Association of Number of Comorbidities and Health-Related Quality of Life in Patients with Rheumatoid Arthritis

by

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Rheumatoid arthritis (RA) is a progressive inflammatory disease that is associated with multiple comorbidities. This study investigated the association between total number of comorbidities and patients' health-related quality of life represented by physical component summary score (PCS) and mental component summary score (MCS), while controlling for rheumatoid arthritis disease activity (RADAI). This study was a cross-sectional, descriptive correlational study and secondary analysis of existing data. A partial correlation was done for the associations between Total Comorbidities and PCS and MCS, while controlling for disease activity. The results showed that Total Comorbidities and PCS were significantly but weakly negatively correlated ($r=-0.228$, $p<0.001$), while Total Comorbidities and MCS were not significantly correlated ($r=-0.041$, $p=0.315$). When RADAI was removed as a control variable, the correlations between Total Comorbidities and PCS improved slightly ($r=-0.314$, $p<0.001$) and Total Comorbidities and MCS became significantly but very weakly negatively correlated ($r=-0.098$, $p=0.017$). RADAI was then investigated as both a moderating and mediating variable in the relationship between Total Comorbidities and PCS and MCS. RADAI was not found to be a moderator; however, mediation analysis showed that there was an indirect mediating effect of RADAI on both PCS and MCS. Increasing disease activity decreased both PCS and MCS, but PCS was more affected. The mediation analysis also showed that there was a significant direct effect of Total Comorbidities on PCS ($p<0.001$), but it was reduced compared to the total effect, which demonstrated the mediating effects of RADAI. In contrast, while the total effect of Total

Comorbidities on MCS was significant (p=0.0167), when the mediating effect of RADAI was removed, the direct effect of Total Comorbidities on MCS was not significant (p=0.3153). This result implies that the apparent association between Total Comorbidities and MCS was largely due to the mediating effect of RADAI. These results suggest that PCS is more directly affected by increases in comorbidities than MCS and emphasizes the importance of treating comorbidities as well as the RA disease in order to improve physical health-related quality of life for patients.

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Preface

This research is a secondary analysis of data from a parent study on Adherence in Rheumatoid Arthritis: Intervention Strategies (NIH Grant R01 NR04554, 1998-2006), for which Dean Jacqueline Dunbar-Jacob was the principal investigator. I have had a personal interest in rheumatoid arthritis and other autoimmune disorders for a long time, and I am very grateful to Dean Dunbar-Jacob for granting me permission to conduct this research using her study database. I also appreciate that she agreed to be on my BSN Thesis Committee and share her expertise in this area.

Thank you also to my external thesis committee member, Dr. Karen Smarr from Harry S. Truman Memorial VA Hospital and University of Missouri, Columbia. Dr. Smarr has studied and published extensively on the health status and quality of life of patients with rheumatoid arthritis, and her insights are most appreciated. The statistical analysis conducted for this project would not have been possible without the guidance and support of Dr. Jeffrey Rohay. I have learned so much from my discussions with him and am grateful for his many suggestions. Lastly, special thanks to my Thesis Advisor Dr. Elizabeth A. Schlenk for her help, guidance, and mentorship over the past three years. We began this project when she was on sabbatical, worked together in Pittsburgh for the middle two years, and completed the last six months remotely due to the COVID-19 pandemic. The potential challenges of distance and pandemic public health emergency could have derailed this project, but Dr. Schlenk's kindness and dedication to helping me reach my goal never wavered. I appreciate her unfailing professionalism, patience, and perseverance, and thank her for generously sharing her knowledge, experience, and guidance with me.

1.0 Introduction

Rheumatoid arthritis (RA) is a chronic progressive systemic inflammatory disease with a prevalence of 1-2% of the population, and a higher prevalence in women and older adults. There is also an increased prevalence among first relatives suggesting some patients may have a genetic predisposition to this autoimmune disease. RA is marked by swelling and progressive destruction of joints, particularly in fingers, wrists, toes, ankles, feet, and knees. The initial pathogenesis of the disorder involves hyperproliferation of synovial cells in joints followed by an immune response from helper T-cells and other immune cells, which causes edema and neovascularization. The cycle of synovium proliferation and immune response eventually causes pannus formation, and consequentially joint destruction and ankylosis (Grossman, 2014).

In addition to joint destruction, one of the most notable complications associated with RA is the prevalence of multiple comorbidities in patients. On average, patients diagnosed with RA have two or more extra-articular comorbidities early in the disease onset and gain additional comorbidities within five years of diagnosis (Innala et al., 2016). These comorbidities contribute to greater disability, costs, and mortality in patients with RA (Michaud & Wolfe, 2007).

1.1 Background

Some of the common comorbidities of RA, including disturbed sleep, fatigue, and depression, may be a reflection of living with a chronic systemic inflammatory disease (Luyster, Chasens, Wasko, & Dunbar-Jacob, 2011). However, research shows that RA patients also have higher than expected prevalence of infections, osteoporosis, chronic obstructive pulmonary disease, hypertension, myocardial infarction, stroke, and specific cancers (Dougados, 2016). An international survey of nearly 4,000 patients found these comorbidities were higher than expected in RA patients, although the prevalence varied considerably between countries. The most common comorbidities in the 400 US patients with RA in Dougados' study were hypertension (39%), hyperlipidemia (38%), depression (33%), hyperglycemia (21%), asthma (21%), gastrointestinal ulcer (11%), chronic obstructive pulmonary disease (8%), coronary heart disease (5%), and stroke (3%) (Dougados et al., 2013). For comparison, the Centers for Disease Control and Prevention reported that the prevalence in the general US population for this time period was 33% with hypertension, 29% with hyperlipidemia, 8% with depression, 14% with hyperglycemia, 8% with asthma, 6% with gastrointestinal ulcer, 4% with chronic obstructive pulmonary disease, 6% with coronary heart disease, and 3% with stroke (Brody, Pratt, & Hughes, 2018; National Center for Health Statistics, 2017; Syamlal, Doney, & Mazurek, 2019; Villarroel, Blackwell, & Jen, 2019a; Villarroel, Blackwell, & Jen, 2019b; Villarroel, Blackwell, & Jen, 2019c). When comparing the prevalence of comorbidities in RA patients in Dougados' study to those in the general US population, there is a higher than expected prevalence ($p \leq 0.01$ in a one-sample chi square test) in Dougados' study for all comorbidities listed above except coronary heart disease ($p=0.40$) and stroke ($p=1.00$). A statistical analysis conducted in a Korean study found that, when adjusted for socioeconomic and lifestyle factors, Korean patients with

RA had a significantly increased prevalence ($p<0.05$) of myocardial infarction or angina, pulmonary tuberculosis, asthma, thyroid disease, depression, and hepatitis B compared with those who did not have RA (Jeong et al., 2017).

While studies have established the higher prevalence of cardiovascular, lung, infection, and cancer comorbidities in RA patients than the general population, the contribution of the RA disease itself to the development of these comorbidities is confounded by patients' increased age, prior health, lifestyle behaviors, and the medications typically used to treat RA. When comparing RA to the general population, there is a higher prevalence of smoking and high lipid levels prior to the diagnosis, which are both risk factors for future cardiac complications. In addition, some of the medications used to treat RA, including glucocorticoids, can increase cardiac risk by stiffening arteries (Crowson et al., 2013). Glucocorticoids have also been associated with increased risk of hyperglycemia, diabetes, osteoporosis, and infection. Other RA drugs like disease-modifying antirheumatic drugs (DMARDs), tumor necrosis factor inhibitors (antiTNF), and nonsteroidal anti-inflammatory drugs (NSAIDs) also increase susceptibility to other comorbidities (Roubille et al., 2015). DMARDs and NSAIDs have been associated with peptic ulcers and other gastrointestinal issues, and DMARDs and antiTNF drugs are associated with infections and cancers, such as lymphomas (Michaud & Wolfe, 2007; Young & Kaduri, 2007).

Since a goal of RA treatment is to slow the disease progression and improve patients' lives, a number of research studies have attempted to quantify and relate RA patients' disability to their health-related quality of life (HRQoL) using various instruments. The degree of disability in RA patients has been measured by many different methods including non-disease specific questionnaires such as the Medical Outcomes Study Short Form-36 (SF-36), the Nottingham Health Profile (NHP), and Sickness Impact Profile (SIP), and more disease specific

questionnaires such as the Stanford Health Assessment Questionnaire (HAQ) and its modified versions like HAQ-II, modified-HAQ (MHAQ), and multidimensional-HAQ (MDHAQ). Visual analog scales (VAS) have also been used to assess physical function, pain, and fatigue. Lastly, performance measures like handgrip strength, walking time, and the button test have been used to measure disability. Some of the same instruments that capture disability can also capture HRQoL in RA patients, including SF-36, NHP, SIP, and VAS-fatigue. Non-disease specific HRQoL has also been measured using health utility scales, including the EuroQoL-5 Dimension (EQ-5D), Finnish 15-Dimension (15D), and Health Utilities Index Mark 2 and 3 (HUI-2 and HUI-3). Arthritis specific HRQoL scales have also been used in some studies, with the most popular being the Arthritis Impact Measurement Scale-2 (AIMS-2) and the Rheumatoid Arthritis Quality of Life (RAQoL) questionnaire (Lillegraven & Kvien, 2007).

