JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2016 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

VOL. 67, NO. 2, 2016
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.10.067

ORIGINAL INVESTIGATIONS

Sex Versus Gender-Related Characteristics

Which Predicts Outcome After Acute Coronary Syndrome in the Young?

Roxanne Pelletier, PhD,* Nadia A. Khan, MD, MSc,† Jafna Cox, MD,‡ Stella S. Daskalopoulou, MD, PhD,§ Mark J. Eisenberg, MD, MPH,‖ Simon L. Bacon, PhD,¶ Kim L. Lavoie, PhD,# Kaberi Daskupta, MD, MSc,** Doreen Rabi, MD, MSc,†† Karin H. Humphries, DSc,‡‡ Colleen M. Norris, PhD,§§ George Thanassoulis, MD,‖‖ Hassan Behlouli, PhD,¶¶ Louise Pilote, MD, PhD,*§ for the GENESIS-PRAXY Investigators

ABSTRACT

BACKGROUND "Gender" reflects social norms for women and men, whereas "sex" defines biological characteristics. Gender-related characteristics explain some differences in access to care for premature acute coronary syndrome (ACS); whether they are associated with cardiovascular outcomes is unknown.

OBJECTIVES This study estimated associations between gender and sex with recurrent ACS and major adverse cardiac events (MACE) (e.g., ACS, cardiac mortality, revascularization) over 12 months in patients with ACS.

METHODS We studied 273 women and 636 men age 18 to 55 years from GENESIS-PRAXY (GENdEr and Sex determInantS of cardiovascular disease: from bench to beyond-Premature Acute Coronary SYndrome), a prospective observational cohort study, who were hospitalized for ACS between January 2009 and April 2013. Gender-related characteristics (e.g., social roles) were assessed using a self-administered questionnaire, and a composite measure of gender was derived. Outcomes included recurrent ACS and MACE over 12 months.

RESULTS Feminine roles and personality traits were associated with higher rates of recurrent ACS and MACE compared with masculine characteristics. This difference persisted for recurrent ACS, after multivariable adjustment (hazard ratio from score 0 to 100: 4.50; 95% confidence interval: 1.05 to 19.27), and was a nonstatistically significant trend for MACE (hazard ratio: 1.54; 95% confidence interval: 0.90 to 2.66). A possible explanation is increased anxiety, the only condition that was more prevalent in patients with feminine characteristics and that rendered the association between gender and recurrent ACS nonstatistically significant (hazard ratio: 3.56; 95% confidence interval: 0.81 to 15.61). Female sex was not associated with outcomes post-ACS.

CONCLUSIONS Younger adults with ACS with feminine gender are at an increased risk of recurrent ACS over 12 months, independent of female sex. (J Am Coll Cardiol 2016;67:127–35) © 2016 by the American College of Cardiology Foundation.

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

From the *Divisions of General Internal Medicine and of Clinical Epidemiology, Department of Medicine, The Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada; †Department of Medicine, Center for Health Evaluation and Outcomes Science, University of British Columbia, Vancouver, British Columbia, Canada; ‡Division of Cardiology, Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, Canada; §Division of Internal Medicine, Department of Medicine, McGill University Health Centre, Montreal, Quebec, Canada; ‖Divisions of Cardiology and Clinical Epidemiology, Department of Medicine, McGill University Health Centre, Montreal, Quebec, Canada; ¶Department of Exercise Science, Concordia University, Montreal, Quebec, Canada; #Department of Psychology, University of Quebec in Montreal, Montreal, Quebec, Canada; **Division of Clinical Epidemiology, McGill University Health Centre, Montreal, Quebec, Canada; ††Department of Community Health Sciences, Faculty of Medicine, University of Calgary, Calgary, Alberta, Canada; ‡‡Division of Cardiology, University of British Columbia, Vancouver, British Columbia, Canada; §§Faculty of Nursing, University of Alberta, Edmonton, Alberta, Canada; ‖‖Division of Cardiology, Department of Medicine, McGill University Health Centre, Montreal, Quebec, Canada; and the ¶¶Division of Clinical Epidemiology, McGill University Health Centre, Montreal, Quebec, Canada. This study was funded by the Heart and Stroke Foundations of

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

CI = confidence interval

CV = cardiovascular

CVD = cardiovascular disease

GRACE = Global Registry of Acute Coronary Events

HR = hazard ratio

MACE = major adverse cardiac events

Gender reflects social norms and expectations ascribed to women and men, in contrast to biological characteristics that are captured by sex. Gender can be referred to as the nonbiological aspects of being male or female (e.g., social roles, personality traits) (1–4). The increased risk of mortality in young females compared with males after acute coronary syndrome (ACS) (5,6) may relate to gender-related characteristics (7–9). For example, hours of paid work have increased significantly among women in the past 20 to 30 years, which in addition to child care responsibilities, may lead to increased psychosocial stress (7,8,10). This stress may be exacerbated post-ACS and may even be a trigger of poor outcomes (11,12).

SEE PAGE 136

Consistent with this idea are the results from the Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients study, demonstrating that women with premature ACS have a worse pre-event mental and physical health status, and a worse quality of life than men, regardless of their history of cardiovascular (CV) disease (13). However, traits typically ascribed to men, including denial of weakness and vulnerability, are thought to undermine health promotion activities (14). Unlike sex characteristics, gender-related characteristics, such as personality traits and social roles, can be present at different levels in both women and men. Therefore, it is possible that there are gender-related attitudes and roles that are important to health behaviors apart from biological sex.

