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Impaired Health Status, Psychological Distress, and Personality in Women and Men With Nonobstructive Coronary Artery Disease

Sex and Gender Differences: The TWIST (Tweesteden Mild Stenosis) Study

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Background—Patients with nonobstructive coronary artery disease (NOCAD; wall irregularities, stenosis <60%), and women with NOCAD in particular, remain underinvestigated. We examined sex and gender (S&G) differences in health status, psychological distress, and personality between patients with NOCAD and the general population, as well as S&G differences within the NOCAD population.

Methods and Results—In total, 523 patients with NOCAD (61±9 years, 52% women) were included via coronary angiography and computed tomography as part of the TWIST (Tweesteden Mild Stenosis) study. Generic health status (12-item Short Form physical and mental scales and fatigue), psychological distress (Hospital Anxiety and Depression Scale anxiety and depressive symptoms and Global Mood Scale negative and positive affect), and personality (Type D personality) were compared between patients with NOCAD and an age- and sex-matched group of 1347 people from the general population. Frequency matching was performed to obtain a similar sex distribution in each age–decile group. Both men and women with NOCAD reported impaired health status, more psychological distress, and Type D personality compared with men and women in the reference group. Women reported more psychosocial distress compared with men, but no significant sex-by-group interaction effects were observed. Women with NOCAD reported impaired health status, more anxiety, and less positive affect, but no differences in depressive symptoms, angina, or Type D personality when compared with men with NOCAD. Age, education, employment, partner, and alcohol use explained these S&G differences within the NOCAD group.

Conclusions—In both men and women, NOCAD was associated with impaired health status, more psychological distress, and Type D personality when compared with a reference population. Factors reflecting S&G differences explained these S&G findings in patient-reported outcomes.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01788241.

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Key Words: anxiety ■ coronary artery disease ■ depression ■ health status ■ quality of life ■ sex ■ Type D personality

Patients with nonobstructive coronary artery disease (NOCAD), or mild stenosis, have detected visible wall irregularities, but no obstructive coronary luminal narrowing (<60% stenosis) in ≥1 epicardial arteries.[1–3] NOCAD has been associated with an elevated risk of major adverse cardiovascular events and all-cause mortality when compared with a reference population without coronary artery disease (CAD).[4,5] Traditional treatment for CAD mainly focuses on functional outcomes, such as survival and mortality. However, these rates do not reflect all aspects of health. Patient-perceived health status, psychological distress, and personality are factors that are known to affect clinical outcomes in patients with established CAD.[4,6–8] As such, these psychosocial factors serve as proxy risk factors for future cardiovascular events.[9]

Health status is a subjective measure of overall well-being and reflects how a disease and its symptoms are interpreted by the patient.[10] Oldridge et al[11] argued that the goal of today's medicine should be to increase patients' quantity of life, as well as their quality of life, or health status. Psychological distress (symptoms of anxiety and depression, and relative

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WHAT IS KNOWN

- Women with cardiovascular disease more often report impaired health status and worse psychological distress.
- Women present more often with nonobstructive coronary artery disease (NOCAD), but sex and gender (S&G) differences in health status and psychological distress are not well investigated in patients with NOCAD.

WHAT THE STUDY ADDS

- In both men and women, NOCAD was associated with impaired health status, more psychological distress, and Type D personality when compared with a reference population, and women reported higher patient-reported outcomes compared with men.
- S&G differences were of similar magnitude in patients with NOCAD and the reference group.
- Age, education, partner, employment, and alcohol use, reflecting S&G differences, explained these S&G differences in patient-reported outcomes.

absence of positive affect [PA]) has been related to cardiac outcomes.[8,12,13] Type D personality represents people who experience negative emotions (negative affectivity [NA]) and at the same time inhibit these emotions in social situations (social inhibition [SI]). Type D personality has been associated with poor physical and mental health status[14,15] and more chest pain in patients with NOCAD.[16]

Patients with established CAD,[17] as well as population-based self-reported CAD which included myocardial infarction (MI) or angina, are known to have significantly impaired health status and more depressive symptoms compared with those without CAD.[18,19] Wheeler et al[20] reported more depressive symptoms and poorer mental health status in patients with NOCAD compared with obstructive CAD and a reference group. However, NOCAD was based on either normal coronary angiographic results in addition to minor lesions (<50%), and some patients with NOCAD had a history of MI. Little is known about impaired health status and psychological distress in patients with NOCAD based on visible coronary irregularities when compared with the general population. Moreover, women tend to report impaired health status and more depressive symptoms when compared with men.[19,21] Measuring health status, psychological distress, and personality among patients with NOCAD provides information about the societal burden of this condition.

There is a lack of knowledge on sex and gender (S&G) differences in patients with NOCAD, which in turn can lead to undertreatment and suboptimal care.[2,22] The increased recognition of S&G differences in patients with NOCAD and health status outcomes, and the implications for clinical practice, has led to calls for more S&G sensitivity and specificity in future research and within clinical practice.[23] Whereas the term sex implies biological differences, gender is a broad term reflecting social and cultural effects.[24] The terms sex and gender are interchangeably used in cardiovascular research because it is difficult to distinguish between both.[22] Moreover, a multitude of other aspects differentiate people, including age, socioeconomic status, and ethnicity. Some of these factors further differentiating S&G differences can be acknowledged in cardiac populations. For example, women are on average 7 to 10 years older when cardiovascular disease emerges, but younger women with CAD are at increased risk for adverse outcomes.[22] Potential factors related to individual differences which may add to explain S&G differences will be examined in this study.

The main objective of this study was to examine S&G differences in health status, psychological distress, and personality subtypes between patients with NOCAD, as part of the TWIST (Tweesteden Mild Stenosis) observational cohort study, and a sex- and age-matched reference group from the general population. We hypothesized that both women and men with NOCAD would have impaired health status scores, more negative psychological distress, reduced PA, and more Type D personality characteristics when compared with the reference group. We further hypothesized that within the NOCAD group, women would report impaired health status, more psychological distress, and more Type D personality when compared with men. We also examine covariates that could provide more insight in the role of S&G differences.

Methods

Patients and Procedure

This study is part of the TWIST observational cohort study. All patients in the TweeSteden Hospital Tilburg, being referred by their cardiologist and receiving coronary angiography (CAG) or 64-slice computed tomography (CT), were screened for eligibility between January 2009 and January 2013. The TWIST study was initiated to study classic and novel risk markers for NOCAD.[15] Patients were eligible if they had a CT calcium score >0 without additional referral to CAG, or CAG diagnosed mild coronary stenosis with visible nonobstructive wall irregularities. Exclusion criteria were severe coronary stenosis (>60%); a previous history of cardiac events, such as MI, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) surgery, or heart failure; and insufficient knowledge of the Dutch language. In total, 883 patients were eligible for participation and received information on the study, as has previously been described in more detail.[16] In total, 547 (62%) patients signed informed consent, of which 523 completed a set of questionnaires which were send and returned by postal mail. The research protocol was approved by the medical ethics committee of the Elisabeth Hospital Tilburg, and written informed consent was obtained from all participants (METC Brabant protocol number: NL22258.008.08).