Although a number of studies have examined the effect of different drug therapies on the level of disability and HRQoL in RA patients, relatively few studies have examined the relationship of comorbidities and HRQoL in patient with RA (van Onna & Boonen, 2016), which is the gap in knowledge the proposed study will attempt to address. Matcham et al. (2014) reported results of a meta-analysis of 31 published studies using SF-36 and found that RA negatively affected both physical component and mental component scores of HRQoL more than other physical illnesses. Rupp, Boshuizen, Jacobi, Dinant, and van den Bos (2004) found that that fatigue, pain, and depression in RA patients were interrelated and negatively affected HRQoL as assessed by RAND-36, which is similar to SF-36. Luyster et al. (2011) also examined the interrelationships between sleep, fatigue, depression, disability, and pain, and found that poor sleep quality was associated with greater functional disability among patients with RA as determined by SF-36, with this relationship being explained by pain severity and fatigue. A 2010

study from Radner, Smolen, and Aletaha identified a significant inverse relationship between number of RA comorbidities and physical function ($p<0.001$). The study demonstrated that an increased number of comorbidities in RA patients decreased HRQoL and ability to conduct physical activities of daily living, such as dressing, hygiene, and eating. However, Radner et al. (2010) did not examine the effect of number of RA comorbidities on the mental domain of HRQoL. Gerhold et al (2015) stratified patients in the RABBIT database to identify HRQoL responders (the 22-37% of patients who had at least an 18-point increase in PCS and 22-point increase in MCS after 12 months of therapy). The percent of patients not meeting their PCS responder criteria increased as comorbidities increased; however, the effect of the number of comorbidities on PCS and MCS in the overall patient population was not characterized. Garip, Eser, and Bodur (2016) found that the presence of comorbidities in RA was associated with a more severe disease state and suggested that the treatment and acknowledgement of these other diseases should play an important role in the care of patients with RA. Although the literature suggests that comorbidities may worsen HRQoL for patients with RA, the association of number of comorbidities and the physical and mental domains of HRQoL in patients with RA has not been fully characterized.

1.2 Purpose

The purpose of this study was to explore the association of number of comorbidities and HRQoL in patients with rheumatoid arthritis controlling for disease activity.

1.3 Research Questions

1. Is the number of comorbidities associated with the physical component summary score of HRQoL controlling for disease activity?
2. Is the number of comorbidities associated with the mental component summary score of HRQoL controlling for disease activity?

2.0 Methods

2.1 Design

This study was a secondary analysis of existing data from a randomized controlled trial of a behavioral intervention to improve medication adherence in patients with RA (NIH, R01 NR04554, 1998-2006). The Principal Investigator of the parent study, Jacqueline Dunbar-Jacob, PhD, RN, FAAN, granted permission for this secondary analysis, and the University of Pittsburgh Human Research Protection Office (HRPO) approved the study (Appendix B). The design was a cross-sectional, descriptive correlational study examining the association of number of comorbidities and HRQoL in RA patients. Disease activity was included as a covariate in the analysis because disease activity varies over time within individuals, which can influence reports of physical and mental HRQoL.

2.2 Sample

The parent study used convenience sampling and screened 645 adults with RA. Inclusion criteria for the current study included male or female adults with RA who were enrolled in the parent study and had complete data on disease activity, comorbidity, and physical and mental HRQoL variables at baseline. Of the 645 adults in the primary study, 590 adults had complete data for the variables of interest and were used as the participants for this secondary analysis. Only baseline data (labelled ADM NUM=0 in the database) were used in this analysis.

2.3 Measures

The total number of comorbidities were determined based on participant's responses in the self-administered Comorbidity Questionnaire developed by the Center for Research in Chronic Disorders at the University of Pittsburgh (Appendix A.1). A comorbidity was counted if a patient self-reported being diagnosed with the condition. Comorbidity count has been shown to correlate well (Spearman $r=.90$, $p<0.001$) with a rheumatoid disease comorbidity index across different races and ethnicities (Dowell et al., 2017).

HRQoL was assessed by the physical component summary score (PCS) and mental component summary score (MCS) from the self-administered SF-36 (Appendix A.2). The PCS and MCS scores are normed to 50 (normal range 40-60), with higher scores indicating better HRQoL. The SF-36 is a non-disease specific quality of life instrument that, in diverse patient populations, has fair test-retest reliability (median $r=.64$ for patients reporting no change between baseline and 2-week administration interval), good internal consistency (median $\alpha=.80$), and evidence of criterion-related and construct validity (McHorney, Ware, Lu, & Sherbourne, 1994; McHorney, Ware, & Raczek, 1993; McHorney, Ware, Rogers, Raczek, & Lu, 1992). The SF-36 has been shown to be a valid and reliable indicator of HRQoL in the RA patient population, with validity established by its ability to discriminate between low, moderate, and high Disease Activity Score 28-joint count (DAS28) and with reliability established by Cronbach alpha>0.85 for the separate scales (Linde, Sorensen, Ostergaard, Horslev-Petersen, & Hetland, 2008). The SF-36 contains eight scales: physical functioning, role functioning-physical, role functioning-emotional, social functioning, bodily pain, mental health, vitality, and general health. PCS is composed of all eight scores with greater weight on physical functioning, role functioning-physical, and bodily pain scores. MCS is composed of all eight scores, weighted more on mental

health, role functioning-emotional, and social functioning scores (Ware, Kosinski, & Keller, 1994).

Disease activity was assessed by a modified version of the self-administered Rapid Assessment of Disease Activity in Rheumatology (RADAR) questionnaire (Appendix A.3). The six-question RADAR assessment includes patient characterization of disease activity over the past six months, as well as current status of the following: joint tenderness and swelling, arthritis pain, morning stiffness, functional activity level, and pain in 10 specific joints on the left and right sides of the body. Patient RADAR scores on each question have been shown to correlate to clinician assessment (ICC=0.57 to 0.87 for specific scale items) and to correlate to change in joint status over six months (ICC=0.83) (Mason et al., 1992). The RADAR questionnaire has been criticized for the lack of a single summed score, requiring comparison of separate scores for each of the six questions (Fransen, Stucki, & van Riel, 2003). Previous studies have circumvented this issue by using partial sum scores from one or five of the RADAR questions. Nicassio used just the joint scores from RADAR Question 6 (4-point Likert scale on 10 joints on the left and right sides of the body, with a sum score of 0-60) as a marker of RA disease activity in a fatigue study (Nicassio et al., 2012). Stucki and colleagues summed five of the six RADAR questions (excluding the functional activity question) to form the Rheumatoid Arthritis Disease Activity Index (RADAI). Since the summed RADAI score has good internal consistency (α=0.91 and 0.87 in studies with 55 and 484 patients, respectively) and good correlations with clinician assessment (Fransen, Langenegger, Michel, & Stucki, 2000; Stucki, Liang, Stucki, Bruhlmann, & Michel, 1995), the RADAI score was calculated and used in this study to assess disease activity. RADAI scores are standardized from 0-10, with higher scores indicating worse disease activity (Fransen et al., 2000).

2.4 Procedures

In the parent study, participants received baseline questionnaires to complete and return by mail, which included the Comorbidity Questionnaire, SF-36, RADAR Questionnaire, and a sociodemographic questionnaire. For the current study, an expedited protocol was reviewed and approved by the University of Pittsburgh HRPO. The study investigator received only the required sociodemographic, comorbidity, disease activity, and HRQoL data listed by patient ID number, and consulted with a statistician to conduct the data analysis to answer the research questions.

2.5 Data Analysis

Data were analyzed using IBM® SPSS® Statistics version 26 (IBM Corp., Armonk, NY). The level of significance was set at 0.05, and 95% was used to estimate confidence intervals. First, the data were carefully screened for any irregularities (e.g., outliers, skewness, and kurtosis). For the variables of interest (PCS, MCS, Total Comorbidities, and RADAI), no outliers were identified, and skewness and kurtosis were within acceptable ranges (skewness ranged from -0.73 to 1.25, kurtosis ranged from -0.77 to 1.71). Second, categorical sociodemographic variables (e.g., race, marital status, household income, and education) were meaningfully categorized as appropriate. Descriptive statistics were summarized for the sociodemographic characteristics of the sample, the Total Comorbidities, the RADAI score, the PCS, and the MCS based on each variable's level of measurement and observed data distribution. Third, participants with complete data in this sample were compared to those with missing data in the parent sample

on all variables using parametric two-sample t-tests for continuous level (ratio or interval scaled) variables and Chi-square tests of independence for nominal-scaled categorical variables. Internal consistency (Cronbach alpha) was assessed on the PCS and MCS of the SF-36.

