HHS Public Access

Author manuscript

J Am Coll Cardiol. Author manuscript; available in PMC 2018 June 13.

Published in final edited form as:

J Am Coll Cardiol. 2017 June 13; 69(23): 2821–2830. doi:10.1016/j.jacc.2017.04.026.

Quality of Life and Associated Factors in Patients with Marfan Syndrome: The GenTAC registry

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Abstract

BACKGROUND—Previous small studies suggested reduced quality of life (QOL) for people with Marfan syndrome (MFS) compared to those without MFS. The national registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC) is a longitudinal observational cohort study of patients with conditions that predispose to thoracic aortic aneurysms and dissections, including MFS. At the time of registry enrollment, GenTAC participants are asked to complete questionnaires about demographics, medical history, health habits, and QOL.

OBJECTIVES—This study assessed QOL in GenTAC participants with MFS and identify associated factors using self-reported data.

METHODS—QOL was assessed using the 4 subscales of the Physical Component Summary (PCS) of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36): physical functioning (PF); role limitations due to physical health (RP); bodily pain (BP); and general health (GH). We studied the association of QOL with self-reported demographics, health behaviors, physical impairments, surgeries, co-morbid medical conditions, medications, and MFS severity.

RESULTS—In the GenTAC registry, 389 adults with MFS completed the SF-36. Mean age was 41, 51% were men, 92% were white, and 65% were college graduates. The mean PCS composite score was 42.3. In bivariate analysis, predictors of better QOL included college education, marital status, higher household income, private health insurance, full-time employment, moderate alcohol use, fewer prior surgeries, fewer comorbid conditions, absence of depression, and less severe MFS

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Disclosures: None of the authors have relationships with industry relevant to the contents of the paper to disclose.

manifestations. In a multivariable analysis, insurance status and employment remained significant predictors of QOL.

CONCLUSIONS—In a large cohort of patients with MFS in the GenTAC registry, health-related QOL was below the population norm. Better QOL was independently associated with socioeconomic factors, not factors related to general health or MFS severity.

Keywords

GenTAC; Marfan syndrome; quality of life; SF-36

INTRODUCTION

Marfan syndrome (MFS) is a hereditary, autosomal dominant disorder due to mutations in the fibrillin 1 gene, that affects connective tissue in multiple organs, most notably the eyes, skeleton, and aorta, with increased risk for thoracic aortic aneurysm and dissection. With advances in aortic surgery over the past 40 years, survival for people with MFS has increased from the third or fourth decade to the eighth (1). However, there continues to be substantial morbidity associated with MFS, including the sequelae of multiple surgeries and lifelong medical therapy (2–4). Not surprisingly, a growing body of literature suggests impaired quality of life (QOL) in patients with MFS (5–11), with most studies using the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) to assess QOL (5–13). Prior studies, however, were limited by small sample sizes and were therefore not able to identify independent factors associated with better or worse quality of life.

The SF-36 is a widely used and extensively validated questionnaire that assesses health related QOL. The questionnaire is subdivided into the Physical Component Score (PCS) and Mental Component Score (MCS). Because previous studies found that MFS predominantly affected the PCS (8,10,12,13), we used the PCS of the SF-36 to assess health related QOL in patients with MFS, and we evaluated the association of QOL with self-reported demographic factors, health behaviors, physical impairments, clinical characteristics, and MFS severity.

METHODS

The development and design of the GenTAC (Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions) registry have been previously described (14,15). Briefly, GenTAC was created as a multicenter, longitudinal, observational cohort study of patients with aortic aneurysm and associated genetic conditions, including MFS. Patients were enrolled at 8 sites: Johns Hopkins University, Baylor College of Medicine, Oregon Health & Sciences University, University of Pennsylvania, University of Texas Health Science Center at Houston, Weill Cornell Medical College, National Institute of Aging-Harbor Hospital and Queen’s Medical Center. Each site obtained Institutional Review Board approval, and each participant patient provided informed consent. Standardized data collection included patient questionnaires, imaging studies, and information about prior surgical procedures. The Research Triangle Institute International in Rockville, Maryland, served as the data coordinating center and was responsible for data management and statistical design and analysis (14,15).