Data were collected ≤3 months after CAG or CT scan and included self-reported demographic variables (sex, age, marital status, and educational level) and lifestyle factors. Disease status and history, medication use, and comorbidity were retrieved from patient hospital records. Biochemical correlates were collected but are not reported in this study.

Reference Group

The reference group of sex- and age-matched controls was selected from a convenience sample of 3389 participants from the Dutch general population residing in the Southern provinces of the Netherlands (population of ≈4 million), collected between 2007 and 2010. Participants were approached personally or by phone by research assistants. Participants received an informed consent form and a questionnaire, which were returned in closed, coded envelopes. Questionnaires used for this study were the 12-item Short Form, Fatigue Assessment Scale, Global Mood Scale, Hospital Anxiety and Depression Scale, and the Type D personality scale, as well as descriptive sociodemographic

information. Comorbid conditions were based on self-reported 'physician or specialist diagnosed presence' of among others cardiovascular disease, lung conditions, diabetes mellitus, dyslipidemia, and hypertension, with an open-ended question to further specify. Cardiac medication use was reported as statins, angiotensin-converting enzyme inhibitors, or β-blockers with examples of brand names provided.

Approval for this study was obtained from a local ethics committee at Tilburg University (protocol number: 2006/1101). The reference group was sex and age matched with the 523 patients with NOCAD as part of the TWIST cohort, ensuring similar sex distribution within each age–decile, providing 1347 matched reference participants.

Measures

Health Status

Health status was measured by the 12-item Short Form in both the reference and the NOCAD group[25] and by the Seattle Angina Questionnaire (SAQ) in the NOCAD group only.[26] The generic 12-item Short Form is a short alternative to the psychometrically sound Short Form-36.[25] It consists of a physical component summary and a mental component summary, which evaluate physical and mental health, respectively. High scores indicate better health status. For the calculation of total scores, normative data presented in a Dutch study were used.[27]

The SAQ was used to measure disease-specific perceived health status.[26] The SAQ is a 19-item, self-administered questionnaire, which has been shown to be a valid, responsive, and reliable instrument.[26] The SAQ measures 5 clinically relevant dimensions: physical limitation, angina stability, angina frequency, treatment satisfaction, and disease and perception. Higher scores indicate fewer complaints and better health status.

Fatigue was assessed with the Fatigue Assessment Scale, which consists of 10 items that are answered on a 5-point rating scale from 1 (never) to 5 (always).[28] Higher fatigue scores indicate more fatigue. The internal consistency of the Fatigue Assessment Scale was 0.88.

Psychological Distress and Personality

Psychological distress was represented by anxiety, depressive symptoms, NA and PA, and personality by Type D personality. Anxiety and depressive symptoms were measured by the Hospital Anxiety and Depression Scale (HADS).[29,30] The HADS contains two 7-item scales: one measuring anxiety (HADS-A), and one measuring depressive symptoms (HADS-D), both with a range of 0 to 21. The internal consistency was 0.85 for HADS-A and 0.84 for HADS-D. Moderate–high anxiety and moderate–high depressive symptoms were calculated using a cutoff of ≥8.[30]

The Global Mood Scale measures NA and PA, using 10 negative (fatigued and listless) and 10 positive (lively and hard working) terms that especially tap vitality concepts that are commonly reported by cardiac patients.[31] The extent to which a respondent has experienced each state is asked on a 5-point Likert scale (ranging from 0, not at all to 4, extremely), and scores on both the NA and PA scales range from 0 to 40.

Type D personality was assessed with the 14-item Type D scale 14, comprising two 7-item subscales measuring NA and SI on a 0 to 4 range.[32] A cutoff of 10 on both NA and SI is used to classify subjects into 4 personality subgroups, Type D personality (high NA and high SI), high NA (with low SI), high SI (with low NA), and a low distress subgroup (low NA and low SI). Cronbach α was 0.88 and 0.86 for NA and SI, respectively.

Statistical Analysis

Statistical Package for Social Sciences version 22 was used for all statistical analysis. χ^2 tests were used for categorical variables and 1-way ANOVA for continuous variables. Because matching does not control for confounding by the matching variable,[33] S&G stratified group differences were additionally examined adjusted for age using logistic and linear regression. Findings showing a different outcome when adjusted for age were reported.

Univariate analyses were done to examine S&G×group interactions for the continuous psychosocial outcomes; logistic regression analyses were performed to examine S&G×group interactions for the dichotomized outcomes (moderate–high anxiety and depressive symptoms); and a multinomial logistic regression was performed to examine S&G×group interactions of the 4 personality subgroups.

Sensitivity analyses were run with the NOCAD patients further stratified by CAG and CT inclusion. Difference between the reference group and either the CAG or the CT NOCAD group was examined for men and women; S&G differences within the CAG or CT group were examined, as well as S&G×group interactions.

In the NOCAD group, patients with a history of MI, PCI, CABG, or heart failure were excluded. Additional analyses were run to compare the NOCAD patients to the reference group omitting people who reported a history of MI, PCI, CABG, or heart failure, those without additional information on the presence of cardiovascular disease, and those who did not further specify cardiovascular disease.

Multivariate analyses split by group were run to examine covariate adjustment for the S&G differences within the NOCAD group with the psychosocial outcomes. The threshold for statistical significance was set at 0.05.

Results

Baseline characteristics of the study populations stratified for men and women are shown in Table 1. Both men and women with NOCAD were less likely to have received college education; were more often overweight or obese; more often reported comorbid hypertension, dyslipidemia, or a history peripheral artery disease, transient ischemic attack, or stroke; and were more likely to use cardiac medications compared with the reference group (Table 1). Men with NOCAD had a higher prevalence of diabetes mellitus (12%) compared with the reference group (7%), but this difference was marginally different between women in both groups (12% versus 8%, χ^2=3.07; *P*=0.080). Women with NOCAD were less often currently employed compared with the reference group, which was no longer significant after additional adjustment for age (findings not shown). No S&G stratified differences between the NOCAD group and the reference group were present for having a partner and lifestyle factors, including smoking, alcohol use, and physical activity (Table 1).

When examining S&G differences within the NOCAD group (Table 1, last column), women were on average 3 years older, less likely to have a partner, and more likely to be either divorced or widowed. Women less often received college education and were less often employed compared with men. Women reported less alcohol use, but no other differences in lifestyle factors, comorbid conditions, or cardiac medication use were present between men and women.

