Cushing syndrome and disease: A study of the diagnosis, treatment, clinical consequences, and Health-related Quality of Life associated with these medical conditions.

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Dr Margot McBride FCR PhD MSc MBA DS DCR(R)

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Conference Presentations & Publications

2019

McBride M: Keynote Lecture: My Patient's Experience: Cushing syndrome and disease. Scottish Clinical Imaging Network Programme, Glasgow, November 2019.

2020

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*McBride M. Patient Unmet Needs: A Patient-Centred Approach to Care. United Kingdom Imaging & Oncology Congress, June 2022, Liverpool,.UK.

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McBride M. Living with Cushing syndrome: The Findings of a Doctor of Philosophy Study. Endocrinology Congress, 2022. Milan, Italy. May 2022.

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Abbreviations

ACTH	Adrenocorticotrophic Hormone
ADR-CS	Adrenal Cushing syndrome
AHP	Allied Health Professional
AI	Adrenal insufficiency
AI	Artificial Intelligence
ANOVA	Analysis of Covariance
ANS	Autonomic nervous system.
APA	Aldosterone producing adenomas
ASE	Appearance Self-Esteem Questionnaire
AST	Attentional Network Test
AVS	Adrenal Venous Sampling
BDI-II	Becks Depression Inventory II
BDNF	Brain-derived neurotrophic factor
BEI	Bern Embitterment Inventory
BHA	Bilateral hyperaldosteronism
BICI	Body Image Concern Inventory
BIPSS	Bilateral inferior petrosal sinus sampling
BMI	Body Mass Index
BMJ	British Medical Journal
BJR	British Journal of Radiology
CBG	Cortisol binding globulin
CCS	Cyclical Cushing syndrome
CD	Cushing disease
CE	Contrast enhanced
CEUS	Contrast enhanced ultrasound.
CESD	Centre for Epidemiological Studies Depression Scale.
CFA	Confirmatory Factor Analysis
CFQ	Cognitive Failures Questionnaire
CG	Clinical Governance
CI	Confidence Interval
CIS	Check Individual Strength Questionnaire
CISS	Constructive interference in steady state
Cm	Centimetre
CMRI	Conventional Magnetic Resonance Imaging
CNC	Carney Complex
CNS	Central Nervous System
COVID-19	Coronovirus-19
CPD	Continuous Professional Development
CPG	Cortisol binding globulin
CPP	Continuous Professional Practice
CSC	Chorioretinopathy
CSI	Cavernous Sinus Invasion
CSRF	Cushing Support and Research Foundation
CT	Computed Tomography
CRH	Cortisone Releasing Hormone
CSRF	Cushing Support Research Foundation
CS	Cushing syndrome
CVE	Cardiovascular Event
dL	Decilitre
DEXA	Dual Energy X-ray Absorptiometry
DI	Digital Imaging
DI	Diabetes Insipidus
DM	Diabetes Mellitus
2D	2 Dimensional

3D	3 Dimensional
Df	Degrees of Freedom
DMRI	Dynamic contrast-enhanced MRI
DNA	Deoxyribonucleic acid
DoH	Department of Health
DSBs	Double-strand breaks
DOTA	DOTATATE
DPTA	Depreotide Octreotide scan
DSM	Diagnostic Statistical Manual of Mental Disorders
DVT	Deep Venous Thrombosis
DWI	Diffusion-weighted Imaging
DWT	Diffusion-weighted
EAS	Ectopic-ACTH syndrome
ECS	Endogenous Cushing syndrome
EEC	European Economic Community
EDI-OCT.	Enhanced depth imaging-ocular coherence tomography.
EuroQoL	European Quality of Life questionnaire (5D).
EFA	Exploratory Factor Analysis
EMD	European Medical Devices
ERCUSYN	European Registry of Cushing syndrome
ESDS	Epidemiological Studies Depression Scale.
ESE	Endocrine Society of Endocrinology
ESECG	Endocrine Society of Endocrinology Clinical Guidelines
EQ-5D	EuroQoL-5D questionnaire
FDA	Food and Drug Administration
FDG-PET	Fluro-deoxy-glucose-Positron Emmis
FKV-LIS	Freiburg questionnaire on coping with illness
FLAIR	Fluid-attenuated inversion-recovery scans
fMRI	Functional Magnetic Resonance Imaging
GA	Gallium
GAD	Generalised anxiety disorder
GCR	Glucocorticosteroids Receptors.
GCs	Glucocorticoids
GHQ	General Health Questionnairei9
GR	Generic questionnaire
GK-RS.	Gamma Knife Radiosurgery
GP	General Practitioner
GCD	Glucocorticoid deficiency
GR	Glucocorticoid receptors
GH	Growth Hormone
GHD	Growth Hormone Deficiency
GIOP	Glucocorticoid-induced osteoporosis
GP	General Practitioner
GSLTPAQ	Godin-Sheppard Leisure-Time Physical Activity questionnaire
GR	Glucocorticoid receptors
GRE	Gradient Echo
GTR	Gross tumour volume
Gy	Gray
HADS	Hospital Anxiety and Depression Scale
HARS	Hamilton Anxiety Rating Scale
HCAHPS	Hospital Consumer Assessment of Healthcare Providers and Systems
HDDST	High dose dexamethasone suppression test
hCG	High human choriogonadotropin
Ho	Hostility subscale.
HPA	Hypothalamic-pituitary-adrenal axis
HRQoL	Health-Related Quality of Life
IBS	Irritable Bowel Syndrome
In	Interleukin
IPQ	Illness perception questionnaire
IPSS	Inferior Petrosal Sinus Sampling

IR	Ionising Radiation
IRR	Ionising Radiation Regulations
IR(ME)R	Ionising Radiation (Medical Exposure) Regulations
Km	Kilometre
KWH	Kruskal-Wallis H-Test
LBNQ	Leiden Bother Needs Questionnaire-Pituitary.
LDDST	Low-dose dexamethasone suppression test
LDL	Low-density lipoprotein
LHCGR	Luteinizing hormone/chorionic gonadotropin receptors
LINAC	Linear Accelerator
LNSC	Late night salivary control
LV	Lumbar Vertebrae
MALDI	Mass spectroscopy
MAS	Mild autonomous cortisol secretion
Max	Maximum
MBSRQ	Multidimensional body-self relations questionnaires
MCS	Mental Summary Scores
MDD	Major depression disorder
MDR	Medical Devices Directive
MEN (1)	Multiple endocrine neoplasia type 1
MET-PET	Methionine-Positron Emission Imaging
Mg	Milligram
MHRR	Mean heart range rate
Min	Minimum
mmoI/L	Millimoles per litre
mm/litre	millimetre per litre
ML	Machine Learning
MLC	Multiple leaf collimators
MR	Magnetic Resonance
MRAs	Mineralocorticoid-receptor antagonists
MRA	Multiple Regression Analysis
MRI	Magnetic Resonance Imaging
MRSA	Methicillin-Resistant Staphylococcus Aureus
MserC.	Midnight serum control
MSV	millisievert
n	Number
nFCS	Normal functional connectivity strength
ng	Nanograms
nM	Nanometres.
NETs	Neuroendocrine tumours
NFPA	Non-functioning pituitary adenoma
NHP	Nottingham Health Profile
NHS	National Health Service
NIR	Near infrared spectroscopy
nmol/L	Nanomoles Per Litre
NMR	Nuclear Magnetic Resonance
NORD	National Organisation for Rare Disorders
NPV	Negative Predictive Value
OB	Obese
OCT	Ocular coherence tomography
ODST	Overnight Dexamethasone Suppression Test
OST	Overnight saliva. Test
OS	Octreotide scintigraphy
PA	Primary Aldosteronism
PANAS	Positive Affect Negative Affect Scale
PCS	Pseudo-Cushing's syndrome
PCS	Physical component summary scores
PET	Positron Emission Tomography
PF, UK	Pituitary Foundation, United Kingdom
PhD	Doctor of Philosophy

PIT-CS	Pituitary Cushing syndrome
PIT-RT	Pituitary radiotherapy
PMT	Pre-operative medical treatment
PPNAD	Primary pigmented nodular adrenocortical disease
PPV	Positive Predictive Value
PRKARIA	Protein kinase, AMP-dependent, regularly, type I
PRO	Patient-reported outcome survey
PSD	Pachychoroid spectrum disease.
PSQI	Pittsburgh Sleep Quality Index
PSS	Perceived Stress Scale
QoL	Quality of Life
QRR	Question Response Rate
RA	Rheumatoid Arthritis.
RBE	Relative-biologic effectiveness
RCR	Royal College of Radiologists
REDCap	Research Electronic Data Capture
Rf	Radio frequency
RR	Relative risk
RT	Radiotherapy
SAS	Social Adjustment scale
SCL	Symptoms check list
SCoR	Society and College of Radiographers
SD	Standard Deviation
SDH	Succinate dehydrogenase
SF	Short form questionnaire
SGE	Spoiled gradient echo
SI	International System of Units
SMD	Standard mean distance
SPECT	Single Photon Emission Computed Tomography
SPSS	Statistical Package for Social Services
SRS	Stereotactic radiosurgery
SS	Sail sign
SSTR	Somatostatin Receptors
STAI	State-Trait Anxiety Inventory
Sv	Sievert
T	Tesla
TBS	Trabecular bone score
TMZ	Temozolomide
TSH	Thyroid stimulating hormone
TSS	Transsphenoidal Surgery
UFC	Urine Free Cortisol
UK	United Kingdom
USA	United States of America
US	Ultrasound
VIBE	Volumetric interpolated breath-hold examination
VTE	Venous thrombosis embolism.
WHO	World Health Organisation
WHOQOL	World Health Organisation Quality of Life questionnaire-BREF

Abstract

Introduction

Cushing syndrome and disease are classified as rare diseases. The estimated incidence of CS (*2021*), was 10 to 15 per million people worldwide per year and can occur in any age group, mostly diagnosed in females with a median age of 41 years. The mortality rate is reported to be between 2-4 times higher than the general population. This study was conducted following my diagnosis of CS to compare other patients experiences of these medical conditions with my own, and the clinical consequences following a diagnosis and treatment of CS.

Methods

A HRQoL survey was conducted on members of the Pituitary Associations using a disease-specific on-line questionnaire. Quantitative and Qualitative analysis was performed.

Semi-structured interviews were also conducted on a range of Health Professions disciplines.

Results

The study population was 86. The 71 female members median age was 42 and the 15 males was 39.4 years. The results showed a strong correlation between age and QoL scores, ($r<1, P < .03$). The median length of time for a diagnosis of CS was 5.4 years (*females*), and 3.7years for the males. The median number of Physicians consulted prior to a diagnosis was 2. The results showed a strong correlation between the number of Physicians and their QoL scores, ($r\ .78, P < .05$). Both genders reported physical and psychological conditions.

Conclusions

The wide clinical spectrum of CS produces medical dilemmas as symptoms vary and therefore patients can be sent to a range of Physicians prior to a definitive diagnosis. The prolonged consequences of excess cortisol affected my own and their HRQoL, even after remission, mainly due to the persistence of physical and neuropsychological morbidity. There remains a lack of psychological support and Health Professionals awareness. A patient's perspective should be recognised to be an integral part of the management of CS.

Title of Study: Cushing syndrome and disease: A study of the diagnosis, treatment, clinical consequences, and Health-related Quality of Life associated with these medical conditions.

Chapter 1

1.0 *Introduction*

Cushing syndrome (*CS*) and Cushing Disease (*CD*), a baffling portmanteau of symptoms, each often ascribed to other medical conditions, but together representing diagnostically, challenging medical conditions which can occur if the body produces too much of the hormone cortisol – sometimes, but not always, due to long term use of steroid medicines. With an estimated incidence of around 10 to 15 million worldwide per year, and often coming, 'disguised,' as other stand-alone conditions such as hypertension, obesity, psychological disorders, diminished libido, infertility, osteoporosis, and even domestic abuse (*due to skin which bruises at the touch*). CS can be present but undiagnosed for many years.[1]

This Doctor of Philosophy (*PhD*), study aims to conduct a systematic search for reliable knowledge to identify the main clinical reasons which can delay the diagnosis and subsequent treatment of these life-threatening medical conditions and to measure the impact that it has on its victims. The objectives being to assess the efficacy of the current clinical working practices i.e., the decision-making related to the diagnostic and therapeutic practices, the reliability of these and the impact these medical conditions have on patients' health-related quality of life (*HRQoL*), before and after diagnosis and treatment.

1.1 What is Cushing syndrome?

Firstly, clarification of the distinction between the 'Syndrome' and the 'Disease'.

Cushing syndrome refers to the rare condition caused by excess cortisol in the body, regardless of the cause. When CS is caused by a pituitary tumour, as opposed for example, to the long-term use of exogenous corticosteroids, it is called CD. Cushing's is mostly caused, by glucocorticoids (*GCs*) prescribed for therapy, an example being prednisolone which is prescribed for a wide range of medical conditions including certain types of cancer. Topical corticosteroids prescribed for example for skin infections can also cause CS.

Symptoms usually develop gradually and so the diagnosis may not be clear for some time. Another reason for CD is primary hypercortisolism which has resulted from an adrenal gland tumour which can be benign or malignant. If the hypercortisolism is untreated, then it can lead to diabetes mellitus (*DM*), and suppression of the immune system. CS and CD are said to be rare, and are clever, deceitful, invasive endocrine disorders that changes

the human body's defence mechanisms. The clinical manifestations of this disorder vary creating challenges for clinicians as patients present with varying symptoms which can be mild to non-specific. Due to this diversity in clinical presentation, it can significantly delay diagnosis and patients may be at a late stage of the disease process before they are diagnosed.

1.2 Background

The condition, CS was first identified by, and named after Harvey Cushing, (*1869-1939*), an eminent American neurosurgeon in 1912. His description was based on a case in 1902 and his experiences which followed. He stated that, "we may perchance be on the way towards the recognition of the consequences of hyperadrenalism."[2]

Over the subsequent years, his theoretical hypothesis was proved to be correct, i.e., that CS is, "linked to minute basophilic adenomas of the pituitary gland."[1] The pluriglandular syndrome became known as CS. Harvey Cushing published an article in 1932 which described the syndrome that was caused by a basophil pituitary adenoma which in turn is caused by hypersecretion from the adrenal cortex. He described these rare tumours of the anterior pituitary gland and their striking clinical manifestations in an article. The manifestations were referred to as Cushingoid features, examples being facial hair, weight gain, hypertension, fatigue, muscle weakness and an increase in the blood cholesterol level. The medical journals of that era named the condition CS.

The patient who most influenced Harvey Cushing, was a sixteen-year-old seamstress, "Minnie G."[2] Cushing removed her pituitary tumour, which was his first neurosurgical experience of this nature, but unfortunately, he failed to remove all the tumour and hence she subsequently died. However, his determination to learn by this experience made him exercise due diligence in ensuring that all specimens taken during his surgical procedures were analysed and the results documented. This is said to have been one of, "Cushing's major legacies to neurosurgery."[2]

He was nominated for the Nobel Prize in surgery and medicine 38 times but never won it although he was one of the foremost neurosurgeons, a world leading teacher of neurosurgery in the first decade of the 20th century and expert in his field. His main aims were to improve the survival rates of patients after complex neurosurgical procedures for intracranial tumours. Cushing himself often discussed CS in its milder form as being not so rare, but a century later the diagnosis remains a challenge for many Physicians and is classified as a rare medical disease.

1.3 Incidence and Prevalence of Cushing syndrome and disease.

Most figures quoted for the incidence and prevalence of CS and CD are extrapolated from hospital and endocrine organizations databases, insurance companies and National patient registry, and are dependent on the methodology of analysing the data which can vary between countries.

The prevalence of CS in Europe is said to be estimated to be between 1.2 to 1.7 million per year and of these, 0.6 million have CD. The CD patients presenting with benign adrenal adenomas and 0.2 per million of those with adrenal carcinomas.

Pituitary micro adenomas account for approximately *70%* in adults, CD is estimated to occur therefore in 10 to 15 million of the population worldwide, women are more likely to have CD than men.[3] These figures extrapolated from the Lindholm et al, 2010 study however were based on the crude incidence rate of CD owing to the uncertainties in establishing the location of the underlying tumour in some of their studies of patients with endogenous CD.[3] The figure quoted for pituitary adenomas was *60%-70%* in children.

A 2015, United States of America (*USA*), study examined the incidence of hypercortisolism, using a commercial claims database, and found the incidence was 6.2-7.6 new CD patients per million population per year. Their results were almost 49 cases per million per year for patients' <65 years old, and substantially higher than previous estimates, which were based primarily on European data.[4]

Using similar methods, the study estimated the incidence of CD at nearly 8 cases per million USA population. This study concluded that these estimates, if further studies were undertaken, would suggest that the incidence of CD is higher than previously thought. [4]

A Swedish study published in 2019 conducted by Ragnarsson et al, assessed the annual incidence in a nationwide cohort of patients with presumed CD.[5] The authors suggested that the reasons why few studies are undertaken into the incidence of CD is due to the limited number of patients who have this medical condition. All their 1317 study cohort was confirmed as having CD. Their clinical, biochemical, imaging, and histopathological data were accessed via the Swedish National Patient Registry. The findings showed that the incidence of CD in Sweden was 1.6 cases per million which agrees with most previous European studies. In the Swedish study, a comparison of incidence was made between 2005-2013 and compared with the 1987-2004 figures. Reflecting on their results the authors wondered if there was a definite increase in the incidence of the disease or was there, "simply an increased awareness, early recognition, and earlier diagnosis." [5] This they could not answer. It was also interesting that this study highlighted the importance and need for validation of the diagnosis of CD in epidemiological research. The latter could suggest that this would be a more accurate method of collecting data.

"Recent studies have advanced the current knowledge on the pathogenesis of a pituitary adenoma, the precise mechanisms and causes have remained elusive." [6] This statement agrees with most current books and publications including the Nieman et al paper in 2015, whereby she stated that the aetiology of the causes of Cushing's can be, "mysterious", and its, "origin complex." [6]

As previously mentioned, approximately *60%* to *70%* of CS patients are found to have developed a small pituitary gland adenoma, (*neuroendocrine tumour*), (*NET*). This gland produces a hormone named adrenocorticotrophic hormone (*ACTH*) which is released into the bloodstream and stimulates the adrenal glands to overproduce cortisol. One or both adrenal glands may then need to be surgically removed. It is often also necessary to remove a NET, and as previously stated, this is then referred to as CD. These NETs are often referred to as spontaneous CS and CD.