We previously observed that poorer access to care for young women compared with men with ACS was partly explained by gender-related attitudes and roles traditionally ascribed to women (15). Whether attitudes and social roles traditionally ascribed to women are associated with adverse CV outcomes after premature ACS is unknown. Our objectives were to determine whether gender-related attitudes and roles and/or sex are associated with recurrent ACS over 12 months following hospital discharge for the index ACS and/or major adverse cardiac events (MACE) and all-cause mortality over 12 months post-ACS, and to explore pathways of these associations. We hypothesized that gender-related attitudes and social roles traditionally ascribed to women would be positively associated with recurrent ACS, MACE, and all-cause mortality at 12 months. We also hypothesized that such patient health behaviors, clinical risk profiles, and medical management characteristics are plausible pathways for these associations.

METHODS

STUDY DESIGN. GENESIS-PRAXY (GENdEr and Sex determInantS of cardiovascular disease: from bench to beyond-Premature Acute Coronary SYndrome) is a multicenter prospective follow-up of young patients (age ≤55 years) with ACS. Between January 2009 and April 2013, a total of 24 centers across Canada, 1 in the United States, and 1 in Switzerland participated in the recruitment of patients. Participants were followed for a 12-month period post-ACS. A detailed description of the design and methods of GENESIS-PRAXY has previously been published (16). The reporting of the present analyses follows the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for observational studies (17).

ETHICS. In Quebec, a multicenter ethics review allowed for the McGill University Heath Centre to act as the central review board and coordinate ethics approval for all centers. All other centers received ethics approval from their respective hospital ethics review boards.

STUDY POPULATION AND DATA SOURCES. Eligible patients were between the ages of 18 and 55 years, fluent in English or French, able to provide

Quebec, Nova Scotia, Alberta, Ontario, Yukon, and British Columbia, Canada, and the Canadian Institutes of Health Research (CIHR). The study sponsors had no role in the design of the study; the collection, analysis, or interpretation of data; the preparation of the report; review; or approval of the manuscript. Dr. Pelletier is supported by a CIHR award. Dr. Khan is supported by a Michael Smith Foundation for Health Research Career Scientist award. Dr. Daskalopoulou is Chercheur-Boursier Clinicien, supported by a Fonds de Recherche du Quebec-Sante (FRQS) salary award. Dr. Bacon is supported by an FRQS salary award; has received investigator initiated grant funding from GlaxoSmithKline and Abbvie; has received personal fees from Kataka Medical Communication; and has received speaker fees from Novartis. Dr. Lavoie is supported by CIHR New Investigator and FRQS salary awards; and has received consultancy and/or presentation fees from Takeda, AbbVie, Boehringer Ingelheim, Janssen, Bayer, Mundi Pharma, AstraZeneca, and Merck. Dr. Daskupta holds a Senior Clinician Scientist salary award from the FRQS. Dr. Thanassoulis is on the speakers bureau of Servier Canada; and has received a grant from ISIS pharmaceuticals. Dr. Pilote holds a James McGill Chair in medicine. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received September 1, 2015; accepted October 20, 2015.

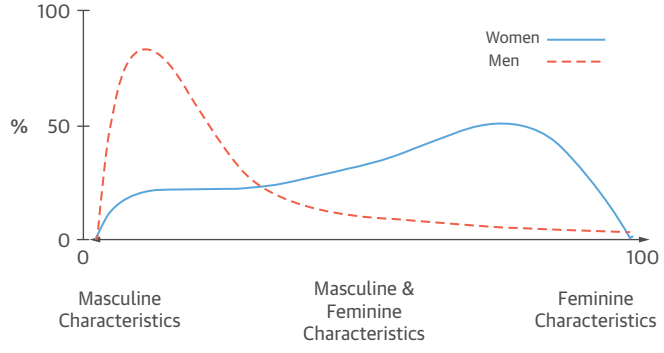
informed consent, and admitted to the hospital with a diagnosis of ACS. On recruitment (within 24 h of admission), participants were asked to complete a self-administered questionnaire (discussed in later text) and anthropometric measurements were obtained. Medical chart reviews undertaken by the research nurse and the self-administered questionnaires were used to collect participants' medical history, health behaviors, and index ACS characteristics; clinical risk profile; and medical management data. At 12 months following ACS, participants' outcome data were reported based on medical chart reviews, and a telephone interview was conducted by the research nurse to complement and/or confirm data. For the present analyses, 909 patients with baseline and follow-up data were included.

GENDER-RELATED FACTORS. According to the Women Health Research Network of the Canadian Institutes of Health Research, the concept of gender includes 4 interrelated aspects that encompass the gender construct: gender roles (e.g., child care), gender identity (e.g., personality traits), gender relationships (e.g., social support), and what is termed "institutionalized gender" (e.g., education level, personal income) (1). As part of the GENESIS-PRAXY study, several gender-related variables relevant to cardiovascular disease (CVD) research were measured to cover most of these 4 aspects. These variables were initially hypothesized to be gender-related as traditionally defined (i.e., historically different in men and women). The following variables were therefore measured using a self-administered questionnaire: household's primary earner status (assessed using the question: "Are you the primary earner in your household?"); employment status; number of hours of work per week; level of responsibility for caring for children (assessed using the question: "For the children that live with you, to what level are you responsible for caring for them" on a scale from 0 to 6); level of responsibility for child discipline (using the same question as the previous but replacing "caring" by "disciplining"); number of hours per week spent doing housework; status of household's primary responsibility; gender-related personality traits assessed using masculinity and femininity scores on the BEM Sex Role Inventory (18); stress level at work, at home, and overall (on a scale from 1 to 10); level of confidence in stress management abilities (assessed using the question: "How confident do you feel in managing your stress?"; participants chose between "Not confident," "A little confident," "Moderately confident," "Very confident"); social support-related variables, found in the items of the ENRICHD Social Support Instrument (19); civil status; personal income; level of education; perceived social standing within patient's community and country, assessed using the MacArthur Perceived Social Standing Scale (20); and job value and job quality deficit-related variables, assessed using a previously modified version of the Canadian Policy Research Network-Ekos Changing Employment Relationships Survey Questionnaire (21).