STUDY SUBJECTS

We included patients in the GenTAC database who had MFS diagnosed by Ghent or revised Ghent criteria and confirmed by confirmed by a core phenotyping laboratory at Johns Hopkins University (16, 17), were age 18 or older, and had completed the SF-36. We excluded patients <18 both to be consistent with the existing literature on QOL in MFS and because parents could complete questionnaires for pediatric patients in GenTAC. This study used de-identified survey data from the GenTAC registry. Patients were enrolled in GenTAC from 2006 through December 31, 2013. The most recent analyses of our data were performed in September 2016.

SF-36 SCALE SCORING

Our analyses focused on QOL, which was measured with the PCS of the SF-36 (18,19). The PCS is comprised of 4 subscales: physical functioning (PF); role limitations due to physical health (RP); bodily pain (BP); and general health (GH). Each score ranges from 0 to 100, and is standardized to the population norm of 50 with a standard deviation of 10; higher scores indicate better QOL (18–20). Each of the 4 SF-36 subscales was standardized using a z-score transformation by subtracting the mean and standard deviation from the 1998 general United States population. Composite PCS was computed using the score coefficients from the 1990 general US population per the standard SF-36 scoring. The composite score is transformed to the norm based scoring, where the norm is set as 50 with a standard deviation of 10 (20).

VARIABLES

Self-reported variables were extracted from the Clinical Evaluation Form and the Enrollment Patient Questionnaire. The Clinical Evaluation Form includes questions about enrollment diagnosis, age at diagnosis, number of prior surgeries, number of medications or use of specific medications. For the Enrollment Patient Questionnaire, patients provided their date of birth and answered multiple choice questions about sex, race/ethnicity (White, Black or African American, Asian, American Indian, Native Hawaiian, or Pacific Islander), education, marital status, household income, health insurance status (employer private health insurance plan, Medicare, Medicaid, other), employment (full time, part time, unable to work, student, homemaker, unemployed, and retired); health behaviors, including use of cigarettes, alcohol and illicit drugs; vision or hearing impairment. This form asks about 47 medical conditions, including the genetic conditions associated with thoracic aortic aneurysms (numbers 1 through 7); cardiovascular history including murmur, palpitation, angina, heart attack, cardiomyopathy and others (numbers 8 through 16); hypertension; stroke; aneurysms; cancer; diabetes; bleeding or clotting disease; gastrointestinal disease; arthritis; autoimmune diseases; joint dislocations; cognitive issues; and depression.

To evaluate QOL data in the presence of phenotypic variability, we created a clinical severity scale to differentiate mild, typical, and severe disease. Two scores have been created previously, but neither has been validated (21,22). For the score used in this paper, we included features of MFS that could be assessed based on the self-reported data included in the questionnaires completed at GenTAC enrollment. We assigned points for features of MFS falling into 4 broad groups: skeletal, ocular, vascular and “other”. Points (in

parentheses) for skeletal features were: scoliosis (1), scoliosis repair (3), pectus excavatum (1), pectus carinatum (1), pectus repair (2), and kyphosis or lordosis (1). Points for ocular features were: lens dislocation (3), retinal detachment (2), early onset glaucoma (2), and early onset cataracts (2). Points for vascular features were: enlarged aorta (1), dissection (4), mitral valve repair (3), aortic root replacement or valve surgery (3), and descending/thoracolumbar aortic repair (3). Points for other features included pneumothorax (1), migraines (1), and joint pain (1). Scores were graded as mild (0 to 2), typical (3 to 8), and severe (≥9). Relative scoring is similar to prior MFS severity scales. Also, similar to other MFS severity scales, prior surgery related to MFS increased severity to greater than mild, and ectopia lentis and aortic dissection each increase severity to greater than mild (21,22).

DATA ANALYSIS

We used SAS software (SAS Institute, Inc., Cary, North Carolina) to extract data from the secure enterprise network database to create reports and summary tables and to perform statistical analyses. To examine between-group differences we used SAS PROC GLM to run solutions for Type III ANOVA models and least squares mean estimates. The Tukey-Kramer test was used for post hoc pairwise comparisons for significant factors with 3 or more level. For data security purposes, all analyses were performed and all data were stored in a password-protected remote workspace. We included variables that were significant in bivariate analysis ($p \leq 0.05$) in a multifactor analysis of variance to identify those most strongly associated with QOL.

RESULTS

Of the 871 patients with MFS in the GenTAC registry 643 were >18 years, of whom 389 (60% of GenTAC MFS patients age 18 or older) completed the PCS of the SF-36 (Table 1) and 254 did not. There was no difference between these 2 groups in gender or race, but the group that completed the SF-36 was older and had more severe MFS (Table 2).