Pituitary adenomas are said to be the most common types of neurological neoplasm, and the third most common type of intracranial tumours and, "a proportion of them exhibit invasive growth towards the surrounding normal structures, including the skull, cavernous sinus, dura, sphenoid bone, the third ventricle, and even the pharyngeal cavity." [7]

According to Professor Newell-Price et al, (*2016*), who is an eminent British Endocrinologist, the statistics for CS are dependent on the population studied and the frequency of the incidence and he estimated that the range for the world is between, 0.7 million to 2.4 million per year. [7] The sources of evidence, however for these figures were dated from the early nineties. (*1990, 1994*), to the early twenty-first. century (*2001*) and undoubtedly the current statistics show an increase in the prevalence of CS and CD, as reported earlier in this section. This 2016 publication, however, accurately describes CS, its causes, the pathogenesis, the biochemical diagnosis of hypercortisolaemia, the diagnostic tests including imaging and the current medical surgeries and therapies. Middle-aged patients i.e., ages. >40-50 more commonly have adrenal carcinoma. The Cushing Support and Research Foundation (*CSRF*) estimates that 10-15 of every million people are affected each year.[8]

There are therefore variations in the current statistics related to CS. In 2018, according to the Virtual Medical Centre, the prevalence was approximately 40 per million and the incidence, 1-2 cases per million of the population.[9] The World population is presently reported to be an estimated 7.9 billion people. The sub-groups from their data, showed CD accounts for *60%* of hypercortisolism, being more common in women than men with

a ratio of 8:1, and their ages between 20-40. It is rare in infants and children. In men, ectopic ACTH production is 10 times more frequently found than in women.[9]

Lacroix et al previously in 2015, reported a global incidence of 0.2-5 million/year and a prevalence of 39-79 million in various populations, with the average age of onset being 41.4 years and a female to male ration of 3:1. Interestingly, Lacroix et al quoted an incidence of approximately 20 per million population in Africa which was extrapolated from the USA Census Bureau.[10]

The Pituitary Foundation, United Kingdom (PF-*UK*), is a national support and information organization for pituitary patients, their families, friends, and carers.[11] The PF is a leading UK charity which provides support to people affected by disorders of the pituitary gland such as acromegaly, CS/CD, prolactinoma, DM, diabetes insipidus (*DI*), and hypopituitarism. The PF statistics are provided by their clinicians which, includes Endocrinologists, Psychologists and Neurosurgeons who are members of the PF committee. The PF quoted incidence of Cushing's in the UK is 1 in 200,000 and they claim that it is now diagnosed more frequently when it is specifically investigated. Like other studies, they also claim that the most common reason for CS overall is GC treatments as previously mentioned, for example the use of a steroid creams. The commonest cause of spontaneous CS (*around 70%*), is a small benign tumour of the pituitary gland. The PF currently estimates that there are approximately 70,000 people with a pituitary condition in the UK.[11]

1.4 Why do we get it?

As previously explained, Cushing's develops because of an excess of the cortisol hormone GC, which is produced by the adrenal glands, which are located at the superior surface of each kidney. Their purpose is to assist in regulating blood pressure, the immune system, and the balance of the effects of insulin which keeps the blood sugar levels normal and helps the body to respond to stress. The "clinical consequences," of this overproduction of GCs result in CS, "irrespective of the underlying cause." [13]

The endogenous causes of CS are said to be rare; they include excess production of the ACTH causing a pituitary adenoma (*CD*) but, "more commonly the prolonged administration of supraphysiological GC treatments." [14] These can be in the form of medication such as tablets, inhalers, skin creams and nasal sprays, and is also known as exogenous or iatrogenic Cushing's. The incidence being 0.7-2.4 million population per year.

Being cortisol-based these GCs increases the exposure to cortisol thus leading to the development of CS. Patients who are prescribed steroids containing GCs for ailments such as arthritis and colitis are said to be the most at risk

of developing Cushing's. Notably, exogenous CS represents the majority of those diagnosed with CS worldwide.[14]

It is interesting that as previously stated, that more women present with Cushing's than men, in the age range between 20-50years. Perhaps this is not surprising as they experience hormonal changes which take place from birth, pregnancy and throughout the perimenopause, menopause and beyond.

CS is said, in most cases not to be congenital or due to any stimulus in our environment. However, some patients may develop CS due to an inherited tendency to develop tumours of one or more of the adrenal glands. These conditions may include primary pigmented micronodular adrenal disease or multiple endocrine neoplasia type 1 (*MEN 1*).[14]

Undoubtedly, the pathophysiology of Cushing's is complex and some of the answers to the origin presents challenges for Endocrinologists and Health Professionals, particularly as the biochemical tests are not always accurate and require careful interpretation.

1.4.1 Genetic Mutations in Tissues (somatic mutations).

Patients, according to Professor J Newell Price, are often asked if CS is a genetically inherited medical condition.[7] Indeed, he suggests that there are several genes which are known to contribute to the pathogenesis of CS, but there are also new genes being discovered that relate to CS.[15] This has been the subject of debate and study for many years.

1.5 *Mortality*

Hypercortisolism, according to a number of studies including Lindholm et al (*2010*), is associated with excess mortality because of cardiovascular disease, stroke and infection.[3] In the era of Harvey Cushing the survival rate was reported to be 5 years but during the 1980's with the advent of adrenalectomy surgery the 5year survival rate exceeded *85%.* Recent studies however for Transsphenoidal surgery (*TSS*), for pituitary adenomas have shown an encouraging survival rate of up to *88.23%* to *99%.*[16] [17] According however to Lindholm, et al, the mortality rate in CD, "remains significantly higher than in the general population." [3] It should be noted however, that the diagnostic criteria used to establish remission varies among individual studies.[18] In some of these studies, patients in remission are said to occasionally experience, "subtle, recurrent hypercortisolism, thereby raising their mortality risk." [18] The other possible mortality risk is the use of supraphysiologic GC replacements.[17] On studying these findings, it is clear that speedy diagnosis and effective management of CD patients is crucial in order to,

reduce the detrimental effects of hypercortisolism and thus reduce mortality.[17] Unfortunately, many studies suggest that the comorbidities associated with CD in all probability continue to persist in patients in remission and subsequently reduce their quality of life (*QoL*).[18]

A multi-centre, multinational, retrospective study (*2009-2014*) found a median survival rate of cure was approximately 40 years in remission. However, patients who had been in remission for more than a period of 10 years were found to have an increased risk of mortality when compared with the general population. This study published in 2016, suggested that the complexity of treatment, number of treatments and varying range of the disease processes created a difficulty in controlling the disease, which appears to have a negative effect on the survival of CS patients.[19.] "Overt CS is a severe condition responsible for *multiple comorbidities and increased mortality." [20] Therefore it is critically important that effective treatment is essential to reduce mortality and reduce the comorbidities associated with CS for long-term QoL.

**Chapter 2, Pages 45-93*, *literature review explores the comorbidities following a Cushing's diagnosis and how these additional medical conditions impact on the patients HRQoL pre- and post CS.*

1.6 Who makes the diagnosis?

The variations in the signs and symptoms of CS and CD can create difficulties for clinicians but the normal pathway for diagnosis is via the General Practitioner (*GP*), who refers the patient to an Endocrinologist, who normally confirms the definitive diagnosis. However, due to the rarity of this condition, many GPs' have little or no experience of patients with these complex conditions. This in turn can cause a major delay for a definitive diagnosis to be made. Patients often mention to their GP one or two or more of their symptoms which are treated but often are not linked to CS. However, Cushing's can be identified often via incidental findings if the patient is referred to hospital clinicians for other reasons. The condition can be found in patients who are referred for example to a psychiatrist for treatment for depression or serious psychological changes, example, hypomanic attacks. Other symptoms can be degenerative changes in bones, examples, rheumatoid arthritis (*RA*), and osteoporosis in which case an orthopaedic surgeon may trace the underlying cause, for example via x-ray imaging of the spine whereby an adenoma of a kidney may be reported. Patients often gain excessive weight, particularly in the abdominal region. There may be weakening of the muscles and the face may become red and rounder, the latter being known as, 'moon face,' and an excess growth of facial hair (*hirsutism*), particularly in women. Patients are often easily bruised and eye conditions such as twitching can be the result of muscle spasms.

A study in 2016 named the 'Patients' Perception on Clinical Outcome and Quality of Life after the diagnosis of Cushing's Syndrome,' is one of the largest studies of its kind, (*269 patients*). The main aim of this study was to measure the QoL, based on the patients' experiences from diagnosis to treatment and the short and long-term effects. Interestingly, the results reported that the time (*median)* taken for confirmation of a diagnosis was 5 years.[21] The authors recommended that Health Professionals and healthcare providers should be taught to recognise the signs and symptoms of CS and concluded that this would lead to earlier diagnosis which would subsequently improve their QoL. [21] A further review of this paper is featured in *Chapter 2, Pages 64-65.*

Cushing's is often accidentally diagnosed in patients who have been referred for diagnostic medical imaging for other reasons, as previously mentioned. For example, a Magnetic Resonance Imaging (*MRI*) scan is recommended for brain scanning and may incidentally detect a pituitary adenoma. Computed Tomography (*CT*), and Ultrasound (*US*), of the abdominal region often identify adrenal adenomas (*kidneys*). X-rays show arthritic changes in the skeletal system caused by Cushing's, including osteoporosis which is a common comorbidity of CS. The latter condition being confirmed using a Dual Energy X-ray Absorptiometry (*DEXA*) scanner

Section 2.0, *Pages 26-35*, of this *Chapte*r discusses in more detail the main imaging modalities for the diagnosis, of CS and CD and the reasons for their choice. There is also a review of literature in *Chapter 2* (*Sections 3,4,5, Pages 71-84),* which highlights the latest developments in imaging for CS and CD.

The Endocrine Society have produced clinical guidelines for the treatment of CS which are aimed at reducing mortality and the associated comorbidities.[22] Recommended treatments include the use of drugs for hypertension (*antihypertensives*) and surgery for the removal of causal lesion(s), this normally being the first-line approach.[6] Surgical procedures include, TSS for pituitary adenomas and adrenalectomies for adrenal adenomas. Medication follows and an oncologist may recommend radiotherapy (*RT*) and/or chemotherapy if a tumour is found to be malignant.

1.7 Hormone Disorders and Cushing syndrome and Pregnancy.

Hormone disorders are abnormalities related to the chemical signalling and the subsequent interaction in the body. For example, high cholesterol levels if left untreated can cause cardiac diseases, high blood sugar levels which lead to diabetes. The endocrine glands which secrete hormones includes not only the pituitary and adrenal glands but the thyroid, pancreas, testicles, and ovaries. Physical and often mental changes occur when there is hormonal in-balance. This is more prevalent in females, particularly during their reproductive years. The hormone

oestrogen, for example is a sex hormone and varies throughout the reproductive cycle and progesterone plays a role in producing these sex hormones and assists in regulating the menstrual cycle. Progesterone levels are found to be high during pregnancy and this hormone is said to aid sleep. Testosterone is widely known as the 'male hormone' but is also present in women and aids muscle growth and libido. Overproduction of this hormone leads to a gain in weight, excess facial and body hair in women and changes the monthly menstrual cycle. It is rare that pregnant women develop CS, but if they do, it can create, "a real medical challenge."[23] The symptoms of pregnancy can closely resemble those of CS and create complexities in screening tests due to an increase in plasma cortisol levels throughout the gestation period.[23] CS during pregnancy can endanger the lives of both mother and foetus. The overall foetal loss is said to be approximately *25%* of the pregnancies. According to Caimari et al, (*2018*), "there is no consensus as to the most effective treatment in these circumstances in terms of improving maternal and foetal outcomes." [23] These authors concluded that this may be due a dearth of studies which compared the different modalities of treatment for CS in pregnancy. The changes therefore in the maternal hormones and their binding proteins cause difficulties for the conventional testing for CS and complicates the assessment of GC hormones during gestation. The most efficient test is the urine free cortisol (*UFC*), and late-night salivary test, (*LNST*), which are recommended in the European Clinical Guidelines.

The difficulty in diagnosing CS in pregnancy is because pregnancy is a state of, "hypercortisolism." [24]

Adrenal adenomas are the most frequent reason for the onset of CS in pregnancy and ACTH hypersecretion from the pituitary gland, less frequent. The low incidence of reported cases during pregnancy and the changes which occur in the hypothalamic-pituitary- axis (*HPA*), in a normal pregnancy means that there is a higher risk of maternal and foetal complications. A recent study showed that the management of pregnant women with CS is similar to non-pregnant women. The authors of this study Kim et al, recommended that any surgical intervention should be performed during the second trimester, before the 24th week of gestation. Notably, ACTH-independent CS accounts for *55%* of the CS cases. Adrenal surgery is suggested to be more successful than medical Therapy.[25]

For CD, TSS and metyrapone is recommended for those who have other comorbidities including diabetes and hypertension, and to ensure better outcomes for mother and child.

The diagnosis and the correct treatment of hormonal in-balance which includes CS and CD is therefore essential to reduce mortality and associated comorbidities. Effective treatment includes the normalization of cortisol levels and includes the normalization of comorbidities via directly treating the cause of CS and by adjunctive treatments (*example, antihypertensives*). Surgical resection of the causal lesion(s) is generally recommended. The choice of second-line treatments, includes medication, bilateral adrenalectomy, and RT, for corticotropic tumours. A

wide variety of current literature agree with Nieman, et al, (*2015*), in that the course of treatment(s), "must be individualized to each patient." [6]

1.7.1 Survival rates

For patients with CD due to a pituitary adenoma and CS due to benign adrenal adenomas survival rates, "have relatively good survival outcomes often mirroring that of the general population."[22] However, ectopic CS and Cushing's caused by an adrenocortical carcinoma, "confer the highest mortality risk among Cushing's etiologies."[22] To decrease the burden of mortality from Cushing's therefore requires not only a prompt diagnosis followed by treatment but regular check-ups in order to monitor associated comorbidities.[22]

On referral to an Endocrinologist, he/she will perform a series of biochemical tests as described in *Section 1.8.1, Pages 22-25* of this *Chapter*. The evaluation of these tests can take time and the medical conditions that a patient can be experiencing can be due to a range of reasons. For example, stress-related, anorexia, alcoholism, pregnancy, infertility, thyroid enlargement, insomnia, arthritis, weight gain, and a life-threatening illness, for example, cancer, cognitive impairment, and mental illnesses. The latter being referred to as pseudo-CS (*PCS*). Most PCS patients are usually found to have some degree of hypercortisolism that, "may biochemically mimic that observed in patients with true CS."[22] This, makes diagnosis complex according to Krystallenia's who presented a paper at the 20th European Congress of Endocrinology in 2018. In his paper, he stated that "no biochemical suppression or stimulation test and no individual clinical feature may warrant a *100%* diagnostic accuracy," for discriminating between a CS diagnosis and PCS.[26] The recommendation being that a combination of tests would enable, "physicians to challenge the differential diagnosis."[26]

Although approximately *78%* of CD patients following pituitary surgery remain in remission during a 10-year period. Around *13%* of patients' relapse and almost a third of these patients experience in the long-term a failure of surgery and require an additional second-line treatment.[22]

It is therefore important that clinicians need to identify the symptoms early, so that patients can be referred for the diagnostic tests. The wide variations in symptoms, as previously stated, create difficulties in decision-making as to the cause and subsequently delays treatment as the symptoms can be associated with other medical illnesses. In endogenously developed CS the signs and symptoms make take years to appear.

Patients may therefore be seen by a myriad of Physicians making it a long, painful, and expensive journey before they are referred to an Endocrinologist whose specialty is to diagnose and treat disorders of the endocrine system and in the case of CD, they may need to be referred to a Neurosurgeon. This highlights the need for awareness of the signs and symptoms within the medical professions.

1.8 The Diagnostic Tests for Cushing syndrome and disease

The diagnostic pathway is decided by the endocrinology team either as a hospital outpatient or inpatient. On studying the main organizations which includes the Endocrine Society. who recommends via their guidelines, the CS and CD tests, they appear to unanimously agree on the methodologies of testing to confirm a CS and/or a CD diagnosis.[6,27,28,29,30,31]

1.8.1 Biochemical Testing

The guidelines recommended by the Endocrine Society have not significantly changed since 2008.[32] For a diagnosis of hypercortisolism at least 3 biochemical tests are initially recommended. A Physician should be alerted to look for biochemical evidence of CS as a first-line screening approach if a patient presents with any of the Cushingoid features including easy skin bruising.[14] However, no single Cushingoid feature is *100%* in predicting CS and therefore this is the reason that it is important to perform more than 1 biochemical test.

Figure 1, Page 26, displays an illustration of the typical Cushingoid features that are often identified during a clinical consultation.

The biochemical testing includes blood, and saliva samples which are normally taken by the endocrine nursing staff. The patient, under instruction is responsible for the collection of their UFC test, the salivary test and self-administration of the dexamethasone and corticotrophin-releasing hormone tablets (*CRH*). All test samples are sent to a hospital laboratory for analysis.

The choice of tests are as follows:

a) A dexamethasone and CRH when prescribed have the physiological effect of suppressing the production of the hormone, cortisol. The test is named the overnight dexamethasone suppression test, (*ODST*). 1mg of dexamethasone, is orally taken by the patient between 23.00 and 00.00 hours. The patient then has a blood test normally at their GP surgery early the next morning. This test is a measure of the serum cortisol taken between 8.00-10.00am. The blood sample is then sent to the hospital for analysis. Cortisol level <50*nmol/L* is the appropriate response after administration of the ODST in normally functioning HPA.

However, inadequate cortisol suppression with higher cortisol levels has a sensitivity *>95%* and a specificity of *80%* for initial diagnosis of CS.[6] If the cut-off value *<140nmol/L* is used, the specificity for this reaches *>95%*, although sensitivity falls significantly.[6] Unfortunately, if a patient is taking various types of medication, then this can affect the test.

b) A low dose ODST (*LDODST*), is conducted in the hospital and can be more specific in the results regarding the exclusion of conditions which are associated with PCS. Dexamethasone is administered over 48 hours in 0.5*mg* doses at 6 intervals over this period of time. On day 3, 6 hours after the previous dose a serum-cortisol measurement is performed. Suppression of cortisol *<50 nmol/L* shows a normal response for non-CS patients. The LDODST has a sensitivity and specificity in diagnosing CS and is said, "to be *100%* and *88%* respectively," and, with a positive predictive value, (*PPV*), of *92%* and negative predictive value (*NPV*), of *89%* respectively.[33] Any additional factors which may interfere with the results should be considered by the endocrine team.

c) Bilateral Inferior Petrosal Sinus Sampling (*BIPSS*) can also help to establish the reason for endogenous CS and identify the root of its cause, example, pituitary or elsewhere. The petrosal sinus veins drain the pituitary gland. In a recent meta-analysis of published literature, the results showed that BIPSS was found to have, "a high diagnostic value for detecting ACTH-dependent CS." [34.] It is also valuable for lateralizing small hormone-producing adenomas within the pituitary gland. BIPSS may be particularly useful when the laboratory evaluation suggests a pituitary source for ACTH, but none can be identified by MRI scanning. Sedation is required for this procedure. The catheter tubes are inserted bilaterally into the femoral veins and by advancing the catheters into the inferior petrosal sinuses via the internal jugular veins, the ACTH levels are measured (*petrosal sinuses*), and a blood sample is taken from the forearm. Baseline ACTH values are obtained from the periphery and the inferior petrosal sinuses both before and after CRH stimulation, (1 μg/kg of body weight). A ratio of 2.0 from the petrosal sinus to the periphery before CRH stimulation, or 3.0 afterwards is felt to be consistent with pituitary CD. In ectopic disease, the ratio is typically less than 2.0 both before and after CRH stimulation.[6] Following this test, it can be established that if the ACTH level is higher from the petrosal sinus sample, then Cushing's has developed from the pituitary gland. However, if both samples are similar then it is highly likely that the source of the problem is elsewhere. According to Vaughan et al, (*2012*), the experience of the practitioner influences the utility of the test, and even some large medical centres may not be able to perform the procedure reliably.[35]

Hypoplastic, ectopic pituitary tumours or anomalous inferior petrosal sinuses can often result in false negative tests. "IPSS results can lateralize those findings and may therefore be misleading and are not highly specific."[31] According to Kyritsi et al, (*2016*), "bilateral sampling of the internal jugular vein is a more simple and safer technique, and it may be used in centres without expertise of BIPSS."[36] This is due to the possible complication

of BIPSS which can range from a hematoma of the groin (*3-4% of cases*), rare complications being deep venous thrombosis (*DVT*), pulmonary thromboembolism pontocerebellar junction stroke, brain stem injury, cranial nerve palsy, venous subarachnoid haemorrhage, and obstructive hydrocephalus.[37]

Notably, according to Nieman (*2017*), approximately only *50%* of tumours are identified by MRI pituitary imaging.[38.] If a tumour is not identified on the MRI images, then BIPSS should be recommended.

d) Adrenal venous sampling (*AVS*) is the gold-standard test used for identifying patients with surgically curable subtype of primary aldosteronism (*PA*), which is the primary cause for hypertension. PA is said to cause between *15%-20%* of drug-resistant hypertension. By measuring the aldosteronism levels from both adrenal veins enables a diagnosis of the adrenal source of excess production. This would be conducted prior to surgery but is also technically challenging and only experienced, 'hands', should perform AVS which is said to be *90%* reliable in diagnosing the aetiology of PA.