GENDER-RELATED SCORE. A detailed description of methodology used to construct the gender index has been published (22). Briefly, a composite measure of the gender-related characteristics was created, whereby the previously named variables were included in a principal component analysis. To determine which variables were actually gender-related in our cohort, the 17 variables identified on the retained components from the principal component analysis (23,24) were included in a logistic regression using biological sex as the dependent variable. This choice of dependent variable was made because to date, gender-related characteristics have mostly been defined historically based on social norms and expectations typically ascribed to men and women (1–4). These norms and expectations are likely to evolve with time, and to differ between subpopulations. We therefore aimed to define objectively the variables that were associated with the reality of being biologically female or male in the GENESIS-PRAXY cohort. For this purpose, a first logistic regression was conducted, including sex as the dependent variable and the variables retained from the principal component analysis as the independent variables.

The 7 variables that were independently associated with biological sex and included in the gender-related score (according to their own weight based on their coefficient estimate) are: 1) status of household

FIGURE 1 Gender Score Distribution in Men and Women With Premature Acute Coronary Syndrome



Adapted with permission from Pelletier et al. (22).

TABLE 1 Baseline Characteristics According to Tertiles of the Gender-Related Score

	Tertile 1 Characteristics Ascribed to Men	Tertile 2 Both Characteristics	Tertile 3 Characteristics Ascribed to Women
Gender-related score	3.3 ± 2.0	18.9 ± 9.0	68.3 ± 17.9
Demographic characteristics			
Median age, yrs (IQR)	48 (8)	48 (7)	48 (7)
Married or common law	258 (86)	116 (58)	186 (60)
Women	6 (2)	60 (20)	207 (66)
Men	294 (98)	240 (80)	102 (34)
White	267 (89)	266 (85)	272 (88)
Poor behaviors			
Cocaine use (ever)	45 (15)	45 (15)	45 (15)
Alcohol, >2 drinks per day	127 (43)	111 (37)	193 (30)
Recreational drug use	120 (40)	122 (41)	113 (37)
Physically active	268 (90)	267 (89)	271 (88)
Current smokers	111 (37)	121 (40)	133 (43)
Clinical profile			
Significant anxiety (score ≥8 on the HADS)	92 (31)	122 (41)	167 (54)
Significant depression (score ≥8 on the HADS)	58 (19)	66 (22)	90 (29)
Diabetes mellitus type 2	37 (12)	38 (13)	71 (23)
Hypertension	132 (44)	133 (43)	173 (56)
Dyslipidemia	175 (59)	165 (55)	162 (52)
Family history of CVD	62 (21)	58 (19)	84 (27)
Obesity	120 (40)	113 (38)	124 (40)
Previous CV event*	45 (15)	71 (23)	84 (28)
STEMI	171 (58)	181 (60)	163 (53)
NSTEMI	102 (34)	101 (34)	105 (34)
Unstable angina	20 (7)	15 (5)	33 (11)
GRACE score	71 ± 17	70 ± 17	71 ± 17
Medical management			
Delay between onset of chest pain and presentation to ED, median (h) (IQR)	3.5 (10.0)	3.2 (7.5)	3.9 (7.4)
Number of medical visits as outpatient at 12 months	1.3 ± 1.9	1.1 ± 1.8	1.3 ± 1.9
Referral for smoking cessation counseling	119 (40)	136 (45)	168 (54)
Referral for diet counseling	206 (69)	213 (71)	221 (72)
Referral for cardiac rehabilitation counseling	234 (78)	212 (71)	224 (72)
Aspirin prescription at discharge	291 (97)	292 (97)	291 (94)
Other antiplatelet prescription at discharge	249 (85)	261 (88)	232 (77)
ACE-inhibitor prescription at discharge	223 (76)	213 (71)	191 (64)
Beta-blockers prescription at discharge	253 (86)	259 (87)	251 (83)
Statins prescription at discharge	285 (97)	277 (93)	277 (92)

Values are mean ± SD or n (%). *Previous CVD event was defined as having a previous myocardial infarction, stroke, percutaneous coronary intervention, or coronary artery bypass grafting, or having peripheral arterial disease.

ACE = angiotensin-converting enzyme; CV = cardiovascular; CVD = cardiovascular disease; ED = emergency department; GRACE = Global Registry of Acute Coronary Events; HADS = Hospital Anxiety and Depression Scale; IQR = interquartile range; NSTEMI = non-ST-segment-elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction.

primary earner; 2) personal income; 3) number of hours per week spent doing housework; 4) status of primary person responsible for doing housework; 5) level of stress at home; 6) Bem Sex Role Inventory masculinity score; and 7) Bem Sex Role Inventory femininity score (Online Tables 1 and 2). The gender-related score represents the probability, between 0% and 100%, for each patient to be a "woman." The lower the score, the more the patient reported characteristics traditionally ascribed to men; and vice versa, the higher the score the more the patient reported characteristics traditionally ascribed to women. Intermediate scores represent patients with an equivalent level of characteristics traditionally ascribed to women and men.

