Health-Related Quality of Life in Premature Acute Coronary Syndrome: Does Patient Sex or Gender Really Matter?

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Background—Limited data exist as to the relative contribution of sex and gender on health-related quality of life (HRQL) among patients with acute coronary syndrome (ACS). This study aims to evaluate the effect of sex and gender-related variables on long-term HRQL among young adults with ACS.

Methods and Results—GENESIS-PRAXY (GENdEr and Sex determInantS of cardiovascular disease: from bench to beyond-Premature Acute Coronary SYndrome) is a multicenter, prospective cohort study (January 2009 to August 2013) of adults aged 18 to 55 years, hospitalized with ACS. HRQL was measured at baseline, 1, 6, and 12 months using the Short Form-12 and Seattle Angina Questionnaire (SAQ) among 1213 patients. Median age was 49 years. Women reported worse HRQL than men over time post-ACS, both in terms of physical and mental functioning. Gender-related factors were more likely to be predictors of HRQL than sex. Femininity score, social support, and housework responsibility were the most common gender-related predictors of HRQL at 12 months. We observed an interaction between female sex and social support (β=0.44 [95% confidence interval, 0.01, 0.88]; *P*=0.047) for the physical limitation subscale of the SAQ.

Conclusions—Young women with ACS report significantly poorer HRQL than young men. Gender appears to be more important than sex in predicting long-term HRQL post-ACS. Specific gender-related factors, such as social support, may be amenable to interventions and could improve the HRQL of patients with premature ACS. (***J Am Heart Assoc***. 2014;3:e000901 doi: 10.1161/JAHA.114.000901)

Key Words: angina • cardiovascular diseases • myocardial infarction • sex

Health-related quality of life (HRQL) is increasingly being used as an outcome measure for the effectiveness of medical treatment and patient recovery in acute coronary syndrome (ACS). Whereas health outcomes in ACS patients have traditionally been measured using mortality and morbidity as primary endpoints, HRQL is an important outcome measure in that it measures illness perception instead of the disease itself.[1] HRQL has been recognized for defining health from the patients' perspective, in terms of how individuals feel (distress and well-being) and how they evaluate their health and prospects for the future.[2]

ACS has been associated with marked impairments in HRQL and considerable loss of productive years.[2–4] In addition, many studies have demonstrated sex differences in HRQL among patients with coronary artery disease (CAD), with women generally reporting lower HRQL than men.[2,5–14] However, inconsistency exists regarding the determinants of HRQL for men and women, and the observed discrepancies in HRQL between sexes are poorly understood.

In addition to biological sex (ie, being male or female), it has been suggested that gender (ie, sociocultural factors related to masculinity and femininity) may influence HRQL.[15] During the past decade, there has been a substantial decrease in gender gap in North America.[16] With more young women gaining access to education and employment, shared household and workplace responsibilities are becoming more common. At the same time, other factors, such as social support and psychological distress, could be equally important in predicting HRQL post-ACS.[8,17] However, the role that

different gender-related factors may play in HRQL remains to be determined, and, to date, there are no comprehensive studies on this subject.

The aim of this study was to examine trends in HRQL and assess the relative contribution of sex and gender among young male and female patients with ACS.

Methods

Study Population

The study population consisted of patients enrolled in GENESIS-PRAXY (GENdEr and Sex determInantS of cardiovascular disease: from bench to beyond-Premature Acute Coronary SYndrome), a multicenter, prospective cohort study of young adults hospitalized with ACS. The methods of the GENESIS-PRAXY study have been previously described.[18] Briefly, eligible participants included patients aged 18 to 55 years, admitted with a diagnosis of ACS to the coronary care units of participating hospitals, fluent in English and/or French, and able to provide informed consent. The study began in January 2009 and includes 24 sites across Canada, one in the U.S., and one in Switzerland. All participating sites received ethics approval from their respective ethics review board, and all participants provided informed consent.

Data Collection

Study participants were approached by a trained research nurse within 48 hours of hospital admission. Patients who gave their consent were asked to complete a self-administered questionnaire at the time of enrolment. They were also mailed questionnaires at 1, 6, and 12 months. Medical chart reviews were carried out by the research nurse at baseline and 12 months.