Various centres throughout the world use different techniques. According to a recent survey, two-thirds of them are using a sequential catheterisation technique.[38] No evidence currently suggests which technique is superior and there is no standardized protocol. A recent review of AVS however, showed that this procedure identifies aldosterone-producing adenomas (*APAs*) and other subtypes with aldosterone production for 1 adrenal gland and this is of great value for surgical planning.[39] In the case of bilateral hyperaldosteronism (*BHA*) it is suggested that this should be treated medically with mineralocorticoid-receptor antagonists (*MRAs*).[40]

e) A 24-hour urine (*UFC*), sample is collected in a special container which is supplied by the hospital with strict instructions given as to how to self-administer this test efficiently so that the sample is accurate and clear of any faecal matter.

The UFC measures the unbound cortisol filtered in the urinary system, which according to Pappachan et al, (*2017*), "provides an integrated assessment of the total urinary cortisol excretion over a 24-hour period, unlike measurement of (*total*) serum cortisol measuring both free hormone and cortisol which is bound to cortisol binding globulin (*CBG*)." [41]

The latter may, however, vary with the alteration in the CBG levels in disease states or the associated use of different types of drugs.

There are, however, variations in the reported efficacy of UFC sampling mainly due to procedural difficulties, for example, children and older patients, contamination before and during processing.

A number of researchers including Guaranotta et al, (*2016*), have found that the degree of urinary hypercortisolism excretion is not correlated with severe CS.[42] According to Persenn et al (*2013*), there exists a high variability in baseline UFC values in patients with CS.[43] A study also by Aranda et al, (*2016*), showed poor diagnostic utility for UFC levels of only *53%* sensitivity and *86%* specificity for initial screening test of CS, thus suggesting that this test is less reliable.[44] These statistics were also quoted in the Pappachan et al paper, (*2017*), which discusses CS and a practical approach to diagnosis and differential diagnosis. Cortisol levels higher than 50-100micrograms per day in adults suggest the presence of CS.[41]

f) A late-night saliva test (*LNST*) is taken and submitted to a hospital laboratory to also measure the cortisol levels. This is carried out late evening as the levels of cortisol can vary throughout the day. This is said to be a highly sensitive test. Plasma cortisol levels in a healthy patient starts rising between 03.00am and 04.00am. At night however, these can be high, and patients are asked to chew a cylindrical cotton swab for a few minutes between 23.00-00.00. The patients are then requested to store the swab in a sterile container at 2-8 degrees Celsius. Most studies have reported the sensitivity and specificity of this test as *>95%* which would suggest the presence of CS. [6 45 46]

The LNST has a better performance than the UFC in the diagnosis of CS, according to Elias et al. [47] It is also important that more than 1 sample should be taken, and clinicians should be aware of, "the importance of pre-test probability, any preanalytical error(s)," and that, "testing/methods/assay differences can significantly influence results accuracy." [48] It is important to note, that there can be cases where a false-negative or false-positive can occur in these diagnostic tests, if sampling conditions are not adhered to. A 2021 paper has suggested that steroid profiling may supplement or improve the existing biochemical tests to diagnose CS and mild autonomous cortisol secretion, (*MAS*). The authors Athimulam et al, in their paper, discuss this method as having diagnostic potential, combining it with customized computational analysis and machine-based learning (*MBL*). This they claim will simplify the hormonal workup and disease subtyping of CS.[49.] Notably, *50%* of patients with incidental adrenal adenomas are found to have MAS.

Display 1

A typical route for a CS diagnostic to treatment pathway is displayed below:

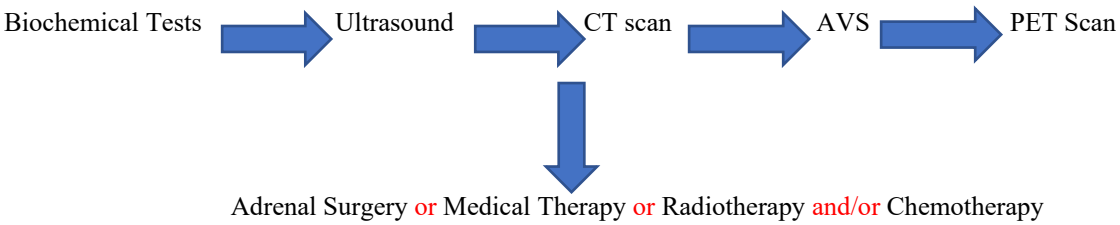
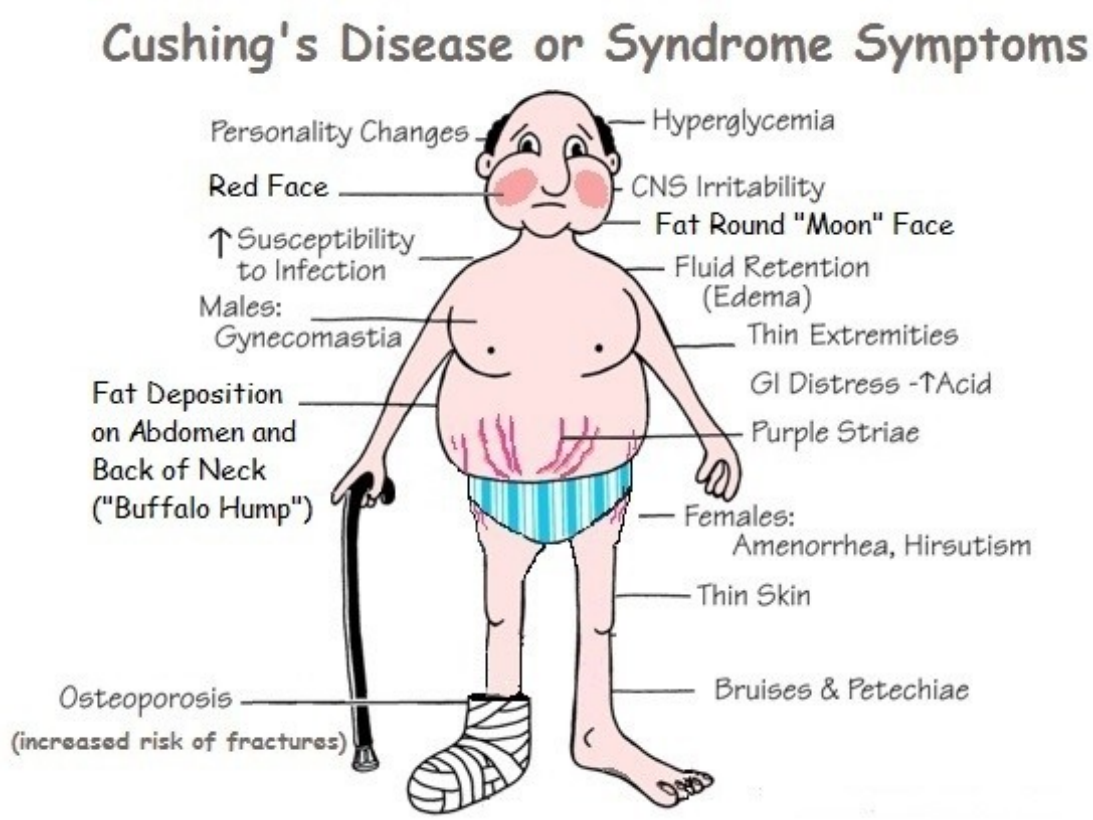


Figure 1 Cushingoid Features



Medical Pictorial Illustration: Courtesy of Quora

Figure 1 displays the Cushingoid features which can be identified during a clinical assessment and should lead to further investigations to establish a CS or CD diagnosis.

2.0 ***Diagnostic Medical Imaging***

Following biochemical testing and depending on the results the patient will be asked to attend the radiology department for imaging of the glands associated with CS and CD, i.e., the pituitary or adrenal glands. The reason for this is to establish the presence of any cysts or adenomas within the pituitary gland and/or adrenal glands. By measuring the size and shape of these glands on the resultant images enables a Radiologist to determine the presence of a tumour. Normal practice is for the Radiologists to report the resultant images and then send the results to the endocrine team with a copy to the patient's GP.

A radiographic image essentially presents visual information of the patients' anatomy and physiology. The observer of the image(s) can for example be a Radiologist, Radiographer or medical doctor who is qualified to undertake the task of making a diagnosis. With the introduction of workstation systems and specially designed software, which enables the production of two dimensional (*2D*), or three-dimensional (*3D*), imaging, these images when displayed, can be manipulated by the operator, and enable anatomical measurements, a prime

example being tumour size and volume. Software is used in CT, MRI, Nuclear Magnetic Resonance (*NMR*), Positron Emission Tomography (*PET*), and ultrasound (*US*), and aids not only diagnosis but pre-surgical planning.

- *Appendix 4, Pages 243-245 features examples of Imaging Modalities and Appendix 5, Pages 246-254, Anatomical illustrations, radiographic images, and case studies.*

2.1 Radiology-Historical Background

Prior to discussing the radiological imaging modalities for a CS and/or CD diagnosis, similar to acknowledging the historical beginnings of CS, it is also important to acknowledge the background of medical imaging as it plays a vital role in the diagnosis of these medical conditions.

Wilhelm Conrad Roentgen in 1895 discovered x-rays while experimenting with a Crook's tube and noticed that "a new kind of rays were emitted that could expose photographic plate even when optically shielded." [50] He named the rays, x-rays and decided to take a radiograph of his wife's hand to view her skeletal anatomy. Shortly after his discovery, x-rays were used in clinical practice (*February,1896*).[50] Since Roentgen's discovery, enormous technological advancements have taken place in medical imaging.

The twenty-first century could be described as the era of the technological revolution.[51] However, with any invention and advancement in technology there is a 'price to pay', not only in terms of financial costs for the research and development, acquisition, installation, and overhead costs of medical devices, but also in the biological effects of ionizing radiation (*IR*). These are the reasons why today's Health Professionals must be compliant with rules and regulations to ensure safe and efficient practice. During their diagnostic journey CS and CD patients are exposed to high doses of radiation, particularly when referred for example for CT examinations and RT.

2.2 Safety Measures for the use of Medical Devices and Prescribing Medical Therapy.

With this in mind, prior to embarking on the literature review for this study (*Chapter 2*), a critical appraisal of the current European and UK Government regulations and laws related to prescribing medication and the use of medical devices for the diagnosis and treatment of CS and CD was conducted. This also assisted in the collation of information for this *Chapter,* which included the application of the ionizing radiation medical exposure regulations (*IR(ME)R*) 2017. [52] The rationale for this was to not only understand the risk benefits for patients who undergo not only biochemical testing, but also medical imaging and sometimes RT which both use IR, and the

prescribed medications and treatments, which can include chemotherapy. This process of study also enabled the author of this thesis to plan the design of the structured questions for the HRQoL survey, i.e., some of the questions were designed to focus on the justification for the diagnostic tests and treatments and how and if these had influenced their HRQoL. This knowledge was also thought to be helpful in preparation for the semi-structured interviews with Health Professionals, which took place during this study.

The present study aims, and objectives of this study are fully described in *Section 7*, *Pages 43-44*, of this *Chapter (1),* and the research methods are fully explained in *Chapter 3*, Research Methodology, *Pages 94-101.*

2.3 Ionising Radiation (Medical Exposure) Regulations, 2017.

The IR(*ME*)Regulations, (*2017*), informs practitioners on the justification for referral of patients. Justification for individual exposures, according to these regulations must show, "a sufficient net benefit, "and that, "the total potential benefits, including diagnostic and therapeutic, including the direct health benefits to the individual and the benefits to society of the exposure." [52]

On referring patients for diagnostic medical imaging, the referrers must therefore consider the reasons why a particular imaging modality is the most appropriate for imaging the area of the body under investigation. During their decision-making processes, they should firstly consider using a non-ionizing radiation modality, examples, MRI or US. The regulations state that**,** "The referrer must supply the practitioner with sufficient medical data, such as previous diagnostic information or medical records, relevant to the exposure requested by the referrer to enable the practitioner to decide whether there is a sufficient net benefit as required by regulation 11(1)(b)." [52]

The practitioner being the person who delivers the radiation dose, examples being a Radiographer, Assistant Radiography Practitioner, Radiologist, or a Surgeon.

However, if non-ionizing imaging modalities are unsuitable for an anatomical area of the body under investigation or a particular pathology, then an IR modality should be chosen. The decisions that referrers and practitioners make regarding their choice of imaging modality should be based on the evidence produced during clinical trials prior to being used in daily clinical practice. The Royal College of Radiologists (*RCR*), evidence-based guidelines help referrers to make the right choice of modality for each radiological investigation, thus providing safe and best practice.[53] Referrers and practitioners, "must ensure that doses arising from the exposure are kept as low as reasonably practicable consistent with the intended purpose." [52 53]

The approximate effective radiation dose from CT for example, is 20milliSieverts (*MSV*), for an abdomen and pelvis repeated with and without contrast media. A PET/CT scan would be approximately 25mSv for a similar

examination. Spine x-ray's approximate radiation dose is 1.5mSv. Dose calculation is, however, complex due to many factors. These doses are the typical values for an average-sized patient therefore, the dose can vary substantially. The effective dose is a calculation which assesses the total risk to the body from IR. This therefore enables medical staff to assess the risk to the patient for each individual x-ray referral. A radiation patients' profile should be kept within their medical records to assess overall the patients' accumulative dose.

The safety aspects related to diagnosing a condition such as CS/CD is important for physicians and surgeons and all those who are referrers to acknowledge. In the case of CS/CD, due often to the large number of radiological investigations required to reach a definitive diagnosis, the radiation dose can be substantial. Unfortunately, this does not cease post diagnosis as RT and additional CT scans, chest x-rays and other radiological investigations due to the long-term comorbidities may be required. Notably, CS and CD patients are given a surveillance plan by their endocrine team to monitor any changes in their health and to ensure that their Cushing's remains under control. It is important therefore that all referrers are not only trained in the IRR but also understand the rules and regulations pertaining to the European Medical Devices Directive.[54]

On May 25th, 2017, the new European Medical Devices (*EMD*) guidelines were published which marked the commencement of the transition period for the manufacturers selling medical devices in Europe, thus allowing them to make changes before selling them to health services. The importance of safety and meeting these standards requires those using medical devices to comply with these safety measures and are of the utmost importance for staff who manufacture, sell, install, and operate the equipment and for patients who are diagnosed and treated using such equipment.

*"MDR replaces the Medical Devices Directive (93/42/EEC) which has a transition period of three years, thus allowing technical documentation and processes to meet the new requirements." [54 55]

2.4 Biological Effects of Medical Exposure to Ionizing Radiation.

The effects and human risk from exposure to IR is dependent on the absorbed dose, dose rate, quality of radiation, specifics of the tissue irradiated and other factors such as the age of the patient. It can take many years for the effects of exposure to IR to manifest itself and cancer can be a result of the stochastic effects of absorbed doses of less than 1Gray (*Gy*).[56] This is a derived unit of IR in the International System of Units (*SI)*. It is defined as the absorption of 1 joule of radiation energy per kilogram of matter. According to Stakiewicz Sherer et al, (*2018*[57]), "the risk of cancer induction varies widely across different tissues: however, the risk of fatal radiation-induced cancer for a general population following chronic exposure is about *5%* Sievert (*Sv*)." [57] The Sv is also

a derived unit of IR dose in SI units and is a measure of the health effects of low levels of IR on the human body.[58] High doses of IR, i.e., over 1Gy, can kill cells within the human body and causes deoxyribonucleic (*DNA*) damage which results in what is known as the deterministic effects. Genetic changes and cancer are examples of the stochastic effects. The non-stochastic effects include, skin erythema, cataracts, bone marrow depression in which case immunosuppression becomes critical. Exposure to IR induces, "various types of DNA damage, including DNA double-strand breaks (*DSBs*)." [59] This damage is normally repaired by the corresponding DNA repair system. However, according to Shi Lin (*2018*), there is substantial evidence that, "if mistakes are made in the repair of the damaged DNA, then the genetic information may be changed leading to health effects," as previously mentioned.[59] The human body's defence mechanisms may repair damaged cells caused by IR, severely damaged cells may however die or proliferate in a modified form of cancer.[59]

Each time the exposure button is pressed on an x-ray system during a radiological investigation the IR penetrates the patients' skin and passes through the tissue and organs. The energy of the radiation imparted along its track, 'excites', the electrons of the molecules within a human cell into motion. The relative-biologic effectiveness (*RBE*) is a ratio which describes the amount of biological damage that a radiation dose can incur, therefore the quality and amount of the radiation is important in determining potential chromosomal damage to a patient.[60]

The biological reactions to IR can therefore result in numerous different effects to the human body and the following examples are summarized:

- Damage to the skin due to low photon energy examples being leukaemia, breast cancer and genetic damage.
- Sterility or the production of mutations.
- Gastrointestinal, central nervous system syndromes.
- Radiation induced cancers.

In *Chapter 2*, the author of this thesis reviews several published works whose authors have studied the types of medical imaging modalities, including IR and non-IR for the diagnosis of CS and CD. These papers discuss the details of the 'gold-standard,' modalities used for these conditions and the justification for their use and focus on the possible side effects which they may induce.

2.5 *Advancements in Technology.*

"Medical diagnostic radiography is the science of producing x-ray images of the human body to aid diagnosis." [60] The growth in radiology services over the past five decades has been exponential, particularly with the introduction of sectional imaging (*CT, NMR, MRI*, *PET*), and US which is also used extensively in many branches of medicine examples are abdominal, cardiology, gynaecology, obstetrics, and the urinary tract.

Since the early nineties, MRI has been the modality of choice for pituitary adenomas and is still the case.[61] Due to their size it is crucial, "to visualize the pituitary gland with the highest spatial resolution, which enables correct delineation of small anatomical structures and pathological lesions." [61]

The use of 3Tesla magnet MRI scanners was hoped to provide a better resolution for minute adenomas but has been found to be in some cases disappointing. However, the recent introduction of the 7T magnet MRI scanners is proving to be hopeful but controversial and is reviewed in *Chapter 2*, *Section 3.4, Pages 75-77.*

* Both MRI and CT, are thought to now be the 'gold standard,' imaging modalities used currently within radiology departments for the diagnosis of CS and CD. The following sections are an overview of these and other imaging modalities which are also used, often as complimentary to obtain and confirm radiological evidence of tumour growth and metastatic spread.

2.6 Adrenal Gland Imaging

Computed Tomography is used to study adrenal masses. Interestingly, prevalence of adrenal masses is reported regularly by Radiologists and is between *1.3%* and *8.7%* among adults with the prevalence increasing up to *10%* as age increases. These incidental adenomas according to Mantero et al, (*2000*), are of, "mild, clinical importance in CS," which is reported in approximately *5%-10%* of these patients.[62] Sherlock et al (*2020*), in their study found that adrenal incidentalomas are now, established as a common endocrine diagnosis and suggested that it requires a multidisciplinary approach for the effective management of CS.[63.] These authors concluded that the advancement of surgical techniques have improved clinical outcomes and new radiological technologies and urinary biomarkers will achieve early detection and patient stratification in future years to come.[63]

A recent 2021 publication in the British Journal of Radiology (*BJR*), suggested that contrast enhanced US (*CEUS*) is currently being evaluated to assess its usefulness as a screening modality to differentiate between benign and malignant adrenal masses.[64] This article describes, CEUS as a relatively safe alternative for patients who perhaps react to contrast-media and may have renal dysfunction or allergy to CT contrast media. With reference to imaging of the adrenal glands, US is normally requested to identify the presence of a benign, or malignant

adenomas.[65] Depending on the result, a CT may be requested to establish tumour volume and the extent of the malignancy. *Figure 39, Appendix 4, Page 244, shows a photograph of an Ultrasonographer scanning a patient, an Ultrasound. Portable unit. Appendix 5, Figure 41, Page 246, displays a CT image of the right adrenal adenoma. Appendix 5, Figure 42, Page 247, displays a CT of the adrenal glands (Normal Anatomy). Appendix 5 Figure 43, Page 248, displays a CT of an adrenal cortical carcinoma.*

2.7 Pituitary Gland, Imaging

- Since its introduction in the 1970s and 1980s, MRI is now widely used in brain scan imaging. The scanner consists of a very large magnet which creates a "strong magnetic field, the nucleus of the hydrogen atoms-proton-tends to align itself with the field." [66] In the human body there are many hydrogen atoms and therefore, this tendency results in a net magnetization of the body. The hydrogen atoms generate a detectable radiofrequency (*Rf*) which is received by antennas in close proximity to the anatomy being examined.[67] "The pulses generated by the radio waves excite the nuclear spin energy transition, and magnetic fields localize the signal in space."[67] Variations in, "the parameters of the pulse sequence, different contrast may be generated between tissues based on the relaxation properties of the hydrogen atoms therein." [67]

  Notably, current research studies are focusing on the MRI techniques to visualize microadenomas of the pituitary gland.[68] A prime example of this is the Grober et al study (*2017*) which, evaluated the use of the 3D volumetric interpolated breath-hold examination, a spoiled-gradient echo 3DT1 sequence (*SGE*) characterized by superior soft tissue contrast and improved resolution and compared this with dynamic contrast-enhanced MRI (*DMRI*), and conventional MRI (*CMRI*) for detecting microadenomas in patients with CD.[68] These researchers concluded that, a SGE should be part of the standard MRI protocol for patients with CD.[68] One could argue however, that this underlines the need for the availability of a stronger magnetic field scanner i.e. 3T or 7T. Apart from the lack of availability within smaller hospitals, there is also an on-going debate as to which level of magnetism is the most efficient for the identification of micro changes in the brain structure.