OUTCOME MEASURES. The primary outcome was recurrent ACS over 12 months, and the secondary outcome measures included MACE and all-cause mortality over 12 months, determined using medical chart review and complemented by a telephone interview conducted by the research nurse. The first occurring event between hospital discharge following the index ACS and 12 months was included in the analyses. MACE included recurrent ACS, cardiac mortality, and revascularization procedures (percutaneous coronary intervention and coronary artery bypass grafting).

POTENTIAL PATHWAYS OF THE ASSOCIATION BETWEEN SEX, GENDER-RELATED SCORE, AND OUTCOMES. Participants' behavior-related variables included cocaine and recreational drug use, alcohol consumption, physical activity, and cigarette smoking. Clinical risk profile-related variables included anxiety and depression symptoms, diabetes, dyslipidemia, family history of CVD, hypertension, obesity, previous CVD events, having been diagnosed with an ST-segment-elevation myocardial infarction as opposed to a non-ST-segment elevation myocardial infarction or unstable angina, and the GRACE (Global Registry of Acute Coronary Events) score (a validated score used to predict in-hospital and long-term mortality or reinfarction). Depression and anxiety symptoms present before the index ACS were assessed using the Hospital Anxiety and Depression Scale (25). Body mass index was calculated from measured height and weight, and obesity was defined as a body mass index ≥30 kg/m^2. Previous CVD events included myocardial infarction, stroke, peripheral arterial disease, coronary artery bypass grafting, and percutaneous coronary intervention. The GRACE score was calculated using chart review data and the Risk Calculator for 6-Month Postdischarge Mortality After Hospitalization for Acute Coronary Syndrome (26). Medical management-related variables included delay between the onset of chest pain and presentation to the emergency department; number of medical visits as outpatient at 12 months; discharge referral for smoking cessation, diet, and cardiac rehabilitation counseling; and discharge medication prescriptions.

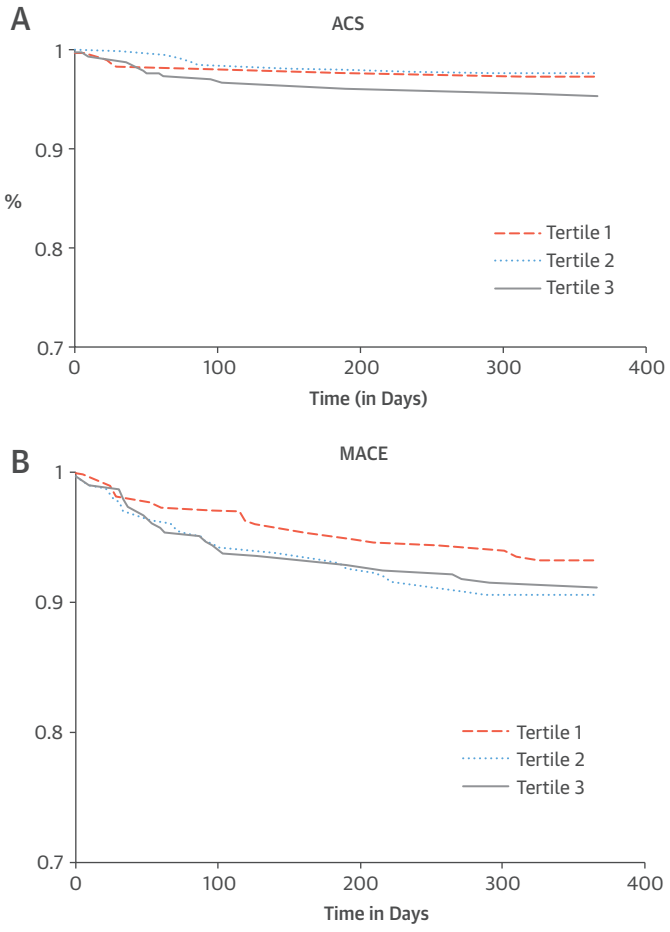
STATISTICAL ANALYSES. Descriptive statistics were used to compare baseline characteristics among patients in the different tertiles of the gender-related score. Tertile 1 included the third of patients (0% to 33.3%) with the highest level of gender-related characteristics traditionally ascribed to men; tertile 2 included the third of patients (33.4% to 66.6%) with an equivalent level of gender-related characteristics traditionally ascribed to women and to men; and tertile 3 included the third of patients (66.7% to 100%) with the highest level of gender-related characteristics traditionally ascribed to women. Rates of recurrent ACS, MACE, and all-cause mortality at 12 months were also compared among tertiles of the gender-related score and between sexes. Continuous variables were compared using Student *t* tests or Wilcoxon tests as appropriate, and dichotomous variables were compared using chi-square tests. Tertiles of the gender-related score were used to compare patients in descriptive analyses, whereas the gender-related score as a continuous variable was used in the Cox proportional hazards regression models.

To assess the relationship of sex and gender-related characteristics with recurrent ACS and MACE, Cox proportional hazards models were constructed. The multivariable models included the gender-related score, sex, age, GRACE score, previous CVD events, and the number of traditional CV risk factors (including diabetes, hypertension, obesity, dyslipidemia, cigarette smoking, and family history of CVD). Regression analyses were not conducted for all-cause mortality because of insufficient statistical power.