S&G Stratified Differences Between the NOCAD and Reference Group

Table 2 describes the S&G stratified differences between the NOCAD versus the reference group. Both women and men in the NOCAD group showed a lower general health status, elevated fatigue, more anxiety, more depressive symptoms, more NA and less PA, and a higher propensity for Type D personality compared with the reference group. There was 1 exception; in women, SI scores were not significantly different between the groups. However, in women, the personality subtype SI only had a lower prevalence in the NOCAD group (11%) versus the reference group (22%), whereas Type

Table 1. Descriptive Characteristics Stratified by S&G, and S&G Differences Within the NOCAD Group

	Men			Women			S&G Differences Within NOCAD
	NOCAD	Reference	F/χ^2	NOCAD	Reference	F/χ^2	F/χ^2
Sex (within each group)	48% (250)	48% (644)		52% (273)	52% (703)		
Sociodemographic factors							
Age, y	59.85 (9.49)	58.65 (10.0)	2.66	62.86 (9.01)	61.73 (9.87)	2.67	13.8*
With partner	88% (220)	89% (573)	0.15	74% (203)	77% (543)	0.91	16.6*
Divorced	4% (10)	3% (16)	5.76	8% (21)	6% (41)	5.38	28.17*
Widowed	2% (6)	3% (22)		14% (38)	13% (89)		
College education or higher	70% (174)	78% (499)	6.80†	45% (122)	57% (396)	11.5†	31.8*
Currently employed	52% (131)	59% (373)	3.12	29% (78)	38% (261)	6.32‡	28.8*
Lifestyle factors							
BMI	27.39 (3.41)	26.08 (3.39)	26.6*	27.75 (4.51)	25.67 (4.20)	45.9*	1.06
Obese (BMI≥30)	21% (53)	12% (76)	12.5*	27% (73)	14% (96)	22.2*	2.19
Smoking (yes)	21% (53)	22% (139)	0.02	18% (48)	17% (116)	0.15	1.10
Alcohol use (yes)	80% (201)	76% (489)	1.84	60% (164)	55% (384)	2.17	25.6*
Physical activity (active)	58% (144)	64% (256)	2.87	67% (183)	66% (286)	0.07	4.71‡
Comorbid conditions							
Diabetes mellitus	12% (31)	7% (43)	6.99†	12% (32)	8% (55)	3.07	0.04
Lung condition	12% (30)	16% (104)	2.51	17% (47)	13% (88)	3.80	3.01
Hypertension	84% (208)	8% (48)	507*	84% (225)	11% (77)	473*	0.01
Dyslipidemia	76% (190)	15% (58)	242*	71% (191)	13% (55)	235*	2.06
History of PAD, TIA, or stroke	11% (27)	2% (13)	28.8*	9% (24)	1% (9)	31.4*	0.54
Cardiac medication use							
Statins	65% (162)	8% (30)	235*	59% (158)	7% (28)	219*	2.37
ACE inhibitors	30% (74)	3% (13)	87.5*	29% (77)	3% (13)	91.0*	0.09
β-blockers	46% (114)	11% (42)	98.0*	46% (123)	9% (38)	120*	<0.01

Mean±SD are reported, or % (n) with effect sizes F/χ^2. ACE indicates angiotensin-converting enzyme; BMI, body mass index; NOCAD, nonobstructive coronary artery disease; PAD, peripheral artery disease; S&G, sex and gender; and TIA, transient ischemic attack.

*P<0.001.

†P<0.01.

‡P<0.05.

D personality was more prevalent in women in the NOCAD group (31%) when compared with the reference group (17%). Additional adjustment for age did not alter these main findings (data not shown).

S&G Differences Within the NOCAD Group

Within the NOCAD group, men and women differed on some, but not all, psychosocial variables (Table 2). Women with NOCAD reported significantly lower physical and mental health status, more fatigue, more physical limitation according to the SAQ, more anxiety, more NA, and less PA compared with men with NOCAD. However, there were no differences in reported angina frequency, angina stability, disease perception, or treatment satisfaction on the SAQ between men and women with NOCAD. Neither were significant S&G differences observed in depressive symptoms, NA of the Global Mood Scale, or personality groups within the NOCAD group.

S&G Differences: Interaction by Group

The NOCAD group reported lower health status and more psychosocial distress compared with the reference group on all variables (data not shown). When examining S&G differences by group (Table 2: S&G×group interaction, last column), S&G differences within the NOCAD group were not significantly different from S&G differences within the reference group for any of the patient-reported outcomes. Thus, S&G differences were not more pronounced in patients with NOCAD when compared with the reference group.

Sensitivity Analyses of CAG and CT Patients With NOCAD

Sensitivity analyses were run to further explore the findings stratified for NOCAD based on either invasive CAG or noninvasive CT scan. In Table I in the Data Supplement, the descriptive characteristics are reported, showing that the

Table 2. S&G Stratified Differences in Health Status, Psychological Distress, and Personality in the NOCAD and Reference Group

	Men			Women			S&G Differences Within NOCAD	S&G by Group Interaction
	NOCAD	Reference	F/χ^2	NOCAD	Reference	F/χ^2	F/χ^2	F/OR (95% CI)
Generic health status* (SF-12)								
Physical health status (PCS)	45.9±10.8	51.8±8.8	72.6†	42.4±10.2	49.0±10.5	76.7†	13.91†	0.31
Mental health status (MCS)	46.1±11.5	51.7±8.5	63.3†	42.4±12.0	49.1±9.7	83.1†	13.09†	1.32
Fatigue (FAS)	22.1±7.2	18.0±5.6	80.3†	23.7±6.7	19.4±5.9	94.3†	7.29‡	0.10
Disease-specific health status* (SAQ)								
Physical limitation (0–100)	55.4±14.4	…	…	49.5±16.7	…	…	18.43†	…
Angina frequency (0–100)	64.8±13.8	…	…	66.2±14.9	…	…	0.63	…
Angina stability (0–100)	61.0±25.0	…	…	60.8±24.9	…	…	≤ 0.01	…
Disease perception (0–100)	58.3±16.1	…	…	58.5±15.1	…	…	0.01	…
Treatment satisfaction (0–100)	64.3±14.2	…	…	63.1±15.5	…	…	0.85	…
Psychological distress								
Anxiety (HADS-A)	5.6±4.1	4.0±3.2	37†	6.9±4.3	5.3±3.9	41.1†	12.6†	0.17
Moderate/high anxiety	29% (73)	14% (88)	29.2†	41% (112)	23% (164)	30.3†	8.17‡	1.13 (0.71–1.80)
Depression (HADS-D)	4.9±4.1	4.1±3.0	10.4†	5.3±3.9	4.1±3.1	23.9†	1.17	1.14
Moderate/high depression	24% (61)	13% (81)	18.7†	27% (74)	14% (95)	25.3†	0.54	0.94 (0.57–1.56)
Negative affect (GMS)	11.1±9.2	6.0±6.7	50.7†	12.2±8.1	7.0±7.0	63.8†	1.89	0.01
Positive affect (GMS)	23.0±8.3	26.1±7.0	20.4†	21.5±8.3	24.8±7.5	23.7†	4.32§	0.06
Personality (DS-14)								
Negative affectivity	8.8±6.0	5.3±4.8	83.7†	10.4±6.4	6.9±5.5	73.7†	8.96‡	<0.01
Social inhibition	9.4±5.9	11.1±9.2	13†	8.9±6.2	8.2±5.9	3.21	0.79	1.63
Type D personality	29% (71)	11% (70)	71.3†	31% (84)	17% (117)	50.4†	6.2	0.64 (0.37–1.09)
NA only (high NA, low SI)	15% (38)	6% (39)		21% (55)	12% (80)			0.64 (0.33–1.22)
SI only (low NA, high SI)	17% (43)	26% (168)		11% (29)	22% (153)			0.67 (0.36–1.23)
Low distress (low NA, low SI)	39% (95)	57% (366)		37% (100)	50% (348)			…