Whilst researchers generally agree that MRI is the safest and most effective method of imaging used for the identification of a pituitary tumour, there are also those who have found false negative and false positive results during their studies, particularly with the use of 1.5T. Vital et al, (*2017*), noted in their study for example, that the smallest of tumours may not be detected by any of these MRI scanners.[69]

Rotte et al previously in their 2016 study of the clinical evaluation in CD using 7T, found when it was compared with 1.5T that 3 out of 5 microadenomas were detected when the 1.5T scanner failed to do so.[61] *Appendix 4, Figure 47, Image 7, Page 251,* displays an MRI scan of the pituitary gland.

2.8 Computed Tomography

- CT is similar in its structural outward appearance to MRI but uses IR to produce two-dimensional (*2D*) images which appear on the resultant images as cross-sections. This modality for example, is used for cardiac imaging, skeletal imaging, suspected brain damage, tumours, and cysts. Similar to MRI, contrast agents are used to demonstrate physiological changes and functional irregularities. MRI and CT both use a computer and keyboard to display the digital images. Once the full processing of the images and data has been stored, a Radiologist for example, then reports their findings, as previously discussed. *Appendix 4, Figure 37, Page 242,* displays a photograph of a CT Scanner.

2.9 Positron Emission Tomography.

- PET scanning is regularly used in cases where adrenocortical carcinoma is suspected which could be based on a suspicious imaging phenotype, large tumour volume, the signs and symptoms for example being hirsutism, hypertension due to CS. A PET scan example: ^{18}F-glurodeoxglucose, is often requested prior to an adrenalectomy to evaluate the possibility of metastases.[70]

  For pituitary gland adenomas, due to the difficulty in proving tumour localization, despite biochemical identification of ectopic -ACTH syndrome (*EAS)*, physicians normally request further imaging to ascertain the presence of a primary tumour a prime example being the lungs which are reported to make up *55%* of these. Further imaging can therefore be in the form of NMR as well as conventional imaging. CT chest imaging has an overall sensitivity of *53%-66%* and for lung tumours, *74.9%,* [71]

2.10 Ocular Coherence Tomography

Another form of imaging is Ocular Coherence Tomography (*OCT*), which is used for CS patients who may develop visual impairments due to a pituitary gland adenoma(s). This is often caused by pressure of a pituitary mass on the optic/retinal nerve.

- OCT is also said to be, “quite useful,” in assessing the thickness of the retinal nerve fibre layer in the optic nerves when they are compressed or distorted by a pituitary tumour.[72]

  The Massachusetts Institute of Technology is presently developing a mini-OCT device which is leading to another possibility which will add to the imaging modalities for pituitary gland imaging. This device is to measure choroidal thickness which increases in the eyes of patients with active CS. A novel

modality is enhanced depth imaging (*EDI-OCT*), which enhances the resultant images and allows eye specialists to measure the anatomy and thickness of the choroid to be assessed and is now being routinely used by many opticians in their clinics.

A research study conducted by Abalem et al (*2016*), compared the choroidal thickness measurement using OCT in patients with EAS, their aim being to evaluate the occurrence of retinal abnormalities in the same group of patients. [73] Their results found that *18.8%* of patients presented with macular changes, possibly secondary to choroidal thickening. Their recommendation was to conduct further research studies which would support their findings. The authors suggested that excess corticosteroid levels seem to have a significant effect on the choroid and might be associated with secondary retinal diseases.[73]

Notably, PET and SPECT are used for the detection of peripheral NETs and can provide an ectopic source of ACTH or CRH, which mimics CD.

Chapter 2 also reviews publications which assesses pituitary and adrenal gland imaging using MRI, CT, US and NMR and the latest advancements in PET scanning.

2.11. Radiotherapy Modalities for the Treatment of Cushing syndrome and disease.

Diagnostic medical imaging also plays an important part in the planning of RT treatment for CS/CD. Radiotherapy is a treatment option for patients who have invasive tumours which are uncurable and have failed to achieve remission. This is normally decided for patients who have had unsuccessful TSS or are not considered to be suitable for this type of surgery, examples being older patients, and those with serious long-term comorbidities.[6]

However, some patients who undergo RT never achieve biochemical remission.[74]

- In 3D MRI-guided RT multi-leaf collimators are used to shape the RT beam to closely match the shape and volume of a tumour, thus reducing the dose to the healthy surrounding tissue.[75] High doses of RT are used to destroy cancer cells in pituitary malignant adenomas. Side effects unfortunately occur during and after RT and its use can also damage healthy cells and tissues near the treatment area. Today, major advances in radiation technology have made its use more precise in defining tumour volume, leading to fewer side effects.[75] The side effects include, cerebrovascular events (*CVEs*), discomfort in swallowing and secondary intracranial tumours, dry mouth, tooth decay, nausea, lymphedema, stiffness in the jaw and long-term arteriosclerosis of the heart.[76] [77] Patients with recurrent CD after surgery are often referred for gamma knife radiosurgery (*GK-RS*). However, according to Cohen-Inbar et al (*2016*), "Patients with

adenoma in the cavernous sinus are more prone to develop loss of pituitary function after GK-RS".[78] This means that there is a risk of long-term hypopituitarism for patients with CD.

2.12 Matrix-assisted laser desorption/ionization- Mass Spectroscopy (MALDI).

Many pituitary tumours invade other areas of the brain causing catastrophic consequences and are sometimes inoperable. New intraoperative techniques are being developed and tested such as MALDI mass spectroscopy. This is used in mapping of the exposed pituitary gland intraoperatively. MALDI geographically maps the gland for the location of clusters of the different types of hormone-expressing cells and tumours composed of these cells.[79] This visualization technique therefore can assist neurosurgeons to define the location of pituitary tumours in near real-time. Calligaris et al, performed imaging analysis using MALDI mass spectroscopy of pituitary adenomas during their 2015 study and were optimistic regarding the potential of this diagnostic method of analysing specific hormones, including growth hormone (*GH)*, and prolactin in tissues. The study conclusion suggested it may be possible to, "determine the composition of such hormones in less than 30 minutes." [80] Thus, giving the surgeons critical information to assist in distinguishing a pituitary tumour from a normal gland.[79] [80]

In Summary: Multi-modality imaging plays a large role in diagnosing CS and CD. Clinicians find it beneficial in their diagnostic assessment to use a combination of these modalities to look for specific patterns associated with the disease processes, and this depends on both the patient, imaging modality and the expert eye of the image reporter.

The number and frequency of imaging examinations and RT treatments are solely dependent on the referring clinicians who must be mindful of the dangers involved, particularly in the use of IR and the long-term biological effects. As previously stated, the justification and benefits must outweigh these dangers. Modalities such as MRI and US should be used as frequently as possible when physicians are striving to make a definitive diagnosis in the safest possible way.

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3.0 *Surgical Techniques for Cushing syndrome and disease.*

3.1 Adrenal Surgery

According to Dalmazi and Reincke (*2018*), "Recent advances in molecular pathogenesis and the natural history of CS have improved the understanding of the management of this disease." [81]

In their paper, the authors discuss the current evaluation of the efficacy of treatments in the long term, including several cortisol-lowering medical therapies.[81] However, adrenal surgery continues to be the safest choice, for the treatment of CS. In the cases of adrenocortical adenomas which are the result of hypercortisolism, unilateral adrenalectomy is said to be the 'gold standard', treatment.[81] To deal with ineffective treatments for CD or CS, i.e., patients who are suffering from elevated serum control may require radical surgery, i.e., bilateral adrenalectomy. This surgery is viewed as, "a last resort," according to Law (*2017*).[18] Cortisol is secreted from the adrenal glands, thus when they are surgically removed the disease is eliminated, but not without consequences. The key points extrapolated from the Dalmazi and Reincke update paper on adrenal surgery is, that laparoscopic surgery should be performed for the surgical removal of adrenal adenomas and that unilateral adrenalectomy should be considered when patients diagnosed with bilateral macronodular adrenal hyperplasia require a surgical option. [81]

Figure 2 ***displays a medical illustration of Adrenal Surgery.***

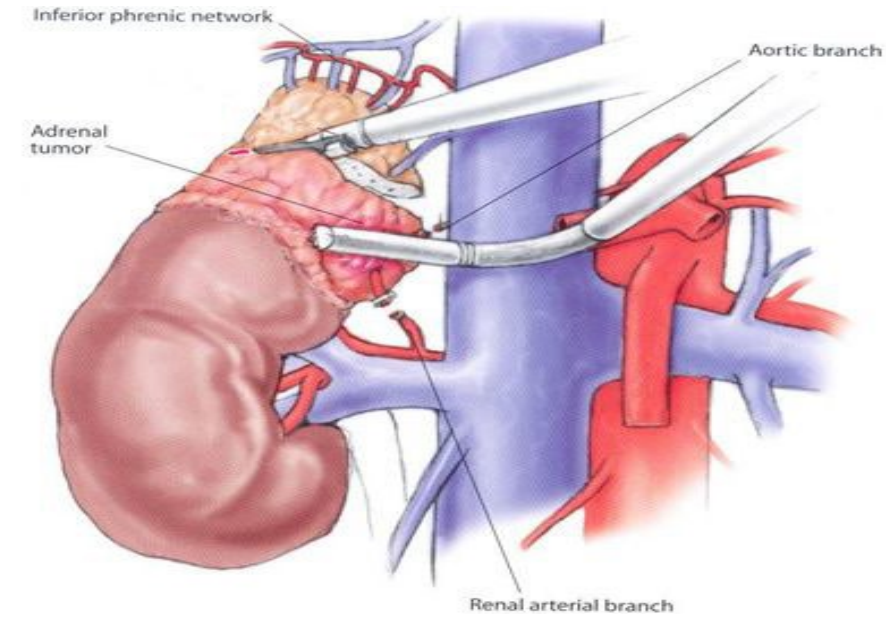


Figure 3 ***Laparoscopic Adrenal Gland Removal (Adrenalectomy).***

Medical Illustrations Courtesy of Medicine.net

Appendix 5, Figure 40, Page 246, displays an illustration of the kidneys, including the adrenal glands.

3.2 Pituitary Surgery

3.2.1 Transsphenoidal Surgery of the Pituitary Gland.

Eighty percent of CD patients are recommended for pituitary surgery. Most Endocrinologists agree that a prime, 'candidate,' for TSS should have completed at least 2 dexamethasone tests including the ODST, LNST and a 24-hour UFC test. In addition to this, patients should undergo a BIPSS study if the initial biochemical tests are inconclusive, and at least a possibility of an MRI scan abnormality within the pituitary region prior to surgery [18]. The endocrine team prior to referring patients for TSS should also consider the comorbidities of individual patients. These include for example, hypertension, cardiac status, presence of DM and glucose metabolism. A recent systematic review by Broersen et al, (*2018*), compared the outcomes of TSS according to tumour size, and evaluated the difference in conducting microscopic with endoscopic TSS. Their findings showed that for CD patients, there was no difference in terms of advantage for either type of surgical techniques.[82] However, in cases of patients with macroadenomas, the endoscopic technique was shown to yield better results regarding remission and recurrence rates. They concluded that, within their study period, "these results are present despite the presumed learning curve of the newer endoscopic technique." [82] These authors recommended, that "although confounding by indication and improved radiological investigations with time", this technique, "cannot be excluded." [82] However, as most patients suffering from CD have microadenomas, the author of the present study tends to agree with the Broersen et als suggestion, that there is no reason for changing techniques. The recommendation being that it is the neurosurgeon's decision as to which surgery is best for a successful clinical outcome.

Figure 4, Page 38, demonstrates the outcomes of TSS according to tumour size and shows the remission and recurrence rates. *Figure 5*, *Page 38*, shows the anatomical area of the pituitary gland and *Figure 6, Page 39,* a pictorial illustration of TSS technique.

Appendix 5, Figure 48, Page 253, displays an MRI image of the pituitary gland prior to surgery and after repeat first and second surgeries. Appendix 5, Figure 49, Page 254, displays a Case Study of a negative MRI.

Display 2

A typical route for a CD diagnostic to treatment pathway is displayed below:

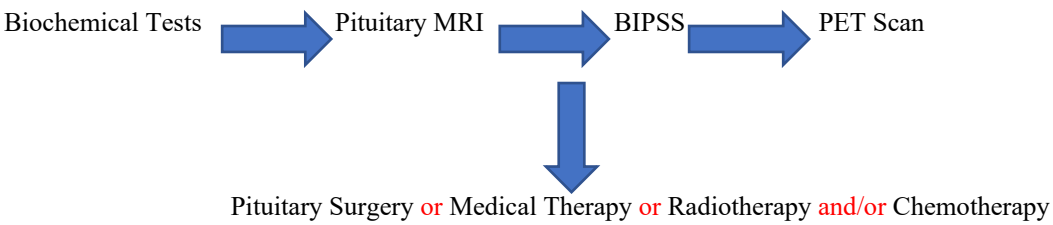
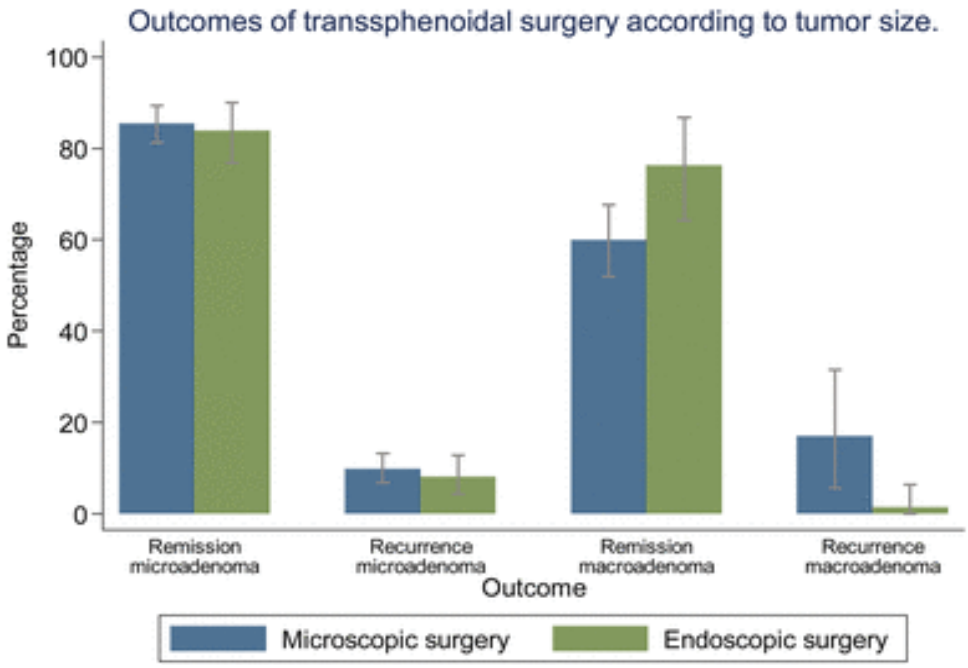
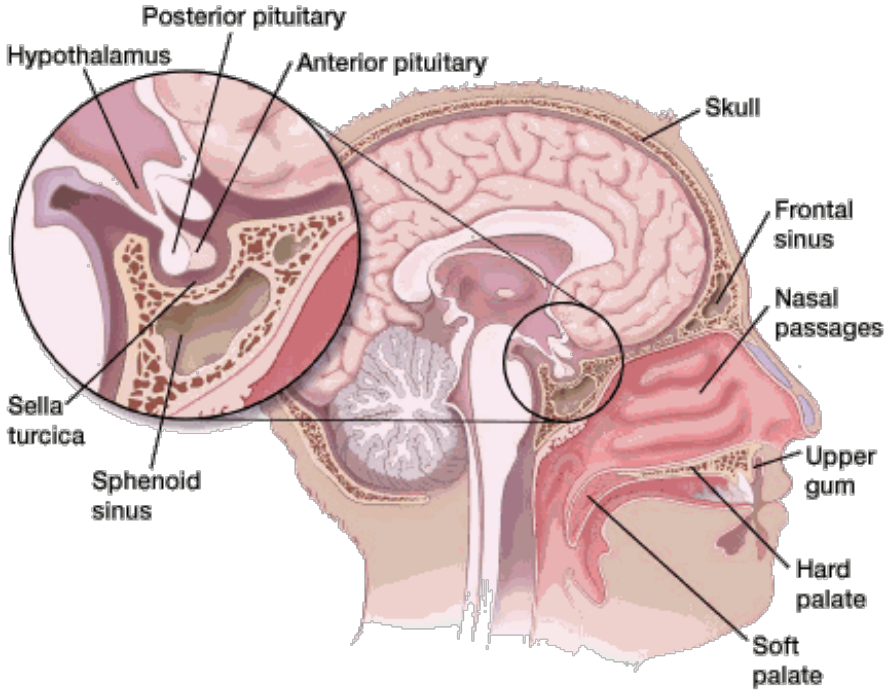


Figure 4 Analysis ***of Complication Rates after TSS for CD. Bars depict: Confidence Levels.***



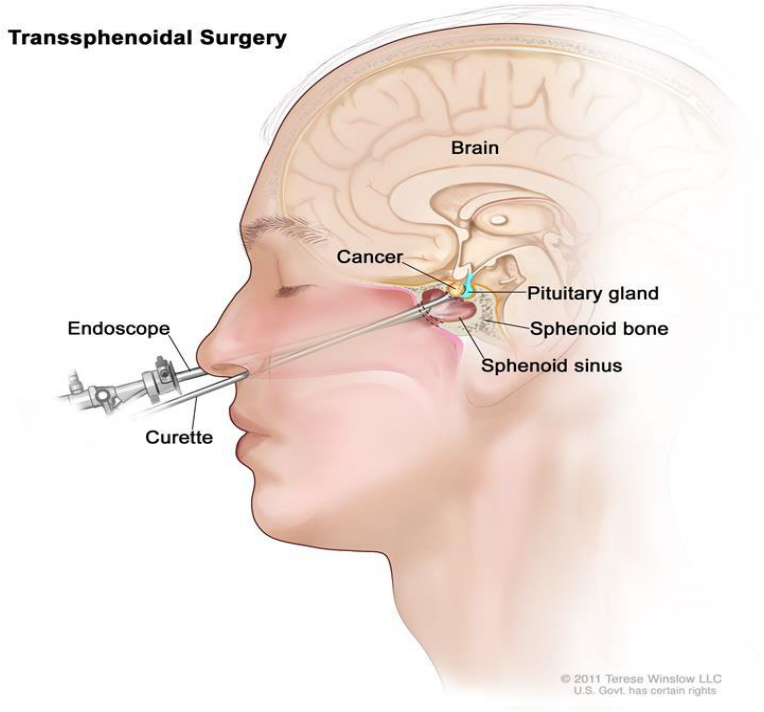
Endoscopic vs Microscopic TSS for CD: a systematic review. Broersen et al, Pituitary, 2018[67]

Figure 5 ***Demonstrates the anatomical of the area of the pituitary gland.***



Medical Illustration: Courtesy of the American Cancer Society.