HRQL was measured using 2 validated instruments: the Short Form-12 (SF-12) version 2.0 and the Seattle Angina Questionnaire (SAQ). The SF-12 includes 2 subscales: the Physical Component Summary (PCS) and Mental Component Summary (MCS) scores, transformed to a 0 to 100 scale, with higher scores representing better health status.[19] The scores can be compared to the general U.S. population with a mean score of 50 and standard deviation (SD) of 10. Clinically significant differences for the SF-12 range from 3 to 5 points.[20] The SF-12 validity, reliability, and responsiveness have been well documented in patients with CAD.[21,22] The SAQ is a 19-item disease-specific functional status measure of CAD using 5 dimensions, namely, physical limitation, angina stability, angina frequency, treatment satisfaction, and disease perception.[23,24] The items are summed within each of the 5 dimensions, and the scale scores are transformed to a 0 to 100 scale. Higher scores represent better health status.

The SAQ is valid, reproducible, and responsive to clinical change.[24] A clinically significant difference in the scores of the SAQ dimensions is between 5 and 8 points.[25]

Our main variables of interest were sex and gender-related variables. According to the Women Health Research Network of the Canadian Institutes of Health Research (CIHR), there are 4 inter-related gender aspects, which are gender roles, gender identity, gender relations, and institutionalized gender.[26] We examined 7 gender-related variables that incorporate these gender aspects, namely, stress level at home, stress management, femininity score, housework responsibility, primary earner status, number of hours worked per week, and social support. Femininity score was measured using the femininity subscale of the Bem Sex Role Inventory (BSRI).[27] Housework responsibility and primary earner status were assessed using the questions, "Are you the primary person responsible for doing the housework in your home? (Yes/No)" and "Are you the primary earner in the house?" (Yes/No). Social support was measured using the ENRICHD Social Support Instrument (ESSI), a valid and reliable 7-item tool among populations with CAD.[28] Low social support is determined based on the score of 5 of the 7 items of the ESSI (items 1, 2, 3, 5, and 6). Patients with a score of ≤3 on at least 2 items or with a total score of ≤18 are considered as having low social support.

Data were additionally collected on sociodemographic factors, including age, marital status, ethnicity, education, and various factors that have been linked to HRQL. These included clinical characteristics, such as anxiety, depression, presence of vascular risk factors, a previous cardiovascular (CV) event (CVE), and type of ACS (ST-elevation myocardial infarction [STEMI], non-STEMI, or unstable angina), as well as treatment procedures (thrombolysis, primary percutaneous coronary intervention [PCI], non-primary PCI, and coronary artery bypass grafting [CABG]). Anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS).[29] Presence of vascular risk factors was defined as having one or more of the following: diabetes, hypertension, dyslipidemia, currently smoking, obesity, and family history of CV diseases. Previous CVE included previous myocardial infarction, stroke, PCI, or CABG or having peripheral arterial disease.

Statistical Analysis

Descriptive statistics were used to report baseline characteristics stratified by tertiles of PCS and MCS scores. Dichotomous variables were presented in percentages, whereas continuous variables were presented as mean± SD.

Descriptive and trend analyses were performed to evaluate the trends in HRQL score. Mean HRQL scores were calculated for men and women, respectively, at the 4 time points

(baseline, 1, 6, and 12 months), and the differences in scores between men and women were assessed using Student t tests. Repeated-measure analyses were done to assess trends in HRQL. We conducted trend analysis on time by using polynomial transformation to account for the different time lapse between the measured time points. Chi-square test was used to compare the percentages of men versus women having angina (score <100).[30]

Multiple linear regression models were created to identify predictors of PCS, MCS, physical limitation, angina stability, treatment satisfaction, and disease perception at 12 months. We used multivariable logistic models to identify predictors of having angina at 12 months. We included sex and the 7 gender-related variables in the multivariable models, together with demographic and clinical variables that were statistically significant at $P<0.10$ in the univariable analyses. Data with missing values were estimated using multiple imputation procedures.[31] We used the false discovery rate method to adjust for multiple testing. In sensitivity analysis, we excluded non-Canadian sites (U.S. and Switzerland).