Mean±SD are reported, or % (n) with effect sizes F/χ^2. CI indicates confidence interval; DS-14, Type D personality; FAS, Fatigue Assessment Scale; GMS, Global Mood Scale; HADS, Hospital Anxiety and Depression Scale; MCS, mental component summary; NA, negative affectivity; NOCAD, nonobstructive coronary artery disease; OR, odds ratio; PCS, physical component summary; S&G, sex and gender; SAQ, Seattle Angina Questionnaire; SF-12 = Short Form 12; and SI, social inhibition.

*A higher score indicates better health.

†P<0.001.

‡P<0.01.

§P<0.05.

CAG group is more often different from the reference group than the CT group. Moreover, S&G differences were more pronounced in the CAG group (Table I in the Data Supplement). No S&G×CAG or CT group interaction effects were observed (data not shown). Table II in the Data Supplement shows health status, psychological distress, and personality differences between the reference group with the CAG and CT group, respectively. Both men and women in the CAG group showed poorer health status, more psychological distress, and more Type D personality compared with the reference group. These differences were either absent or less pronounced in the male CT group and less likely to be present in the female CT group when compared with the reference group. Within the NOCAD group, S&G differences were more likely to be present in the CT group rather than the CAG group. No significant interaction effects of S&G×CAG or CT group were observed (data not shown).

Additional Analyses Excluding Cardiovascular Disease From the Reference Group

In the reference group, 1309 people filled out the question on cardiovascular disease absence or presence, of whom 128 people further specified their condition as an open-ended question. In total, 46 (3.4%) people reported a previous history of MI, PCI, CABG, or heart failure. Additional analyses were run comparing the NOCAD group to a selection of the reference group (n=1201, 53% women) after excluding people with a history of MI, PCI, CABG, or heart failure (n= 46), as well as those who did not report the presence or absence of CVD (n=38), or who did not further specify their cardiac

conditions (n=62). Exclusion of the group did not alter the main findings (data not shown).

The Impact of S&G: Post Hoc Covariate Adjustment Within the NOCAD Group

Within the NOCAD group, significant S&G differences were present for the covariates age, partner, college education, employment, and alcohol use (Table 1). Neither of these variables represents random error but rather represents S&G as well as other individual differences. Women are older on average when cardiovascular disease emerges, are more often either widowed or divorced, less often have received college education, and are less likely to be employed compared with men (Table 1). Moreover, less alcohol use is reported in women. Multivariate adjustment for these covariates rendered all S&G differences in the NOCAD group nonsignificant (Table 3, first column). Age, college education, employment, and alcohol use were significantly associated with impaired physical health status, fatigue, physical limitation, anxiety, PA, and NA (Table 3). Having a partner was significantly associated with better mental health status, but not with the other psychosocial factors. The findings show that these covariates are relevant determinants of S&G differences in psychosocial factors in patients with NOCAD.

Discussion

Patients with NOCAD reported significantly impaired physical and mental health status, more fatigue, anxiety, depressive symptoms, NA, a higher propensity for Type D personality, and less PA, when compared with an age- and sex-matched reference group of the general population. Women in the NOCAD group reported poorer physical and mental health status, more physical limitation, fatigue, anxiety, NA, and less PA compared with men in the NOCAD group. No significant S&G differences in the NOCAD group were present for angina frequency, angina stability, disease perception, treatment satisfaction, depressive symptoms, or Type D personality. There were no significant S&G by group interactions, showing that the observed S&G differences in psychosocial factors were not different between the NOCAD and the reference groups. Within the NOCAD group, S&G differences became nonsignificant when adjusting for age, partner, college education, employment, and alcohol use, showing the importance of covariates in S&G differences in psychosocial factors in patients with NOCAD.

Both men and women with NOCAD report impaired health status, more psychological distress, and more Type D personality compared with an age- and sex-matched reference group of the general population, with women reporting overall higher levels of impaired health status, psychological distress, and Type D personality. These findings are in line with the results of 2 previous studies in patients with CAD.[18,19] Ford et al[19] reported impaired health status in women compared with men and in patients with CAD compared with people without CAD, but there was no significant interaction between sex and CAD for health status. Xie et al[18] reported impaired health status in patients with CAD compared with the NOCAD group and in women compared with men. Moreover, women had an impaired physical, but not mental, health status in the CAD group.[18] Attention for women and men with a poor health status is needed because impaired health status has been associated with adverse

Table 3. Multivariate Associations of S&G on Psychosocial Factors Adjusted for Covariates in Patients With NOCAD

		Covariates				
	Sex	Age, y	College Education	With Partner	Currently Employed	Alcohol Use (Yes)
Health status						
Physical health status (PCS)*	−0.025	0.132†	0.209‡	0.071	0.254‡	0.145§
Mental health status (MCS)*	−0.064	0.122†	0.139§	0.142§	0.121†	0.104†
Physical limitation (SAQ)	−0.052	−0.106†	0.152§	0.074	0.106†	0.131§
Fatigue (FAS)	0.014	−0.204‡	−0.138§	−0.082	−0.200‡	−0.159‡
Psychological distress						
Anxiety (HADS-A)	0.065	−0.112†	−0.158§	−0.073	−0.120†	−0.091†
Positive affect (GMS)	−0.005	0.114†	0.161§	0.047	0.153§	0.111†
Personality						
Negative affectivity (DS-14)	0.068	−0.112†	−0.167‡	−0.009	−0.118†	−0.038

Standardized β scores are reported. DS-14 indicates Type D personality; FAS, Fatigue Assessment Scale; GMS, Global Mood Scale; HADS, Hospital Anxiety and Depression Scale; MCS, mental component summary; NOCAD, nonobstructive coronary artery disease; PCS, physical component summary; S&G, sex and gender; and SAQ, Seattle Angina Questionnaire.