To answer the two research questions, partial correlations were performed on the association between Total Comorbidities and the two measures of HRQoL (PCS and MCS), while controlling for disease activity (RADAI). Additional analyses were conducted by repeating the correlation analysis without controlling for disease activity, and by performing partial correlations on the association of RADAI with the two measures of HRQoL (PCS and MCS) with and without controlling for Total Comorbidities. To test whether RADAI moderated the relationship between Total Comorbidities and HRQoL, regression models were run with Total Comorbidities, RADAI, and the interaction term as predictors for the two measures of HRQoL. To test whether RADAI mediated the relationship between Total Comorbidities and the two measures of HRQoL, the PROCESS macro for SPSS (Version 3.5) was downloaded and Model 4 (a simple mediation model) was run within SPSS (Hayes, 2020). PROCESS is a modeling tool that uses bootstrapping to estimate the direct and indirect effects in mediation models (Appendix C). In this model, the total effect, "c", is the extent to which Total Comorbidities influences HRQoL (PCS or MCS) in the absence of a mediator. The indirect effect is the extent to which the dependent variable (HRQoL) changes when the independent variable (Total Comorbidities) is constant and the mediating variable (RADAI) varies. The indirect effect is represented by variable "a*b", where "a" is the effect of Total Comorbidities on Disease Activity (RADAI) and "b" is the effect of the mediator Disease Activity (RADAI) on HRQoL. The direct effect, " c' ", measures the extent to which the dependent variable (HRQoL) changes when the mediator (RADAI) is constant and the independent variable (Total Comorbidities) changes. The total

effect “c” is the sum of the direct and indirect effects. The significance of the total, direct, and indirect effects were determined by computing the 95% confidence intervals of 5,000 bootstrapped samples. The effects were considered significant if the 95% confidence interval did not include zero (Field, 2013; Hayes & Rockwood, 2016).

3.0 Results

3.1 Demographic Characteristics of Sample

A total of 645 subjects were screened in the parent study. Subject demographics are shown in Table 1. The majority of subjects were women (80%), white (92%), and non-Latino (96%). Subjects had a mean age of 59 years (SD=12), with a range of 19 to 85 years. Subjects were well educated with 19% completing a 2- or 4-year college degree, and 9% completing a graduate or professional degree. While most subjects were currently married (65%), a total of 32% of subjects were never married, divorced, separated, or widowed. Household incomes were less than or equal to $30,000 for 43% of subjects, $30,001 to $50,000 for 22% of subjects, and over $50,000 for 27% of subjects.

Table 1 Parent Study Demographics (N=645)

Demographic Characteristic	n (%)
Sex	
Male	124 (19.2)
Female	517 (80.2)
Missing	4 (0.6)
Age (years)	Mean = 59.3, Range = 19-85, SD = 11.9
Race	
White	594 (92.1)
Black or African American	24 (3.7)
Asian	3 (0.5)
Other (Including multi-racial and unknown)	12 (3.1)
Missing	4 (0.6)
Ethnicity	
Non-Latino	620 (96.2)
Latino	6 (0.9)
Missing	19 (2.9)
Marital Status	
Never married	61 (9.4)
Currently married	421 (65.3)
Living with partner/significant other	13 (2.0)
Widowed	85 (13.2)
Separated	9 (1.4)
Divorced	52 (8.1)
Missing	4 (0.6)
Highest Level of Education Completed	
Grade school	35 (5.4)
High school or GED	300 (46.5)
Vocational/Technical School	72 (11.2)
2-year college	33 (5.1)
4-year college	89 (13.8)
Graduation/Professional School	58 (9.0)
Other	54 (8.4)
Missing	4 (0.6)
Household Income	
≤ $10,000	37 (5.7)
$10,001 to $13,000	37 (5.7)
$13,001 to $20,000	87 (13.5)
$20,001 to $30,000	119 (18.5)
$30,001 to $50,000	140 (21.7)
> $50,000	172 (26.7)
Missing	53 (8.2)

3.2 Treatment of Missing Data

Although 645 subjects were initially screened in the parent study, 55 subjects (8.5%) had missing data in the variables of interest (Total Comorbidities, PCS, MCS, and/or RADAI). As shown in Table 2, parametric two sample t-tests showed no significant differences in the variances and means for those with complete and those with missing data for the Total Comorbidities, PCS, and RADAI variables. For MCS, there was no significant difference in the variances for complete and missing data, but there was a significant difference in the means, with a p-value of 0.046 and a 95% confidence interval that did not include zero (0.060-5.884). The results of the Chi-Square analysis for the nominal-scaled variables are shown in Table 3. There were no significant differences for missing versus complete data for sex, race, marital status, education level, and household income. The mean age for those with complete data was 59.3 years versus a mean age of 62.2 years for those with missing data, which was not significantly different (p=0.098). Since only 8.5% of the total data were missing for the variables of interest (55 of 645 subjects) and the mean of MCS was likely minimally affected with a p-value close to 0.05, it was decided to proceed using only complete data for the analysis.

Table 2 Parametric t-tests of Complete versus Missing Data

Variable	t-test for Equality of Means					Levene's Test for Equal Variances	
	Mean Difference	95% CI[4] (Lower)	95% CI[4] (Upper)	t	p-Value	F	p-Value
Total Comorbidities	0.415	-0.157	0.988	1.425	0.155	2.492	0.115
PCS[1]	0.518	-2.678	3.713	0.318	0.750	0.127	0.722
MCS[2]	2.972	0.060	5.884	2.000	0.046	0.665	0.415
RADAI[3]	-0.172	-0.954	0.611	-0.431	0.666	<0.001	0.984

[1] PCS (Physical Component Summary Score) from SF-36 HRQoL questionnaire
[2] MCS (Mental Component Summary Score) from SF-36 HRQoL questionnaire
[3] RADAI (Rheumatoid Arthritis Disease Activity Index)
[4] 95% Confidence Interval on Mean Difference

Table 3 Chi-Square Analysis of Complete versus Missing Data

Variable	Complete Data	Missing Data	Chi-Square (p-Value)
Sex			**0.12 (p=0.73)**
Male	113 (91%)	11 (9%)	
Female	476 (92%)	41 (8%)	
Race			**1.00 (p=0.32)**
White	562 (88%)	48 (7%)	
Non-white	27 (4%)	4 (1%)	
Marital Status			**0.43 (p=0.51)**
Married	389 (61%)	32 (5%)	
Non-married	200 (31%)	20 (3%)	
Education level			**2.92 (p=0.88)**
High school completed	514 (80%)	41 (6%)	
High school not completed	75 (12%)	11 (2%)	
Household Income			**2.15 (p=0.14)**
Income above $30,001	293 (46%)	19 (3%)	
Income ≤ $30,000	254 (40%)	26 (4%)	

3.3 Data Distribution and Reliability

The most common comorbidities were hypertension (n=218, 34%), anemia (n=131, 21%), intermittent claudication (n=127, 20%), asthma (n=73, 11%), and arrhythmias (n=68, 11%). Other comorbidities included heart attack (n=40, 6%), heart failure (n=42, 7%), coronary artery disease (n=43, 7%), valve disorders (n=38, 6%), other heart disorders (n=36, 6%), other blood disorders (n=19, 3%), emphysema (n=24, 4%), pneumonia (n=43, 7%), pulmonary fibrosis (n=12, 2%), and tuberculosis (n=2, <1%). The prevalence of most of these comorbidities were not significantly different compared to the general US population rates; however, asthma ($p=0.027$) and anemia ($p<0.001$) were significantly higher than the national rates (Seitz, Chen, & Lukacs, 2018; Villarroel et al., 2019a; Villarroel et al., 2019b).

Table 4 shows descriptive summary statistics for Total Comorbidities, PCS, MCS, and RADAI. The MCS mean score of 52.1 +/- 9.8 was within the normal range of 40-60, while the PCS mean score of 33.3 +/- 10.9 indicated a worse physical than mental HRQoL. The mean of Total Comorbidities was 1.4 and the mean of RADAI was 4.2, which imply the sample had relatively few comorbidities with low to moderate disease activity. Internal consistency of the PCS and MCS of the SF-36 was analyzed using Cronbach alpha. The Cronbach alpha for PCS, which heavily weights Physical Functioning, Role-Physical, Bodily Pain, and General Health, was 0.753. MCS, which heavily weights Vitality, Social Functioning, Role-Emotional, and Mental Health, had a Cronbach alpha of 0.714. These results indicated that PCS and MCS values had acceptable internal consistency reliability in measuring physical and mental HRQoL, respectively.

Table 4 Descriptive Statistics for Variables of Interest (N=590)

Variable	Mean	Standard Deviation	Range
Total Comorbidities	1.4	1.4	0-7
PCS[1]	33.3	10.9	9.2-59.8
MCS[2]	52.1	9.8	19.6-68.6
RADAI[3]	4.2	2.2	0-9.9

[1] PCS (Physical Component Summary Score) from SF-36 HRQoL questionnaire
[2] MCS (Mental Component Summary Score) from SF-36 HRQoL questionnaire
[3] RADAI (Rheumatoid Arthritis Disease Activity Index)

3.4 Results for Research Questions

Table 5 addresses the research questions of whether the number of comorbidities is associated with physical and mental HRQoL (PCS and MCS, respectively) when controlling for disease activity (RADAI). When RADAI was the control variable, Total Comorbidities and PCS

were significantly but weakly negatively correlated (r=-0.228, p<0.001). When controlling for RADAI, Total Comorbidities and MCS were not significantly correlated (r=-0.041, p=0.315). When the correlation was rerun without RADAI as a controlling variable, the results showed slight improvements in the correlations between Total Comorbidities and PCS (r=-0.314, p<0.001) and MCS became significantly but very weakly negatively correlated (r=-0.098, p=0.017). Since the model correlation improved slightly and MCS became significant when RADAI was removed from the model, the relationship between RADAI and Total Comorbidities was further explored.

