# THE IMPACTS OF DIFFERENT STAGES OF CHRONIC KIDNEY DISEASE, AS WELL AS THE CO-MORBIDITIES OF DIABETES AND HEART DISEASE, ON PATIENTS' QUALITY OF LIFE.

**by**

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**A Thesis submitted to the School of Graduate Studies towards partial fulfilment of the requirements for obtaining the degree of Master of Science (Medicine).**

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**October, 2014.**

**St. John's, Newfoundland & Labrador.**

# ABSTRACT

**Background:** Health-related Quality of Life (QoL) pertains to how medical conditions affect the lives of people suffering from those respective conditions, and QoL measurements therefore help to define the everyday impacts of the conditions; understanding these impacts can lead to improvements in the healthcare provisions for patients with each condition. There is yet to be a large-sample Study that compares QoL across different stages of Chronic Kidney Disease (CKD) while (i) utilizing a predominantly North American adult population, and (ii) factoring in commonly-associated co-morbidities (i.e. Diabetes and Heart Disease).

**Methods:** A Retrolective Cross-sectional Observational Study utilizing historical baseline data from 1135 anonymous adult CKD patients was performed; CKD Stages 3 and 5 were predominant, and every selected patient had answered to a comparable version of the Short Form 36 (SF-36) Health Survey, having had CKD with/without a co-morbidity at baseline. SF-36 Domain and Summary scores were compared, across the stages of CKD (in terms of medians, as distributions were skewed); similar comparisons were also performed with co-morbidities and demographic factors as respective grouping variables. Regression models were subsequently built to analyse the associations between relevant SF-36 scores and each of these independent variables – Stage of CKD, Diabetes, Heart Disease, Age, and Gender.

**Results:** The Physical Component Summary (PCS) score was significantly ($p < 0.05$) lowest among patients with Stage 5 CKD, while patients with Stage 4 CKD, in turn, exhibited significantly lower PCS scores than patients with Stage 3 CKD; Stage 5 CKD patients - who were all on Hemodialysis therapy - also scored lowest (significantly) on five of the eight SF-36 Domains. Coexisting Diabetes and Heart Disease were each associated with further significant

decreases in the PCS score and three physical health-related Domain scores. Compared to females, males scored significantly higher on the PCS measure and on four Domains. Patients' Age did not impact QoL, definitively - while the Mental Component Summary (MCS) score and mental health-related Domain scores were seen to gradually but inconsistently increase with Age, physical health-related QoL was generally unaffected by Age. Regression models, by and large, confirmed the findings from the comparisons of medians.

**Conclusions:** Greater negative impacts on physical health appear to occur, as CKD progresses from stage to stage, but the effects of CKD progression on mental health seem to be negligible. Among CKD patients, Diabetes and Heart Disease appear to further reduce patient perceptions of physical health. Male patients with CKD appear to have more favourable perceptions of their overall health status, as compared to female patients with CKD.

**Recommendations:** Regarding future research - a prospective longitudinal study that periodically assesses QoL across a cohort with CKD would be advisable (in order to further assess the impact of CKD progression on QoL, and to overcome the issues of "missing" data that were encountered during this Study). Regarding the clinical perspective - considerable efforts should be made to prevent (or slow) the progression of CKD towards the final stage of the disease, while enabling patient education, too.

# ACKNOWLEDGEMENTS

I would like to thank Dr. Brendan Barrett for kindly agreeing to be my Supervisor, and for guiding me through this project with both his patience and his expertise. I am deeply grateful to him for making time, in order to provide me with numerous suggestions that each focused my thought processes.

I am also grateful to Dr. Patrick Parfrey for placing me on this path, in the first place, and for helping me to obtain most of the data and information that I needed to carry out my analyses.

I would also like to thank Dr. William Midodzi for his expert advice, regarding the statistical analyses that have been necessary during the course of this project.

I would also like to convey my gratitude to Dr. Gerry Mugford who enabled me to embark on a career in Clinical Epidemiology, and to Dr. Bryan Curtis who helped me to extract the relevant data from one of the three original datasets, in order for this project to go ahead.

Finally, with regards to my general career, I would like to extend my gratitude to my professors/tutors/colleagues, past and present (in India, Russia, Maldives, Saudi Arabia, Philippines, and Canada) who have all helped to further my interest and accomplishments in the field of Medicine.

# FUNDING

Funding for this thesis has been forthcoming from the following sources –

- Research and Graduate Studies, Faculty of Medicine, Memorial University of Newfoundland.
- Research Grants Accounts of members of my Supervisory Committee, which included unencumbered funds from Janssen Ortho (i.e. the company responsible for one of the three historical datasets, which were utilized for this particular Study).

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# LIST OF ABBREVIATIONS

QoL = (Health-related) Quality of Life

CKD = Chronic Kidney Disease

SF-36 = Short Form 36 (questionnaire)

PCS = Physical Component Summary (score)

MCS = Mental Component Summary (score)

SPSS = Statistical Product and Service Solutions

KDQOL/KDQOL-SF = Kidney Disease Quality Of Life-Short Form (questionnaire)

CIHI = Canadian Institute for Health Information

ARF = Acute Renal Failure

GFR = Glomerular Filtration Rate

mL = Millilitre

min = Minute

$m^2$ = Square metres

LADA = Latent Autoimmune Diabetes of Adults

IHD = Ischemic Heart Disease

DALY = Disability Adjusted Life Years

PVD = Peripheral Vascular Disease

WHO = World Health Organization

CDC = Centers for Disease Control and Prevention

QLQ-LC13 = Quality of Life Questionnaire-Lung Cancer 13 (module)

WHOQOL-BREF = World Health Organization Quality of Life-Brief (questionnaire)

IQOLA = International Quality Of Life Assessment (project)

MOS = Medical Outcomes Study

PF = Physical Functioning (SF-36 Domain)

RP = Role limitations due to Physical health (SF-36 Domain)

BP = Bodily Pain (SF-36 Domain)

GH = General Health (SF-36 Domain)

VT = Vitality (SF-36 Domain)

SF = Social Functioning (SF-36 Domain)

RE = Role limitations due to Emotional health (SF-36 Domain)

MH = Mental Health (SF-36 Domain)

SF-2 = Question # 2 in SF-36 questionnaire

NBS = Norm-Based Scoring

HIV = Human Immunodeficiency Virus

AIDS = Acquired Immuno-Deficiency Syndrome

FWBP = Functioning and Well-Being Profile (questionnaire)

GPWBI = General Psychological Well-Being Inventory (questionnaire)

IRT = Item Response Theory

PUBMED = a search engine that mainly accesses the Medical Literature Analysis and Retrieval System Online

ANOVA = Analysis Of Variance

HUI-3/HUI Mark 3 = Health Utilities Index 3 (questionnaire)

TTO = Time Trade Off (questionnaire)

DSI = Dialysis Symptom Index (questionnaire)

PHQ-9 = Patient Health Questionnaire 9 (questionnaire)

QWB = Quality of Well-Being scale (questionnaire)

SCL-90R = Symptom Check-List 90R (questionnaire)

PSF = Patient Symptom Form

PPHS = Patient's Perception of life on Hemodialysis Scale (questionnaire)

SAS = Statistical Analysis System

HREA = Health Research Ethics Authority

# I. AN INTRODUCTION

With regards to the Study Design, this Study was – a Retrolective Cross-sectional Observational Study.

The ultimate objective of this particular project was to ascertain if there are significant differences in health-related Quality of Life (QoL) between predominantly Canadian adult patients who have different stages of Chronic Kidney Disease (CKD); additionally, another major objective was to ascertain if the presence of coexisting conditions (specifically - Diabetes Mellitus and/or symptomatic Heart Disease) in these CKD patients would lead to them experiencing a significantly different QoL, as compared to the QoL of CKD patients without those coexisting conditions (i.e. co-morbidities). In case significant differences in patients' QoL would be shown to exist, modifications in Patient Care could then be suggested, based on which particular stage of CKD (and/or which associated co-morbidity) a patient is known to have.

Prior to any data analysis, an exhaustive search of the literature concerning this Research Question was performed, in order to ascertain – (a) any similarities/differences between this Study and related studies from the past, (b) the advantages and disadvantages of this Study, as compared to related studies from the past, and (c) the best methods for analysing the available data. A search of the literature was also performed, in order to understand the relative strengths/weaknesses of the QoL-measuring instrument being used (i.e. the SF-36 Health Survey). Finally, there was a brief perusal of published papers and/or drafts that arose out of the analyses of the three previously-compiled datasets (note - each of those datasets from the past contributed data that was used during this particular Study, and it was necessary to understand the definition of each variable within each of those three "source" datasets).

As a result of the available data, the final dataset used for analysis comprised patients who were known to have had Stage 2, Stage 3, Stage 4, or Stage 5 of CKD, at baseline (i.e. at the time of first measurement of QoL); these patients had no personal identifiers (just as in the "source" datasets), and were all pooled from those three already-existing datasets. It should be noted that the "source" datasets each arose out of separate multi-centre studies that were conducted at different time periods. The majority of patients in the final dataset had been on Hemodialysis therapy at baseline, as a result of suffering from Stage 5 CKD (i.e. "end-stage" Kidney Disease); the bulk of the remaining patients had been suffering from Stage 3 CKD at baseline, while those who had had Stage 4 CKD or Stage 2 CKD constituted a small minority. Some of the patients in the final dataset had one or both of the co-morbidities of interest (Diabetes Mellitus and symptomatic Heart Disease), as well.

With a very few exceptions, all of the patients in the final dataset had answered to a QoL-measuring Health Survey (in its entirety), at the time of their first entry into the respective original Study that they were a part of, and the Health Survey was either the Short Form 36 (SF-36) instrument or the Kidney Disease Quality Of Life (KDQOL) instrument (note – all of the questions in the former instrument are included within the latter one, too). Since only SF-36 information was common across the three "source" datasets, only SF-36 answers were subsequently utilized for the analyses during this particular Study. In addition, except when impossible in certain cases, the answers of each patient to the various questions in the SF-36 instrument were combined into two "Summary" scores (representing overall physical and overall mental perceptions of health, respectively); this was performed for individual patients before final analyses (i.e. Comparisons of Means/Medians and Multiple Linear Regression modelling) were carried out. As per the characteristics of the available data, primary analyses were

performed to look for significant differences in QoL between the following groups of patients – (a) Hemodialysis (i.e. Stage 5 CKD) patients and non-Hemodialysis (i.e. Stage 2/3/4 CKD) patients, (b) CKD patients with Diabetes and CKD patients without Diabetes, and (c) CKD patients with symptomatic Heart Disease and CKD patients without symptomatic Heart Disease. In addition, any QoL trends that were based on the respective variables of "Stage of CKD", "Age", and "Gender" were also looked for.

Prior to statistical analyses, the three "source" datasets were deemed to be comparable, after ensuring that the definitions of the relevant variables (e.g. the definition of symptomatic Heart Disease) were, as far as practically possible, the same across all of the datasets. In addition, as far as possible, all necessary calculations (e.g. calculations to recode, transform and aggregate the "raw" QoL scores) were performed in exactly the same way across all three datasets.

All of the statistical analyses were carried out, using Statistical Product and Service Solutions (SPSS) software (note – this software used to be known as Statistical Package for the Social Sciences, but with the same acronym). After obtaining the relevant Descriptive Statistics, final statistical analyses were performed, and these included – (a) Comparisons of Means/Medians between groups (accomplished by either parametric tests or non-parametric tests, based on whether the distributions of data points were normal, or not), and (b) Multiple Linear Regression modelling. It may be mentioned that performing both the Comparisons of Means/Medians and the Multiple Linear Regression ought to assist in verifying the results from each respective form of analysis.

At the end of all of the analyses, an understanding of the findings would lead to – (a) definitions of trends, based on significant differences in SF-36 (Domain/Summary) scores between the

relevant groups, (b) interpretation of the observed trends, based on the available data, (c) comparisons of the results with results from related past studies, and (d) suggestions for further research on this topic, and (where applicable) suggestions for improved care of patients who may have one or more of the conditions that were compared, here.

# II. CHRONIC KIDNEY DISEASE AND POSSIBLE ASSOCIATED CO-MORBIDITIES

## II.1 CHRONIC KIDNEY DISEASE

### Definition

Chronic Kidney Disease (CKD) is a loss of kidney function over a period of time, which can range from months to years (note – while progression does occur at some point, progression may have ceased by the time of diagnosis). A lower than normal Glomerular Filtration Rate (GFR) occurs in patients with CKD - this means that the capability of the kidneys to excrete waste products is decreased, and this reduced capability is classified into different stages that will be described in due course.

### Prevalence

In Canada, 1.9 to 2.3 million people are estimated to suffer from CKD.[1] According to a progress report (that is periodically updated, following initiation in 2009) from the Canadian Institute for Health Information (CIHI), the number of patients with Stage 5 CKD (i.e. Kidney Failure) in Canada steadily increased for 20 years before stabilizing at about 40000 patients, from 2009 onwards; the largest increase occurred in patients aged 75 and above who account for about 20% of all Stage 5 CKD patients. The CIHI also reported that, in 2009, out of the total number of Stage 5 CKD patients, approximately 60% were on Dialysis (with about 80% of these being treated with Hemodialysis), and approximately 8% were waiting for a Kidney Transplant. As elsewhere, CKD in Canada is mostly a disease of the elderly with no notable gender-based

differences (note – these CKD patients include those on Dialysis, those who have Kidney Transplants, and those who are waiting for either Dialysis or Kidney Transplantation).

## Causes

The causes of CKD can be classified, as follows (based largely on which particular part of the renal anatomy is involved) –

- Vascular (i.e. a large or small blood vessel supplying or draining the kidney is affected).
- Glomerular (i.e. the glomeruli are involved) – this can be primary (e.g. focal glomerulosclerosis), or secondary due to other diseases (e.g. Diabetes, certain autoimmune disorders, etc.).
- Tubular or tubulointerstitial (i.e. the tubules and interstitium of the kidney are affected by toxins, polycystic disease, etc.).
- Obstructive (i.e. drainage from the kidney is impaired - by kidney stones, for example).
- Infections.

(Note: The most common specific causes of CKD have been shown to be – Diabetes, Hypertension, and Glomerulonephritis[2]).

## Signs

Laboratory and clinical tests may indicate the following (with the frequency and severity of each sign being influenced by both the stage of CKD and the underlying etiology) –

- Increased serum Creatinine.

- Proteinuria, or an increased amount of Protein in the urine (this is prognostically important during all of the stages of CKD).
- Increased blood Urea, which can lead to the more serious conditions of Azotemia, and Uremia.
- Hyperkalemia (i.e. an increase in blood Potassium).
- Hyperphosphatemia (i.e. an increase in blood Phosphates).
- Hypocalcemia (i.e. a reduction in blood Calcium).
- Fluid overload in the body.
- Decreased amounts of Erythropoietin, which leads to Anemia.
- Metabolic acidosis.
- Hypertension.

## Symptoms

Symptoms are uncommon during the early stages of CKD, and the non-specific nature of several symptoms can lead to even patients with advanced CKD being unaware of their condition. However, any symptoms experienced may relate to the issues that are listed, above. The commoner symptoms include the following –

- Lethargy, reduced appetite, and general malaise.
- Symptoms of high blood pressure, such as headaches.
- Fatigue (due to Anemia, among other reasons).

- Nausea.
- Weight loss.
- Itching.
- Bone pain.
- Edema.

## Complications

Several complications (often impacting the heart) can develop, as a consequence of even the initial effects of CKD; the more serious complications include –

- Congestive Heart Failure.
- Pericarditis.
- Cardiac Arrhythmias.
- Ischemic Heart Disease (often leading to "heart attacks"), as a result of increased Atherosclerosis.
- Pulmonary Edema.
- Encephalopathy.
- Secondary Hyperparathyroidism and Renal Osteodystrophy.
- Bleeding from the gastro-intestinal tract.
- Liver damage/failure.

- Infertility/miscarriages.
- Increased risk for cancer, according to certain studies.[3]

## Diagnostic Tests

In the few patients who develop CKD without any prior kidney disease (or any CKD-precipitating disorder), it may be necessary to perform diagnostic tests. It is also important to differentiate CKD from Acute Renal Failure (ARF) because the latter is potentially reversible. Some of the common tests that are used to diagnose CKD (when necessary) are, as follows –

- Measurement of serum Creatinine levels (with gradually increasing levels over months/years being suggestive of CKD).
- Urine analysis for protein, along with measurement of the Albumin to Creatinine ratio in urine (progressive loss of protein indicates worsening of CKD, as well as an increasing risk for Cardiovascular Disease).
- Measurement of blood Urea Nitrogen levels.
- Measurement of serum Electrolyte levels.
- Abdominal ultrasound or Computed Tomography - to check for kidney size and structure.
- Nuclear Imaging (i.e. radio-isotope) scans - to check for kidney function.

## Stages of CKD

Individuals who have a Glomerular Filtration Rate (GFR) <60 mL/min/1.73m$^2$ for, at least, 3 months and/or clear kidney damage are classified as having CKD. These patients are thereby at a

higher risk for total loss of kidney function, along with cardiovascular complications and earlier death.

***TABLE II.1: Summary of the main differentiating features of the various stages of CKD***

| | **Stage 1** | **Stage 2** | **Stage 3** | **Stage 4** | **Stage 5** |
|---|---|---|---|---|---|
| **Amount of kidney function remaining** | More than 90% | 60 to 89% | 30 to 59% | 15 to 29% | Less than 15% |
| **Description** | Early kidney damage with normal or even increased function | Worse kidney damage with reduced function | Even worse kidney damage with less function than during the preceding stage | Severe kidney damage with poor function that is barely enough to keep the patient alive | End-Stage Kidney Disease with kidney function that is insufficient to keep the patient alive |
| **Symptoms** | No symptoms observed; Urea and Creatinine levels are normal (although other markers of kidney damage are seen) | No symptoms observed; Urea and Creatinine levels are normal, or mildly elevated | Early symptoms (e.g. lethargy, itching, and poor appetite) appear; Creatinine level rises, Urea level is high, and Anemia may begin to appear | Symptoms (e.g. lethargy, itching, and poor appetite) may worsen | Symptoms include – poor sleep, difficulty breathing, severe itchiness, and frequent vomiting; Creatinine and Urea levels are very high |
| **GFR level ($mL/min/1.73m^2$)** | 90 or more | 60 to 89 | 30 to 59 | 15 to 29 | Less than 15 |
| **Treatment options** | Identify cause and try to reverse it | Monitor Creatinine, blood pressure, and general health; try to stop/slow the worsening kidney function | Continue to try to stop/slow the worsening kidney function; educate patient about disease / treatment options | Plan and create access site for Dialysis; receive assessment for possible Transplant | Commence Renal Replacement Therapy (Dialysis or Transplantation) |

[*Table is courtesy of – "Clinical Practice Guidelines for Chronic Kidney Disease: evaluation, classification and stratification"; American Journal of Kidney Disease (2002); 39 (Supplement Number 1): S19].

It may be noted that individuals with Stages 1-4 CKD are also sometimes said to have Non-Dialysis Dependent CKD, while those with Stage 5 CKD (who require Dialysis or Renal Transplantation) are said to have End-Stage Kidney Disease.

## Management and Prognosis

There is no true cure for CKD, at present. However, patients with Stages 1–4 CKD require the progression of their disease to Stage 5 to be slowed or halted, and they need to be protected from potential Cardiovascular Disease, too. Some of the common treatments advocated for Stages 1–4 CKD patients (inclusive of treatment for common coexisting conditions, such as Hyperlipidemia and Hypertension) are, as follows –

- Lifestyle changes, such as - dietary modifications, regular exercise, cessation of smoking, control of blood sugar levels, etc.
- Anti-Hypertensive drugs (commonly - Angiotensin Converting Enzyme Inhibitors, or Angiotensin II Receptor Antagonists).
- Erythropoietin Replacement Therapy.
- Calcitriol Replacement Therapy.
- Phosphate Binders.
- Supplementation of certain Vitamins (e.g. Vitamin D) and minerals (e.g. Iron).

However, these medications rarely slow the progression of CKD into Stage 5, for which the only possible treatment is one of these two forms of Renal Replacement Therapy –

- Dialysis (the usual forms of which are – (a) Conventional Hemodialysis, which is performed in a hospital setting for 3-4 hours, three times a week, (b) Daily Hemodialysis, which is usually performed at home for 2 hours on six days per week, (c) Nocturnal Hemodialysis, which is usually performed during sleep in a home or hospital setting for 6-10 hours on three to six days per week, and (d) Peritoneal Dialysis, which is carried out at home by the patient, but which usually requires 4-5 repetitions per day).

- Renal Transplantation (which involves a compatible donor providing a well-functioning kidney).

The prognosis is not good for CKD patients. It has been shown that mortality increases as kidney function decreases, with Cardiovascular Disease being the leading cause of death.[4] While forms of Renal Replacement Therapy (especially Renal Transplantation) significantly prolong the life of Stage 5 CKD patients, they are known to also negatively affect the patients' QoL (especially in the short term, after the particular therapy).[5] However, high intensity "Home Hemodialysis" is reported to both increase survival and provide a better QoL, as compared to other forms of Dialysis.[6]

## Risk and Screening

Studies have shown a higher prevalence of CKD among African-Americans, which could be explained by a higher prevalence of Hypertension in this group; treating Hypertension in those African-Americans who are afflicted with CKD does not appear to slow the progression of the CKD, and this is different from what generally occurs in Caucasians.[7,8] Another pointer to a genetic basis is the higher risk of CKD in individuals who have had close relatives suffer from CKD, too.[8]

Screening for CKD is suggested for people who have the following risk factors –

- Hypertension.
- History of Cardiovascular Disease.
- Diabetes.
- Obesity.
- Age >60 years.
- Certain ethnic groups (African-Americans, First Nations communities, etc.).
- History of past Kidney Disease.
- Close relatives with a history of Kidney Disease.

A referral to a nephrologist would be especially advisable, if the following signs (among others) are present –

- Low and/or progressively decreasing GFR, which is estimated from the serum Creatinine level.
- High Albumin to Creatinine ratio, in the urine.
- Hematuria.
- Uncontrollable high blood pressure.

## II.2 CO-MORBIDITIES THAT ARE FREQUENTLY ASSOCIATED WITH CHRONIC KIDNEY DISEASE

### Diabetes Mellitus

**Definition:** Diabetes Mellitus (simply referred to as – Diabetes) is a metabolic disorder that is characterized by high blood sugar levels, in the affected individual. This occurs due to either insufficiency of the hormone called Insulin, or non-responsiveness of body cells to the effects of Insulin.

**Prevalence:** 285 million people are estimated to be affected by Diabetes, worldwide, with approximately 9 million people in Canada being affected.[9] Type 2 Diabetes in particular is seeing a major increase in industrialized countries, with further great increases envisaged in Asia and Africa.[9]

**Types:** There are three main forms of the disease, plus miscellaneous variants. The types of Diabetes are summarized, as follows –

- Type 1 Diabetes occurs due to insufficient production of Insulin from the pancreas, has a strong genetic basis, is often diagnosed during childhood, and is the type seen in approximately 10% of patients with Diabetes.
- Type 2 Diabetes occurs when the body's cells fail to respond to Insulin, usually manifests itself in older age groups, is often due to lifestyle-related issues like unhealthy diets, and accounts for approximately 90% of all Diabetes cases.
- Gestational Diabetes occurs in women during pregnancy, is often transient, can lead to fetal complications/anomalies, and is reported to occur in 2 to 10% of all pregnancies,

with 5 to 10% of women with Gestational Diabetes being shown to have Type 2 Diabetes, post-pregnancy.[10]

- Other forms of Diabetes include - (a) Latent Autoimmune Diabetes of Adults (LADA), and (b) Prediabetes (which often precedes the manifestation of Type 2 Diabetes).

**Prognosis:** The Canadian Diabetes Association reports that approximately 80% of people with Diabetes will die due to Heart Disease or Stroke, and that Diabetes is a contributing factor in the deaths of about 41,500 Canadians, each year. The life expectancy of people with Diabetes may be shortened by 5 to 15 years, with the greatest reductions in individual life expectancies occurring due to Type 1 (rather than Type 2) Diabetes.[9]

**Effects of Diabetes on the kidneys:** It is estimated that approximately 30% of patients with Type 1 Diabetes will eventually develop Stage 5 CKD, while about 10-40% of patients with Type 2 Diabetes will do so.[11] Diabetes can affect the kidneys (and other components of the urinary tract) in the following ways –

- Diabetic Nephropathy: The small blood vessels in the kidneys are damaged, which leads to salt and water retention in the body, as well as to Proteinuria and decreased excretion of waste products.

- Diabetic Neuropathy: The nerve damage caused by Diabetes can lead to inadequate emptying of urine from the urinary bladder, which can then lead onto kidney damage (due to the back pressure of the urine, and also due to the retrograde infections that may be precipitated by the urinary stasis).

**Signs of Kidney Disease in patients with Diabetes:** When patients with Diabetes develop Kidney Disease, they may exhibit the following signs –

- Albumin and other proteins in the urine (this is usually an early sign of coexistence of both conditions).
- High blood pressure (this is usually an early sign of coexistence of both conditions).
- Edema.
- Increased Urea in blood and increased Creatinine in serum (these are usually late signs of coexistence of both conditions).
- Anemia (this is usually a late sign of coexistence of both conditions).

**Symptoms of Kidney Disease in patients with Diabetes:** When patients with Diabetes develop Kidney Disease, they may experience the following symptoms –

- Swelling and cramps.
- Nocturnal polyuria.
- Nausea and vomiting.
- Weakness, paleness, and itching.
- Lesser need for anti-Diabetic medications.

**Management of patients who have both CKD and Diabetes:** The management of patients with both CKD and Diabetes usually involves the following –

- Anti-Diabetic medication (e.g. Insulin, Metformin, etc.).

- Anti-Hypertensive medication (e.g. Angiotensin Converting Enzyme Inhibitors).
- Specific treatments for any disorders of the urinary tract (such as – infections).
- Following a healthy diet (e.g. restricting the intake of protein, and sugars).
- Ensuring home monitoring (and general awareness) of blood glucose levels and blood pressure.
- Avoidance of any potentially nephrotoxic drugs.
- Renal Replacement Therapy for those patients who have both Diabetes and Stage 5 CKD (Steroid therapy is required, post-transplant, and a higher dose of Insulin is required by some of those who receive donor kidneys, too).
- Pancreatic Transplantation (although rare, this can be done in conjunction with Kidney Transplantation).

## Heart Disease

While Heart Disease actually includes a large number of different sub-divisions, only those specific conditions that come under the heading of "symptomatic Heart Disease" and that could be accurately utilized as variables during this Study will be described in detail. This is advisable because only those CKD patients who have active Heart Disease at the time when their QoL is measured can definitely be said to have both CKD and the co-morbidity of Heart Disease (however, the form of Heart Disease cannot be truly acute because patients will not be expected to have their QoL measured during medical emergencies). The conditions in focus are – Ischemic Heart Disease and Heart Failure, which together are estimated to affect 5% of all Canadians aged greater than 12 years (based on prior cross-sectional self-reporting).[12]

## ***Ischemic Heart Disease***

***Definition:*** Ischemic Heart Disease (IHD) is characterized by a reduction in the blood flow to the muscle of the heart. This reduced blood flow is due to spasm or obstruction of the coronary arteries that supply the muscle of the heart.

***Prevalence:*** Based on cross-sectional self-reporting in Canada, it was once estimated that (among Canadians of 12 years of age, and older) 2.1% had had a Myocardial Infarction, with 1.9% having Angina Pectoris.[12] The incidence of IHD increases as age increases, and IHD is commoner in males, overall (however the incidence rates in males and females become similar, after menopause).

***Manifestations:*** IHD can lead to – (a) Angina Pectoris, which can range in severity from the stable form to the unstable form, and which basically is chest pain due to ischemia of the heart muscle (breathlessness, nausea, and sweating may be associated with this chest pain, too) and/or (b) Acute conditions (which are medical emergencies), with Myocardial Infarction being the most serious of these because it involves death of part of the heart muscle, and often precipitates the following symptoms – severe radiating chest pain, breathlessness, palpitations, sweating, nausea, and even loss of consciousness that may be followed by death (however, non-symptomatic Myocardial Infarctions are known to occur, as well[13]).

***Prognosis:*** The prognosis varies according to the symptoms of the individual patient, as well as the presence/absence of various risk factors. General prognostic trends include –

- Angina Pectoris is often the presenting symptom of IHD (especially in women); the mortality rate at 5 years, post-onset of Angina is approximately 5%, and men with Angina

are at a greater risk (compared to women with Angina) for Myocardial Infarction and IHD-related death.[14]

- The prognosis after a Myocardial Infarction varies. Predictive prognostic value is assigned to factors like - age, hemodynamic parameters (systolic blood pressure, left ventricular ejection fraction, etc.), ST-segment changes on the Electrocardiogram, elevated cardiac markers, and a few others.[15] The mortality rate after Myocardial Infarctions has decreased over time, but it is estimated that just over 12% of all annual deaths (worldwide) are due to Myocardial Infarctions, with it being the leading cause of death in "high/middle income" countries.[16] In the United States, median mortality at 30 days after a Myocardial Infarction ranges from 10 to 25%.[17] In Canada, it is estimated that there are 70000 Myocardial Infarctions per year, with 16000 Canadians dying each year, as a result of that (the majority of deaths are out of hospital).[18]

Globally, approximately 7 million people suffer IHD-related acute events, each year,[19] and it is predicted that Disability Adjusted Life Years (DALYs) lost to IHD will account for 5.5% of total DALYs in 2030 (making IHD the second leading cause of disability, and the leading cause of death, at that time).[16] In total, slightly more women than men die of IHD due to women generally living for longer, as compared to men.[20]

## ***Heart Failure***

***Definition:*** Heart Failure (also known as - Congestive Heart Failure) refers to a serious condition in which the heart is unable to pump out sufficient amounts of blood to meet the body's requirements.

***Prevalence:*** It is estimated that about 500000 Canadians are living with Heart Failure, with 50000 being newly diagnosed with the condition, each year.[18] Based on cross-sectional self-reporting in Canada, it was once estimated that (among Canadians of 12 years of age, and older) 1% were living with Heart Failure.[12] The prevalence rate is much higher in those over 65 years of age, and certain ethnic groups (e.g. African-Americans) have higher prevalence rates, too.

***Types:*** Based on anatomy, there are two types of Heart Failure, which are the following –

- Right-sided Failure, in which the heart cannot pump out sufficient blood to the lungs for the purpose of getting oxygenated (this is often due to incomplete filling up of the heart with blood).
- Left-sided Failure, in which the heart cannot pump out sufficient oxygenated blood to the rest of the body.

***Prognosis:*** The prognosis for patients with Heart Failure is generally not good. The following statistics from the Canadian Cardiovascular Society would support the preceding statement[18] –

- The average annual mortality rate for Heart Failure is 10% per year.
- The five-year survival rate for Heart Failure is 50%.
- Severity of presenting symptoms, level of heart dysfunction, age, and some other factors all help to determine the prognosis for individual patients, but up to 50% of patients with Heart Failure will die within 5 years of the diagnosis.

**Relationship between CKD and Heart Disease:** It has been shown that chronic dysfunction of the kidneys is closely associated with the following disorders that (i) affect the vasculature, and (ii) can lead to serious heart-related conditions –

- Atherosclerosis (i.e. thickening of the walls of arteries due to the formation of "plaques", which are accumulations of cholesterol plus other fatty substances and calcium) – this can lead to a compromise in the arterial blood supply to the heart muscle.

- Hypertension (i.e. increased pressure required to propel the blood within arteries) – this can weaken the walls of arteries, and also compromise the arterial blood supply to the heart muscle.

(It should be mentioned that certain less-conspicuous abnormalities that are associated with CKD can also increase the risk of developing Heart Disease, and these abnormalities are – (a) Dyslipidemia; as a result of lipoprotein metabolism being altered during CKD, increases of fatty substances like Cholesterol can occur within the blood, and those increases can subsequently lead to Atherosclerosis and IHD, and (b) Inflammation; as a result of certain metabolic pathways being altered during CKD, inflammatory changes that affect the arterial walls can follow, thereby potentially leading to arterial damage and IHD, in due course).

**Specific complications of CKD that have an impact on the heart:** CKD can lead to certain complications (which can indirectly impact the workings of the heart); the notable complications are explained, as follows –

- Hypertension – A hormone called Renin is produced by the kidneys, and Renin is part of a hormone chain that acts to increase blood pressure whenever necessary; however, impaired kidneys can over-secrete Renin, leading to unnecessarily high blood pressure (this can then cause IHD, Heart Failure, Strokes, and even reduce arterial blood perfusion to the kidneys in a round-about way).

- Anemia – A hormone called Erythropoietin is produced in the kidneys, and is responsible for stimulating the production of Red Blood Cells from the bone marrow, but impaired production of Erythropoietin due to dysfunctional kidneys can ultimately lead to a deficiency of Red Blood Cells and Hemoglobin; thus, the heart muscle may receive insufficient oxygen, while parts of the heart muscle may also hypertrophy when the heart attempts to compensate for the systemic oxygen deficit by pumping out more blood (note - IHD can result from the impaired oxygenation of the heart muscle, while Heart Failure can result from the hypertrophy of the heart muscle).

- Hyperglycemia: If Diabetes already exists in a patient with CKD, the increased blood sugar can result in damage to the arteries that supply the heart (as well as the kidneys, and other organs); this can lead on to IHD, and potentially to Heart Failure, after that.

- Mineral imbalance: High levels of Calcium and Phosphorous in the blood have been linked to Atherosclerosis of the coronary arteries (and even to bone formation within the walls of said arteries);[21] therefore, when improperly-functioning kidneys are unable to excrete excess amounts of Calcium and Phosphorus, IHD could result.

- Homocysteine imbalance: Excess levels of an amino-acid called Homocysteine have been linked to Atherosclerosis and clot formation because high levels of this amino-acid can lead to both the build-up of "plaques" on the walls of arteries, and the damage of the arterial walls;[22] as dysfunctional kidneys cannot adequately regulate the amounts of Homocysteine in the blood, IHD (including Myocardial Infarctions) and Strokes could result when CKD is associated with high Homocysteine levels.

**Management of patients who have both CKD and Heart Disease:** The management of patients who have both CKD and Heart Disease usually includes the following guidelines, irrespective of how each of the conditions are caused -

- Regular monitoring of – (a) Renal parameters (primarily - Urea and Creatinine levels), (b) Heart function, (c) Serum electrolytes, and (d) Blood pressure.
- A prescribed regimen of exercise and diet (usually designed with the help of a dietician).
- Medications for any complications (such as - Hypertension, Diabetes, Hypercholesterolemia, etc.).
- Renal Replacement Therapy when the kidneys go into "failure" mode (i.e. Stage 5 CKD).
- Treatments for IHD can vary from anti-Angina medications (e.g. Nitroglycerin and other Vasodilators, Calcium Channel Blockers, Beta Blockers, etc.) to immediate treatments for Myocardial Infarctions (e.g. Fibrinolysis, and even interventional procedures to remove coronary artery clots), while Heart Failure is usually treated with medications (e.g. Angiotensin Converting Enzyme Inhibitors, Diuretics, Vasodilators, etc.).

## Other Cardiovascular conditions (associated with Chronic Kidney Disease) that can be analysed

Based on the available data, the Cardiovascular conditions of Stroke and Peripheral Vascular Disease could also be used as independent variables to predict respective aspects of the QoL of CKD patients. It ought to be mentioned that both Stroke and Peripheral Vascular Disease (particularly when the latter involves arteries) are often due to Atherosclerosis, Hypertension, and Hypercholesterolemia (which are all associated with CKD); as a result, just as CKD patients

are at an increased risk for Heart Disease, they are also at an increased risk for other forms of Cardiovascular Disease, such as Stroke and Peripheral Vascular Disease. The hemostatic imbalances associated with CKD and the reduced amounts of physical activity that is associated with any chronic disorder could also lead to venous conditions, which are part of the Peripheral Vascular Disease spectrum.

## ***Stroke***

A Stroke occurs when the blood supply to a part of the brain ceases, leading to death of the brain cells in that area of supply. Strokes are medical emergencies.

There are approximately 50000 Strokes in Canada, every year, and about 315000 Canadians are living with the effects of Strokes.[18]

CKD is associated with a high risk for Strokes, considering that several of the CKD-associated factors (Hypertension, Atherosclerosis, Anemia, Diabetes, Hypercholesterolemia, Hyperhomocystinemia, etc.) are risk factors for Strokes.[23]

There are generally three types of Strokes – (a) Ischemic Strokes, which are the commonest type, and which occur when a blood clot (thrombus or embolus) blocks an artery that supplies the brain (or a region of the brain), (b) Hemorrhagic Strokes, which occur when a blood vessel ruptures and bleeds into the brain, and (c) Transient Ischemic Attacks, which are brief interruptions of the blood flow to the brain (or a region of the brain) that do not cause lasting cell death or symptoms, but do indicate an impending major Stroke. The origins of up to 40% of ischemic Strokes are unknown.[24]

Strokes are usually caused by cardiac disorders and/or vascular disorders, and the common causes include – (a) Atherosclerosis in arteries, (b) Sickle-cell Anemia, (c) Arrhythmias, (d) Dysfunctions of Heart Valves, (e) Endocarditis, (f) Hypertension, and (g) Vascular Malformations within the brain.

The signs and symptoms depend on which regions of the brain are specifically affected. The commonest symptoms of a Stroke are – (a) weakness and/or numbness on one side of the body, (b) confusion and lack of comprehension, (c) difficulty in speaking, (d) visual problems, (e) loss of balance and coordination, (f) dizziness, (g) loss of sensation on one side of the body, and (h) severe headaches.

After immediate medical or surgical treatment to remove the thrombus/embolus (or to treat the cause of the bleed when a Hemorrhagic Stroke occurs), long-term management of Stroke patients involves Rehabilitation Therapy, which includes – (a) nursing care, even when at home, (b) physical therapy, (c) speech therapy, (d) occupational therapy, (e) use of artificial appliances (e.g. Wheelchairs), and (f) elimination or control of the risk factors for a subsequent Stroke (e.g. Diabetes, Hypertension, Heart Disease, Hypercholesterolemia, etc.).

The prognosis for Stroke patients is generally not good. In about 75% of patients, Strokes cause disabilities that are sufficient to reduce employability.[25] Apart from physical and mental problems, Strokes also lead to emotional problems, with 30 to 50% of Stroke survivors suffering from post-Stroke depression.[26] Cognitive deficits and psychological problems (post-Stroke) are more likely in older patients, in patients with pre-Stroke brain pathology, and in patients with pre-Stroke psychiatric problems.[27] Up to 10% of patients suffer seizures, post-Stroke, too.[28] Worldwide, Stroke is the second most frequent cause of death (after Heart Disease), and

accounted for about 11% of total deaths in 2008.[29] In Canada, Stroke is the third leading cause of death (6% of all deaths), and approximately 14000 Canadians die from Strokes, each year. The risk of a Stroke increases with age, and men are more likely than women to suffer Strokes (although more women die from Strokes because they are usually older when afflicted).[30]

## ***Peripheral Vascular Disease***

Peripheral Vascular Disease (PVD) is a spectrum that refers to damage or blockage of blood vessels (arteries or veins) that are distant from the heart.

The prevalence of PVD worldwide is 12 to 14%, with up to 20% of those over 70 years of age being affected; up to 80% of affected individuals are asymptomatic, though.[31]

PVD can be arterial or venous.[32] The commonest arterial diseases classified under PVD include – Arterial Blockages, and Aortic Aneurysms (i.e. bulges in the wall of the aorta, usually involving the abdominal portion of that large vessel). The commonest venous diseases classified under PVD involve blood clots in veins, with Deep Vein Thrombosis (i.e. clot formation in the deep veins of the leg) being the most serious condition out of those; Deep Vein Thrombosis affects 1 in 1000 adults, per year.[33]

Peripheral Arterial Blockages (and the resulting ischemia) often begin in the legs and are usually caused by Atherosclerosis, which indicates that patients with CKD are at risk for PVD. Aortic Aneurysms can result from Atherosclerosis, high blood pressure, certain infections, and smoking; however, they can also be congenital in origin, or be precipitated by certain predisposing diseases (e.g. Marfan's Syndrome). Venous clots are commonly caused by slow blood flow to the lower extremities, and the slow flow (in turn) could be caused by physical inactivity, smoking, high blood pressure, Diabetes, Heart Disease, pregnancy, tumors, or certain hormones.

Depending on where the block is, Peripheral Arterial Blockages can lead to pain that gets worse during exertion; this pain (the severity of which indicates the seriousness of the block) is called Intermittent Claudication, and disease progression can lead on to Cyanosis and Gangrene, with the latter necessitating an amputation. Other serious conditions that can be linked to blockages in peripheral arteries include – Strokes, Transient Ischemic Attacks, Kidney Disease, and Heart Disease. An Aortic Aneurysm can cause breathlessness, pain in the back, and referred pain to the shoulders; rupture of an Aortic Aneurysm is a life-threatening emergency due to the massive bleeding. Clots in the deep veins of the leg can cause pain, swelling, redness and warmth around the affected areas (usually – calves and ankles); these clots can break free, travel to the lungs, and cause death by impeding the blood flow to the lungs (i.e. Pulmonary Embolism).

Peripheral Arterial Blockages that are not severe can be managed by controlling the risk factors (e.g. Diabetes, excess weight associated with Hypercholesterolemia, smoking, etc.); in more severe cases, Angioplasty/Stent Procedures or Bypass surgeries are performed. Surgery is required for Aortic Aneurysms that are close to the heart; for Aneurysms further away from the heart, the size determines whether surgery (to strengthen the weak arterial wall with a graft) or simple monitoring is the best option. Venous clots in the legs require anticoagulant therapy, as well as rest (lying down with raised legs during the periods of continuous rest is also helpful).

# III. QUALITY OF LIFE WITHIN THE FIELD OF HEALTHCARE

## III.1 CONCEPTS

In 1946, the constitution of the World Health Organization (WHO) defined health as "a state of complete physical, mental, and social well-being, and not merely the absence of disease or infirmity".

Quality of Life (QoL) generally refers to someone's well-being as a whole, and it includes all aspects of that person's life (i.e. the physical, mental, and social aspects, plus the correlates of those aspects – socioeconomic status, health risk factors, etc.). In the field of healthcare, QoL generally refers to how an individual's well-being is affected by a specific medical condition.

Unlike earlier when public health was evaluated using measures of mortality and morbidity, public health is now understood to comprise several dimensions. Therefore, as treatments to save lives improved over time, it was also deemed important to improve the QoL of those individuals under care – this way, both the years of survival and the QoL during those years would increase, together. And, measuring the QoL of such patients is a necessary first step.

It is now accepted that the measurement of an individual's QoL should be based on that individual's own perceptions. This prevents the inconsistent subjectivity that is associated with any external rating (by a physician, for instance), and it also means that a subject can rate his/her situation based on his/her own expectations. So, QoL for practical purposes can be defined as – "a broad multi-dimensional concept that usually includes subjective evaluations of both positive and negative aspects of life".[34] The Centers for Disease Control and Prevention (CDC) in the

U.S. has defined Health-Related Quality of Life as – "an individual's or group's perceived physical and mental health over time."

It is often advantageous to measure the QoL of an individual at different points in time (while he/she is still affected by the same medical condition), in order to see if changes in lifestyle or treatment have a positive/negative effect on his/her QoL; for this reason, as well, self-rating is best because it maintains the consistency of the rater.