Figure 6 ***Transsphenoidal surgery is performed through the sphenoid sinus, a hollow space in the skull behind the nasal passage and below the brain. The back wall of the sinus covers the pituitary gland.***



Pictorial Illustration: Courtesy of the National Cancer Institute

4.0 ***Other Treatments for Cushing syndrome and disease.***

Physicians and scientists are continuously trying to reduce the mortality rates due to CS and CD. "The genetic basis of neoplasia within the pituitary gland is under continuous investigation." [18]

Earlier in this introductory *Chapter*, the genetic characteristics of certain pituitary tumours, including those associated with CD which may have potential therapeutic targets were discussed. Chemotherapy for example, using Temozolomide (*TMZ)*, to treat refractory tumours of the pituitary which are aggressive or malignant.[18] However, TMZ, is said to be only used for life-threatening pituitary tumours, and the duration of therapy must be determined on a patient-by-patient basis.[18] There remains a dearth of prospective clinical trial data for rare aggressive pituitary tumours which undoubtedly require multidisciplinary patient care teams to provide them with the most informed treatment options. According to Bush et al (*2010*), this requires a multi-centre approach which would support future clinical research with the aim of developing guidelines for treatment of aggressive pituitary tumours.[83] Bush et al, also suggests that complete remission is not an expected outcome from this form of therapy, but a reduction in tumour volume and stabilization has the potential to improve the clinical outcomes. [83]

According to Halevy et al (*2017*), TMZ, has an accepted role in treating pituitary carcinoma and adenomas if RT and surgery have failed to control tumour growth. However, the authors agree with the Bush et al study that its use, "as a primary therapy, or in preference to RT remains controversial." [84]

Treatment options in CS and CD are increasing with some Endocrinologists preferring to refer patients for medical therapy prior to the surgical options in order to achieve control of hypercortisolism. Treatment options are discussed in *Chapters 3* and *5*.

5.0 *The Validation of Clinical Practice.*

The quality of care is of great importance within daily clinical practice. Health Professionals and medical researchers continually seek ways of improving the quality of care whilst ensuring that the health policies are delivered within their departmental budgets. Clinical audits are conducted to measure the clinical outcomes using standards which have been set, on the principles of evidence-based medicine. This assists in regularly measuring clinical outcomes and assessing the competency to practice in each field of health care.

Clinical governance (*CG*) has been implemented since 1999 (*DoH,1999*). Continuous Professional Practice (*CPP, Dearing, 1997*) and Continuous Professional Development (*CPD-Henwood, 2000*), were all introduced to ensure that medical staff continually update their clinical knowledge and skills. [85] [86] [87]

All Health Professionals as part of their professional registration must now provide evidence that they are attending courses and keeping up to date with the relevant regulations which includes the codes of practice and conduct set by their professional bodies.

Undoubtedly the introduction of CG has enabled clinicians to be more involved in defining the quality of service by the development of guidelines and setting standards of care. This was the conduit that changed the "prescriptive nature of healthcare", and thus created, "a desire amongst staff to change as a result of benchmarking and to balance the ideology of an improved clinical service for patients." [85]

The rationale for discussing CG within this thesis is to ensure that, whilst engaging with Health Professions staff and CS patients during the present study, that the guidelines and codes of practice relative for each area of clinical practice were explored to compare their differences in experiences and opinions.

Since the introduction of CG there have been many changes to the delivery of health care services. The DoH's definition is that "CG is the system through which NHS organisations are accountable for continuously improving the quality of their services and safeguarding high standards of care by creating an environment in which clinical excellence will flourish." [89.]

The views and decisions made by the multi-disciplinary team who are involved with diagnosing and treating CS and CD are crucial to the successful clinical outcomes. With reference to the surgeons, not only, "surgical skills alone", are required but the, "leadership skills of the surgeon," according to Latifi et al (*2016*).[90] In their publication they described the importance of leadership, and how the processes of managing patients should be, " seamless," and how this can affect the overall clinical outcomes.[90] The authors also discuss how change that is managed efficiently improves organizational performance. These leadership skills are required of today's Health Professions staff, including the endocrinology teams who should be encouraged to adopt a more creative, innovative, problem-solving approach to the delivery of their services. and not only manage change but also seek to improve their staff retention. The important roles played by the healthcare team must include leading research projects which focus on using new techniques and technologies for the diagnosis and treatment of CS.

During the present study, the demands of the delivery of endocrinology services, the quality of care and support mechanisms for those diagnosed with Cushing's was observed to appreciate why it can take so long to diagnose and if and how this service can be improved.

6.*0* *Cushing syndrome– The Author's Personal Journey*

The following is an account of my personal journey from diagnosis to treatment.

Diagnosis

I contracted Methicillin-Resistant Staphylococcus Aureus (*MRSA*) in 2007, the source was unconfirmed but thought to be the result of an infected skin cut. This is a serious illness causing impairment of the lymphatic system and can weaken the immune system. Shortly after recovery I was diagnosed with Barrett's Esophagus (*2008*), which is a life-threatening inflammatory disease and then diverticulosis and irritable bowel syndrome (*IBS*) (*2009/2010*). The latter is often associated with stress which results in inflammation of the bowel. In 2009, I suffered a mild stroke which was thought to be the result of hypertension.

Before my diagnosis, I experienced psychological effects which manifested itself, in my case, with bouts of anxiety, emotionalism, depression and hypomanic attacks (*2014*). I was hospitalized for six weeks, and my Consultant Psychiatrist began to consider that CS was possibly the cause of my hypomania.

Prior to being diagnosed with CS, I was informed by my Orthopaedic Consultant that I was suffering from severe compression of Lumber Vertebrae (*LV*) 4 to LV5 which resulted in severe sciatica. I had experienced back pain for three years and my right lower leg had begun to swell and my skin slowly developed rashes. A Radiologist's

report confirmed that I was suffering from degenerative spondylolisthesis which caused my severe sciatica, a swelling was also identified in my right kidney. This incidental finding which was an adenoma in my right adrenal gland resulted in a referral to an Endocrinologist who prescribed a dexamethasone blood test, LDDST, AVS, UFC and salivary samples, (*LNST*), US, and CT scan (*2015*).

Treatment

These tests identified that I had CS, the adenoma turned out to be benign, and was subsequently removed. My right lower leg pain persisted and, following several x-rays and eventually an MRI scan, I was diagnosed as having a musculo-skeletal aggressive soft tissue sarcoma. My leg was subsequently amputated (*2016*). This was not the end of my surgical journey as my follow-up biochemical tests, MRI pituitary scan and BIPSS confirmed a diagnosis of CD. I was then referred to a Consultant Neurosurgeon (*2017*). The combination of the biochemical tests and imaging procedures therefore identified the presence of a benign pituitary cyst which was removed and following TSS surgery, I was informed 1year later by my Neurosurgeon and Endocrinologist that I was in remission from CD (*2018*). Slowly my medication (*Hydrocortisone*) was reduced and in January 2019, my cortisol levels returned to normal, and I was withdrawn from this medication being declared, "cured."

Recovery

On reading the evidence presented by other Cushing's patients in numerous research papers, and my attendance at the PF UK conference (*2019*), the diagnostic odysseys resemble many of my own. My Cushingoid features included truncal obesity, excess hair growth, hypertension, and skin bruising. I also experienced bone pain, insomnia, fatigue, emotional lability, depression leading to suicidal ideation and generally was very weak. According to Law[18] *61%* of patients are reported has having emotional lability, *49%* of these have cognitive difficulties. Most of these patients experience a lack of concentration and memory loss and out of *17%* per cent of these patients, at least 1 is admitted to hospital for psychiatric care prior to their diagnosis of CS.[18] Similar to other Cushing's patients, I recognized that my proficient verbal skills were lacking, and I began to lose confidence in public-speaking and my academic activities. I was most fortunate in that I had a loving family and colleagues who supported me through the many dark days of my illness. Cushing disease and CS can be a devastating diagnosis for anyone, but young adults are said to be particularly vulnerable to the ridicule and abuse they experience due to their personality changes and physical appearances. I found that when my diagnosis was finally made, I knew nothing about what it really was both as a patient and Health Professional. The brief explanation I was given did not reassure me that I would get better. I felt angry, confused as to, 'why me,'? Most of all why

had it taken so long to diagnose! However, similar to many patients eventually I accepted the diagnosis and it somehow reassured me that it was this hormonal in-balance, i.e., my elevated cortisol levels that had driven my body to experience extreme pain, disorientation, psychosocial issues, hypomania, facial and body changes. I found difficulty in accepting the loss of my right lower leg and the painful journey of having to learn to walk with a prosthetic leg. The post amputation however, relieved me of the excruciating pain that I had experienced for many years. My sarcoma has not to date been associated with my Cushing's conditions.

After my TSS these changes rapidly began to reverse, my self-respect and esteem returned albeit slowly. The effects of steroids and its withdrawal syndrome can affect patients in a wide variety of ways. Several published articles related to the remission of patients suggest often physicians can be inexperienced regarding the advice and importance of patient information in what to look for i.e., the expected post illness signs and symptoms and the unexpected. Patients should not have to wait so long for a diagnosis and thus avoid this tortuous road to treatment. I continue to meet with my endocrine team yearly. Prior these appointments, I have a dexamethasone blood test, LDDST and an MRI (*Pituitary*) scan. My comorbidities include osteoporosis and RA. I will always have a fear of recurrence, but I am also happy and found, an inner peace, a need to pass on my experiences and a passion to raise public awareness. Hence my desire to use my patient experiences and this is the reason I felt compelled to undertake this PhD study.

Although this study was of a personal nature, driven by a desire to find answers as to why I developed CS and CD, it gave me a unique opportunity to compare my experiences with other Cushing's patients, particularly the impact factors and consequences of a CS diagnosis. My personal experience admittedly could have influenced the narrative within the present study. However, my insight into these medical conditions, provided contextualisation and support for this research study and helped formulate the research methodology, including the research questions and the design of the survey questionnaire. I would suggest that my personal experience brought a benefit to this study in terms of understanding of the nature of this condition and a context to the clinical evidence and outcomes, which helped inform the dissemination of this study.

7.0 *The Present Study Outcome, Aim and Objectives.*

The main outcome of this study is to add to the existing body of knowledge through my personal experiences. This was an evidence-based study, robust in its nature and thought provoking in its processes of uncovering the range

of opinions of the health care team, the patients', and the public's perceptions of this condition and their HRQoL due to having been diagnosed with CS and/or CD.

7.1 Aim of Study:

The aim of this study was to appraise the current methodology of diagnosing and treating CS and CD and to evaluate the clinical consequences of the disease processes in terms of HRQoL.

7.2 Study Objectives:

To achieve this aim, the following objectives are summarized below:

1. Review the current methods of diagnosis and treatments.
2. Explore the consequences of being diagnosed with CS and/or CD.
3. Conduct a HRQoL survey on members of the Pituitary Foundation UK who have been diagnosed with CS and/or CD.

As <u>part</u> of the HRQ0L survey:

4. Establish how aware and informed Health Professionals are when diagnosing and treating a patient with CS and CD.
5. Identify methods of accelerating the diagnostic processes which may lead to earlier reviews by the multi-disciplinary teams.

*The recommendations which emerged from the aim and objectives of this study, are listed in *Chapter 7, Pages 207-208.*

Chapter 2

Cushing syndrome and Cushing disease- a narrative review of the past and current literature

1.0 Introduction

Since CS and CD were named after Harvey Cushing in 1902, as previously mentioned in *Chapter 1*, (*Section 1.2, Page 9*), of this thesis, there has been a plethora of books and journal publications related to the many reasons for its diagnosis, subsequent treatments, current clinical practices, and what impact it has on the daily lives of its victims (*HRQoL*). To explore these topics a narrative review of literature, was conducted at the onset of this study.

A narrative review, (*sometimes referred to as a traditional literature review*), is a comprehensive, critical, and objective analysis of the current knowledge on a topic. The review of literature being defined according to Fink, (*2005*), "as a systematic, explicit, and reproducible method for identifying, evaluating, and synthesising the existing body of completed and recorded work produced by researchers, scholars and practitioners." [91]

This definition summarises the fundamental aim of researchers and the author of this thesis sought to achieve these valuable core elements of research by designing a strategic research framework prior to the commencement of this study. Using this framework, a comprehensive preliminary search strategy enabled a scoping exercise to ascertain, "what is known and what is not known," in relation to the research question and the aims and objectives of this study set out in; *Chapter 1, Sections 7.1 and 7.2, Pages 43-44.* [91]

1.1 Search Strategy

A search strategy requires a focused approach when reviewing a vast range of data. Reference screening and data extraction requires a clear methodology of search which involves a process known as decomposition. This is used widely by researchers as a method of breaking down a problem into more manageable parts. The author found no paucity in acquiring published literature related to CS and CD subject topics. The selection criteria were therefore modified during the review process to be more restrictive, and systematic. This posed challenges as the computer databases generated a generous body of published material. Hence, the search included keywords, subject headings, Thesaurus searching, and short focused questions which were related to each of the subject areas under review. During the early stages of the electronic database search, the author studied the hierarchical order in relation to each topic which assisted in the development of an inclusion/exclusion criterion. This proved sufficient to cover the review focus and created an awareness that the initial data extraction was the first key step in

identifying suitable material. This scoping exercise increased the author's appetite to question the authenticity and validity of the prime material which emerged from the search. The interdisciplinary nature of the study also warranted an electronic database search of different medical disciplines. The search was undertaken using web-based search engines as the gateway for accessing academic material. Google Scholar, PubMed, MEDLINE, ResearchGate, the Cochrane Library, British National Library, Universities of St. Andrews, Dundee, and Cumbria libraries websites are examples of the main sources used. A range of internet sites were also accessed, examples being the Department of Health (*DoH*), NHS, Government statistic databases, Society and College of Radiographers (*SCoR*), British Medical journals, National and International Radiology and endocrinology journals and conference papers. The author found visiting the universities libraries helpful in allowing access to current books and journals. Browsing the library shelves helped enormously in finding new sources of information and frequently allowed the tracking of the published work of experts in the fields for examples, of endocrinology, radiology, other healthcare disciplines and HRQoL research studies.

This process assisted the evaluation and analysis of the progress of diagnosing and treating patients with CS and CD and the constantly evolving changes being made for the delivery of current endocrinology, neurosurgery, psychology, and radiology services. The mission being to evaluate what impact these changes have made which has led to the change management for staff, and the matrix of public opinions and patients' experiences.

Being aware that potential bias might be present when studying the reading material, particularly with the author's healthcare background and having been diagnosed and treated for CS and CD, she therefore sought to ensure that each source of information was chosen for its relevance and rigour and not based, "on an argument fabricated to support a prior conclusion." [92]

Bias can be defined as any systematic error in the design, conduct, or analysis of a study. In health studies, bias can arise from two different sources; the approach adopted for selecting subjects for a study or the approach adopted for collecting or measuring data from a study. These are, respectively, termed as selection bias and information bias. [93] For example, Althubaiti's (*2016*), paper, discusses the need for researchers to acknowledge the, "sources of bias," and emphasized that this, "is a key element for drawing valid conclusions, bias in health research continues to be a very sensitive issue that can affect the focus and outcome of investigations." [93] Information bias, otherwise known as misclassification, is one of the most common sources of bias that affects the validity of health research.

Fisher's (*1990*), theories remain relevant today for current research methodology.[94] He believes, "experimental observations are only experienced carefully planned in advance and designed to form a secure basis for new

knowledge." [94] This statement underpins the author of this thesis belief, that the investigation and observation of the researchers' findings, must be pivotal during the process of reviewing their work. Reading the experiences of researchers in the field of endocrinology, nurtured a quest for developing this research framework strategy with the ultimate aim of adding to the existing body of knowledge.

In *Chapter 3*, *Pages 94-101,* the research methods are fully explained and how empirical guidance from experienced researchers aided this process.

The author believes that information gathering becomes knowledge and that to use the knowledge and personal experience is a keystone for acquiring evidence and taking actions which would be a pre-requisite for reaching final conclusions for the present study. Critical thinking was indeed a process the author embraced to ensure that her personal feelings and opinions did not affect the interpretation of the acquired knowledge. The intention of this narrative review of literature was therefore to describe and synthesise the available knowledge objectively, thus providing a conclusion from this evidence.

Firstly, however, and foremost was the need to unfold the theoretical evidence on which the research question fulfilled the aim and objectives of this study (*Chapter 1, Section 7.1 and 7.2, Pages 43-44*).

After the initial literature search, the preliminary findings showed a large variation in the volume of data available in each of the subject topics. The author therefore acknowledged the need to limit the data to manageable proportions which required finding a balance between sensitivity and specificity. Setting the parameters for the literature search was therefore necessary by delimiting the boundaries to retrieve relevant studies, whilst ensuring that the search terms would be recognised by the vocabulary of the database, i.e., key words and additional words where appropriate, as previously explained. The search was restricted to articles written in the English language.

*Readers of this thesis should note that a critical review of the literature was an on-going process which was undertaken throughout the entire PhD study.

1.2 Summary of Results from the Literature Searches for Chapters

The initial literature search for the Chapters yielded 890 articles and abstracts related to CS and CD. After screening, 302 full-text articles were reviewed for eligibility. The references are listed for each *Chapter in Pages 209-224* and the *Recommendations and Limitations Chapter 7, Pages 207-208.*

The following sections present a narrative review of the past and current research and synthesises the information retrieved in the literature search.

2.0 Health-Related Quality of Life in patients with Cushing syndrome and disease.

Numerous studies over the past few decades have sought to establish the reasons why CS and CD patients experience a significant change in their QoL post diagnosis. As discussed in *Chapter 1*, hypercortisolism significantly impacts on a patient's health and subsequently on their HRQoL[94] Remission following cure of CS does not eliminate these systemic complications completely. Pivonello et als (*2005*), HRQoL paper for example discusses abdominal obesity, systematic arterial hypertension, impairment of glucose tolerance, dyslipidaemia, and thrombotic diathesis, which increases cardiac risk in CS patients.[95]

2.1 Remission and Recurrence

Pivonello et al continued their HRQoL studies in 2007 and described remission in their paper as a normalisation of cortisol levels and for some patients the occurrence of hypercortisolism requires specific replacement treatment.[96] This recovery therefore can show improvement but can result in complications which can develop post remission and over time persist. These complications, following successful treatment are responsible therefore for the relevant impairments which are experienced by CS/CD patients post remission. Pivonello et al interestingly, describes this as the "Cushing's Cure Syndrome." [96]

***Figure 7* is Pivonello et als exemplary scheme.**[96]

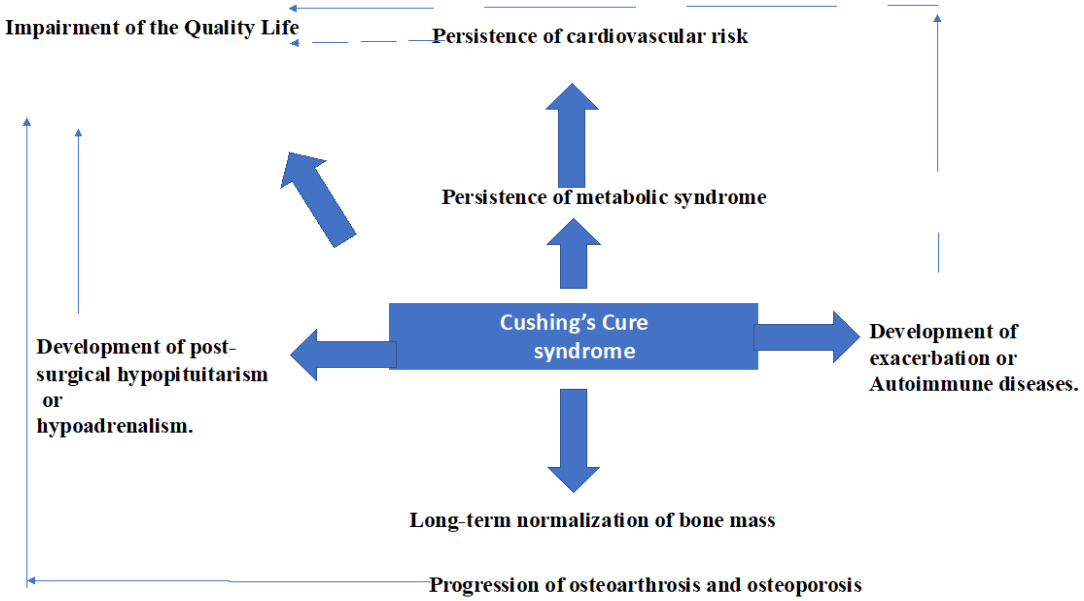


Figure 7. Exemplary scheme of clinical manifestations of the, 'Cushing's cure syndrome.' Pinovello et al, 2007

In 2008, Pivonello et al wrote a follow-up paper which discussed the prognosis of CS and acknowledged that this is mainly affected by the diagnostic challenges presented in each individual patient.[97]

In 2016, Pivonello et al continued to emphasise the need to speed up treatment for CS patients to avoid the detrimental effects of hypertension whose multifactorial pathogenesis contributes to the risk of cardiac failure, myocardial infarction, and stroke. If patients develop life-threatening conditions these can be, "exacerbated by prothrombotic diathesis and hypokalaemia." [98] These authors also highlighted that CS remission can also exacerbate underlying autoimmune disease and recommended, that quicker treatment of excess cortisol could lead to a reduction in these serious complications and reduce the mortality rates, this being reflected in all their publications.[95 96 97 98]

Interestingly, earlier, Tahir and Sheeler's in their 1992 study, reported a recurrence rate of *20%* and previously, Pieters et al in their 1989 study reported that *25%* of their remission patients relapsed after 4.5 years for TSS surgery [99].[100]

However, Rees et al in 2002 showed that in their long-term follow-up study of 54 patients' post-remission after TSS, found that the initial remission rate was *77%,* with the median follow-up of 6 years showing only a *5%* recurrence rate.[101]

The remission and recurrence rates post TSS for CS patients, according to Semple and Carter (*2010*), varies from *64%* to *93%.* This paper reported on the result findings of the success rates of TSS by reviewing many publications. Their findings revealed that the rates of remission differed between short-term to long-term follow-up and that the postoperative remission rates varied between *70%* to *93%.*[102] The differences in remission rate percentages reported in this paper, however, vary between authors. Sonino et al (*2003*), for example, similarly reported that the cumulative percentage of patients remaining in remission after 2 years was *93%* but after 10 years this had decreased to *70%.*[103]

Blevins et al previously in 2009, found that CS patients in initial remission experienced a lower rate for macroadenomas (*67%*), than microadenomas (*91%*), and the recurrence rate was higher for macroadenomas (*35%*), than microadenomas being *12%.* [104.]