Of the respondents who completed the SF-36, mean age was 41, half were women, and most self-identified as white. Most had some college education, one-third earned more than $100,000 annually, and nearly three-fourths had private health insurance. Scores for each subscale were PF 72.6 (or 45.6 with norm-based scoring), RP 46.2 (41.0), BP 65.9 (48.2), and GH51.3 (41.2). Using norm-based scoring, the composite PCS was 42.3, within 1 standard deviation from the population norm of 50.

In bivariate analysis (Table 3), better QOL, as indicated by higher scores across all 4 subscales and a higher PCS composite score, was associated with college education (PCS composite score 38.9 for education less than college vs. 44.3 for college graduates; $p = 0.001$), marital status (34.6 for divorced or separated, 42.0 for married or in a partnership, 44.3 for never married; $p = 0.001$), higher household income (35.7 for ≤$25,000, 42.0 for $25,001–100,000, and 44.2 for >$100,000; $p < 0.0001$), private insurance (33.7 for Medicare or Medicaid vs. 44.8 for private insurance; $p < 0.0001$), working as opposed to unable to work, unemployed, or retired ($p < 0.0001$), moderate alcohol use (38.5 for rare alcohol, 42.9 for near daily or daily, 45.1 for more than monthly but less than daily; $p < 0.0001$), fewer comorbid medical conditions (46.7 for 0 to 2, 43.0 for 3 to 6, and 33.9 for ≥7; $p < 0.0001$),

less severe MFS based on our scale (48.7 for mild, 44.6 for typical, 38.3 for severe; p <0.0001), and absence of depression (44.0 if no depression vs. 36.8 if depressed; p <0.0001).

Those unable to work due to disability had significantly lower scores on the PCS composite and each subscale, as compared to those who were retired, unemployed, or working. The working group scored highest on the composite and all subscales. Those unable to work due to disability also scored higher on the MFS severity score, had more MFS related surgeries, and had more comorbid conditions (Table 4).

Four variables were associated with better QOL in the PCS composite, but not across all 4 subscales: younger age (score of 44.4 for ages 18 to 39 vs. 40.4 for >40; p =0.0022), with 2 subscales significant (PF and RP) and 2 subscales trending toward significant (BP with p =0.0594 and GH, p =0.054); unimpaired hearing (43.0 vs. 36.8; p =0.0052); non-smokers (43.2 vs. 40.4; p =0.046); and fewer prior surgeries (no surgeries 44.8, 1 or 2 surgeries 43.1, ≥3 surgeries 39.1; p =0.002), with 3 subscales significant (PF, p =0.0012; BP, p =0.0084; and RP, p =0.04) and GH not significant (p =0.06).

Gender, race, recreational drug use, vision impairment, use of beta-blockers, and use of angiotensin receptor blockers were not significantly different across the composite or any of the subscales.

In the multivariate model (Table 5), only private insurance status (p =0.013) and employment (p <0.0001) were associated with better QOL as assessed by the composite PCS. In addition to the PCS score remaining significant, employment status also remained significant across all 4 subscales whereas insurance status was only significant across the PF and RP subscales. Marital status (p =0.057) and alcohol use (p =0.053) were no longer significant.

Tukey-Kramer post-hoc tests were performed on variables with ≥3 levels that were significant in the multivariate model. While the post hoc test for income showed significant differences in the PF subscale between the 2 higher income groups ($25,000 to $100,000 and >$100,000, p =0.02), the lower income group did not differ significantly from the other 2 categories. In the case of employment, QOL was significantly lower for those unable to work compare to the other employment categories but there was no significant difference between the other groups.

DISCUSSION

In this largest study to date of QOL in adults with MFS, using the extensively validated SF-36, health-related QOL was 42.3, below the population norm of 50 but within 1 standard deviation of the mean (18–20). The PCS composite score of 42.3 is better than scores seen in previous smaller studies of MFS patents (Table 6), including scores of 34.7 in Foran (22 patients with MFS) (8) and 36 in Rand-Hendriksen (84 patients with MFS) (12), but lower than the composite score of 45.5 in Schoormans's study (121 patients with MFS) (10). Despite small sample sizes, nearly all of the prior studies of MFS patients found a reduction in the PCS composite or in the 4 component subscales (5,8–10,12,13) Three of these studies