## III.2 QUESTIONNAIRES

As a result of the benefits of self-rating, hundreds of patient-based questionnaires have been created to measure (health-related) QoL. These questionnaires are usually all-encompassing, covering the physical, emotional, social, and cognitive aspects of a patient's life; in addition, specific questions (disorder-related, medication-related, profession-related, finance-related, etc.) are also included in some of these QoL questionnaires.

Since subjective evaluations of several different dimensions (physical health, mental health, etc.) have to be part of any QoL measurement, techniques must be designed to define and measure these dimensions; the ways by which the respective dimensions relate to each other must be understood, too. In the field of healthcare, many QoL questionnaires have been developed, tested for validity/reliability, and then used as QoL-measuring instruments. These questionnaires generally fall into one of the following two categories –

- Generic instruments that include general health-related questions - these are relevant to patients suffering from almost any medical condition (examples of these instruments are -

the Ferrans and Powers Quality of Life Index, the Sickness Impact Profile, the Nottingham Health Profile, the Health Utilities Index, and the various Medical Outcomes Study Short Form (SF) questionnaires).

- Disorder-specific instruments - these include questions, which only pertain to one particular medical condition (examples of this are - the Migraine-Specific Quality of Life Questionnaire, the Adult Asthma Quality of Life Questionnaire, and the QLQ-LC13 Module for patients with Lung Cancer).

It may be noted that certain QoL instruments include both general health-related questions and disorder-specific questions in the same questionnaire (an example of this is the Kidney Disease Quality Of Life or KDQOL instrument).

Some simple generic QoL questionnaires that are frequently used (due to their short length and the simplicity of their questions) are – (a) Healthy Day Measures (which is used by the CDC, and which has only four basic questions), (b) Manchester Short Assessment of Quality of Life (which has sixteen questions, and which is used among psychiatric patients), and (c) WHOQOL-BREF (which has been translated for use in several different countries/languages, and which contains twenty-six basic questions).

## III.3 BENEFITS

Measuring QoL is useful for these reasons – (a) Measurement of QoL shows the levels of impact that various diseases/disabilities have on the population, (b) Treatment options for future patients can be better defined when treatment effects on the QoL of historical patients are understood, (c)

QoL data are important to obtain while conducting certain forms of research (e.g. during randomized controlled studies about community health services, and during clinical trials to test experimental therapies), (d) QoL data are necessary when comparing the effectiveness (including the cost-effectiveness) of various forms of therapy, (e) Tracking a community's overall health over a period of time requires QoL data, in addition to the statistics of mortality and morbidity, (f) Identifying population sub-groups with poor perceived health requires an analysis of QoL data, (g) Health policy decisions (e.g. decisions pertaining to fund allocation when attempting to enhance the health of a particular population sub-group) require QoL data as a guide, (h) Analysis of QoL data provides useful insights about the relationship between QoL trends and the risk factors for certain diseases, and this, in turn, can lead to initiatives to combat those diseases, (i) QoL data can also relate self-reported chronic diseases (Diabetes, Hypertension, etc.) to respective risk factors (smoking, sedentary lifestyle, etc.) because personal habits are covered by several QoL-measuring instruments,[35] (j) Surveillance in a community to see if certain healthcare interventions are being successful also requires QoL data, (k) QoL measurements are particularly important in the elderly - as life expectancy increases, ways to make the increased living years more worthwhile are sought after, as well, (l) Health-related QoL information can help to co-ordinate the different forms of medical services (psychiatric, physical, etc.), along with social services, (m) QoL information also helps those who are indirectly involved with healthcare (e.g. community planners, investors in pharmaceutical companies, charities, etc.) to contribute superior services and policy ideas,[36] (n) Self-assessed health status has also been shown to be a more powerful predictor of mortality and morbidity than many objective measurements,[37] and (o) In several jurisdictions, QoL improvement is now a central public health goal (in the U.S., this is evidenced by the government's Healthy People 2020 publication).

## III.4 DRAWBACKS

As with any kind of measurement, there are obvious limitations, with regards to QoL measures, too, and these include – (a) Perceptions of life and health can vary widely among individuals with even the exact same disease/symptoms (especially when subjective self-ratings are concerned), thus potentially leading to "outliers" in datasets, (b) Allowance has to be made for the fact that even though different dimensions of health (physical, mental, social, etc.) may be measured separately, they all correlate with each other to varying extents, in every individual, (c) Since (health-related) QoL-measuring instruments almost exclusively comprise health-related questions, other factors (e.g. jobs, religious beliefs, family support, neighbourhoods, ethnicity-based culture, etc.) that can also cause variations in an individual's QoL are often left unaccounted for, (d) It has been theorized that the "channel capacity" (i.e. the maximum amount of information that can be assimilated) of humans can impede the consistency of responses and skew the results, especially when long/complex questionnaires are used,[38] (e) In cross-sectional studies where answers to a QoL questionnaire are only utilized from one point in time, more allowances must be made for inconsistency of answers (as a discomfort may affect the individual at that particular moment, for example), (f) In longitudinal studies, there is always the possibility that an individual's views/perceptions/expectations will change over the course of a Study (this is called "Response Shift Bias"),[39] (g) In longitudinal studies that look at the effects of interventions, there are potential issues during statistical analysis, as a result of "ceiling" effects (i.e. patients who start with a higher QoL than the average patient do not have much room for post-intervention improvement, but have more chances of post-intervention worsening) and "floor" effects (i.e. patients who start with a lower QoL than the average patient have much more room for post-intervention improvement, but have less chances of post-intervention

worsening),[40] (h) The determination of which one of the many QoL questionnaires to administer to a particular sample population is rarely perfect because (especially in the elderly) two or more medical conditions can co-exist at the same time, thus necessitating questions that can somehow cover disparate symptoms, (i) Confounding variables (e.g. Age, Income, etc.) often need to be accounted for before the relationship between QoL and a medical condition is suggested, and (j) Summary scores are frequently calculated, in order obtain a single representative value for several QoL Domains (i.e. aspects) combined; however, these Summary scores must be calculated and interpreted with care because they can be influenced by Domains that they are not actually summarizing (Summary scores are also computed via comparisons with "norm" scores, but the "norm" scores are based on relatively small "non-diseased" population samples, which vary from country to country).

## III.5 ENHANCEMENTS

To overcome the difficulties associated with QoL measurements, the following steps can be taken whenever possible – (a) Increase the sample size for the Study, so that any discrepancies/outliers do not exert undue influence on the overall results, (b) Adhere to strict pre-defined inclusion/exclusion criteria, (c) In the case of longitudinal studies, try to ensure that the follow-up period and the number of times when the questionnaire is administered are exactly the same for everyone in the sample, (d) Analyse not just any Summary outcome variables (e.g. the Physical Component Summary and Mental Component Summary scores that arise from the SF-36 instrument's eight Domains), but also the constituent Domains (e.g. Pain, Vitality, etc.) of those Summary scores – that way, a broader picture of how a certain medical condition affects

each individual Domain can also be ascertained, (e) If applicable, use more than one method for statistical analysis to answer an identical question, just to reinforce/crosscheck the results of each method, (f) Compare and contrast the results of the QoL analysis with the results from other similar studies, so that the validity of the latest results can be demonstrated (the similarity of studies will be determined by – demographic factors, the medical condition being studied, the QoL questionnaire being used, the patient setting, etc.), (g) Whenever QoL Summary scores need to be calculated, it is best to compute them, based on "norm" values from the same country that the population being studied is in, and (h) Design a new QoL-measuring instrument and test it for reliability and validity, in case no satisfactory instrument currently exists for individuals with a particular medical condition of interest.

## III.6 PROGRESS

There have been many advancements with the aim of improving QoL-measuring practices, and examples of these include – (a) Attempts to standardize QoL measures in certain jurisdictions (e.g. the Healthy Day Measures was developed and validated, thanks to a coordinated effort by five U.S. government bodies, in the 1990s[41]), (b) More and more research is being done to study various QoL-measuring instruments, in order to check their respective benefits and drawbacks, (c) New techniques are being developed to better understand the various dimensions that constitute QoL, and to see how these dimensions relate to each other, and (d) The ethics governing studies that measure QoL have progressed over time, and some now argue that decisions on the continuation/termination of a life should be based on the QoL that the individual can potentially have, rather than on the "sanctity of life" concept.[42]

# IV. INSTRUMENTS USED TO MEASURE HEALTH-RELATED QUALITY OF LIFE

## IV.1 CONCEPTS

A questionnaire used in a clinical setting that elicits responses directly from the patient can be classified under the umbrella of – "Patient Reported Outcomes". As such, it is designed to only obtain the views of the patient (about certain outcomes), and can be administered via an interview, in case the patient cannot fill out the answers to the survey on his/her own.

A questionnaire can assess a single construct (or characteristic), or multiple constructs. If it measures a single construct, it is called uni-dimensional. However, in healthcare, the most frequently used QoL-measuring instruments are multi-dimensional questionnaires with several Domains (which are also known as – Scales or Subscales, depending on the literature); each Domain is scored and reported, differently. In some instances, one final "Summary" score can be derived from several individual Domain scores with the help of the procedure known as Factor Analysis.[43] Generic Health-Related Quality of Life questionnaires usually include Domains that cover – general health perceptions, physical/mental/social functioning, non-specific symptoms (e.g. Pain), and overall quality of life (based on - ability to perform day-to-day activities, emotional status, etc.). Disease-specific questionnaires, in addition to the afore-mentioned Domains, usually focus on – health status, specific symptoms of the disease, impairments associated with the disease, and perceptions of the care being provided. Attempts are being made to create shorter and easier-to-use questionnaires that can effectively and regularly monitor patients' QoL.[44] The objective of these attempts is to have a simple and easy way for patients to assess their own health status, all while the data is being aggregated and checked for sensitivity.

Of course, advances in psychometrics will also be necessary to ensure that the psychometric properties (reliability, internal consistency, validity, and responsiveness) of these newer questionnaires meet the appropriate standards.

## IV.2 REQUIREMENTS

Before any QoL-measuring instrument (i.e. questionnaire) can be used in a population, it must meet certain standards, pertaining to its development, its psychometric properties, and its scaling/scoring methods. The requisites for a satisfactory QoL-measuring instrument include – (a) A sound theoretical basis; the definition of what QoL means to the instrument's architects has to be shown to be reasonable, and the theory/model behind the instrument will be important when the instrument is subsequently checked for validity,[45] (b) Relevant content/wording in the instrument; this ought to be based on interview responses from the target population,[46] thus ensuring that specific concerns of the relevant population (in their own words) are included,[47] while also ensuring that linguistic and cultural factors in the target population are taken into account, (c) Acceptability of the instrument to the target group(s); the response rate will be greater whenever a target population believes that the instrument is truly relevant to their particular health status (therefore, it is sometimes unwise to use a generic QoL-measuring instrument on a group of patients with one specific disease), (d) Equivalence of subsequent translations into other languages; a validated instrument can be translated into another language, as long as the psychometric properties do not change, and as long as the translation's wording/format accommodates local linguistic idiosyncrasies and culture (therefore, technical word-for-word translations are often inappropriate), (e) Reliability; the results of the measuring

instrument must be reproducible (i.e. with negligible differences during random measurements on the same population) for it to correctly show changes in anyone's QoL, and this means that scores ought to be consistent, after repeated use of the instrument on a target population, (f) Internal consistency, which can be evaluated by the Cronbach's Alpha coefficient; it is important to ascertain how closely items (i.e. questions) that measure the same construct are related (an interrelationship between items is necessary, but a very strong relationship means that an item in the instrument is redundant[45]), (g) Uni-dimensionality, which should be assessed by Rasch analysis;[48] every Domain in an instrument must cover only one construct because each Domain score should indicate valid changes in only one particular construct, (h) Face validity; members of the target populations should be interviewed to ensure that the instrument is understandable, suitable, comprehensive, and relevant (as per the perceptions of said target populations), (i) Construct validity, which means that the instrument measures the construct that is was designed to measure; this can be verified via comparison with other similar instruments (as long as the comparators are themselves valid and reliable), or via correlations with the status of patients who are at different stages of the disease in question, (j) Sensitivity; an instrument should be able to detect even small changes in any construct that it is designed to measure (therefore, it should be reliable, and also cover all aspects of the construct), and (k) Feasibility, which means that the instrument must be easy to administer, and also easy for the target individuals to answer; in order to minimize "missing" or inaccurate data points, the mode of administration ought to be simple (e.g. self-administration) and consistent, in all situations.

## IV.3 THE MEDICAL OUTCOMES STUDY SHORT FORM 36 (SF-36) HEALTH SURVEY

For this Study, the instrument of principal interest is the SF-36, which is a multi-purpose Health Survey that was developed as part of the Medical Outcomes Study – this was a two-year Study of patients with chronic conditions (Ware J.E. and Sherbourne C.D.; Health Institute, Boston; 1992). Following the design of the SF-36, the RAND Corporation[49] (a non-profit American research institution that was part of the original Study) put out a version of the original SF-36 instrument called the RAND SF-36. This RAND SF-36 instrument contains the exact same questions as the original SF-36 instrument, although the scoring instructions recommended for the RAND SF-36 are slightly different. The original SF-36 instrument (and the proprietary software for scoring it) can only be obtained commercially by an individual/group with a pre-approved license from the Medical Outcomes Trust, which comprises a group of researchers from the original Study; it may be noted that the Medical Outcomes Trust has subsequently merged their SF-36 licensing/registration programs with Qualitymetric Incorporated[50] (who are now responsible for evaluating SF-36 license applications). On the other hand, the RAND SF-36 questionnaire (and the scoring instructions for it) can be obtained for free by any interested individual/group. As a result of being freely available, the RAND SF-36 is now purported to be the most widely-used generic (health-related) QoL measure in the world.[51] Earlier, in 2002, De Haan stated that the SF-36 (all versions) was the most commonly used generic instrument for measuring (health-related) QoL.[52] The RAND SF-36 instrument has been translated into many languages, although not all translations have been deemed to be equivalent to the original; the most systematic efforts to produce equivalent, validated and culturally-cognizant translations were undertaken by the International Quality of Life Assessment (IQOLA) Project, which

enabled satisfactory translations to be used in more than fifty countries (including in other English-speaking countries).[53] As compared to version 1 (which was released in standard form, in 1990)[54], version 2 of the SF-36 (which was released in standard form, in 1996)[54] is supposed to enable more precise scoring, while being easier to understand/answer;[55] version 2 also has a better layout, improved wording, and more uniform response options[54] (for example – the phrase "full of pep" was changed to "full of life" in the latter version, while sixteen items were made to be more consistent with other items in the instrument by having their 2-level and 6-level response options all changed to 5-level response options). The RAND SF-36 instrument takes about 7-10 minutes to self-administer, although it can also be administered via a computer, or by a trained interviewer (in person or via telephone).[51] All of the SF-36 questionnaires (including the RAND SF-36) have been designed with both 1-week recall and 4-week recall options for twenty of the thirty-six items (i.e, subjects have to answer those questions, based on their experiences during either the preceding week, or the preceding 4 weeks). In addition to being more commonly used and totally free to obtain, the RAND SF-36 also uses a simpler and more straightforward scoring algorithm that has been deemed to be superior to the original SF-36 scoring algorithm[56].

This Study will be based on - (i) the RAND SF-36 4-week recall questionnaire (as dictated by the Study data), (ii) the format of version 1 of the SF-36 (as dictated by the Study data), and (iii) the RAND SF-36 scoring instructions (as dictated by the majority of the Study data, and also by the recommendations from the literature).

The RAND SF-36 instrument is a 36-item generic measure of Health-related Quality of Life (QoL) that measures eight constructs via eight different Domains (or Scales), which are –

- Physical Functioning (PF): Calculated from the answers to questions 3 to 12.
- Role limitations due to Physical Health (RP): Calculated from the answers to questions 13 to 16.
- Bodily Pain (BP): Calculated from the answers to questions 21 to 22.
- General Health (GH): Calculated from the answers to questions 1, 33, 34, 35 and 36.
- Vitality or Energy/Fatigue (VT): Calculated from the answers to questions 23, 27, 29 and 31.
- Social Functioning (SF): Calculated from the answers to questions 20 and 32.
- Role limitations due to Emotional Health (RE): Calculated from the answers to questions 17 to 19.
- Mental Health or Emotional Well-being (MH): Calculated from the answers to questions 24, 25, 26, 28 and 30.

All thirty-six questions are scored on a scale from 0 to 100, although the pattern of scoring varies from question to question. The scores from a subject's answers to the various questions under each particular Domain are averaged to create an aggregate score for each Domain (PF, RP, etc.); each of the eight Domains can have a minimum aggregate score of 0 and a maximum aggregate score of 100. The answers to thirty-five out of the thirty-six questions in the instrument are used to calculate the respective Domain scores via the specialized scoring algorithm; however Question # 2 is only aimed at finding out how the subject rates his/her current overall health status, in comparison to his/her overall health status at a year ago. For each question and also for each Domain, a score of 100 represents the highest possible level of functioning, and a score of 0

represents the lowest possible level of functioning; therefore, a score that is 100 or close to 100 indicates a favourable perception by the subject of his/her status, regarding that particular question or Domain. In case a subject fails to answer all of the questions that come under a particular Domain, the aggregate score for that Domain can still be calculated, as long as a majority of questions that constitute that Domain have been answered (for example – if only two of the three questions under the Domain of RE have been answered, the aggregate score for RE can be computed by averaging the scores for the available two answers).[57]

The eight Domains listed above can be used to calculate two psychometrically-based "Summary" scores. These Summary scores were created, in order to simplify the statistical comparisons required during any analysis of SF-36 scores (i.e. instead of comparing all eight Domain scores between respective populations, just two Summary scores would suffice for the same purpose). These two Summary scores/measures are –

- Physical Component Summary (PCS) score.
- Mental Component Summary (MCS) score.

The PCS and MCS scores for each subject are calculated, based on country-based "norms" where 50 (Standard Deviation = 10) is taken to be the mean of the "norm" (i.e. non-diseased) population. These PCS and MCS scores can be calculated via computerized Norm-Based Scoring (NBS) calculators, or manually. In any event, the calculation of the Summary scores for each subject involves this 3-step process[58] – (i) Firstly, all eight Domain scores are standardized using a linear Z-score transformation (while calculating the Z-scores, only Domain means and standard deviations pertaining to the Study population's own country should be used); (ii) Secondly, the Z-scores are multiplied by the Domain factor score coefficients for PCS and MCS (which are

available in Tables from J. E. Ware, et al.) and summed over all eight Domains, so that there is a PCS summed score and an MCS summed score; (iii) Thirdly, T-scores are calculated by multiplying the respective PCS and MCS sums (which were just obtained) by 10, before adding 50 to the respective products (thereby ensuring a mean of 50 and a Standard Deviation of 10 for the "norm" population).

The PCS score is primarily dependent on the Domains of PF, RP, and BP (as these Domains correlate most strongly with physical health), while the MCS score is primarily dependent on the Domains of MH, RE, and SF (as these Domains correlate most strongly with mental health). The GH and VT Domains correlate strongly with both physical and mental health. It should also be mentioned that the Domain of SF has a significant correlation with physical health, too.

Some other noteworthy points about the SF-36 instrument are –

- Even though the SF-36 instrument is a generic one, it has been used in both general and disease-specific populations to compare relative burdens of diseases, and also to compare the benefits of different forms of treatment in a population; the conditions most often studied with the help of the SF-36 instrument are chronic conditions (e.g. Cancer, Cardiovascular Disease, Chronic Kidney Disease, Diabetes, HIV/AIDS, Hypertension, Rheumatoid Arthritis, Stroke, etc.).[54]

- By 2003, the SF-36 had been mentioned in more than 4000 articles covering more than 200 different conditions (with more than 500 articles in more than 20 countries mentioning a translated version of the SF-36 as a primary QoL-measuring instrument).[54]

- The SF-36 was designed to be a relatively short Health Survey, and was based on the 149-item Functioning and Well-Being Profile (FWBP)[59], which was itself based on

previously-constructed and widely-used instruments, such as the General Psychological Well-Being Inventory (GPWBI).[60]

- Out of forty constructs measured in the Medical Outcomes Study, the final eight Domains chosen for the SF-36 were deemed to be the most commonly measured constructs in existing popular Health Surveys, and also the constructs that exhibited greatest changes due to disease and treatment; items representing various health indicators (e.g. behavioral changes, objective assessments, distress, etc.) were found to be important and included in the instrument, too.[61]

- Apart from the improvements that version 2 of the SF-36 is said to have (i.e. greater comparability with translations, better wording/layout, more consistent response options, smaller standard deviation, smaller "floor" and "ceiling" effects for the RP/RE Domains, etc.), other advances concerning the instrument included – (i) the introduction of Norm-Based Scoring (NBS) algorithms for the eight Domains, which permitted NBS-based comparisons of the Domain scores and the Summary scores, and (ii) Re-estimation of "norms", so that (via NBS algorithms) results from version 1 of the SF-36 could still be directly comparable with results from version 2.

- To make the instrument more capable of detecting recent/acute changes in health status (as can occur during Asthma, for instance), the 1-week recall SF-36 instrument was created; in this adaptation, each of the Domains that have a recall period (i.e. RP, BP, VT, SF, RE, and MH) have a 1-week recall period, instead of a 4-week recall period.

- Psychometric testing of the SF-36 instrument has been performed on several occasions (and in several different countries), and has led to the following findings – (i) 80-85% of

the reliable variance in the eight Domains is due to physical health and mental health factors, which were corroborated by Factor Analytical studies[54] (this had been verified in more than ten countries, by 1998), (ii) Extensive testing of the scaling and scoring assumptions in the SF-36 was performed using guidelines from various American research bodies, and all items in the instrument have been shown to correlate strongly (correlation factor >0.4) with their respective Domains, on almost all occasions,[62] (iii) Many studies have also confirmed that items can be aggregated without weighing the items, or standardizing the scores,[61] (iv) Studies using Item Response Theory (IRT) have shown that improvements in the scaling/scoring of the PF Domain are possible, although these studies have also shown that the summated (Domain) scores have strong linear associations with scores from IRT models,[63] (v) Test-retest and internal consistency methods have shown that the reliability statistics for the eight Domains and two Summary measures are >0.8 in most publications (with the Summary measures actually having very high reliability statistics), and this is well above the minimum standard reliability statistic for instruments of this type (i.e. 0.7),[64] (vi) 95% Confidence Intervals around individual scores were found to be much smaller for the Summary scores, as opposed to the Domain scores,[64] (vii) The validity of the SF-36 has been proven in many studies that have compared it with other commonly-used generic (health-related) QoL-measuring instruments - SF-36 Domains have been seen to achieve 80-90% of their empirical validity in studies that cover the criteria for physical health and mental health,[65] (viii) The sensitivity and specificity of the SF-36 for certain conditions has been shown to be high, too (for example – the MCS measure had a specificity of 81% and a sensitivity of 74% in detecting patients with a diagnosis of depressive disorder),[64] (ix) Cross-

sectional and longitudinal studies have shown that there is no significant loss of information when only the Summary scores (rather than the Domain scores) are utilized for statistical comparisons between groups[64] (although there remain advantages to analysing each Domain score, too), (x) Available information indicates high completion rates for the items in the SF-36, as well as adequate response consistency,[61] (xi) Interpretation of results is now easier, thanks to Norm-Based Scoring (as standardized mean scores and standard deviations help during the interpretation of differences across Domains, and also help when longitudinally studying a diseased population), and (xii) Subsequent advances have led to the creation of the SF-12 instrument (which is shorter, but still covers the same constructs that the SF-36 covers), to the creation of the SF-10 instrument for children, and to the development of a preference-based Health Utility Index that can be used during economic evaluations.

It should be mentioned that a common disorder-specific instrument that is used for measuring the QoL of patients with Kidney Disease is the Kidney Disease Quality of Life Short Form (KDQOL-SF) Health Survey; this instrument was originally developed for patients with Stage 5 CKD, but can be used for other CKD patients, as well.[66] The first part of this instrument is actually the SF-36 instrument (i.e. it contains the exact same thirty-six generic-based items that have been described, earlier), while the second part contains items that are specific to Kidney Disease. The second part comprises forty-three items that help constitute the following eleven Domains – (a) Symptoms, (b) Effects of Kidney Disease, (c) Burden of Kidney Disease, (d) Work Status, (e) Cognitive Function, (f) Quality of Social Interaction, (g) Sexual Function, (h) Sleep, (i) Social Support, (j) Dialysis Staff Encouragement, and (k) Patient Satisfaction. In a few instances, the first part of the KDQOL-SF (i.e. the generic part) is made to be the SF-12

questionnaire, instead of the SF-36 questionnaire; however, the Domains and Summary measures are the same for both the SF-36 and SF-12, even though the number of items is different. The KDQOL-SF instrument is also free to obtain from the RAND Corporation. However, as the disease-specific components of the KDQOL-SF are out of the realm of this Study, this instrument will not be discussed, further.

## IV.4 ARTICLES ABOUT THE SF-36 INSTRUMENT

Publications that provided insights into the SF-36 QoL-measuring instrument would be useful, particularly in terms of – (a) understanding how results obtained through it can be interpreted, (b) confirming the validity of it, (c) understanding how the normative SF-36 data for Canada were obtained, and (d) understanding the usefulness of the Domain scores and Summary scores, respectively.

The reasons for searching for such articles about the SF-36 are –

- It is vital to (i) know how to interpret the Domains and Summary measures of the SF-36 instrument, (ii) understand how to relate the SF-36 Domain and Summary scores to real life events, and (iii) know how to compare the SF-36 scores of a group or individual having a certain medical condition with the SF-36 scores of a general non-diseased population.

- The SF-36 instrument must be proven to be an acceptable, widely-used, valid, and reliable QoL-measuring instrument before the results from this Study can be deemed to be useful.

- The methods by which the Canadian normative SF-36 data were compiled assume importance because the Norm Based Scoring method will be used to calculate the PCS and MCS scores during this Study, and it is worth knowing how these two Summary scores will actually be computed; it is also important to understand the theory behind the computations, and the strengths/weaknesses of the Study that was performed to compile the normative data for Canada.

- It is important to know (i) how the SF-36 Domain scores and Summary scores relate to each other, (ii) what the Domain and Summary scores respectively signify, and (iii) where it is better to emphasize Domain scores instead of Summary scores (and vice versa).

**Interpretation of the SF-36 instrument:** Using the search terms of "SF-36" and "Interpretation", a search was performed in the PUBMED health database. Of the 280 publications retrieved, only 1 publication was an article from Canada that described in detail how SF-36 results can be related to everyday life. As other health databases (i.e. EMBASE, COCHRANE LIBRARY, and UPTODATE) and general search engines did not provide any more informative publication that originated from Canada, the article found in the PUBMED database is summarized, as follows –

***TABLE IV.1: Interpreting the SF-36 Health Survey, 2002 (Canadian Association of Cardiac Rehabilitation)***[A]

*Barbara Gandek*

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| Objective | To help explain what the numbers associated with the SF-36 instrument actually mean. |
| Interpretation Strategies | Content-based interpretation.<br>Construct-based interpretation. |

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| | Criterion-based interpretation. |
| *Content-based interpretation* | Meaning is assigned to scores, based on information about item content and patterns of response options.<br>For example – an individual who is not limited in physical activities (e.g. bathing, dressing, etc.) due to his/her health will score highly on the PF Domain, while the reverse is true for someone who is limited in his/her physical activities, as a result of health issues.<br>A research-based example using understandable figures is – 81% of people scoring less than 30 on the PCS measure had some limitation in walking a block, while only 0.6% of people scoring 60 or more on the PCS measure had such a limitation. |
| *Construct-based interpretation* | This indicates how a Domain (i.e. a Scale) fits into the general health model.<br>It has been shown that the PF, RP, and BP Domains have strong correlations with each other, while on the other hand, the SF, RE, and MH Domains have strong correlations with each other. Therefore, the first three are related to the construct of physical health, and the latter three are related to the construct of mental health.<br>Research has also proved that the Domains that strongly measure physical health do well in detecting the impact of interventions that primarily affect physical health; the same applies to the Domains that strongly measure mental health. |
| *Criterion-based interpretation* | This utilizes information about the relationship between scores and external variables (e.g. job loss, death, etc.) to determine the meaning of scores.<br>For example - U.S. data showed that 48% of those who scored between 30 and 34 on the PCS measure visited a doctor during the past month, while only 26% of those who scored between 45 and 49 on the PCS measure did so.<br>Norm-Based Scoring helps to understand how all scores relate to scores of the general population. This helps to determine how different a Study population is from the general population. Normative values are usually listed separately for different Age Groups, and Genders. The main advantage of Norm-Based Scoring is - it makes it possible to infer that a score above 50 (for any Domain or Summary measure) is better than the average score of a general population, while a score below 50 is worse; this is so, even if the actual average Domain/Summary score of the |

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| | general population is any number between 0 and 100 (before conversion). Therefore, the way in which an individual's score for (say) the PF Domain differs from 50 can also indicate the level of physical function that he/she is capable/incapable of. This advantage of Norm Based Scoring holds value while measuring the impacts of interventions, too. |
| Conclusion | Interpretation of results from specific studies can be done via the three techniques described, above. However, more evidence and details, regarding the interpretation of the SF-36 will be obtained over time. |

- This article adequately explains how to understand and interpret the various scores obtained via an SF-36 measurement (in terms of real life activities).

**Validity, reliability, and acceptability of the SF-36 instrument:** Using the search terms of "SF-36", "Validity", "Reliability", and "Acceptability", a search was performed in the PUBMED health database. Of the 57 publications retrieved, only 1 publication described a Study where the primary objective was to test the validity of the SF-36 instrument in an English-speaking country. As other health databases (i.e. EMBASE, COCHRANE LIBRARY, and UPTODATE) and general search engines did not provide any other similar publication, the publication found in the PUBMED database is summarized, as follows –

***TABLE IV.2: Validating the SF-36 health survey questionnaire: new outcome measure for primary care, 1992 (British Medical Journal, 1992 July 18, 305 (6846): 160 – 164)***[B]

*J. E. Brazier, R. Harper, N. M. Jones, A. O'Cathain, K. J. Thomas, T. Usherwood, and L. Westlake*

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| Objectives | To test the acceptability, validity, and reliability of the SF-36 Health Survey, and compare it with another generic Health Survey being commonly used in Britain (i.e. the Nottingham |

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| | Health Profile). |
| Country where the Study was based | United Kingdom (city of Sheffield). |
| Study design | Cross-sectional Analysis. |
| Number of subjects | 1980 patients of ages 16-74 randomly selected from lists of current patients at two general medical practices. |
| Instrument(s) used | Medical Outcomes Study SF-36 version 1 (note - the wordings of six questions in the original U.S. version were modified before the instrument was used on British patients).<br>Nottingham Health Profile. |
| Methods | Both questionnaires were mailed out to the patients' homes, along with questions about recent use of health services, and socio-demographic characteristics.<br>The response rate, internal consistency, test-retest reliability, validity, and discriminatory power were subsequently checked for. |
| Main statistical method(s) used | Cronbach's Alpha and two-way ANOVA for internal consistency.<br>Bland-Altman technique[67] for test-retest reliability.<br>Kruskal-Wallis test and the Multitrait Multimethod Matrix[68] (which is specifically used to test convergent and discriminant validity) for construct validity.<br>(To determine discriminant power, the frequency distributions of scores obtained by the respective measures were scrutinized, with less skewed distributions indicating greater discriminatory power). |
| Results | The overall response rate was 83%, and the rate of completion for each SF-36 Domain was >95%; the proportion of missing data for the SF-36 was only 0.5-4% (as opposed to 4-7% for the Nottingham Health Profile).<br>Internal consistency of the SF-36 was acceptable (item to own Domain correlations were >0.5 for 33 of the 36 items). Cronbach's Alpha was >0.85 (as required), and reliability coefficients were >0.75 for all Domains, except SF.<br>Test-retest scores were highly correlated with those from the main survey. For all Domains, 91- |

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| | 98% of cases fell within the 95% Confidence Interval constructed for a normal distribution.<br>Validity was satisfied. The distribution of scores was as expected. Men perceived their health to be slightly better than women ($p < 0.001$) on all Domains, except GH. Significant age gradients were found for the Domains of PF and BP ($p < 0.001$), but there was no gradient for MH ($p = 0.585$). Health perceptions decreased as socio-economic class decreased ($p < 0.05$) across all Domains, except GH. For 77 patients who had been diagnosed with, at least, one chronic physical condition, health was perceived to be worse ($p < 0.001$) across all Domains, except MH (i.e. when they were compared to a chronic disease-free patient sample that was matched for Age, Sex, and Medical Centre). Discriminant validity was also satisfied with Correlation Coefficients for four comparable Domains on the SF-36 and Nottingham Health Profile being higher than the Correlation Coefficients for non-comparable Domains.<br>Discriminatory Power of the SF-36 was also good because the frequency distributions of SF-36 scores were less skewed than the frequency distributions of comparable scores from the Nottingham Health Profile.<br>(Patients were grouped into two groups, based on their health perceptions – the group consisting of patients with poorer health perceptions had a higher proportion of women, an older mean age, a lower proportion of full-time employed people, and a greater number of medical consultations; however, between the two groups, the only significantly different Domain scores were those for PF, BP, and SF ($p < 0.05$). |
| Conclusions | The SF-36 is a suitable instrument for measuring (health-related) QoL in a general population because it is easy to use, acceptable to patients, and fulfils strict criteria for reliability and validity. It was also superior to the Nottingham Health Profile, overall. |
| Recommendations | Further studies are required to demonstrate that the SF-36 can be used to study patient groups with specific diseases.<br>The higher level of missing data in the 65-74 Age Group may mean that caution should be applied when using the SF-36 on elderly patients.<br>It would be advisable to design one valid health-related QoL score, which can replace the two Summary scores. |

- This Study adequately proves that the SF-36 is a valid, reliable, and acceptable QoL-measuring instrument; it is also worth noting that the usefulness and strengths of the SF-36 instrument were proven, reasonably early after its creation (and when version 1 of the SF-36 was the only available version).

- Even though the Study took place in the United Kingdom, the analysis has an important bearing on the utilization of the SF-36 in Canada, too because it has been shown that SF-36 normative data are similar for both Canadian and British general populations.[69]

- The large sample size and the wide-ranging analyses used indicate that the Study was robust.

- The favourable comparison of the SF-36 with the Nottingham Health Profile further strengthened the relevance of the Study's results because the latter instrument had been widely and commonly used in Britain, prior to the creation of the SF-36 (as noted by the authors).

**Preparation of Canadian normative data for the SF-36:** Using the search terms of "SF-36", "Normative", and "Canada", a search was performed in the PUBMED health database. Of the 39 publications retrieved, only 1 publication described the Study through which the first (and, so far, only) normative Canadian data for the SF-36 were prepared and published. As other health databases (i.e. EMBASE, COCHRANE LIBRARY, and UPTODATE) and general search engines did not provide any other publication about the compilation of Canadian SF-36 normative data, the publication found in the PUBMED database is summarized, as follows –

***TABLE IV.3: Canadian normative data for the SF-36 health survey, 2000 (Canadian Medical Association Journal, 2000 August 8, 163 (3): 265 – 271)***[C]

*Wilma M. Hopman, Tanveer Towheed, Tassos Anastassiades, Alan Tenenhouse, Suzette Poliquin, Claudie Berger, Lawrence Joseph, Jacques P. Brown, Timothy M. Murray, Jonathan D. Adachi, David A. Hanley, Emmanuel Papadimitropoulos, and the Canadian Multicentre Osteoporosis Study Research Group*

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| Objective | To publish the first normative Canadian data for the SF-36 because only normative data can show whether an individual/group is scoring above or below an average SF-36 score for their country (and, for their Age and Gender). |
| Country where the Study was based | Canada (multiple cities). |
| Study design | Cross-sectional Analysis. |
| Number of subjects | 9423 subjects (aged 25 years, or more) that formed the prospective cohort for the Canadian Multi-centre Osteoporosis Study; the sample (men = 30.6 %; women = 69.4 %; mean age = 62.1 years with a Standard Deviation of 13.4) was drawn from residents within a 50 kilometre radius of the following nine Canadian cities – St. John's, Halifax, Quebec City, Kingston, Toronto, Hamilton, Saskatoon, Calgary, and Vancouver. |
| Instrument(s) used | Medical Outcomes Study SF-36 (the U.S. English version was used for English-speaking subjects, as only "mile" had to be changed to "kilometre" for Canadians, while the Canadian French-language version from the IQOLA Project Group was used for French speakers). |
| Methods | The main Study was aimed at estimating the incidence and prevalence of Osteoporosis and osteoporotic fractures in the Canadian population, and to check for any regional variation, regarding the rates for those conditions. During the collection of baseline data for the main Study, the SF-36 instrument was administered at the end of that interview (this therefore presented a unique opportunity to develop normative SF-36 data). |

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| | To develop normative data for the general Canadian population that was adjusted for Age and Gender, only data from those who fully participated in the main Study were analysed. However, to estimate any selection bias, Regression models were used to predict whether results would have been any different, if the data points of those who did not fully participate were also included (there was subsequently shown to be no difference). |
| Results | The normative scores for all eight Domains and two Summary measures were obtained.<br>Just as in the U.S., men scored higher than women in Canada on all eight Domains and on both Summary measures (with the difference being most pronounced on the RP, VT, and RE Domains).<br>The physical health-related Domains and the PCS score decreased with increasing Age, while there was no definitive age-related pattern for the mental health-related Domains and the MCS score.<br>Several Domains (especially the RE Domain) exhibited a "ceiling" effect, but there was no strong "floor" effect for any Domain.<br>(Incidentally, Canadians scored higher than Americans on all eight Domains and on both Summary measures, although the differences were small). |
| Inferences | The differences in SF-36 scores across Ages, Genders, and Nations prove that Canadian SF-36 norms are very important to have whenever the SF-36 is used to compare (health-related) QoL among Canadian populations.<br>These norms will be useful (in Canada) when looking into the health status of the general population and specific patient populations, and also while monitoring the effects of interventions in a population. |

- The sample is large and includes people from the various regions of Canada (individuals from anywhere within a 50-kilometre radius of the cities were selected, so that there would be a balance between rural and urban residents).

- A complex sampling framework was also employed to ensure that the sample was truly representative.

- The authors state that multiple imputation methods proved that selection bias could not have substantially changed the mean values, even though participation in the Study was voluntary (it is worth mentioning that normative SF-36 data for the U.S. and the U.K. were also derived via voluntary participants).

- Prior to conversion into a "norm" mean score (i.e. 50) for the purposes of Norm Based Scoring, each Domain has a mean score of between 0 and 100 for the Canadian general population, and as per this Study, those values are – (a) PF: 85.8, (b) RP: 82.1, (c) BP: 75.6, (d) GH: 77, (e) VT: 65.8, (f) SF: 86.2, (g) RE: 84, and (h) MH: 77.5.

**Domain (or Subscale) and Summary scores of the SF-36:** Using the search terms of "SF-36", "Subscale", "Summary", and "Scores", a search was performed in the PUBMED health database. Of the 96 publications retrieved, only 1 publication described a Study that primarily looked into the relationship between the SF-36 Domain scores and Summary scores (all within a normative sample population, so that the effects of any medical condition did not come into play). Substituting the keyword "Domain" for "Subscale" and performing the same search in the PUBMED health database did not lead to any more relevant publication being found. As other health databases (i.e. EMBASE, COCHRANE LIBRARY, and UPTODATE) and general search engines did not provide any other publication that looked into the relationship between the SF-36 Domain and Summary scores (without considering any disease-specific variables), the publication found in the PUBMED database is summarized, as follows –

***TABLE IV.4: Do SF-36 summary component scores accurately summarize subscale scores?, 2001 (Quality of Life Research, 2001, 10: 395 – 404)***[D]

*Charles Taft, Jan Karlsson & Marianne Sullivan*

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| Objectives | To analyse and understand - (i) the relationships between the eight Domain scores and the two Summary scores, (ii) the relationships between the two Summary scores, and (iii) the implications of the two Summary scores (and their respective relationships) during the interpretation of research results. |
| Country where the Study was based | Sweden. |
| Study design | Cross-sectional Analysis |
| Number of subjects | 8930 subjects who constitute the Swedish SF-36 normative sample (however, as not all of these subjects had been scored on each of the eight Domains, only the 8004 subjects with computable PCS/MCS scores were ultimately utilized for this Study). |
| Methods | Firstly, theoretical analyses to describe how the SF-36 scoring algorithm influences the relationships between Domain and Summary scores were completed.<br>Secondly, correlations between the two Summary scores were calculated, at different intervals of the scoring range.<br>Thirdly, step-wise Regression analysis was performed to find out the proportion of the variance in PCS and MCS scores that is explained by each Domain, at different scoring levels. |
| Results | All eight Domain scores are required for the computation of the PCS and MCS scores; the greater the deviation of an individual's Domain score from the general population's mean Domain score and the smaller the variance for that particular Domain, the greater will be the impact of scoring coefficients on the Summary scores.<br>Significant correlations were found between PCS and MCS scores, at their respective upper scoring intervals (therefore, they are not totally independent of each other). Regression analyses showed that, in these upper ranges, PCS primarily measures aspects of mental health, while MCS primarily measures aspects of physical health. The implications of those analyses |

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| | are - the computation procedure for the PCS and MCS scores can sometimes inaccurately summarize the Domain scores. |
| Recommendations | Until further revisions are made to the computation procedure for the SF-36 Summary scores, PCS and MCS scores must be interpreted with caution, and also be always interpreted in combination with the respective Domain scores. |

- The Study is relevant and instructional, as it was based on a large number of people who were already part of a national SF-36 normative sample.
- The recommendation to never discard the Domain scores in favour of the Summary scores, alone is worth following, as far as possible.

**Footnote to Chapter IV:**

- **Appendix I** – RAND SF-36 Questionnaire.
- **Appendix II** – Scoring Instructions for the RAND SF-36 Instrument.
- **Appendix III –** Reliability, Central Tendency, and Variability of the RAND SF-36 Domains.
- **Appendix IV** – Summary of Information about the SF-36 Domains and the SF-36 Summary measures.

# V. CHRONIC KIDNEY DISEASE AND ITS POTENTIAL IMPACTS ON QUALITY OF LIFE

## V.1 OVERVIEW

Health is now said to be more than just a means to a longer life, and its objective is also to make life more satisfying and meaningful while improving the Quality of Life (QoL).

Improved healthcare has led to longer lifespans, which have led to greater susceptibilities to chronic diseases, which have led to relatively lower QoL levels in the elderly of today. Increasing age in tandem with the progression of various chronic diseases provides many challenges to QoL because each factor is capable of reducing QoL levels, on its own. A survey of "healthy days" by the Centers for Disease Control and Prevention (CDC) in the U.S. has indicated that self-rated "healthy" days decrease, as age increases (particularly after 65 years).[70] And, Canadian statistics indicate that the number of patients with Stage 5 Chronic Kidney Disease (CKD) who require Renal Replacement Therapy is increasing by approximately 10%, each year.[71] It should be noted that every chronic disease can impact a patient's QoL in a different way, and as the manifestations of the same disease can also vary among individuals, QoL can even diverge among those with an identical condition.

However, based on knowledge of the symptomatology (but prior to any in-depth perusal of the literature concerning the relationships between CKD and QoL), it would be prudent to state some expectations/hypotheses, with regards to how QoL may be affected by CKD.

## V.2 CHRONIC KIDNEY DISEASE

Based on just knowledge of the symptomatology, the respective stages of CKD would be expected to lead to the following general impacts on QoL -

- Stages 1 and 2 of CKD should have no significant impacts on any of the physical health-related Domains of an individual's QoL due to the paucity of symptoms during the early stages of the disease; while Social Functioning ought not to be affected, there could be a short-term negative impact on emotional health due to the stress of a serious new diagnosis.