To explore potential pathways of the association between gender-related characteristics and recurrent ACS, only the health behaviors, clinical risk profile, and medical management characteristics that were associated with the gender-related score in univariate analyses were used. These variables included anxiety; depression; family history of CVD; smoking; dyslipidemia; hypertension; diabetes mellitus; and prescription of angiotensin-converting enzyme inhibitor, antiplatelet, and statin medications at hospital discharge. As such, 10 Cox regression models were conducted, where each of the previous 10 variables were included, in rotation, in the initial multivariable model (see previous paragraph). In these models, changes in the effect size of the gender-related score that were induced by the inclusion of each potential pathway-related variable were assessed.

Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina). Statistical tests were 2-sided; differences with $p \leq 0.05$ were considered statistically significant.

FIGURE 2 Unadjusted Proportions of Patients Free of Recurrent Events According to the Tertiles of the Gender-Related Score



(A) Unadjusted proportions of patients free of recurrent acute coronary syndrome (ACS) over 12 months according to tertiles of the gender-related score. **(B)** Unadjusted proportions of patients free of major adverse cardiac events (MACE) over 12 months according to tertiles of the gender-related score.

RESULTS

BASELINE CHARACTERISTICS. Our study population included 273 (30%) women and 636 (70%) men (Online Figure 1), for whom the gender-related score distribution is presented in **Figure 1**. In our cohort, the mean gender-related score was 30.5 ± 30.2, and the median age was 48 years (interquartile range: 6 years). Recurrent ACS at 12 months occurred in 35 (3%) patients, and 75 (8%) and 9 (<1%) patients sustained a MACE and died, respectively. Patients with characteristics traditionally ascribed to women (tertile 3 of the gender-related score) were more likely to be women, unmarried, to report high levels of anxiety and depression, to be smokers, have diabetes,

TABLE 2 Multivariable Cox Proportional Hazards Regressions: Association Between the Gender-Related Score and Recurrent ACS

	Recurrent ACS HR (95% CI)	p Value
Gender-related score (from score 0 to 100)	4.50 (1.05–19.27)	0.04
Female sex	0.50 (0.18–1.40)	0.18
Age	1.01 (0.94–1.10)	0.77
GRACE score, for each point increment	1.00 (0.97–1.02)	0.70
Previous CV event	2.13 (0.94–4.80)	0.07
Number of CV risk factors	1.02 (0.77–1.35)	0.92

ACS = acute coronary syndrome; CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

TABLE 3 Stepwise Proportional Hazard Regressions: Potential Pathways of the Association Between the Gender-Related Score and Recurrent ACS

	Recurrent ACS* HR (95% CI)	p Value
Initial model		
Gender-related score (from score 0 to 100)	4.50 (1.05–19.27)	0.04
Exploratory Model 1		
Significant anxiety (score ≥8 on the HADS)	1.96 (0.90–4.29)	0.09
Gender-related score	3.56 (0.81–15.61)	0.09
Exploratory Model 2		
ACE-inhibitors prescription at discharge	0.88 (0.40–1.92)	0.74
Gender-related score	4.49 (1.05–19.25)	0.04
Exploratory Model 3		
Antiplatelet prescription at discharge	0.64 (0.27–1.63)	0.32
Gender-related score	4.47 (1.05–19.07)	0.04
Exploratory Model 4		
Statins prescription at discharge	0.60 (0.18–2.03)	0.41
Gender-related score	4.44 (1.04–19.02)	0.04
Exploratory Model 5		
Family history of CVD	0.55 (0.19–1.56)	0.26
Gender-related score	4.59 (1.08–19.54)	0.04
Exploratory Model 6		
Current smoking	0.53 (0.23–1.24)	0.53
Gender-related score	4.64 (1.07–20.04)	0.04
Exploratory Model 7		
Significant depression (score ≥8 on the HADS)	1.33 (0.60–2.99)	0.48
Gender-related score	4.37 (1.01–18.85)	0.04
Exploratory Model 8		
Dyslipidemia	1.09 (0.42–2.84)	0.86
Gender-related score	4.55 (1.06–19.61)	0.04
Exploratory Model 9		
Hypertension	1.71 (0.68–4.28)	0.25
Gender-related score	4.64 (1.04–19.18)	0.04
Exploratory Model 10		
Diabetes mellitus type 2	2.65 (0.98–7.20)	0.06
Gender-related score	4.44 (1.03–19.14)	0.04

*All models are also adjusted for sex, age, GRACE score, previous events, and the number of CVD risk factors.
Abbreviations as in Tables 1 and 2.

hypertension, family history of CVD, and prior CV events before the index ACS than patients in tertiles 2 and 1. Patients with characteristics traditionally ascribed to women were also less likely to be prescribed antihypertensive, antiplatelet, and statin medication at hospital discharge (Table 1).