*A higher score indicates better health.

†$P<0.05$.

‡$P<0.001$.

§$P<0.01$.

prognosis in patients with CAD.[4,6,7] There is currently no guideline-recommended therapy for patients with NOCAD, other than symptom relief and cardiovascular disease risk factor management.[2,34]

In this study, no S&G differences in patients with NOCAD were observed for most health status measures of the disease-specific SAQ, depressive symptoms, and Type D personality. Moreover, whereas patients with NOCAD who were included via CAG showed more cardiac risk factors and adverse patient-reported outcomes than patients included via CT, sex differences were more often present within the CT group. A higher cardiac risk factor burden in the CAG group than the CT group is in line with the findings by Huang et al.[5] The absence of S&G differences contrasts findings in patients with CAD, showing a higher prevalence of depressive symptoms in women compared with men[35] and poor disease-specific health status according to the SAQ in women compared with men.[36] This discrepancy could be attributed to various factors; CAD affects women later in life than men,[37,38] and women are more likely to have comorbid conditions such as diabetes mellitus, hypertension, hypercholesterolemia, and peripheral vascular disease.[39]

Comorbidity can increase disease-specific physical limitations,[40] but in our study, the prevalence of comorbid conditions was not different between men and women with NOCAD. Neither were S&G differences observed in cardiac medication use, which points toward a similar treatment profile for men and women with NOCAD. Moreover, no S&G by group interactions were observed, indicating that S&G differences may be attributed to the overall S&G differences rather than being related to CAD.

Sex refers to biological differences between women and men, whereas gender implies the role of social, societal, and environmental factors.[22,24] On a broad level, there is a multitude of aspects representing diversity of an individual. S&G differences in psychosocial factors within the NOCAD group were explained by age, partner, employment status, college education, and alcohol use. The finding that these covariates are associated with psychosocial variables suggests a role for gender and other covariates as explanatory factors for differences in psychosocial variables.

It is noteworthy that in this study, over 1 in 5 women (22%) was either widowed or divorced compared with 1 in 17 (6%) widowed/divorced men. A recent study showed that marital disruption was associated with a higher allostatic load burden, neuroendocrine pathways which have found to be elevated in cardiovascular disease.[41] It remains to be examined whether the sex differences observed in this study are predictive of future cardiovascular events. Psychosocial factors have previously been found to be related to adverse outcomes in cardiovascular disease,[9] but whether these differences are consistently different for men and women with NOCAD is currently unknown.

The rate of eligible patients willing to participate was 64%. No information is present for nonresponders, which may limit the generalizability of the results toward the NOCAD population. It is possible that a volunteer bias has been introduced in the reference group, although exclusion of people with a possible history of obstructive CAD did not alter the main findings. The absence of the SAQ in the general population limits the comparability of these findings. Another limitation of this study is that various aspects of patient-perceived health are subjectively assessed by self-report questionnaires.

About half the patients with NOCAD were women (52%), which was similar in other studies of patients without obstructive CAD (40%–55%).[3–5,42] The prevalence of women is higher in patients with NOCAD (≈50%) compared with studies in patients with obstructive CAD, where women comprise ≈25% of the study population. This discrepancy may be because of the presence of coronary microvascular disease in patients with NOCAD, leading to ischemia in the microvasculature, without the presence of significant obstructions in the major coronary arteries.[23,43] Routine CAG or CT scans cannot detect coronary microvascular disease, although endothelial dysfunction and coronary microvascular disease are likely to be present in patients with NOCAD.[44] Novel techniques will need to become incorporated in routine clinical practice to distinguish NOCAD with subsequent endothelial dysfunction and coronary microvascular disease. It is currently unknown whether these patients' groups report differences in psychosocial functioning.

Clinicians involved in cardiovascular care need to be aware that differences in health status between male and female patients exist. In spite of evidence that women benefit from the same therapies as men, they continue to receive less aggressive therapy, which is reflected in higher healthcare resource utilization and adverse health status outcomes.[2,22]

This study shows that patients with NOCAD have adverse health status and more psychosocial distress compared with the general population. Women showed impaired health status and more psychosocial distress compared with men, but these differences were not exclusive for patients with NOCAD. Additional adjustment for age, education, partner, employment, and alcohol use showed that these other factors explained the S&G differences in psychosocial factors in the NOCAD group.

Disclosures

None.

References

1. Ambrose JA, Srikanth S. Vulnerable plaques and patients: improving prediction of future coronary events. *Am J Med*. 2010;123:10–16. doi: 10.1016/j.amjmed.2009.07.019.
2. Pepine CJ, Ferdinand KC, Shaw LJ, Light-McGroary KA, Shah RU, Gulati M, Duvernoy C, Walsh MN, Bairey Merz CN; ACC CVD in Women Committee. Emergence of nonobstructive coronary artery disease: a woman's problem and need for change in definition on angiography. *J Am Coll Cardiol*. 2015;66:1918–1933. doi: 10.1016/j.jacc.2015.08.876.
3. Patel MR, Dai D, Hernandez AF, Douglas PS, Messenger J, Garratt KN, Maddox TM, Peterson ED and Roe MT. Prevalence and predictors of nonobstructive coronary artery disease identified with coronary angiography in contemporary clinical practice. *Am Heart J*. 2014;167:846.e2–852.e2.
4. Jespersen L, Hvelplund A, Abildstrøm SZ, Pedersen F, Galatius S, Madsen JK, Jørgensen E, Kelbæk H, Prescott E. Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events. *Eur Heart J*. 2012;33:734–744. doi: 10.1093/eurheartj/ehr331.
5. Huang FY, Huang BT, Lv WY, Liu W, Peng Y, Xia TL, Wang PJ, Zuo ZL, Liu RS, Zhang C, Gui YY, Liao YB, Chen M, Zhu Y. The prognosis of patients with nonobstructive coronary artery disease versus normal arteries