- Stage 3 CKD patients should start to perceive physical limitations due to the associated lethargy and poor appetite while their work/employment may also be adversely affected, but certain physical health-related Domains (e.g. Pain) should not be impacted; the onset of physical limitations, the worry about the disease's progression, and the inherent lifestyle changes could all negatively affect certain mental health-related Domains (e.g. Vitality), although Social Functioning ought not to be affected, as yet.

- Stage 4 CKD patients should perceive even greater negative impacts on the same physical health-related Domains that are affected by Stage 3 CKD (e.g. everyday Physical Functioning and General Health) because the symptoms of Stage 3 and Stage 4 of CKD are quite similar, but more pronounced in the latter; patients whose mental health-related Domains were negatively impacted by Stage 3 CKD ought to perceive further negative impacts on those same Domains (especially - Vitality) when they have Stage 4 of the disease, and Social Functioning should be negatively impacted in these patients during

Stage 4 CKD, too (note - plans to treat the impending Stage 5 CKD with Renal Replacement Therapy are usually made when patients have Stage 4 of the disease).

- In comparison with the other stages of CKD, Stage 5 CKD (i.e. "end-stage" kidney disease) should lead to the greatest negative impacts on all physical health-related Domains (with the possible exception of Pain), as this is the stage when most patients are on a form of Dialysis therapy; while Vitality ought to be more severely impacted, other mental health-related Domains including Social Functioning should be impacted to a relatively lesser degree by Stage 5 of the disease, and mental health-related QoL scores in general would be expected to stabilize and even improve, as patients adjust to living long-term with Stage 5 CKD.

**Notes:** The following noteworthy points should also be mentioned -

- Patients with CKD should exhibit lower QoL scores across all Domains when compared with the general population (note - the most significant differences should be observed under the physical health-related Domains, with the possible exception of Pain).

- Patients with CKD should exhibit sequentially lower physical health-related QoL scores, as their disease progresses from Stage 1 to Stage 5, while mental-health related QoL scores, though negatively impacted in general, are unlikely to follow such a clear-cut pattern (for instance – getting used to a life on Dialysis or getting used to a donor kidney could lead to better perceptions of mental health by Stage 5 CKD patients, as compared to patients with the preceding stages of the disease, but on the other hand, the actual initiation of Dialysis therapy could lead to depressive symptoms,[72] and lower mental-health related QoL scores at that time).

## V.3 CHRONIC KIDNEY DISEASE ASSOCIATED WITH DIABETES

Based on just knowledge of the symptomatology, a combination of CKD and Diabetes would be expected to lead to the following general impacts on QoL -

- Patients with CKD and uncomplicated Diabetes should generally not have significantly different QoL scores, as compared to patients with only CKD (because Diabetes per se is usually both non-debilitating, and controllable); however, the stress of being diagnosed with two serious coexisting diseases could lower the mental health-related QoL scores of these patients, in the short-term.

- Patients with CKD and the complications of Diabetes (e.g. ulcers, dysfunctional nerves, visual disturbances, etc.) should have lower QoL scores across all Domains, as compared to patients with only CKD (and, due to the added external aggravation that Dialysis entails, this negative impact would be accentuated in those patients who are on Dialysis while suffering from diabetic complications); the complications of Diabetes should cause the greatest impacts on the physical health-related Domains, rather than on the mental health-related Domains.

## V.4 CHRONIC KIDNEY DISEASE ASSOCIATED WITH HEART DISEASE

Based on just knowledge of the symptomatology, a combination of CKD and Heart Disease would be expected to lead to the following general impacts on QoL -

- Patients with CKD and non-acute IHD (without Heart Failure) should generally not have significantly different QoL scores, as compared to patients with only CKD (because

stable Angina is usually both non-debilitating, and controllable); however, the stress of being diagnosed with two serious coexisting diseases should lower the mental health-related QoL scores of these patients, in the short-term.

- Patients with CKD plus acute manifestations of IHD and/or recent Myocardial Infarction (without Heart Failure) should have lower QoL scores across all Domains, as compared to patients with only CKD; relatively greater impacts on the physical health-related Domains would be expected in this case, too.

- Patients with CKD and Heart Failure (without IHD) should have lower QoL scores, as compared to patients with only CKD, and this ought to be equally true across all Domains, with the exception of Pain; overall, physical health-related QoL should be impacted to a greater degree, as compared to mental health-related QoL.

**Notes:** The following noteworthy points should also be mentioned -

- In patients who already have CKD, conditions such as Stroke and Peripheral Vascular Disease (PVD) would likely lead to further decreases in QoL scores, across all Domains; in general, Stroke should impact each Domain more severely than PVD due to the greater degree of debilitation that is usually caused by the former condition.

- Due to the combined debilitation, patients with CKD plus both IHD and Heart Failure should have physical health-related QoL scores that are among the lowest within any cohort of CKD patients; however, mental health-related QoL scores would not follow a definitive pattern due to differing individual traits.

- The general QoL in patients with CKD plus both Diabetes and Heart Disease cannot be adequately compared to the QoL in other groups because the symptoms among patients with all three diseases (CKD, Diabetes, and Heart Disease) would be widely disparate.

## V.5 CHRONIC KIDNEY DISEASE AND DEMOGRAPHIC FACTORS

The demographic factors of Age and Gender would also significantly contribute to differences in QoL, among patients with the conditions discussed in the preceding paragraphs. Based on clinical experience, the potential impacts of these two demographic factors may be summarized, as follows –

- The perceptions of QoL in patients with chronic diseases should be worse in younger Age Groups (where general expectations include having full-time occupations and active family lives), as compared to older age groups (where responsibilities are fewer, expectations are more modest, and medications for other concurrent age-related conditions may provide additional palliation).

- Women (especially working women who have to invest time toward family affairs, too) generally have more responsibilities than men, and since women also generally live longer (therefore being susceptible to more age-related disabilities), women with chronic diseases may perceive their QoL to be worse than that of comparable men; however, a significant difference in QoL between men and women with an identical disease may be unlikely without other coexisting factors playing a part, too.

# VI. LITERATURE REVIEW

## VI.1 OVERVIEW

The search for past publications was performed, in order to find articles on studies/research that looked at –

- QoL among (preferably) North American adult patients afflicted with different stages of CKD (note - the presence and evaluation of associated co-morbidities would be advantageous but not mandatory).
- QoL among (preferably) North American adult patients with CKD or (if necessary) even other chronic conditions, along with particular evaluation of the effects of Age and Gender on QoL (note - the presence and evaluation of associated co-morbidities would be advantageous but not mandatory).

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## VI.2 STUDIES THAT COMPARED QUALITY OF LIFE ACROSS ADULT PATIENTS SUFFERING FROM DIFFERENT STAGES OF CHRONIC KIDNEY DISEASE

Utilizing both healthcare-related web-sites and general search engines, online searches were conducted, in order to find - Studies in English that compared QoL across adult patient groups in North America where each group had a different stage of CKD (with or without co-morbidities), and where a version of the SF-36 was one of the instruments (or the only instrument) used for the measurement of QoL. If a Study primarily looked into the effects of Diabetes and/or Heart Disease on the QoL of CKD patients, that Study would be worth perusing, too.

The reasons for the rationale stated above are –

- This Study is not trying to compare the QoL of a group of CKD patients with the QoL of a non-CKD sample; therefore, studies that have done so (e.g. compared the QoL of a specific ethnic group with CKD to the QoL of the general population, or compared the QoL of Hemodialysis patients to the QoL of the general population, and so on) would not provide many useful insights.

- Unless a complete English translation is available, publications in other languages would be undecipherable.

- Analyses of QoL in countries outside of North America would likely be based upon SF-36 normative scores that are significantly different from Canadian norms (while QoL data from outside of North America might also reflect medical care, which is not comparable with the care that is generally provided to CKD patients in Canada); therefore, such studies will not be extensively dissected, although their salient features could be instructive, and will be summarized.

- If a Study used a QoL-measuring instrument other than the SF-36, the interpretation and comparison of results from that Study would require an in-depth understanding of the other instrument (in terms of – scales, computations, validity, reliability, etc.), and that is outside the scope of this particular Study; however, the salient features of instructive studies that evaluated QoL without using the SF-36 would still be summarized.

- Those studies that only looked into QoL differences within a particular stage of CKD (e.g. only across patients on different forms of Dialysis) would not be very relevant to this particular Study.

- Those studies that tried to ascertain whether QoL among CKD patients was affected by the use/non-use of a certain intervention would not be very relevant to this particular Study.

- Publications about how a particular co-morbidity (other than Diabetes, or Heart Disease) impacts the QoL of CKD patients would also provide few valuable insights, regarding the current analyses.

- Studies that attempted to connect QoL information from CKD patients with other outcomes (e.g. utility, daily activities, disease coping methods, etc.) would not be of much relevance to the current analyses, unless QoL across the stages of CKD was also incidentally evaluated.

- Studies that compared only one dimension of health (i.e. only Pain, only Sleep, etc.) across groups of CKD patients would provide few relevant insights; however, such studies may be used as references during the interpretations of results from the current analyses.

- Studies that looked into QoL differences among CKD patients as a non-primary outcome (e.g. during validation studies on the SF-36 instrument) would also not be of much assistance, unless the relevant analyses were explained in detail; however, those studies could be used as references during the interpretations of results from the current analyses.

The search for relevant publications was conducted, as follows –

- Using the search terms of “Chronic”, “Kidney Disease”, and “SF-36”, a search was performed in the PUBMED health database.

- Of the 298 publications that were retrieved in the PUBMED health database, only 3 publications were about studies that used a version of the SF-36 to measure QoL across North American patients with two or more stages of CKD.
- Using the same search terms ("Chronic", "Kidney Disease", and "SF-36"), searches were also performed in the EMBASE, COCHRANE LIBRARY, and UPTODATE health databases; however, no additional studies of relevance were discovered.
- A general Google search found no further studies of relevance, either.

The 3 publications that were found to be the most relevant to this particular Study are summarized, as follows –

***TABLE VI.1: Quality of life in Chronic Kidney Disease (CKD): A cross-sectional analysis in the Renal Research Institute-CKD study, April 2005 (American Journal of Kidney Diseases 45 (4): 658 – 666)***[E]

*(Rachel L. Perlman, Fredric O. Finkelstein, Lei Liu, Erik Roys, Margaret Kiser, George Eisele, Sally Burrows-Hudson, Joseph M. Messana, Nathan Levin, Sanjay Rajagopalan, Friedrich K. Port, Robert A. Wolfe, Rajiv Saran)*

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| Objective | To compare the QoL of non-Dialysis CKD patients with the QoL of both (a) CKD patients on Hemodialysis and (b) Healthy controls. |
| Country where the Study was based | U.S.A. (state of Michigan). |
| Study design | Cross-sectional Observational Study. |

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| Number of subjects | 634 subjects with CKD, of whom only 505 completed the SF-36 questionnaire in full - 2 had Stage 2, 151 had Stage 3, 360 had Stage 4, 118 had Stage 5 but were not on Dialysis, and 3 had an unknown stage (the main inclusion criterion was – a GFR of 50 mL/min/1.73m$^2$, or less). |
| Instrument(s) used | Medical Outcomes Study 4-week recall SF-36. |
| Methods | The QoL of patients enrolled in a multi-center prospective observational study about CKD was compared with (i) the QoL of a prevalent cohort of Hemodialysis patients (from U.S. historical data) and (ii) the QoL of healthy controls (from U.S. historical data).<br>Correlations of QoL with Age, Sex, Race, Marital Status, Education, GFR levels, Diabetes, Heart Disease, Hypertension, Body Mass Index, Hemoglobin levels, and Albumin levels were checked for within the CKD cohort, as well.<br>*P* values <0.05 were indicative of statistical significance. |
| Main Statistical Analytical Method(s) | Fisher's Exact tests and Student's T tests to compare the respective demographic factors, biochemical markers, and co-morbidities for all of the patients who were surveyed (i.e. all of those in the CKD cohort).<br>Student's T tests to compare the mean QoL scores of CKD patients with the mean QoL scores of each of the other 2 groups (i.e. the Hemodialysis group, and the healthy controls group), in turn.<br>Multiple Linear Regression to study how the ten scales (i.e. the Domain and Summary measures) of the SF-36 were related to biochemical parameters, while controlling for demographic factors, and co-morbidities. |
| Results | Non-Dialysis CKD patients had significantly higher QoL scores on all eight Domains and on both Summary scales, when compared with patients on Hemodialysis ($p < 0.0001$), but they had significantly lower QoL scores on seven Domains (all except MH) and on one Summary scale (PCS), when compared with the healthy controls ($p < 0.0001$).<br>The only other significant finding was that higher Hemoglobin levels (which are directly related to Erythropoietin levels) were associated with higher scores, across both Summary scales and across all Domains, except Pain ($p < 0.05$). |

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| | Within the CKD cohort, patients with Stage 4 CKD actually had lower scores on most Domains and across both Summary scales, as compared to patients with Stage 5 CKD; however, none of these differences were statistically significant. Even when GFR was used as a continuous variable (instead of "Stage of CKD"), there was no linear or quadratic relationship between that and QoL (probably because Kidney Disease is usually "silent" until the latter stages).<br>Effects of demographic factors and co-morbidities on Domain and Summary scores were also checked for; there were no significant correlations, although patients with Heart Failure were seen to have lower scores on several Domains and on the MCS measure, as compared to patients without Heart Failure. |
| Conclusions | SF-36 scores for the CKD cohort were higher than those for Hemodialysis patients.<br>SF-36 scores for the CKD cohort were lower than those for the healthy controls, especially with regards to the measures of physical health.<br>Hemoglobin level significantly predicted Domains related to both mental health and physical health (with the exception of Pain). |
| Recommendations | Longitudinal studies are required to better define changes in QoL during the course of CKD, and also to explore interventions to improve the QoL of these patients. |

Critical appraisal of this Study identified the following noteworthy points –

- The Study primarily compared the QoL of CKD patients on Hemodialysis with the QoL of CKD patients who were not on Hemodialysis, but comparisons of QoL across the various stages of CKD were not actually performed (except for the incidental comparison between Stage 4 CKD and Stage 5 CKD patients).
- The sample size was relatively small, in comparison with other such studies, with only 80% (505) of the original 634 subjects actually completing the survey and being part of

the final analyses; in addition, only 222 out of those 505 subjects had absolutely no "missing" data.

- The Study considered co-morbidities, such as Diabetes and Heart Disease; however, by the authors' own admissions, Diabetics were under-represented in the sample that completed the SF-36 (just 35%).

- The lack of centralized laboratory testing was cited by the authors as another weakness, along with the number of subjects who had "missing" data points.

- It would have been preferable to obtain the data for the Hemodialysis group from a prospective cohort, rather than from a historical dataset (note - in terms of QoL, a group of Stage 5 CKD patients on Hemodialysis could be very distinct from a group of Stage 5 CKD patients not on Hemodialysis because the latter group would likely consist of less symptomatic patients).

***TABLE VI.2: Health-related quality of life and estimates of utility in chronic kidney disease, 2005 (Kidney International 68: 2801–2808)***[F]

*(Irina Gorodetskaya, Stefanos Zenios, Charles E. McCulloch, Alan Bostrom, Chi-Yuan Hsu, Andrew B. Bindman, Alan S. Go, and Glenn M. Chertow)*

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| Objective | To determine the relations among kidney function, health-related QoL, and estimates of utility. |
| Country where the Study was based | U.S.A. (state of California). |
| Study design | Cross-sectional Observational Study (for all CKD patients), and Longitudinal Analysis (with |

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| | readings 2-8 times over the following two years) for only those patients with CKD stages 4 and 5 (i.e. those patients with GFR <30 mL/min/1.73m$^2$). |
| Number of subjects | 205 patients with CKD (GFR <70 mL/min/1.73m$^2$), 38 of whom were on Hemodialysis. |
| Instrument(s) used | KDQOL-SF (with the generic part being the 1-week recall RAND SF-12 questionnaire).<br>Health Utilities Index (HUI-3).<br>Time Trade Off (TTO) Questionnaire. |
| Methods | Cross-sectional analysis was performed using the whole sample (which was pooled from two prospective cohorts that were both under one research team), in order to see if differences in the stage of CKD had a significant impact on QoL and Utility; measurements using each of the three instruments were performed.<br>Longitudinal analyses were performed to evaluate self-reported outcomes among those with GFR <30 mL/min/1.73m$^2$, with administration of all three questionnaires attempted at 3-month intervals, even after any patient initiated Dialysis. 115 patients in total were longitudinally evaluated (with, at least, two measurements over two years).<br>All analyses were adjusted for - Age, Sex, Race/Ethnicity, and Diabetes.<br>*P* values <0.01 were considered to be statistically significant.<br>(Covariates included – Age, Sex, Race/Ethnicity, Socio-economic Status, select Medications, and some Laboratory Values, as well as multiple co-morbidities that were all summarized into the Charlson Co-morbidity Index[73]). |
| Main Statistical Analytical Method(s) | ANOVA tests (normal distributions) and Kruskal-Wallis test (non-normal distributions) for comparisons of the means/medians between groups.<br>Spearman Rank Correlation Coefficient to analyse trends between categories (adjustments were made for Age, Sex, Race/Ethnicity, and Diabetes).<br>Mixed Effect Regression models to analyse the change in QoL and utility over time (longitudinal analysis), with GFR being a time-varying covariate. |
| Results | Cross-sectional analyses showed that the lower levels of kidney function (based on GFR values, rather than the "Stage of CKD" variable) were associated with significantly lower PCS scores (p = 0.002), as well as significantly lower Burden of Kidney Disease and Effects of |

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| | Kidney Disease Domain scores (both of the latter two Domains with $p < 0.0001$, and both of those Domains being from the KDQOL-SF Questionnaire). In addition - hospitalization was associated with further declines in the PCS score, while Emergency Department visits were associated with declines in the MCS score; the initiation of Dialysis for some of those who were being longitudinally studied did not significantly impact either Summary score.<br>The other noteworthy findings (with an emphasis on QoL) were – (a) Longitudinal decline in GFR significantly impacted the Burden of Kidney Disease Domain in a negative way, (b) Mean scores across all three instruments suggested considerable loss of function and well-being in CKD patients, as compared to general population norms, (c) No significant changes in the PCS and MCS scores were observed during longitudinal analyses, and (d) Results from both the cross-sectional and longitudinal analyses were not affected significantly by Age, Sex, Race/Ethnicity, or Diabetes. |
| Conclusions | Health-related QoL and estimates of utility are extremely low in CKD patients (with the PCS score being <43, which indicates a perception that physical health problems are definitely impeding normal life functioning[74]). |
| Recommendations | Health policy decisions affecting CKD patients should take self-reported outcomes into consideration. |

Critical appraisal of this Study identified the following noteworthy points –

- The total sample size was very small; however, the study population was still reasonably diverse, and it was possible to obtain multiple measurements of QoL and Utility for the purpose of analysis.
- The sample size of the group that was longitudinally followed was even smaller than the initial sample, although several analyses were still performed using the available data,

and the face validity of scores in response to major life events (e.g. initiation of Dialysis) was evaluated, too.

- One of the limitations was that all of the subjects were from an ambulatory nephrology clinic in a single institution, thereby restricting generalizability.

- The sample was slightly skewed towards younger Age Groups (while non-responders were older), and this could have led to more favourable perceptions of health among the sample.

- There was a relatively high proportion of patients of Asian descent (25%) in the sample.

- The authors state that there might have been misclassification of some subjects within the "GFR category" variable due to imprecision in determining the change in kidney function, based on the change in GFR; this may have reduced the power of the longitudinal analysis.

- A relatively large faction of the sample (25%) was lost to follow-up, which may have biased the longitudinal analyses, too.

- While the SF-12 (which was used for this Study) is comparable to the SF-36, using the SF-36 is still preferable because the greater number of items in it lead to slightly more representative Domain and Summary scores.

- The administration of three questionnaires at the same time to each patient could have created response inconsistencies due to "channel capacity" issues.

- The results were primarily reported in terms of the continuous variable of "GFR value", rather than the ordinal variable of "Stage of CKD"; using the latter would have provided clearer delineations, with regards to QoL trends.

***TABLE VI.3: Symptom Burden, Depression, and Quality of Life in Chronic and End-Stage Kidney Disease, 2009 (Clinical Journal of the American Society of Nephrology, June 2009, 4 (6): 1057 – 1064)***[G]

*Khaled Abdel-Kader, Mark L. Unruh, Steven D. Weisbord*

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| Objective | To compare (i) symptom burden, (ii) levels of depression, and (iii) QoL between those with advanced CKD (i.e. CKD just prior to Stage 5) and those with Stage 5 CKD (i.e. End-Stage Kidney Disease). |
| Country where the Study was based | U.S.A. (state of Pennsylvania). |
| Study design | Cross-sectional Prospective Observational Study. |
| Number of subjects | 177 patients - 90 with Stage 5 CKD (70 were on Hemodialysis, and 20 were on Peritoneal Dialysis), and 87 with either Stage 4 CKD or severe Stage 3 CKD (note - patients' GFR levels and patients' functional status were estimated, prior to inclusion).<br>(4 patients from the Stage 5 CKD group and 7 patients from the Stage 3-4 CKD group did not complete the SF-36, and were subsequently excluded from final QoL analysis; patients who had severe co-morbidities, patients who were not 18-90 years of age, and patients who were not residing at home were all excluded from the start of the Study). |
| Instrument(s) used | Dialysis Symptom Index (DSI).<br>Patient Health Questionnaire–9 (PHQ-9).<br>Medical Outcomes Study 4-week recall SF-36. |
| Methods | Cross-sectional analysis was performed to compare differences between the two groups (i.e. |

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| | the Stage 5 CKD group and the Stage 3-4 CKD group), with regards to - demographic characteristics, clinical variables, individual symptoms, overall symptom burden, overall symptom severity, depression, and QoL.<br>Impacts of demographic and clinical variables on group differences (pertaining to - symptoms, depression, and QoL) were also studied.<br>Correlations in each group among overall symptom burden, overall symptom severity, depression, and QoL were studied, as well.<br>Except when analysing the differences in prevalence/severity of individual symptoms on the DSI instrument (for which a $p$ value <0.002 was indicative of statistical significance), a $p$ value of <0.05 indicated significance during all of the other analyses.<br>(It should be noted that, with regards to QoL, all eight Domains and two Summary scores of the SF-36 were compared between the two groups; however, during correlation analysis, only the PCS and MCS scores of the SF-36 were relevant). |
| Main Statistical Analytical Method(s) | Student's T tests or Mann-Whitney U tests for the comparison of means (continuous variables) between the two groups; Fisher's Exact test or Chi-Square Statistic for the comparison of means (categorical variables) between the two groups.<br>Multiple Linear Regression, Logistic Regression, or the Wilcoxon-Mann-Whitney Rank Sum test for analysing the impacts of demographic and clinical variables on group differences, regarding – (i) symptoms, (ii) depression, and (iii) QoL (which was indicated by the respective PCS and MCS scores).<br>Spearman's Correlation Coefficient for assessing the correlations within each group among (i) overall symptom burden, (ii) overall symptom severity, (iii) depression, (iv) PCS, and (v) MCS.<br>(Also – Cronbach's Alpha for assessing the internal consistency of the DSI instrument, and Bonferroni Correction for analysing the differences in individual symptoms on the DSI instrument). |
| Results | QoL-related scores (as well as symptom-related and depression-related scores) were similar, across both groups (Stage 5 CKD patients had lower scores than Stage 3-4 CKD patients on |

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| | the PF Domain of the SF-36, but this did not translate into a significant difference in the PCS score).<br>Adjustment for demographic and clinical variables did not unmask differences in overall symptom burden/severity, depression, or QoL, and did not attenuate the mild difference in the PF Domain of the SF-36.<br>Overall symptom burden and overall symptom severity were correlated with (i) depression in both patient groups, (ii) PCS scores in patients with Stage 5 CKD, and (iii) MCS scores in patients with Stage 3-4 CKD.<br>Depression was strongly correlated with MCS scores in both groups. |
| Conclusions | A comparable low QoL is seen in the following groups - (i) patients with Kidney Failure and (ii) patients with advanced stages of CKD who do not yet have Kidney Failure.<br>(The burden of symptoms and the prevalence of depression are similar across both of these groups, too). |
| Recommendations | Significant attention should be paid to health-related Domains in the growing number of patients who suffer from advanced CKD, even before their kidneys go into failure mode. |

Critical appraisal of this Study identified the following noteworthy points –

- The sample size was relatively small, which may hinder the generalizability of the results.
- The CKD cohort included a disproportionate number of men (66%), while the Dialysis cohort included a relatively high proportion of African-American patients (41%).
- The exclusion of patients with severe co-morbidities may have led to the Dialysis (i.e. Kidney Failure) cohort that was selected being healthier than Dialysis patients in general.

- The cross-sectional nature of the Study did not permit any evaluation of the evolution of QoL (as well as – symptoms and depression) over a period of time, and across potential future adverse events.

- The questionnaires were all administered in the selected patients' homes, which could have led to those patients having more favourable perceptions of their health status, as compared to CKD/Dialysis patients in general.

- The administration of three questionnaires at the same time might have hampered the consistency of responses due to "channel capacity" issues.

In addition to the studies that have already been summarized, the following 4 studies from outside of North America (which also compared QoL in adult patients across the stages of CKD, while using the SF-36) will be briefly summarized, too –

***Health-related quality of life in different stages of chronic kidney disease and at initiation of dialysis treatment, 2012 (Health and Quality of Life Outcomes, June 18 2012, 10: 71)***[H]

*Pagels A.A., Söderkvist B.K., Medin C., Hylander B., Heiwe S.*

- This cross-sectional Study in Sweden utilized the SF-36 to compare (health-related) QoL among 535 CKD patients with stages 2-5 of the disease (inclusive of some patients who were at the start of Dialysis therapy), while also exploring possible correlating and influencing factors; 55 healthy controls were part of the Study, too.

- All Domain and Summary scores significantly deteriorated, as the stage of CKD worsened, with greatest impacts on physical health perceptions (i.e. the PF, RP, and GH

Domains, plus the PCS score), and the smallest impacts on the Domains of MH and BP. Even patients with stages 2-3 of CKD had much lower scores than healthy controls, with regards to the GH Domain and the PCS score. Stage 4 CKD patients had much lower PF, GH, and PCS scores, as compared to those with stages 2-3 of CKD. Stage 5 CKD patients even had lower RE and MCS scores than Stage 4 CKD patients. QoL deteriorated further, as Dialysis was initiated. GFR values of around 45 mL/min/1.73m$^2$ seemed to be a demarcating line for a fall in QoL (particularly with regards to the PCS score). All of the considered co-existing conditions were significant predictors of impaired QoL (note - Cardiovascular Disease and Inflammation were slightly stronger predictors than Diabetes).

Critical appraisal of this Study identified the following noteworthy points –

- The sample size was relatively small, which may hinder the generalizability and accuracy of the results.
- The subjects (both patients and healthy controls) were not randomly selected, and this fact would have increased the risk of biases.
- The group sizes (with regards to the different stages of CKD) were disproportionate, with most patients having had Stage 5 CKD and with no patients having had a GFR of between 31 and 50 mL/min/1.73m$^2$; however, the authors state that Regression analyses were performed with more proportionate group sizes.
- There was a majority of males in the Study, although the percentages of each Gender were similar to the general male-female distribution of CKD patients.

- The usual limitations of any cross-sectional QoL analysis ("ceiling and floor" effects, "response shift" phenomenon, effects of a known diagnosis on the health perceptions of asymptomatic patients, etc.) were present, as well.

***Quality of life in patients with chronic kidney disease, 2011 (Clinics–Sao Paolo, 2011, 66 (6): 991-995)*** [I]

*Cruz M.C., Andrade C., Urrutia M., Draibe S., Nogueira-Martins L.A., Sesso R de C.*

- This cross-sectional Study of 155 patients in Brazil utilized the SF-36 to compare the dimensions of (health-related) QoL in patients with the respective stages (1-5) of CKD, while also evaluating the influences of socio-demographic, clinical, and laboratory data on QoL; in addition, the Karnofsky Performance Scale was used to measure functional status.

- QoL in this cohort of CKD patients was lower than the QoL of the general population. The PF, RP, and PCS scores were seen to progressively decrease, as the stage of CKD worsened, but these decreases were not statistically significant. Older patients performed worse on the PCS measure, but better on the MCS measure. Higher Hemoglobin levels were associated with better PCS scores. Males had significantly higher MCS scores than females. Regarding co-morbidities - only patients with three or more associated co-morbidities showed significant decreases in their PF, RP, and PCS scores, as compared to those without co-morbidities. Professionally active individuals with higher education levels displayed higher PCS scores, while individuals with higher incomes had higher MCS scores.

Critical appraisal of this Study identified the following noteworthy points –

- The sample size was relatively small, which may hinder the generalizability and accuracy of the results.
- The lack of a significant difference in any Domain score between the "Stage of CKD" groups could be due to the small sample size.
- The authors admit that it was extremely difficult to recruit subjects with the early stages of CKD.
- The cross-sectional study design prevented any causal relationships being determined.

***Quality of life in chronic kidney disease, 2011 (Nefrologia, 2011, 31 (1): 91-96)***[J]

*Fructuoso M., Castro R., Oliveira L., Prata C., Morgado T.*

- This cross-sectional Study of 111 patients in Brazil utilized the KDQOL-SF to compare (health-related) QoL between four groups – (i) patients with stages 1-4 of CKD, (ii) patients who had undergone Kidney Transplants, (iii) patients who were on Hemodialysis, and (iv) patients who were on Peritoneal Dialysis.
- There were no significant differences in Domain scores between the four groups, but the scores for the SF Domain were highest, in each of the four groups, while the scores for the GH Domain were lowest, in each of the four groups. Peritoneal Dialysis patients scored significantly higher on the PCS measure (as well as on the PF and BP Domains) when compared to the other three groups, but even these differences disappeared when adjustments were made for confounding factors. Age, Gender, and Hemoglobin levels

were significant predictors of the PF, BP, and PCS scores. Only Peritoneal Dialysis patients indicated a significant improvement in their health, relative to a year ago. In terms of KDQOL-SF Domains that were not part of the SF-36 – Peritoneal Dialysis patients had significantly better scores when compared to Hemodialysis patients, on the Domains of "Effects of Kidney Disease", "Burden of Kidney Disease", and "Patient Satisfaction".

Critical appraisal of this Study identified the following noteworthy points –

- The sample size was extremely small, which may hinder the generalizability and accuracy of the results.
- There was no actual comparison of QoL across the respective stages of CKD, which makes any inference (even if there had been a significant difference in an SF-36 Domain score between any of the analysed groups) not very constructive.
- The small sample size (due to the low power) probably also contributed to the lack of a significant difference in an SF-36 Domain score between any of the analysed groups.

***Moderately decreased renal function negatively affects the health-related quality of life among the elderly Korean population: a population-based study, 2008 (Nephrology, Dialysis, Transplantation – official publication of the European Dialysis and Transplant Association, September 2008, 23 (9): 2810-2817)***[K]

*Chin H.J., Song Y.R., Lee J.J., Lee S.B., Kim K.W., Na K.Y., Kim S., Chae D.W.*

- This cross-sectional Study (which was part of a larger longitudinal Study) of 944 CKD patients in a South Korean city looked at the impact of kidney function on (health-

related) QoL, and the risk factors for poor QoL in an elderly population (all patients in the Study were >65 years of age).

- Five groups were defined, based on GFR levels - those with a GFR of 90 mL/min/1.73m$^2$ or more made up the first group, while those with a GFR <45 mL/min/1.73m$^2$ made up the last group. All of the SF-36 Domain and Summary scores (except for the GH and MH scores) were significantly reduced in the last group, as compared to the other four groups; even after adjusting for confounders, the PCS score was still much lower in the last group, as compared to the other four groups. Across the sample, physical health-related QoL scores were lower than mental health-related QoL scores with the VT and BP scores being similar for the last group, only. A GFR value of <45 mL/min/1.73m$^2$ was an independent predictor of poor physical health-related QoL. Apart from GFR levels, the other significant predictors of the PCS and/or MCS score were – Age, Gender, Duration of Education, Living Spouse, Income Status, Regular Exercise Habits, Depression, History of Stroke, Serum Albumin levels, Serum Hemoglobin levels, and Serum Cholesterol levels (in general, lower scores on one or both of the Summary measures were associated with older Age Groups, females, lower levels of education/income, less settled home life, less exercise, associated physical/mental debilitation, and worse laboratory-based parameters).

Critical appraisal of this Study identified the following noteworthy points –

- The sample was not totally representative of all age groups, as all of the subjects were >65 years of age.

- Of the 1000 subjects initially selected for the Study, the 56 who did not complete the SF-36 questionnaire and had to be excluded were all relatively older, less educated, poorer, and more anemic than those who actually completed the questionnaire; this fact may have skewed some of the results.

- The groups were created, based on GFR values that do not actually correlate with the GFR values used to determine the five stages of CKD; therefore, direct comparisons with existing CKD stage-related QoL data would not be appropriate.

- Due to high degrees of imprecision associated with estimating GFR levels >60, there would have been greater chances of patient misclassification occurring among the GFR-based groups.

- The Study was planned to be a prospective one, but the analyses were only carried out using data from the first year of the Study.

- The authors state that the sample was too small to be demarcated into a greater number of groups (which had been the original intention).

- The sample was not very representative of Stage 4 and Stage 5 of CKD (note - all of the subjects with a GFR <45 mL/min/1.73m$^2$ were combined into a single group).

In addition to the studies that have already been summarized, the following 2 studies from North America that compared QoL in adult patients across the stages of CKD with the help of instruments other than the SF-36 will be briefly summarized, too –

***Cross-sectional study of quality of life and symptoms in chronic renal disease patients: the Modification of Diet in Renal Disease Study, 1997 (American Journal of Kidney Diseases, June 1997, 29 (6): 888-896)***[L]

*Rocco M.V., Gassman J.J., Wang S.R., Kaplan R.M.*

- The aim of this cross-sectional study in the U.S. was to measure (health-related) QoL in the 1284 CKD patients who were enrolled during the baseline period of the Modification of Diet in Renal Disease Clinical Trial. Each of the patients had to have completed a measurement of QoL/symptoms using one of the following questionnaires – (a) Quality of Well-Being (QWB) scale, (b) Symptom Checklist-90R (SCL-90R), and (c) Patient Symptom Form (PSF).
- This Study did not categorize patients by the stage of CKD. However, multivariate analyses indicated that QoL (measured either by the QWB, or the SCL-90R) worsened as GFR decreased. QoL was also generally worse in older Age Groups, female patients, those with lower levels of education, those with lower incomes, and those with lower serum Albumin levels. The commonest symptoms reported in this cohort were – difficulty sleeping, fatigue, and abdominal bloating. The overall conclusion was that those with moderate-to-severe renal insufficiency had a reduced QoL, as well as more frequent (and severe) symptoms and psychological distress; the magnitude of these effects was negatively correlated with GFR.

Critical appraisal of this Study identified the following noteworthy points –

- Despite the satisfactory sample size, there was no demarcation of patients by stage of CKD (to be fair, the staging approach towards CKD was not routine at the time of this particular Study).
- Some patients (though a minority, overall) had completed just one out of the three measuring instruments, which meant that it was not possible to correlate QoL and symptomatology for every subject in the Study.

***Quality of life and psychosocial relationships in patients with chronic renal insufficiency, 1998 (American Journal of Kidney Diseases, October 1998, 32 (4): 557-566)***[M]

*Shidler, N.R., Peterson R.A., Kimmel P.L.*

- The aim of this cross-sectional study involving 50 outpatients with CKD (prior to Stage 5) in the U.S. was to assess the psychological functioning level, and the relationship between - (a) psychosocial variables, (b) psychological functioning, and (c) social support buffering effects. The measuring instruments used were - (a) Beck Depression Inventory, (b) Illness Effects Questionnaire, (c) Multidimensional Scale of Social Support, and (d) Satisfaction With Life Scale (in addition to the Karnofsky scale rating that a nephrologist provided for the assessment of physical functioning). This cohort was compared with – (a) a previously reported sample of non-Dialysis Stage 5 CKD patients, and (b) a previously reported sample of patients who had just been started on Hemodialysis therapy.

- Satisfaction with life and cognitive depression scores were similar across all of the groups (i.e. the CKD prior to Stage 5 group, the non-Dialysis Stage 5 CKD group, and the Dialysis Stage 5 CKD group). Even in the first group, there was minimal depression, as well as significant inter-correlations between – (a) perception of illness, (b) depression, and (c) QoL. The mean level of perceived social support was highest in the Dialysis group, though. In conclusion, higher negative perception of illness is associated with higher depression scores and lower QoL (even in early-stage CKD patients); however, social support may play an important role in the perceptions of those beginning to experience kidney impairment.

Critical appraisal of this Study identified the following noteworthy points –

- The sample size of the main cohort was very small, which may hinder the generalizability and accuracy of the results.
- Only aspects of mental-health related QoL were analysed; however, the inference that these aspects do not vary to a great degree across patients with different degrees of kidney impairment is noteworthy.
- The comparisons between groups were not straightforward, as each of the three groups had been measured at different times, and each of the sample sizes was different, too.
- The respective stages of CKD were not mentioned in this publication, and it should be noted that two of the three groups both contained Stage 5 CKD patients, while the other group was defined as the CRI (Chronic Renal Insufficiency) group.

- Several instruments were used during the same Study, which might have led to ``channel capacity`` issues.

## VI.3 STUDIES THAT COMPARED THE QUALITY OF LIFE OF ADULT PATIENTS HAVING CHRONIC KIDNEY DISEASE (OR EVEN OTHER CHRONIC CONDITIONS) WITH THE QUALITY OF LIFE OF A GENERAL POPULATION, ALONG WITH EVALUATION OF THE EFFECTS OF AGE, GENDER AND CO-MORBIDITIES

Utilizing both healthcare-related web-sites and general search engines, online searches were conducted, in order to find - Studies in English that compared the QoL of North American adult patients afflicted with CKD (or even other chronic conditions) with the QoL of a "norm" (i.e. disease-free) population, while using a version of the SF-36 QoL-measuring instrument, and while also evaluating the effects of the variables of Age, Gender, and Co-morbidities on QoL. Specific efforts were also made to find a Study that was conducted in Canada during the past five years.

The reasons for the rationale stated above are –

- Before the results of this particular Study are interpreted, it would be helpful to understand how CKD (or even chronic conditions, in general) can affect (health-related) QoL, particularly in relation to the general Canadian population.

- Before the results of this particular Study are interpreted, it would be helpful to know how Age, Gender, and Co-morbidities can affect the QoL of Canadians with CKD (or even chronic conditions, in general).

- Understanding some of the methods that were used (e.g. to categorize the variable of Age into groups, to build the predictor models, etc.) would be very helpful before the current analyses are carried out.

- Studies that used the SF-36 QoL-measuring instrument and Canadian SF-36 normative data would be primarily sought for, so that comparisons with this particular Study could be straightforward.

- Studies from the recent past would be much preferred because only recent studies could reflect how present-day trends in healthcare and disease progression (with regards to – CKD in Canada) might be impacting patients' QoL.

The search for relevant publications was conducted, as follows –

- Using the search terms of "Quality of Life", "SF-36", "Chronic", "Kidney Disease", "Age", and "Gender", a search was performed in the PUBMED health database.
- Of the 57 publications that were retrieved in the PUBMED health database, only 1 publication was about a Study that utilized the SF-36 to compare the QoL of Canadian patients having one or more chronic conditions (CKD being one such condition) with the Canadian normative SF-36 data, while also evaluating the effects of co-morbidities on QoL; none of the other retrieved studies were performed on Canadian patients.
- Using the same search terms ("Quality of Life", "SF-36", "Chronic", "Kidney Disease", "Age", and "Gender"), searches were also performed in the EMBASE, COCHRANE

LIBRARY, and UPTODATE health databases; however, no additional studies of relevance were discovered.

- A general Google search found no further studies of relevance, either.

The single publication that has been found to have the most relevance to this Study is summarized, as follows -

***TABLE VI.4: Associations between chronic disease, age and physical and mental health status, 2009 (Chronic Diseases in Canada 29 (3): 108-116)***[N]

*W. M. Hopman; M. B. Harrison; H. Coo; E. Friedberg; M. Buchanan; E. G. Van Den Kerkhof*

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| Objective | To examine the associations between chronic disease, Age, and QoL (both physical health-related and mental health-related). |
| Country where the Study was based | Canada (province of Ontario). |
| Study design | Cross-sectional Analysis |
| Number of subjects | 2418 patients aged 25 years, or more (129 had Kidney Failure, 366 had Osteoarthritis, 487 had Heart Failure, 1160 had chronic Leg Ulcer, and 276 had Multiple Sclerosis). |
| Instrument(s) used | Medical Outcomes Study 4-week recall SF-36 (or SF-12, in some cases). |
| Methods | Age was categorized in 10-year increments (just as the Canadian normative data is categorized for the variable of Age).<br>Five condition-specific databases were created, and the mean PCS and MCS scores (graphed by Age Group and Condition) were compared with the Canadian normative data that were adjusted for Age and Gender.<br>Multiple Linear Regression models were created to predict PCS and MCS scores, while controlling for – Condition, Age Group, Gender, Living Circumstances, Cardiovascular |

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| | Disease, Diabetes, and any other Co-morbidities (note - Diabetes and Cardiovascular Disease were the predominant co-morbidities in these patients).<br>Two-way interactions were also assessed.<br>(During comparison with the normative data, the reference Age Group was set as 25-34 years, while Heart Failure was set as the reference Condition because it had the highest mean Age, out of all five chronic conditions). |
| Main Statistical Analytical Method(s) | Multiple Linear Regression. |
| Results | The respective mean PCS scores for those with the chronic diseases were much lower than the mean PCS score from the Canadian normative data; the respective mean MCS scores for those with the chronic diseases were only slightly lower than the mean MCS score from the Canadian normative data (note - the mean MCS score for CKD patients was actually near identical to the mean MCS score from the Canadian normative data).<br>Further decreases in both the PCS and MCS scores were observed in female patients.<br>Further decreases in both the PCS and MCS scores (with greater decreases on the PCS measure) were observed in patients with co-morbid conditions.<br>Increased Age was significantly associated with decreased PCS scores (even after controlling for - Condition, Gender, and Co-morbidities); on the other hand, increased Age was significantly associated with increased MCS scores.<br>(There was no significant difference in PCS or MCS scores between the condition-based sub-groups; however, on the PCS measure, it is worth mentioning that Osteoarthritis patients scored lowest, while Leg Ulcer patients scored highest, with CKD and Heart Failure patients scoring similarly - in between Leg Ulcer and Osteoarthritis patients). |
| Conclusions | Chronic diseases caused great impairments in physical health, but only mild impairments in mental health (as per patients' perceptions).<br>Female patients with chronic conditions perceived their health (physical and mental) to be worse than that of their male counterparts, which is consistent with other studies (note - QoL |

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| | in acute conditions does not appear to involve any Gender-based difference[75]).<br>Co-morbidities (Diabetes and Cardiovascular Diseases, in particular) led to further decreases in both physical and mental health perceptions, which is also consistent with the results from most other studies on this topic.<br>Increasing Age by itself leads to more physical hardships, even in disease-free individuals, which may explain why older persons with chronic diseases have worse PCS scores than younger individuals; mental health stabilizes over time, as individuals learn to cope with their ailments and therapies, and this may help to explain the increases in the MCS scores of older patients. |
| Recommendations | Additional research on patients with other chronic conditions, as well as longitudinal studies would be useful in better defining the complex relationship between chronic disease, physical health, mental health, and advancing age.<br>A validated co-morbidity index would be advantageous, too. |

Critical appraisal of this Study suggested the following noteworthy points –

- Since the Study data had to be extracted from ten databases, only six variables that were common to each database could be used (with no obtainable information about socio-economic status and illness severity, for example).
- A large proportion of the total sample (48%) had Leg Ulcer as their chronic condition, thus limiting the generalizability of the results, even though the sample size was large.
- The number of co-morbidities entered in each of the ten "source" databases was different; in addition, the severity of the co-morbid conditions in each patient (though important) could not be defined before analysis.