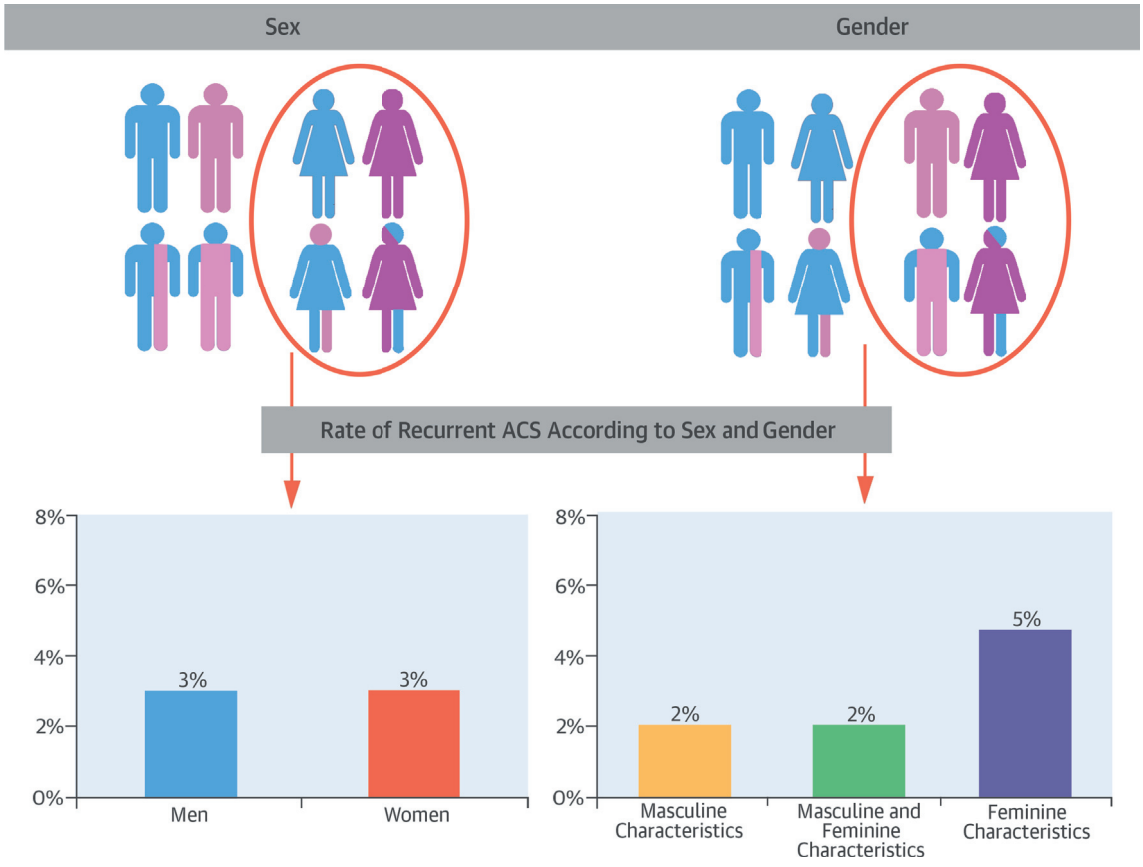
SEX, GENDER, AND OUTCOMES. The proportions of men and women with recurrent ACS (3% for both), MACE (8% for both), and all-cause mortality (<1% for both) at 12 months were similar. The risk of events according to sex in adjusted Cox proportional hazards regressions for recurrent ACS (hazard ratio [HR]: 0.93; 95% confidence interval [CI]: 0.45 to 1.92; p = 0.85) and for MACE (HR: 0.71; 95% CI: 0.41 to 1.23; p = 0.22) was inconclusive.

In contrast, when patients were categorized according to tertiles of the gender-related score, the rate of recurrent ACS in patients with characteristics traditionally ascribed to women was 5% compared with 2% in the other 2 groups. Results of the multivariable Cox regression analysis adjusted for sex, age, ethnicity, previous CV events, the GRACE score, and the number of traditional CV risk factors further supported the univariate results: patients with characteristics traditionally ascribed to women were more likely to experience a recurrent ACS than patients with characteristics traditionally ascribed to men (HR: 4.50; 95% CI: 1.05 to 19.27; p = 0.04) (Figure 2A, Table 2).

The rate of MACE was 9% in patients in tertiles 3 and 2 of the gender-related score, whereas it was 6% in patients from tertile 1. Results of the multivariable Cox regression analysis adjusted for sex, age, ethnicity, previous CV events, the GRACE score, and the number of traditional CV risk factors yielded a trend toward patients with characteristics traditionally ascribed to women to be more likely to experience a MACE than patients with characteristics traditionally ascribed to men (HR: 1.54; 95% CI: 0.90 to 2.66; p = 0.12) (Figure 2B). In addition, mortality rate was 1% in patients in tertile 3 and in tertile 2 of the gender-related score, whereas it was 0% in patients in tertile 1. No multivariable analyses were conducted because of insufficient statistical power.

POTENTIAL PATHWAYS OF ASSOCIATION BETWEEN GENDER-RELATED CHARACTERISTICS AND OUTCOMES. Results of our exploratory analyses indicated that higher levels of anxiety decreased the effect size of the gender-related score by over 10%, and rendered its association with recurrent ACS nonstatistically significant. No other variables had a notable decremental effect on the effect size (range of decrease for other plausible pathways, 0% to 3%). This result indicates that elevated anxiety may be a pathway

CENTRAL ILLUSTRATION **Gender-Related Characteristics Versus Sex: Cardiovascular Outcomes**



Pelletier, R. et al. J Am Coll Cardiol. 2016; 67(2):127–35.

Gender identifies both men and women who are at increased risk through their high level of characteristics traditionally attributed to women. Sex distinguishes between males and females independent of their gender-related characteristics. ACS = acute coronary syndrome.

through which personality traits and social roles traditionally ascribed to women increase the risk of recurrent ACS (Table 3).

DISCUSSION

This study suggests that personality traits and social roles traditionally ascribed to women are associated with adverse CV outcomes in young patients with ACS. Specifically, event rates at 12 months were higher in patients with personality traits and roles traditionally ascribed to women compared with patients with personality traits and roles traditionally ascribed to men. In contrast, event rates did not differ between sexes (Central Illustration). This study also indicates that reported increased anxiety may represent a means by which gender-related characteristics are associated with adverse CV outcomes.

