularization due to the nature of the disease.

The results of worse perceived HRQoL among patients with angina compared to patients without angina support previous findings. ^{7,17,25} Although the present study supports these findings, the results add to the notion that angina patients do have a worse HRQoL, and that this functional status remains impaired on all of the multi-dimensional subscales 6 months post-cardiac event. This study indicates that this group of patients may not be recovering as quickly as the other patients in the sample. This study supports the idea that patients with angina should be frequently monitored in the months after a post-cardiac event, and not just before or immediately after an MI or invasive procedure. The evaluation of physical and mental health remains an important task when managing angina patients. It is important that patients with stable angina do not get lost to follow-up, as these patients are indeed as important to manage as patients with an acute cardiac event.

States of distress (inclusive of depression), have been shown in recent studies to be associated with myocardial ischemia, ^{18,26} as well as an increased rate of morbidity and mortality from cardiac events. ^{13–15,18,27} Therefore, it is important to recognize that CHD patients with angina may be at a higher risk for future complications, and even death. A study by Springer et al. [18] states that 'refractory angina, in which pain continues to occur even after medication and surgical remedies, can worsen a patient's functional disability and lead to heightened negative emotional states of stress, anxiety, and depression'. The authors also state that if these conditions continue, then they may negatively affect morbidity and mortality.

Although there seems to be a consensus that angina is associated with depression, ¹¹ the direction of this relationship remains unclear. The present study suggests that depression may be the result of angina; however, the review by Ketterer et al. [11] shows that depression was a predictor of anginal chest pain symptoms in at least two studies. ^{28,29} In fact, it may be proposed from the results of the present study and previous studies, that there is an indication of a vicious circle in the CHD population. A number of studies show that depression may be a predictor of angina, and in other cases, depression may be the result of the angina condition. Ketterer et al. [11] state that depression is common in pain syndromes, specifically angina, and that these psychiatric conditions may worsen symptoms experienced by angina patients. In any case, it seems that research indicates that states of depression and angina influence one another.

Whether a predictor or the result of angina, the treatment of depression is important in patients that are admitted to comprehensive CR programs. The treatment of depression (and also targeting other emotional components such as anger and anxiety) has been shown to reduce anginal symptoms, ^{30–34} hospital readmissions, and recurring cardiac events in angina patients. ¹¹ The results of these studies demonstrate the treatment of depression may help break the vicious circle (in which angina symptoms and depression influence one another) in order to prevent, control, and reduce anginal symptoms that are intensified by depression (and other psychiatric conditions).

Limitations of this Study

The results of this study should be interpreted with some caution. Firstly, we did not collect objective medical information such as the presence of comorbid medical conditions (e.g. diabetes mellitus) or family history of heart disease, which are known prognostic indicators. This may have somewhat biased our results. Therefore, future studies within this domain should control for these factors. Secondly, angina status was not assessed in the regression analysis at baseline due to logistical reasons. Thus we do not know what differences - if any - existed between angina and angina-free patients at the first measurement. Nevertheless, assessment of psychological symptoms at the time of a cardiac procedure has not been shown to be an optimal time point, as symptoms may reflect distress related to the procedure.³⁵ In the early months following a cardiac event, it may be difficult for patients to distinguish between chest discomfort caused by anxiety and depression rather than by angina. It is however important to mention that angina has been an established predictor of HRQoL and psychological distress, therefore the results of the current study may not have been affected due to this missing data. Another limitation of the study is that the sample consists of many more men than women. There may be several reasons for the higher inclusion of men in the sample population. Firstly, patients were recruited partly from one of two cardiac rehabilitation (CR) centers. It has been shown in the literature that fewer female patients participate in CR, ^{36,37} thus this could have been part of the reason that fewer women were recruited to participate in this study. Secondly, women are generally older and have more comorbidities than men with heart disease. Older women (over the age of 70) and women with other serious diseases (i.e. cancer or renal failure) would have been excluded from participating. As literature indicates that women are less likely to participate in research that evaluates heart disease, future studies should actively recruit women to be included in the study population.

Conclusions

Implications for Future Research and Clinical Practice

In the current study, angina was measured by self report. It would be useful for future research to consider tracking cardiac patients observationally over time, and having participants wear a Holter monitoring device and/or by administering ECGs at several time points to assess ischemia. Along with self report, these tests may help accurately define angina at an earlier stage after a cardiac event. Further, future research should collect thorough clinical data, and objectively assess anginal frequency at several time points.