- The authors state that there were too few young patients with Osteoarthritis and Heart Failure, and too few older patients with Multiple Sclerosis.
- The cross-sectional nature of the Study meant that Age had to be stratified, but this is inferior to following the same cohort, longitudinally, and looking at how QoL changes along with ageing.

## VI.4 SUMMARY OF THE NOTEWORTHY POINTS FROM THE LITERATURE REVIEW

Based on the literature that has been reviewed, the following impressions should be briefly stated -

- Physical health-related QoL appears to significantly and progressively worsen, as CKD advances from the early stages to Stage 5; this appears to particularly be true, with regards to the SF-36 Domains of PF, RP, and GH.
- Mental health-related QoL appears to be impacted to a mild degree (if at all) by CKD with no definitive pattern of QoL change being obvious, as CKD advances from the early stages to Stage 5; this appears to be the case, especially with regards to the SF-36 Domains of MH, RE, and SF.

**Additional notes:** The following observations should also be mentioned -

- Ageing appears to generally worsen physical-health related QoL in CKD patients, although the perception of pain does not appear to be significantly affected by ageing; on

the other hand, mental health-related QoL generally appears to improve, as CKD patients become older.

- Across the board, male CKD patients appear to perceive their QoL as being better (when compared to corresponding female patients).
- In general, associated co-morbidities appear to lead to further decreases in the QoL of CKD patients, with greater impacts on physical health-related QoL; however, it has not been possible to clearly ascertain how each respective co-morbidity impacts the QoL of CKD patients.

# VII. DATA AND DESIGN

## VII.1 DATA

The data used for this Study were amalgamated from three existing datasets that were each part of a Medical Research Study, in the past. These three datasets will now be described, along with the pertinent points, regarding each of the three studies.

### Dataset from the Patient's Perception of life on Hemodialysis Scale (PPHS) Study

This dataset was obtained from my supervisor (Dr. Brendan Barrett) who was one of the Primary Investigators on this project (note - Dr. Patrick Parfrey who is another member of my Supervisory Committee was also a Primary Investigator on this project). The complete dataset was obtained in April, 2012, at the Patient Research Centre, Faculty of Medicine, Memorial University of Newfoundland, St. John's, Newfoundland and Labrador. Clarifications (regarding - the compilation of the dataset, the structure of the dataset, and the definitions of the various variables in the dataset) were subsequently obtained over the next few weeks via Dr. Barrett, as well.

The important features of this particular dataset were, as follows -

- The dataset was in SPSS format, and it contained a total of 236 subjects with no personal identifiers.
- All of the subjects in this dataset had been on Hemodialysis therapy, at the time of data collection.

- The subjects in this dataset had been enrolled from five Hemodialysis centres (located in Newfoundland & Labrador, Quebec, and Ontario, respectively), and the time that patients had been on Hemodialysis therapy ranged from 3 months to 276 months.

- The entry dates of subjects (into this dataset) ranged from July, 1998 to February, 2000.

- All of the subjects in this dataset had been interviewed in their respective centres (to ascertain their perceptions of their own QoL); 120 of these subjects had answered to the RAND SF-36 instrument, while 71 had answered to the Ferrans and Powers Quality of Life Index instrument, and 45 had answered to both of those instruments.

- For every subject who had answered to the SF-36 instrument - the "raw" scores, the recoded "raw" scores (as per RAND SF-36 scoring instructions), and the eight SF-36 Domain scores were available.

- There were two "missing" data points for each of the two demographic variables of interest (i.e. Age and Gender), but no further "missing" data points were present.

The relevant aspects of the Study from which this dataset was derived could be summarized, as follows –

***TABLE VII.1: Psychometric Properties of the Patient's Perception of life on Hemodialysis Scale, 2012 (Thesis - Extract)***[O]

*(J. Creina Twomey, Brendan J. Barrett, Christine Y. Way, Tom A. Hutchinson, David N. Churchill, and Patrick S. Parfrey)*

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|---|---|
| Objectives | To assess the reliability and validity of the revised Patient's Perception of life on Hemodialysis Scale (PPHS) instrument. |

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| Country where the Study was based | Canada. |
| Study design | Cross-sectional Observational Study. |
| Number of subjects | 236 patients on Hemodialysis (in five respective centres) – all of the patients contributed towards the testing of the psychometric properties of the revised PPHS instrument, while data from just 30 of them were used to examine the stability of said instrument. |
| Instruments used | PPHS (revised version).<br>RAND SF-36.<br>Ferrans and Powers Quality of Life Index. |

***Note:*** *It should be mentioned that along with the Study that has just been described, a subset of 85 patients from the original sample was also assessed, longitudinally (with two measurements taken, six months apart), in order to (i) evaluate the changes in physical health, psycho-social health, and quality of supports among these Hemodialysis patients, at the two different time periods, (ii) evaluate the inter-relationship among patients' experiences, demographics, illness characteristics, and biochemical indicators, and (iii) determine the sensitivity of the PPHS instrument, while evaluating its ability to measure changes. However, these 85 patients included the 71 patients whose QoL was solely measured by the Ferrans and Powers Quality of Life Index; therefore, the data from most of these patients was unusable during the current Study.*

**Inclusion Criteria:** The data collection for the PPHS Study was conducted in five Hemodialysis centres (three in Newfoundland & Labrador, one in Quebec, and one in Ontario), and data was only collected from patients who met the following criteria –

- Were on in-centre Hemodialysis therapy for, at least, 12 weeks.

- Were mentally competent.
- Were not experiencing any episode of acute illness.
- Were over the age of 19.
- Were able to understand and speak English.

The variables of interest in this dataset were only those entered at Time 1 (i.e. the initial time when patients' QoL was measured), and they were the following –

- "Age": Defined as - "Age in years, at Time 1".
- "Sex": Defined as - "Gender of subject".
- "CHF1": Defined as – "Presence of Congestive Heart Failure on exertion, at Time 1".
- "CHF2": Defined as – "Presence of Congestive Heart Failure during rest, at Time 1".
- "Unstable": Defined as – "Attack of Angina and/or Myocardial Infarction event within the 6 months prior to Time 1".
- "IHD": Defined as - "Attack of Angina and/or Myocardial Infarction event in the past history, but with no such episode occurring within the 6 months prior to Time 1".
- "Diabetes": Defined as – "Presence of diabetic symptoms and/or reliance on anti-diabetic medication(s), at Time 1".
- "PVD": Defined as – "Presence of symptoms of Peripheral Vascular Disease, at Time 1".
- "Stroke": Defined as – "Occurrence of a thrombotic Stroke event within the 6 months prior to Time 1".

- "Sf361", "Sf362", etc.: Defined as – "The 'raw' scores for each respective answer to the SF-36 questionnaire, at Time 1".

- "ReSf1", "ReSf2", etc.: Defined as – "The recoded 'raw' scores for each respective answer to the SF-36 questionnaire, at Time 1".

- "Tpf", "Trp", "Tbp", "Tgh", "Tvt", "Tsf", "Tre", and "Tmh": Defined as – "The respective SF-36 Domain scores, as derived from the subjects' original answers to the SF-36 questionnaire, at Time 1".

(It should be noted that, due to being irrelevant to the question being posed and/or incompatibility with the other "source" datasets, there was no further use of the variables in the PPHS dataset that concerned the following – (a) time on Dialysis, (b) native language, (c) province of residence, (d) living arrangements, (e) cause of the Kidney Failure, (f) laboratory-based parameters, (g) Cancer, and (h) Lung Disease).

**Dataset from the CANPREVENT Study**

This dataset was obtained from my supervisor (Dr. Brendan Barrett) who was one of the Primary Investigators on this project (note - Dr. Patrick Parfrey who is another member of my Supervisory Committee was also a Primary Investigator on this project). The complete dataset was obtained in February, 2012, at the Patient Research Centre, Faculty of Medicine, Memorial University of Newfoundland, St. John's, Newfoundland and Labrador. Clarifications (regarding - the compilation of the dataset, the structure of the dataset, and the definitions of the various variables in the dataset) were subsequently obtained over the next few weeks via Dr. Barrett, as well.

The important features of this particular dataset were, as follows –

- The dataset was in SPSS format, and it contained a total of 474 subjects with no personal identifiers.

- All of the subjects in this dataset had had Stage 2, Stage 3, or Stage 4 of CKD when they were surveyed.

- The subjects in this dataset were selected from five urban centres in Canada.

- The entry dates of subjects (into this dataset) ranged from May, 2005 to June, 2008, and the subjects had also had their QoL measured, longitudinally (four measurements were taken, with an interval of four months between each measurement).

- Co-morbidity information for each subject in this dataset was based on that patient's medical history, alone; a perusal of the dataset showed that the dates of diagnosis (for respective co-morbidities) ranged from 1 year prior to a subject's first measurement of QoL to 25 years prior to said measurement.

- Each subject in this dataset had been required to answer to three respective QoL-measuring instruments, which were – (a) KDQOL-SF, (b) WHOQOL-BREF, and (c) HUI Mark 3.

- While none of the subjects had absolutely no "raw" SF-36 scores entered, at Time 1 (i.e. at the first time when their QoL was measured), some "raw" SF-36 scores had not been entered for a few subjects, at Time 1.

- 55 subjects did not have the stage of their CKD entered and/or could not have their SF-36 Summary scores calculated, as a result of insufficient "raw" scores under a particular SF-36 Domain, at Time 1 (this was particularly the case when just one of the two questions under the BP Domain or the SF Domain had been answered).

- For every subject who had provided sufficient "raw" SF-36 scores for the calculation of the SF-36 Domain scores - the recoded "raw" scores (as per RAND SF-36 scoring instructions) and the eight SF-36 Domain scores were also available.

- 8 subjects did not have any information entered, with regards to the status of their hearts.

The Study from which this dataset was derived led to the following publication (and the relevant aspects of that Study are subsequently summarized, too) –

***TABLE VII.2: A Nurse-coordinated Model of Care versus Usual Care for Stage 3/4 Chronic Kidney Disease in the Community: A Randomized Controlled Trial, February 2011 (Clinical Journal of the American Society of Nephrology 6: 1241-1247)***[P]

*(Brendan J. Barrett, Amit X. Garg, Ron Goeree, Adeera Levin, Anita Molzahn, Claudio Rigatto, Joel Singer, George Soltys, Steven Soroka, Dieter Ayers, and Patrick S. Parfrey)*

| | |
|---|---|
| Objectives | To compare a new coordinated model of care for CKD patients with the usual care that CKD patients receive. |
| Country where the Study was based | Canada. |
| Study design | Randomized Unblinded Controlled Trial. |
| Number of subjects | 474 patients with median estimated GFR of 42 mL/min/1.73m$^2$ (as identified by laboratory criteria) – of these patients, 32% had Diabetes and 60% had Cardiovascular Disease. |

| | |
|---|---|
| Instruments used | KDQOL-SF (including the RAND SF-36).<br>WHOQOL-BREF.<br>HUI Mark 3. |

**Inclusion Criteria:** The data collection for the CANPREVENT Study was conducted in five urban Canadian centres, and data was only collected from patients who met the following criteria –

- Were between 40 and 75 years of age.
- Had documented CKD with a GFR of between 25 and 60 mL/min/1.73m$^2$.

**Exclusion Criteria:** Patients who met the following criteria were excluded from the Study -

- Were expected to die within 6 months.
- Had either advanced Cardiovascular Disease, or had recent unstable Cardiovascular Disease.
- Were being treated for malignancy.
- Were receiving immunotherapy for Kidney Disease.
- Were either on Dialysis, or had received an organ transplant (already, or even with transplant surgery being planned within the next 6 months).
- Were already enrolled in a Kidney/Cardiovascular Disease management program (or in another interventional clinical trial).
- Were residing in a location that was too distant for them to attend Study visits.

The variables of interest in this dataset were only those entered at Time 1 (i.e. the initial time when their QoL was measured), and they were the following –

- "Age": Defined as - "Age in years, at Time 1".
- "Gender": Defined as - "Gender of subject".
- "Angina": Defined as – "Diagnosis of Angina Pectoris in subject's history".
- "HeartAttack": Defined as – "Diagnosis of a Myocardial Infarction in subject's history".
- "HeartFailure": Defined as – "Diagnosis of Congestive Heart Failure in subject's history".
- "Diabetes": Defined as – "Diagnosis of Diabetes Mellitus in subject's history".
- "Stroke": Defined as – "Diagnosis of a thrombotic Stroke in subject's history".
- "AORAN": Defined as – "Diagnosis of an Aortic Aneurysm in subject's history".
- "INTCL": Defined as – "Diagnosis of Intermittent Claudication in subject's history".
- "GANG": Defined as - "Diagnosis of Gangrene in subject's history".
- "DVT": Defined as – "Diagnosis of Deep Vein Thrombosis in subject's history".
- "MDRD0_stage": Defined as – "Stage of CKD, at Time 1".
- "a_KDQOLQ1", "a_KDQOLQ2", etc.: Defined as – "The 'raw' scores for each respective answer to the SF-36 portion of the KDQOL-SF questionnaire, at Time 1".

- "a_KDQOLQ1_rec", "a_KDQOLQ2_rec", etc.: Defined as – "The recoded 'raw' scores for each respective answer to the SF-36 portion of the KDQOL-SF questionnaire, at Time 1".

- "a_SF36PFscale", "a_SF36RPscale", "a_SF36Painscale", "a_SF36GHscale", "a_SF36EnergyFatiguescale", "a_SF36SFscale", "a_SF36REscale", and "a_SF36Emotionalscale": Defined as - "The respective SF-36 Domain scores, as derived from the subjects' original answers to the SF-36 portion of the KDQOL-SF questionnaire, at Time 1".

(It should be noted that, due to being irrelevant to the question being posed and/or incompatibility with the other "source" datasets, there was no further use of the variables in the CANPREVENT dataset that concerned the following – (a) randomization methods, (b) race/ethnicity, (c) education, (d) employment/occupation, (e) living arrangements, (f) marital status, (g) answers to questions in the KDQOL-SF questionnaire that were not part of the SF-36 instrument, (h) history of medical conditions that were not related to either Diabetes, or Heart Disease (e.g. Asthma, Tuberculosis, etc.), (i) history of heart-related conditions/procedures that did not clearly indicate symptomatic Heart Disease (e.g. Congenital Heart Disease, Heart Valve Replacement, etc.), and (j) laboratory-based parameters).

## **Dataset from the EPO-INTERNATIONAL Study**

This dataset was obtained from Dr. Patrick Parfrey (a member of my Supervisory Committee who was also a Primary Investigator on this project) with the permission of Janssen Ortho (the company that both owns and is responsible for this dataset). The complete dataset was obtained in April, 2012, at the Patient Research Centre, Faculty of Medicine, Memorial University of

Newfoundland, St. John's, Newfoundland and Labrador. While a "dictionary of variables" for this dataset was indeed accessible, further clarifications about this particular dataset were unobtainable due to the set-out regulations of Janssen Ortho.

The important features of this particular dataset were, as follows –

- The dataset was in Statistical Analysis System (SAS) format, and it contained a total of 596 subjects with no personal identifiers.
- All of the subjects in this dataset had been on Hemodialysis therapy, at the time of data collection.
- The subjects in this dataset were from the following countries - Canada, Austria, Germany, United Kingdom, Belgium, Poland, Hungary, Spain, France, and Greece.
- The entry dates of subjects into this dataset ranged from February, 2000 to February, 2003, and most of the subjects had had their QoL measured, longitudinally (eight separate measurements were attempted - at the time of entry into the Study, and subsequently at 24, 36, 48, 60, 72, 84, and 96 weeks).
- For the purpose of ascertaining their QoL, all of the subjects in this Study had answered to the KDQOL-SF instrument.
- Heart Disease (not including Arrhythmias) was part of the exclusion criteria for this Study; while there was no specific labelling of patients with Diabetes in this dataset, those subjects whose CKD had been caused by Diabetic Nephropathy could be identified as Diabetics because the "Primary Cause of Kidney Disease" was actually a variable in this dataset.

- Only the Domain scores for each subject were available in this dataset, with no "raw" scores or recoded "raw" scores being available for any subject; upon detailed perusal, it was confirmed that the SF-36 Domain scores for every subject had been obtained via the original (i.e. MOS) SF-36 scoring algorithm.

- In this dataset, there were absolutely no SF-36 scores for 45 subjects, while SF-36 scores from the first time of entry into the Study were not included for another 58 subjects (however, SF-36 scores from, at least, one subsequent visit were entered for those 58 subjects).

The Study from which this dataset was derived led to the following publication (and the relevant aspects of that Study are subsequently summarized, too) –

***TABLE VII.3: Erythropoietin therapy, hemoglobin targets, and quality of life in healthy hemodialysis patients: a randomized trial, April 2009 (Clinical Journal of the American Society of Nephrology 4 (4): 726-733)***[Q]

*(Robert N. Foley, Bryan M. Curtis, Patrick S. Parfrey)*

| | |
|---|---|
| Objectives | To analyse the effects of different Hemoglobin targets (when using Erythropoiesis-stimulating agents) on QoL because predictors of change in QoL during end-stage Kidney Disease have not been well characterized, thus far. |
| Countries where the Study was based | Canada, Austria, Germany, United Kingdom, Belgium, Poland, Hungary, Spain, France, and Greece. |
| Study design | Randomized Double-Blind Controlled Trial. |
| Number of subjects | 596 patients on Hemodialysis, in the respective countries that are mentioned, above. |

| | |
|---|---|
| Instrument used | KDQOL-SF (including the Medical Outcomes Study SF-36). |

**Inclusion Criteria:** The data collection for the EPO-INTERNATIONAL Study was conducted in the ten respective countries, and data was only collected from patients who met the following criteria –

- Were 18 years of age, or older.
- Had been started on Maintenance Hemodialysis Therapy, 3 to 18 months before the first measurement of their QoL.
- Had a pre-dialysis Hemoglobin reading of between 8 and 12 g/dl.
- Had a Left Ventricular Volume Index <100 ml/$m^2$.
- Had a pre-dialysis Diastolic Blood Pressure reading <100 mmHg.

**Exclusion Criteria:** Patients who met the following criteria were excluded from the Study -

- Clinical evidence or history of symptomatic Cardiac Failure or Ischemic Heart Disease.
- Daily Prednisone dose that was 10 mg, or more.
- Medical conditions likely to reduce Erythropoietin responsiveness (including uncorrected Iron Deficiency).
- Concurrent malignancy.
- Blood transfusion in the preceding month.
- Therapy with cytotoxic agents.

- Seizure in the preceding year.
- Hypersensitivity to intravenous Iron.
- Current pregnancy or breastfeeding.

The variables of interest in this dataset were only those entered at Time 1 (i.e. the initial time of entry into the Study), and they were the following –

- "AGE": Defined as - "Age in years, at Time 1".
- "SEX": Defined as - "Gender of subject".
- "PRIM": Defined as – "Primary cause of the Chronic Kidney Disease" (note – this variable was only beneficial, in terms of identifying the subjects who definitely had Diabetes, at Time 1).
- "PHYFUN10", "ROLEP4", "PAIN2", "GENH5", "ENFAT4", "SOCFUN2", "ROLEE3", and "EMOT5": Defined as - "The respective SF-36 Domain scores, as derived from the subjects' original answers to the SF-36 portion of the KDQOL-SF questionnaire, at Time 1".

(It should be noted that, due to being irrelevant to the question being posed and/or incompatibility with the other "source" datasets, there was no further use of the variables in the EPO-INTERNATIONAL dataset that concerned the following – (a) randomization methods, (b) time on Dialysis, (c) country of residence, (d) race/ethnicity, (e) answers to questions in the KDQOL-SF questionnaire that were not part of the SF-36 instrument, and (f) laboratory-based parameters).

**The combination of variables from the three datasets into the final dataset:** The variables of interest were pooled and combined from the three described datasets, based on the following guidelines –

- The demographic variables ("AGE" and "GENDER") were combined into the final dataset in a straightforward manner, as they were each defined in the exact same way across each of the three "source" datasets; it was only necessary to ensure that the abbreviations (i.e. codes) for each of these demographic variables were exactly the same in the "source" datasets, prior to the combination.

- The relevant variables concerning the SF-36 scores (i.e. the Domain scores, and where available, the "raw" scores) were combined into the final dataset in a straightforward manner, as they were each defined in the exact same way across each of the three "source" datasets; it was only necessary to ensure that the abbreviations (i.e. codes) for these QoL variables were exactly the same in the "source" datasets, prior to the combination.

- The variable of "STAGE OF CKD" was created in the final dataset in the following manner – (i) all subjects from the PPHS and EPO-INTERNATIONAL datasets were labelled as having Stage 5 CKD, and (ii) each subject from the CANPREVENT dataset was labelled as having the stage of the disease that matched the entry for him/her under the "MDRD0_stage" variable in the CANPREVENT dataset.

- The variable of "DIABETES" was created in the final dataset in the following manner – it was constituted from (i) the Presence/Absence variable of "Diabetes" in the PPHS dataset, (ii) the Presence/Absence variable of "Diabetes" in the CANPREVENT dataset,

and (iii) the variable of "PRIM" in the EPO-INTERNATIONAL dataset, from which only those subjects who had had Diabetic Nephropathy were extracted (note – only the CANPREVENT dataset contained a variable that described the specific type of Diabetes present).

- The variable of (symptomatic) "HEARTDISEASE" was created in the final dataset in the following manner – it was constituted from (i) the Presence/Absence variables of "CHF1", "CHF2", "Unstable", and "IHD" in the PPHS dataset, and (ii) the Presence/Absence variables of "Angina", "HeartAttack", and "HeartFailure" in the CANPREVENT dataset (note – these constituent variables were used due to being available, and also because patients with IHD and/or Heart Failure were specifically excluded from the EPO-INTERNATIONAL Study).

- The variable of "HEARTFAILURE" was created in the final dataset in the following manner – it was constituted from (i) the Presence/Absence variables of "CHF1", and "CHF2" in the PPHS dataset, and (ii) the Presence/Absence variable of "HeartFailure" in the CANPREVENT dataset.

- The variable of "ANGINA" was created in the final dataset in the following manner – it was constituted from (i) the Presence/Absence variable of "Unstable" in the PPHS dataset, and (ii) the Presence/Absence variable of "Angina" in the CANPREVENT dataset (note – the "IHD" variable in the PPHS dataset was neglected because that variable encompassed subjects who had experienced symptoms of IHD >6 months prior to their baseline QoL measurement, and it was also unclear whether these subjects who

were labelled as having IHD had experienced Angina, or a Myocardial Infarction, or both).

- The variable of symptomatic "PVD" was created in the final dataset in the following manner – it was constituted from (i) the Presence/Absence variable of "PVD" in the PPHS dataset, and (ii) the Presence/Absence variables of "AORAN", "INTCL", "GANG", and "DVT" in the CANPREVENT dataset.

- The variable of (thrombotic) "STROKE" was created in the final dataset in a straightforward manner, as it was a 'Presence/Absence" variable in the two datasets that included patients with thrombotic Strokes.

## VII.2 DESIGN

The Study Design being employed for this particular analysis is a – Retrolective Cross-sectional Observational Study (note – it is "retrolective" because, while this Study is utilizing data from historical studies, each of those already-completed studies was actually a Prospective Study, at the time).

### Cross-sectional study

A cross-sectional study is basically a "snapshot" at a specific point in time of an outcome and the factors that are associated with that particular outcome[76]. A cross-sectional study is descriptive in nature, and survey-based data is commonly the focus of cross-sectional studies. Cross-sectional studies are usually conducted when a given population needs to be described in terms of an outcome and a set of risk factors for that outcome, but they can also be used when the prevalence

of a particular outcome of interest (within a given population) needs to be determined[76]. Cross-sectional studies are rarely used to prove/disprove hypotheses, as they cannot conclusively prove causality. Cross-sectional studies also cannot describe associations between an outcome and risk factors over a long period of time; however, repeated cross-sectional studies with the same variables (e.g. looking into the annual prevalence of CKD in Canada by analysing a different randomly-selected sample, every year) could still provide valuable information for the longer term.

In the field of medicine, cross-sectional studies are primarily used for the generation of hypotheses and/or the development of public health policy (regarding certain medical conditions).

Ideally, for it to be truly representative, a cross-sectional study should be based on a large sample that has been selected at random[77]. In addition, whenever cross-sectional analyses are being performed using responders to a survey, the response rate to the survey must not be connected in any way to something that may skew the results[77] (e.g. a survey should not be exclusively completed at a clinic because a disproportionate majority of the responders would then be ambulatory patients, rather than bed-ridden patients who would be relatively more debilitated). Therefore, survey-based cross-sectional studies should involve multiple methods of survey-taking, in order to ensure both a high response rate, and a non-biased sample of responders.

The main advantages of a cross-sectional study design are – (a) it is relatively inexpensive, (b) it is less time-consuming than most other study designs, and (c) loss to follow-up does not occur, thus allowing many variables to be part of the study (as opposed to a longitudinal study where it makes more sense to have a small number of both independent and dependent variables).

The main disadvantages of a cross-sectional study design are – (a) two cross-sectional studies on the same population (with identical variables) that are conducted at different times may each produce significantly different results, (b) results of a single "snapshot" are insufficient to concretely prove any etiology, and (c) particularly when chronic diseases are being studied, any risk factor that may cause death will not be well-represented among those afflicted with the disease.

**Reasons for the cross-sectional study design in this case (taking the available datasets into account):** The utilization of a cross-sectional design for this particular Study was appropriate due to the following main reasons –

- Despite only historical data being available, the fact that data from Time 1 (in each "source" Study) could be satisfactorily extracted made a cross-sectional approach possible.

- Each of the three historical studies were disparate, in terms of times and locations; this fact means that any present/future follow-up of the included subjects would be unfeasible.

- The dataset from the PPHS Study did not permit any longitudinal evaluation for 151 out of the 165 patients who had answered to the SF-36 instrument (note - the majority of those who had been followed, longitudinally had only been measured by the Ferrans and Powers Quality of Life Index instrument).

- The available historical data made using a cross-sectional design to compare QoL across the stages of CKD more logical because, for one thing, subjects from the PPHS and EPO-INTERNATIONAL datasets had Stage 5 CKD (and were on Dialysis) throughout the

period of their QoL measurements, whereas many subjects from the CANPREVENT dataset did not have the exact same CKD stage throughout the period when their QoL was measured, longitudinally.

- Each of the three studies had followed different criteria for the follow-up of patients during longitudinal assessments (for example – the time intervals between consecutive surveys and the durations of follow-up were different, in each of the three studies).

# VIII. METHODS

## VIII.1 STEPS

The analysis associated with this Study was conducted while following these steps (in sequential order) -

- Although a cross-sectional study cannot prove/disprove any hypothesis, the basic objectives of the Study (which had to be borne in mind) were to find out whether the following statements may be true, or not - (i) The QoL of patients with Stage 3 CKD is the same as the QoL of patients with Stage 4 CKD, and is also the same as the QoL of patients with Stage 5 CKD, (ii) the QoL of patients who have both CKD and Diabetes is the same as the QoL of patients who have CKD but not Diabetes, and (iii) the QoL of patients who have both CKD and symptomatic Heart Disease is the same as the QoL of patients who have CKD but not symptomatic Heart Disease.
- Ethics approval for this project was obtained from the Health Research Ethics Authority (HREA), in St. John's, Newfoundland and Labrador.
- The three (PPHS, CANPREVENT, and EPO-INTERNATIONAL) datasets were collected, following which it was determined that, with regards to QoL info, only the SF-36 Domain scores were common to each of those datasets (note - the “raw” SF-36 scores and the recoded “raw” SF-36 scores were only available for subjects in the PPHS and CANPREVENT datasets).
- As the dataset from the EPO-INTERNATIONAL Study was originally in SAS format, it was converted into SPSS format (using an option available within the SPSS program), so that it could be compatible with the other two “source” datasets.

- All QoL-related data points in the three datasets that were obtained via instruments other than the SF-36 were deleted because those data points would not be compatible with the information obtained via the SF-36 questionnaire (note - different questionnaires comprise different questions, dimensions, scoring patterns, etc.). It should be mentioned that this requisite led to the removal of (i) 71 out of 236 subjects in the PPHS dataset who had had their QoL measured solely by the Ferrans and Powers Quality of Life Index, and (ii) all QoL-related scores in the CANPREVENT and EPO-INTERNATIONAL datasets that were obtained via questions 12–24 of the KDQOL-SF Instrument (i.e. the questions in that instrument that are distinct from the SF-36 questions).
- With regards to the data points that were only based on the SF-36 instrument, several errors of entry and/or calculation were corrected, following a perusal of each subject's (i) "raw" scores, (ii) re-coded "raw" scores, and (iii) Domain scores. This was done, specifically with regards to – (i) several random wrongly-calculated GH Domain scores in the PPHS dataset, and (ii) the recoded scores for Answer # 3 to SF-36 Questions # 34 and # 36 in the CANPREVENT dataset (note - this particular answer had been consistently recoded as "30", instead of the correct "50").
- Variables from each of the three "source" datasets that would have no bearing on the particular research question behind this Study were deleted, except for a few variables (e.g. the "raw" SF-36 scores from the PPHS and CANPREVENT datasets), which could be used for cross-check purposes, later.
- Any information (for each subject across all three datasets) that was not collected at baseline (i.e. not collected at first "visit") was deleted; however, for a few subjects in the EPO-INTERNATIONAL dataset whose baseline SF-36 Domain scores were unavailable,

it was decided to include the SF-36 Domain scores from the subjects' earliest subsequent visit when those scores were actually obtained/entered (this was possible and done for 58 subjects). It was necessary to delete non-baseline information because (i) only baseline information was available for most of the subjects in the PPHS dataset who had answered to the SF-36 instrument, thereby preventing any worthwhile longitudinal analysis, and (ii) in such a cross-sectional evaluation, applying uniform criteria (such as – only including QoL info from the time of first "visit") is more logical, and also more beneficial during the interpretation of results.

- A small number of cases for whom the stage of CKD was not entered at baseline were deleted (this was only true for a few cases in the CANPREVENT dataset); it may be noted that two subjects in the PPHS dataset had not had their Age and Gender entered, but it was decided to include these two cases in the final dataset because they would still be useful data points when QoL across the stages of CKD (and across each co-morbidity) was compared.
- The eight variables comprising baseline data that were common to and comparable across all three "source" datasets (i.e. Age, Gender, PF Domain score, RP Domain score, VT Domain score, SF Domain score, RE Domain score, and MH Domain score) were combined in the merged dataset, such that each of these variables would singly encompass all of the relevant cases from the "source" datasets.
- The three variables comprising baseline data that were common to and comparable across only the PPHS and CANPREVENT datasets (i.e. BP Domain score, GH Domain score, and Recoded SF-2 Question score) were also combined in the merged dataset, such that each of these variables would singly encompass all of the relevant cases from the two

"source" datasets; it may be noted that while BP and GH Domain scores were also present in the EPO-INTERNATIONAL dataset, they were calculated there via the MOS SF-36 scoring algorithm (rather than via the RAND SF-36 scoring algorithm, which was the method used in the other two datasets), and this fact plus the lack of "raw"/recoded "raw" SF-36 scores in the EPO-INTERNATIONAL dataset precluded the use/comparison of the differently-calculated Domain scores from the EPO-INTERNATIONAL dataset.

- Stage of CKD was created as a variable in the merged dataset by (i) labelling all of the subjects from the PPHS and EPO-INTERNATIONAL datasets as having Stage 5, and (ii) labelling each subject from the CANPREVENT dataset as having the stage of the disease that he/she had at the time of his/her first QoL measurement.
- Diabetes was constituted as a Yes/No variable in the merged dataset after combining (i) the subjects from the PPHS and CANPREVENT datasets who were labelled as having Diabetes at baseline, and (ii) the subjects in the EPO-INTERNATIONAL dataset for whom Diabetic Nephropathy was entered as the cause of their CKD (note - the specific type of Diabetes was a variable in only the CANPREVENT dataset, which meant that that piece of information was unusable in a merged dataset).
- Heart Disease was constituted as a new Yes/No variable in the merged dataset, after combining the constituents of Heart Disease in the PPHS and CANPREVENT datasets that were (i) present as individual variables, (ii) suggestive of symptomatic Heart Disease at baseline, and (iii) definitely part of the exclusion criteria during the EPO-INTERNATIONAL Study (notes – (a) in the merged dataset, all of the EPO-INTERNATIONAL subjects were labelled as being free of Heart Disease due to the exclusion criteria of that particular Study, and (b) Arrhythmia was a variable in both the

PPHS and CANPREVENT datasets, but it was decided to completely exclude this constituent of Heart Disease from the merged dataset because, unlike all of the other Heart-related disorders, Arrhythmia was not part of the exclusion criteria during the EPO-INTERNATIONAL Study).

- Four Cardiovascular Disease-related variables comprising baseline data that were common to and comparable across the PPHS and CANPREVENT datasets (i.e. Heart Failure, Angina, Peripheral Vascular Disease, and Stroke) were also constituted as Yes/No variables in the merged dataset, such that each variable would singly encompass all of the relevant cases from the two "source" datasets. It should be mentioned that, in the CANPREVENT dataset, the variable of Peripheral Vascular Disease had to be constituted from these separate variables – (a) Aortic Aneurysm, (b) Gangrene, (c) Intermittent Claudication, and (d) Deep Vein Thrombosis (note - while the last mentioned condition is the only venous disorder out of the four, it has been recently classified as a Peripheral Vascular Disease[32]).
- The PCS score and the MCS score were individually calculated (using the Norm Based Scoring (NBS) calculator) for each subject who had been in the PPHS and CANPREVENT datasets. It was not possible to calculate Summary scores for the EPO-INTERNATIONAL subjects because of (i) the incompatible BP Domain scores and GH Domain scores in the EPO-INTERNATIONAL dataset, and (ii) the non-availability of "raw"/recoded "raw" SF-36 scores in the EPO-INTERNATIONAL dataset. It may be noted that the NBS calculator is freely available online at www.SF-36.org, which is a web-site that is run by Qualitymetric Incorporated (i.e. the company that took over all of the SF-36 processes from the Medical Outcomes Trust); this calculator can compare the

entered Domain scores with Canadian "norm" Domain scores, and then extrapolate that information into the two respective Summary scores. The NBS calculator was used to calculate the Summary scores because (i) the purchasable proprietary scoring software from Qualitymetric Incorporated does not work with RAND SF-36 scoring instructions, does not work with SF-36 version 1 answers, and also does not work with Canadian "norm" scores (unlike the NBS calculator, which does), (ii) it is important to obtain Summary scores, but as this Study is only comparing QoL scores between diseased groups, it is not really important to understand how patients' Domain scores differ from "norm" Domain scores, and (iii) the Summary scores for every patient are computed identically by the NBS calculator, after first comparing the entered Domain scores with the "norm" Domain scores for Canada (this ensures that all calculations are consistent with each other, as long as all entered Domain values come via one particular scoring algorithm).

- A variable that indicated the specific cause of CKD could not be included in the merged dataset due to it being absent in the CANPREVENT dataset, while a variable that indicated a past history of Heart Disease could not be included in the merged dataset due to it being absent in the PPHS dataset.
- A new variable was created in the merged dataset, in order to indicate which original Study each individual subject had been extracted from.
- After being created, the merged dataset was cross-checked for errors, while the codes (and answers) for all of the variables were verified to make sure that they were consistent with the entries in the respective "source" datasets. For a few variables that were coded differently in their respective original datasets, a new coding system was created to

encompass all of the subjects in the merged dataset (for example – for medical condition-related variables in the PPHS dataset, "1" indicated "presence of disease", while "0" indicated "absence of disease", but the opposite was true in the CANPREVENT dataset; in the merged dataset, it was decided to follow the coding system used in the PPHS dataset because "0" seemed to be more appropriate for an absence).

- All of the respective Domain scores (in addition to the two Summary scores, and the Recoded SF-2 Question score) would be utilized as Outcome variables because (i) no general trend can be expected in advance across the Study sample, with regards to either physical health, or mental health, and (ii) nothing concerning this particular Study necessitates a restriction of the number of Outcome variables.
- To permit bivariate comparison of "outcome by age", the continuous variable of Age was broken down into the ordinal variable of Age Category (with six respective categories).
- Statistical significance was inferred if the *p* value was $<0.05$.
- Descriptive Statistics (overall numbers, means, medians, standard deviations, variances, as well as informative bar charts and histograms) were obtained for all of the relevant Grouping variables (i.e. Age Category, Gender, Stage of CKD, Diabetes, and Heart Disease).
- Descriptive Statistics (overall numbers, means, medians, standard deviations, variances, as well as informative bar charts and histograms) were obtained for all of the relevant Outcome variables (i.e. PF Domain score, RP Domain score, VT Domain score, SF Domain score, RE Domain score, MH Domain score, BP Domain score, GH Domain score, Recoded SF-2 Question score, PCS score, and MCS score). It may be noted that

the latter five of these variables were not applicable to subjects from the EPO-INTERNATIONAL dataset due to reasons that have already been explained.

- Means were obtained (without any statistical tests) for all of the Outcome variables, across each of the Grouping variables, just to get a general sense of the data patterns; means were similarly obtained for all of the Outcome variables with the Grouping variable being – the Original Study.
- For the purpose of providing a diagrammatic overview - bar charts were plotted, in order to indicate what the means of each of the relevant Outcome variables were for (i) CKD patients with no co-morbidities, (ii) CKD patients with Diabetes, but not Heart Disease, (iii) CKD patients with Heart Disease, but not Diabetes, and (iv) CKD patients with both Diabetes and Heart Disease.
- Tests of Normality were performed (each Outcome variable versus each Grouping variable), in order to determine whether the means/medians were best compared by parametric or non-parametric methods.
- As non-parametric comparisons of medians/ranks were indicated by the Tests of Normality, the Kruskal-Wallis Test (for Grouping variables – Age Category and Stage of CKD) and the Mann-Whitney U Test (for Grouping variables – Gender, Diabetes, Heart Disease, Heart Failure, Angina, Peripheral Vascular Disease, and Stroke) were performed, in order to find out which differences in mean ranks were actually significant. It may be noted that (i) the Levene's Non-parametric Test was performed for each comparison, in order to test the assumption of "homogeneity of variance", and (ii) medians for each Outcome variable (across each Grouping variable) were also subsequently obtained, in order to bolster the results of the non-parametric comparisons of mean ranks.

- Multiple Linear Regression models were built for each one of the eleven Outcome variables (i.e. PF Domain score, RP Domain score, VT Domain score, SF Domain score, RE Domain score, MH Domain score, BP Domain score, GH Domain score, Recoded SF-2 Question score, PCS score, and MCS score), in order to see which of the five Grouping variables (i.e. Age, Gender, Stage of CKD, Diabetes, and Heart Disease), if any, were significant predictors of each of the outcomes. Any non-significant predictors of each outcome were eliminated, step-by-step until only the significant predictor(s) remained in the final model (for each of the eleven Outcome variables); these final models were each subsequently evaluated for validity and "fit".
- Results primarily from (i) the Kruskal-Wallis/Mann-Whitney U Tests, and (ii) the Multiple Linear Regression models were analysed and interpreted.

**Notes:** Other points that are related to the described steps (and worth mentioning) are, as follows -

- The variables of "Heart Failure", "Angina", and "PVD" were each defined in the merged dataset as – "presence or history of (the respective condition)"; the variable of "Stroke" was defined in the merged dataset as - "history of (the condition)".

- The only variable in any of the "source" datasets that definitely indicated a Myocardial Infarction (in the patient's history) was the variable called "HeartAttack" in the CANPREVENT dataset; therefore, a single variable in the merged dataset to indicate a prior Myocardial Infarction was unfeasible, although the "HeartAttack" variable in the CANPREVENT dataset did help to constitute the variable of Heart Disease, in the merged dataset.

- For the purpose of getting a general impression, the mean Age was obtained for each of the following – (i) the respective genders, (ii) the respective stages of CKD, (iii) CKD patients with and without Diabetes, and (iv) CKD patients with and without Heart Disease.

- For the purpose of getting a general impression, the gender distribution was obtained across each of the following – (i) the respective stages of CKD, (ii) CKD patients with and without Diabetes, and (iii) CKD patients with and without Heart Disease.

- For all of the "Yes/No" variables: 0 = No (or Absent) while 1 = Yes (or Present); similarly, with regards to Gender: 0 = Female, while 1 = Male.

- As per the requisites of the respective statistical tests - Age (continuous variable) was used as a Predictor variable during the Multiple Linear Regression analyses, while Age Category (ordinal variable) was used as a Grouping variable during the Kruskal-Wallis Test.

- Prior to the Multiple Linear Regression analyses, the Stage of CKD variable was re-coded, as follows: Stage 2/3/4 = 0, and Stage 5 = 1; this was done due to the relatively small number of patients with Stage 2 and Stage 4 CKD (i.e. a total of 19 out of the 1135 patients in the whole sample), and also because it will be of greater interest in clinical settings to know if QoL significantly differs between CKD patients on Dialysis and CKD patients not on Dialysis.

- Prior to the Kruskal-Wallis/Mann-Whitney U Tests, the Stage of CKD variable was re-coded for the single case with Stage 2 CKD, as follows: 2 = 3; this was done because there was just one case in the final dataset with Stage 2 CKD, and this was proving

difficult to handle, statistically (e.g. during the Levene's Non-Parametric Test, following the comparison of medians/ranks).

## VIII.2 SUMMARY OF RELEVANT VARIABLES IN THE FINAL (MERGED) DATASET

**Codes and explanations for the Grouping variables:** The respective Grouping variables would be, as follows -

- AGE (continuous variable) = Age in years, at Time 1 (i.e. at baseline).
- AGEGROUPS (ordinal variable) = Age Category, at Time 1 (i.e. at baseline): 30 years and under (coded as "1"), 31 to 40 years (coded as "2"), 41 to 50 years (coded as "3"), 51 to 60 years (coded as "4"), 61 to 70 years (coded as "5"), and 71 years and over (coded as "6").
- SEX (binary variable) = Gender: Female (coded as "0"), or Male (coded as "1").
- STAGECKD (ordinal variable) = Stage of Chronic Kidney Disease, at Time 1 (i.e. at baseline): Stage 2 or mild decrease in kidney function (coded as "2"), Stage 3 or moderate decrease in kidney function (coded as "3"), Stage 4 or severe decrease in kidney function (coded as "4"), and Stage 5 or Kidney Failure (coded as "5").
- DIABETES (binary variable) = Presence/absence of any type of Diabetes, at Time 1 (i.e. at baseline): No (coded as "0"), or Yes (coded as "1").

- HEARTDISEASE (binary variable) = Presence/absence of (symptomatic) Heart Disease or history of (symptomatic) Heart Disease, at Time 1 (i.e. at baseline): No (coded as "0"), or Yes (coded as "1").

- HEARTFAILURE (binary variable) = Presence/absence of Congestive Heart Failure or history of Congestive Heart Failure, at Time 1 (i.e. at baseline): No (coded as "0"), or Yes (coded as "1").