The reason why characteristics traditionally ascribed to women increase the risk of adverse CV outcomes after a premature ACS independent of biological sex is likely multifactorial. One possibility is that in younger adults, personality traits, family, and institutional roles influence CV health more substantively than biological/anatomic sex characteristics. An association between gender roles and coronary heart disease incidence has previously been reported in middle-aged women (27). In this study, Japanese women living with both a spouse and children had a 2.1-fold higher risk of coronary heart disease compared with women living with a spouse but no children. It is noteworthy that the expectations with regards to family roles may differ between Japanese and American culture. Nonetheless, results of this Japanese study suggest that an increased children-related burden may adversely affect CV

health. Previous studies have further shown that being married is associated with a better prognosis after myocardial infarction in men, whereas married middle-aged women have a greater fatality risk than unmarried women (28,29). The discrepancy between married women and men is thought to be partly explained by men enjoying social support and control provided by the wife, because women have the tendency to take greater responsibility over organizing health care and providing care (30). However, such feminine gender roles (i.e., the organizing and care tendency toward the husband) may represent a burden and a daily stress for married cardiac women. Moreover, in the last decades, there has been a continuous increase in women's economic participation and opportunities, and educational attainment (7,9). Nevertheless, in today's high-performance and consumer-focused era, most women continue to retain some of the traditional "feminine" responsibilities (e.g., child care) even when employed outside the home. Similarly, men whose wives work outside the home are also likely to be faced with increased household and childcare responsibilities (7). Middle-aged men and women also often face divorce and have to deal with single parenting, debts, and/or lack of resources (31). These gender-related characteristics are present at different levels in both women and men, and in the present study, they adversely affect health processes, independent of biological sex.

In our cohort, characteristics traditionally ascribed to females seemed to adversely affect health outcomes potentially through increased levels of anxiety. Previous studies have shown that anxiety increases the risk of CVD via excessive activation of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system, and via poor health behaviors (32). There are likely multiple and various reasons to explain the presence of increased anxiety in men and women with characteristics traditionally ascribed to women in our sample. For example, marital strain as described previously, and financial difficulties and/or the need to manage housework, child care, and work may represent a daily burden and chronic anxiety may result.

STUDY LIMITATIONS. This study contains some methodological limitations. First, the low mortality rate at 12 months led to low statistical power. This limitation may explain why we did not observe significant associations between sex and adverse CV outcomes, which is in contrast to previous studies with higher ACS rates and comparable proportions of men and women (1). Second, given the limited numbers of recurrent ACS, the interpretation of the stepwise analyses is limited. Insufficient statistical power may be a reason why anxiety was not associated with the outcome in the multivariable model. As such, we hypothesized that increased anxiety may represent a pathway for the association between gender-related characteristics and recurrent ACS, but larger studies are needed to replicate this finding. Third, a small proportion of our patients were recruited in the United States and in Switzerland. Despite the fact that gender-related characteristics are culturally sensitive, only 19 (2%) and 42 (5%) patients were recruited in the United States and in Switzerland, respectively, and thus it is unlikely that our results have been affected. We still cannot exclude possible cultural differences within Canada. Fourth, participants who did not complete follow-up were more likely to be diabetic, smokers, depressed, obese, and nonwhite than those with follow-up data who were included in the analyses. Three of these variables (diabetes, depression, and cigarette smoking) were associated with gender-related characteristics traditionally attributed to women in our study. As such, the inclusion of patients with missing follow-up data would have likely increased the outcomes risk in the group of patients with more feminine gender-related score and would have likely strengthened even more the association we observed between the gender-related score and the risk of recurrent ACS. Finally, there exists no gold standard for a measure of gender and as such, our gender-related score is internally derived without external validation.

CONCLUSIONS

Overall, our study allowed the assessment of the role of variables that are traditionally ascribed to each sex in society, and may shed light on unexplained sex differences in ACS. Specifically, this study shows that personality traits, such as being shy and sensitive to the needs of others, and social roles, such as being responsible for housework, which are traditionally ascribed to women, increase the risk of adverse CV outcomes in young patients with ACS. Gender-related characteristics might impact adverse CV outcomes through increased anxiety.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Louise Pilote, Division of Clinical Epidemiology and General Internal Medicine, McGill University and McGill University Health Centre, 1001 Decarie Boulevard, Room D05.5021, Montreal, Quebec H4A 3J1, Canada. E-mail: louise.pilote@mcgill.ca.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Gender-related characteristics like personality traits and social roles (psychosocial sex) may be as important as biological sex in predicting adverse cardiovascular outcomes in young patients with acute coronary syndromes. Both women and men with personality traits and social roles traditionally attributed to women are at increased risk of subsequent adverse events.

TRANSLATIONAL OUTLOOK: Further studies in larger cohorts are needed to confirm these findings and explore the mechanisms responsible for the associations between feminine gender scores and adverse cardiovascular outcomes.

REFERENCES

1. Johnson JL, Greaves L, Repta R. Better science with sex and gender: a primer for health research: Vancouver: Women's Health Research Network, 2007. Available at: http://bccewh.bc.ca/wp-content/uploads/2012/05/2007_BetterSciencewithSexandGenderPrimerforHealthResearch.pdf. Accessed March 5, 2014.

2. Phillips SP. Defining and measuring gender: a social determinant of health whose time has come. Int J Equity Health 2005;4:11.