determined by invasive coronary angiography or computed tomography coronary angiography: a systematic review. *Medicine*. 2016;95:e3117. doi: 10.1097/MD.0000000000003117.
6. Grool AM, van der Graaf Y, Visseren FL, de Borst GJ, Algra A, Geerlings MI; SMART Study Group. Self-rated health status as a risk factor for future vascular events and mortality in patients with symptomatic and asymptomatic atherosclerotic disease: the SMART study. *J Intern Med*. 2012;272:277–286. doi: 10.1111/j.1365-2796.2012.02521.x.
7. Mommersteeg PM, Denollet J, Spertus JA, Pedersen SS. Health status as a risk factor in cardiovascular disease: a systematic review of current evidence. *Am Heart J*. 2009;157:208–218. doi: 10.1016/j.ahj.2008.09.020.
8. Hoen PW, Denollet J, de Jonge P, Whooley MA. Positive affect and survival in patients with stable coronary heart disease: findings from the Heart and Soul Study. *J Clin Psychiatry*. 2013;74:716–722. doi: 10.4088/JCP.12m08022.
9. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corra U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FD, Lochen ML, Lollgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WM, De Backer G, Roffi M, Aboyans V, Bachl N, Bueno H, Carerj S, Cho L, Cox J, De Sutter J, Egidi G, Fisher M, Fitzsimons D, Franco OH, Guenoun M, Jennings C, Jug B, Kirchhof P, Kotseva K, Lip GY, Mach F, Mancia G, Bermudo FM, Mezzani A, Niessner A, Ponikowski P, Rauch B, Ryden L, Stauder A, Turc G, Wiklund O, Windecker S, Zamorano JL. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. *Eur J Prevent Cardiol*. 2016;23:np1–np96.
10. Swenson JR, Clinch JJ. Assessment of quality of life in patients with cardiac disease: the role of psychosomatic medicine. *J Psychosom Res*. 2000;48:405–415.
11. Oldridge N, Saner H, McGee HM; HeartQoL Study Investigators. The Euro Cardio-QoL Project. An international study to develop a core heart disease health-related quality of life questionnaire, the HeartQoL. *Eur J Cardiovasc Prev Rehabil*. 2005;12:87–94. doi: 10.1097/01.hjr.0000159408.05180.0e.
12. de Miranda Azevedo R, Roest AM, Hoen PW, de Jonge P. Cognitive/affective and somatic/affective symptoms of depression in patients with heart disease and their association with cardiovascular prognosis: a meta-analysis. *Psychol Med*. 2014;44:2689–2703. doi: 10.1017/S0033291714000063.
13. Roest AM, Martens EJ, de Jonge P, Denollet J. Anxiety and risk of incident coronary heart disease: a meta-analysis. *J Am Coll Cardiol*. 2010;56:38–46. doi: 10.1016/j.jacc.2010.03.034.
14. Middel B, El Baz N, Pedersen SS, van Dijk JP, Wynia K, Reijneveld SA. Decline in health-related quality of life 6 months after coronary artery bypass graft surgery: the influence of anxiety, depression, and personality traits. *J Cardiovasc Nurs*. 2014;29:544–554. doi: 10.1097/JCN.0b013e3182a102ae.
15. Mommersteeg PM, Pot I, Aarnoudse W, Denollet J, Widdershoven JW. Type D personality and patient-perceived health in nonsignificant coronary artery disease: the TWeesteden mIld STenosis (TWIST) study. *Qual Life Res*. 2013;22:2041–2050. doi: 10.1007/s11136-012-0340-2.
16. Mommersteeg PM, Widdershoven JW, Aarnoudse W, Denollet J. Personality subtypes and chest pain in patients with nonobstructive coronary artery disease from the TweeSteden Mild Stenosis study: mediating effect of anxiety and depression. *Eur J Pain*. 2016;20:427–437. doi: 10.1002/ejp.743.
17. De Smedt D, Clays E, Annemans L, Pardaens S, Kotseva K, De Bacquer D. Self-reported health status in coronary heart disease patients: a comparison with the general population. *Eur J Cardiovasc Nurs*. 2015;14:117–125. doi: 10.1177/1474515113519930.
18. Xie J, Wu EQ, Zheng ZJ, Sullivan PW, Zhan L, Labarthe DR. Patient-reported health status in coronary heart disease in the United States: age, sex, racial, and ethnic differences. *Circulation*. 2008;118:491–497. doi: 10.1161/CIRCULATIONAHA.107.752006.
19. Ford ES, Mokdad AH, Li C, McGuire LC, Strine TW, Okoro CA, Brown DW, Zack MM. Gender differences in coronary heart disease and health-related quality of life: findings from 10 states from the 2004 behavioral risk factor surveillance system. *J Womens Health*. 2008;17:757–768. doi: 10.1089/jwh.2007.0468.
20. Wheeler A, Schrader G, Tucker G, Adams R, Tavella R, Beltrame JF. Prevalence of depression in patients with chest pain and non-obstructive coronary artery disease. *Am J Cardiol*. 2013;112:656–659. doi: 10.1016/j.amjcard.2013.04.042.
21. Norris CM, Ghali WA, Galbraith PD, Graham MM, Jensen LA, Knudtson ML; APPROACH Investigators. Women with coronary artery disease report worse health-related quality of life outcomes compared to men. *Health Qual Life Outcomes*. 2004;2:21. doi: 10.1186/1477-7525-2-21.
22. Regitz-Zagrosek V, Oertelt-Prigione S, Prescott E, Franconi F, Gerdts E, Foryst-Ludwig A, Maas AH, Kautzky-Willer A, Knappe-Wegner D, Kintscher U, Ladwig KH, Schenck-Gustafsson K, Stangl V. Gender in cardiovascular diseases: impact on clinical manifestations, management, and outcomes. *Eur Heart J*. 2016;37:24–34.
23. Crea F, Battipaglia I, Andreotti F. Sex differences in mechanisms, presentation and management of ischaemic heart disease. *Atherosclerosis*. 2015;241:157–168. doi: 10.1016/j.atherosclerosis.2015.04.802.
24. Schiebinger L. Scientific research must take gender into account. *Nature*. 2014;507:9. doi: 10.1038/507009a.
25. Ware J Jr, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care*. 1996;34:220–233.
26. Spertus JA, Winder JA, Dewhurst TA, Deyo RA, Prodzinski J, McDonell M, Fihn SD. Development and evaluation of the Seattle Angina Questionnaire: a new functional status measure for coronary artery disease. *J Am Coll Cardiol*. 1995;25:333–341.
27. Mols F, Pelle AJ, Kupper N. Normative data of the SF-12 health survey with validation using postmyocardial infarction patients in the Dutch population. *Qual Life Res*. 2009;18:403–414. doi: 10.1007/s11136-009-9455-5.
28. Michielsen HJ, De Vries J, Van Heck GL. Psychometric qualities of a brief self-rated fatigue measure: The Fatigue Assessment Scale. *J Psychosom Res*. 2003;54:345–352.
29. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67:361–370.
30. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res*. 2002;52:69–77.
31. Denollet J. Emotional distress and fatigue in coronary heart disease: the Global Mood Scale (GMS). *Psychol Med*. 1993;23:111–121.
32. Denollet J. DS14: standard assessment of negative affectivity, social inhibition, and Type D personality. *Psychosom Med*. 2005;67:89–97. doi: 10.1097/01.psy.0000149256.81953.49.
33. Pearce N. Analysis of matched case-control studies. *BMJ*. 2016;352:i969.
34. Bugiardini R, Bairey Merz CN. Angina with "normal" coronary arteries: a changing philosophy. *JAMA*. 2005;293:477–484. doi: 10.1001/jama.293.4.477.
35. Shanmugasegaram S, Russell KL, Kovacs AH, Stewart DE, Grace SL. Gender and sex differences in prevalence of major depression in coronary artery disease patients: a meta-analysis. *Maturitas*. 2012;73:305–311. doi: 10.1016/j.maturitas.2012.09.005.
36. Norris CM, Spertus JA, Jensen L, Johnson J, Hegadoren KM, Ghali WA; APPROACH Investigators. Sex and gender discrepancies in health-related quality of life outcomes among patients with established coronary artery disease. *Circ Cardiovasc Qual Outcomes*. 2008;1:123–130. doi: 10.1161/CIRCOUTCOMES.108.793448.
37. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Soliman EZ, Sorlie PD, Sotoodehnia N, Turan TN, Virani SS, Wong ND, Woo D, Turner MB; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics–2012 update: a report from the American Heart Association. *Circulation*. 2012;125:e2–e220. doi: 10.1161/CIR.0b013e31823ac046.
38. Anand SS, Xie CC, Mehta S, Franzosi MG, Joyner C, Chrolavicius S, Fox KA, Yusuf S; CURE Investigators. Differences in the management and prognosis of women and men who suffer from acute coronary syndromes. *J Am Coll Cardiol*. 2005;46:1845–1851. doi: 10.1016/j.jacc.2005.05.091.
39. Mikhail GW. Coronary heart disease in women. *BMJ*. 2005;331:467–468. doi: 10.1136/bmj.331.7515.467.
40. Rushton CA, Kadam UT. Impact of non-cardiovascular disease comorbidity on cardiovascular disease symptom severity: a population-based study. *Int J Cardiol*. 2014;175:154–161. doi: 10.1016/j.ijcard.2014.05.001.
41. Rote S. Marital disruption and allostatic load in late life [published online ahead of print April 13, 2016]. *J Aging Health*. doi: 10.1177/0898264316641084. Accessed October 2016. http://www.ncbi.nlm.nih.gov/pubmed/27079918.
42. Bittencourt MS, Hulten E, Ghoshhajra B, O'Leary D, Christman MP, Montana P, Truong QA, Steigner M, Murthy VL, Rybicki FJ, Nasir K, Gowdak LH, Hainer J, Brady TJ, Di Carli MF, Hoffmann U, Abbara S, Blankstein R. Prognostic value of nonobstructive and obstructive coronary