Table 5 Correlation[1] Analysis for Research Questions (N=590)

Controlling Variable	Variable of Interest	PCS[2] Correlation	PCS[2] Two Tailed Significance	MCS[3] Correlation	MCS[3] Two Tailed Significance
RADAI[4]	Total Comorbidities	-0.228	<0.001	-0.041	0.315
None	Total Comorbidities	-0.314	<0.001	-0.098	0.017

[1] Pearsons zero-order correlation
[2] PCS (Physical Component Summary Score) from SF-36 HRQoL questionnaire
[3] MCS (Mental Component Summary Score) from SF-36 HRQoL questionnaire
[4] RADAI (Rheumatoid Arthritis Disease Activity Index)

First, a correlation was performed with no control variable and with PCS, MCS, and RADAI as dependent variables. As seen in Table 6, Total Comorbidities was weakly but significantly positively correlated with RADAI (r=0.226, p<0.001), suggesting more comorbidities occur in those with more disease activity. When Total Comorbidities was used as the controlling variable and RADAI was the independent variable, the correlations slightly improved for both PCS (r=-0.575, p<0.001) and MCS (r=-0.249, p<0.001).

Table 6 Correlation Analysis of Comorbidities, RADAI and PCS/MCS (N=590)

Control Variable	Variable of Interest		PCS[1]	MCS[2]	RADAI[3]
None	Total Comorbidities	Correlation	-0.314	-0.098	0.226
		2-Tailed Significance	<0.001	0.017	<0.001
RADAI[3]	Total Comorbidities	Correlation	-0.228	-0.041	-
		2-Tailed Significance	<0.001	0.315	-
Total Comorbidities	RADAI[3]	Correlation	-0.575	-0.249	-
		2-Tailed Significance	<0.001	<0.001	-

[1] PCS (Physical Component Summary Score) from SF-36 HRQoL questionnaire
[2] MCS (Mental Component Summary Score) from SF-36 HRQoL questionnaire
[3] RADAI (Rheumatoid Arthritis Disease Activity Index)

The role of RADAI in the association between Total Comorbidities and HRQoL was further explored by testing if RADAI moderated or mediated the relationship between Total Comorbidities and HRQoL. The results of the moderation analysis with an interaction term for Total Comorbidities*RADAI are shown in Table 7 for PCS and Table 8 for MCS, respectively. The interaction term was not significant for PCS (p=0.093) or MCS (p=0.504), suggesting that RADAI does not moderate the relationship between Total Comorbidities and HRQoL.

Table 7 Moderation Analysis with Interaction Term for PCS (N=590)

Predictors	Unstandardized Beta[2]	Unstandardized Standard Error[3]	Standardized Beta[4]	t	p-Value
(Constant)	47.7	0.991	-	48.2	<0.001
RADAI[1]	-3.0	0.225	-0.615	-13.4	<0.001
Total Comorbidities	-2.3	0.568	-0.298	-4.0	<0.001
Interaction term (Total Comorbidities * RADAI[1])	0.2	0.112	0.145	1.7	0.093

[1] RADAI (Rheumatoid Arthritis Disease Activity Index)
[2] Unstandardized Beta from regression: Slope of line between predictor and dependent variable
[3] Unstandardized Standard Deviation: Standard error for Unstandardized Beta above
[4] Standardized Beta: on scale of -1 to 1

Table 8 Moderation Analysis with Interaction Term for MCS (N=590)

Predictors	Unstandardized Beta[2]	Unstandardized Standard Error[3]	Standardized Beta[4]	t	p-Value
(Constant)	56.7	1.115	-	50.8	<0.001
RADAI[1]	-1.0	0.253	-0.227	-4.0	<0.001
Total Comorbidities	0.1	0.639	0.014	0.2	0.879
Interaction term (Total Comorbidities * RADAI[1])	-0.1	0.127	-0.072	-0.7	0.504

[1] RADAI (Rheumatoid Arthritis Disease Activity Index)
[2] Unstandardized Beta from regression: Slope of line between predictor and dependent variable
[3] Unstandardized Standard Deviation: Standard error for Unstandardized Beta above
[4] Standardized Beta: on scale of -1 to 1

The preconditions to conduct a mediation analysis were that Total Comorbidities had to predict both dependent variables (PCS and MCS), as well as the potential mediating variable (RADAI). The first line in Table 6 shows that this precondition was met, as Total Comorbidities was significantly correlated with PCS ($p<0.001$), MCS ($p =0.017$), and RADAI ($p<0.001$).

The mediation effect was analyzed using the PROCESS macro to estimate the total effect (not considering any mediator), direct effect (effect of Total Comorbidities on HRQoL controlling for RADAI) and indirect effect (mediation effect of Total Comorbidities on HRQoL via RADAI). Table 9 shows the results for the mediation of RADAI on the effect of Total Comorbidities on PCS. Total Comorbidities had a significant and negative total effect on PCS when RADAI was not considered ($p<0.001$). Total Comorbidities also had a significant negative direct effect on PCS when controlling for RADAI ($p<0.001$). The indirect effect via RADAI as a mediating variable was also considered significant because the bootstrapped 95% confidence interval of -1.3593 to -0.6152 did not contain zero. The results in Table 9 indicate that RADAI is a mediator for the association between Total Comorbidities and PCS, and that it increases the significant negative relationship between them.

Table 9 Mediation Analysis For Total Comorbidities and PCS (N=590)

Predictors	Unstandardized Effect	Unstandardized Standard Error	t	p	95% CI[6] (Lower)	95% CI[6] (Upper)
Total effect (c)[1]	-2.4119	0.3010	-8.0121	<0.001	-3.0031	-1.8207
Direct effect (c')[2]	-1.4378	0.2530	-5.6832	<0.001	-1.9347	-0.9409
Indirect effect via RADAI (a*b)[3]	-0.9740	0.1851[*]	-	-	-1.3593[*]	-0.6152[*]
Effect of RADAI on PCS (b)[4]	-2.7359	0.1606	-	-	-3.0513	-2.4205
Effect of Total Comorbidities on RADAI (a)[5]	0.3560	-	-	-	-	-

[1] Total effect (c) not considering RADAI as mediator
[2] Direct effect (c') holding RADAI constant and varying Total Comorbidities
[3] Indirect effect (a*b) via RADAI, holding Total Comorbidities constant and varying RADAI
[4] b is effect of RADAI on PCS (Physical Component Score)
[5] a is effect of Total Comorbidities on RADAI where a=a*b/b
[6] 95% Confidence Intervals
[*] Bootstrapped 95% Confidence Intervals

Table 10 shows the results for the mediation of RADAI on the association between Total Comorbidities and MCS. While Total Comorbidities had a significant and negative total effect on MCS (p=0.0167), it did not have a significant direct effect (p=0.3153). Since the bootstrapped 95% confidence intervals of -0.0607 to -0.0328 for the indirect effect via RADAI did not include zero, Table 10 shows that RADAI was a significant negative mediator of the association between Total Comorbidities and MCS.

Table 10 Mediation Analysis For Total Comorbidities and MCS (N=590)

Predictors	Unstandardized Effect	Unstandardized Standard Error	t	p	95% CI[6] (Lower)	95% CI[6] (Upper)
Total effect (c)[1]	-0.6856	0.2857	-2.4	0.0167	-1.2467	-0.1245
Direct effect(c')[2]	-0.2857	0.2843	1.0050	0.3153	-0.8441	0.2726
Indirect effect via RADAI (a*b)[3]	-0.4000	0.0096	-	-	-0.0607*	-0.0328*
Effect of RADAI on PCS (b)[4]	-1.1233	0.1804	-6.2253	<0.001	-1.4777	-0.7689
Effect of Total Comorbidities on RADAI (a)[5]	0.3560	-	-	-	-	-

[1] Total effect (c) not considering RADAI as mediator
[2] Direct effect (c') holding RADAI constant and varying Total Comorbidities
[3] Indirect effect (a*b) via RADAI holding Total Comorbidities constant and varying RADAI
[4] b is effect of RADAI on MCS (Mental Component Score)
[5] a is effect of Total Comorbidities on RADAI where a=a*b/b
[6] 95% Confidence Intervals
* Bootstrapped 95% Confidence Intervals

4.0 Discussion

4.1 Demographics and Variables of Interest

The majority of subjects in this study were white (92.1%) women (80.2%) with a mean age of 59 years. This sample was relatively representative of the general RA population, as it most commonly affects Caucasian (64.2%) women (77.8%) and prevalence increases with age. However, Caucasians were overrepresented in the study (92.1% versus 64.2%), which led to other races being underrepresented. Only 4% of subjects were Black/African American, less than 1% were Asian, and 1% were Latino/Hispanic. Although Black/American Americans, Asian, and Hispanic patients are less likely to be diagnosed with RA compared to Caucasian patients, they make up more of the RA population than represented in this study (Kawatkar, Portugal, Chu, & Iyer, 2012). Additionally, Black/African American and Hispanic patients are more likely to be severely impacted by the disease due to health disparities and genetics. Hispanic patients often have higher levels of disease activity compared to other groups, even with higher uses of biologic treatments. Both Black/African American and Hispanic RA patients report worse functional status compared to Caucasian patients (Greenberg et al., 2013).