- ANGINA (binary variable) = Presence/absence of Angina or history of Angina, at Time 1 (i.e. at baseline): No (coded as "0"), or Yes (coded as "1").

- PVD (binary variable) = Presence/absence of Peripheral Vascular Disease or history of Peripheral Vascular Disease, at Time 1 (i.e. at baseline): No (coded as "0"), or Yes (coded as "1").

- STROKE (binary variable) = Presence/absence of history of Stroke, at Time 1 (i.e. at baseline): No (coded as "0"), or Yes (coded as "1").

**Codes and explanations for the Outcome variables:** The respective Outcome variables would be, as follows -

- PHYFUNC (continuous variable, but with mild ordinal characteristics) = Transformed Physical Functioning Domain score.

- ROLEPHY (continuous variable, but with mild ordinal characteristics) = Transformed Role-Physical Domain score.

- ENERFAT (continuous variable, but with mild ordinal characteristics) = Transformed Vitality Domain score.
- SOCIALFUNC (continuous variable, but with mild ordinal characteristics) = Transformed Social Functioning Domain score.
- ROLEEMOTION (continuous variable, but with moderate ordinal characteristics) = Transformed Role-Emotional Domain score.
- EMOTION (continuous variable, but with mild ordinal characteristics) = Transformed Mental Health Domain score.
- PAIN (continuous variable, but with mild ordinal characteristics) = Transformed Bodily Pain Domain score.
- GENHEALTH (continuous variable, but with mild ordinal characteristics) = Transformed General Health Domain score.
- SF2_RECODED (continuous variable, but with pronounced ordinal characteristics) = Transformed score that pertains to the perception of current health, as compared to health at a year ago.
- PCS (continuous variable) = Physical Component Summary score.
- MCS (continuous variable) = Mental Component Summary score.

**Other variables:** The other variables that require a mention would be, as follows -

- PATIENTID = Patient Identification Number (note – as it was luckily appropriate, the respective number for each subject in the merged dataset was exactly the same number

that he/she had been designated with in his/her "source" dataset; no number identified more than a single patient in the merged dataset).

- ORIGIN = Original dataset from which the case was obtained: PPHS (coded as "1"), EPO-INTERNATIONAL (coded as "2"), and CANPREVENT (coded as "3").

- SF1, SF2, SF3, and so on… up to SF36 = The "raw" SF-36 scores (i.e. the answers at baseline to each of the thirty-six questions in the SF-36 instrument); it may be noted that the questions in the SF-36 instrument are actually numbered, as follows – 1, 2, 3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j, 4a, 4b, 4c, 4d, 5a, 5b, 5c, 6, 7, 8, 9a, 9b, 9c, 9d, 9e, 9f, 9g, 9h, 9i, 10, 11a, 11b, 11c, and 11d.

# IX. RESULTS

## IX.1 DESCRIPTIVE STATISTICS

### General numbers for all of the relevant variables

The numbers of subjects within each of the relevant variables of interest are detailed in the following tables -

***TABLE IX.1: Main Grouping variables (at baseline)***

| | | Age in Years | Gender | Stage of Chronic Kidney Disease | Diabetes | Heart Disease |
|---|---|---|---|---|---|---|
| N | Valid | 1133 | 1133 | 1135 | 1135 | 1127 |
| | Missing | 2 | 2 | 0 | 0 | 8 |
| Range | | 73 | N/A | 3 | N/A | N/A |
| Minimum | | 18 | N/A | 2 | N/A | N/A |
| Maximum | | 91 | N/A | 5 | N/A | N/A |

***TABLE IX.2: Outcome variables (at baseline)***

| | PF Domain score | RP Domain score | VT Domain score | SF Domain score | RE Domain score | MH Domain score | BP Domain score | GH Domain score | Recoded SF-2 Question score | PCS score | MCS score |
|---|---|---|---|---|---|---|---|---|---|---|---|
| N Valid | 1135 | 1135 | 1135 | 1135 | 1135 | 1135 | 584 | 584 | 584 | 584 | 584 |
| Missing | 0 | 0 | 0 | 0 | 0 | 0 | 551 | 551 | 551 | 551 | 551 |
| Range | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 | 96.00 | 100.00 | 100.00 | 100.00 | 61.0 | 65.7 |
| Percentile - 25 | 45.00 | 0.00 | 40.00 | 62.50 | 66.67 | 64.00 | 45.00 | 40.00 | 50.00 | 28.73 | 45.83 |
| Percentile - 50 | 70.00 | 50.00 | 55.00 | 75.00 | 100.00 | 76.00 | 68.75 | 55.00 | 50.00 | 39.15 | 53.90 |
| Percentile - 75 | 85.00 | 100.00 | 73.33 | 100.00 | 100.00 | 88.00 | 90.00 | 70.00 | 75.00 | 48.53 | 58.90 |

***TABLE IX.3: Other Grouping variables (sub-categories of Cardiovascular Disease, at baseline)***

| | | Heart Failure | Angina | Peripheral Vascular Disease | Stroke |
|---|---|---|---|---|---|
| **N** | Valid | **1127** | **1127** | **582** | **576** |
| | Missing | **8** | **8** | **553** | **559** |

***Notes:*** *(1) 2 subjects in the PPHS dataset did not have any information about their ages, or their genders entered into said dataset; (2) 8 subjects in the CANPREVENT dataset did not have any information about the status of their hearts entered into said dataset (also in said dataset - a further 2 subjects had no information entered about the presence/absence of PVD, while a further 8 subjects had no information entered about the presence/absence of a history of Stroke); (3) The 551 subjects from the EPO-INTERNATIONAL dataset had to constitute "missing" data points under the variables of Peripheral Vascular Disease and Stroke because, while these two conditions were not part of the exclusion criteria during that particular Study, no information about the respective conditions was entered into said dataset, either; (4) The 551 subjects from the EPO-INTERNATIONAL dataset had to remain without entries for two Domain scores (BP and GH), the Recoded SF-2 Question score, and the two Summary scores because of the different scoring algorithm used during the compilation of said dataset, and also because of the total lack of "raw" scores in said dataset.*

**General numbers for each Grouping variable (including subdivisions) of interest**

The numbers of subjects within the subdivisions of each relevant Grouping (i.e. Independent) variable are detailed in the following table -

*TABLE IX.4: Sub-classification of each Grouping variable (at baseline)*

| | | |
|---|---|---|
| **Age Category** (N = 1133) | **30 and under** | 70 |
| | **31-40** | 108 |
| | **41-50** | 148 |
| | **51-60** | 238 |
| | **61-70** | 342 |
| | **71 and over** | 227 |
| **Gender** (N = 1133) | **Male** | 609 |
| | **Female** | 524 |
| **Stage of Chronic Kidney Disease** (N = 1135) | **Stage 2** | 1 |
| | **Stage 3** | 400 |
| | **Stage 4** | 18 |
| | **Stage 5** | 716 |
| **Presence of Diabetes** (N = 1135) | **Yes** | 281 |
| | **No** | 854 |
| **Presence of Heart Disease** (N = 1127) | **Yes** | 164 |
| | **No** | 963 |
| **Presence of Heart Failure** (N = 1127) | **Yes** | 67 |
| | **No** | 1060 |
| **Presence of Angina (no Myocardial Infarction)** (N = 1127) | **Yes** | 51 |
| | **No** | 1076 |
| **Presence of PVD** (N = 582) | **Yes** | 84 |
| | **No** | 498 |
| **History of Stroke** (N = 576) | **Yes** | 28 |
| | **No** | 548 |

## General view of the mean SF-36 scores across the respective datasets

The mean SF-36 scores, as per each of the three "source" datasets (individually) are detailed in the following tables -

***TABLE IX.5: Means for the scores that are common to all three datasets***

| Original Study/Dataset | | PF | RP | VT | SF | RE | MH |
|---|---|---|---|---|---|---|---|
| **PPHS** | **Mean** | **52.09** | **44.70** | **47.46** | **70.15** | **76.36** | **74.35** |
| | Std. Deviation | 29.31 | 41.12 | 24.43 | 28.68 | 38.44 | 20.05 |
| **EPO-INTERNATIONAL** | **Mean** | **65.90** | **49.62** | **56.43** | **72.44** | **68.30** | **70.33** |
| | Std. Deviation | 24.81 | 42.05 | 22.37 | 24.77 | 41.09 | 20.79 |
| **CANPREVENT** | **Mean** | **65.22** | **64.26** | **57.29** | **83.23** | **82.70** | **77.93** |
| | Std. Deviation | 26.66 | 40.01 | 20.58 | 21.44 | 32.01 | 15.87 |
| **Total** | **Mean** | **63.64** | **54.31** | **55.44** | **76.09** | **74.79** | **73.72** |
| | Std. Deviation | 26.60 | 41.87 | 22.28 | 24.83 | 38.13 | 19.31 |

***TABLE IX.6: Means for the scores that are common to only two datasets***

| Original Study/Dataset | | BP | GH | Recoded SF-2 Question | PCS | MCS |
|---|---|---|---|---|---|---|
| **PPHS** | **Mean** | **68.67** | **45.58** | **65.00** | **34.20** | **49.22** |
| | Std. Deviation | 28.68 | 22.36 | 32.53 | 11.82 | 12.78 |
| **CANPREVENT** | **Mean** | **66.49** | **58.08** | **53.52** | **39.71** | **52.03** |
| | Std. Deviation | 25.60 | 20.52 | 21.69 | 12.27 | 10.44 |
| **Total** | **Mean** | **67.11** | **54.55** | **56.76** | **38.15** | **51.23** |
| | Std. Deviation | 26.50 | 21.78 | 25.72 | 12.39 | 11.21 |

***Notes:*** *(1) Subjects from the PPHS dataset had Stage 5 CKD at baseline, having been on Hemodialysis therapy for anywhere between 3 and 276 months; (2) Subjects from the EPO-INTERNATIONAL dataset had Stage 5 CKD at baseline, having been on Hemodialysis therapy for 3-18 months; (3) Subjects from the CANPREVENT dataset had CKD Stage 2/3/4 at baseline, and were not on any form of Dialysis therapy.*

**Observations (with regards to general relationships between each dataset and the SF-36 scores):** Patients on Hemodialysis therapy appear to be clearly scoring lower (compared to non-Dialysis patients) on the Domains of Role-Physical, Social Functioning, Role-Emotional, and General Health, as well as on the Physical Component Summary measure; these patients on Hemodialysis therapy also appear to be scoring marginally lower on the Domains of Vitality and Mental Health, as well as on the Mental Component Summary measure. There appears to be no distinct difference between Dialysis and non-Dialysis patients, with regards to the Domains of Physical Functioning and Bodily Pain. There is a suggestion that patients on Hemodialysis therapy perceived a greater improvement (in QoL) than those not on Dialysis when current health status was compared to health status at one year ago (however, the answer to this question was only available from 23% of the total number of patients who had been on Hemodialysis therapy).

## General relationships between mean SF-36 scores and each relevant Grouping variable

Prior to in-depth statistical analyses, a general idea of how each relevant Grouping variable (i.e. Stage of CKD, Age Category, Gender, Diabetes, and Heart Disease) impacts each SF-36 score was obtained via the following observations -

***TABLE IX.7: Means (across each stage of Chronic Kidney Disease) for the scores that are common to all three datasets***

| STAGE OF CHRONIC KIDNEY DISEASE | | PF | RP | VT | SF | RE | MH |
|---|---|---|---|---|---|---|---|
| **CKD - STAGE 2** | **Mean** | **50.00** | **100.00** | **50.00** | **100.00** | **100.00** | **76.00** |
| | Std. Deviation | - | - | - | - | - | - |
| **CKD – STAGE 3** | **Mean** | **65.56** | **64.13** | **57.35** | **83.31** | **82.46** | **77.72** |
| | Std. Deviation | 26.68 | 40.21 | 20.82 | 21.47 | 32.21 | 15.97 |
| **CKD – STAGE 4** | **Mean** | **58.49** | **65.28** | **56.39** | **80.56** | **87.04** | **82.89** |
| | Std. Deviation | 26.66 | 36.52 | 15.42 | 21.53 | 28.33 | 13.50 |
| **CKD – STAGE 5** | **Mean** | **62.72** | **48.49** | **54.36** | **71.91** | **70.16** | **71.25** |
| | Std. Deviation | 26.54 | 41.86 | 23.16 | 25.72 | 40.61 | 20.68 |
| **TOTAL** | **Mean** | **63.64** | **54.31** | **55.44** | **76.09** | **74.79** | **73.72** |
| | Std. Deviation | 26.60 | 41.87 | 22.28 | 24.83 | 38.13 | 19.31 |

***TABLE IX.8: Means (across each stage of Chronic Kidney Disease) for the scores that are common to only two datasets***

| STAGE OF CHRONIC KIDNEY DISEASE | | BP | GH | Recoded SF-2 Question | PCS | MCS |
|---|---|---|---|---|---|---|
| **CKD – STAGE 2** | **Mean** | **70.00** | **65.00** | **50.00** | **40.80** | **55.30** |
| | Std. Deviation | . | . | . | . | . |
| **CKD – STAGE 3** | **Mean** | **66.88** | **58.30** | **53.56** | **39.90** | **51.89** |
| | Std. Deviation | 25.44 | 20.52 | 21.57 | 12.31 | 10.52 |
| **CKD – STAGE 4** | **Mean** | **57.78** | **52.78** | **52.78** | **35.46** | **54.86** |
| | Std. Deviation | 29.00 | 21.09 | 25.57 | 11.35 | 8.62 |
| **CKD – STAGE 5** | **Mean** | **68.67** | **45.58** | **65.00** | **34.20** | **49.22** |
| | Std. Deviation | 28.68 | 22.36 | 32.53 | 11.82 | 12.78 |
| **TOTAL** | **Mean** | **67.11** | **54.55** | **56.76** | **38.15** | **51.23** |
| | Std. Deviation | 26.50 | 21.78 | 25.72 | 12.39 | 11.21 |

**Observations (with regards to general relationships between the Stage of CKD and the SF-36 scores):** Neglecting the single patient with Stage 2 CKD, patients with Stage 5 CKD appear to be scoring markedly lower on five of the Domains (Role-Physical, Social Functioning, Role–Emotional, Mental Health, and General Health) when compared to patients with Stage 3 CKD and Stage 4 CKD. There is no clear trend across the three stages, with regards to the other three Domains (Physical Functioning, Vitality, and Bodily Pain). Stage 5 CKD patients appear to be scoring marginally lower on each of the two Summary measures when compared to patients with the preceding two stages of the disease, but on the other hand, Stage 5 CKD patients exhibit relatively higher scores when rating their current health (compared to their health at one year ago).

Stage 4 CKD patients appear to be clearly scoring lower than Stage 3 CKD patients on the Domains of Physical Functioning, Bodily Pain, and General Health (but also lower than Stage 5 CKD patients on the former two Domains, strangely). It should, however, be remembered that (i) the latter two Domain scores were measured across a smaller sample, and (ii) the total number of Stage 4 CKD patients in the sample was small (N = 18).

**Observations (with regards to general relationships between the Age Category of CKD patients and the SF-36 scores):** There is no clear trend for any of the Domain/Summary/Recoded SF-2 Question scores, across the six Age Categories, except that (i) CKD patients >50 years of age appear to have lower Physical Functioning Domain scores when compared to CKD patients who are 50 years of age and under, and (ii) CKD patients >50 years of age appear to have higher General Health Domain scores, compared to those who are 50 years of age and under (however, General Health Domain scores were only obtainable from a smaller overall sample, of course).

***[See Appendix VII.1 & VII.2 for Tables]***

**Observations (with regards to general relationships between the Gender of CKD patients and the SF-36 scores):** Male CKD patients appear to have a marginally better QoL on each of the Summary measures when compared to female CKD patients. Across the Domain scores (and the Recoded SF-2 Question score), there appears to be little difference between male CKD patients and female CKD patients, except for the Domains of Physical Functioning, Vitality and Bodily Pain where male patients appear to be clearly scoring higher (however, it should be emphasized, again that Bodily Pain Domain scores were only obtainable from a smaller overall sample).

***[See Appendix VII.3 & VII.4 for Tables]***

**Observations (with regards to general relationships between Diabetes in CKD patients and the SF-36 scores):** CKD patients with Diabetes appear to score lower than CKD patients without Diabetes on the Domains of Physical Functioning, Role–Physical, and General Health, as well as on the Physical Component Summary measure; mental health-related QoL in general appears to not be clearly impacted by the presence/absence of Diabetes (in CKD patients), though.

***[See Appendix VII.5 & VII.6 for Tables]***

**Observations (with regards to general relationships between Heart Disease in CKD patients and SF-36 scores):** As compared to CKD patients without Heart Disease, CKD patients with Heart Disease appear to clearly score lower on all of the primary physical health-related Domains (Physical Functioning, Role–Physical, and Bodily Pain), as well as on the General Health Domain and the Physical Component Summary measure. However, there is no obvious difference between the two groups, regarding the Domain scores that primarily relate to mental health, to the Mental Component Summary score, or to the Recoded SF-2 Question score.

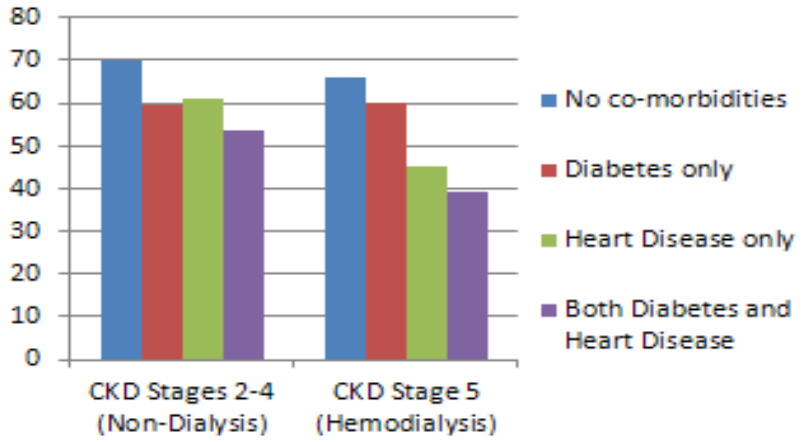
***[See Appendix VII.7 & VII.8 for Tables]***

## IX.2 ILLUSTRATIONS OF THE GENERAL RELATIONSHIPS BETWEEN SF-36 SCORES AND CHRONIC KIDNEY DISEASE (WITH AND WITHOUT CO-MORBIDITIES)

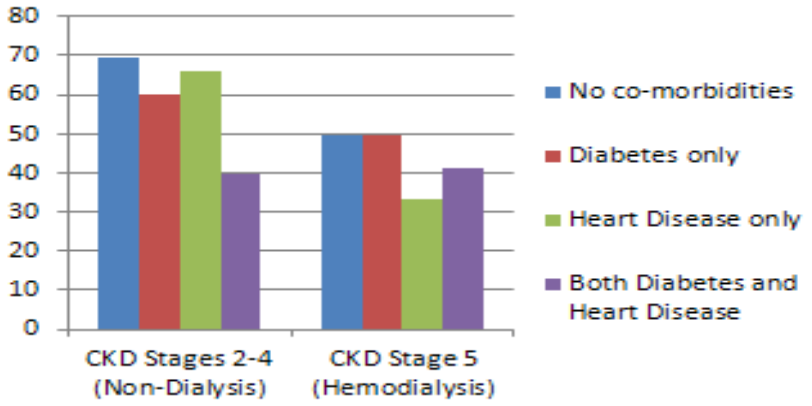
Mean SF-36 scores (for each Domain, each Summary measure, and the Recoded SF-2 Question) were compared across the sample, with respect to (i) patients with CKD and no co-morbidities, (ii) patients with CKD and Diabetes, (iii) patients with CKD and Heart Disease, and (iv) patients

with CKD and both Diabetes and Heart Disease; these are the diagrammatic representations of the general relationships -

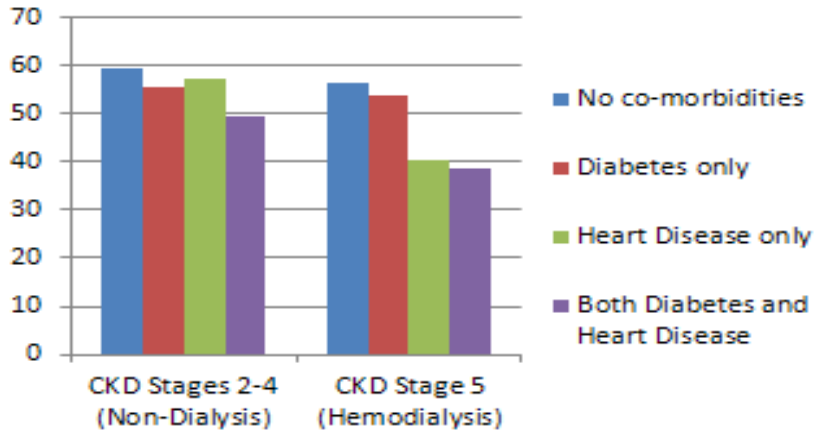
**(a) <u>PHYSICAL FUNCTIONING Domain Score [N = 411 (CKD Stages 2-4); N = 716 (CKD Stage 5)]</u>**



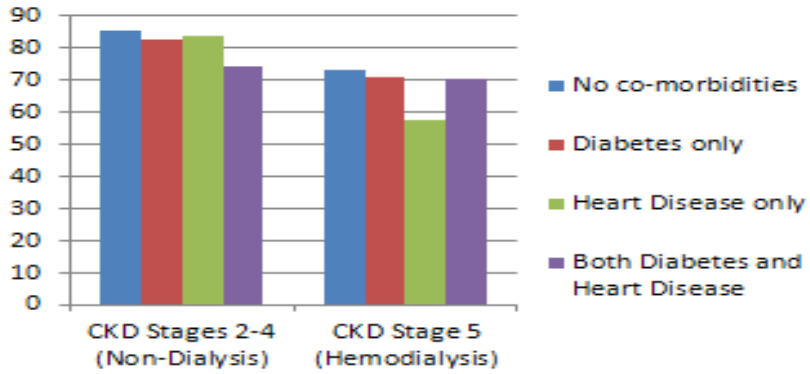
**(b) ROLE-PHYSICAL Domain Score [N = 411 (CKD Stages 2-4); N = 716 (CKD Stage 5)]**



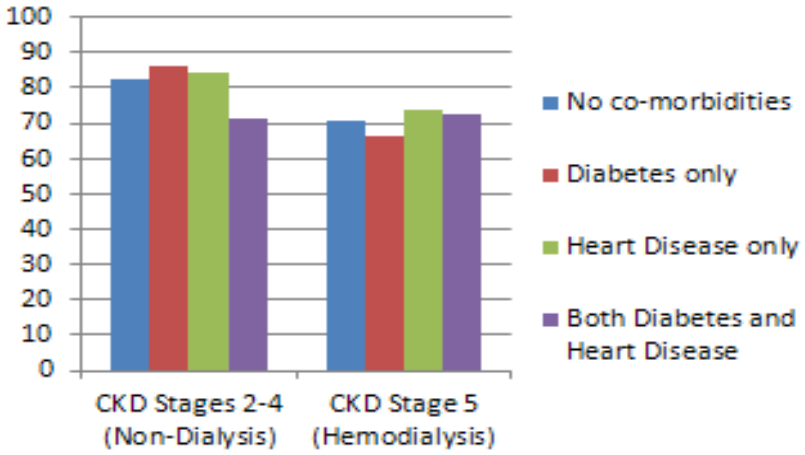

**(c) VITALITY Domain Score [N = 411 (CKD Stages 2-4); N = 716 (CKD Stage 5)]**



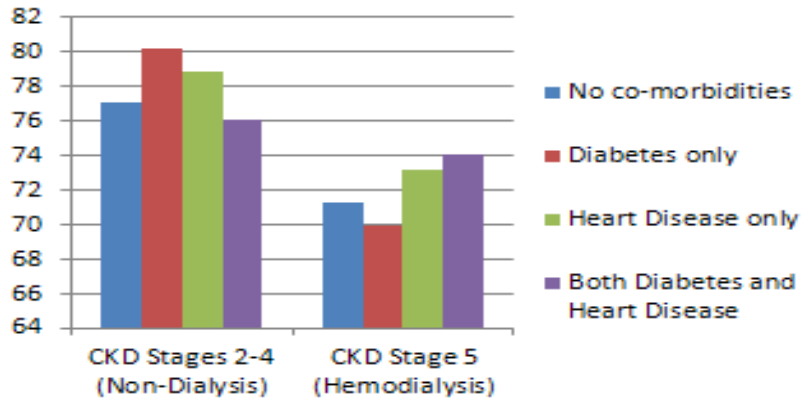
**(d) <u>SOCIAL FUNCTIONING Domain Score [N = 411 (CKD Stages 2-4); N = 716 (CKD Stage 5)]</u>**



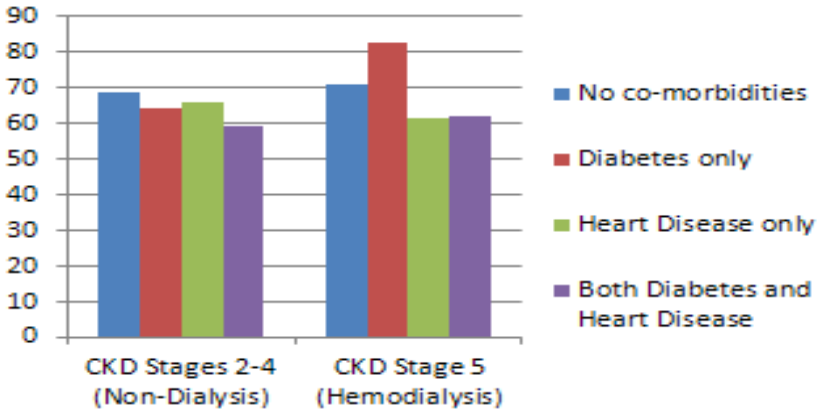

**(e) <u>ROLE-EMOTIONAL Domain Score [N = 411 (CKD Stages 2-4); N = 716 (CKD Stage 5)]</u>**



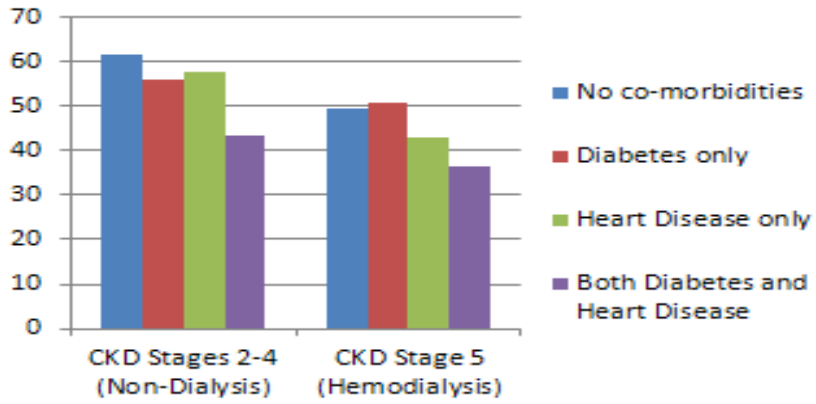
**(f) MENTAL HEALTH Domain Score [N = 411 (CKD Stages 2-4); N = 716 (CKD Stage 5)]**



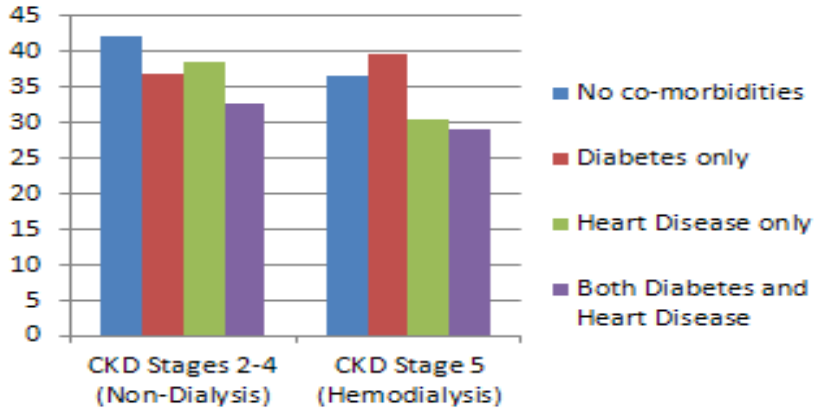

**(g) BODILY PAIN Domain Score [N = 411 (CKD Stages 2-4); N = 165 (CKD Stage 5)]**



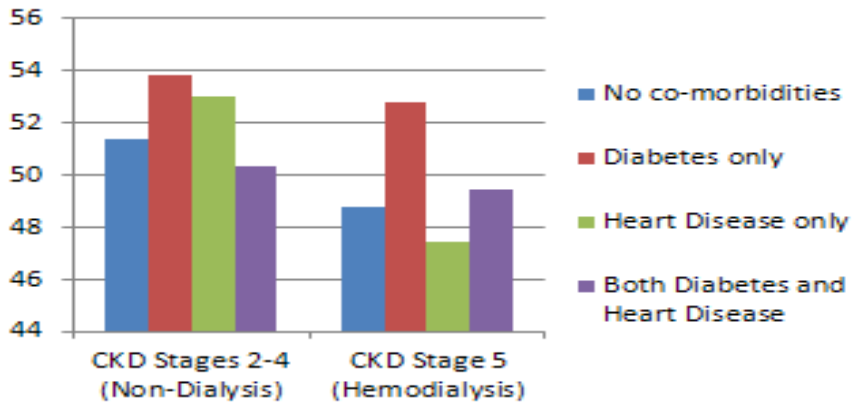
**(h) GENERAL HEALTH Domain Score [N = 411 (CKD Stages 2-4); N = 165 (CKD Stage 5)]**



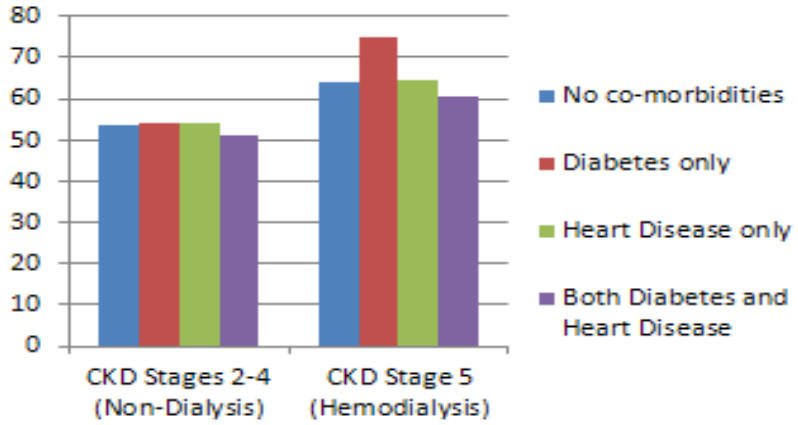

**(i) PHYSICAL COMPONENT SUMMARY Score [N = 411 (CKD Stages 2-4); N = 165 (CKD Stage 5)]**



**(j) MENTAL COMPONENT SUMMARY Score [N = 411 (CKD Stages 2-4); N = 165 (CKD Stage 5)]**




**(k) RECODED SF-2 QUESTION Score [N = 411 (CKD Stages 2-4); N = 165 (CKD Stage 5)]**



## IX.3 COMPARISONS OF SF-36 SCORES ACROSS THE GROUPING VARIABLES

As none of the respective distributions were normal, non-parametric comparisons of median SF-36 scores (along with mean ranks of those scores) were performed across the primary Grouping variables of (i) Stage of Chronic Kidney Disease, (ii) Age Category, (iii) Gender, (iv) Diabetes, and (v) Heart Disease; the observations are, as follows –

### Kruskal-Wallis Test (Grouping Variable – Stage Of Chronic Kidney Disease)

***TABLE IX.9: Significance of each Outcome variable (i.e. each SF-36 score)***

| | PF | RP | VT | SF | RE | MH | BP | GH | Recoded SF-2 Question | PCS | MCS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Chi-Square | 4.362 | 37.416 | 5.248 | 58.772 | 25.690 | 26.888 | 3.480 | 41.102 | 22.479 | 27.295 | 5.456 |
| Df | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| **Asymp. Sig.** | .113 | **.000** | .073 | **.000** | **.000** | **.000** | .176 | **.000** | **.000** | **.000** | .065 |

***TABLE IX.10: Significantly different Mean Ranks and Medians (N = 1135)***

| | Stage of Chronic Kidney Disease | N | Mean Rank | Median |
|---|---|---|---|---|
| ROLE-PHYSICAL | CKD STAGES 2-3 | 401 | 642.66 | 75 |
| | CKD STAGE 4 | 18 | 644.64 | 75 |
| | CKD STAGE 5 | 716 | 524.26 | 50 |
| SOCIAL FUNCTIONING | CKD STAGES 2-3 | 401 | 664.39 | 100 |
| | CKD STAGE 4 | 18 | 612.39 | 87.5 |
| | CKD STAGE 5 | 716 | 512.90 | 75 |
| ROLE-EMOTIONAL | CKD STAGES 2-3 | 401 | 621.20 | 100 |
| | CKD STAGE 4 | 18 | 652.92 | 100 |
| | CKD STAGE 5 | 716 | 536.07 | 100 |
| MENTAL HEALTH | CKD STAGES 2-3 | 401 | 627.62 | 80 |
| | CKD STAGE 4 | 18 | 725.92 | 84 |
| | CKD STAGE 5 | 716 | 530.64 | 76 |

***TABLE IX.11: Significantly different Mean Ranks and Medians (N = 584)***

| | Stage of Chronic Kidney Disease | N | Mean Rank | Median |
|---|---|---|---|---|
| GENERAL HEALTH | CKD STAGES 2-3 | 401 | 322.04 | 60 |
| | CKD STAGE 4 | 18 | 276.81 | 50 |
| | CKD STAGE 5 | 165 | 222.41 | 40 |
| RECODED SF-2 QUESTION | CKD STAGES 2-3 | 401 | 273.05 | 50 |
| | CKD STAGE 4 | 18 | 271.72 | 50 |
| | CKD STAGE 5 | 165 | 342.03 | 75 |
| PHYSICAL COMPONENT SUMMARY | CKD STAGES 2-3 | 401 | 317.08 | 41.9 |
| | CKD STAGE 4 | 18 | 252.53 | 35.15 |
| | CKD STAGE 5 | 165 | 237.12 | 34.1 |

***Notes:*** *(1) The Levene's Non-parametric Test results proved the Homogeneity of Variance, with regards to this analysis; (2) For reasons already discussed, the comparisons of the GH Domain Score, the Recoded SF-2 Question score, and the PCS score during this analysis could only be performed across a smaller sample (utilizing only 23% of the total number of Hemodialysis patients from the whole dataset).*

**Observations:** The significantly different SF-36 scores are those that pertain to - (1) ROLE-PHYSICAL (RP): As compared to patients with the preceding stages of CKD, Stage 5 CKD patients appear to perceive greater limitations in their life roles (due to their poor physical health); (2) SOCIAL FUNCTIONING (SF): In a systematic manner – the worse the stage of the disease (CKD), the worse the social functioning abilities appear to be; (3) ROLE-EMOTIONAL (RE): Stage 5 CKD patients appear to perceive comparatively greater limitations in their life roles (due to their poor emotional health), although the degree of difference across the stages is mild; (4) MENTAL HEALTH (MH): Patients with Stage 5 CKD appear to perceive their mental/emotional health as being worse, in relation to CKD patients with the preceding stages of CKD; (5) GENERAL HEALTH (GH): In a systematic manner – the worse the stage of the

disease (CKD), the worse the perceptions of overall health appear to be; (6) RECODED SF-2 QUESTION: Unlike patients with the preceding stages of CKD, patients with Stage 5 CKD appear to perceive their current health status as being better than their health status at one year ago (this could be due to Stage 5 CKD patients' lesser worries of disease progression and/or greater satisfaction with their Hemodialysis therapy); (7) PHYSICAL COMPONENT SUMMARY (PCS): Patients with Stage 3 CKD appear to perceive their overall physical health as being better than that of patients with the subsequent stages of the disease (note – the PCS scores for Stage 4 CKD patients and Stage 5 CKD patients in this analysis are similar).

**Kruskal-Wallis Test (Grouping Variable – Age Category)**

***TABLE IX.12: Significance of each Outcome variable (i.e. each SF-36 score)***

| | **PF** | **RP** | **VT** | **SF** | **RE** | **MH** | **BP** | **GH** | **Recoded SF-2 Question** | **PCS** | **MCS** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Chi-Square | 64.624 | 3.548 | 6.653 | 20.058 | 8.908 | 32.264 | 2.170 | 28.503 | 11.154 | 6.543 | 26.301 |
| Df | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| **Asymp. Sig.** | **.000** | .616 | .248 | **.001** | .113 | **.000** | .825 | **.000** | **.048** | .257 | **.000** |

***Notes:*** *(1) The Levene's Non-parametric Test results proved the Homogeneity of Variance, with regards to this analysis; (2) For reasons already discussed, the comparisons of the GH Domain score, the Recoded SF-2 Question score, and the MCS score during this analysis could only be performed across a smaller sample (utilizing only 23% of the total number of Hemodialysis patients from the whole dataset).*

**Observations:** The significantly different SF-36 scores are those that pertain to - (1) PHYSICAL FUNCTIONING (PF): CKD patients' physical functioning capacities appear to have a uniformly inverse relationship with age (note - almost every older Age Category comprises a worse median

PF score than the preceding younger Age Category); (2) SOCIAL FUNCTIONING (SF): Up to 50 years of age, CKD patients' social functioning abilities appear to remain stable and similar across the various Age Categories, but >50 years of age, these abilities seem to improve with age (note - >50 years of age, each older Age Category appears to comprise a better SF score than the preceding younger Age Category); (3) MENTAL HEALTH (MH): Mental/emotional health appears to have an inverse relationship with age among CKD patients of 50 years of age and younger, but the reverse appears to be true among CKD patients who are >50 years of age (note – up to 50 years of age, median MH scores appear to get gradually worse when going from one Age Category to the next oldest Age Category, but >50 years of age, median MH scores appear to get gradually better when going from one Age Category to the next oldest Age Category); (4) GENERAL HEALTH (GH): CKD patients who are >60 years of age appear to perceive their overall health as being better, in relation to CKD patients who are <60 years of age; (5) RECODED SF-2 QUESTION: CKD patients across all of the stated Age Categories seem to rate their baseline health status as being similar to their health status at one year ago, with the exception of those who were 31-40 years of age who rated their current health status as being better (however, the significance level of this SF-2 Question-based variable in the above analysis is borderline); (6) MENTAL COMPONENT SUMMARY (MCS): Similar to the afore-mentioned observation pertaining to the more specific (and less comprehensive) Mental Health Domain, overall mental/emotional health appears to have an inverse relationship with age among CKD patients of 50 years of age and younger, but the reverse appears to be true among CKD patients who are >50 years of age (note – up to 50 years of age, median MCS scores appear to get gradually worse when going from one Age Category to the next oldest Age Category, but >50

years of age, median MCS scores appear to get gradually better when going from one Age Category to the next oldest Age Category).

***[See Appendix IX.1 for Table]***

## Mann-Whitney U Test (Grouping Variable – Gender)

***TABLE IX.13: Significance of each Outcome variable (i.e. each SF-36 score)***

| | **PF** | **RP** | **VT** | **SF** | **RE** | **MH** | **BP** | **GH** | **Recoded SF-2 Question** | **PCS** | **MCS** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Mann-Whitney U | 132991.5 | 154404.5 | 141858.5 | 153511.0 | 157714.0 | 147092.0 | 34949.5 | 41250.5 | 40999.0 | 38409.5 | 39211.0 |
| Wilcoxon W | 270541.5 | 340149.5 | 279408.5 | 291061.0 | 295264.0 | 284642.0 | 81920.5 | 88221.5 | 79225.0 | 85380.5 | 86182.0 |
| Z | -4.846 | -.977 | -3.230 | -1.136 | -.395 | -2.276 | -3.617 | -.484 | -.646 | -1.885 | -1.489 |
| **Asymp. Sig. (2-tailed)** | **.000** | .329 | **.001** | .256 | .693 | **.023** | **.000** | .629 | .518 | **.059** | .136 |

***Notes:*** *(1) The Levene's Non-parametric Test results proved the Homogeneity of Variance, with regards to this analysis; (2) For reasons already discussed, comparisons of the BP Domain score and the PCS score during this analysis could only be performed across a smaller sample (utilizing only 23% of the total number of Hemodialysis patients from the whole dataset).*

**Observations:** The significantly different SF-36 scores are those that pertain to - (1) PHYSICAL FUNCTIONING (PF): Male CKD patients appear to have greater physical functioning capacities when compared to female CKD patients; (2) VITALITY (VT): Male CKD patients appear to have more energy (and less fatigue) when compared to female CKD patients; (3) MENTAL

HEALTH (MH): Male CKD patients appear to perceive their mental/emotional health as being better when compared to female CKD patients; (4) BODILY PAIN (BP): Male CKD patients appear to experience less pain when compared to female CKD patients; (5) PHYSICAL COMPONENT SUMMARY (PCS): Male CKD patients appear to have better physical health, overall when compared to female CKD patients (however, the significance level of the PCS variable in the above analysis is borderline).

***[See Appendix IX.2 for Table]***

## Mann-Whitney U Test (Grouping Variable – Diabetes)

***TABLE IX.14: Significance of each Outcome variable (i.e. each SF-36 score)***

| | **PF** | **RP** | **VT** | **SF** | **RE** | **MH** | **BP** | **GH** | **Recoded SF-2 Question** | **PCS** | **MCS** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Mann-Whitney U | 95373.0 | 112265.5 | 105778.5 | 116915.5 | 119135.5 | 113896.0 | 35443.5 | 29408.0 | 36517.0 | 28754.5 | 34149.5 |
| Wilcoxon W | 134994.0 | 151886.5 | 145399.5 | 156536.5 | 158756.5 | 478981.0 | 53209.5 | 47174.0 | 115123.0 | 46520.5 | 112755.5 |
| Z | -5.173 | -1.686 | -2.988 | -.665 | -.210 | -1.281 | -.941 | -4.112 | -.395 | -4.446 | -1.614 |
| **Asymp. Sig. (2-tailed)** | **.000** | .092 | **.003** | .506 | .834 | .200 | .347 | **.000** | .693 | **.000** | .107 |

***Notes:*** *(1) The Levene's Non-parametric Test results proved the Homogeneity of Variance, with regards to this analysis; (2) For reasons already discussed, comparisons of the GH Domain score and the PCS score during this analysis could only be performed across a smaller sample (utilizing only 23% of the total number of Hemodialysis patients from the whole dataset).*

**Observations:** The significantly different SF-36 scores are those that pertain to - (1) PHYSICAL FUNCTIONING (PF): CKD patients with Diabetes appear to have lesser physical functioning capacities when compared to CKD patients without Diabetes; (2) VITALITY (VT): CKD patients with Diabetes appear to have less energy (and more fatigue) when compared to CKD patients without Diabetes; (3) GENERAL HEALTH (GH): CKD patients with Diabetes appear to perceive their overall health as being worse, in relation to CKD patients without Diabetes; (4) PHYSICAL COMPONENT SUMMARY (PCS): CKD patients with Diabetes appear to have worse physical health, overall when compared to CKD patients without Diabetes.