used control groups derived from national datasets as comparators (8,10,12). Fusar-Poli et al. found a reduction in MCS but not PCS, but their study was limited by a low response rate, with only 36 MFS patients enrolled out of 380 families who were approached (9). When Lane et al. looked at QOL in adults with congenital heart disease, only 6 of 276 patients had MFS, and so the authors could not comment about QOL in MFS (6). In a study of 174 MFS patients that assessed QOL with a different scale, the Ferrans and Powers Quality of Life Index, Cardiac Version III (QLI-Cardiac III) (7,23), QOL scores were low but comparable to adults with cardiovascular disease, while scores on the psychological/spiritual subscale were significantly lower than for cardiovascular disease (23).

In the current study, variables associated with worse QOL in the bivariate model were less education, being divorced (as opposed to married, in a partnership, or never married), lower household income, public health insurance (as opposed to private), and inability to work due to disability (as opposed to working, unemployed, or retired). Interestingly, MFS severity, number of MFS-related surgeries, and number of comorbid conditions did not impact QOL as independent variables. However, people who were unable to work due to disability were more likely to score in the severe range on the MFS severity score. Of that group, 56.9% had a score of severe MFS, whereas only 29.7% of those in other employment categories had severe MFS, $p = 0.0002$), to have had >3 surgeries (53.5% vs. 31.3%, $p = 0.002$), and to have >7 comorbid conditions (53.5% vs. 13.7%, $p < 0.0001$). This suggests that MFS patients in this study who were unable to work due to disability represent a category of patients with more severe disease.

Bathen et al. looked at fatigue in 73 adults with MFS, and were surprised to find no correlation between fatigue and MFS-related health problems, like aortic dissection or vision impairment. Instead, chronic pain and being unable to work (vs. employed or in school) were associated with increased fatigue (24). It is possible that those with chronic pain who were unable to work may also fall into this category of disability preventing employment.

In Rand-Hendriksen's study of 84 MFS patients, a low PCS composite and low subscale scores were not associated with any of the variables assessed, which included gender, body mass index, ascending aortic surgery, use of beta-blockers, visual acuity, joint hypermobility, or number of Ghent criteria fulfilled (12). In a study of 121 MFS patients, a low PCS and low subscale scores did not correlate with disease severity (10). Similarly, in a study of 857 MFS patients that used a nonvalidated questionnaire, 26.5% of the 857 respondents thought they were severely affected by MFS, which did not correlate with MFS severity (22). In semi-structured interviews with 17 MFS patients, childhood teasing, concerns about physical appearance, and, for women, concerns about childbearing impacted QOL (25). These features were unfortunately not captured by the GenTAC registry.

In the multivariate model, registry participants with private health insurance, compared to public health insurance, and those who were working or retired, compared to unable to work due to disability, had better quality of life.

There was borderline significance to better quality of life with more frequent alcohol use ($p = 0.053$) and with marital status ($p = 0.057$). The divorced or separated group had the lowest

PCS composite score, and the lowest scores for 3 of the 4 subscales. The widowed group had the highest scores, but it is premature to draw any conclusions about the widowed group, as it included only 5 patients (1.3% of study participants). While being married would seem to be a surrogate marker for presence of social support, studies in patients with acute coronary syndromes (26), congestive heart failure (27), and colorectal cancer (28) show that being married or in a partnership does not necessarily connote social support, and the relationship between social support and QOL is not linear.

Having private health insurance has correlated with improved QOL in patient groups as diverse as pediatric patients with sickle cell disease (29), >5.7 million adults with arrhythmias (30), adult survivors of colorectal cancer (31), a predominantly Black and Latino group of stroke survivors (32), and men with prostate cancer (33). Higher household income was not significantly associated with better QOL in our study, despite being associated with better QOL in a broad range of studies in non-MFS patients, including a nationwide sample of 2,700 American children (34), Chinese survivors of stroke (35), and lung cancer survivors (36).

STUDY LIMITATIONS

Limitations of the current study include the use of registry data. There is the possibility of selection bias as only 60% of MFS patients in GenTAC who were 18 or older completed the questionnaire, although prior studies of QOL in MFS also had low response rates (9,11,22–24). Those who completed the SF-36 tended to be older than those who did not, and had more severe MFS, as 41.7% of the completers had severe MFS, compared to 29.5% of those who did not complete the SF-36. As with all GenTAC studies, there may be differences between MFS patients that enroll in GenTAC and those who do not. GenTAC enrollees are seen at 1 of 8 major medical centers, which are referral centers for patients with genetic diseases that predispose to aortic aneurysms. While patients seen at these centers may not reflect MFS patients seen at local centers, each site strives to recruit all eligible patients to GenTAC. There may be limits to generalizability, as this population was predominantly white and well educated. Also, all variables were self-reported, although this has been previously validated.