The results of the present study indicate that the presence of continuing or recurrent angina symptoms six months after a cardiac event is predictive of worse overall HRQoL and higher levels of depression in CHD patients. In order to prevent the development of a vicious circle characterized by the fact that angina and depression continuously influence each other in a negative way, psychological assessment and interventions are considered to be important components of CR. They may especially be vital in the first months after a cardiac event as patients are beginning their recovery and adjusting to new lifestyle changes. The impact of cardiac history on depression six months after a cardiac event should be further explored, as it may reveal itself to be an important prognostic factor for the development of psychological distress in CHD patients.

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Patients with no cardiac history

Patients with a cardiac history

SCL-90 Depression

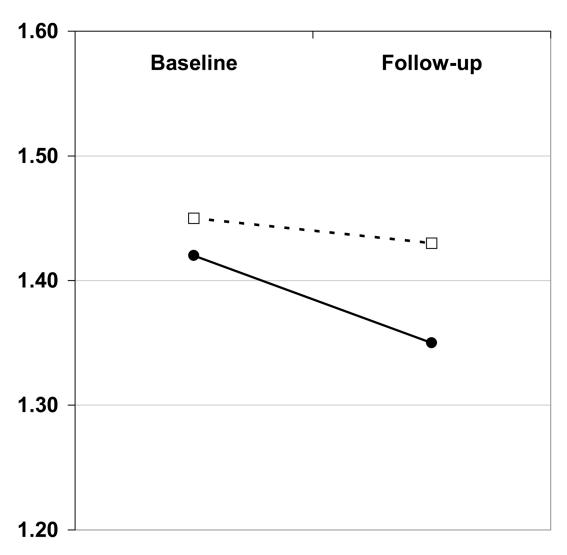


Figure 1. Presence Versus Absence of Previous Cardiac Events Give Rise to Distinct Trajectories of Recovery on Depression Mean Subscale Scores.

Depression at 6 Months stratified by Previous Cardiac History*

^{*} Linear Regression. A higher score indicates higher depression levels.

Table 1
Sociodemographic and Medical Characteristics of the Patient Sample at Baseline and Follow-up

Sociodemographic characteristics	Baseline (N = 171)	Follow-up (N = 121)
Age, mean (SD)	53.98 (8.29)	54.91 (8.00)
Gender		
Male, n (%)	144 (84.0)	104 (86.0)
Living Situation*		
Living Alone	12.0	9.0
Living with Partner and/or Children	88.0	91.0
Education*		
Primary Education	12.3	11.6
Lower Secondary Education	46.8	51.2
Higher Secondary Education	25.7	23.1
Higher Education	12.9	13.2
Employment Status * a		
Not working	28.1	30.6
1–20	10.6	9.9
21+	57.8	57.0
Medical characteristics		
Reason for admittance * b		
CABG	19.0	23.0
PCI	36.0	41.0
MI	45.0	36.0
Previous cardiac event *c		
Presence of a previous cardiac event	22.8	22.3
Angina Pectoris (AP)*		
Presence of AP	32.0	24.8
Location of Recruitment*		
Hospital	67.0	N/A
CR site * d	33.0	N/A

^{*}Numbers are percentages. Those percentages that do not add to 100% may have missing values.

^aNumber of hours worked per week,

 $^{{}^{}b}_{\text{Myocardial infarction (MI), percutaneous coronary intervention (PCI), coronary artery bypass grafting surgery (CABG)}.$

cardiac event = MI, PCI, or CABG,

 $^{^{}d}$ Cardiac Rehabilitation (CR).

Table II

Cardiac history as a predictor of impaired HRQL at baseline: A comparison between patients with and without a previous cardiac event (adjusted analyses)

	β	sr ²	95% Confidence Interval	
Emotional HRQoL			Lower Bound	Upper Bound
Previous Event (cardiac history)	006	006	-5.118	4.768
Gender	207 ⁺	208	-11.920	-1.768
Age	052	052	311	.157
PCI	112	048	-12.051	6.445
CABG	.026	.013	-8.632	10.215
MI	046	020	-10.265	7.998
Physical HRQoL				
Previous Event (cardiac history)	004	004	-4.532	4.327
Gender	199*	203	-10.538	-1.440
Age	069	069	302	.117
PCI	095	041	-10.467	6.109
CABG	.114	.059	-5.282	11.607
MI	138	059	-11.276	5.090
Social HRQoL				
Previous Event (cardiac history)	.001	.001	-3.317	3.357
Gender	210 ⁺	211	-8.224	-1.290
Age	056	055	213	.102
PCI	.013	.005	-6.073	6.506
CABG	.132	.067	-3.684	9.190
MI	.023	.010	-5.836	6.627
SCL-90 Depression				
Previous Event (cardiac history)	.023	.021	056	.073
Gender	.174*	.175	.009	.143
Age	.001	.001	003	.003
PCI	.295	.125	024	.218
CABG	.138	.070	069	.180
MI	.230	.097	046	.195

 $MI = myocardial\ infarction;\ PCI = percutaneuous\ coronary\ intervention;\ CABG = coronary\ artery\ bypass\ grafting$

The SCL-90R depression subscale was transformed using LOG10 in order to normalize the data.