***[See Appendix IX.3 for Table]***

## Mann-Whitney U Test (Grouping Variable – Heart Disease)

***TABLE IX.15: Significance of each Outcome variable (i.e. each SF-36 score)***

| | **PF** | **RP** | **VT** | **SF** | **RE** | **MH** | **BP** | **GH** | **Recoded SF-2 Question** | **PCS** | **MCS** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Mann-Whitney U | 55465.5 | 71402.0 | 61955.0 | 74038.0 | 77123.0 | 73462.0 | 29283.0 | 24380.5 | 33483.5 | 23332.5 | 32104.5 |
| Wilcoxon W | 68995.5 | 84932.0 | 75485.0 | 87568.0 | 541289.0 | 537628.0 | 42813.0 | 37910.5 | 118561.5 | 36862.5 | 45634.5 |
| Z | -6.110 | -2.043 | -4.425 | -1.319 | -.562 | -1.432 | -2.514 | -5.228 | -.178 | -5.798 | -.932 |
| **Asymp. Sig. (2-tailed)** | **.000** | **.041** | **.000** | .187 | .574 | .152 | **.012** | **.000** | .859 | **.000** | .351 |

***Notes:*** *(1) The Levene's Non-parametric Test results proved the Homogeneity of Variance, with regards to this analysis; (2) For reasons already discussed, comparisons of the BP Domain score, the GH Domain score, and the PCS score during this analysis could only be performed*

*across a smaller sample (utilizing only 23% of the total number of Hemodialysis patients from the whole dataset).*

**Observations:** The significantly different SF-36 scores are those that pertain to - (1) PHYSICAL FUNCTIONING (PF): CKD patients with Heart Disease appear to have lesser physical functioning capacities when compared to CKD patients without Heart Disease; (2) ROLE-PHYSICAL (RP): CKD patients with Heart Disease appear to perceive marginally more limitations in their life roles (due to their poor physical health), as compared to CKD patients without Heart Disease; (3) VITALITY (VT): CKD patients with Heart Disease appear to have less energy (and more fatigue) when compared to CKD patients without Heart Disease; (4) BODILY PAIN (BP): CKD patients with Heart Disease appear to experience more pain when compared to CKD patients without Heart Disease; (5) GENERAL HEALTH (GH): CKD patients with Heart Disease appear to perceive their overall health as being worse, in relation to CKD patients without Heart Disease; (6) PHYSICAL COMPONENT SUMMARY (PCS): CKD patients with Heart Disease appear to have worse physical health, overall when compared to CKD patients without Heart Disease.

***[See Appendix IX.4 for Table]***

***As the available data permitted comparisons of median/mean rank SF-36 scores across certain Grouping variables that were each a subdivision of Cardiovascular Disease, these supplementary comparisons were performed, as well; the respective Grouping variables were (i) Heart Failure, (ii) Angina, (iii) Peripheral Vascular Disease, and (iv) Stroke, and all comparisons were performed while using non-parametric tests due to the respective distributions not being normal.***

## Mann-Whitney U Test (Grouping Variable – Heart Failure)

***TABLE IX.16: Significance of each Outcome variable (i.e. each SF-36 score)***

| | **PF** | **RP** | **VT** | **SF** | **RE** | **MH** | **BP** | **GH** | **Recoded SF-2 Question** | **PCS** | **MCS** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Mann-Whitney U | 19069.5 | 27031.0 | 23737.0 | 28170.0 | 34281.0 | 34083.0 | 15401.0 | 10692.5 | 16421.5 | 9755.5 | 15963.5 |
| Wilcoxon W | 21347.5 | 29309.0 | 26015.0 | 30448.0 | 36559.0 | 596413.0 | 17679.0 | 12970.5 | 146216.5 | 12033.5 | 18241.5 |
| Z | -6.374 | -3.415 | -4.566 | -2.930 | -.559 | -.554 | -1.298 | -4.977 | -.524 | -5.698 | -.850 |
| **Asymp. Sig. (2-tailed)** | **.000** | **.001** | **.000** | **.003** | .576 | .580 | .194 | **.000** | .600 | **.000** | .396 |

***Notes:*** *(1) The Levene's Non-parametric Test results proved the Homogeneity of Variance, with regards to this analysis; (2) For reasons already discussed, comparisons of the GH Domain score and the PCS score during this analysis could only be performed across a smaller sample (utilizing only 23% of the total number of Hemodialysis patients from the whole dataset).*

**Observations:** The significantly different SF-36 scores are those that pertain to - (1) PHYSICAL FUNCTIONING (PF): CKD patients with Heart Failure appear to have lesser physical functioning capacities when compared to CKD patients without Heart Failure; (2) ROLE-PHYSICAL (RP): CKD patients with Heart Failure appear to perceive more limitations in their life roles (due to their poor physical health), as compared to CKD patients without Heart Failure;

(3) VITALITY (VT): CKD patients with Heart Failure appear to have less energy (and more fatigue) when compared to CKD patients without Heart Failure; (4) SOCIAL FUNCTIONING (SF): CKD patients with Heart Failure appear to have lesser social functioning abilities when compared to CKD patients without Heart Failure; (5) GENERAL HEALTH (GH): CKD patients with Heart Failure appear to perceive their overall health as being worse, in relation to CKD patients without Heart Failure; (6) PHYSICAL COMPONENT SUMMARY (PCS): CKD patients with Heart Failure appear to have worse physical health, overall when compared to CKD patients without Heart Failure.

***[See Appendix IX.5 for Table]***

## Mann-Whitney U Test (Grouping Variable – Angina)

***TABLE IX.17: Significance of each Outcome variable (i.e. each SF-36 score)***

| | **PF** | **RP** | **VT** | **SF** | **RE** | **MH** | **BP** | **GH** | **Recoded SF-2 Question** | **PCS** | **MCS** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Mann-Whitney U | 19162.5 | 25127.5 | 20139.5 | 27226.5 | 26052.0 | 26539.5 | 9866.5 | 10050.5 | 11187.5 | 9291.5 | 12280.0 |
| Wilcoxon W | 20488.5 | 26453.5 | 21465.5 | 28552.5 | 27378.0 | 605965.0 | 11192.5 | 11376.5 | 12513.5 | 10617.5 | 13606.0 |
| Z | -3.650 | -1.059 | -3.221 | -.096 | -.717 | -.397 | -3.124 | -2.947 | -2.065 | -3.610 | -.976 |
| **Asymp. Sig. (2-tailed)** | **.000** | .290 | **.001** | .923 | .473 | .692 | **.002** | **.003** | **.039** | **.000** | .329 |

***Notes:*** *(1) The Levene's Non-parametric Test results proved the Homogeneity of Variance, with regards to this analysis; (2) For reasons already discussed, comparisons of the BP Domain score, the GH Domain score, the Recoded SF-2 Question score, and the PCS score during this analysis could only be performed across a smaller sample (utilizing only 23% of the total number of Hemodialysis patients from the whole dataset).*

**Observations:** The significantly different SF-36 scores are those that pertain to - (1) PHYSICAL FUNCTIONING (PF): CKD patients with Angina appear to have lesser physical functioning capacities when compared to CKD patients without Angina; (2) VITALITY (VT): CKD patients with Angina appear to have less energy (and more fatigue) when compared to CKD patients without Angina; (3) BODILY PAIN (BP): CKD patients with Angina appear to experience more pain when compared to CKD patients without Angina; (4) GENERAL HEALTH (GH): CKD patients with Angina appear to perceive their overall health as being worse, in relation to CKD patients without Angina; (5) RECODED SF-2 QUESTION: In relation to health status at one year ago, CKD patients with Angina appear to rate their current health status as being marginally worse when compared to CKD patients without Angina; (6) PHYSICAL COMPONENT SUMMARY (PCS): CKD patients with Angina appear to have worse physical health, overall when compared to CKD patients without Angina.

***[See Appendix IX.6 for Table]***

## Mann-Whitney U Test (Grouping Variable – Peripheral Vascular Disease)

***TABLE IX.18: Significance of each Outcome variable (i.e. each SF-36 score)***

| | **PF** | **RP** | **VT** | **SF** | **RE** | **MH** | **BP** | **GH** | **Recoded SF-2 Question** | **PCS** | **MCS** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Mann-Whitney U | 15834.0 | 17686.0 | 18528.0 | 20875.0 | 20048.5 | 19235.0 | 18982.5 | 16818.5 | 19398.0 | 16271.0 | 20647.0 |
| Wilcoxon W | 19404.0 | 21256.0 | 22098.0 | 24445.0 | 23618.5 | 22805.0 | 22552.5 | 20388.5 | 22968.0 | 19841.0 | 144898.0 |
| Z | -3.570 | -2.373 | -1.679 | -.030 | -.767 | -1.184 | -1.365 | -2.881 | -1.135 | -3.258 | -.189 |
| **Asymp. Sig. (2-tailed)** | **.000** | **.018** | .093 | .976 | .443 | .237 | .172 | **.004** | .257 | **.001** | .850 |

***Notes:*** *(1) The Levene's Non-parametric Test results proved the Homogeneity of Variance, with regards to this analysis; (2) For reasons already discussed, comparisons of the GH Domain score and the PCS score during this analysis could only be performed across a smaller sample (utilizing only 23% of the total number of Hemodialysis patients from the whole dataset).*

**Observations:** The significantly different SF-36 scores are those that pertain to - (1) PHYSICAL FUNCTIONING (PF): CKD patients with Peripheral Vascular Disease appear to have lesser physical functioning capacities when compared to CKD patients without Peripheral Vascular Disease; (2) ROLE-PHYSICAL (RP): CKD patients with Peripheral Vascular Disease appear to perceive much more limitations in their life roles (due to their poor physical health), as compared

to CKD patients without Peripheral Vascular Disease; (3) GENERAL HEALTH (GH): CKD patients with Peripheral Vascular Disease appear to perceive their overall health as being worse, in relation to CKD patients without Peripheral Vascular Disease; (4) PHYSICAL COMPONENT SUMMARY (PCS): CKD patients with Peripheral Vascular Disease appear to have worse physical health, overall when compared to CKD patients without Peripheral Vascular Disease.

***[See Appendix IX.7 for Table]***

## Mann-Whitney U Test (Grouping Variable – Stroke)

***TABLE IX.19: Significance of each Outcome variable (i.e. each SF-36 score)***

| | **PF** | **RP** | **VT** | **SF** | **RE** | **MH** | **BP** | **GH** | **Recoded SF-2 Question** | **PCS** | **MCS** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Mann-Whitney U | 5804.0 | 6688.0 | 5814.5 | 6663.5 | 7392.5 | 7347.5 | 6960.0 | 6298.0 | 7596.0 | 5994.5 | 7554.5 |
| Wilcoxon W | 6210.0 | 7094.0 | 6220.5 | 7069.5 | 157818.5 | 7753.5 | 7366.0 | 6704.0 | 158022.0 | 6400.5 | 157980.5 |
| Z | -2.178 | -1.199 | -2.168 | -1.234 | -.410 | -.379 | -.835 | -1.603 | -.094 | -1.953 | -.137 |
| **Asymp. Sig. (2-tailed)** | **.029** | .231 | **.030** | .217 | .682 | .705 | .404 | .109 | .925 | **.051** | .891 |

***Notes:*** *(1) The Levene's Non-parametric Test results proved the Homogeneity of Variance, with regards to this analysis; (2) For reasons already discussed, comparisons of the PCS score during*

*this analysis could only be performed across a smaller sample (utilizing only 23% of the total number of Hemodialysis patients from the whole dataset).*

**Observations:** The significantly different SF-36 scores are those that pertain to - (1) PHYSICAL FUNCTIONING (PF): CKD patients with a history of Stroke appear to have lesser physical functioning capacities when compared to CKD patients without a history of Stroke; (2) VITALITY (VT): CKD patients with a history of Stroke appear to have less energy (and more fatigue) when compared to CKD patients without a history of Stroke; (3) PHYSICAL COMPONENT SUMMARY (PCS): CKD patients with a history of Stroke appear to have worse physical health, overall when compared to CKD patients without a history of Stroke.

***[See Appendix IX.8 for Table]***

## IX.4 MULTIPLE LINEAR REGRESSION MODELS

*Prior to the Multiple Linear Regression modelling, it should be noted that a higher score for any of the SF-36 Domains/Summary measures (as well as for the Recoded SF-2 Question) indicates a superior QoL with respect to that particular Domain/Summary measure (or Recoded SF-2 Question); therefore, a higher score on the Physical Functioning Domain indicates a greater physical functioning capacity, a higher score on the Role-Physical Domain indicates a lower level of limitation due to poor physical health, a higher score on the Bodily Pain Domain indicates less pain being experienced, and so on.*

The respective Multiple Linear Regression models led to the following observations -

***TABLE IX.20: Significant predictors of the Physical Functioning Domain score***

| Model | Unstandardized Coefficients | | Standardized Coefficients | t | Sig. | 95% Confidence Interval for B | |
|---|---|---|---|---|---|---|---|
| | B | Std. Error | Beta | | | Lower Bound | Upper Bound |
| (Constant) | 96.841 | 3.745 | | 25.856 | .000 | 89.492 | 104.190 |
| **Age in Years** | **-.486** | .055 | -.272 | -8.836 | **.000** | -.594 | -.378 |
| **Stage of CKD** | **-11.518** | 1.682 | -.209 | -6.846 | **.000** | -14.819 | -8.217 |
| **Gender** | **9.644** | 1.491 | .181 | 6.467 | **.000** | 6.718 | 12.571 |
| **Diabetes** | **-7.017** | 1.747 | -.114 | -4.018 | **.000** | -10.444 | -3.590 |
| **Heart Disease** | **-10.400** | 2.194 | -.137 | -4.740 | **.000** | -14.705 | -6.095 |

***Notes:*** *(1) The overall significance of the model is proven (as per the ANOVA Test); (2) Only 15% of the Variability in the PF Domain score can be explained by Age In Years, Gender, Stage Of CKD, Diabetes, and Heart Disease (as per the $R^2$ Value); (3) There is no significant correlation between residuals (as per the Durbin-Watson Test Value, which is = 1.997); (4) Tolerance values are all >0.1 by a large degree, which means that none of the predictors in the model are redundant; (5) All values for Cook's Distance are <1, which indicates that there is no undue influence on the model by any leverage point, while <5% of cases have Standardized Residuals >2, which indicates that the data fits the model well; (6) Residuals are normally distributed (as per the histogram and P-P plots).*

**Observations:** The significant predictors of the Physical Functioning (PF) Domain score are - (1) AGE: As the age of CKD patients increases by one year, the PF score decreases by a factor of 0.5; (2) GENDER: Male CKD patients have higher PF scores than female CKD patients by a factor of 9.6; (3) STAGE OF CKD: Kidney Failure (i.e. Stage 5 CKD) patients have lower PF

scores than Non-Kidney Failure CKD patients by a factor of 11.5; (4) DIABETES: CKD patients with Diabetes have lower PF scores than CKD patients without Diabetes by a factor of 7; (5) HEART DISEASE: CKD patients with Heart Disease have lower PF scores than CKD patients without Heart Disease by a factor of 10.4.

***TABLE IX.21: Significant predictors of the Role-Physical Domain score***

| Model | Unstandardized Coefficients | | Standardized Coefficients | t | Sig. | 95% Confidence Interval for B | |
|---|---|---|---|---|---|---|---|
| | B | Std. Error | Beta | | | Lower Bound | Upper Bound |
| (Constant) | 66.810 | 2.186 | | 30.563 | .000 | 62.521 | 71.099 |
| **Stage of CKD** | **-17.201** | 2.587 | -.198 | -6.650 | **.000** | -22.276 | -12.126 |
| **Heart Disease** | **-11.812** | 3.531 | -.099 | -3.345 | **.001** | -18.740 | -4.884 |

***Notes:*** *(1) The overall significance of the model is proven (as per the ANOVA Test); (2) Only 4% of the Variability in the RP Domain score can be explained by Stage Of CKD and Heart Disease (as per the $R^2$ Value); (3) There is no significant correlation between residuals (as per the Durbin-Watson Test Value, which is = 1.928); (4) Tolerance values are all >0.1 by a large degree, which means that none of the predictors in the model are redundant; (5) All values for Cook's Distance are <1, which indicates that there is no undue influence on the model by any leverage point, while no cases have Standardized Residuals >2, which indicates that the data fits the model well; (6) Residuals are not normally distributed (as per the histogram and P-P plots); this means that an assumption has been violated.*

**Observations:** The significant predictors of the Role-Physical (RP) Domain score are - (1) STAGE OF CKD: Kidney Failure (i.e. Stage 5 CKD) patients have lower RP scores than Non-Kidney Failure CKD patients by a factor of 17.2; (2) HEART DISEASE: CKD patients with Heart Disease have lower RP scores than CKD patients without Heart Disease by a factor of 11.8.

*(Caveat: Due to the violation of an assumption, as well as due to the low $R^2$ value, the results of this particular Multiple Linear Regression model are likely to comprise a high degree of inaccuracy; therefore, more weight should be give to the results of the non-parametric comparisons of medians/mean ranks, with regards to the relationship between (i) the RP Domain score and the Stage of CKD, and (ii) the RP Domain score and Heart Disease in CKD patients).*

***TABLE IX.22: Significant predictors of the Vitality Domain score***

| Model | Unstandardized Coefficients | | Standardized Coefficients | t | Sig. | 95% Confidence Interval for B | |
|---|---|---|---|---|---|---|---|
| | B | Std. Error | Beta | | | Lower Bound | Upper Bound |
| (Constant) | 58.364 | 1.349 | | 43.280 | .000 | 55.718 | 61.010 |
| **Stage of CKD** | **-5.513** | 1.393 | -.119 | -3.958 | **.000** | -8.246 | -2.780 |
| **Gender** | **5.467** | 1.318 | .122 | 4.148 | **.000** | 2.881 | 8.053 |
| **Diabetes** | **-4.243** | 1.533 | -.083 | -2.767 | **.006** | -7.251 | -1.234 |
| **Heart Disease** | **-9.406** | 1.906 | -.149 | -4.935 | **.000** | -13.145 | -5.666 |

***Notes:*** *(1) The overall significance of the model is proven (as per the ANOVA Test); (2) Only 5% of the Variability in the VT Domain score can be explained by Gender, Stage Of CKD, Diabetes, and Heart Disease (as per the $R^2$ Value); (3) There is no significant correlation between residuals*

*(as per the Durbin-Watson Test Value, which is = 1.932); (4) Tolerance values are all >0.1 by a large degree, which means that none of the predictors in the model are redundant; (5) All values for Cook's Distance are <1, which indicates that there is no undue influence on the model by any leverage point, while <5% of cases have Standardized Residuals >2, which indicates that the data fits the model well; (6) Residuals are normally distributed (as per the histogram and P-P plots).*

**Observations:** The significant predictors of the Vitality (VT) Domain score are - (1) GENDER: Male CKD patients have higher VT scores than female CKD patients by a factor of 5.5; (2) STAGE OF CKD: Kidney Failure (i.e. Stage 5 CKD) patients have lower VT scores than Non-Kidney Failure CKD patients by a factor of 5.5; (3) DIABETES: CKD patients with Diabetes have lower VT scores than CKD patients without Diabetes by a factor of 4.2; (4) HEART DISEASE: CKD patients with Heart Disease have lower VT scores than CKD patients without Heart Disease by a factor of 9.4.

***TABLE IX.23: Significant predictors of the Social Functioning Domain score***

| Model | Unstandardized Coefficients | | Standardized Coefficients | t | Sig. | 95% Confidence Interval for B | |
|---|---|---|---|---|---|---|---|
| | B | Std. Error | Beta | | | Lower Bound | Upper Bound |
| (Constant) | 83.215 | 1.433 | | 58.066 | .000 | 80.403 | 86.027 |
| **Gender** | **3.814** | 1.456 | .076 | 2.619 | **.009** | .957 | 6.671 |
| **Stage of CKD** | **-12.957** | 1.535 | -.251 | -8.440 | **.000** | -15.969 | -9.945 |
| **Heart Disease** | **-6.882** | 2.082 | -.097 | -3.306 | **.001** | -10.967 | -2.798 |

***Notes:*** *(1) The overall significance of the model is proven (as per the ANOVA Test); (2) Only 6% of the Variability in the SF Domain score can be explained by Gender, Stage Of CKD, and Heart Disease (as per the $R^2$ Value); (3) There is no significant correlation between residuals (as per the Durbin-Watson Test Value, which is = 2.006); (4) Tolerance values are all >0.1 by a large degree, which means that none of the predictors in the model are redundant; (5) All values for Cook's Distance are <1, which indicates that there is no undue influence on the model by any leverage point, while <5% of cases have Standardized Residuals >2, which indicates that the data fits the model well; (6) Residuals are normally distributed (as per the histogram and P-P plots).*

**Observations:** The significant predictors of the Social Functioning (SF) Domain score are - (1) GENDER: Male CKD patients have higher SF scores than female CKD patients by a factor of 3.8; (2) STAGE OF CKD: Kidney Failure (i.e. Stage 5 CKD) patients have lower SF scores than Non-Kidney Failure CKD patients by a factor of 13; (3) HEART DISEASE: CKD patients with Heart Disease have lower SF scores than CKD patients without Heart Disease by a factor of 6.9.

***TABLE IX.24: Significant predictor of the Role-Emotional Domain score***

| Model | Unstandardized Coefficients | | Standardized Coefficients | t | Sig. | 95% Confidence Interval for B | |
|---|---|---|---|---|---|---|---|
| | B | Std. Error | Beta | | | Lower Bound | Upper Bound |
| (Constant) | 82.697 | 1.840 | | 44.944 | .000 | 79.087 | 86.307 |
| **Stage of CKD** | **-12.539** | 2.317 | -.159 | -5.412 | **.000** | -17.084 | -7.993 |

***Notes:*** *(1) The overall significance of the model is proven (as per the ANOVA Test); (2) Only 3% of the Variability in the RE Domain score can be explained by the Stage Of CKD (as per the* $R^2$ *Value); (3) There is no significant correlation between residuals (as per the Durbin-Watson Test Value, which is = 1.979); (4) Tolerance values are all >0.1 by a large degree, which means that the predictor in the model is not redundant; (5) All values for Cook's Distance are <1, which indicates that there is no undue influence on the model by any leverage point, while <5% of cases have Standardized Residuals >2, which indicates that the data fits the model well; (6) Residuals are not normally distributed (as per the histogram and P-P plots); this means that an assumption has been violated.*

**Observations:** The only significant predictor of the Role-Emotional (RE) Domain score is - STAGE OF CKD: Kidney Failure (i.e. Stage 5 CKD) patients have lower RE scores than Non-Kidney Failure CKD patients by a factor of 12.5.

*(Caveat: Due to the violation of an assumption, as well as due to the low* $R^2$ *value, the results of this particular Multiple Linear Regression model are likely to comprise a high degree of inaccuracy; therefore, more weight should be give to the results of the non-parametric comparisons of medians/mean ranks, with regards to the relationship between the RE Domain score and the Stage of CKD).*

***TABLE IX.25: Significant predictors of the Mental Health Domain score***

| Model | Unstandardized Coefficients | | Standardized Coefficients | t | Sig. | 95% Confidence Interval for B | |
|---|---|---|---|---|---|---|---|
| | B | Std. Error | Beta | | | Lower Bound | Upper Bound |
| (Constant) | 70.691 | 2.864 | | 24.685 | .000 | 65.072 | 76.310 |
| **Age in Years** | **.085** | .041 | .066 | 2.077 | **.038** | .005 | .166 |
| **Stage of CKD** | **-6.291** | 1.277 | -.157 | -4.928 | **.000** | -8.796 | -3.786 |
| **Gender** | **3.797** | 1.140 | .098 | 3.332 | **.001** | 1.561 | 6.033 |

***Notes:*** *(1) The overall significance of the model is proven (as per the ANOVA Test); (2) Only 4% of the Variability in the MH Domain score can be explained by Age In Years, Gender, and Stage Of CKD (as per the $R^2$ Value); (3) There is no significant correlation between residuals (as per the Durbin-Watson Test Value, which is = 1.911); (4) Tolerance values are all >0.1 by a large degree, which means that none of the predictors in the model are redundant; (5) All values for Cook's Distance are <1, which indicates that there is no undue influence on the model by any leverage point, while <5% of cases have Standardized Residuals >2, which indicates that the data fits the model well; (6) Residuals are normally distributed (as per the histogram and P-P plots).*

**Observations:** The significant predictors of the Mental Health (MH) Domain score are - (1) AGE: As the age of CKD patients increases by one year, the MH score increases by a factor of 0.09 (however, this increase is an all-encompassing average, and greater weight should be given to the results of the Kruskal-Wallis Test, which suggest that the relationship between the MH score and Age is not quite so monotonic); (2) GENDER: Male CKD patients have higher MH scores than female CKD patients by a factor of 3.8; (3) STAGE OF CKD: Kidney Failure (i.e.

Stage 5 CKD) patients have lower MH scores than Non-Kidney Failure CKD patients by a factor of 6.3.

***TABLE IX.26: Significant predictors of the Bodily Pain Domain score***

| Model | Unstandardized Coefficients | | Standardized Coefficients | t | Sig. | 95% Confidence Interval for B | |
|---|---|---|---|---|---|---|---|
| | B | Std. Error | Beta | | | Lower Bound | Upper Bound |
| (Constant) | 64.943 | 1.617 | | 40.173 | .000 | 61.768 | 68.118 |
| **Gender** | **8.529** | 2.194 | .161 | 3.887 | **.000** | 4.219 | 12.839 |
| **Heart Disease** | **-7.472** | 2.431 | -.127 | -3.074 | **.002** | -12.247 | -2.697 |

***Notes:*** *(1) This model had to exclude the 551 subjects from the EPO-INTERNATIONAL dataset for whom scores for this particular Domain were unavailable; (2) The overall significance of the model is proven (as per the ANOVA Test); (3) Only 4% of the Variability in the BP Domain score can be explained by Gender and Heart Disease (as per the $R^2$ Value); (4) There is no significant correlation between residuals (as per the Durbin-Watson Test Value, which is = 1.885); (5) Tolerance values are all >0.1 by a large degree, which means that none of the predictors in the model are redundant; (6) All values for Cook's Distance are <1, which indicates that there is no undue influence on the model by any leverage point, while <5% of cases have Standardized Residuals >2, which indicates that the data fits the model well; (7) Residuals are not normally distributed (as per the histogram and P-P plots); this means that an assumption has been violated.*

**Observations:** The significant predictors of the Bodily Pain (BP) Domain score are - (1) GENDER: Male CKD patients have higher BP scores than female CKD patients by a factor of 8.5; (2) HEART DISEASE: CKD patients with Heart Disease have lower BP scores than CKD patients without Heart Disease by a factor of 7.5.

*(Caveat: Due to the violation of an assumption, as well as due to the low $R^2$ value, the results of this particular Multiple Linear Regression model are likely to comprise a high degree of inaccuracy; therefore, more weight should be give to the results of the non-parametric comparisons of medians/mean ranks, with regards to the relationship between (i) the BP Domain score and Gender, and (ii) the BP Domain score and Heart Disease in CKD patients).*

***TABLE IX.27: Significant predictors of the General Health Domain score***

| Model | Unstandardized Coefficients | | Standardized Coefficients | t | Sig. | 95% Confidence Interval for B | |
|---|---|---|---|---|---|---|---|
| | B | Std. Error | Beta | | | Lower Bound | Upper Bound |
| (Constant) | 36.218 | 5.280 | | 6.859 | .000 | 25.847 | 46.589 |
| **Age in Years** | **.401** | .080 | .198 | 4.984 | **.000** | .243 | .559 |
| **Stage of CKD** | **-9.374** | 1.918 | -.195 | -4.888 | **.000** | -13.140 | -5.607 |
| **Diabetes** | **-6.103** | 1.801 | -.132 | -3.389 | **.001** | -9.640 | -2.566 |
| **Heart Disease** | **-9.893** | 1.936 | -.205 | -5.110 | **.000** | -13.695 | -6.091 |

***Notes:*** *(1) This model had to exclude the 551 subjects from the EPO-INTERNATIONAL dataset for whom scores for this particular Domain were unavailable; (2) The overall significance of the model is proven (as per the ANOVA Test); (3) Only 16% of the Variability in the GH Domain score can be explained by Age In Years, Stage Of CKD, Diabetes, and Heart Disease (as per the*

*$R^2$ Value); (4) There is no significant correlation between residuals (as per the Durbin-Watson Test Value, which is = 1.968); (5) Tolerance values are all >0.1 by a large degree, which means that none of the predictors in the model are redundant; (6) All values for Cook's Distance are <1, which indicates that there is no undue influence on the model by any leverage point, while <5% of cases have Standardized Residuals >2, which indicates that the data fits the model well; (7) Residuals are normally distributed (as per the histogram and P-P plots).*

**Observations:** The significant predictors of the General Health (GH) Domain score are - (1) AGE: As the age of CKD patients increases by one year, the GH score increases by a factor of 0.4; (2) STAGE OF CKD.: Kidney Failure (i.e. Stage 5 CKD) patients have lower GH scores than Non-Kidney Failure CKD patients by a factor of 9.4; (3) DIABETES: CKD patients with Diabetes have lower GH scores than CKD patients without Diabetes by a factor of 6.1; (4) HEART DISEASE: CKD patients with Heart Disease have lower GH scores than CKD patients without Heart Disease by a factor of 9.9.

***TABLE IX.28: Significant predictor of the Recoded SF-2 Question score***

| Model | Unstandardized Coefficients | | Standardized Coefficients | t | Sig. | 95% Confidence Interval for B | |
|---|---|---|---|---|---|---|---|
| | B | Std. Error | Beta | | | Lower Bound | Upper Bound |
| (Constant) | 53.520 | 1.232 | | 43.439 | .000 | 51.100 | 55.940 |
| **Stage of CKD** | **11.480** | 2.318 | .201 | 4.953 | **.000** | 6.927 | 16.032 |

***Notes:*** *(1) This model had to exclude the 551 subjects from the EPO-INTERNATIONAL dataset for whom scores for this particular Question were unavailable; (2) The overall significance of the model is proven (as per the ANOVA Test); (3) Only 4% of the Variability in the Recoded SF-2 Question score can be explained by Stage Of CKD (as per the $R^2$ Value); (4) There is no*

*significant correlation between residuals (as per the Durbin-Watson Test Value, which is = 2.163); (5) Tolerance values are all >0.1 by a large degree, which means that the predictor in the model is not redundant; (6) All values for Cook's Distance are <1, which indicates that there is no undue influence on the model by any leverage point, while <5% of cases have Standardized Residuals >2, which indicates that the data fits the model well; (7) Residuals are normally distributed (as per the histogram and P-P plots).*

**Observations:** The only significant predictor of the Recoded SF-2 Question score is - STAGE OF CKD: When compared to Non-Kidney Failure CKD patients, Kidney Failure (i.e. Stage 5 CKD) patients are more likely (by a factor of 11.5) to rate their current overall health as being better than their overall health at one year ago; this could possibly be due to perceived success of their Hemodialysis therapy (along with adequate adjustments of their lives around said therapy).

***TABLE IX.29: Significant predictors of the Physical Component Summary score***

| Model | Unstandardized Coefficients | | Standardized Coefficients | t | Sig. | 95% Confidence Interval for B | |
|---|---|---|---|---|---|---|---|
| | B | Std. Error | Beta | | | Lower Bound | Upper Bound |
| (Constant) | 47.124 | 3.119 | | 15.110 | .000 | 40.998 | 53.249 |
| **Age in Years** | **-.102** | .047 | -.088 | -2.158 | **.031** | -.196 | -.009 |
| **Gender** | **3.541** | .990 | .142 | 3.576 | **.000** | 1.596 | 5.486 |
| **Stage of CKD** | **-5.113** | 1.125 | -.185 | -4.545 | **.000** | -7.323 | -2.903 |
| **Diabetes** | **-4.106** | 1.056 | -.155 | -3.888 | **.000** | -6.181 | -2.032 |
| **Heart Disease** | **-4.959** | 1.134 | -.180 | -4.373 | **.000** | -7.187 | -2.731 |

***Notes:*** *(1) This model had to exclude the 551 subjects from the EPO-INTERNATIONAL dataset for whom scores for this particular measure were incalculable; (2) The overall significance of the model is proven (as per the ANOVA Test); (3) Only 12% of the Variability in the PCS score can be explained by Age In Years, Gender, Stage Of CKD, Diabetes, and Heart Disease (as per the* $R^2$ *Value); (4) There is no significant correlation between residuals (as per the Durbin-Watson Test Value, which is = 1.969); (5) Tolerance values are all >0.1 by a large degree, which means that none of the predictors in the model are redundant; (6) All values for Cook's Distance are <1, which indicates that there is no undue influence on the model by any leverage point, while <5% of cases have Standardized Residuals >2, which indicates that the data fits the model well; (7) Residuals are normally distributed (as per the histogram and P-P plots).*

**Observations:** The significant predictors of the Physical Component Summary (PCS) score are - (1) AGE: As the age of CKD patients increases by one year, the PCS score decreases by a factor of 0.1; (2) GENDER: Male CKD patients have higher PCS scores than female CKD patients by a factor of 3.5; (3) STAGE OF CKD: Kidney Failure (i.e. Stage 5 CKD) patients have lower PCS scores than Non-Kidney Failure CKD patients by a factor of 5.1; (4) DIABETES: CKD patients with Diabetes have lower PCS scores than CKD patients without Diabetes by a factor of 4.1; (5) HEART DISEASE: CKD patients with Heart Disease have lower PCS scores than CKD patients without Heart Disease by a factor of 5.

***TABLE IX.30: Significant predictors of the Mental Component Summary score***

| Model | Unstandardized Coefficients | | Standardized Coefficients | t | Sig. | 95% Confidence Interval for B | |
|---|---|---|---|---|---|---|---|
| | B | Std. Error | Beta | | | Lower Bound | Upper Bound |
| (Constant) | 39.508 | 2.854 | | 13.843 | .000 | 33.902 | 45.113 |
| **Age in Years** | **.193** | .043 | .184 | 4.465 | **.000** | .108 | .278 |
| **Stage of CKD** | **-2.129** | 1.027 | -.085 | -2.073 | **.039** | -4.146 | -.112 |

***Notes:*** *(1) This model had to exclude the 551 subjects from the EPO-INTERNATIONAL dataset for whom scores for this particular measure were incalculable; (2) The overall significance of the model is proven (as per the ANOVA Test); (3) Only 4% of the Variability in the MCS score can be explained by Age In Years and Stage Of CKD (as per the $R^2$ Value); (4) There is no significant correlation between residuals (as per the Durbin-Watson Test Value, which is = 1.907); (5) Tolerance values are all >0.1 by a large degree, which means that none of the predictors in the model are redundant; (6) All values for Cook's Distance are <1, which indicates that there is no undue influence on the model by any leverage point, but 6% of cases have Standardized Residuals >2, which indicates that the data may not perfectly fit the model (however, the value of 6% is only marginally above the ideal value of something <5%); (7) Residuals are normally distributed (as per the histogram and P-P plots).*

**Observations:** The significant predictors of the Mental Component Summary (MCS) score are - (1) AGE: As the age of CKD patients increases by one year, the MCS score increases by a factor of 0.2 (however, this increase is an all-encompassing average, and greater weight should be given to the results of the Kruskal-Wallis Test, which suggest that the relationship between the MCS score and Age is not quite so monotonic); (2) STAGE OF CKD: Kidney Failure (i.e. Stage

5 CKD) patients have lower MCS scores than Non-Kidney Failure CKD patients by a factor of 2.1.

**Footnote to Chapter IX:**

- **Appendix V** – Histograms for the respective Outcome variables in the analyses.
- **Appendix VI** – Means of each Demographic Factor across each of the other Grouping variables of interest.
- **Appendix VII -** General relationships between mean SF-36 scores and the Grouping variables of (i) Age Category, (ii) Gender, (iii) Diabetes, and (iv) Heart Disease.
- **Appendix VIII** – Tests of Normality (Kolmogorov-Smirnov and Shapiro-Wilk), prior to comparisons of mean ranks/medians.
- **Appendix IX –** Comparisons of SF-36 mean rank/median scores across the Grouping variables of (i) Age Category, (ii) Gender, (iii) Diabetes, (iv) Heart Disease, (v) Heart Failure, (vi) Angina, (vii) Peripheral Vascular Disease, and (viii) Stroke.

# X. DISCUSSION

## X.1 SAMPLE CHARACTERISTICS

With regards to the general characteristics of the sample used for this Study, the following important points should be appreciated -

- The mean age of the Study sample (57 years) was lower than the average age of CKD patients in general,[78] and the mean age of Stage 5 CKD patients in the Study sample (53 years) was lower than the average age of Stage 5 CKD patients in general.[78] Although CKD can occur at any age, the risk for CKD increases with age; CKD is predominantly seen in those who are 60 years and over[78], and the average age of CKD patients generally increases, as the stage of the disease worsens (note - as life expectancy has increased, approximately 25% of individuals aged >60 years in the U.S. are now affected by CKD, while CKD rates among those <40 years of age has remained virtually unchanged during the past two decades[78]). However, the relatively lower mean age of the Study sample could be explained by the exclusion of Heart Disease patients from the EPO-INTERNATIONAL Study, which provided 48.6% of the patients for this particular Study (note - CKD patients with one or more co-morbidities are generally older than CKD patients without a co-morbidity[79]). It may be emphasized that the mean age of non-Stage 5 CKD patients in the Study sample was in line with general trends.

- As per trends among CKD patients in Canada and elsewhere[80], the mean age of males in the Study sample was marginally lower than the mean age of females in the Study sample (with 57 years being the approximate mean age of each of the gender-based groups).

- As per trends among CKD patients in Canada and elsewhere[80], patients with Diabetes and/or Heart Disease were older when compared to patients without either one of those co-morbidities (in the Study sample).

- There were more males than females (by approximately 7.5%) in the Study sample, which is dissimilar to the general gender-based prevalence of CKD; in various historical studies, CKD has been reported to be more common in females by between 2 and 7%.[81] However, the fact that Stage 5 CKD patients outnumbered Stage 2-4 CKD patients (63.1% to 36.9%) within the Study sample could explain the greater number of males in said sample (note – while CKD is more prevalent among females in general, the proportion of males increases at more advanced stages[82], and males have been reported to constitute a majority of the patients on Dialysis[83]). It may be emphasized that (just as in general trends) the majority of non-Stage 5 CKD patients in the Study sample were female.

- As per trends in Canada and elsewhere among patients with Diabetes and/or Heart Disease[84,85], males constituted a majority among patients having one or both of those conditions (in the Study sample). Therefore (based on these variables, at least), the sample analyzed during this Study is similar to most populations with CKD, with the exception of the many patients on Dialysis who were free of Heart Disease.

## X.2 RESULTS

It was determined that performing non-parametric comparisons of medians/mean ranks, and then verifying/substantiating the results of those comparisons via Multiple Linear Regression analyses would be most prudent.

**Comparisons of medians/mean ranks:** The non-parametric tests (Kruskal-Wallis or Mann-Whitney U) were the primary statistical tests performed, and they resulted in observations that should be dissected, as follows -

- Similar to the results from most of the studies that were summarized in Chapter VI, Stage 5 CKD patients had (i) significantly more role limitations due to poor physical health, (ii) significantly lower perceptions of their general health, and (iii) significantly lower PCS scores, as compared to patients with the preceding stages of CKD. While Stage 5 CKD patients also exhibited significantly greater negative impacts on their social functioning abilities and mental health (as compared to patients with Stage 2-4 CKD), these observations are not consistent with the results of most similar studies from the past; however, a noteworthy exception is the previously-summarized Swedish Study by Pagels et al. in 2012, which did indeed lead to such results (i.e. significant negative impacts on aspects of mental health-related QoL). The GH and SF Domain scores, as well as the PCS score were (i) significantly lower for Stage 4 CKD patients when compared to Stage 3 CKD patients, and (ii) significantly lower for Stage 5 CKD patients when compared to Stage 4 CKD patients; even though the total number of Stage 4 CKD patients in the Study sample was very small, the stage-wise decrease in physical health-related QoL is consistent with the results of most of the studies that were summarized in Chapter VI.

While CKD is generally associated with fatigue (and, therefore, loss of energy), the fact that the VT Domain score was not significantly impacted by the stage of the disease suggests that the degree of fatigue does not differ greatly across the various stages of CKD. Another interesting observation was that when current health status was compared with health status at a year ago, Stage 5 CKD patients rated their current health status as being better to a greater extent than Stage 2-4 CKD patients did (note - Stage 2-4 CKD patients provided a significantly lower rating on this matter); this could be because the vast majority of Stage 5 CKD patients in the Study sample had already been on Hemodialysis therapy for more than 3 months, thereby having had sufficient time to get accustomed to a beneficial therapy (in addition – unlike patients with the preceding stages of CKD, Stage 5 CKD patients may value the stability that comes with the natural end of disease progression).

- As observed during similar studies from the past, the co-morbidities of Diabetes and Heart Disease were both associated with further (significant) reductions in physical health-related QoL (with the PF, GH, and VT Domains, as well as the PCS measure being negatively impacted by Diabetes and Heart Disease, respectively); it ought to be remembered that the GH and VT Domains each comprise aspects of both physical health and mental health, which means that the impacts of the co-morbidities on these Domains is not unexpected. Perceptions of pain were significantly higher in those CKD patients with Heart Disease, which is explained by the fact that a majority (64%) of the Heart Disease patients in the Study sample had been diagnosed with pain-associated IHD (i.e. Angina and/or Myocardial Infarction), prior to their baseline QoL measurement. As would be expected, CKD patients with any one of the analysable components of

Cardiovascular Disease (i.e. Heart Failure, Angina, PVD and Stroke) had significantly worse physical health-related QoL than CKD patients who did not have the respective component of Cardiovascular Disease; it may also be mentioned that Angina, as expected, was the only one of the four named conditions to be significantly associated with increased perceptions of pain (note – while PVD is also often associated with pain, it is possible that an impressive number of patients in the CANPREVENT dataset who had a diagnosis of PVD in their histories did not have active symptoms of PVD at the time of baseline QoL measurement; however, there was no way to verify this supposition).

- The demographic factor of Age appeared to significantly impact the QoL of CKD patients in ways that are not totally consistent with the results of past studies on the topic. Mental health-related QoL (including social functions) was observed to be progressively worse in every succeeding group of older patients within the <50 years of age subset, but mental health-related QoL (including social functions) was then seen to be progressively better in every succeeding group of older patients within the >50 years of age subset; this could be due to patients discovering better coping mechanisms (to deal with CKD-associated discomforts/disabilities) as time passes, after struggling to cope during their early years with the disease. On the other hand, physical functions (as per the PF Domain score) were observed to be progressively worse in absolutely every succeeding group of older patients; this is consistent with logical expectations because increasing age is naturally associated with decreasing physical capabilities, but even this observation is not totally consistent with the existing literature on CKD patients. While patients >60 years of age seemed to perceive their general health as being better when compared to patients <60 years of age, this appears to be due to a correlation with the mental health-related QoL

trends within the Study sample (note – the GH Domain score reflects perceptions of both physical health and mental health). A caveat worth bearing in mind is that the EPO-INTERNATIONAL dataset contained individuals who were relatively younger and relatively healthier (at least, in terms of co-morbidities); this fact could have led to the results of this Study being rather different from the results of prior studies that looked into age-based effects on CKD patients' QoL.

- Male CKD patients appeared to experience a significantly better QoL, across the board when compared to female CKD patients (with the difference in physical health-related QoL being slightly greater than the difference in mental health-related QoL). This observation is consistent with not only the existing literature that pertains to QoL in CKD patients, but also that which pertains to QoL in patients with other chronic diseases (the previously-summarized publication by Hopman et al. from 2009 is one such piece of evidence).