CONCLUSIONS

In a large cohort of adults with MFS, health-related QOL was 42.3, below the population norm of 50 but within 1 standard deviation of the mean. Registry participants with private health insurance, as opposed to public health insurance, and those who were working or retired, compared to unable to work due to disability, had better QOL. Notably, factors related to health and MFS severity did not correlate with better or worse QOL.

Acknowledgments

Grants/Contracts/financial support: The GenTAC Registry has been supported by US Federal Government contracts HHSN268200648199C and HHSN268201000048C from the National Heart Lung and Blood Institute and the National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health (Bethesda, MD).

Abbreviations

BP	Bodily Pain (subscale of PCS)
GenTAC	Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions
FH	General Health (subscale of PCS)
MFS	Marfan syndrome
PCS	Physical Component Summary (PCS) of the MOS 36-Item Short-Form Health Survey
PF	Physical functioning (subscale of PCS)
RP	Role limitations due to physical health (subscale of PCS)
QOL	Quality of life
SF-36	Medical Outcomes Study 36-Item Short-Form Health Survey

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CLINICAL PERSPECTIVES

COMPETENCY IN SYSTEMS-BASED PRACTICE

Health-related quality of life in patients with Marfan syndrome is below the population norm and more closely associated with socioeconomic factors, specifically employment and medical insurance, than with disease severity or general health status.

TRANSLATIONAL OUTLOOK

Factors that influence the quality of life should be considered in the design of clinical trials and systems of care to improve clinical outcomes for patients with Marfan syndrome.

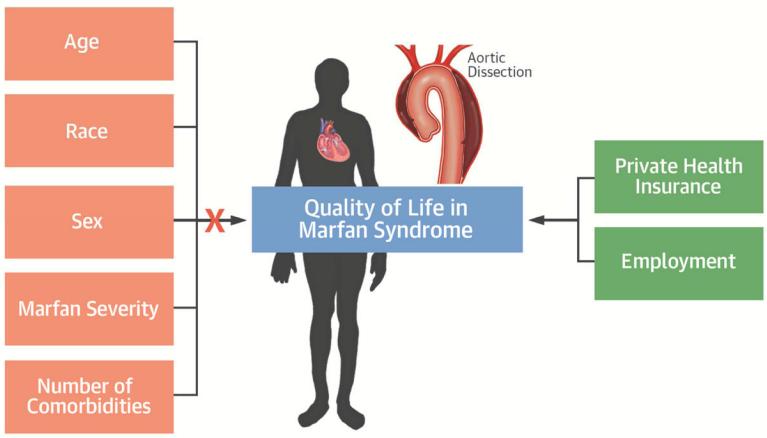

FIGURE 1.
Central Illustration. Factors that Impact Quality of Life in Marfan Syndrome

Table 1

Patient Characteristics

Age	18–39 years	192 (49.4%)
	40–69 years	183 (47.0%)
	≥70 years	14 (3.6%)
Gender	Male	199 (51.2%)
Race	White	356 (91.5%)
	Black	16 (4.1%)
	Asian	10 (2.6%)
	Other	7 (1.8%)
Education	Post-college	127 (34.1%)
	College graduate	116 (31.2%)
	Some college	75 (20.2%)
	High school graduate/GED	54 (14.5%)
Marital status	Married/unmarried partners	214 (56.9%)
	Divorced or separated	37 (9.8%)
	Widowed	5 (1.3%)
	Never married	120 (31.9%)
Household income	≤$25,000	63 (18.2%)
	$25,001 – 50,000	51 (14.7%)
	$50,0001–$75,000	72 (20.8%)
	$75,0001–$100,000	48 (13.9%)
	>$100,000	112 (32.4%)
Health insurance	Private coverage	282 (78.3%)
	Non-private	78 (21.7%)
Employment	Full-time	178 (48%)
	Part-time	23 (6.2%)
	Student	35 (9.4%)
	Self-employed	21 (5.7%)
	Retired	27 (7.3%)
	Unable to work/disabled	58 (15.6%)
	Unemployed	17 (4.6%)
	Homemaker	12 (3.2%)
Alcohol Use	Never or once monthly	161 (42.1%)
	>1 monthly but not daily	192 (50.3%)
	Almost everyday	29 (7.6%)
Hearing impairment	Yes	39 (10.3%)