artery disease detected by coronary computed tomography angiography to identify cardiovascular events. *Circ Cardiovasc Imaging*. 2014;7:282–291. doi: 10.1161/CIRCIMAGING.113.001047.

43. Vaccarino V, Badimon L, Corti R, de Wit C, Dorobantu M, Hall A, Koller A, Marzilli M, Pries A, Bugiardini R; Working Group on Coronary Pathophysiology and Microcirculation. Ischaemic heart disease in women: are there sex differences in pathophysiology and risk factors? Position paper from the working group on coronary pathophysiology and microcirculation of the European Society of Cardiology. *Cardiovasc Res*. 2011;90:9–17. doi: 10.1093/cvr/cvq394.
44. Lee BK, Lim HS, Fearon WF, Yong AS, Yamada R, Tanaka S, Lee DP, Yeung AC, Tremmel JA. Invasive evaluation of patients with angina in the absence of obstructive coronary artery disease. *Circulation*. 2015;131:1054–1060. doi: 10.1161/CIRCULATIONAHA.114.012636.

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Impaired Health Status, Psychological Distress, and Personality in Women and Men With Nonobstructive Coronary Artery Disease: Sex and Gender Differences: The TWIST (Tweesteden Mild Stenosis) Study

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SUPPLEMENTAL MATERIAL

Supplemental Table S1. Descriptive characteristics stratified by sex & gender (S&G) and NOCAD group (CAG and CT), and S&G differences within the NOCAD group stratified for CAG and CT group.

	MEN			WOMEN			MEN: Reference versus NOCAD		WOMEN: Reference versus NOCAD		S&G differences within the NOCAD group	
	Reference	NOCAD CAG	NOCAD CT	Reference	NOCAD CAG	NOCAD CT	CAG F/X^2	CT F/X^2	CAG F/X^2	CT F/X^2	CAG F/X^2	CT F/X^2
Sex	644 (48%)	177 (48%)	73 (46%)	703 (52%)	189 (52%)	84 (54%)						
Sociodemographic factors												
Age [years]	58.7 (10.0)	61.3 (9.5)	56.5 (8.6)	61.7 (9.9)	64.4 (8.7)	59.3 (8.9)	**9.60****	**3.26**$^{+}$	**11.6****	**4.53***	**11.1****	**4.24***
With partner	89% (573)	88% (156)	89% (64)	77% (543)	74% (139)	76% (64)	0.18	0.01	1.13	0.05	**12.5*****	**4.25***
Divorced	2% (16)	4% (7)	4% (3)	6% (41)	7% (6)	6% (41)	4.28	7.09	4.92	4.92	**18.8****	**10.8**$^{+}$
Widowed	3% (22)	3% (6)	0% (0)	13% (89)	12% (10)	13% (89)						
College education or higher	78% (499)	67% (118)	77% (56)	57% (396)	40% (74)	57% (48)	**9.38****	0.09	**17.9*****	0	**26.5*****	**6.69***
Currently employed	59% (373)	46% (81)	68% (50)	38% (261)	21% (39)	46% (39)	**9.73****	2.5	**17.6*****	2.3	**24.2*****	**7.75****
Lifestyle factors												
BMI	26.1 (3.4)	27.7 (3.6)	26.7 (2.9)	25.7 (4.2)	28.2 (4.6)	26.9 (4.1)	**29.6*****	2.31	**49.4*****	**5.90***	1.24	0.06
Obese [BMI ≥ 30]	12% (76)	24% (42)	15% (11)	14% (96)	29% (55)	21% (18)	**15.6*****	0.61	**24.0*****	**3.35**$^{+}$	1.35	1.05
Smoking (yes)	22% (139)	19% (34)	26% (19)	17% (116)	18% (34)	17% (14)	0.48	0.74	0.22	0	0.09	2.06
Alcohol use (yes)	76% (489)	79% (140)	84% (61)	55% (384)	58% (109)	65% (55)	0.67	2.02	0.48	3**.43**$^{+}$	**19.3*****	**6.62***
Physical activity (active)	64% (256)	55% (97)	64% (47)	66% (286)	66% (124)	70% (59)	**4.53***	0	0.01	0.56	**4.20***	0.61
Comorbid conditions												
Diabetes mellitus	7% (43)	16% (28)	4% (3)	8% (55)	14% (26)	7% (6)	**13.6*****	0.82	**5.69***	0.11	0.24	0.67
Lung condition	16% (104)	12% (22)	11% (8)	13% (88)	22% (40)	8% (7)	1.53	1.37	**9.5****	1.27	**5.28***	0.31
Hypertension	8% (48)	85% (150)	82% (58)	11% (77)	90% (166)	70% (59)	**450*****	**277*****	**450*****	**181*****	2.03	**2.73**$^{+}$
Dyslipidemia	15% (58)	77% (137)	74% (53)	13% (55)	75% (140)	61% (51)	**212*****	**115*****	**225*****	**94.1*****	0.23	**2.90**$^{+}$
History of PAD, TIA, or stroke	2% (13)	13% (23)	5% (4)	1% (9)	10% (19)	6% (5)	**35.6*****	**2.81**$^{+}$	**35.2*****	**8.40****	0.69	0.02
Cardiac medication use												
Statins	8% (30)	68% (121)	58% (41)	7% (28)	62% (115)	51% (43)	**225*****	**113*****	**213*****	**111*****	1.53	0.67
ACE inhibitors	3% (13)	32% (56)	25% (18)	3% (13)	31% (58)	23% (19)	**88.3*****	**44.8*****	**95.8*****	**43.3*****	0	0.16
Beta blockers	11% (42)	47% (84)	42% (30)	9% (38)	49% (91)	38% (32)	**91.4*****	**43.4*****	**120*****	**47.8*****	0.11	0.28