The prevalence of different comorbidities in this study were relatively representative of those reported for the RA population with hypertension as the most common comorbidity (34% versus reported 39%). Coronary artery disease had a similar prevalence (7% versus reported 5%) but asthma did not occur as frequently in this study as reported in the RA population (11% versus reported 21%) (Dougados et al., 2013). The mean Total Comorbidities in this study (1.4 +/- 1.4) was similar to the mean of 1.6 comorbidities reported in 17,738 patients (Wolfe & Michaud, 2008). The RADAI (4.2 out of 10) score in this study suggests the population had low

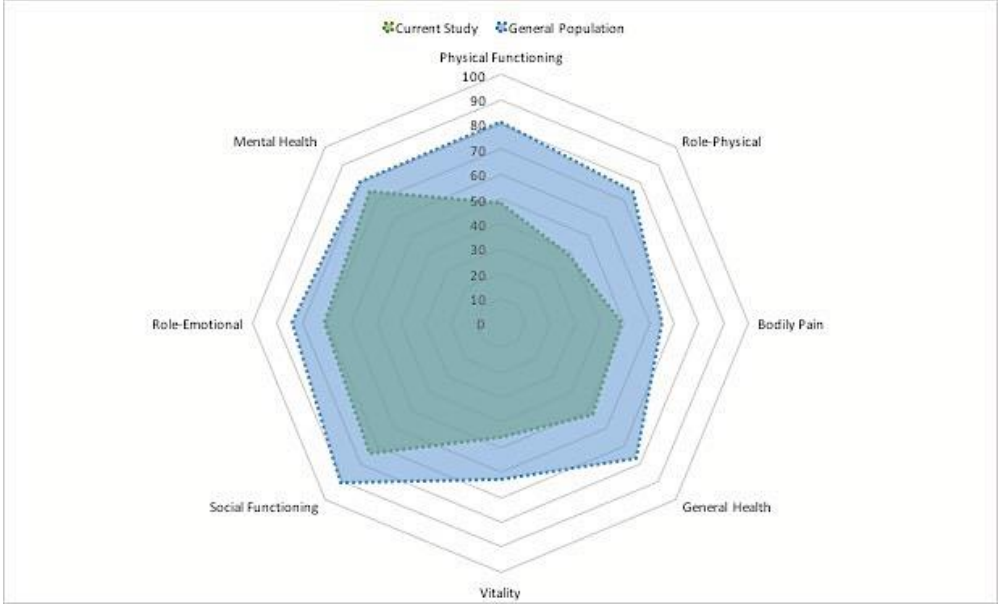
to moderate disease compared to the general RA population. The mean PCS (33.3 +/- 10.9) and MCS (52.1 +/- 9.8) in the study were slightly higher (implying better HRQoL) than the mean PCS (29-33) and mean MCS (41-51) reported for US studies with similar numbers of RA patients (Strand, Burmester et al., 2012; Strand, Sharp et al., 2012).

4.2 Research Questions: Association of Total Comorbidities with HRQoL Measures

When controlling for disease activity (RADAI) in this study, Total Comorbidities had weak negative associations with both measures of HRQoL (PCS and MCS), but only PCS was significant ($p<0.001$). A significant association of PCS but not MCS with RA disease activity was seen in a large tociluzimab study, although Total Comorbidities was not measured (Strand, Burmester et al., 2012). The greater influence on PCS than MCS may be partially explained by the orthogonal weighting calculation applied to the SF-36 domains to calculate the normed PCS and MCS scores. In the calculation, three mental scores (SF: social functioning, RE: role limitations due to emotional problems, and MH: mental health) have negative weighting on PCS. Three physical scores (PF: physical functioning, RP: role limitations due to physical health problems, and BP: bodily pain) have negative weighting on MCS. For diseases with considerable physical burden like RA, the net effect of the negative weighting for three physical scores raises the MCS (Laucis, Hays, & Bhattacharyya, 2015). This scoring effect may underestimate the actual mental HRQoL burden as well as decrease the likelihood of detecting significant changes in MCS in RA patients. Figure 1 compares the means for the eight normed SF-36 domains in this study to the US means for a population of healthy women with a mean age of 62 years (Yost, Haan, Levine, & Gold, 2005). All eight domains in this study were lower than in healthy women

of a similar age, but the most significant impacts on HRQoL were in the four physical domains and vitality, with lesser impacts on mental health, role limitations due to emotional problems, and social functioning. This finding suggests that overall HRQoL was lower for this RA population than for healthy peers, with physical HRQoL being more severely impacted than mental HRQoL.

Figure 1 Mean of Normed SF-36 Domains for Study Sample versus US Females

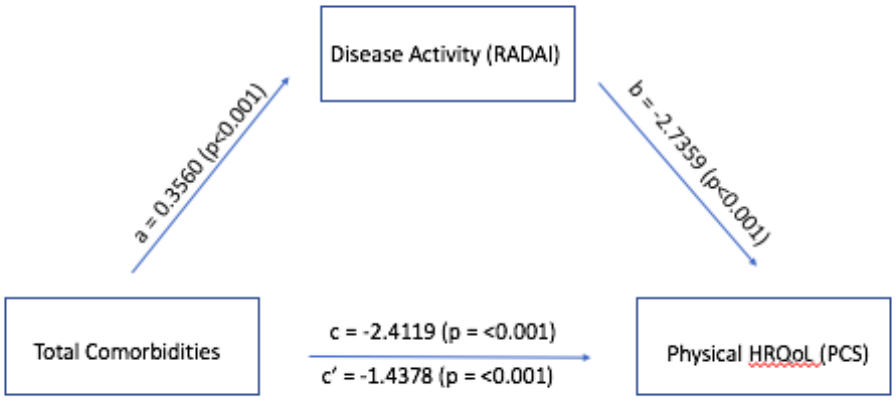


Physical component summary score (PCS): Physical Functioning, Role-Physical, Bodily Pain, General Health
Mental component summary score (MCS): Vitality, Social Functioning, Role-Emotional, Mental Health

In this study, higher number of Total Comorbidities were significantly associated with greater disease activity as measured by RADAI ($p<0.001$). In fact, when controlling for Total Comorbidities, disease activity was significantly negatively correlated with both PCS and MCS ($p<0.001$). The stronger association of disease activity (RADAI) than Total Comorbidities with both measures of HRQoL raised the possibility that disease activity (RADAI) could be moderating or mediating the association between the Total Comorbidities and HRQoL. RADAI did not act as a moderator, but analysis via PROCESS showed it was acting as a mediator in the relationship between Total Comorbidities and the two measures of HRQoL (PCS and MCS).

Figure 2 shows a model of RADAI as a mediator of the association between Total Comorbidities and PCS using the PROCESS effects values. The significant indirect effect via RADAI from Table 9 (-0.9740, bootstrapped 95% confidence interval of -1.3593 to -0.6152) was the product of the significant positive effect of Total Comorbidities on RADAI (0.3560, $p<0.001$) and the significant negative effect of RADAI on PCS (-2.7359, $p<0.001$). The direct effect of Total Comorbidities on PCS (-1.4378, $p<0.001$) was significant but considerably reduced compared to the total effect (-2.4119, $p<0.001$), showing the RADAI mediation effect. The results indicate that patients with more total comorbidities tend to have decreased physical functioning, which is further exacerbated by increases in disease activity.

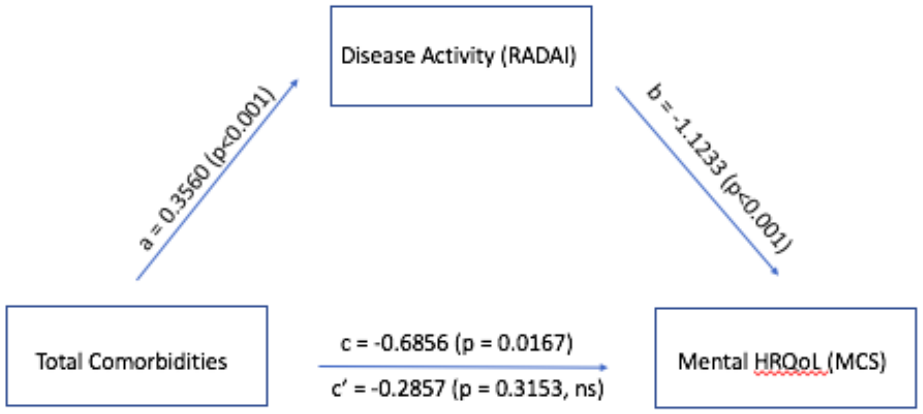
Figure 2 Mediation Model for PCS (Physical Component Summary Score from SF-36)



a is effect of Total Comorbidities on Disease Activity (RADAI)
b is effect of mediator, Disease Activity (RADAI), on PCS
a*b (not shown in Figure) is indirect effect of mediator, Disease Activity, on PCS where a*b = (0.3560*-2.7359) = -0.9740
c is total effect of Total Comorbidities on PCS
c' is direct effect of Total Comorbidities on PCS, calculated by c' = (c - indirect effect a*b)

Figure 3 showed RADAI's mediation of the relationship between Total Comorbidities and MCS. The significant indirect effect of RADAI shown in Table 10 (-0.4000, bootstrapped 95% confidence interval of -0.0607 to -0.0328) was the product of the significant positive effect of Total Comorbidities on RADAI (0.3560, p<0.001) and the significant negative effect of RADAI on MCS (-1.1233, p<0.001). Although the total effect of number of Total Comorbidities on MCS (-0.6856, p=0.0167) was significant, when it was reduced by the mediation effect of RADAI, the direct effect was not significant (-0.2857, p=0.3153). As with PCS, as the number of Total Comorbidities increased, disease activity (RADAI) increased. As disease activity increased, the MCS measure of HRQoL decreased. However, for MCS, RADAI more completely mediated the relationship, so that there was no significant direct effect of Total Comorbidities on the MCS measure of HRQoL.