Vision impairment	Yes	317 (83.4%)
Smoking	Smoker (>100 cigarettes)	132 (34.6%)
	Non-smoker	250 (65.4%)
Recreational drug use	Never	256 (65.8%)
	Past	72 (18.5%)
	Current	61 (15.7%)
Prior surgeries	0	105 (27.0%)
	1–2	154 (39.6%)
	3+	130 (33.4%)
Co-morbid conditions	0–2	113 (29%)
	3–6	199 (51.2%)
	7+	77 (19.8%)
Beta blocker use	Yes	313 (80.5%)
ARB use	Yes	142 (36.5%)
Age at diagnosis (years)	<5	52 (15.0%)
	5–17	122 (35.2%)
	18–39	127 (36.6%)
	40+	46 (13.3%)
Depression (Ever)	Yes	79 (24.8%)
MFS severity score	Mild (0–2)	27 (6.9%)
	Typical (3–8)	200 (51.4)
	Severe (9+)	162 (41.7%)

Table 2

Comparison of Marfan patients in GenTAC who completed the SF-36 versus those who did not

		Completed SF-36	No SF-36	p-value
Age at enrollment	18–39 years	192 (49.4%)	158(62.2%)	
	40–69 years	183 (47.0%)	92 (36.2%)	
	≥70 years	16 (4.2%)	4 (1.6%)	0.004
Gender	Male	199 (51.2%)	142 (55.9%)	0.2
Race	White	356 (91.5%)	217 (85.4%)	
	Black	16 (4.1%)	19 (7.5%)	
	Asian	10 (2.6%)	10 (3.9%)	
	Other	7 (1.8%)	8 (3.1%)	0.1
MFS severity score	Mild (0–2)	27 (6.9%)	33 (13%)	
	Typical (3–8)	200 (51.4)	146 (57.5%)	
	Severe (9+)	162 (41.7%)	75 (29.5%)	0.001
Age at diagnosis	mean (standard deviation)	21 (15.8)	18.1 (14.2)	0.03

Table 3

Bivariate analysis of PCS subscale scores and composite scores with GenTAC variables

		PF score	p-value	RP score	p-value	BP score	p-value	GH score	p-value	PCS composite	p-value
Age			0.0003		0.0085		0.06		0.054		0.0022
	18–39	47.7		42.9		49.5		42.3		44.4	
	≥40	43.8		39.4		47.1		40		40.4	
Gender			NS		NS		NS		NS		NS
	Male	46.2		40.9		48.6		41.5		42.7	
	Female	45		41.2		47.8		40.9		41.8	
Race			NS		NS		NS		NS		NS
	White	45.6		40.8		48.4		41.4		42.3	
	Non-White	45.6		43		45.9		39		41.6	
Education			0.0297		0.004		<0.0001		0.004		0.001
	<College graduate	44.2		38.5		44.2		39.2		38.9	
	College graduate	46.7		42.6		50.5		42.7		44.3	
Marital status			0.019		0.018		0.001		0.022		0.001
	Married or partnership	45		40.8		48.5		41.6		42	
	Divorced or separated	41.6		35		40.1		36.3		34.6	
	Never married	47.5		42.7		49.3		41.8		44.3	
	Widowed	48.6		43.5		54.6		48.9		48.3	
Household income			<0.0001		0.0004		<0.0001		0.0084		<0.0001
	≤ 25 K	41.6		35.8		42.7		37.5		35.7	
	25–100 K	45		40.7		48		41.8		42	
	>100K	49.1		43.8		52.6		42.9		44.2	
Health insurance			<0.0001		<0.0001		<0.0001		<0.0001		<0.0001
	Private	47.5		42.9		50.3		42.6		44.8	
	Non-private	39.5		34.4		41.3		36.1		33.7	
Employment			<0.0001		<0.0001		<0.0001		<0.0001		<0.0001
	Working/Student/Home maker	48.9		43.8		51.4		43.6		46.1	
	Unable to work due to disability	33.4		29.5		35.7		32.1		26.4	