We also investigated for interactions between sex and gender-related variables when they were found to be statistically significant in the same model. When there was a significant interaction effect, post-hoc analyses were conducted to compare the HRQL scores of men and women for the concerned gender-related variable.

All statistical analyses were performed using the SAS (version 9.2) statistical software package (SAS Institute Inc, Cary, NC).

Results

Among 1410 eligible patients who were approached, participation refusal rates were 18% in men and 10% in women, for an overall participation rate of 86% or 1213 enrolled patients (68% men). Data at 12 months were available for 65% patients. Of these, there were an average of 11% missing data per outcome.

Baseline characteristics are presented by tertiles of PCS and MCS scores (Table). Median age was 49 years (inter-quartile range, 45 to 53 years). There were more men in the highest PCS and MCS tertiles. There also appeared to be a pattern among gender-related factors. Those in the highest PCS and MCS tertiles had lower levels of stress at home, better stress management ability, and higher social support. Those in the highest MCS tertiles were also less likely to have housework responsibilities, but were more likely to be the family's primary earners. Femininity score was nonetheless similar across PCS and MCS tertiles. Additionally, there were fewer patients with low education, depression, anxiety, vascular risk factors, and previous CVEs in the highest

tertiles. Except for primary PCI, other revascularization treatments (thrombolysis, non-primary PCI, and CABG), as well as type of ACS, did not appear to have any specific pattern across tertiles of PCS and MCS.

Trends in HRQL

At every point in time (baseline, 1, 6, and 12 months), the mean PCS and MCS scores of this population of young ACS patients were lower than the mean score of 50 of the general population, and lower in women compared to men (Figure 1). An improving trend was observed for both PCS and MCS among men ($P<0.01$ and $P=0.01$, respectively), whereas an improvement was observed only for PCS and not MCS among women ($P<0.01$ and $P=0.55$, respectively). Men consistently reported higher scores than women, with the difference in scores being clinically significant (>3 points for SF-12 and >5 points for SAQ). Furthermore, a significantly higher proportion of women compared to men had angina. The proportion of men with angina decreased consistently over time, and in the long-term, women reported more angina than men (48.2% versus 29.4%; $P<0.01$ at 12 months).

Predictors of HRQL

In multivariable linear and logistic regressions, gender-related variables were more likely than sex to be significant predictors of HRQL (Figure 2). Femininity score and social support appeared to be particularly important, being statistically significant for 4 (PCS, physical limitation, angina frequency, and disease perception) and 3 (PCS, physical limitation, and disease perception) outcomes, respectively. Housework responsibility was also found to be an important determinant of PCS and physical limitation. Conversely, sex was not a predictor for any of the outcomes, except physical limitation ($\beta=-5.37$ [95% CI, -8.94, -1.79]; $P=0.003$). After adjustment for multiple testing, statistical significance persisted for most variables. In two cases where the variable of interest was no longer statistically significant, similar trends in the results were nonetheless observed. Moreover, in sensitivity analysis, which included Canadian sites only, we obtained similar results.

We tested for interactions between sex and femininity score, sex and social support, and sex and housework responsibility in predicting physical limitation. We did not find an interaction between sex and femininity score or sex and housework responsibility, but found a statistically significant interaction between sex and social support ($\beta=0.44$ [95% CI, 0.01, 0.88]; $P=0.047$). In post-hoc analyses, there was a clinically significant difference in the physical limitation score of high versus low social support

Table. Baseline Characteristics According to Tertiles of Physical Component Summary and Mental Component Summary Scores