Valassi et al conducted a retrospective case series at 3 tertiary care centres to study 620 TSS patients who did not experience post-surgery remission and on biochemical testing did not show a decrease to normal or low cortisol levels without requiring further therapy, (*1982-2007*).[105] The data was divided into 3 groups i.e., delayed control group, normal group, and an immediate control group for analyses. The outcome classification was based upon the postoperative pattern of cortisol testing. Recurrence was found in *13%* of the studies at a median follow-up

of 66 months post TSS, the cumulative rate of recurrence at 4.5 years was found to be significantly higher in the delayed control group vs the immediate control group (*43 vs 14%; P>.02*). The delayed control group being, 35 of the 620 patients who had early elevated or normal UFC levels. These patients had developed a delayed and persistent cortisol decrease after an average of 38 ± 50 postoperative days.[104] The immediate control group contained 437 of the 620 patients with hypercortisolism and/or cortisol normalization throughout their post-surgery follow-up. Over *23%* of the normal control patient group experienced persistent hypercortisolism. The authors concluded that biochemical testing post TSS could be, "misleading," as remission can be delayed in some patients.[104] Similar to other authors, Valassi et al recommended continuous follow-up for CD patients and suggested that this may avoid unnecessary further treatment and recommend optimal timing to determine the requirement for further therapy post-surgery.[105]

Hugeut et al (*2015*), reported that TSS with immediate post-operative remission rates, ranges from *59%* to *94%* and recurrence rates, *3%* to *46%*.[106]

These figures quoted in the various papers, however, are difficult to compare. The limitations being the definition of remission/recurrence criteria, the length of follow-up which varies between centres, and the study population in terms of numbers and severity of the disease, for example micro vs macroadenomas.

An interesting retrospective analysis of 61 patients with CD post TSS, was conducted by Serban et al, and published in 2019.[107] The aim was to analyse the recovery of patients from adrenal insufficiency (*AI)*. The strict criteria included age, presence of AI, follow-up 2 months post-surgery and a minimum follow-up of 3 years after their surgery. The study findings reported that 10 (*16.4%*), patients had a recurrence after 6 years (*median*) post TSS. The patients who had restored adrenal function did so after a median time of 19 months, with a significantly shorter time in the recurrence group (*12.5 vs 25 months, P>.008*). However, all 10 patients who experienced recurrence did recover adrenal function within 22 months. AI recovery rate at 3 years was found to persist in the remission group *(37.3% and 55.8% at 5 years).* In all patients the duration of AI was negatively associated with disease recurrence. These findings suggest that the length of post-surgical AI in patients who experienced recurrence, CD is significantly shorter than patients with persistent remitted CD. The authors suggested that this could provide, "a useful predictor of recurrence," and recommended that surveillance of patients showing a normal pituitary-adrenal axis, with 2 years post-surgery, must be conducted, as they may have a higher risk of recurrence.[107]

2.2 Evaluation of Health-Related Quality of Life in patients with Cushing Syndrome.

Webb et al, in 2008 designed, a disease-specific questionnaire to evaluate HRQoL in patients who were diagnosed with CS. The authors named it the CushingQoL questionnaire [108] This questionnaire is now widely used in Cushing's studies; their rationale for designing a specific questionnaire was that they felt there was no disease-specific questionnaire available for these rare conditions. In their paper they acknowledged that previous researchers had used the Hospital Anxiety and Depression scale (*HADS*), the General Health Questionnaire-28, the World Health Organisation QoL questionnaire (*WHOQOL-BREF*), the SF-36 questionnaire and the Social Adjustment Scale (*SAS1 and SAS2*). However, the authors took the initiative to design their own which they felt reflected, "aspects of greatest concern for the patients," and used a scoring system to measure the QoL.[108] To validate this questionnaire, Webb et al conducted an international observational cross-sectional study with a study population of 125 patients. The aim of the study was to conduct an evaluation of the psychometric properties of the CushingQoL questionnaire, i.e., its *validity and reliability* and its correlation with the clinical parameters relevant to patients with CS. [108]

The range of questions were extensive, and the experience of previous studies had assisted in the compilation of their questions which covered both physical and psychological conditions pre, during and post diagnosis. The main results demonstrated the length of time for diagnosis was between 65 months to 24 years. A third of the participants felt that they were not experiencing good health, *80%* of them developed several medical conditions which included DM, high blood pressure, depression, and osteoporosis. On comparing the CushingQoL score with the patients self-perceived general health status and dimensions of the SF-36, the results demonstrated a significant correlation (*P >.001*, *Pearson correlation coefficient= r.597*). A Linear Aggression analysis test results showed that female patients' health was poorer than the males and patients who had been hospitalised and had experienced hypercortisolism showed a worse score in the CushingQoL questionnaire, experiencing psychological and cognitive changes. Limitations were due to the time frame, which was short for a longitudinal study, which if conducted over a longer period, might have altered the QoL score as patients can improve or deteriorate over time. The authors' conclusion was that the CushingQoL questionnaire was, "feasible, reliable and valid instrument for measuring HRQoL in patients with CS; the short unidimensionality contributes to facilitate its scoring and interpretation." [108] The scores correlated with the clinical parameters, in this short study but longitudinal studies would validate the usefulness of this questionnaire, this being recommended by the authors'.

2.3 Impaired quality of life in patients in long-term remission of Cushing's Syndrome of both Adrenal and Pituitary Origin.

In CS HRQoL research studies, the main aim is to evaluate the long-term effects from being exposed to high levels of cortisol which ultimately reduce HRQoL in patients with CS.[96 108]

Wagenmakers et al, in their 2012 paper, discuss the impaired QoL in patients in long-term remission of CS of both adrenal and pituitary origin and reported on their remaining effects of long-standing hypercortisolism. These authors stated that, "the determinants that cause impaired long-term remission of CS are unknown." [109.] The Wagenmaker et al study differed from the Webb et al study as 7 validated questionnaires, including the CushingQoL questionnaire, were used. The aim of this study was to gain a greater understanding of the disease characteristics which impact on CS patients QoL post-remission.[109] The background to this study was a result of the authors having studied previous QoL studies but found that they had major limitations. These included, small study populations, QoL was not the main purpose of the study, there were no control groups, the questionnaires were unvalidated, missing data regarding the characteristics and no details as to the biochemical follow-up.

The authors also acknowledged that most previous research had only investigated QoL in patients in remission of pituitary CD and these studies did not include patients in remission of adrenal CS.[109]

However, they did mention in their published report, the Tiemensa et al, 2011 study which discussed the negative illness perceptions associated with impaired QoL in patients after long-term remission in CS. Tiemensa et als publication describes how 11 (*25%*) of their patients who had been treated by adrenalectomy, found that after long-term remission of CS, they unfortunately reported more negative illness perceptions when compared with patients with other acute and chronic conditions.[110]

Similar to the Webb et al, and Tiemensa et al studies, the Wagenmakers et al study was a national cross-sectional study with a study population of 123 patients (*106 women, 17 men*), all of whom were in remission. To compare the biometric and socio-economic characteristics of the patients and the control groups, unpaired *t*-tests and c^2 tests were applied to the data. The authors also chose to apply the Kruskal-Wallis rank test of equality-of-populations to compare the results of the 7 questionnaires. This test is a valid method of testing the data which has emerged from the result of several questionnaires where the results do not have a normal distribution. By applying multiple regression analysis (*MRA*), to the data for example, where there are differences in the duration of time in remission, age, sex, significant differences can then be defined as a $P>.05$ value. The results of this study showed that *80%* of the patients were in remission from pituitary CS. A total of *85%* of them had undergone TSS. Bilateral adrenalectomy had been performed on *12%* of the patients and only *3%* had RT of the pituitary

gland. Approximately, *49%* of the patients had experienced persistent or recurrent hypercortisolism and/or developed Nelson's syndrome. The latter is a rare disorder than can occur in CS patients due to the removal of the adrenal glands. An estimated *15%-25%* who undergo adrenalectomy develop Nelson's. Unfortunately, for patients who develop this condition, the pituitary tumour continues to enlarge. In the Wagenmakers er al study *51%* of the patients in remission of adrenal CS and who had unilateral adrenalectomies experienced partial or total hypopituitarism, even though they had been treated for pituitary CS. Blood tests taken during this study showed that the hormonal deficiencies due to any cause, including pituitary, Adrenal insufficiencies following surgery and primary hypothyroidism remained present in *65%* (*n=81*) of all patients, 4 having been treated for adrenal CS. A contrasting result showed that *74%* (*n=74*), patients who were in remission from pituitary CS, the presence of Growth Hormone deficiency (*GHD)*, was present in *53%* of these patients. All 7 questionnaires demonstrated that the QoL in all patient groups was lower compared with the health control groups. The Rand-36 questionnaire however, revealed that there exists a significant difference between the patients and the control group when it came to their educational level, which resulted in a lack of earning potential, as more of the CS patients were unable to work. The CushingQoL questionnaire score showed similar findings to the Rand-36 compared with the overall results of the Webb et al study.[108] The length of remission was found to affect the patients QoL in several dimensions, the longer in remission the better QoL. The female population in this study scored a worse QoL score compared with the men in remission in approximately *60%* of the items of the QoL questionnaires.

This was a complex study in nature due to the number of questionnaires. However, comparing the different elements contained within each of the 7 questionnaires allowed a comparative amalgam of constructive information for future QoL CS studies. The experience of previous QoL studies had focused mainly on patients in remission of pituitary CS, but none had specifically compared patients in long-term remission of both adrenal and pituitary origin. Although Webb et al in their 2008 study compared 18 patients with adrenal CS and 107 with pituitary CS, they did not find any evidence of the difference in the QoL between the two groups. This as previously mentioned, was a short, disease-specific study and may account for their results. Notably, their results concur with the Wagenmaker et al study in that no difference in QoL was found between pituitary vs adrenal patients.[109] This cannot be conclusive however, in terms of equality in these studies populations.

2.4 Incidence and late prognosis of Cushing syndrome.

Lindholm et al in 2001, assessed the late outcome of CS, particularly in CD during a 11-year period in Denmark. The results showed that, "the incidence was 1.2-1.7/million/year (*CD*), 0.6/million/year (*adrenal adenomas*) and 0.2 million/year (*adrenal carcinoma*)." [111]

The Lindholm et al study found that other conditions of CD were rare. Interestingly, Wagenmakers et al, referenced this study in their 2012 publication and commented that although the results from the Lindholm et al study were, "sparse," their findings however, showed that patients with a malignancy increased the mortality ratio and that the excess mortality rate was mainly found in patients in their first year of being diagnosed. [109]

The inherent weakness of the Lindholm et. al study was that there was no direct comparison with age, or a sex-matched control group and lacked details of the patients' clinical characteristics. Wagenmakers et al study had concluded that patients in long-term remission of CS regardless of the presence of hormonal deficiencies, treatment regimens and aetiology, had impaired QoL. The latter authors suggested that there are, "multifactorial," reasons for this and they, "remain unclear," and recommended that additional research into the QoL in patients with long-term remission of CS would, "provide targets for interventions that can improve their QoL." [109] This comprehensive, comparative review of previous studies undoubtedly added to the body of evidence, i.e. that long-term hypercortisolism can cause, irreversible damage to the human body which includes not only cardiovascular disease but also inflammatory conditions which can only be measured over time.

A previous study conducted by Barahona et al, in 2009 for example, investigated abdominal fat in CS patients in long-term remission, as in active hypercortisolaemia with consequent unfavourable adipokine profile. This state leads to what is termed as low-grade inflammation and subsequently increases the chance of cardiovascular disease.[112.] Interestingly, QoL studies up until 2009 had mainly concentrated on the causes of CS and identified the causal effects.

Researchers clearly recognise that the comorbidities due to CS/CD, creates a raft of physical and psychological differences within individual patients. To find an accurate, reliable instrument to measure, HRQoL and to understand the precise mechanism by which Cushing's affects an individual, several researchers during the early 2000s began to concentrate their studies on individual physical and mental changes in the active and non-active phases of these rare diseases.

- *The following sections present papers which concentrate on some of the individual common signs and symptoms, and how they affect the HRQoL in Cushing's patients.*

2.5 Quality of Life in Obesity and Cushing syndrome patients.

As previously mentioned, one of the clinical signs of CS is an increase in abdominal fat. A direct comparison of QoL in obese (*OB)* and CS patients was the subject of a study conducted by Abraham et al in 2013.[113]

Patients presenting with OB can often be diagnosed as genetically induced or over-eating and therefore this can create a medical challenge for physicians with the question of, "whom to screen for CS." [113]

Prior to this study in 2009, Baid et al published a paper which discussed, the specificity of screening tests for CS in overweight patients and the OB population. The findings demonstrated that by screening OB patients for CS showed *16%* false-positive results. [114]

This study was followed up by Tirakioglue et al in 2010 who studied the frequency of CS in patients who were OB but did not present with any other clinical signs of having Cushing's, but often present with psychological conditions due to their weight.[115] By screening CS and OB patients biochemically, they found that there was a significant proportion (*9.34%*) of their patient population (*n=150*) with simple OB who had CS. This led to the recommendation to screen OB patients routinely to establish whether they had CS. This was a unique study and identified that previous studies had not directly compared the HRQoL of OB patients with CS patients.[115]

It is medically accepted that OB and CS patients experience similar medical conditions with subsequent impaired QoL. The determinants found in OB patients for example, is their intolerance for exercise, pain, cardiovascular disease and often the development of DM.

The study conducted by Abraham et al in 2013 consisted of 327 OB patients, showing at least 2 of the typical Cushingoid features were recruited in an outpatient weight-management clinic in the Washington DC non-surgical clinic. The study population age range was 18-75years. Those excluded from the study were patients below159kgs, the maximum weight allowed on the imaging tables, serum creatinine 02mg./dl, pregnancy, and any serious medical conditions affecting GC physiology.[113] A series of biochemical CS tests were performed including the ODST, UFC, the measurement of LNST and their Body Mass index (*BMI*) measurement. The SF-36 questionnaire and locally created symptoms questionnaires were used to evaluate their HRQoL with the aim of assessing any differences between OB and CS patients.

The SF-36 applies 8 sub-scales of HRQoL; questions include, physical fitness and role, pain, general health, vitality, social functioning, emotional state, and psychological health.[113] On completing the SF-36, the participants then completed the locally developed symptoms questionnaires which asked them to explain their signs and symptoms. Both quantitative and qualitative analysis were performed on the data. For assessing the difference between OB and CS patients from the SF-36 subscale, *t*-tests were applied to examine the component scores. The

differences in age, sex, BMI, biochemical test measurements, percentage of symptom count and DM were evaluated as potential covariates and were included in the full model. It should be noted that this was only if they were significantly associated with the physical component summary scores (*PCS*), and the mental component scores (*MCS*) in OB vs CS patients.

The analysis of covariance, (*ANOVA*), was also used to test the differences between OB and CS patients to establish any significant difference in each of these. The study sample was then analysed to assess the between-group differences in the demographic variables which were examined using *t*-tests for continuous variables and c^2 analysis for categorical variables. A high score was a better QoL. The results were clearly reported. OB patients were found to be significantly older, with a higher BMI than CS patients, the latter group however, showed a higher prevalence of DM. This is a surprising result as DM (*Type 2*), is claimed to be the most common form of diabetes and is currently a major worldwide cause of morbidity and mortality. [113] This type of diabetes is most common in patients with CS. Patients with type 1 diabetes also may develop Cushing's. following their diagnosis or if there is difficulty in controlling pre-existing diabetes.[18]

According to Law, almost *75%* of CS patients develop an insulin resistance or glucose intolerance. Prevalence of diabetes can be between *20%* to *47%* of patients, therefore if they do develop diabetes then this has a profound consequence on their therapy options and prognosis. [18]

Biochemical testing for DM poses challenges in CS and CD patients due to the possibility of, "misinterpretation of markers of cortisol hypersecretion."[116] Due to the complexities associated with controlling hypersecretion in active Cushing's the therapeutic treatment must be chosen carefully for each individual patient. The presence of DM, according to Mazziotti et al (*2017*), is said to be significant when referring patients for medical therapy as drugs can have a variable influence on glucose homeostasis, regardless of controlling hypercortisolism.[116]

With reference to the Abraham et al study, 3 of the OB patients only completed 1 of the CS tests and their results were negative. The remaining patients were thought to have a low probability of having CS; 72 of them having at least 1 abnormal screening test result. However, on further testing none of them were diagnosed with CS. The surgical pathology confirmed that out of the 66 CS patients, 49 had CD.[113] Differences were found to be significant in 22 of the 39 individual symptoms between OB and CS groups with all 22 being more common in the CS group. Post adjustment of the symptoms count demonstrated that the OB patients results showed a significantly higher mean PCS score than the CS patients which indicated that they had a better HRQoL (*P>.001*). The MCS score for the OB patients however was lower, showing a poor HRQoL (*P>.0001*). Notably, the Abraham et al study provided relevant information and suggests, that it could be beneficial to Physicians who are seeking to find an

individual patient-specific plan for the management of weight loss for OB patients, and that CS should be considered as the differential diagnosis. This study also showed that CS patients have significantly poorer physical HRQoL when compared with the OB patients. The main strength of this study was the comparison of these 2 groups who presented with similar clinical appearances, but significantly different aetiologies; unlike the Tiryakioglu et al study, whereby no clinical signs were identified in the OB patients. The measurement of the level of emotional tolerance in OB patients was thought to be the key to their treatment regime, according to Abraham et al. A limitation however being that the results demonstrated insufficient data regards to the psychological impairment(s), particularly depression.[113.]