		PF score	p-value	RP score	p-value	BP score	p-value	GH score	p-value	PCS composite	p-value
	Retired	40.4		40.2		49.7		40.7		40.7	
	Unemployed	48.5		39.4		43.1		38.5		40.4	
Alcohol use			0.0001		0.0004		0.0003		0.0058		<0.0001
	Never or once/month	43		37.8		45.1		39		38.5	
	>1/month but not daily	47.7		43.2		50.4		42.8		45.1	
	Almost daily	44.6		42.4		49		43		42.9	
Vision impairment			0.65		0.69		0.19		0.36		0.68
	No	46.3		40.4		46.4		42.4		41.7	
	Yes	45.6		41.1		48.7		41		42.5	
Hearing impairment			NS		0.015		0.0001		0.05		0.0052
	No	46		41.6		49		41.8		43	
	Yes	43.2		36.2		41.8		38.1		36.8	
Smoking			0.044		0.06		0.09		0.65		0.046
	Smoker (>100 cigarettes)	44.1		39.3		46.6		40.9		40.4	
	Non-smoker	46.4		41.8		48.9		41.4		43.2	
Recreational drug use			0.18		0.58		0.26		0.066		0.18
	Never	45.2		41.1		47.9		41.7		42.1	
	Past	47.7		41.9		50.1		42.2		44.5	
	Current	45.1		39.6		46.8		38.1		40.3	
Number of prior MFS-related surgeries			0.0012		0.0084		0.04		0.06		0.002
	0	47.4		44.1		49.3		42.4		44.8	
	1–2	46.7		40.7		49.3		42.1		43.1	
	3 or more	42.9		38.9		45.9		39.3		39.1	
Number of comorbid conditions			<0.0001		<0.0001		<0.0001		<0.0001		<0.0001
	0–2	49.1		44.4		51.5		44.2		46.7	
	3–6	46.1		41.5		48.5		41.9		43	
	7 or more	39.4		34.9		42.5		35.1		33.9	
Beta blocker use			0.68		0.95		0.43		0.72		0.99
	No	46.1		40.9		47.1		40.8		42.2	

		PF score	p-value	RP score	p-value	BP score	p-value	GH score	p-value	PCS composite	p-value
	Yes	45.5		41		48.4		41.3		42.3	
Angiotensin receptor blocker use			0.13		0.13		0.62		0.69		0.37
	No	46.3		41.8		47.9		41.4		42.7	
	Yes	44.6		39.7		48.6		40.9		41.5	
Age at MFS diagnosis			NS		0.0256		NS		NS		0.10
	<5	45.4		40.8		47.2		38.8		40.9	
	5–17	47.4		43.7		49.6		42.1		44.6	
	18–39	45		38.9		46.9		41.1		40.8	
	40+	45.8		39.6		49.5		42.8		42.6	
MFS Severity score			<0.0001		<0.0001		0.0085		0.0003		<0.0001
	Mild (0–2)	49.7		48.9		50.5		46.0		48.7	
	Typical (3–8)	47.3		43.2		49.7		42.6		44.6	
	Severe (9+)	42.9		37.1		45.9		38.7		38.3	
Depression			<0.0001		0.0211		<0.0001		<0.0001		<0.0001
	No	47.1		41.9		49.7		42.1		44	
	Yes	42.3		38		43.1		35.7		36.8	

PF = Physical functioning, RF = Role physical BP = Bodily pain, GH = General health, NS = not significant

Table 4

Association of Unable to work due to disability and other variables

		Unable to work due to disability		
		No	**Yes**	**p-value**
MFS Severity score	Mild (0–2)	27 (8.6%)	1 (1.7%)	
	Typical (3–8)	193 (61.7%)	24 (41.4%)	
	Severe (9+)	93 (29.7%)	33 (56.9%)	0.0002
Number of MFS-related surgeries	0	89 (28.4%)	7 (12.1%)	
	1–2	126 (40.3%)	20 (34.5%)	
	3 or more	98 (31.3%)	31 (53.5%)	0.002
Number of comorbid conditions	0–2	102 (35.6%)	9 (15.5%)	
	3–6	168 (53.7%)	18 (31.0%)	
	7 or more	43 (13.7%)	31 (53.5%)	<0.0001