Characteristics	All Patients (N=1123)					
	PCS Tertile			MCS Tertile		
	≤40.7	40.7 to ≤50.8	>50.8	≤40.5	40.5 to ≤52.5	>52.5
Sex (male), %	58.9	70.1	74.3	58.4	66.5	78.2
Gender-related factors						
Femininity score, mean±SD	5.7±1.0	5.7±0.9	5.7±0.9	5.7±1.0	5.6±0.9	5.7±0.9
Stress level at home, mean±SD	4.8±2.6	4.5±2.6	4.2±2.4	5.8±2.5	4.6±2.4	3.2±2.0
Stress management, %	2.8±0.9	3.0±0.9	3.1±0.9	2.5±0.9	2.9±0.8	3.4±0.7
Housework responsibility, %	50.6	41.2	41.4	52.6	45.7	35.3
Primary earner, %	63.6	69.4	66.2	62.9	65.5	70.6
No. of hours worked/week, mean±SD	43.0±15.3	44.4±12.7	46.0±13.7	44.1±15.6	44.8±12.4	44.9±13.9
Low social support, %	33.8	30.1	17.8	36.4	29.3	16.2
Sociodemographic factors						
Age, mean±SD	48.6±5.6	48.1±5.9	47.9±6.0	47.8±5.6	48.3±5.9	48.4±6.0
Marital status (married versus not), %	48.2	46.6	56.1	44.3	51.9	56.8
Ethnicity (Caucasian vs not), %	87.4	89.1	91.8	89.1	90.0	89.1
Low education (<post-secondary), %	42.2	38.5	31.5	40.6	40.0	31.6
Clinical characteristics						
Depression, %	38.8	19.2	12.7	54.3	13.9	3.0
Anxiety, %	60.2	38.7	32.6	78.7	40.7	12.5
Presence of vascular risk factors, %	97.0	90.0	86.6	94.3	91.3	88.1
Previous cardiovascular event, %	35.1	18.1	12.5	29.5	20.1	16.3
Type of ACS						
STEMI, %	49.4	64.1	61.8	54.2	56.6	64.2
Non-STEMI, %	35.5	27.3	32.9	33.9	37.1	26.8
Unstable angina, %	14.0	4.9	3.5	9.7	5.0	7.6
Treatment						
Thrombolysis, %	9.2	16.3	14.9	13.3	12.3	14.8
Primary PCI, %	32.1	39.6	40.2	34.0	36.8	41.0
Non-primary PCI, %	41.7	38.7	36.4	37.4	40.1	39.2
CABG, %	11.0	5.4	5.0	7.2	6.9	7.3

ACS indicates acute coronary syndrome; CABG, coronary artery bypass grafting; MCS, Mental Component Summary; PCI, percutaneous coronary intervention; PCS, Physical Component Summary; STEMI, ST-elevation myocardial infarction.
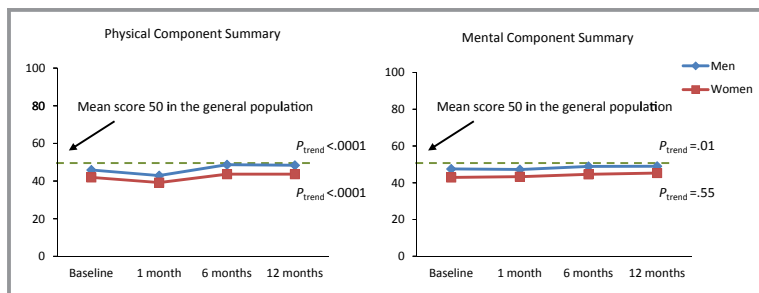

Figure 1. Trends in Physical Component Summary and Mental Component Summary scores. Note: Difference >3 points and *P*<0.01 between men and women at all points in time.

among women (82 versus 66; difference >5 points), but not among men (Figure 3).

Discussion

Our study found that young male and female patients with ACS had poorer HRQL, compared to the general population, both in terms of physical and mental functioning. Importantly, our findings demonstrated that the long-term impact of ACS on HRQL among young adults depends more strongly on gender than on sex. Even when adjusting for clinical characteristics and treatment, several gender-related factors were found to be significant in predicting HRQL, particularly femininity score, social support, and housework responsibility. Sex was not found to be an important predictor, except for physical limitation. We also found that social support was more important among women than men to increase their physical limitation score.