This study was similar to the Valassi et al study in 2011, which found that depression in patients was less documented in previous QoL studies.[117] The latter study used the CushingQoL questionnaire score for depression, this being a negative predictor. However, for example other variables such as a delay in diagnosis, hypertension or DM did not significantly affect the type of measurements applied to the data.[117] Interestingly, the Valassi et al study also showed that significant weight gain in CS patients was found in *80%* of women compared with *62%* of men (*P>.01*).[117]

When a patient presents with a clear diagnosis, Physicians can choose from many protocol references that prescribe the necessary treatment. However, in the case of CS, when the patient presents with a symptom, as is often the case, the Physician needs a resource which is well-organised, straightforward and contains manageable information that will expedite the appropriate differential diagnosis. Patients presenting therefore with OB could be an indicator, which may lead to the diagnosis of CS. The Abraham et al study, recommended the QoL questionnaires should be of interest to Physicians and used to assist in the screening of both CS and OB patients.[113]

2.6 Disease-Specific Quality of Life evaluation and its determinants in Cushing syndrome: What we have learnt?

Since Webb et al designed the CushingQoL questionnaire in 2008, HRQoL studies have steadily increased. [108]

A prime example is the Badia et al study published in 2014. This study was in the form of a review whose purpose was to summarise the characteristics of 7 QoL studies which had used 2 disease-specific questionnaires, the CushingQoL and the Tuebingen CD-25 questionnaire.[118]

The characteristics of these 7 studies were *a)* the determinants of the disease-specific HRQoL in patients with CS and *b)* the impact of treatment for CS on disease-specific HRQoL. Interestingly, the results found that the 25 items within the Tuebingen CD-25 questionnaire, provided a study of technical literature and enabled patients via

interviews in their study, to rate their Neurosurgeons, Endocrinologists, and a Neuropsychologist.[118] The subdomains of, depression, sexual anxiety environment, eating behaviours, bodily restrictions and cognitive response option were measured on a 5-point Likert scale having a 10-100 scoring scale. A higher score representing a lower HRQoL. Their overall findings revealed that studying the clinical factors showed, for example, a possible association between UFC levels and disease specific HRQoL. Currently, according to the ERCUSYN, the diagnostic criteria that suggest CS, is that the UFC levels are greater than the normal range when testing the assay serum cortisol measurements.[117]

As discussed for example, in *Chapter 1*, *Section 1.8.1, Page 24e)*, a weakness of the UFC test is that the daily variations both methodologically and physiologically can influence the results.[6]

Caloa et al previously in 2012 conducted a 12-month, 3 phase study, which was reported in the Badia et al review, of pasireotide in CD.[119] Pasireotide is said, "to be a potential therapy, has a unique broad somatostatin-receptor binding profile, with high binding affinity for somatostatin-receptor subtype 5."[119] Caloa et al described the participants in their study as having a measurable pituitary tumour on MRI baseline. After 12 months of treatment, 12 patients showed that, "the mean percentage change in tumour volume was *9.1%* (*95% CI, -46.3 to 28.0*), in the 600-mg group *-43.8%* (*95% CI, -68.4 to -19.2*), in the 900mg group." [118] The UFC levels showed that out of 72 patients (*46%*), with the uncontrolled hypercortisolism during the first 2 months of medication, hypercortisolism remained uncontrolled and in 66 of those patients, 6 months and continued in 64 patients after 1 year. The adverse effects of pasireotide varied and was reported as being similar to the other somatostatin analogues, examples being gastrointestinal symptoms and gallstones.[119] More serious effects included hyperglycaemia and DM which was found in *31%* and *7%* respectively. A total of 118 patients had a hyperglycaemia-related adverse effect and *6%* resulted in them discontinuing their pasireotide treatment. The study concluded that, hypercortisolism was reduced in patients with CD and that pasireotide treatment could be a potential agent as a pituitary-specific treatment for CD.[119] Although Badia et al admitted that the Caloa study was another example of a small population study (*n=162*), it proved to be a useful form of testing. The recommendation from this study was the need to conduct regular blood tests and monitor UFC levels.[119]

Extrapolating the findings from each of the 7 studies, Badia et al concluded that active AIs, recent diagnoses (*last 2 years*), depression, active hypopituitarism were factors which affected the CS patients resulting in a lower QoL score. Interestingly however, that there was at that time no current evidence which showed lower QoL based on the impact of aetiology or signs and symptoms associated with CS.[118] A limitation in each of the 7 studies was the small population and previous studies had found that this was not always the case. The ERCUSYN data

demonstrated for example that TSS improved QoL significantly, particularly 12 months post-surgery.[117] This concurred with Santos et al (*2012*), whose study investigated the psychometric performance of the CushingQoL questionnaire in conditions described as, "real clinical practice," and found that post TSS patients had an improved QoL.[120] Badia et al found that 3 studies included repeat measurements with the CushingQoL questionnaire which examined the impact of different interventions on patient- specific HRQoL.[118] However, when this paper was published no longitudinal studies had been performed using the Tuebingen CD-25 questionnaire. One main finding demonstrated however, that there was clinical evidence which suggested that elevated UFC levels are associated with poor QoL resulting in physical and psychological changes. Notably, this has been highlighted within other CS QoL studies [117] [120] [6]

The forementioned authors recommended that further studies are required to acquire more robust evidence into the signs, symptoms, and aetiology of disease- specific HRQoL questionnaires to establish more significant conclusions. In terms of clinical factors there was certainly evidence for an association between UFC levels and disease- specific HRQol however, the strength of this association varied between studies. Until 2012, the HRQoL in CS patients were shown to have subsequent consequences even those patients in total remission. Generic health questionnaires, (*GHQ-28, GHQ-12*), 12 items did not address specific problems related to CS and these problems can be, "sensitive to clinical change." [122]

Arguably, the CushingQoL questionnaire, however, is specifically designed for CS patients and this is demonstrated in the success of the Calao[119] Santos[120] and Valassi[117]studies. Santos et al for example suggested, "the CushingQoL questionnaire shows good test-retest reliability and sensitivity to change in clinical practice conditions." [120]

The Tuebingen CD-25 questionnaire is also a feasible instrument to assess HRQoL in CD in a clinical and investigative setting and provides normative data for all age groups and genders. [122]

Both questionnaires demonstrate feasibility, reliability and are valid instruments for both physiology and psychometric measures of the HRQoL in CS studies.

2.7 From First symptoms to Final diagnosis of Cushing disease.

A study in 2015 conducted by Kreitschmann-Andermahr et al focused on how long it can take to diagnose CD using the experiences of 176 patients.[123] In their publication, the authors discussed the prevalence of CD as quoted in the Excabe et al, 1994[124], study and how Lindholm et al in 2001 had studied the mortality and morbidity and the late prognosis of CD.[111] Kreitschmann-Andermahr et al therefore concentrated their study on the length

of time it takes in diagnosing CS and the legacy which this condition leaves post diagnosis. This retrospective study was conducted in 3 large German Neurosurgical University referral centres, over a period of 15 months, (*2013-2014*).[123] This research compared 2 groups of patients using a self-reported questionnaire to establish how informed medical doctors are regards CD and patients who had eventually had a confirmed diagnosis. What emerged from this paper suggests that there is a common theme which flows throughout CS and CD surveys, i.e., that there exists a lack of awareness regarding the signs and symptoms of CD, particularly from GPs and patients. This study included a rural population where the findings showed a significant difference between the patients in this group whereby some patients consulted up to 8 Physicians before a diagnosis of CD ($P>.05$). It took an average of 0.9 to 2 years, before they sought medical advice and *69.9%* of the 179 patients were eventually diagnosed by an Endocrinologist. Many patients described their, "general discomfort," as a symptom, which could be suggested, nurtures a sense of confusion when Physicians, particularly GPs make their clinical decisions as to where and whom they should be referred. Patients reported, "isolated symptoms," and this prompted their GPs to send them to a particular medical specialist and occasionally it was they who made the CD diagnosis.[123] Unfortunately, there are limitations to this study which included, Physician bias particularly with regards to women who present with physical changes, example weight gain, mood swings and on occasions they reported that they were, "dismissed or belittled." [123] The authors recommended that further research was required to study the difference between the, "self-and-proxy observed symptoms which did not result in different diagnostic latencies between males and females."[123] The overall results with regards to the median of 2 years from the on-set of CD symptoms were found to match those of the ERCUSYN database.[32]

***In summary*:** The Kreitschmann-Andermahr et al study sought to obtain structured information on why there is a delay in diagnosing patients with CD and highlighted the broad variation of the on-set of diagnosis and the urgency of a quicker diagnosis for CD.[123]

Interestingly, Bolland et al previously in 2011, also conducted a retrospective study but it differed in that it was a, "symptom-onset study," conducted by Physicians based on chart records and demonstrated that more than half of the patients were diagnosed within 1 year.[125]

2.8. Neuropsychiatric Disorders in Cushing syndrome.

In 1952, Starr wrote a paper regarding personality changes, depression and mental disturbances which were reported as being often observed in CS patients, albeit only, "causal references," were made.[126] In this paper, he

referred to Maclay and Stokes and Schlesinger and Horwitz who, "were among the first to suggest specificity in the relationship between psychosis and endocrine dysfunction," in CS.[127 128]

In 1938, Maclay and Stokes acknowledged that, "both the endocrine state and mental illness may be expressions of an underlying cause, either of pathological genetic disposition or an environmental noxa." [127] Schlesinger and Horiwitz in 1940 had theorized that, "mental symptoms may be a direct manifestation of the underlying specific endocrinopathy, although the mechanism of their production remains obscure." [128.] These theories have evolved over the years, and formed the basis of current clinical practice whereby patients presenting with depressive psychoses should be tested for CS. However, this is sadly not always practiced and therefore a CS diagnosis is missed.

It is now well documented that excess GCs can lead to both, "structural and functional changes in the central nervous system (*CNS*), which are mainly based on brain atrophy," according to Sonio et al (*2010*). [129] These changes unfortunately generate neuropsychiatric disorders. Forget et al in 2015 for example, studied the long-term cognitive effects of GC excess in CS.[130] Pivonello et al also in 2015, conducted a brief mini review of the common neuropsychiatric and neurocognitive disorders observed in patients with endogenous CS during active disease and their development after disease remission.[131] This mini review explored the disorders that impacted on patients QoL with the aim of highlighting the important role of long-term follow-up in terms of diagnostic assessment and treatment success. The review also focused on the careful periodical investigation of psychiatric and neurocognitive disorders in the management of CS. The authors found that major depression (*60%*), in CS patients is thought to be induced by stress and anxiety.[131]

As previously mentioned, regardless of etiology there are several psychiatric and psychological issues which in all probability are due to an active hypercortisolaemic state. Patients in long-term remission find that their cognitive function improves but in some it can deteriorate thus effecting their QoL and their on-going treatment regimes. Unfortunately, there is evidence that even post treatment irreversible physiological impairment can lead to psychiatric and psychological problems and may result in a reduced QoL. Depressive symptoms in some cases can have subtle-to-severe cognitive decrements. [131 108 09 98]

Neuropsychiatric conditions were originally observed by Harvey Cushing when he noticed that his patients experienced mood swings, irritability, insomnia, and reduced libido (*Chapter 1, Section 1.2, Page 13*). The Pinovello et al review therefore served to remind Health Professionals including the endocrinology team, the importance of recognizing not only physical signs but any psychological changes early when diagnosing CS and CD.[131] The high prevalence of neurocognitive and psychiatric disorders can, according to these authors cause life-

threatening impairments in *50%-60%* of the CS population. Hypomania, mental disturbances, anxiety attacks, depression and suicidal ideation are reported in some of these patients and by many CS researchers who have studied the HRQoL in CS and CD patients.[98 102 103 106 108 113 119 1250 127 128 130 131]

Moraitis et al published a paper in 2017 which acknowledged the increase in CS research studies and focused on the effects of glucocorticoid receptors (*GR*), and their involvement with the "physiological changes with metabolic syndrome and certain psychiatric illnesses." [132] This paper discusses the impact on the pathophysiology and development of CS and CD and are presented in a review of how it can be affected by, "GR mutations on metabolic syndrome and psychotic depression."[132] The review discusses how genetic polymorphism of the GCs, and the large array of GR related cofactors can directly or indirectly affect the pathophysiology and evolution of these conditions.[132] The GR polymorphisms can therefore increase the sensitivity or resistance to GCs and this can directly affect patients psychological state, in a range of different, complex ways, as previously discussed.

2.9 Using subscales when scoring the Cushing Quality of Life questionnaire.

CS and CD present Physicians with a set of questions which could be suggested as having several competing epistemologies and ontologies. Answering questions in HRQoL studies are dependent on the habituation nature of an individual which can often create unreliable data. How to numerically evaluate HRQoL is complex as the questionnaire instrument must reflect all aspects of the disease processes and how it affects QoL. Prior to commencing their 2016 study into the use of subscales when scoring HRQoL for patients experiencing long-term remission, Tiemensma et al studied different scoring systems and compared their performance in determining which method of scoring was optimal for the Webb et al, CushingQoL questionnaire.[133.]

Prior to their study and similar to the Webb et al study in 2008 [108] and other QoL studies, researchers in the early 2000s, had reviewed other HRQoL studies, including the WHO QoL study which recommended in 1995 that QoL studies, "should be "treated as a multi-dimensional construct containing aspects of QoL referring to physical, psychological and social issues." [134] Webb et al for example, had recommended, using the global score when assessing QoL over a period of time.[108.] However, the disadvantage of using the WHO global score is that all constructs are combined in the global scores, therefore this makes it impossible to extract the information which reflects the different dimensions of QoL. [134]

The Tiemensma et al, 2015 study accessed the CSRF database of Cushing's members. A total of 341 members (*female=305, male=25, unknown=11*), aged 18 plus years accessed an on-line version of the Webb et al CushingQoL questionnaire which as previous mentioned, contains 12 questions which ask the participants their

clinical characteristics. These questions were analysed using a 5-point Likert scale. A demographic survey was also used containing 20 questions (*Part 2*), which asked for details of their physical and psychological changes and if CS had an impact on their social activities. The scoring system ranged from 10-100, a lower scale indicating a poor QoL. The data was split into 2 separate data files so that they could fully examine the possible scoring options for the CushingQoL questionnaire.[133]

An exploratory factor analysis (*EFA*) was used for the first file to determine scale dimensionality. This is applied when there is hardly ever, or no knowledge known about the dimension of a measure.[133]

This form of analysis is used when a large, complex set of variable data is gathered. A confirmatory factor analysis (*CFA*) was also used, "to test the hypothesis about generalizability of scale dimension as well as to compare alternative scoring options." [133] The results of the EFA analysis revealed that 2 subscales (*psychosocial issues and physical disabilities*) were optimal when compared to the global CushingQoL score.[133] The third subscale (*global)*, made it, impossible to compare the physical problems from psychosocial ones. [133] The published results showed good examples of the potential benefits of using 2-subscale options of the CushingQoL questionnaire in comparison with the global scores. The model-fit was assessed to establish the degree to which each scoring method for the questionnaire reflected the CSRF members responses to the questions. A notable example of these results was the CFA coefficient related to the question of pain where the single global coefficient was 0.717, and subscale 1-psychosocial issues was 0.716 showing therefore a significant difference in the result (*P>.05*). A comparative fit index Table demonstrated that the 2-scale option was found to significantly improve the detail of information in comparison to the total score model for the CushingQoL questionnaire when compared with the two-factor model. The benefit for clinicians who wish to use this model of questionnaire was displayed in a sample of 9 scores which was also shown in a Table which demonstrated that by using the 2-scales in conjunction with the global score helped to evaluate the QoL. The 2-scale CushingQoL showed, "good psychometric properties," particularly for the evaluation of physical and psychological conditions.[133] Using their 2011 study experiences, this was the first CushingQoL survey conducted to explore different scoring options for the Webb et al 2008 CushingQoL questionnaire.[108 133]

The Tiemensa et al cross-sectional study's aim was to explore illness perceptions as potential modifiable psychological factors, in relation to QoL in patients in long-term remission of CS. The methodology adopted to evaluate these was to use the Illness Perception Questionnaire (*IPQ)*-Revised, and the QoL was measured using the physical symptom checklist, the EuroQoL-5D (*EQ-5D*), and the Webb CushingQoL questionnaire. This was the first study of its kind in patients with endocrine diseases and the authors admit that the study was complex in

nature. Applying a range of analytical tools which measured all dimensions of the Cushing's physical and psychological comorbidities, the authors concluded, "that there is a strong correlation between illness perception and decreased QoL."[133] Comparing all items within each of the questionnaires, the CushingQoL questionnaire results for the physical, psychological, and social issues was found to be a valuable method of highlighting the divergent factors which influence the negative illness perceptions in CS patients.[133] Tiemensa et al recommended that doctors and researchers who wished, to differentiate between physical and psychosocial issues, the 2-sub-scale scoring solution should be applied.[133.]

2.10 Patients Perception on Clinical Outcomes and Quality of Life after a diagnosis of Cushing's syndrome.

Previous QoL studies have enabled endocrine research centres to provide evidence in relation to the QoL during the different phases of patients' illnesses with those, diagnosed with CS and/or CD. In 2016, as mentioned in *Chapter 1, Section 1.6*, *Page 19,* a QoL study was conducted by Papoian et al in collaboration with the CSRF, with the aim of providing patients' perceptions of their QoL and their clinical outcomes post treatment.[21]

The study population consisted of 240 females, 27 males and 2 patients with non-sex specification, all being members of the CSRF.[8] This study claims to be the largest study of this nature. The CushingQoL questionnaire was used, and the resultant data analysed for, "associations between QoL and demographic treatment and disease factors."[21] The main results extrapolated from their publication was that patients who were referred to an Endocrinologist with regular consultations, did not show any significant improvement in their QoL (*P>.05*), but those who were regularly seen by a CS specialist did (*P>.37*). Interestingly, no definition was given as to the difference between a CS specialist and Endocrinologist. The median time for remission was 4 years (*mean of 6± 6years*) with a range of 1-40years. However, when 195 patients who were in, or had been in remission were compared with 69 patients who had never been in remission, these 2 cohorts showed a highly significant difference in their QoL scores (*P>.001*). Treatment for CS varied and depended on the causal effects and the severity. CD patients (*185)* with hypopituitarism or hormone deficiency, experienced no significant difference in their QoL score (*P>.05*) as did those who were in remission but on long-term steroid medication (*P>.05*). Patients who had undergone TSS once or more showed no difference in their reported QoL score (*P>.05*). Similar results for adrenalectomies were reported (*P>.05*). Notably, the published results lacked detail in some of the information and no question was asked as to whether their participants had received chemotherapy.[21]

According to Rappana et al in 2010 an estimated *9%-37%* macroadenomas were diagnosed in patients with CD and patients with ACTH-secreting microadenomas after TSS have a *65%-90%* remission rate comparable with

GH-secreting microadenomas (*>85%*).[135] The GH-secreting adenomas, however, are found mostly to be macroadenomas and require either RT or chemotherapy. Notably, the biological effects of RT in the long-term have a 10-year cumulative risk of *2%* and a 20-year risk of *2.4%* for secondary malignancies.[135] Examples of these malignancies are sarcomas, meningiomas and gliomas.

In 2010, Bush et al studied the use of TMZ, which is a chemical treatment for malignant pituitary adenomas, as previously mentioned in *Chapter 1*, *Section 4.0*, *Pages 39-40*.[83] The recommendation from this study was patients with complications post-surgery and RT should be considered for chemotherapy, and TMZ but other chemical inhibitors and, "targeted therapies," should be explored, "urgently." [83]

With reference to the Papoain cross-sectional study there were limitations, the major one being the inability to longitudinally compare the QoL of individual patients. [21] This meant that the QoL could not be measured over specific time periods and had similar limitation which were found in the Webb et al, 2008 study.[108] Important to note that the QoL scores were associated with the standard deviations, (*SDs*), that ranged from 16-24 points and was therefore consistent with the CushingQoL instrument in the Webb et al study. An interesting recommendation that emerged from the Papoain. et al study was that healthcare providers must be, "educated," on how to identify the signs and symptoms and this they suggested would lead to earlier diagnosis and treatment of CS.[21] Notably, this recommendation is highlighted in several publications of this nature, particularly from 2015 onwards.