Table 5

Adjusted model of PCS composite and subscale scores

	PF	*p-value*	*RP (n = 249)*	*p-value*	*BP*	*p-value*	*GH*	*p-value*	*PCS Composite*	*p-value*
Age		0.38		0.7		0.44		0.47		0.65
18 – 39	45.8		39.0		46.3		38.0		40.1	
≥ 40	44.7		38.4		45.2		39.0		39.5	
Education		0.67		0.89		0.043		0.67		0.37
Not a college graduate	45.5		38.6		44.3		38.2		39.3	
College graduate	45.0		38.8		47.4		38.8		40.4	
Marital Status		0.13		0.14		0.08		0.43		0.057
Married or living with a partner	43.2		38.2		44.1		37.0		37.9	
Never married	46.2		40.9		46.8		37.1		40.9	
Widowed	47.1		40.9		50.7		44.6		44.4	
Divorced or separated	44.3		34.8		41.6		35.3		36.0	
Household income, annual		0.022		0.59		0.07		0.97		0.10
≤ $25K	44.5		37.8		44.8		38.1		38.6	
$>25–100K	43.8		38.2		44.4		38.7		38.8	
>$100K	47.4		40.1		48.2		38.6		42.1	
Health insurance		0.033		0.042		0.07		0.18		0.013
Private coverage	47.0		41.1		47.7		39.9		42.3	
Non-Private	43.5		36.3		43.9		37.1		37.4	
Employment		<0.0001		0.0007		0.0001		0.012		<0.0001
Working/Student/H omemaker	48.1		40.5		47.7		39.7		42.4	
Unable to work due to disability	37.0		31.2		38.5		33.6		30.4	
Retired	45.3		43.8		51.3		43.0		44.3	
Unemployed	50.5		39.3		45.7		37.6		42.1	
Alcohol Use in last 12 months		0.045		0.24		0.19		0.41		0.053
0 or <1 per month	43.3		37.0		43.9		38.6		37.8	
>1 month to 4 per week	45.8		39.6		46.1		39.9		40.9	
Almost every day or everyday	46.6		39.4		47.4		36.9		40.8	

	PF	*p-value*	*RP (n = 249)*	*p-value*	*BP*	*p-value*	*GH*	*p-value*	*PCS Composite*	*p-value*
Hearing impairment		0.99		0.10		0.09		0.16		0.12
Yes	45.2		42.5		43.9		37.0		38.2	
No	45.2		45.3		47.7		40.0		41.4	
Number of prior MFS related surgeries		0.32		0.56		0.55		0.50		0.69
None	44.2		*38.1*		*45.5*		*38.7*		*39.1*	
1–2 surgeries	46.3		38.0		46.8		39.3		40.5	
3+ surgeries	45.2		40.0		45.1		37.4		39.8	
Number of comorbid conditions		0.18		0.37		0.54		0.25		0.12
0–2	47.0		40.6		47.0		39.9		42.1	
3–6	45.0		38.3		45.3		39.3		39.7	
7+	43.7		37.2		45.2		36.3		37.7	
Depression		0.29		0.65		0.14		0.07		0.21
Yes	44.5		39.1		44.5		36.9		38.8	
No	46.0		38.3		47.1		40.0		40.8	
MFS severity score		0.39		0.035		0.86		0.52		0.13
Mild (0–2)	45.7		41.7		45.3		40.1		41.4	
Typical (3–8)	45.8		39.2		46.4		38.2		40.4	
Severe (9+)	44.2		35.2		45.7		37.1		38.7	

NS = not significant

Table 6

Comparison of SF-36 PCS scores in MFS patients across different studies

Study first author and year	Number of patients	PF	RP	BP	GH	PCS composite
Verbraecken J, 2001(5)	15 MFS	71	60	71	57	*Not reported*
	24 healthy controls	97	96	92	84	*Not reported*
Foran JR, 2005(8)	22 MFS	*Not reported*				34.7
	Normal controls	*Not reported*				50 (population norm)
Fusar-Poli P, 2008(9)	36 MFS	77.9	70.8	67.5	51.6	50.4
	No control group					50 (population norm)
Rand-Hendriksen S, 2010(12)	84 MFS	70	43	55	47	36
	Control, n = 420 (dataset derived)	90	83	77	79	51
Schoormans, 2012(10)	121 MFS	79.2	68.8	70.6	57.0	45.5
	Control, n = 1742 (Dutch population)(37)	83	76	75	71	50 (population norm)
Current study	389 MFS	72.6	46.2	65.9	51.3	42.3