**Regression analyses:** Multiple Linear Regression models were principally built to strengthen the results of the non-parametric comparisons of medians/mean ranks, although any additional pertinent information was looked for in the models, as well. Prior to discussing the results of the Multiple Linear Regression analyses, it is worth emphasizing that for five Outcome variables (i.e. BP Domain score, GH Domain score, PCS score, MCS score, and Recoded SF-2 Question score), the 551 subjects from the EPO-INTERNATIONAL Study could not be part of the analyses; in addition, SF-36 Domain scores (especially those for RP, BP, SF and RE) and the Recoded SF-2 Question score have ordinal characteristics, which impede truly accurate results coming out of those Multiple Linear Regression models. In any case, the results of the Multiple Linear Regression analyses should be dissected, as follows -

- Stage of CKD was a significant predictor for all of the SF-36 Domain scores (except the BP score), as well as for both of the Summary scores, and the Recoded SF-2 Question score. Each of the significantly predicted SF-36 scores worsened along with the worsening of the Stage of CKD, except for the Recoded SF-36 Question score (which did the reverse, thus being consistent with the previously-explained results of the Kruskal-Wallis Test). It may be noted that pain is not usually associated with CKD unless there is an associated pain-inducing co-morbidity; therefore, it is not surprising that perceptions of pain are not significantly impacted in CKD patients (whatever the stage of the disease might be). Overall, these results corroborate the results of the non-parametric comparisons of medians/mean ranks where Stage of CKD was the variable (out of all of the Grouping variables) that led to significantly different scores for the greatest number of Outcome variables.

- Similar to the results of the non-parametric comparisons of medians/mean ranks, co-morbidities were generally associated with further worsening of physical health-related QoL among CKD patients (note - both Diabetes and Heart Disease were significantly predictors of the PF, VT, and GH Domain scores, plus the PCS score, while Heart Disease alone was a significant predictor of the RP and BP Domain scores). The fact that Heart Disease and not Diabetes was significantly associated with worse BP Domain scores is, once again, likely because IHD was the commonest form of Heart Disease in patients labelled as having Heart Disease (note - 64% of Heart Disease patients in the Study sample had had pain-associated IHD). In addition, the fact that Heart Disease (compared to Diabetes) was associated with greater negative impacts on QoL could be explained by (i) the comparatively more debilitating nature of the Heart Disease

symptomatology, and (ii) a large percentage (46.3%) of Diabetics in the Study sample not being on Dialysis therapy (note – Dialysis therapy is specifically purported to lead to severe impacts on the QoL of Diabetics[86]).

- Consistent with the observations derived from the non-parametric comparisons of medians/mean ranks, increasing age among CKD patients was significantly associated with (i) a worsening of physical functions (i.e. the PF Domain score), and (ii) an improvement in some aspects of mental health (however, this improvement in mental health-related QoL shown by the Regression models is just an overall trend, and is less informative than the Kruskal-Wallis Test, which indicated one trend for those <50 years of age, and another trend for those >50 years of age).

- Just as indicated by the non-parametric comparisons of medians/mean ranks, male CKD patients perceived their QoL to be significantly better than that of female CKD patients; this was observed across the board with a slightly greater difference between the genders being noted in aspects of physical health-related QoL.

*It should be noted that, as per each Regression model, the Variability in each of the SF-36 scores was due in relatively small part (range: 3-16%) to the significant predictor variables (i.e. one or more of - Age, Gender, Stage of CKD, Diabetes, and Heart Disease); this indicates that there are other factors, which affect CKD patients' QoL to a great degree (and, those factors are potentially stronger predictors of QoL than any of the five predictor variables used during these analyses). However, it should be emphasized that the Variability in three SF-36 scores (i.e. the PF Domain score, the GH Domain score, and the PCS score) was explained by the significant predictor variables to a much greater extent (i.e. 12-16%) when compared to each of the other*

*SF-36 scores, for which the Variability was explained by the significant predictor variables to a very small extent (i.e. 3-6%); this observation also helps one to infer that the stages of CKD and the main CKD-associated co-morbidities lead to greater impacts on physical health-related QoL, rather than mental health-related QoL.*

## X.3 LIMITATIONS

While interpreting the results of the various analyses performed during this particular Study, it is also important to consider the limitations of the Study, which include the following -

- As a result of being based on historical data from three separate studies, the definitions of several variables of interest were not identical across the three original datasets; this limitation led to - (a) the possibility that Diabetics from the EPO-INTERNATIONAL Study were slightly under-represented, in the merged dataset, (b) the possibility that some patients with no symptoms of Heart Disease during baseline QoL measurement were labelled as symptomatic Heart Disease patients, in the merged dataset (note – the opposite form of this misclassification was also possible, but much less likely), (c) a disproportionately large number of patients in the merged dataset being free of Heart Disease (as a result of the exclusion criteria of the EPO-INTERNATIONAL Study), and (d) the SF-36 Domain scores for GH and BP being absent for 48.6% of the patients in the merged dataset due to the different scoring algorithm used during the EPO-INTERNATIONAL Study.

- Not only were the BP and GH Domain scores unavailable for 48.6% of patients in the merged dataset, the two Summary scores and the Recoded SF-2 Question score were also

unavailable for those same patients; this was due to both the lack of "raw" SF-36 scores from the EPO-INTERNATIONAL Study, as well as the different SF-36 scoring algorithm used during that particular Study (note – the scoring algorithm used during both the PPHS and CANPREVENT studies is the recommended scoring algorithm, as per the relevant literature[56]).

- Due to the small proportion of patients with Stage 2 CKD (0.09%) and Stage 4 CKD (1.6%) in the merged dataset, this Study was basically a comparison of QoL between Stage 3 CKD patients and Stage 5 CKD patients; in addition, the Stage 5 CKD patients in this Study were all on Hemodialysis therapy, which means that that particular stage of CKD was not as well represented as it could have been (note – in general, Stage 5 CKD patients would also include those who are on other forms of Renal Replacement Therapy, as well as those who are yet to be started on a form of Renal Replacement Therapy).

- The mean age of the Study sample was lower than the mean age of CKD patients in general; this difference was accentuated, with regards to Stage 5 CKD patients in the sample.

- There was a majority of males in the Study sample, which is different from the gender-based distribution among CKD patients in the general population.

- The disparate settings in which data had been collected during the original studies may have impacted subjective evaluations of health differently, thus leading to widely different QoL scores, even among patients with similar symptoms (note – each of the three original studies, in turn, involved data collection from several different locations).

- In the merged dataset, only 12% of the total number of patients on Hemodialysis (i.e. those with Stage 5 CKD) had been started on Hemodialysis therapy >18 months prior to their baseline QoL measurement; this meant that a meaningful comparison of QoL between incident and prevalent Hemodialysis patients was untenable.

- The usual disadvantages of a cross-sectional study (such as - not being able to make inferences about cause, not being able to track QoL along with the course of illness, etc.) were present, as well.

- Any analysis that is based on a QoL-measuring instrument involves certain inherent limitations (such as – "ceiling" and "floor" effects of the instrument, subjective evaluations that are based on each patient's surroundings and/or beliefs, perceptions of health that derive only from the diagnosis that the patient is labelled with, patients' differing adaptations to similar symptoms, etc.); these issues mean that caution should be applied when interpreting the results.

- The QoL data was all based on a generic QoL-measuring instrument (i.e. the SF-36), which meant that many specific dimensions of health (e.g. Sleep, Cognitive Functions, Sexual Functioning, etc.) could not be assessed, even though they also contribute to a patient's QoL; in addition, variables that often influence mental health-related QoL (e.g. self-management, psycho-social supports, etc.) could not be part of the Study.

- The SF-36 Domain scores are not purely continuous variables because they contain ordinal characteristics, too; therefore, caution is required while interpreting the results of the Multiple Linear Regression analyses that were performed to predict each SF-36 Domain score (note - Discriminant Function tests for those semi-ordinal variables could

be performed, later, but said tests would be superfluous in this case because the results of the non-parametric comparisons of medians/mean ranks take precedence over and carry more weight than the results of the Regression analyses).

## X.4 STRENGTHS

The obvious strengths of this particular Study must also be stated, and they are -

- The total sample size of 1135 subjects was large, especially in comparison with previous studies that have specifically compared QoL among CKD patients (note – even excluding the subjects from the EPO-INTERNATIONAL Study for whom some of the SF-36 scores were unavailable, the remaining sample size of 584 is still relatively large).

- The fact that the data were collected via three different studies (which were each conducted in vastly different settings) can also be called a strength because the resultant final sample will potentially consist of a more diverse population than would otherwise be the case.

- A Study that compares QoL between predominantly Stage 3 and Stage 5 CKD patients (with very few Stage 2 and Stage 4 CKD patients included in the Study) is still clinically important, considering that the majority of reported CKD cases (i.e. 5-6% of the general population) have stages 3-5 CKD.[82]

- A look into how the co-morbidities of Diabetes and Heart Disease impact the QoL of CKD patients has not been performed in such an elaborate manner, to date; this objective is clinically important because of the extra risk of disability/death that is involved with

the co-morbidities (note - Heart Disease is the leading cause of mortality in CKD patients, and for CKD patients, the risk of dying from Heart Disease is greater than the risk of ever requiring Renal Replacement Therapy[82]).

- The use of more than one form of statistical analyses to relate QoL dimensions to CKD (with/without co-morbidities) provides an extra layer of validation to the final results.

## X.5 INCIDENTAL OBSERVATIONS

Even though this particular Study was never intended to compare the QoL of CKD patients with the QoL of a non-diseased population sample (and, even though the two Summary scores could not be calculated for 48.6% of the patients in the Study sample due to already-stated reasons), it is still worth pointing out the following incidental observations -

- The mean PCS score for the sample used during this Study was 38.2, while the mean MCS score for the sample was 51.2; this suggests that CKD patients generally have a much lower physical health-related QoL than the Canadian "norm" population, while the same CKD patients apparently have a mental health-related QoL that is mildly but not significantly higher than that of the Canadian "norm" population (note – as per the Canadian Norm-Based Scores that were utilized for computations during this Study, 50 indicates the Canadian "norm" population's mean score for the PCS and MCS measures, respectively). These observations are also consistent with findings listed in the previously-summarized Study by Hopman et al. (published in 2009).

- Taking the afore-mentioned observation a bit further, it should also be stated that the mean PCS scores were well below 50, across all of the stages of CKD; on the other hand, the mean MCS score for Stage 5 CKD patients was slightly <50 while the mean MCS scores for patients with the preceding stages of CKD was slightly >50 (and, this could indicate a mild negative impact of Dialysis therapy on mental health-related QoL).

# XI. CONCLUSIONS

As a result of the observations obtained via this particular Study, the following points may be inferred -

- Stage 5 CKD is associated with a significantly worse physical health-related QoL, as compared to Stage 3 CKD (and, there is also a suggestion that progression of CKD from stage to stage is directly associated with worsening of physical health-related QoL).

- The co-morbidities of Diabetes and Heart Disease are associated with further decrements of physical health-related QoL in CKD patients (and, Heart Disease is associated with slightly greater negative impacts on QoL, as compared to Diabetes).

- Female CKD patients are associated with significantly worse physical and mental health-related QoL, as compared to male CKD patients (when the gender-based comparison groups are similar, in terms of age-range and prevalent co-morbidities).

- CKD patients over 50 years of age are associated with mildly better mental health-related QoL, as compared to CKD patients below 50 years of age.

# XII. RECOMMENDATIONS

With the conclusions of this Study in mind, the following recommendations may be put forward -

- From the perspective of a clinician, it is clear that substantive efforts must be made to prevent the progression of CKD towards Stage 5, and great efforts must also be made to prevent/control the co-morbidities of Diabetes and Heart Disease; when this approach is successful, not only would the QoL of affected patients be negatively impacted to a lesser degree, but the burden and cost of care would also come down because more advanced/complicated disease entails more time and effort on the part of healthcare workers.

- From the perspective of a present or future CKD patient, more information can and should be accessed by him/her, with regards to how CKD during each of its stages will potentially affect his/her QoL (and therefore, his/her physical abilities, family life, work situation, employment prospects, etc.).

- From the perspective of a health policy-maker, investing more to prevent the progression of CKD towards Stage 5 would be wise because (i) the poor QoL of Stage 5 CKD patients greatly reduces their productivity in the community, and (ii) the cost involved with Renal Replacement Therapy (which is the usual treatment for Stage 5 CKD patients) is far higher than the costs involved with other treatments for kidney ailments; considering the relatively long life expectancies and the relatively large ageing populations in countries like Canada, this approach should be emphasized because the financial burden placed on the healthcare system by all forms of Renal Replacement Therapy (i.e. Dialysis and Kidney Transplantation) is immense.[78]

- From the perspective of a researcher, it would be advisable to answer this Study's fundamental question by carrying out a Prospective Longitudinal Observational Study using a single large cohort of CKD patients who would answer to a kidney-specific health survey, such as - the KDQOL (the timings and settings for each survey administration would have to be based on the characteristics of the available sample, of course); this approach would naturally (i) include more specific dimensions of health, (ii) indicate the perceptions of patients, as time passes, (iii) indicate the perceptions of patients, as symptomatology changes, (iv) circumvent many of the shortcomings that are associated with cross-sectional studies, and (v) circumvent many of the shortcomings that are associated with the use of historical datasets.

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# SUMMARIZED STUDIES

**A**. Interpreting the SF-36 Health Survey, 2002 – Gandek B. (Canadian Association of Cardiac Rehabilitation).

**B**. Validating the SF-36 health survey questionnaire: new outcome measure for primary care, 1992 – Brazier J.E. et al. (British Medical Journal).

**C**. Canadian normative data for the SF-36 health survey, 2000 – Hopman W.M. et al. (Canadian Medical Association Journal).

**D**. Do SF-36 summary component scores accurately summarize subscale scores?, 2001 – Taft C. et al. (Quality of Life Research).

**E.** Quality of life in Chronic Kidney Disease (CKD): A cross-sectional analysis in the Renal Research Institute-CKD study, 2005 – Perlman R.L. et al. (American Journal of Kidney Diseases).

**F.** Health-related quality of life and estimates of utility in chronic kidney disease, 2005 – Gorodetskaya I. et al. (Kidney International).

**G**. Symptom Burden, Depression, and Quality of Life in Chronic and End-Stage Kidney Disease, 2009 – Abdel-Kader K. et al. (Clinical Journal of the American Society of Nephrology).

**H.** Health-related quality of life in different stages of chronic kidney disease and at initiation of dialysis treatment, 2012 – Pagels A.A. et al. (Health and Quality of Life Outcomes).

**I.** Quality of life in patients with chronic kidney disease, 2011 – Cruz M.C. et al. (Clinics–Sao Paolo).

**J.** Quality of life in chronic kidney disease, 2011 – Fructuoso M. et al. (Nefrologia).

**K.** Moderately decreased renal function negatively affects the health-related quality of life among the elderly Korean population: a population-based study, 2008 – Chin H.J. et al. (Nephrology, Dialysis, Transplantation – official publication of the European Dialysis and Transplant Association).

**L.** Cross-sectional study of quality of life and symptoms in chronic renal disease patients: the Modification of Diet in Renal Disease Study, 1997 – Rocco M.V. et al. (American Journal of Kidney Diseases).

**M.** Quality of life and psychosocial relationships in patients with chronic renal insufficiency, 1998 – Shidler N.R. et al. (American Journal of Kidney Diseases).

**N.** Associations between chronic disease, age and physical and mental health status, 2009 – Hopman W.M. et al. (Chronic Diseases in Canada).

**O.** Psychometric Properties of the Patient's Perception of life on Hemodialysis Scale, 2012 (Thesis) – Twomey J.C. et al.

**P.** A Nurse-coordinated Model of Care versus Usual Care for Stage 3/4 Chronic Kidney Disease in the Community: A Randomized Controlled Trial, 2011 – Barrett B. J. et al. (Clinical Journal of the American Society of Nephrology).

**Q.** Erythropoietin therapy, hemoglobin targets, and quality of life in healthy hemodialysis patients: a randomized trial, 2009 – Foley R.N. et al. (Clinical Journal of the American Society of Nephrology).

# APPENDIX

## I. RAND SF-36 Questionnaire (Version 1; 4-week recall)

*[courtesy of the Workplace Safety & Insurance Board, Ontario (wsib.on.ca)]*

**1. In general, would you say your health is:**

Excellent = 1

Very good = 2

Good = 3

Fair = 4

Poor = 5

**2. Compared to one year ago, how would your rate your health in general now?**

Much better now than one year ago = 1

Somewhat better now than one year ago = 2

About the same = 3

Somewhat worse now than one year ago = 4

Much worse now than one year ago = 5

**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?**

**3. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports**

**4. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf**

**5. Lifting or carrying groceries**

**6. Climbing several flights of stairs**

**7. Climbing one flight of stairs**

**8. Bending, kneeling, or stooping**

**9. Walking more than a mile**

**10. Walking several blocks**

**11. Walking one block**

**12. Bathing or dressing myself**

(For Questions 3-12: Yes, limited a lot = 1; Yes, limited a little = 2; No, not limited at all = 3).

**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?**

**13. Cut down the amount of time you spent on work or other activities**

**14. Accomplished less than you would like**

**15. Were limited in the kind of work or other activities**

**16. Had difficulty performing the work or other activities (for example, it took extra effort)**

(For Questions 13-16: Yes = 1; No = 2).

**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)?**

**17. Cut down the amount of time you spent on work or other activities**

**18. Accomplished less than you would like**

**19. Didn't do work or other activities as carefully as usual**

(For Questions 17-19: Yes = 1; No = 2).

**20. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?**

Not at all = 1

Slightly = 2

Moderately = 3

Quite a bit = 4

Extremely = 5

**21. How much bodily pain have you had during the past 4 weeks?**

None = 1

Very mild = 2

Mild = 3

Moderate = 4

Severe = 5

Very severe = 6

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

Not at all = 1

A little bit = 2

Moderately = 3

Quite a bit = 4

Extremely = 5

**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 . . .**

**23. Did you feel full of pep?**

**24. Have you been a very nervous person?**

**25. Have you felt so down in the dumps that nothing could cheer you up?**

**26. Have you felt calm and peaceful?**

**27. Did you have a lot of energy?**

**28. Have you felt downhearted and blue?**

**29. Did you feel worn out?**

**30. Have you been a happy person?**

**31. Did you feel tired?**

(For Questions 23-31: 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).

**32. 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.)?**

All of the time = 1

Most of the time = 2

Some of the time = 3

A little of the time = 4

None of the time = 5

**How TRUE or FALSE is each of the following statements for you?**

**33. I seem to get sick a little easier than other people**

**34. I am as healthy as anybody I know**

**35. I expect my health to get worse**

**36. My health is excellent**

(For Questions 33-36: Definitely true = 1; Mostly true = 2; Don't know = 3; Mostly false = 4; Definitely false = 5).

## II. Scoring Instructions for the RAND SF-36 Questionnaire

*[courtesy of the Workplace Safety & Insurance Board, Ontario (wsib.on.ca)]*

### Step 1: Recoding Items (i.e. Questions)

For Questions 1, 2, 20, 22, 34, 36: 1 = 100; 2 = 75; 3 = 50; 4 = 25; 5 = 0

For Questions 3-12: 1 = 0; 2 = 50; 3 = 100

For Questions 13-19: 1 = 0; 2 = 100

For Questions 21, 23, 26, 27, 30: 1 = 100; 2 = 80; 3 = 60; 4 = 40; 5 = 20; 6 = 0

For Questions 24, 25, 28, 29, 31: 1 = 0; 2 = 20; 3 = 40; 4 = 60; 5 = 80; 6 = 100

For Questions 32, 33, 35: 1 = 0; 2 = 25; 3 = 50; 4 = 75; 5 = 100

### Step 2: Averaging Items (i.e. Questions) To Form Subscales (i.e. Domains)

**Physical Functioning (PF):** After recoding the answers, average these 10 Items (i.e. Questions) – Questions 3-12.

**Role limitations due to Physical health (RP):** After recoding the answers, average these 4 Items (i.e. Questions) – Questions 13-16.

**Bodily Pain (BP):** After recoding the answers, average these 2 Items (i.e. Questions) – 21-22.

**General Health (GH):** After recoding the answers, average these 5 Items (i.e. Questions) – 1, 33, 34, 35, 36.

**Vitality (VT):** After recoding the answers, average these 4 Items (i.e. Questions) – 23, 27, 29, 31.

**Social Functioning (SF):** After recoding the answers, average these 2 Items (i.e. Questions) – 20, 32.

**Role limitations due to Emotional problems (RE):** After recoding the answers, average these 3 Items (i.e. Questions) – 17-19.

**Mental Health (MH):** After recoding the answers, average these 5 Items (i.e. Questions) – 24, 25, 26, 28, 30.

## III. Reliability, Central Tendency and Variability of the RAND SF-36 Domains

*[courtesy of the Workplace Safety & Insurance Board, Ontario (wsib.on.ca)]*

| Domains | Questions | Alpha | Mean | Standard Deviation |
|---|---|---|---|---|
| PF | 10 | 0.93 | 70.61 | 27.42 |
| RP | 4 | 0.84 | 52.97 | 40.78 |
| BP | 2 | 0.78 | 70.77 | 25.48 |
| GH | 5 | 0.78 | 56.99 | 21.11 |
| VT | 4 | 0.86 | 52.15 | 22.39 |
| SF | 2 | 0.85 | 78.77 | 25.43 |
| RE | 3 | 0.83 | 65.78 | 40.71 |
| MH | 5 | 0.90 | 70.38 | 21.97 |
| Health Change | 1 | - | 59.14 | 23.12 |

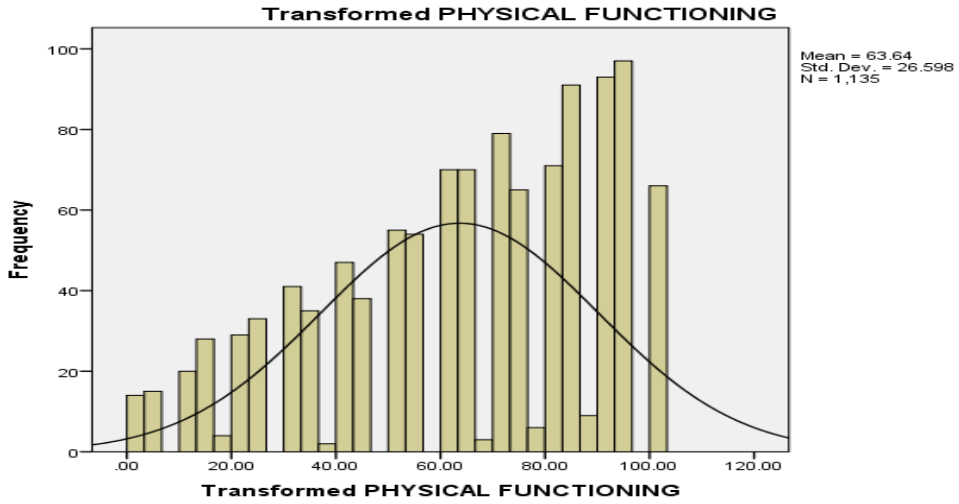
## IV. Summary of Information about the SF-36 Domains and Summary measures

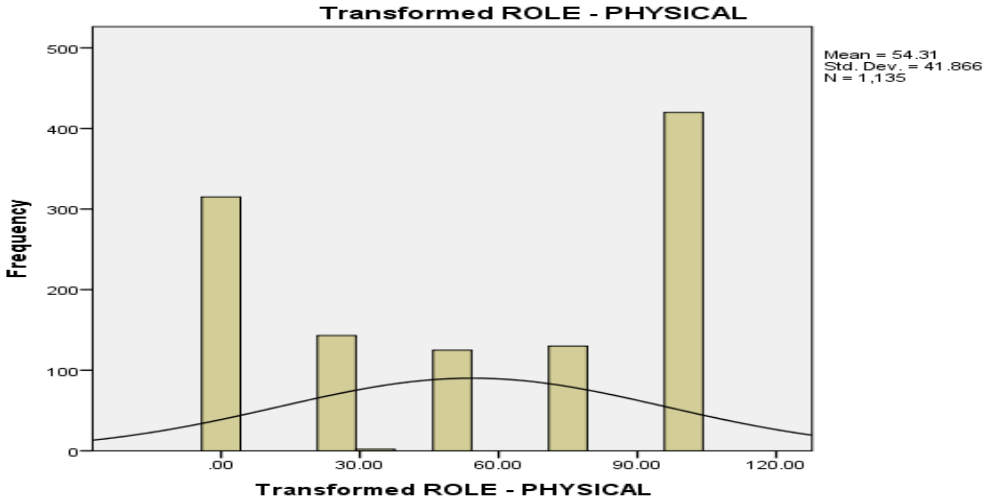
*[courtesy of Ware, Kosinski & Keller (1994)]*

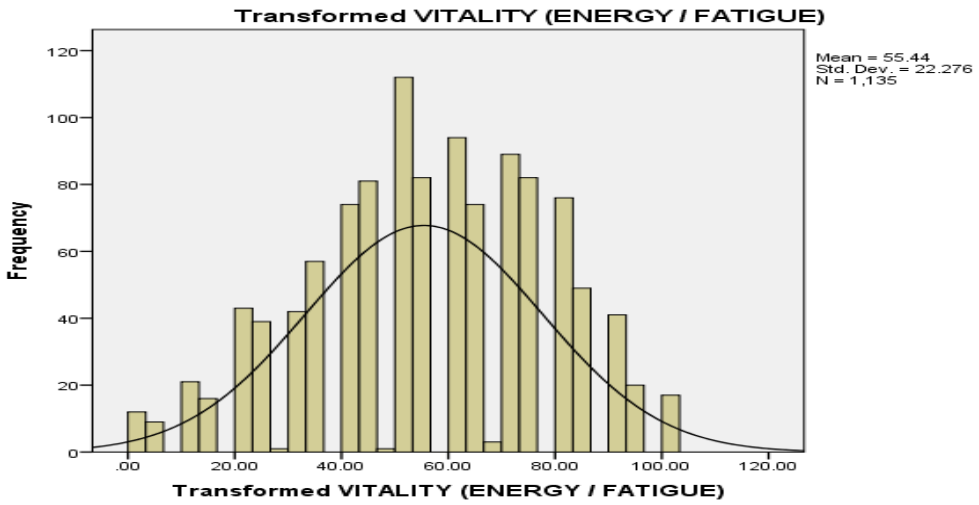
| Scales | Correlations with PCS | Correlations with MCS | Number of Items | Levels | Mean | SD | Reliability | 95% C.I. | Lowest Possible Score (Floor) | Highest Possible Score (Ceiling) |
|---|---|---|---|---|---|---|---|---|---|---|
| Physical Functioning (PF) | 0.85 | 0.12 | 10 | 21 | 84.2 | 23.3 | 0.93 | 12.3 | Very limited in performing all physical activities, including bathing or dressing (0.8%) | Performs all types of physical activities including the most vigorous without limitations due to health (38.8%) |
| Role-Physical (RP) | 0.81 | 0.27 | 4 | 5 | 80.9 | 34.0 | 0.89 | 22.6 | Problems with work or other daily activities as a result of physical health (10.3%) | No problems with work or other daily activities (70.9%) |
| Bodily Pain (BP) | 0.76 | 0.28 | 2 | 11 | 75.2 | 23.7 | 0.90 | 15.0 | Very severe and extremely limiting pain (0.6%) | No pain or limitations due to pain (31.9%) |
| General Health (GH) | 0.69 | 0.37 | 5 | 21 | 71.9 | 20.3 | 0.81 | 17.6 | Evaluates personal health as poor and believes it is likely to get worse (0.0%) | Evaluates personal health as excellent (7.4%) |
| Vitality (VT) | 0.47 | 0.65 | 4 | 21 | 60.9 | 20.9 | 0.86 | 15.6 | Feels tired and worn out all of the time (0.5%) | Feels full of pep and energy all of the time (1.5%) |
| Social Functioning (SF) | 0.42 | 0.67 | 2 | 9 | 83.3 | 22.7 | 0.68 | 25.7 | Extreme and frequent interference with normal social activities due to physical and emotional problems (0.6%) | Performs normal social activities without interference due to physical or emotional problems (52.3%) |
| Role-Emotional (RE) | 0.16 | 0.78 | 3 | 4 | 81.3 | 33.0 | 0.82 | 28.0 | Problems with work or other daily activities as a result of emotional problems (9.6%) | No problems with work or other daily activities (71.0%) |
| Mental Health (MH) | 0.17 | 0.87 | 5 | 26 | 74.7 | 18.1 | 0.84 | 14.0 | Feelings of nervousness and depression all of the time (0.0%) | Feels peaceful, happy, and calm all of the time (0.2%) |
| Physical Component Summary | | | 35 | 567 | 50.0 | 10.0 | 0.92 | 5.7 | Limitations in self-care, physical, social, and role activities, severe bodily pain, frequent tiredness, health rated "poor" (0.0%) | No physical limitations, disabilities, or decrements in well-being, high energy level, health rated "excellent" (0.0%) |
| Mental Component Summary | | | 35 | 493 | 50.0 | 10.0 | 0.88 | 6.3 | Frequent psychological distress, social and role disability due to emotional problems, health rated "poor" (0.0%) | Frequent positive affect, absence of psychological distress and limitations in usual social/role activities due to emotional problems, health rated "excellent" (0.0%) |

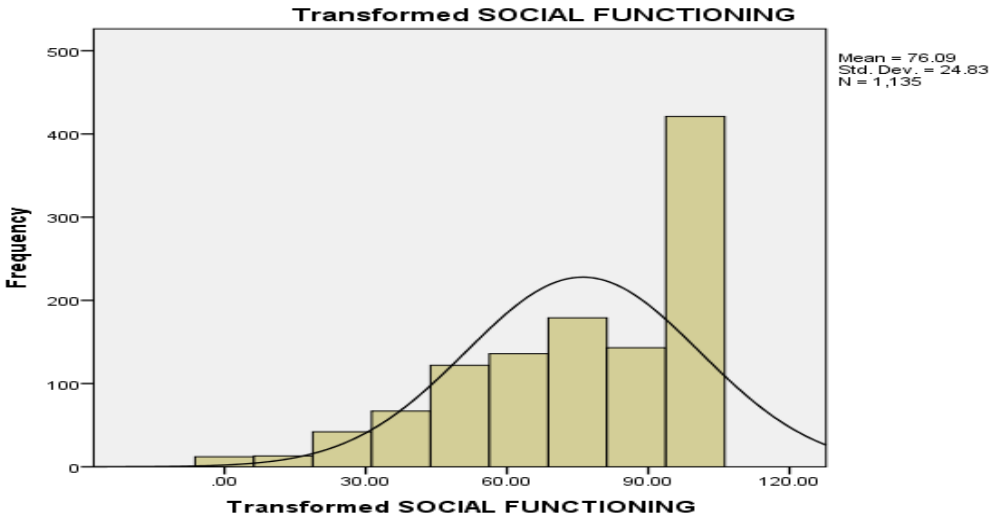
*[Notes: (1) The percentages of observed "floor" and "ceiling" scores are from the general U.S. population sample (n = 2474); (2) Scores for the eight Domains are the percentage of the total possible score achieved for each of these Domains; scores for PCS and MCS are T-scores].*

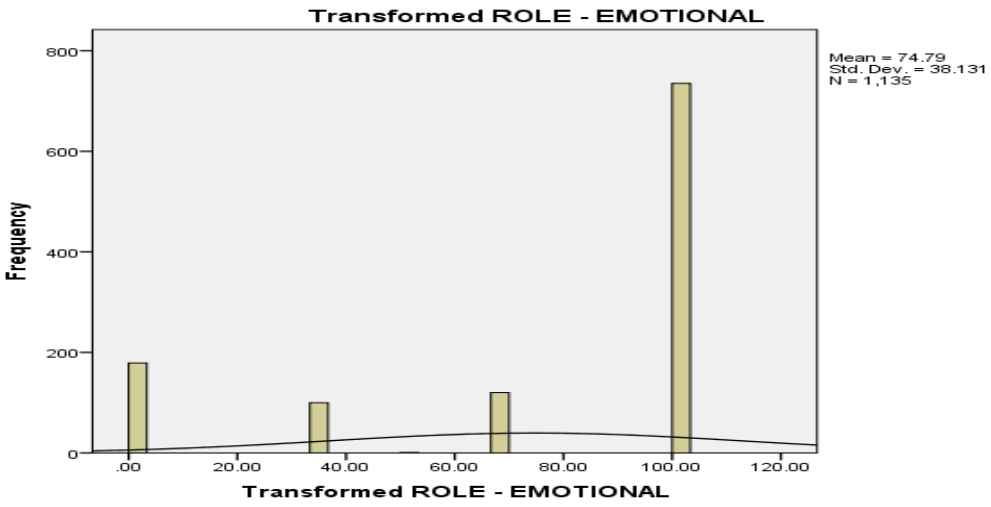
## V. Histograms for respective Outcome variables in the analyses

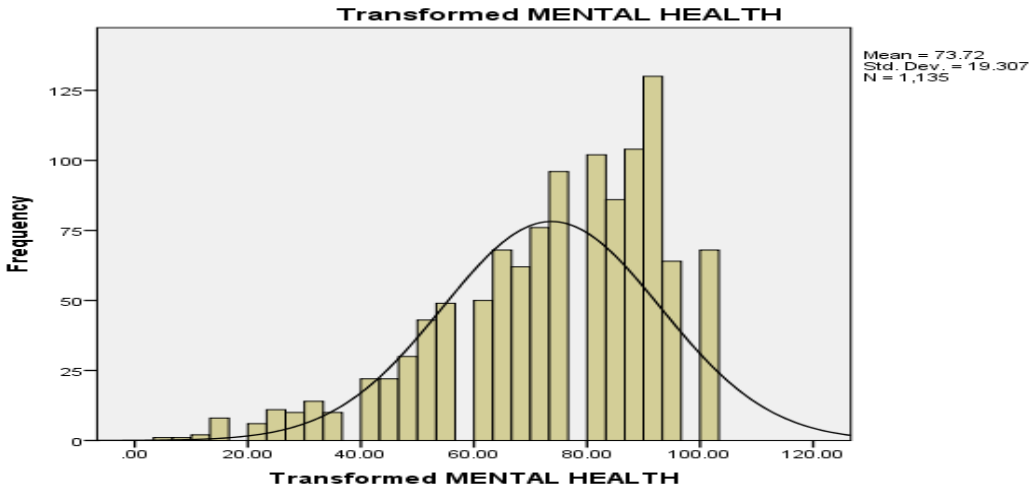


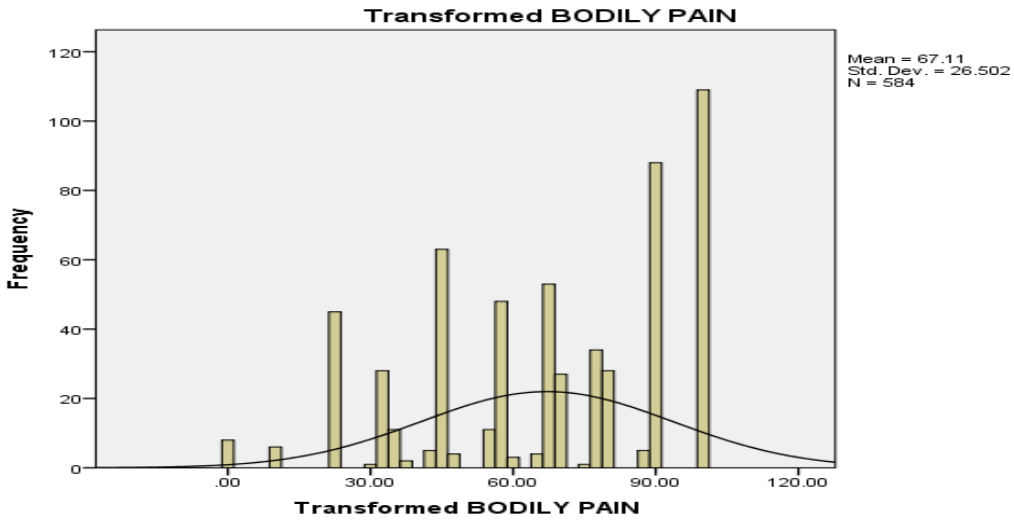



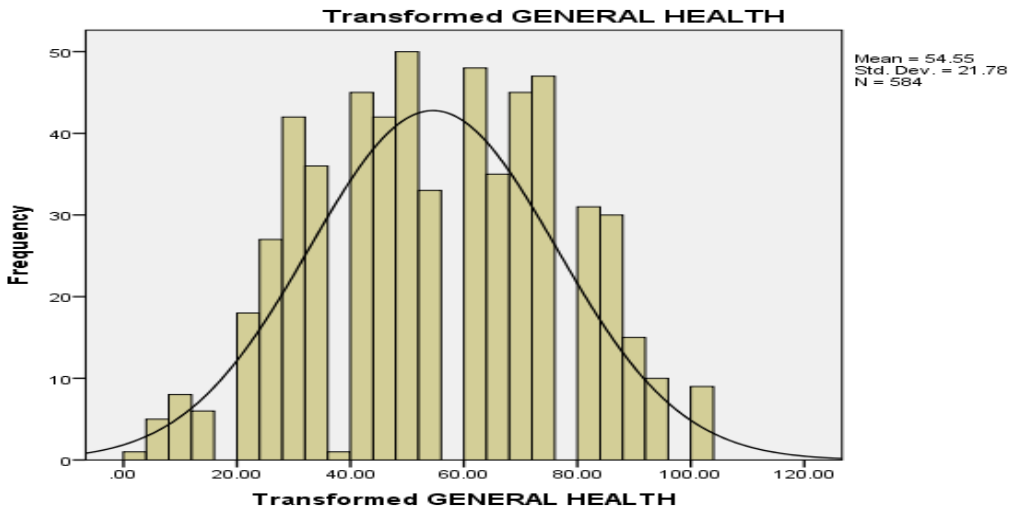

Transformed VITALITY (ENERGY / FATIGUE)
Mean = 55.44
Std. Dev. = 22.276
N = 1,135
Frequency
0
20
40
60
80
100
120
.00
20.00
40.00
60.00
80.00
100.00
120.00
Transformed VITALITY (ENERGY / FATIGUE)

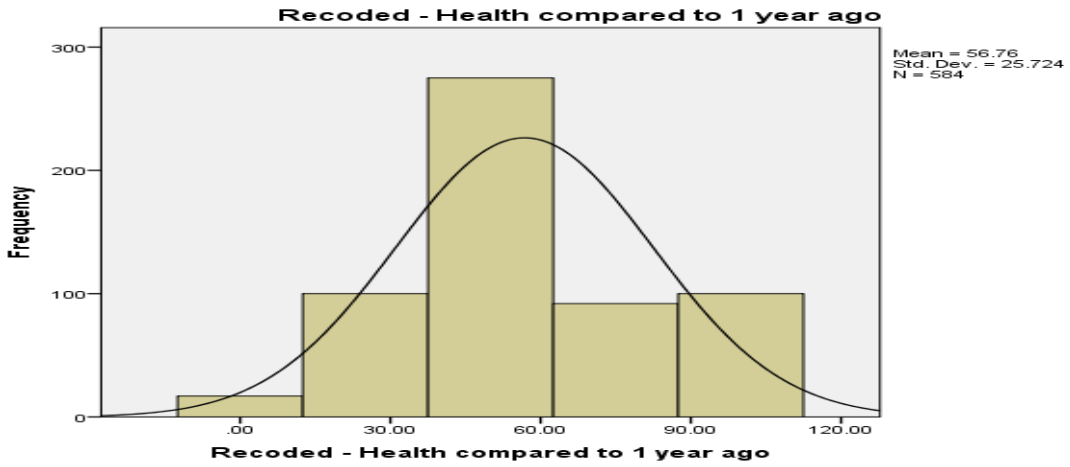

Transformed SOCIAL FUNCTIONING
Mean = 76.09
Std. Dev. = 24.83
N = 1,135
Frequency
0
100
200
300
400
500
.00
30.00
60.00
90.00
120.00
Transformed SOCIAL FUNCTIONING

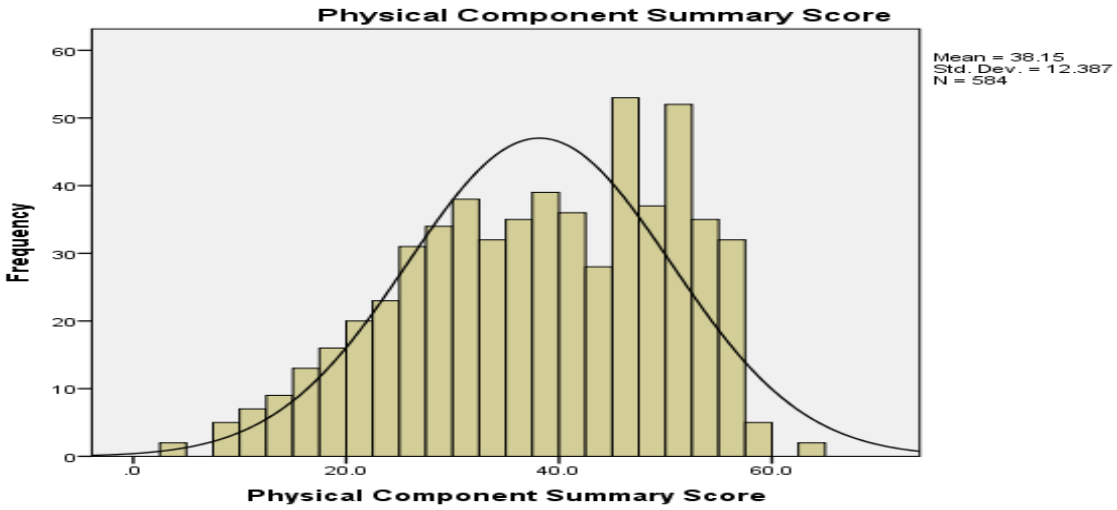

Transformed ROLE - EMOTIONAL
Mean = 74.79
Std. Dev. = 38.131
N = 1,135
Frequency
0
200
400
600
800
.00
20.00
40.00
60.00
80.00
100.00
120.00
Transformed ROLE - EMOTIONAL

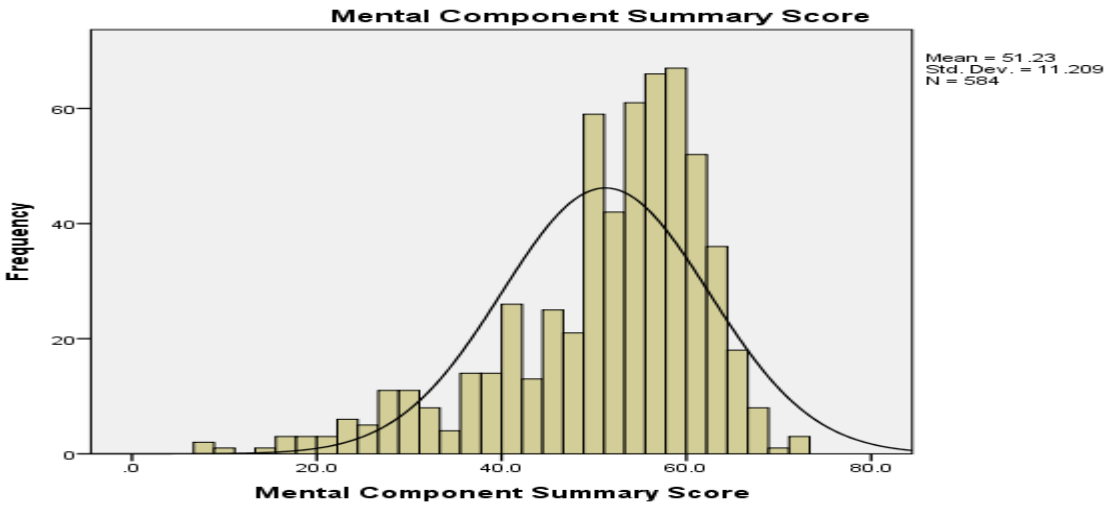

Transformed MENTAL HEALTH
Mean = 73.72
Std. Dev. = 19.307
N = 1,135
Frequency
125
100
75
50
25
0
.00
20.00
40.00
60.00
80.00
100.00
120.00
Transformed MENTAL HEALTH