3. Ristvedt SL. The evolution of gender. JAMA Psychiatry 2014;71:13–4.

4. Unger RK. Toward a redefinition of sex and gender. Am Psychol 1979;34:1085–94.

5. Claassen M, Sybrandy KC, Appelman YE, Asselbergs FW. Gender gap in acute coronary heart disease: myth or reality? World J Cardiol 2012;4:36–47.

6. Vaccarino V, Parsons L, Peterson ED, Rogers WJ, Kiefe CI, Canto J. Sex differences in mortality after acute myocardial infarction: changes from 1994 to 2006. Arch Intern Med 2009;169:1767–74.

7. Marshall K. Generational change in paid and unpaid work. Canadian Social Trends: Statistics Canada, 2011. Available at: http://www.statcan.gc.ca/pub/11-008-x/2011002/article/11520-eng.pdf. Accessed October 10, 2014.

8. Väänänen A, Kevin MV, Ala-Mursula L, Pentti J, Kivimaki M, Vahtera J. The double burden of and negative spillover between paid and domestic work: associations with health among men and women. Women Health 2004;40:1–18.

9. World Economic Forum. The global gender gap report 2013. World Economic Forum, Geneva Switzerland, 2013. Available at: http://www3.weforum.org/docs/WEF_GenderGap_Report_2013.pdf. Accessed October 10, 2014.

10. Nordenmark M. Balancing work and family demands: Do increasing demands increase strain? A longitudinal study. Scand J Public Health 2004;32:450–5.

11. Norris CM, Murray JW, Triplett LS, Hegedoren KM. Gender roles in persistent sex differences in health-related quality-of-life outcomes of patients with coronary artery disease. Gend Med 2010;7:330–9.

12. Edmondson D, Green P, Ye S, Halazun HJ, Davidson KW. Psychological stress and 30-day all-cause hospital readmission in acute coronary syndrome patients: an observational cohort study. PLoS One 2014;9:e91477.

13. Dreyer RP, Smolderen KG, Strait KM, et al. Gender differences in pre-event health status of young patients with acute myocardial infarction: a VIRGO study analysis. Eur Heart J Acute Cardiovasc Care 2015 Feb 13 [E-pub ahead of print].

14. Courtenay WH. Constructions of masculinity and their influence on men's well-being: a theory of gender and health. Soc Sci Med 2000;50:1385–401.

15. Pelletier R, Humphries KH, Shimony A, et al. Sex-related differences in access to care among patients with premature acute coronary syndrome. CMAJ 2014;186:497–504.

16. Pilote L, Karp I. GENESIS-PRAXY (GENdEr and Sex determInantS of cardiovascular disease: From bench to beyond-Premature Acute Coronary SYndrome). Am Heart J 2012;163:741–6.

17. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Ann Intern Med 2007;147:573–7.

18. Bem S. The measurement of psychological androgyny. J Consult Clin Psychol 1974;42:155–62.

19. The ENRICHD investigators. Enhancing recovery in coronary heart disease patients (ENRICHD): study design and methods. Am Heart J 2000;139:1–9.

20. Adler NE, Epel ES, Castellazzo G, Ickovics JR. Relationship of subjective and objective social status with psychological and physiological functioning: preliminary data in healthy white women. Health Psychol 2000;19:586–92.

21. CPRN - Ekos Changing Employment Relationships Survey Questionnaire. [Announcement posted on the World Wide Web]. 2008. Available at: http://www.cprn.org/doc.cfm?doc=762&l=en. Accessed October 10, 2014.

22. Pelletier R, Ditto B, Pilote L. A composite measure of gender and its association with risk factors in patients with premature acute coronary syndrome. Psychosom Med 2015;77:517–26.

23. Cattell RB. The screen test for the number of factors. Multivariate Behav Res 1966;1:245–76.

24. SAS Institute Inc. SS. Procedure user's guide. Cary, NC: SAS Institute Inc., 2009.

25. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361–70.

26. Eagle KA, Lim MJ, Dabbous OH, et al. A validated prediction model for all forms of acute coronary syndrome estimating the risk of 6-month postdischarge death in an international registry. JAMA 2004;291:2727–33.

27. Ikeda A, Iso H, Kawachi I, Yamagishi K, Inoue M, Tsugane S. Living arrangement and coronary heart disease: the JPHC study. Heart 2009;95:577–83.

28. Mehta PK, Wei J, Wenger NK. Ischemic heart disease in women: a focus on risk factors. Trends Cardiovasc Med 2015;25:140–51.

29. Kilpi F, Konttinen H, Silventoinen K, Martikainen P. Living arrangements as determinants of myocardial infarction incidence and survival: a prospective register study of over 300,000 Finnish men and women. Soc Sci Med 2015;133:93–100.

30. Bird CE, Rieker PP. Gender and Health: The Effects of Constrained Choices and Social Policies. Cambridge, UK: Cambridge University Press, 2008.

31. Statistics Canada. Women in Canada: a gender-based statistical report. Statistics Canada: Ottawa, Canada; 2011.

32. Thurston RC, Rewak M, Kubzansky LD. An anxious heart: anxiety and the onset of cardiovascular diseases. Prog Cardiovasc Dis 2013;55:524–37.

KEY WORDS adverse cardiovascular outcomes, epidemiology, feminine gender roles and traits, premature acute coronary syndrome, stress, women

APPENDIX For supplemental tables and figures as well as a complete list of GENESIS-PRAXY Investigators and participating centers, please see the online version of this article.