^{*}p < 0.05;

⁺p < 0.01;

 $[\]frac{1}{p}$ < 0.001

 $\label{eq:Table 3}$ Means and Standard Deviations for HRQoL at Baseline and 6-Month Follow-up, Broken Down by Cardiac History and Gender (N = 121)

		Baseline Mean Score (SD)	Follow-up Mean Score (SD)
Emotional HRQoL		` ,	•
No previous events	men	54.19 (12.20)	60.40 (11.71)
	women	48.69 (9.01)	56.45 (13.50)
	Total	53.32 (11.89)	59.79 (12.01)
At least 1 previous event	men	51.27 (11.27)	54.62 (13.30)
	women	46.00 (5.29)	51.00 (9.17)
	Total	50.61 (10.77)	54.17 (12.75)
Physical HRQoL			
No previous events	men	49.44(10.83)	56.35 (10.47)
	women	43.00 (10.82)	52.08 (11.21)
	Total	48.41(11.82)	55.71 (10.63)
At least 1 previous event	men	46.70 (10.35)	50.00 (13.15)
	women	43.00 (6.83)	47.00 (5.00)
	Total	46.24 (9.90)	49.64 (12.42)
Social HRQoL			
No previous events	men	37.35 (8.09)	41.10 (7.01)
	women	31.88 (9.76)	37.14 (9.11)
	Total	36.48 (8.56)	40.50 (7.44)
At least 1 previous event	men	36.01(8.10)	37.82 (7.06)
	women	32.17 (2.57)	35.33 (3.51)
	Total	35.54 (7.72)	37.52 (6.73)
SCL-90 Depression			
No previous events	men	1.39 (0.14)	1.34 (0.13)
	women	1.45 (0.17)	1.39 (0.17)
	Total	1.40 (0.15)	1.35 (0.14)
At least 1 previous event	men	1.45 (0.13)	1.44 (0.13)
	women	1.51 (0.11)	1.47 (0.11)
	Total	1.45 (0.13)	1.44 (0.13)

 $^{^{*}}$ The SCL-90R depression subscale was transformed using LOG10 in order to normalize the data.

Of note, p values were not incorporated into this table. Significant differences can be found in Table 2.

Table 4

Cardiac history and angina as predictors of impaired HRQL and psychological distress at follow-up

	β	sr ²	95% Confidence Interval	
Emotional HRQoL			Lower Bound	Upper Bound
Cardiac history	090	089	-8.552	3.149
Angina Pectoris	.304-1	.305	3.391	13.581
Gender	134	145	-10.666	1.464
Age	029	031	327	.237
PCI	329	149	-18.718	2.253
CABG	367*	193	-21.869	208
MI	232	109	-16.607	4.531
Physical HRQoL				
Cardiac history	113	115	-8.206	2.094
Angina Pectoris	.336⊥	.341	4.004	13.249
Gender	137	151	-9.995	1.204
Age	028	030	294	.215
PCI	377	176	-18.092	.744
CABG	311	169	-18.161	1.156
MI	249	120	-15.386	3.564
Social HRQoL				
Cardiac history	113	110	-5.511	1.520
Angina Pectoris	.261+	.260	1.212	7.523
Gender	187*	195	-7.733	089
Age	013	014	186	.161
PCI	.015	.007	-6.206	6.652
CABG	.070	.037	-5.334	7.852
MI	.069	.032	-5.391	7.545
SCL-90 Depression				
Cardiac history	.206 *	.199	.003	.137
Angina Pectoris	204 *	206	125	005
Gender	.127	.135	021	.120
Age	.019	.020	003	.004
PCI	.287	.121	048	.211
CABG	.220	.107	059	.207
MI	.246	.107	058	.203

^{*}p < 0.05;

The SCL-90R depression subscale was transformed using LOG10 in order to normalize the data.

 $p^{+} < 0.01;$

 $^{^{ \}rlap{\perp} }p < 0.001$