Our study encompasses extensive measures of gender-related factors among young patients with ACS, which have not been examined in previous studies. Although most studies
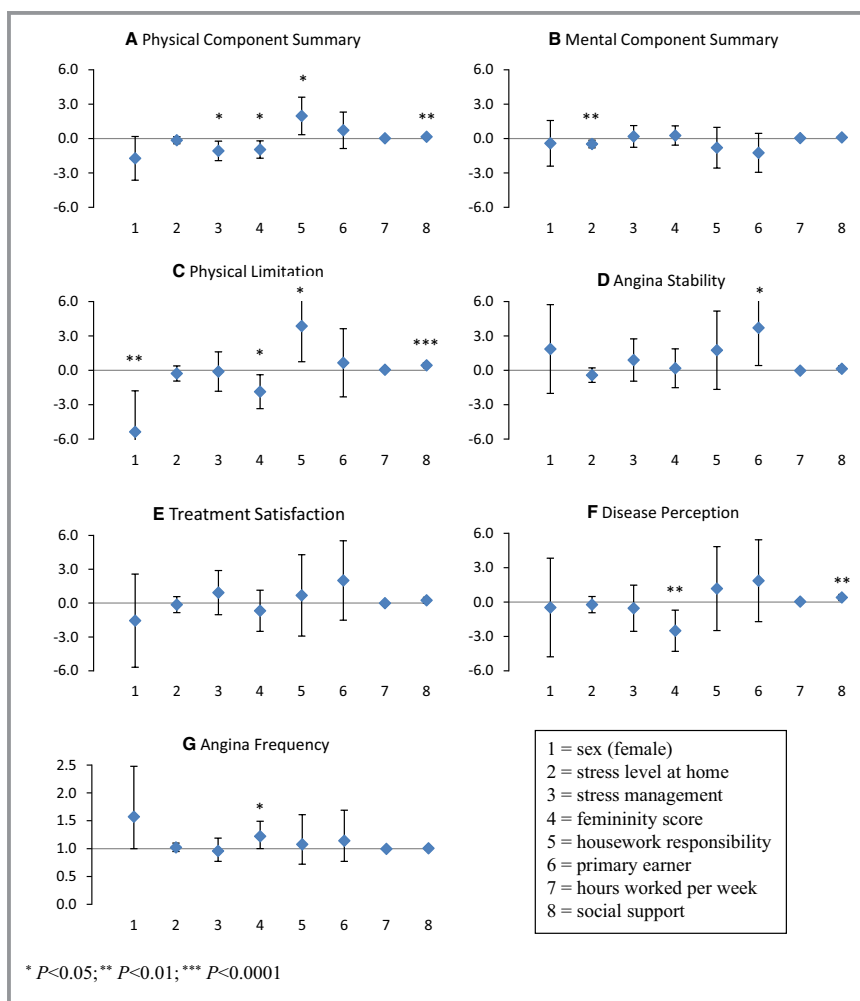

Figure 2. Multivariable regressions of predictors of health-related quality of life. Note: Figure 2A through 2F indicate β coefficients; Figure 2G indicates odds ratio (OR). Adjustments were made for variables significant at *P*<0.10 in univariable analyses: (A) education, presence of vascular risk factors, previous cardiovascular event, depression, anxiety, nonprimary percutaneous coronary intervention, type of acute coronary syndrome, and baseline score; (B) education, previous cardiovascular event, depression, anxiety, and baseline score; (C) education, previous cardiovascular event, depression, anxiety, type of acute coronary syndrome, and baseline score; (D) depression and baseline score; (E) education, depression, anxiety, and baseline score; (F) education, presence of vascular risk factors, previous cardiovascular event, depression, anxiety, and baseline score; and (G) education, previous cardiovascular event, depression, anxiety, and baseline score.
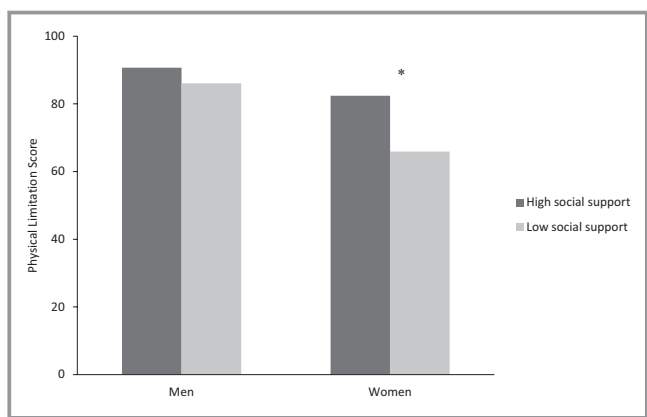
Figure 3. Effect of sex and social support on physical limitation score. *Difference >5 points and $P=0.047$ for high versus low social support.