Bold typeface represents significant differences, with $^{+}$p<.10, *p<.05, **p<.01, ***p<.001

Supplemental Table S2. Sex & gender (S&G) and NOCAD (CAG and CT) stratified differences in health status, psychological distress, and personality in the reference and NOCAD CAG and CT group.

	MEN			WOMEN			MEN: Reference versus NOCAD		WOMEN: Reference versus NOCAD		Sex differences within the NOCAD group	
	Reference	NOCAD CAG	NOCAD CT	Reference	NOCAD CAG	NOCAD CT	CAG F/X^2	CT F/X^2	CAG F/X^2	CT F/X^2	CAG F/X^2	CT F/X^2
Generic health status1 [SF-12]												
Physical health status [PCS]	51.8 (8.8)	44.0 (10.8)	50.3 (9.3)	49.0 (10.5)	41.0 (9.9)	45.6 (10.4)	**98.8*** **	1.83	**87.2*** **	**7.5** **	**7.7** **	**8.8** **
Mental health status [MCS]	51.7 (8.5)	44.3 (12.1)	50.5 (8.3)	49.1 (9.7)	41.2 (12.4)	45.0 (10.6)	**86.2*** **	1.3	**87.2*** **	**13.5*** **	**5.7***	**13.0*** **
Fatigue [FAS]	18.0 (5.6)	23.2 (7.6)	19.4 (5.2)	19.4 (5.9)	24.2 (6.8)	22.7 (6.3)	**101*** **	**3.92***	**88.1*** **	**22.3*** **	1.65	**12.7*** **
Disease-specific health status (SAQ)												
Physical limitation (0-100)		53.0 (15.5)	61.2 (9.3)		46.8 (1.74)	55.5 (13.5)					**12.7** **	**9.2** **
Angina frequency (0-100)		57.8 (25.5)	68.5 (22.0)		58.2 (25.1)	66.7 (23.6)					0.02	0.25
Angina stability (0-100)		63.5 (14.2)	69.1 (11.6)		65.0 (15.5)	70.1 (12.1)					0.52	0.1
Disease perception (0-100)		63.6 (14.8)	66.2 (12.6)		62.4 (15.7)	64.7 (15.0)					0.5	0.44
Treatment satisfaction (0-100)		56.3 (17.0)	63.3 (12.4)		57.1 (15.8)	61.7 (13.2)					0.22	0.62
Psychological distress												
Anxiety [HADS-A]	4.0 (3.2)	6.0 (4.4)	4.6 (3.3)	5.2 (3.6)	7.2 (4.4)	6.2 (3.9)	**45.7*** **	2.05	**42.6*** **	**6.8** **	**6.6***	**8.3** **
Moderate/high anxiety	14% (88)	33% (58)	21% (15)	23% (164)	44% (82)	36% (30)	**34.4*** **	2.49	**30.2*** **	**6.1***	**4.5***	**4.39***
Depression [HADS-D]	4.1 (3.0)	5.4 (4.2)	3.5 (3.5)	4.1 (3.1)	5.6 (4.0)	4.5 (3.7)	**23.6*** **	2.09	**30.3*** **	1.45	0.13	**2.96**$^{+}$
Moderate/high depression	13% (81)	29% (51)	14% (10)	14% (95)	29% (54)	24% (20)	**26.9*** **	0.07	**24.4*** **	**6.3***	<0.01	2.58
Negative affect [GMS]	6.0 (6.7)	12.4 (9.6)	8.3 (7.5)	7.0 (7.0)	12.8 (8.5)	10.8 (6.9)	**64.5*** **	**5.97***	**64.0*** **	**18.9*** **	0.22	**4.8***
Positive affect [GMS]	26.1 (7.0)	21.8 (8.5)	26.0 (7.3)	24.8 (7.5)	20.9 (8.4)	22.8 (8.2)	**33.5*** **	0.03	**27.2*** **	**4.4***	0.92	**6.4***
Personality [DS-14]												
Negative affectivity	5.3 (4.8)	9.4 (6.2)	7.3 (5.4)	6.9 (5.5)	10.6 (6.7)	10.0 (5.8)	**91.7*** **	**11.07** **	**61.9*** **	**23.8*** **	**3.08**$^{+}$	**9.4** **
Social inhibition	7.9 (5.6)	9.8 (6.1)	8.5 (5.3)	8.2 (5.9)	9.5 (6.3)	7.7 (6.0)	**15.7*** **	0.726	**7.2** **	0.43	0.25	0.66
Type D personality	11% (70)	32% (55)	22% (16)	17% (117)	34% (62)	26% (22)	**79.5*** **	**9.65***	**40.3*** **	**22.7*** **	0.76	**11.6** **
NA only [high NA, low SI]	6% (39)	18% (31)	10% (7)	11% (80)	19% (35)	24% (20)						
SI only [low NA, high SI]	26% (168)	16% (28)	21% (15)	22% (153)	13% (24)	6% (5)						
Low distress [low NA, low SI]	57% (366)	34% (60)	48% (35)	50% (348)	34% (63)	44% (37)						

Bold typeface represents significant differences, with $^{+}$p<.10, *p<.05, **p<.01, ***p<.001