Figure 3 Mediation Model for MCS (Mental Component Summary Score from SF-36)



a is effect of Total Comorbidities on Disease Activity (RADAI)
b is effect of mediator, Disease Activity (RADAI), on MCS
a*b (not shown in Figure) is indirect effect of mediator, Disease Activity, on MCS where a*b = (0.3560*-1.1233) = -0.4000
c is total effect of Total Comorbidities on MCS
c' is direct effect of Total Comorbidities on MCS, calculated by c'= (c - indirect effect a*b)

Comparing Figure 2 and Figure 3, RADAI had a stronger effect on the physical component summary score (PCS) than the mental component summary score (MCS) of HRQoL (-2.7359 vs -1.1233, respectively). This implies that as disease activity (RADAI) became more severe, PCS worsened more than MCS. Total Comorbidities also had a stronger direct effect on PCS than MCS (-1.4378 vs -0.2857, respectively), which implies that with increasing Total Comorbidities, PCS worsens more than MCS. As noted previously, the weighted calculation of HRQoL component scores may artificially raise the MCS in physically burdensome diseases like RA (Laucis et al., 2015), but the comparison with the individual HRQoL domains in Figure 1 supports the conclusion that the RA disease activity and total comorbidities had a stronger effect on physical than mental HRQoL.

4.3 Implications

The significant direct association between increases in Total Comorbidities and decreases in the physical component summary score of HRQoL in this study shows the importance of preventing, monitoring, and treating common comorbidities in RA. This finding is particularly important for comorbidities directly related to RA, such as cardiovascular complications and anemia. Effective treatment of RA is also very important, since increases in disease activity are associated with decreased HRQoL physical and mental component summary scores.

4.4 Research Next Steps

There are several results from this study that could be further investigated in future studies. The demographics of those involved in the study were skewed towards white, well-educated, married women with low-moderate disease activity and relatively few comorbidities. Although RA is more prevalent in women, the demographics are not fully representative of the RA population. It would be interesting to compare these results with subjects of a lower socioeconomic status with similar or greater disease activity to see if MCS is more affected by Total Comorbidities in patients who have lower income, and less resources/treatment options. It would also be interesting to include more subjects from different races or ethnicities, especially those who are Black or Hispanic, as these individuals are more likely to have lower reported functional ability in RA, as well as the presence of health disparities. These disparities could further impact their ability to treat comorbidities and RA, and could lead to worsening disease activity, physical health, and mental health.

4.5 Limitations

As stated above, the lack of demographic diversity is a limitation of this study and more diverse racial, ethnic, and socioeconomic groups could be further investigated in future studies. Additionally, patients in this study had relatively low Total Comorbidities (mean=1.4) and low-moderate disease activity (mean=4.2), which might have limited the ability to detect changes in the mental component summary score of HRQoL. Another limitation is that this study was

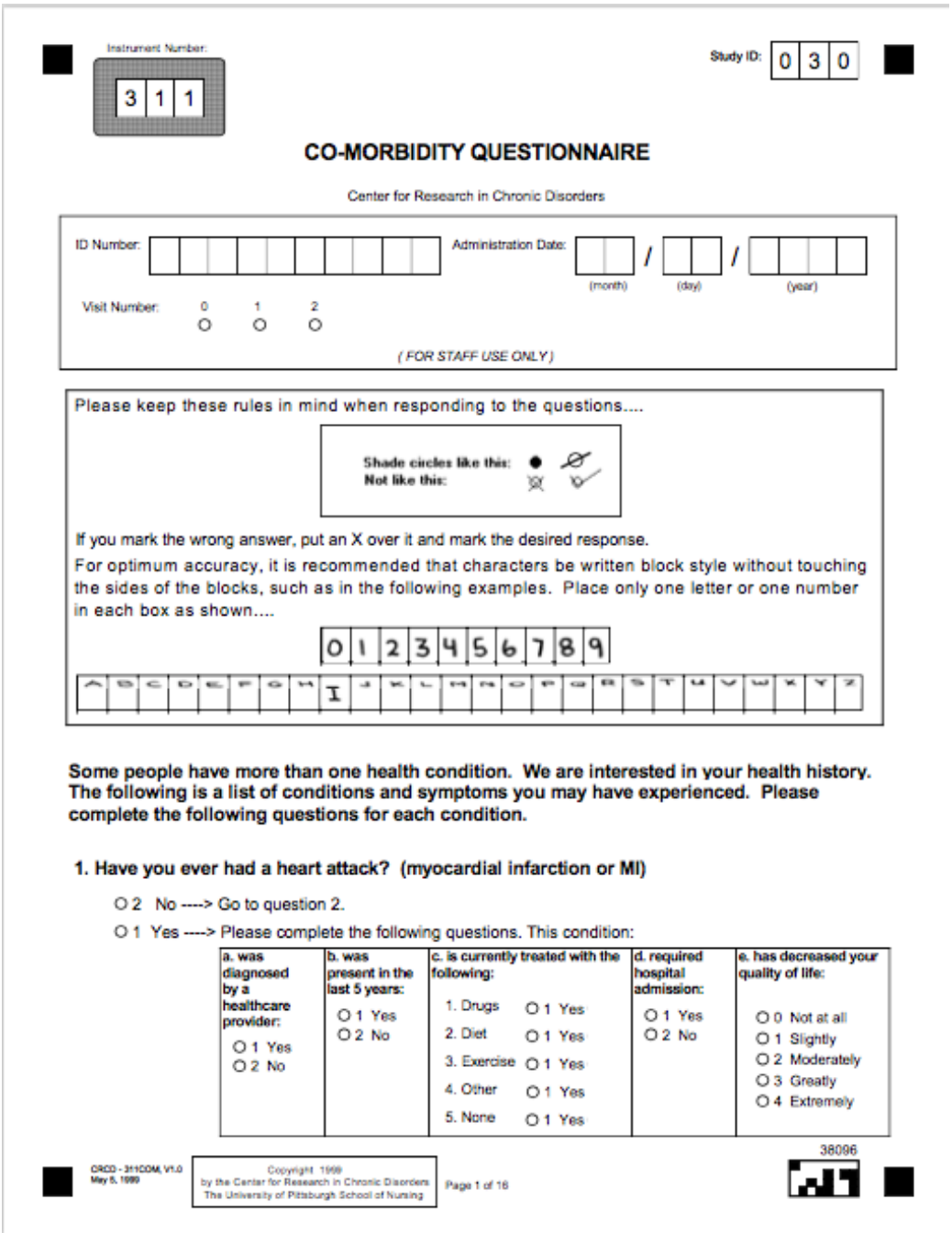
conducted prior to the wider use of biologic DMARDs. It is also important to note that the comorbidity questionnaire mainly focused on physical illnesses, rather than mental illnesses.

5.0 Conclusion

This study explored if the number of Total Comorbidities in patients with RA was associated with HRQoL through physical (PCS) and mental (MCS) domains when controlling for disease activity (RADAI). When controlled for disease activity, increases in the number of Total Comorbidities led to significant decreases in physical HRQoL, but not mental HRQoL. With no control for disease activity, the number of Total Comorbidities appeared to have a better correlation to physical and mental HRQoL, with both significantly decreasing with increasing Total Comorbidities. Disease activity was found to be a significant mediator of the relationship between the number of Total Comorbidities and both physical and mental HRQoL. When the mediating effect of disease activity was removed, the number of Total Comorbidities was still significantly and negatively correlated with physical HRQoL. Although number of comorbidities appeared to be significantly negatively correlated with mental HRQoL based on the Total Effect model, this result was largely due to the mediating effect of disease activity. When disease activity was removed from the model, the direct effect of Total Comorbidities on mental HRQoL was no longer significant. The results of this study indicate that, when including disease activity as a mediating variable, there is a direct association between comorbidities and physical HRQoL. When the number of Total Comorbidities increased, the physical HRQoL of a patient decreased. As the number Total Comorbidities increased, the mental HRQoL is not significantly directly affected, as most of the apparent effect is due to the mediating effect of disease activity. These results emphasize the importance of treating the patient's comorbidities, in addition to their primary disease, in order to improve their physical HRQoL.