have consistently shown that women generally have poorer HRQL after an ACS event, the reasons for this are not well understood. Studies that have attempted to investigate sex differences in the predictors of HRQL have mostly focused on clinical characteristics and treatment procedures. Yet, these only partially explain the observed sex discrepancies in HRQL, and gender has been suggested as accounting for the residual discrepancies.[32] Furthermore, angina frequency is an important characteristic of HRQL in ACS. The prevalence of angina tends to be higher in women, compared to men.[33] Hence, it is possible that societal views on the acceptability of residual angina in women versus men may, in part, account for less aggressive treatments among women.

In addition, studies investigating HRQL post-ACS have typically included older adults and few have focused on younger patients with ACS.[4,34,35] Some studies have investigated social support as a determinant of HRQL and have found it to be particularly important for women.[8,36] These studies have been mostly conducted among older populations, but younger populations are a particularly vulnerable population who may have persisting disease burden leading to a loss of many years of productivity. In the MONIKA/KORA population-based registry, it was demonstrated that HRQL is greatly impaired post-ACS, especially among young adults (aged 45 to 54 years), compared to their same age-group counterparts in the general population.[4] Our results, based on a younger population, are concordant with previous findings and sustain the importance of social support in long-term HRQL among young women after an ACS event. Low social support appears to be more detrimental to women than men. This may be because of the fact that women, especially younger ones, may have higher combined occupational and household responsibilities than men and thus may require more social support. It is plausible that these young women who have low social support will face greater difficulties re-immersing into their normal routine and re-establishing an

adequate HRQL post-ACS. Therefore, the value of social support post-ACS also needs to be underlined among such young adult populations.

The importance of studying gender-related factors as separate entities from sex has been increasingly emphasized in health research.[37,38] In fact, different gender-related factors, including family and societal roles, have been suggested as being key to the psychosocial response that one may have after having a CVE.[39] It has been suggested that women may have more difficulty coping after a cardiac event than men.[40] In our young population of patients with ACS, we interestingly observed that a higher femininity score may be linked to poorer HRQL. The BRSI considers traits such as "sensitive to the needs of others," "compassionate," and "loves children," among others, as being feminine characteristics. These can be thought of as being linked to higher household responsibilities and roles traditionally occupied by women. Considering an evolving society with closing gender gaps, particularly among younger generations, further research is imperative to evaluate how these changing roles may affect CV health and HRQL among young patients. Furthermore, in an older population with ACS, higher femininity among women may be even more impactful. Additional investigations in other study groups may also better show the influence of gender-related factors on HRQL in ACS.

Our study is unique in that it is a large-scale prospective cohort study of patients with premature ACS. Nonetheless, there are certain limitations to our study. The sample size for women was smaller than that for men. As data were incomplete on some variables, we used multiple imputation. Although the results may not be as accurate as with a complete data set, we obtained very similar results to those yielded from the non-imputed models. Therefore, it is unlikely that the multiple imputation procedures have biased our results. Also, there are many possible determinants of HRQL, and the use of many variables in the multivariable models may have reduced the power to detect statistical significance. However, our results were similar after adjustment for multiple testing, with nearly all of the variables retaining statistical significance. As well, it would have been interesting to address medication use, but we had insufficient data to conduct these analyses. It is also possible that among eligible participants, those enrolled were in a more favorable clinical situation. Moreover, because various questions on the SF-12 and SAQ refer to questions on health status over the past 4 weeks, there is the possibility of poor recall.

Conclusions

Female patients with premature ACS report significantly poorer HRQL than male patients, both in terms of physical

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and mental functioning. Gender appears to be more important than sex in predicting long-term HRQL post-ACS. Future research should aim to address gender-related factors as a means to improve HRQL among young patients recovering from ACS. Specific gender-related factors, such as social support, may be amenable to interventions and could improve the HRQL of patients with premature ACS.

Appendix

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Disclosures

None.

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