Transformed BODILY PAIN
Mean = 67.11
Std. Dev. = 26.502
N = 584
Frequency
120
100
80
60
40
20
0
.00
30.00
60.00
90.00
120.00
Transformed BODILY PAIN


Transformed GENERAL HEALTH
Mean = 54.55
Std. Dev. = 21.78
N = 584
Frequency
50
40
30
20
10
0
.00
20.00
40.00
60.00
80.00
100.00
120.00
Transformed GENERAL HEALTH


Recoded - Health compared to 1 year ago
Mean = 56.76
Std. Dev. = 25.724
N = 584
Frequency
300
200
100
0
.00
30.00
60.00
90.00
120.00
Recoded - Health compared to 1 year ago


Physical Component Summary Score
Mean = 38.15
Std. Dev. = 12.387
N = 584
Frequency
60
50
40
30
20
10
0
.0
20.0
40.0
60.0
Physical Component Summary Score


Mental Component Summary Score
Mean = 51.23
Std. Dev. = 11.209
N = 584
Frequency
60
40
20
0
.0
20.0
40.0
60.0
80.0
Mental Component Summary Score

## VI. Means of each Demographic Factor across each of the other main Grouping variables

### *VI.1: Age across Gender*

| Gender | Mean Age | N | Std. Deviation |
|---|---|---|---|
| Female | 57.99 | 523 | 14.140 |
| Male | 56.82 | 609 | 15.420 |
| Total | 57.36 | 1132 | 14.847 |

### *VI.2: Age across Stage of Chronic Kidney Disease*

| Stage of Chronic Kidney Disease | Mean Age | N | Std. Deviation |
|---|---|---|---|
| CKD Stage 2 | 62.00 | 1 | . |
| CKD Stage 3 | 64.74 | 400 | 7.605 |
| CKD Stage 4 | 68.61 | 18 | 5.962 |
| CKD Stage 5 | 52.89 | 714 | 16.243 |
| Total | 57.33 | 1133 | 14.866 |

### *VI.3: Age across Diabetes*

| Diabetes | Mean Age | N | Std. Deviation |
|---|---|---|---|
| No | 55.84 | 853 | 15.554 |
| Yes | 61.88 | 280 | 11.417 |
| Total | 57.33 | 1133 | 14.866 |

### *VI.4: Age across Heart Disease*

| Heart Disease | Mean Age | N | Std. Deviation |
|---|---|---|---|
| No | 55.78 | 963 | 15.004 |
| Yes | 66.44 | 162 | 10.424 |
| Total | 57.31 | 1125 | 14.908 |

***VI.5: Gender across Age Categories***

| | | Age Categories | | | | | | Total |
|---|---|---|---|---|---|---|---|---|
| | | 30 and under | 31-40 | 41-50 | 51-60 | 61-70 | 71 and above | |
| Gender | Female | 27 | 40 | 71 | 114 | 173 | 98 | 523 |
| | Male | 42 | 68 | 77 | 124 | 169 | 129 | 609 |
| Total | | 69 | 108 | 148 | 238 | 342 | 227 | 1132 |

***VI.6: Gender across Stage of Chronic Kidney Disease***

| | | Stage of Chronic Kidney Disease | | | | Total |
|---|---|---|---|---|---|---|
| | | CKD Stage 2 | CKD Stage 3 | CKD Stage 4 | CKD Stage 5 | |
| Gender | Female | 0 | 221 | 11 | 292 | 524 |
| | Male | 1 | 179 | 7 | 422 | 609 |
| Total | | 1 | 400 | 18 | 714 | 1133 |

***VI.7: Gender across Diabetes***

| | | Diabetes | | Total |
|---|---|---|---|---|
| | | No | Yes | |
| Gender | Female | 407 | 117 | 524 |
| | Male | 445 | 164 | 609 |
| Total | | 852 | 281 | 1133 |

***VI.8: Gender across Heart Disease***

| | | Heart Disease | | Total |
|---|---|---|---|---|
| | | No | Yes | |
| Gender | Female | 446 | 71 | 517 |
| | Male | 516 | 92 | 608 |
| Total | | 962 | 163 | 1125 |

## VII. General relationships between mean SF-36 scores and the main Grouping variables

## (except - Stage of CKD)

***VII.1: Means (across each stated Age Category) for the scores that are common to all datasets***

| AGE CATEGORIES | | PF | RP | VT | SF | RE | MH |
|---|---|---|---|---|---|---|---|
| **30 AND UNDER** | **Mean** | **75.89** | **57.50** | **56.83** | **74.64** | **77.62** | **74.20** |
| | Std. Dev. | 21.85 | 40.01 | 21.19 | 23.50 | 37.09 | 16.70 |
| **31-40** | **Mean** | **70.82** | **54.40** | **53.75** | **71.07** | **72.53** | **69.82** |
| | Std. Dev. | 23.94 | 40.56 | 22.66 | 26.23 | 39.95 | 21.16 |
| **41-50** | **Mean** | **70.43** | **49.55** | **54.21** | **70.52** | **67.79** | **68.81** |
| | Std. Dev. | 22.97 | 43.37 | 23.29 | 25.59 | 41.22 | 20.10 |
| **51-60** | **Mean** | **65.54** | **54.73** | **53.56** | **76.16** | **72.83** | **71.24** |
| | Std. Dev. | 25.78 | 41.23 | 23.63 | 25.31 | 39.44 | 20.21 |
| **61-70** | **Mean** | **61.63** | **56.82** | **57.43** | **79.39** | **77.68** | **76.21** |
| | Std. Dev. | 26.11 | 42.19 | 21.71 | 23.23 | 36.45 | 18.46 |
| **71 AND ABOVE** | **Mean** | **53.43** | **52.64** | **55.55** | **77.48** | **77.46** | **77.36** |
| | Std. Dev. | 28.86 | 42.18 | 21.15 | 25.19 | 35.92 | 17.70 |
| **TOTAL** | **Mean** | **63.71** | **54.41** | **55.43** | **76.08** | **74.83** | **73.70** |
| | Std. Dev. | 26.56 | 41.84 | 22.29 | 24.85 | 38.09 | 19.31 |

***VII.2: Means (across each stated Age Category) for the scores that are common to only two datasets***

| AGE CATEGORIES | | BP | GH | Recoded SF-2 Question | PCS | MCS |
|---|---|---|---|---|---|---|
| **30 AND UNDER** | **Mean** | **73.57** | **39.29** | **53.57** | **40.84** | **47.33** |
| | Std. Dev. | 32.34 | 10.18 | 39.34 | 12.51 | 12.93 |
| **31-40** | **Mean** | **65.16** | **38.13** | **70.31** | **36.72** | **44.12** |
| | Std. Dev. | 24.62 | 20.07 | 33.19 | 12.29 | 13.90 |
| **41-50** | **Mean** | **72.37** | **48.46** | **55.13** | **42.09** | **44.68** |
| | Std. Dev. | 20.95 | 20.33 | 29.35 | 10.65 | 12.28 |
| **51-60** | **Mean** | **66.28** | **49.72** | **51.58** | **38.26** | **49.59** |
| | Std. Dev. | 24.82 | 22.52 | 23.66 | 12.33 | 12.87 |
| **61-70** | **Mean** | **66.75** | **56.84** | **57.44** | **38.50** | **52.40** |
| | Std. Dev. | 26.20 | 21.70 | 24.56 | 12.46 | 10.08 |
| **71 AND ABOVE** | **Mean** | **66.47** | **57.73** | **58.23** | **36.76** | **52.95** |
| | Std. Dev. | 29.09 | 20.50 | 25.95 | 12.67 | 10.12 |
| **TOTAL** | **Mean** | **66.99** | **54.45** | **56.70** | **38.17** | **51.22** |
| | Std. Dev. | 26.48 | 21.73 | 25.70 | 12.40 | 11.21 |

***VII.3: Means (across each Gender) for the scores that are common to all datasets***

| GENDER | | PF | RP | VT | SF | RE | MH |
|---|---|---|---|---|---|---|---|
| **FEMALE** | **Mean** | **59.46** | **55.71** | **53.06** | **75.05** | **74.43** | **72.19** |
| | Std. Deviation | 27.64 | 42.04 | 22.54 | 25.52 | 38.28 | 20.00 |
| **MALE** | **Mean** | **67.38** | **53.12** | **57.43** | **76.95** | **75.18** | **74.99** |
| | Std. Deviation | 25.05 | 41.69 | 21.87 | 24.23 | 37.96 | 18.62 |
| **TOTAL** | **Mean** | **63.71** | **54.32** | **55.41** | **76.07** | **74.83** | **73.69** |
| | Std. Deviation | 26.56 | 41.85 | 22.28 | 24.84 | 38.09 | 19.31 |

***VII.4: Means (across each Gender) for the scores that are common to only two datasets***

| GENDER | | BP | GH | Recoded SF-2 Question | PCS | MCS |
|---|---|---|---|---|---|---|
| **FEMALE** | **Mean** | **63.52** | **54.18** | **57.27** | **37.26** | **50.48** |
| | Std. Deviation | 26.17 | 21.48 | 26.36 | 12.45 | 11.61 |
| **MALE** | **Mean** | **70.88** | **54.88** | **56.07** | **39.18** | **52.01** |
| | Std. Deviation | 26.36 | 22.00 | 24.99 | 12.30 | 10.69 |
| **TOTAL** | **Mean** | **67.01** | **54.51** | **56.70** | **38.17** | **51.21** |
| | Std. Deviation | 26.50 | 21.71 | 25.70 | 12.41 | 11.20 |

***VII.5: Means (across presence/absence of Diabetes) for the scores that are common to all datasets***

| DIABETES | | PF | RP | VT | SF | RE | MH |
|---|---|---|---|---|---|---|---|
| **NO** | **Mean** | **64.63** | **61.49** | **55.92** | **80.05** | **81.06** | **76.30** |
| | Std. Deviation | 27.65 | 41.15 | 21.44 | 24.58 | 34.26 | 17.16 |
| **YES** | **Mean** | **54.93** | **52.93** | **51.54** | **78.46** | **80.59** | **78.22** |
| | Std. Deviation | 27.79 | 40.94 | 23.40 | 24.07 | 33.64 | 17.29 |
| **TOTAL** | **Mean** | **61.51** | **58.73** | **54.51** | **79.54** | **80.91** | **76.92** |
| | Std. Deviation | 28.04 | 41.24 | 22.16 | 24.41 | 34.03 | 17.21 |

***VII.6: Means (across presence/absence of Diabetes) for the scores that are common to only two datasets***

| DIABETES | | BP | GH | Recoded SF-2 Question | PCS | MCS |
|---|---|---|---|---|---|---|
| **NO** | **Mean** | **68.02** | **57.05** | **56.50** | **39.69** | **50.79** |
| | Std. Deviation | 25.99 | 21.05 | 25.35 | 12.13 | 11.17 |
| **YES** | **Mean** | **65.19** | **49.27** | **57.31** | **34.92** | **52.17** |
| | Std. Deviation | 27.53 | 22.40 | 26.55 | 12.34 | 11.26 |
| **TOTAL** | **Mean** | **67.11** | **54.55** | **56.76** | **38.15** | **51.23** |
| | Std. Deviation | 26.50 | 21.78 | 25.72 | 12.39 | 11.21 |

***VII.7: Means (across presence/absence of Heart Disease) for the scores that are common to all datasets***

| HEART DISEASE | | PF | RP | VT | SF | RE | MH |
|---|---|---|---|---|---|---|---|
| **NO** | **Mean** | **65.59** | **55.24** | **56.69** | **76.57** | **74.35** | **73.30** |
| | Std. Deviation | 25.99 | 41.80 | 22.00 | 24.43 | 38.52 | 19.57 |
| **YES** | **Mean** | **51.51** | **47.87** | **48.04** | **73.17** | **76.73** | **75.99** |
| | Std. Deviation | 27.20 | 41.94 | 22.44 | 27.11 | 36.30 | 17.60 |
| **TOTAL** | **Mean** | **63.55** | **54.16** | **55.43** | **76.08** | **74.70** | **73.69** |
| | Std. Deviation | 26.63 | 41.89 | 22.27 | 24.86 | 38.20 | 19.31 |

***VII.8: Means (across presence/absence of Heart Disease) for the scores that are common to only two datasets***

| HEART DISEASE | | BP | GH | Recoded SF-2 Question | PCS | MCS |
|---|---|---|---|---|---|---|
| **NO** | **Mean** | **68.79** | **57.46** | **56.80** | **39.89** | **51.57** |
| | Std. Deviation | 26.12 | 20.95 | 24.65 | 12.29 | 11.12 |
| **YES** | **Mean** | **62.52** | **46.89** | **56.86** | **33.48** | **50.47** |
| | Std. Deviation | 27.25 | 22.05 | 28.42 | 11.50 | 11.39 |
| **TOTAL** | **Mean** | **67.0052** | **54.4531** | **56.8142** | **38.063** | **51.253** |
| | Std. Deviation | 26.58 | 21.78 | 25.75 | 12.41 | 11.20 |

# VIII. Tests of Normality (prior to comparisons of mean ranks/medians)

## VIII.1 Outcome variable - Physical Functioning Domain score

**Grouping variable - Age Categories**

| | Age Categories | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| PHYSICAL FUNCTIONING | 30 AND UNDER | .378 | 6 | **.007** | .751 | 6 | **.020** |
| | 31-40 | .203 | 16 | **.076** | .876 | 16 | **.034** |
| | 41-50 | .174 | 38 | **.005** | .883 | 38 | **.001** |
| | 51-60 | .158 | 108 | **.000** | .926 | 108 | **.000** |
| | 61-70 | .134 | 238 | **.000** | .943 | 238 | **.000** |
| | 71 AND OVER | .089 | 167 | **.003** | .951 | 167 | **.000** |

**Grouping variable - Gender**

| | Gender | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| PHYSICAL FUNCTIONING | FEMALE | .103 | 298 | **.000** | .948 | 298 | **.000** |
| | MALE | .141 | 275 | **.000** | .919 | 275 | **.000** |

**Grouping variable - Stage of CKD**

| | Stage of Chronic Kidney Disease | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| PHYSICAL FUNCTIONING | STAGE 2-3 CKD | .120 | 393 | **.000** | .932 | 393 | **.000** |
| | STAGE 4 CKD | .189 | 18 | **.088** | .908 | 18 | **.078** |
| | STAGE 5 CKD | .125 | 162 | **.000** | .941 | 162 | **.000** |

**Grouping variable - Diabetes**

| | Diabetes | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| PHYSICAL FUNCTIONING | NO | .121 | 386 | **.000** | .923 | 386 | **.000** |
| | YES | .116 | 187 | **.000** | .956 | 187 | **.000** |

**Grouping variable - Heart Disease**

| | Heart Disease | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| PHYSICAL FUNCTIONING | NO | .142 | 411 | **.000** | .918 | 411 | **.000** |
| | YES | .095 | 162 | **.001** | .968 | 162 | **.001** |

## VIII.2 Outcome variable – Role-Physical Domain score

**Grouping variable - Age Categories**

| | Age Categories | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| ROLE-PHYSICAL | **30 AND UNDER** | .315 | 6 | **.063** | .753 | 6 | **.021** |
| | **31-40** | .201 | 16 | **.083** | .828 | 16 | **.007** |
| | **41-50** | .253 | 38 | **.000** | .808 | 38 | **.000** |
| | **51-60** | .245 | 108 | **.000** | .804 | 108 | **.000** |
| | **61-70** | .260 | 238 | **.000** | .785 | 238 | **.000** |
| | **71 AND OVER** | .250 | 167 | **.000** | .796 | 167 | **.000** |

**Grouping variable - Gender**

| | Gender | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| ROLE-PHYSICAL | **FEMALE** | .244 | 298 | **.000** | .798 | 298 | **.000** |
| | **MALE** | .261 | 275 | **.000** | .790 | 275 | **.000** |

**Grouping variable - Stage of CKD**

| | Stage of Chronic Kidney Disease | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| ROLE-PHYSICAL | **STAGE 2-3 CKD** | .285 | 393 | **.000** | .772 | 393 | **.000** |
| | **STAGE 4 CKD** | .218 | 18 | **.024** | .838 | 18 | **.005** |
| | **STAGE 5 CKD** | .203 | 162 | **.000** | .814 | 162 | **.000** |

**Grouping variable - Diabetes**

| | Diabetes | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| ROLE-PHYSICAL | **NO** | .267 | 386 | **.000** | .779 | 386 | **.000** |
| | **YES** | .222 | 187 | **.000** | .819 | 187 | **.000** |

**Grouping variable - Heart Disease**

| | Heart Disease | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| ROLE-PHYSICAL | **NO** | .271 | 411 | **.000** | .783 | 411 | **.000** |
| | **YES** | .206 | 162 | **.000** | .808 | 162 | **.000** |

## VIII.3 Outcome variable – Vitality Domain score

**Grouping variable - Age Categories**

| | Age Categories | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| VITALITY | **30 AND UNDER** | .184 | 6 | **.200** | .925 | 6 | **.543** |
| | **31-40** | .130 | 16 | **.200** | .970 | 16 | **.840** |
| | **41-50** | .088 | 38 | **.200** | .976 | 38 | **.572** |
| | **51-60** | .092 | 108 | **.026** | .977 | 108 | **.053** |
| | **61-70** | .103 | 238 | **.000** | .975 | 238 | **.000** |
| | **71 AND OVER** | .084 | 167 | **.006** | .979 | 167 | **.011** |

**Grouping variable - Gender**

| | Gender | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| VITALITY | **FEMALE** | .082 | 298 | **.000** | .982 | 298 | **.001** |
| | **MALE** | .091 | 275 | **.000** | .973 | 275 | **.000** |

**Grouping variable - Stage of CKD**

| | Stage of Chronic Kidney Disease | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| VITALITY | **STAGE 2-3 CKD** | .085 | 393 | **.000** | .976 | 393 | **.000** |
| | **STAGE 4 CKD** | .161 | 18 | **.200** | .973 | 18 | **.847** |
| | **STAGE 5 CKD** | .072 | 162 | **.040** | .983 | 162 | **.039** |

**Grouping variable - Diabetes**

| | Diabetes | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| VITALITY | **NO** | .094 | 386 | **.000** | .974 | 386 | **.000** |
| | **YES** | .115 | 187 | **.000** | .980 | 187 | **.010** |

**Grouping variable - Heart Disease**

| | Heart Disease | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| VITALITY | **NO** | .086 | 411 | **.000** | .976 | 411 | **.000** |
| | **YES** | .087 | 162 | **.005** | .981 | 162 | **.027** |

## VIII.4 Outcome variable – Social Functioning Domain score

**Grouping variable - Age Categories**

| | Age Categories | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| SOCIAL FUNCTIONING | 30 AND UNDER | .172 | 6 | **.200** | .912 | 6 | **.452** |
| | 31-40 | .205 | 16 | **.071** | .868 | 16 | **.025** |
| | 41-50 | .186 | 38 | **.002** | .888 | 38 | **.001** |
| | 51-60 | .279 | 108 | **.000** | .778 | 108 | **.000** |
| | 61-70 | .266 | 238 | **.000** | .804 | 238 | **.000** |
| | 71 AND OVER | .236 | 167 | **.000** | .790 | 167 | **.000** |

**Grouping variable - Gender**

| | Gender | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| SOCIAL FUNCTIONING | FEMALE | .225 | 298 | **.000** | .833 | 298 | **.000** |
| | MALE | .263 | 275 | **.000** | .784 | 275 | **.000** |

**Grouping variable - Stage of CKD**

| | Stage of Chronic Kidney Disease | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| SOCIAL FUNCTIONING | STAGE 2-3 CKD | .286 | 393 | **.000** | .777 | 393 | **.000** |
| | STAGE 4 CKD | .238 | 18 | **.008** | .827 | 18 | **.004** |
| | STAGE 5 CKD | .181 | 162 | **.000** | .883 | 162 | **.000** |

**Grouping variable - Diabetes**

| | Diabetes | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| SOCIAL FUNCTIONING | NO | .249 | 386 | **.000** | .798 | 386 | **.000** |
| | YES | .232 | 187 | **.000** | .836 | 187 | **.000** |

**Grouping variable - Heart Disease**

| | Heart Disease | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| SOCIAL FUNCTIONING | NO | .270 | 411 | **.000** | .786 | 411 | **.000** |
| | YES | .183 | 162 | **.000** | .869 | 162 | **.000** |

## VIII.5 Outcome variable – Role-Emotional Domain score

**Grouping variable - Age Categories**

| | Age Categories | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| ROLE-EMOTIONAL | 30 AND UNDER | .401 | 6 | **.003** | .702 | 6 | **.007** |
| | 31-40 | .405 | 16 | **.000** | .631 | 16 | **.000** |
| | 41-50 | .364 | 38 | **.000** | .695 | 38 | **.000** |
| | 51-60 | .430 | 108 | **.000** | .590 | 108 | **.000** |
| | 61-70 | .450 | 238 | **.000** | .563 | 238 | **.000** |
| | 71 AND OVER | .417 | 167 | **.000** | .614 | 167 | **.000** |

**Grouping variable - Gender**

| | Gender | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| ROLE-EMOTIONAL | FEMALE | .417 | 298 | **.000** | .618 | 298 | **.000** |
| | MALE | .443 | 275 | **.000** | .572 | 275 | **.000** |

**Grouping variable - Stage of CKD**

| | Stage of Chronic Kidney Disease | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| ROLE-EMOTIONAL | STAGE 2-3 CKD | .435 | 393 | **.000** | .588 | 393 | **.000** |
| | STAGE 4 CKD | .454 | 18 | **.000** | .540 | 18 | **.000** |
| | STAGE 5 CKD | .415 | 162 | **.000** | .621 | 162 | **.000** |

**Grouping variable - Diabetes**

| | Diabetes | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| ROLE-EMOTIONAL | NO | .435 | 386 | **.000** | .587 | 386 | **.000** |
| | YES | .419 | 187 | **.000** | .616 | 187 | **.000** |

**Grouping variable - Heart Disease**

| | Heart Disease | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| ROLE-EMOTIONAL | NO | .442 | 411 | **.000** | .571 | 411 | **.000** |
| | YES | .399 | 162 | **.000** | .654 | 162 | **.000** |

## VIII.6 Outcome variable – Mental Health Domain score

**Grouping variable - Age Categories**

| | Age Categories | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| MENTAL HEALTH | 30 AND UNDER | .156 | 6 | **.200** | .965 | 6 | **.860** |
| | 31-40 | .135 | 16 | **.200** | .911 | 16 | **.121** |
| | 41-50 | .131 | 38 | **.099** | .972 | 38 | **.459** |
| | 51-60 | .139 | 108 | **.000** | .909 | 108 | **.000** |
| | 61-70 | .125 | 238 | **.000** | .921 | 238 | **.000** |
| | 71 AND OVER | .152 | 167 | **.000** | .907 | 167 | **.000** |

**Grouping variable - Gender**

| | Gender | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| MENTAL HEALTH | FEMALE | .113 | 298 | **.000** | .928 | 298 | **.000** |
| | MALE | .147 | 275 | **.000** | .914 | 275 | **.000** |

**Grouping variable - Stage of CKD**

| | Stage of Chronic Kidney Disease | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| MENTAL HEALTH | STAGE 2-3 CKD | .140 | 393 | **.000** | .916 | 393 | **.000** |
| | STAGE 4 CKD | .199 | 18 | **.057** | .877 | 18 | **.023** |
| | STAGE 5 CKD | .133 | 162 | **.000** | .932 | 162 | **.000** |

**Grouping variable - Diabetes**

| | Diabetes | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| MENTAL HEALTH | NO | .139 | 386 | **.000** | .924 | 386 | **.000** |
| | YES | .136 | 187 | **.000** | .908 | 187 | **.000** |

**Grouping variable - Heart Disease**

| | Heart Disease | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| MENTAL HEALTH | NO | .132 | 411 | **.000** | .908 | 411 | **.000** |
| | YES | .147 | 162 | **.000** | .934 | 162 | **.000** |

## VIII.7 Outcome variable – Bodily Pain Domain score

**Grouping variable - Age Categories**

| | Age Categories | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| BODILY PAIN | 30 AND UNDER | .271 | 6 | **.190** | .814 | 6 | **.079** |
| | 31-40 | .140 | 16 | **.200** | .940 | 16 | **.354** |
| | 41-50 | .167 | 38 | **.009** | .933 | 38 | **.025** |
| | 51-60 | .123 | 108 | **.000** | .940 | 108 | **.000** |
| | 61-70 | .135 | 238 | **.000** | .933 | 238 | **.000** |
| | 71 AND OVER | .162 | 167 | **.000** | .905 | 167 | **.000** |

**Grouping variable - Gender**

| | Gender | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| BODILY PAIN | FEMALE | .130 | 298 | **.000** | .939 | 298 | **.000** |
| | MALE | .154 | 275 | **.000** | .903 | 275 | **.000** |

**Grouping variable - Stage of CKD**

| | Stage of Chronic Kidney Disease | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| BODILY PAIN | STAGE 2-3 CKD | .132 | 393 | **.000** | .935 | 393 | **.000** |
| | STAGE 4 CKD | .226 | 18 | **.016** | .931 | 18 | **.204** |
| | STAGE 5 CKD | .172 | 162 | **.000** | .896 | 162 | **.000** |

**Grouping variable - Diabetes**

| | Diabetes | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| BODILY PAIN | NO | .150 | 386 | **.000** | .922 | 386 | **.000** |
| | YES | .123 | 187 | **.000** | .932 | 187 | **.000** |

**Grouping variable - Heart Disease**

| | Heart Disease | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| BODILY PAIN | NO | .159 | 411 | **.000** | .918 | 411 | **.000** |
| | YES | .118 | 162 | **.000** | .941 | 162 | **.000** |

## VIII.8 Outcome variable – General Health Domain score

**Grouping variable - Age Categories**

| | Age Categories | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| GENERAL HEALTH | **30 AND UNDER** | .366 | 6 | **.012** | .822 | 6 | **.092** |
| | **31-40** | .275 | 16 | **.002** | .860 | 16 | **.019** |
| | **41-50** | .100 | 38 | **.200*** | .977 | 38 | **.605** |
| | **51-60** | .129 | 108 | **.000** | .955 | 108 | **.001** |
| | **61-70** | .082 | 238 | **.001** | .984 | 238 | **.009** |
| | **71 AND OVER** | .091 | 167 | **.002** | .980 | 167 | **.015** |

**Grouping variable - Gender**

| | Gender | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| GENERAL HEALTH | **FEMALE** | .082 | 298 | **.000** | .981 | 298 | **.001** |
| | **MALE** | .082 | 275 | **.000** | .981 | 275 | **.001** |

**Grouping variable - Stage of CKD**

| | Stage of Chronic Kidney Disease | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| GENERAL HEALTH | **STAGE 2-3 CKD** | .086 | 393 | **.000** | .981 | 393 | **.000** |
| | **STAGE 4 CKD** | .164 | 18 | **.200** | .983 | 18 | **.973** |
| | **STAGE 5 CKD** | .143 | 162 | **.000** | .959 | 162 | **.000** |

**Grouping variable - Diabetes**

| | Diabetes | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| GENERAL HEALTH | **NO** | .094 | 386 | **.000** | .978 | 386 | **.000** |
| | **YES** | .092 | 187 | **.001** | .979 | 187 | **.006** |

**Grouping variable - Heart Disease**

| | Heart Disease | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| GENERAL HEALTH | **NO** | .087 | 411 | **.000** | .980 | 411 | **.000** |
| | **YES** | .110 | 162 | **.000** | .978 | 162 | **.011** |

## VIII.9 Outcome variable – Recoded SF-2 Question score

**Grouping variable - Age Categories**

| | Age Categories | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| RECODED SF-2 QUESTION | **30 AND UNDER** | .251 | 6 | **.200** | .869 | 6 | **.223** |
| | **31-40** | .244 | 16 | **.012** | .808 | 16 | **.003** |
| | **41-50** | .212 | 38 | **.000** | .879 | 38 | **.001** |
| | **51-60** | .286 | 108 | **.000** | .870 | 108 | **.000** |
| | **61-70** | .298 | 238 | **.000** | .858 | 238 | **.000** |
| | **71 AND OVER** | .271 | 167 | **.000** | .877 | 167 | **.000** |

**Grouping variable - Gender**

| | Gender | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| RECODED SF-2 QUESTION | **FEMALE** | .249 | 298 | **.000** | .890 | 298 | **.000** |
| | **MALE** | .300 | 275 | **.000** | .858 | 275 | **.000** |

**Grouping variable - Stage of CKD**

| | Stage of Chronic Kidney Disease | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| RECODED SF-2 QUESTION | **STAGE 2-3 CKD** | .319 | 393 | **.000** | .837 | 393 | **.000** |
| | **STAGE 4 CKD** | .265 | 18 | **.002** | .902 | 18 | **.062** |
| | **STAGE 5 CKD** | .216 | 162 | **.000** | .861 | 162 | **.000** |

**Grouping variable - Diabetes**

| | Diabetes | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| RECODED SF-2 QUESTION | **NO** | .277 | 386 | **.000** | .875 | 386 | **.000** |
| | **YES** | .267 | 187 | **.000** | .880 | 187 | **.000** |

**Grouping variable - Heart Disease**

| | Heart Disease | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| RECODED SF-2 QUESTION | **NO** | .300 | 411 | **.000** | .857 | 411 | **.000** |
| | **YES** | .210 | 162 | **.000** | .904 | 162 | **.000** |

## VIII.10 Outcome variable – Physical Component Summary score

**Grouping variable - Age Categories**

| | Age Categories | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| PHYSICAL COMPONENT SUMMARY | 30 AND UNDER | .214 | 6 | **.200** | .902 | 6 | **.386** |
| | 31-40 | .136 | 16 | **.200** | .958 | 16 | **.620** |
| | 41-50 | .095 | 38 | **.200** | .968 | 38 | **.341** |
| | 51-60 | .092 | 108 | **.025** | .965 | 108 | **.006** |
| | 61-70 | .085 | 238 | **.000** | .964 | 238 | **.000** |
| | 71 AND OVER | .093 | 167 | **.001** | .969 | 167 | **.001** |

**Grouping variable - Gender**

| | Gender | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| PHYSICAL COMPONENT SUMMARY | FEMALE | .091 | 298 | **.000** | .970 | 298 | **.000** |
| | MALE | .072 | 275 | **.002** | .967 | 275 | **.000** |

**Grouping variable - Stage of CKD**

| | Stage of Chronic Kidney Disease | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| PHYSICAL COMPONENT SUMMARY | STAGE 2-3 CKD | .098 | 393 | **.000** | .959 | 393 | **.000** |
| | STAGE 4 CKD | .143 | 18 | **.200** | .955 | 18 | **.512** |
| | STAGE 5 CKD | .052 | 162 | **.200** | .984 | 162 | **.057** |

**Grouping variable - Diabetes**

| | Diabetes | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| PHYSICAL COMPONENT SUMMARY | NO | .098 | 386 | **.000** | .960 | 386 | **.000** |
| | YES | .051 | 187 | **.200** | .983 | 187 | **.020** |

**Grouping variable - Heart Disease**

| | Heart Disease | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| PHYSICAL COMPONENT SUMMARY | NO | .098 | 411 | **.000** | .957 | 411 | **.000** |
| | YES | .054 | 162 | **.200** | .988 | 162 | **.185** |

## VIII.11 Outcome variable – Mental Component Summary score

**Grouping variable - Age Categories**

| | Age Categories | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| MENTAL COMPONENT SUMMARY | 30 AND UNDER | .279 | 6 | **.159** | .795 | 6 | **.053** |
| | 31-40 | .270 | 16 | **.003** | .882 | 16 | **.042** |
| | 41-50 | .110 | 38 | **.200** | .948 | 38 | **.078** |
| | 51-60 | .171 | 108 | **.000** | .889 | 108 | **.000** |
| | 61-70 | .114 | 238 | **.000** | .915 | 238 | **.000** |
| | 71 AND OVER | .121 | 167 | **.000** | .913 | 167 | **.000** |

**Grouping variable - Gender**

| | Gender | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| MENTAL COMPONENT SUMMARY | FEMALE | .131 | 298 | **.000** | .920 | 298 | **.000** |
| | MALE | .135 | 275 | **.000** | .901 | 275 | **.000** |

**Grouping variable - Stage of CKD**

| | Stage of Chronic Kidney Disease | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| MENTAL COMPONENT SUMMARY | STAGE 2-3 CKD | .127 | 393 | **.000** | .908 | 393 | **.000** |
| | STAGE 4 CKD | .155 | 18 | **.200** | .944 | 18 | **.337** |
| | STAGE 5 CKD | .138 | 162 | **.000** | .921 | 162 | **.000** |

**Grouping variable - Diabetes**

| | Diabetes | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| MENTAL COMPONENT SUMMARY | NO | .131 | 386 | **.000** | .905 | 386 | **.000** |
| | YES | .129 | 187 | **.000** | .915 | 187 | **.000** |

**Grouping variable - Heart Disease**

| | Heart Disease | Kolmogorov-Smirnov | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | DF | Sig. | Statistic | DF | Sig. |
| MENTAL COMPONENT SUMMARY | NO | .135 | 411 | **.000** | .901 | 411 | **.000** |
| | YES | .132 | 162 | **.000** | .924 | 162 | **.000** |

## IX. Comparisons of SF-36 scores across Grouping variables (except - Stage of CKD)

***IX.1: Significantly different Mean Ranks and Medians (Grouping variable – Age Category)***

| | Age Categories | N | Mean Rank | Median |
|---|---|---|---|---|
| PHYSICAL FUNCTIONING | 30 & UNDER | 70 | 723.01 | 82.5 |
| | 31-40 | 108 | 654.14 | 75 |
| | 41-50 | 148 | 644.05 | 75 |
| | 51-60 | 238 | 587.60 | 70 |
| | 61-70 | 342 | 537.32 | 65 |
| | 71 & OVER | 227 | 450.32 | 55 |
| SOCIAL FUNCTIONING | 30 & UNDER | 70 | 537.14 | 75 |
| | 31-40 | 108 | 504.04 | 75 |
| | 41-50 | 148 | 492.38 | 75 |
| | 51-60 | 238 | 570.51 | 81.25 |
| | 61-70 | 342 | 608.88 | 87.5 |
| | 71 & OVER | 227 | 588.04 | 87.5 |
| MENTAL HEALTH | 30 & UNDER | 70 | 558.27 | 76 |
| | 31-40 | 108 | 507.83 | 74 |
| | 41-50 | 148 | 479.89 | 72 |
| | 51-60 | 238 | 527.58 | 76 |
| | 61-70 | 342 | 610.55 | 80 |
| | 71 & OVER | 227 | 630.36 | 84 |
| GENERAL HEALTH | 30 & UNDER | 7 | 162.36 | 40 |
| | 31-40 | 16 | 164.63 | 35 |
| | 41-50 | 39 | 246.88 | 45 |
| | 51-60 | 111 | 254.09 | 45 |
| | 61-70 | 242 | 310.30 | 57.5 |
| | 71 & OVER | 167 | 317.11 | 60 |
| RECODED SF-2 QUESTION | 30 & UNDER | 7 | 271.71 | 50 |
| | 31-40 | 16 | 385.44 | 75 |
| | 41-50 | 39 | 275.95 | 50 |
| | 51-60 | 111 | 260.88 | 50 |
| | 61-70 | 242 | 295.49 | 50 |
| | 71 & OVER | 167 | 301.54 | 50 |
| MENTAL COMPONENT SUMMARY | 30 & UNDER | 7 | 218.64 | 50.3 |
| | 31-40 | 16 | 187.84 | 48.75 |
| | 41-50 | 39 | 194.88 | 45.9 |
| | 51-60 | 111 | 277.40 | 53.7 |
| | 61-70 | 242 | 305.56 | 54.7 |
| | 71 & OVER | 167 | 316.04 | 55.4 |

*IX.2: Significantly different Mean Ranks and Medians (Grouping variable – Gender)*

| | Gender | N | Mean Rank | Sum of Ranks | Median |
|---|---|---|---|---|---|
| PHYSICAL FUNCTIONING | FEMALE | 524 | 516.30 | 270541.50 | 65 |
| | MALE | 609 | 610.62 | 371869.50 | 70 |
| VITALITY (ENERGY/FATIGUE) | FEMALE | 524 | 533.22 | 279408.50 | 54.17 |
| | MALE | 609 | 596.06 | 363002.50 | 60 |
| MENTAL HEALTH | FEMALE | 524 | 543.21 | 284642.00 | 76 |
| | MALE | 609 | 587.47 | 357769.00 | 80 |
| BODILY PAIN | FEMALE | 306 | 267.71 | 81920.50 | 67.5 |
| | MALE | 276 | 317.87 | 87732.50 | 77.5 |
| PHYSICAL COMPONENT SUMMARY | FEMALE | 306 | 279.02 | 85380.50 | 38.2 |
| | MALE | 276 | 305.34 | 84272.50 | 40.6 |

*IX.3: Significantly different Mean Ranks and Medians (Grouping variable – Diabetes)*

| | Diabetes | N | Mean Rank | Sum of Ranks | Median |
|---|---|---|---|---|---|
| PHYSICAL FUNCTIONING | NO | 854 | 596.82 | 509686.00 | 70 |
| | YES | 281 | 480.41 | 134994.00 | 60 |
| VITALITY (ENERGY/FATIGUE) | NO | 854 | 584.64 | 499280.50 | 60 |
| | YES | 281 | 517.44 | 145399.50 | 50 |
| GENERAL HEALTH | NO | 396 | 312.24 | 123646.00 | 60 |
| | YES | 188 | 250.93 | 47174.00 | 50 |
| PHYSICAL COMPONENT SUMMARY | NO | 396 | 313.89 | 124299.50 | 41.35 |
| | YES | 188 | 247.45 | 46520.50 | 35 |

*IX.4: Significantly different Mean Ranks and Medians (Grouping variable – Heart Disease)*

| | Heart Disease | N | Mean Rank | Sum of Ranks | Median |
|---|---|---|---|---|---|
| PHYSICAL FUNCTIONING | NO | 963 | 588.40 | 566632.50 | 70 |
| | YES | 164 | 420.70 | 68995.50 | 50 |
| ROLE-PHYSICAL | NO | 963 | 571.85 | 550696.00 | 50 |
| | YES | 164 | 517.88 | 84932.00 | 50 |
| VITALITY (ENERGY/FATIGUE) | NO | 963 | 581.66 | 560143.00 | 60 |
| | YES | 164 | 460.27 | 75485.00 | 50 |
| BODILY PAIN | NO | 412 | 299.42 | 123363.00 | 70 |
| | YES | 164 | 261.05 | 42813.00 | 66.25 |
| GENERAL HEALTH | NO | 412 | 311.32 | 128265.50 | 60 |
| | YES | 164 | 231.16 | 37910.50 | 45 |
| PHYSICAL COMPONENT SUMMARY | NO | 412 | 313.87 | 129313.50 | 41.85 |
| | YES | 164 | 224.77 | 36862.50 | 32.75 |

*IX.5: Significantly different Mean Ranks and Medians (Grouping variable – Heart Failure)*

| | Heart Failure | N | Mean Rank | Sum of Ranks | Median |
|---|---|---|---|---|---|
| PHYSICAL FUNCTIONING | NO | 1060 | 579.51 | 614280.50 | 70 |
| | YES | 67 | 318.62 | 21347.50 | 40 |
| ROLE-PHYSICAL | NO | 1060 | 572.00 | 606319.00 | 50 |
| | YES | 67 | 437.45 | 29309.00 | 25 |
| VITALITY (ENERGY/FATIGUE) | NO | 1060 | 575.11 | 609613.00 | 55 |
| | YES | 67 | 388.28 | 26015.00 | 45 |
| SOCIAL FUNCTIONING | NO | 1060 | 570.92 | 605180.00 | 87.5 |
| | YES | 67 | 454.45 | 30448.00 | 75 |
| GENERAL HEALTH | NO | 509 | 300.99 | 153205.50 | 55 |
| | YES | 67 | 193.59 | 12970.50 | 40 |
| PHYSICAL COMPONENT SUMMARY | NO | 509 | 302.83 | 154142.50 | 40.6 |
| | YES | 67 | 179.60 | 12033.50 | 27.7 |

*IX.6: Significantly different Mean Ranks and Medians (Grouping variable – Angina)*

| | Angina | N | Mean Rank | Sum of Ranks | Median |
|---|---|---|---|---|---|
| PHYSICAL FUNCTIONING | NO | 1076 | 571.69 | 615139.50 | 70 |
| | YES | 51 | 401.74 | 20488.50 | 50 |
| VITALITY (ENERGY/FATIGUE) | NO | 1076 | 570.78 | 614162.50 | 55 |
| | YES | 51 | 420.89 | 21465.50 | 50 |
| BODILY PAIN | NO | 525 | 295.21 | 154983.50 | 70 |
| | YES | 51 | 219.46 | 11192.50 | 45 |
| GENERAL HEALTH | NO | 525 | 294.86 | 154799.50 | 55 |
| | YES | 51 | 223.07 | 11376.50 | 43.75 |
| RECODED SF-2 QUESTION | NO | 525 | 292.69 | 153662.50 | 50 |
| | YES | 51 | 245.36 | 12513.50 | 50 |
| PHYSICAL COMPONENT SUMMARY | NO | 525 | 296.30 | 155558.50 | 39.9 |
| | YES | 51 | 208.19 | 10617.50 | 32.5 |

*IX.7: Significantly different Mean Ranks and Medians (Grouping variable – Peripheral Vascular Disease)*

| | Peripheral Vascular Disease | N | Mean Rank | Sum of Ranks | Median |
|---|---|---|---|---|---|
| PHYSICAL FUNCTIONING | NO | 498 | 301.70 | 150249.00 | 70 |
| | YES | 84 | 231.00 | 19404.00 | 50 |
| ROLE-PHYSICAL | NO | 498 | 297.99 | 148397.00 | 75 |
| | YES | 84 | 253.05 | 21256.00 | 25 |
| GENERAL HEALTH | NO | 498 | 299.73 | 149264.50 | 55 |
| | YES | 84 | 242.72 | 20388.50 | 47.5 |
| PHYSICAL COMPONENT SUMMARY | NO | 498 | 300.83 | 149812.00 | 40.2 |
| | YES | 84 | 236.20 | 19841.00 | 33.25 |

*IX.8: Significantly different Mean Ranks and Medians (Grouping variable – Stroke)*

| | Stroke | N | Mean Rank | Sum of Ranks | Median |
|---|---|---|---|---|---|
| PHYSICAL FUNCTIONING | NO | 548 | 291.91 | 159966.00 | 65 |
| | YES | 28 | 221.79 | 6210.00 | 50 |
| VITALITY (ENERGY/FATIGUE) | NO | 548 | 291.89 | 159955.50 | 55 |
| | YES | 28 | 222.16 | 6220.50 | 50 |
| PHYSICAL COMPONENT SUMMARY | NO | 548 | 291.56 | 159775.50 | 39.35 |
| | YES | 28 | 228.59 | 6400.50 | 36 |