Appendix A Assessment Instruments

Appendix A.1 Co-Morbidity Questionnaire



Instrument Number: 311

Study ID: 030

CO-MORBIDITY QUESTIONNAIRE

Center for Research in Chronic Disorders

ID Number: _____ Administration Date: ___ / ___ / ___ (month) (day) (year)

Visit Number: 0 ○ 1 ○ 2 ○

(FOR STAFF USE ONLY)

Please keep these rules in mind when responding to the questions....

Shade circles like this: ● Not like this: ⊘ ✓ ⊗

If you mark the wrong answer, put an X over it and mark the desired response.

For optimum accuracy, it is recommended that characters be written block style without touching the sides of the blocks, such as in the following examples. Place only one letter or one number in each box as shown....

0 1 2 3 4 5 6 7 8 9

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

Some people have more than one health condition. We are interested in your health history. The following is a list of conditions and symptoms you may have experienced. Please complete the following questions for each condition.

1. Have you ever had a heart attack? (myocardial infarction or MI)

○ 2 No ----> Go to question 2.

○ 1 Yes ----> Please complete the following questions. This condition:

a. was diagnosed by a healthcare provider:	b. was present in the last 5 years:	c. is currently treated with the following:	d. required hospital admission:	e. has decreased your quality of life:
○ 1 Yes ○ 2 No	○ 1 Yes ○ 2 No	1. Drugs ○ 1 Yes 2. Diet ○ 1 Yes 3. Exercise ○ 1 Yes 4. Other ○ 1 Yes 5. None ○ 1 Yes	○ 1 Yes ○ 2 No	○ 0 Not at all ○ 1 Slightly ○ 2 Moderately ○ 3 Greatly ○ 4 Extremely

38096

CRCD - 311COM, V1.0 May 5, 1999

ID Number: _ _ _ _ _ _ _ _ _ _ (for internal use only) Date: _ _ / _ _ / _ _ (for internal use only) Study ID: 0 3 0

2. Have you ever been hospitalized or treated for heart failure? (You may have felt more short of breath and the doctor may have told you that you had fluid in your lungs or that your heart was not working efficiently.)

○ 2 No ----> Go to question 3.

○ 1 Yes ----> Please complete the following questions. This condition:

a. was diagnosed by a healthcare provider:	b. was present in the last 5 years:	c. is currently treated with the following:	d. required hospital admission:	e. has decreased your quality of life:
○ 1 Yes ○ 2 No	○ 1 Yes ○ 2 No	1. Drugs ○ 1 Yes 2. Diet ○ 1 Yes 3. Exercise ○ 1 Yes 4. Other ○ 1 Yes 5. None ○ 1 Yes	○ 1 Yes ○ 2 No	○ 0 Not at all ○ 1 Slightly ○ 2 Moderately ○ 3 Greatly ○ 4 Extremely

f. Did you ever have any of the following with your hospitalization for heart failure?

1. Heart attack	○ 1 Yes	○ 2 No	○ 3 Don't know
2. Rapid irregular heart beat	○ 1 Yes	○ 2 No	○ 3 Don't know
3. Total body infection (Sepsis)	○ 1 Yes	○ 2 No	○ 3 Don't know
4. Inflammation of the heart muscle wall (Endocarditis)	○ 1 Yes	○ 2 No	○ 3 Don't know
5. Pregnancy	○ 1 Yes	○ 2 No	○ 3 Don't know

Directions for questions beginning on the next page:

For the questions that look like this:

	Medical Condition	a. Do you have this condition? Yes 1 No 2	b. was diagnosed by a healthcare provider: Yes 1 No 2	c. was present in the last 5 years: Yes 1 No 2	d. is currently treated with the following: 1 = Drugs 2 = Diet 3 = Exercise 4 = Other 5 = None 1 2 3 4 5	e. required hospital admission: Yes 1 No 2	f. has decreased your quality of life: 0 = Not at all 1 = Slightly 2 = Moderately 3 = Greatly 4 = Extremely 0 1 2 3 4
	Example:	○ ●	○ ○	○ ○	○ ○ ○ ○ ○	○ ○	○ ○ ○ ○ ○
1.	Headaches	→ *If your response is "No," DO NOT ANSWER b through f and go to the next question.*					
	Example:	● ○	● ○	○ ●	● ○ ● ● ○	○ ●	○ ○ ○ ● ○
2.	Tuberculosis	→ *If your response is "Yes," PLEASE ANSWER b through f and then go to the next question.*					

38096

ID Number: _ _ _ _ _ _ _ _ _ _ _ _ (for internal use only) Date: _ _ / _ _ / _ _ (for internal use only) Study ID: 0 3 0

Please answer the following questions regarding the medical conditions listed below as they pertain to you.

	Medical Condition	a. Do you have this condition? Yes 1 / No 2	b. was diagnosed by a healthcare provider: Yes 1 / No 2	c. was present in the last 5 years: Yes 1 / No 2	d. is currently treated with the following: 1 = Drugs, 2 = Diet, 3 = Exercise, 4 = Other, 5 = None — 1 2 3 4 5	e. required hospital admission: Yes 1 / No 2	f. has decreased your quality of life: 0 = Not at all, 1 = Slightly, 2 = Moderately, 3 = Greatly, 4 = Extremely — 0 1 2 3 4
3.	Coronary Artery Disease	○ ○	○ ○	○ ○	○ ○ ○ ○ ○	○ ○	○ ○ ○ ○ ○
4.	Irregular Heart Rate	○ ○	○ ○	○ ○	○ ○ ○ ○ ○	○ ○	○ ○ ○ ○ ○
5.	Heart Valve Disorders	○ ○	○ ○	○ ○	○ ○ ○ ○ ○	○ ○	○ ○ ○ ○ ○
6.	Other Heart Disorders *Specify condition(s):* _____	○ ○	○ ○	○ ○	○ ○ ○ ○ ○	○ ○	○ ○ ○ ○ ○
7.	High Blood Pressure	○ ○	○ ○	○ ○	○ ○ ○ ○ ○	○ ○	○ ○ ○ ○ ○
8.	Anemia	○ ○	○ ○	○ ○	○ ○ ○ ○ ○	○ ○	○ ○ ○ ○ ○
9.	Other Blood Disorders *Specify condition(s):* _____	○ ○	○ ○	○ ○	○ ○ ○ ○ ○	○ ○	○ ○ ○ ○ ○

10. Do you cough first thing in the morning in the winter? (Exclude clearing the throat.)

○ 2 No ----> Go to question 11.

○ 1 Yes ----> Please complete the following questions:

a. Do you cough during the day in the winter?	○ 1 Yes	○ 2 No
b. Do you cough during the night in the winter?	○ 1 Yes	○ 2 No
c. Do you cough like this for most days for 3 months every year?	○ 1 Yes	○ 2 No
d. Do you cough up mucus on most of these days?	○ 1 Yes	○ 2 No
e. Has this gone on for at least 2 years?	○ 1 Yes	○ 2 No

Please answer the following questions regarding the medical conditions listed below as they pertain to you.

	Medical Condition	a. Do you have this condition? Yes 1	a. No 2	b. was diagnosed by a healthcare provider: Yes 1	b. No 2	c. was present in the last 5 years: Yes 1	c. No 2	d. is currently treated with the following: 1 = Drugs 2 = Diet 3 = Exercise 4 = Other 5 = None 1	2	3	4	5	e. required hospital admission: Yes 1	e. No 2	f. has decreased your quality of life: 0 = Not at all 1 = Slightly 2 = Moderately 3 = Greatly 4 = Extremely 0	1	2	3	4
11.	Asthma or Wheezing	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
12.	Emphysema	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
13.	Pneumonia	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
14.	Tuberculosis	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
15.	Pulmonary Fibrosis ("stiff lungs")	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○

16. Have you had pain in either leg when walking other than pain in your joints?

O 2 No ----> Go to question 17.

O 1 Yes ----> Please complete the following questions. This condition:

a. was diagnosed by a healthcare provider as Peripheral Vascular Disease (PVD) or Claudication:	b. was present in the last 5 years:	c. is currently treated with the following:	d. required hospital admission:	e. has decreased your quality of life:
O 1 Yes O 2 No	O 1 Yes O 2 No	1. Drugs O 1 Yes 2. Diet O 1 Yes 3. Exercise O 1 Yes 4. Other O 1 Yes 5. None O 1 Yes	O 1 Yes O 2 No	O 0 Not at all O 1 Slightly O 2 Moderately O 3 Greatly O 4 Extremely

f. Does the leg pain begin when you are standing still?

O 1 Yes
O 2 No

g. Where in your leg does the pain begin?

O 1 Calf included
O 2 Does not include calf

h. Do you get leg pain if you walk uphill or hurry?

O 1 Yes
O 2 No
O 3 Do not walk up hill

i. Does standing still relieve your leg pain?

O 1 Yes
O 2 No

j. What do you do when you get leg pain while walking?

O 1 Stop or slow down
O 2 Keep walking at the same pace

k. How soon until your leg pain goes away?

O 1 More than 10 minutes
O 2 Less than 10 minutes

l. Have you had a peripheral bypass operation for this problem?

O 1 Yes
O 2 No

Appendix A.2 Medical Outcomes Questionnaire (MOS-SF-36)

Instrument Number: 202

Study ID: 030

MEDICAL OUTCOMES QUESTIONNAIRE (MOS-SF-36)

ID Number: Administration Date: (month) / (day) / (year)

0 1 2

Administration Time: (hr) : (min)

(FOR STAFF USE ONLY)

Please use the following example to answer all questions:

Shade circles like this: ●
Not like this: ⊗ ✓

INSTRUCTIONS: **This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.**

1. In general, would you say your health is: (choose one response only...)

   O 1 excellent
   O 2 very good
   O 3 good
   O 4 fair
   O 5 poor

2. Compared to one year ago, how would you rate your health in general now? (choose one response only...)

   O 1 much better now than 1 year ago
   O 2 somewhat better now than 1 year ago
   O 3 about the same
   O 4 somewhat worse now than 1 year ago
   O 5 much worse now than 1 year ago

3. The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much? (choose one response on each line...)

	Yes, limited a lot 1	Yes, limited a little 2	No, not limited at all 3
a. vigorous activities, such as running, lifting heavy objects, or participating in strenuous sports	O	O	O
b. moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	O	O	O
c. lifting or carrying groceries	O	O	O
d. climbing several flights of stairs	O	O	O
e. climbing one flight of stairs	O	O	O
f. bending, kneeling, or stooping	O	O	O
g. walking more than a mile	O	O	O
h. walking several blocks	O	O	O
i. walking one block	O	O	O
j. bathing or dressing yourself	O	O	O

4. During the **past 4 weeks,** have you had any of the following problems with your work or other regular daily activities **as a result of your physical health?** (choose one response only...)

	1	2
a. cut down the amount of time you spent on work or other activities	O Yes	O No
b. accomplished less than you would like	O Yes	O No
c. were limited in the kind of work or other activities	O Yes	O No
d. had difficulty performing the work or other activities (for example, it took extra effort)	O Yes	O No

5. During the **past 4 weeks,** have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?
(choose one response on each line...)

	1	2
a. cut down the amount of time you spent on work or other activities	O Yes	O No
b. accomplished less than you would like	O Yes	O No
c. did not do work or other activities as carefully as usual	O Yes	O No

6. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups? (choose one response only...)

O 1 not at all
O 2 slightly
O 3 moderately
O 4 quite a bit
O 5 extremely

7. How much **bodily** pain have you had during **the past 4 weeks**? (choose one response only...)

O 1 none
O 2 very mild
O 3 mild
O 4 moderate
O 5 severe
O 6 very severe

8. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside home and housework)? (choose one response only...)

O 1 not at all
O 2 a little bit
O 3 moderately
O 4 quite a bit
O 5 extremely

9. These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the **past 4 weeks**...? (choose one response on each line...)

	All of the time 1	Most of the time 2	A good bit of the time 3	Some of the time 4	A little of the time 5	None of the time 6
a. did you feel full of pep	O	O	O	O	O	O
b. have you been a nervous person	O	O	O	O	O	O
c. have you felt so down in the dumps nothing could cheer you up	O	O	O	O	O	O
d. have you felt calm and peaceful	O	O	O	O	O	O
e. did you have a lot of energy	O	O	O	O	O	O
f. have you felt down-hearted and blue	O	O	O	O	O	O
g. did you feel worn out	O	O	O	O	O	O
h. have you been a happy person	O	O	O	O	O	O
i. did you feel tired	O	O	O	O	O	O

10. During the **past 4 weeks**, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)? (choose one response only...)

O 1 all of the time
O 2 most of the time
O 3 some of the time
O 4 a little of the time
O 5 none of the time

11. Please choose the answer that best describes how **true** or **false** each of the following statements are for you: (choose one response on each line...)

	Definitely true 1	Mostly true 2	Don't know 3	Mostly false 4	Definitely false 5
a. I seem to get sick a little easier than other people	○	○	○	○	○
b. I am as healthy as anybody I know	○	○	○	○	○
c. I expect my health to get worse	○	○	○	○	○
d. My health is excellent	○	○	○	○	○

Appendix A.3 RADAR/RADAI Questionnaire

Instrument Number: 367

Study ID: 030

RAPID ASSESSMENT OF DISEASE ACTIVITY IN RHEUMATOLOGY

ID Number: _____ Administration Date: ___ / ___ / ____ (month) (day) (year)

0 1 2

(FOR STAFF USE ONLY)

Please use the following example to answer all questions:

Shade circles like this: ●
Not like this: ⊗ ✓

Please answer these questions about your arthritis.

1. In general, how active has your arthritis been **over the past six months?**
   Mark **X** on the scale below at the point which best describes the level of arthritis activity you have had.

   Not Active At All —————— ***Extremely Active***

2. How active is your arthritis **today** in terms of joint tenderness and swelling?
   Mark **X** on the scale below at the appropriate point.

   Not Active At All —————— ***Extremely Active***

3. How much arthritis pain do you feel **today?**
   Mark **X** on the scale below at the appropriate point.

   No Pain —————— ***Very severe pain***

(for internal use only)

(for internal use only)

(for internal use only)

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4. Were your joints stiff when you woke up today?

O 1 Yes ---->a.) How long did this extra stiffness last?

O 2 No

- O 1 Less than 30 minutes
- O 2 30 minutes to an hour
- O 3 1-2 hours
- O 4 2-4 hours
- O 5 More than 4 hours
- O 6 All day

5. Which statement best describes your abilities **today**?

- O 1 Able to carry on all usual duties without limitations.
- O 2 Able to conduct normal activities despite handicap of discomfort or limited mobility of one or more joints.
- O 3 Able to perform few or none of the duties of your usual occupation.
- O 4 Largely confined to bed and chair with little or no self care.

6. Please indicate below the amount of pain and / or tenderness you are having today in each of the joint areas listed below:

Fill in the circle that corresponds to the amount you are having today. The choices are:

0 = no pain / tenderness
1 = mild pain / tenderness
2 = moderate pain / tenderness
3 = severe pain / tenderness

For the areas which are marked with an * think of one joint in the group that bothers you the most today, and give a score for that joint. Be sure to mark both left and right sides separately.

Joints	Left Side None 0	Mild 1	Moderate 2	Severe 3	Right Side None 0	Mild 1	Moderate 2	Severe 3
a.) Shoulders	O	O	O	O	O	O	O	O
b.) Elbows	O	O	O	O	O	O	O	O
c.) Wrists	O	O	O	O	O	O	O	O
d.) Hand knuckles*	O	O	O	O	O	O	O	O
e.) Finger knuckles*	O	O	O	O	O	O	O	O
f.) Hips	O	O	O	O	O	O	O	O
g.) Knees	O	O	O	O	O	O	O	O
h.) Ankles	O	O	O	O	O	O	O	O
i.) Ball of foot*	O	O	O	O	O	O	O	O
i.) Toe knuckles*	O	O	O	O	O	O	O	O

Appendix B IRB Approval Letter

University of Pittsburgh
Institutional Review Board

Human Research Protection Office
3500 Fifth Avenue, Suite 106
Pittsburgh, PA 15213
Tel (412) 383-1480
www.hrpo.pitt.edu

APPROVAL OF SUBMISSION (Exempt)

Date:	March 23, 2020
IRB:	STUDY20010183
PI:	Kalaina Corbo
Title:	Association of Number of Comorbidities and Health-Related Quality of Life in Patients with Rheumatoid Arthritis
Funding:	None

The Institutional Review Board reviewed and approved the above referenced study. The study may begin as outlined in the University of Pittsburgh approved application and documents.

Approval Documentation

Review type:	Initial Study
Approval Date:	3/23/2020
Exempt Category:	(4) Secondary research on data or specimens (no consent required)
Approved Documents:	• IRB#970380ConsentGoodAdherers10-05-2006, Category: Other; • IRB#970380ConsentRandomized10-05-2006, Category: Other;

As the Principal Investigator, you are responsible for the conduct of the research and to ensure accurate documentation, protocol compliance, reporting of possibly study-related adverse events and unanticipated problems involving risk to participants or others. The HRPO Reportable Events policy, Chapter 17, is available at http://www.hrpo.pitt.edu/.

Clinical research being conducted in an UPMC facility cannot begin until fiscal approval is received from the UPMC Office of Sponsored Programs and Research Support (OSPARS).

If you have any questions, please contact the University of Pittsburgh IRB Coordinator, Larry Ivanco.

Please take a moment to complete our Satisfaction Survey as we appreciate your feedback.

Pitt_510_Exempt

Appendix C PROCESS Copyright Permission

The PROCESS macro for SPSS, SAS, and R

PROCESS operates on both Windows and Mac versions of SPSS and SAS. PROCESS for SPSS requires SPSS version 19 or later but works best on versions 22 and above. PROCESS for SAS requires PROC IML. PROCESS for R was written in R base 3.6.1 and requires no additional packages. Downloading this software implies you have familiarized yourself with and understand the copyright notice and disclaimer below and will comply. This notice is available in the zip archive.

PROCESS for R is not yet publicly available. A beta version will be provided to students who attend one of these PROCESS workshops in the first half of 2020.

COPYRIGHT AND DISCLAIMER NOTICE

As with all statistical software, all attempts are made to make sure that the computations programmed are performed correctly. When bugs are found or reported, they are eliminated as quickly as possible. This software is offered to the research community free of charge and "as is." The user accepts all responsibility for any negative consequences that might result from its use. Always use the most current release of the software.

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