The common theme of addressing and controlling excess production of cortisol is the key to improving QoL which will undoubtedly assist in the management and care of CS patients. This is conducive for example, with the Neiman et al 2015 paper which emphasised the need to treat the cause of CS with for example antihypertensives and suggested that this would help to reduce comorbidities.[6] Neiman et. al, acknowledged that there was a dearth of publications of this nature, particularly cross-sectional studies in relation to patients QoL following treatment regimens for CS. However, Arnaldi et al previously in 2003 conducted 2 large cross-sectional CS QoL studies and found that the long-term effects of high cortisol levels produced residual impairments of physical and social functioning thus creating a poorer QoL, despite being treated. The consequences being significant in terms of their social and working lives.[137]

2.11 The Development and Validations of the Leiden Bother and Needs Questionnaire for patients with pituitary disease.

A paper published in 2016 written by Andela et al reported the results of their qualitative study of patients with pituitary disease. The questionnaire which was named the Leiden Bother Needs Questionnaire (*LBNQ-Pituitary*).[138] The authors acknowledged that until their study period, no suitable questionnaire had been developed to assess *a)* whether pituitary patients were, "bothered," by the consequences of their illness and *b)* their needs for support. A total of 49 questions were designed for the LBNQ-Pituitary questionnaire and completed by 337 patients. Six other, validated QoL questionnaires, including the Webb et al Cushing|QoL questionnaire were also used in their study. Construct validity using the EFA was conducted for 26 of the questions in parallel with reliability testing of the subscales (*Cronbach's alphas*). Concurrent validity being assessed by calculating the Spearman's correlation between the LBNQ-Pituitary and the other measures. A total of 5 subscales were produced (*EFA*), from the 26 questions. Examples of these questions were, mood swings, negative illness perceptions such as fear of adenoma recurrence and anxiety over sexual function and physical and cognitive impairments. This study could be said to be ground-breaking at this time, as it captured a more personalised approach to explore the underlying emotions and physical symptoms that are experienced in CS remission. Prior to this study, very few studies had encapsulated the need to support these patients and to ensure that their QoL could be improved. The author concluded that, "Exploration of the patient's perspective is crucial in identifying potential unmet needs and aspects for improvement in QoL." [138]

2.12 Do coping strategies have a strong impact on quality of life, depression, and embitterment in patients with Cushing's disease?

The recognition that psychological conditions created by hypercortisolism prompted a study in 2016 conducted by Siegel et al, which focused on CS patients' psychosocial impairments and their coping strategies following surgical interventions at 3 large tertiary centres.[139] This study was another example of using multiple questionnaires to establish the emotional reactions to a negative life event. The average years post-surgery of the study population was 6.8 ± 6.66 years. The self-assessment inventories were the HADS QoL, SF-36, Tuebingen CD-25, coping style, the Freiburg questionnaire on coping illness (*FKV-LIS*), and the Bern Embitterment Inventory (*BEI*). Regression analysis was applied to the data, so that the predictors of psychosocial impairment could be identified. The results showed that *21.8%* of the patients were suffering from anxiety, *31.1%* from depression and *18.7%,* had an above-average feeling of embitterment. [139]

The researchers acknowledged that patients' reactions to cope with stressful situations vary and therefore some adapt their lifestyles, for example, take up sports and hobbies. Maladaptive coping styles (*FKV-LIS*) confirmed that their results were accurate and strong predictors of psychosocial impairments, age, sex, and hydrocortisone intake however, the researchers failed to explain the reasons for the variance in these measurements. The Siegel et al study concluded that psychological training of positive coping styles could be helpful for patients with difficulty in coping with stress and anxiety caused by CD.[139]

This study of patients' psychological changes caused by pituitary origin is similar to the Nelson et al 2013 study, which evaluated the psychometric aspects of the CushingQoL questionnaire.[140] The aim of the latter study was to evaluate the reliability, validity, the ability to detect change and if there was a minimal important difference, during and after treatment. The latter study was also similar to the Calao et al 2012 study, as previously discussed where their study population (*n=162*) participated in a clinical trial having been treated with pasireotide (*600mg or 900 mg*) for their pituitary adenomas. The Calao et al results showed that this type of therapy significantly reduced the tumour volume during their treatment and this in turn led to improvements in their physical and psychological impairments.[119]

In the Siegel study, the patients completed the CushingQoL questionnaire 4 times over the clinical trial year. This enabled a robust method of testing the reliability of internal consistency (*coefficient alphas*), and test re-test (*intra-class correlation coefficients*), for the patients who were experiencing hypercortisolism (*3/6months*).[139]

A weakness however was identified with applying this type of methodology. That is being the reliability of the patients' answers which can vary over time, i.e., recall bias and this can influence the research outcomes. Notably, in this study, physical measurements were also taken to measure any changes in Cushingoid features, BMI, and cortisol levels. The results of the CushingQoL scores in the Siegel et al study showed a moderate correlation for patients with depressive symptoms, the mean scores being significantly higher indicating a better QoL when compared with patients who were severely depressed.[139]

In summary*:* The findings of the Siegel et al study is comparable with other non-pituitary patient illnesses and quoted multiple sclerosis and lower back pain as comparative examples of physical medical conditions. The results being that QoL is partially based on how patients deal with their illness (*both physical and psychological*) and should be encouraged to adopt copying strategies as part of their overall treatment.[139]

CS patients often feel panic, fear, anger, jealousy, sadness and frustration, and experience mood changes and social avoidance. However, they rarely share these psychological issues with their Physicians, according to Andela et al (*2016*).[138] Lack of time during the visit, embarrassment over their own feelings and thoughts, and concerns

about bothering their healthcare provider with, "minor," problems are some reasons why certain psychosocial needs and coping strategies remain unaddressed.[141]

2.13 Hippocampal volume, cognitive functions, depression, anxiety, and quality of life in patients with Cushing's Syndrome.

Frimodt-Mellor et al published in 2019, a paper which reported the results of their systematic review.[142] The main objectives were to assess hippocampal volume, cognitive functioning, depression, anxiety, and QoL in CS patients. Two reviewers took part and the review consisted of case-controlled studies which compared CS patients with healthy control groups and studies to assess CS patients prior to and post-surgery. Meta-analysis of 18 studies were performed using a random effect model. When compared with the healthy group, the CS patients' right hippocampal volume was significantly reduced to a Standard Mean Distance (*SMD*) of 0.68, (*95% CI; -1.12 to -0.24; P>.002, I^2=0%*). Interestingly, it was also found that the CS patients had a reduced HRQoL experiencing depressive symptoms, impaired cognitive functioning despite their surgery having favourable outcomes .[142] This was interestingly defined as no clinical presence of anxiety post-surgery which was similar to the Cole et al (*2011*), study, which performed a random-effects meta-analysis to establish whether hippocampal atrophy exists from disease onset.[143] The Cole et al study included MRI imaging of the hippocampal in patients with first episode major depression disorder (*MDD*), and compared them with matched healthy controls. Results showed that the hippocampal volume was significantly reduced in patients with first episode depression. This result was consistent with a neurodevelopmental model of depression thus recommending that hippocampal structure is a potential diagnostic neuro-biomarker for depression.[143]

In 2017, Santos et al published a paper reporting their meta-analysis study, the aim being to analyse amygdala volume in patients with CS and its relationship with anxiety, depression, and hormone levels.[144] The conclusion to this study was that CS patients in the active phase of disease have a smaller right amygdala volume when compared to their study's control group and the left amygdala volumes are associated with mood state in both of their patient groups.[144] Santos et al previously in 2014, had studied cerebellar cortex volume in CS patients and found that it is significantly smaller in the active phase of CS when compared with their control group.[145] The association with visual memory and QoL was also found to be significantly changed in the CS patients, particularly in the older patients and those with pronounced higher triglyceride levels.[144] Similar therefore also to Cole and the Santos studies, their studies concur with the Frimodt-Mellor 2019 findings in that structural changes in the brain of CS patients cause neuropsychiatric conditions.[143] [144] [145]

2.14 Elevated resting-state connectivity in the medial temporal lobe and the prefrontal cortex among patients with Cushing's Syndrome in remission.

Further evidence of these conditions was highlighted by Stomby et al (*2019*), who conducted a cross-sectional case-control study into the long-term cognitive deficits and affective symptoms, (*examples, anxiety, depression*), in 19 CS female patients in remission for a median time of 7 years.[146] The mean age of the patients was 45years, the study population was chosen from the database of 3 university clinics. All 19 patients plus age-matched female controls underwent fMRI at a single radiology centre, the main outcome being the "measure of functional connectivity at rest." [146] The reported results identified that the medial temporal lobe and prefrontal cortex networks exhibited elevated connectivity among the Cushing's patients when compared with the control group. The authors concluded that their study had revealed that in resting-state functional connectivity within GCR-rich regions, particularly the medial temporal lobe and medial prefrontal cortex, was increased in the CS patients. Stomby et al suggested that, "these differences in connectivity may provide a neural basis for the cognitive deficits and affective symptoms," which are often experienced by patients with CS in remission.[146]

In contrast to this study, Wang et al (*2019*), explored the anatomical distance-dependent functional connectivity patterns in patients with active phase CD. The authors aim, was to evaluate the associations between hypercortisol exposure and regional normalized function connectivity strengths using fMRI. The fMRI results of the database of 32 CD patients and 32 healthy controls were compared for normalized functional connectivity strength (*nFCs*), for each voxel in the brain and further divided them into long-range and short-range nFCSs. To investigate between-group differences in these nFCSs metrics general linear models were used and the correlations between the nFCSs and the clinical variables were calculated. [147.] On comparing the fMRI, the CD patients results from the imaging studies showed that the discrepant functional connectivity patterns indicated hypercortisolism, this being associated with distance-dependent disruption of resting-state functional connectivity in patients with active CD. The results confirming that the patients right parahippocampal cortex and serum cortisol levels at 08.00am were shown to remain significant after taking the anatomic distance into consideration. The authors concluded that this study provided a method of identifying the impact of hypercortisolism and the pathophysiologic mechanism of CD and suggested that this may eventually facilitate advances in CD intervention.[147]

Until recently there has been limited evidence available regarding the effects of GC excess on brain metabolism. According to Law, (*2017*), "primate studies using exogenous GCs show that the hippocampal changes are present within 1 year of GC exposure," but there remains little data which suggests exposure to GCs causes brain atrophy.[18] However, interestingly a previous limited study in 2012 conducted by Langenecker er al using fMRI,

indicated alterations in brain activity in adolescents with active CD. The areas of the brain affected were regions used for perception, processing, and regulation of emotions.[148]

The exponential use of fMRI studies over the past few years have confirmed those of the limited previous studies and provided concrete evidence in measuring brain atrophy. Cerebral atrophy in CD patients, using fMRI has been shown to be, "at least partially reversible." [148] Following normalization of cortisol levels, the brain volume is said to increase but does not return to normal state.

A more recent study in 2019, conducted by Brzozowska et al reported a case of a CS female patient who had experienced severe cognitive defect and functional decline over a 10-year period.[149] Following treatment for her CS and successful cure she experienced a significant recovery in her neurocognitive function. This was reflected in the structural brain changes reported in her MRI scans. The patient had presented with the long-term effects of cortisol exposure on her brain function but Brzozowska et al, suggested that an improvement over time post treatment could significantly improve the recovery of neurocognitive impairment in patients with endogenous CS.[149] The authors acknowledged that patients may not regain their premorbid level of function and they may experience a reduced QoL due to persistent cognitive impairment(s). Transient hypercortisolism remains a challenge to fully understand but this study underlines the importance of early diagnosis and treatment.[149]

Several studies prior to and most recently therefore agree with Frimodt-Mellor in that patient following biochemical remission find that there is a marked increase in hippocampal volume *(>10%),* which correlates with the UFC excretion levels. A decrease in cortisol levels, correlates with an improvement in memory in relationship to an increase in hippocampal volume thus indicating that the effects from prolonged cortisol exposure on the hippocampal volume are reversible following treatment.[142] [149]

The psychological and cognitive impairments which reduce the QoL in CS and CD patients as reported in numerous QoL studies, may improve with biochemical control of hypercortisolism, but sadly may persist. The minor to major changes within the brain (*anatomic, cerebral, and hippocampal atrophy*), and in the site-specific cerebral metabolism, may explain the signs and symptoms associated with Cushing's. The school of thought from this must be that further research may be important in defining the structural and clinical manifestations which emerge from hypercortisolism combined with interventions that may improve these findings. fMRI has a significant part to play in future investigations.

*In Chapter 1, Sections 2,3.4**,** Pages 26-40, the imaging modalities used in the diagnosis and treatment of CS and CD are discussed and includes the physical principles, safety guidelines and biological hazards. The following*

section of this narrative review presents a wide range of literature which focuses on the use of the main imaging modalities for the diagnosis of CS and CD.

3.0 *Pituitary Imaging.*

3.1 MRI Pituitary Studies

Many researchers over the past decade have highly recommended and validated the use of MRI for pituitary studies. The main purpose of these studies was to develop MRI-specific sequences, reduced contrast medium dose and develop high-field technology with the aim of better localization of ACTH-secreting microadenomas. Kasaliwal et al, (*2013*), for example studied MRI volume interpolated 3D-echo sequence and the results of their study claimed that it was better than dynamic contrast spin echo sequence for MRI detection of ACTH-secreting pituitary microadenomas. [150]

Stobo et al previously published a paper in 2011 which discussed the initial experience of using 3T MRI for small functioning pituitary tumours.[151] The results of their study concluded that the stronger magnet increased the likelihood of detecting GH and ACTH-secreting pituitary microadenomas. The recommendations were to use 3TMRI if available, and in cases where 1.5T MRI was negative or equivocal.[151]

Neiman, and Gharib in 2016, then recommended the use of structural imaging for the diagnosis of tumours suggesting functional imaging with somatostatin analogues.[152] The authors also however, recommended taking a cautious approach as they suggested that even the best protocols do not always identify more than *80%* of pituitary tumours.[152]

Vitale et al, in 2017 (*Chapter 1, Section 2.7, Page 32-33*), agreed that MRI is the 'gold standard,' imaging modality for the detection of pituitary tumours.[69] However, they established that between *30%-60%* of ACTH-secreting pituitary microadenomas often go unreported due to their location, enhancing characteristics and their size. These figures are however notably lower when compared with some of the previous publications. Vitale et al subsequently recommended that by adjusting the MRI protocols for these microadenomas leads to improving the quality of images for the diagnosis of pituitary diseases.[69] This paper presented an overview of MRI for pituitary disease related to CD and according to the authors, provides a protocol to be followed when an ACTH-secreting pituitary adenoma is suspected. [69]

Grober et al (*2018*), also previously mentioned in *Chapter 1, Section 2.7*, *Page 32-33,* evaluated the use of 3D volumetric interpolated breath-hold examination (*VIBE*), a spoiled-gradient echo 3D T1 SGE characterized by superior soft tissue contrast, and this improved image resolution. [68] The authors compared images produced with

DMRI and CMRI for the detection of microadenomas in patients diagnosed with CD and their study suggested that SGE shows higher sensitivity for detecting and localizing pituitary microadenomas. However, the authors concluded that it is rare that an adenoma is detected using DMRI alone and recommended that the standard protocol should include SGE for CS patients.[68]

A retrospective study conducted in 2018 by Lang et al, compared T2-gradient echo sequence, constructive interference in steady state (*CISS)*, with contrast-enhanced (*CE*), T1-weighted sequence and VIBE, for the diagnosis of pituitary adenomas in 12 patients who had undergone TSS for CD. Two Neuroradiologists took part in the study and had no access to the patients clinical and surgical findings prior to independently reporting the resultant images.[153] The results showed that the average sensitivity for the detection of pituitary adenomas was not significantly different between CE-VIBE sequence (*63%*), and CISS sequence, this being *54%.* Interestingly, the PPV was *75%* (*Observer A*), and the CE-VIBE sequence was *100%* (*Observer B*), and *64%* (*Observer A*) and *100%* (*Observer B*) with the CISS sequence.[153] The observers found that 2 of the patients' pituitary adenomas were clearly identified with the CISS sequence but on the CE-VIBE produced images, the adenomas were more difficult to detect. However, in 2 of the other patients their adenomas were clearly identified on the CE-VIBE. The authors concluded that CISS sequence to T1-weighted MRI protocols improved the detection of pituitary adenomas and that the CISS sequence could be a useful addition to T1-weighted MRI protocols for pituitary imaging, making an alternative option for patients with gadolinium contraindications." [153]

Several authors including Chatain et al (*2017*), have sought to establish the reasons why MRI-negative pituitary microadenomas present a challenge for accurate pre-surgical localization in CD.[154] The importance of recognising the harmful effects caused by surgical inaccuracies are paramount in pre-surgical planning to reduce the risks. An example being paraneoplastic syndrome of ectopic ACTH production from NETs, such as small-cell lung carcinoma.[155] It is widely accepted that accurate location improves remission rates and decreased comorbidities. 3D-GRE MRI identifies *50%-80%* of microadenomas.

3.1.1 MRI and Transsphenoidal Surgery

In *Chapter 1*, *Section 3.2.1, Pages 37-39,* the importance of MRI in pituitary studies was discussed and how a subset of patients with CD who have no evidence of an adenoma, undergo other radiological investigations for example, BIPSS prior to their surgery to confirm a CD diagnosis.

Congxin et al, studied the outcomes of TSS in CD of 125 patients with negative pituitary MRI scans between 2000 and 2019 by accessing their medical records at the Peking Union Medical College Hospital. Interestingly,

they found that the remission rate was *73.3%* after TSS and *11.8%* of patients experienced recurrence.[156] These rates were found to be the same between patients with negative MRI findings compared with those with positive MRI findings, recommending that TSS remains the first-line treatment for CD patients, even if their MRI results are negative.

A recent novel research study into an innovative method of analysing a large and complex data set was used to evaluate the use of machine learning (*ML*), to identify predictors of early postsurgical and long-term outcomes of TSS. This study involved 151 patients, with a gross-tumour removal (*GTR*) and surgery was successful in 137 of them. The medical records which the researchers Zoli et al, at the time of their study (*2020*), showed that 116 patients were still in remission post-surgery and 21 their CD was controlled with complimentary therapy.[157] The tumour volume i.e., size and invasiveness, combined with the biopsy results of the ACTH-secreting cells were the main 3 predictors i.e., endpoints of interest. The ML algorithms were applied to train and internally validate robust models for all 3 endpoints., thus achieving accurate outcomes predictions in the CD cases. The authors highlighted that this analytical method could improve patient care, including counselling but warned that accuracy in clinical interpretation of the results remains important before adopting this method in clinical practice.[157]

3.2 Cavernous Sinus Sampling in Cushing disease.

Cavernous sinus invasion (*CSI*), in patients with CD, "apparently affects the probability of complete resection, biochemical cure and the need for adjuvant therapy." [158] Mastorakos et al (*2018*), discuss in their paper, the difficulties encountered in the prediction of CSI based on CD patients MRI results, and had noted that they have in the past been inconsistent and therefore unreliable.[158] The Knosp classification is the most widely used radiographic predictor of CSI.[158] This classification relates to the work undertaken by Knosp et al (*1993*), who constructed a grading system for predicting CSI caused by pituitary microadenomas.[160] However, this method is limited in its ability to accurately predict CSI and the probability of gross-total resection for microadenomas or Knosp grade 0-2 macroadenomas.[159]

Mastorakos et al observed that on viewing the coronal MRI images of patients with pituitary lesions, the presence of a triangular shape of adenomas adjacent to the cavernous sinus which are often associated with CSI. [158] The aim of their study being to determine the correlation of this radiographic find ("sail sign" {SS}), with CSI." [158]

This retrospective review consisted of 115 patients with a *<20mm* pituitary lesion and a biochemical diagnosis of CD post TSS (*2007-2017*). Patients were chosen using an inclusion/exclusion criterion. CSIs which were inoperative were prospectively evaluated at the time of surgery by 1 Neurosurgeon and the MRI results were

reported retrospectively by a Neurosurgical resident and a Neuroradiologist, blinded to the intraoperative results. The results of 23 patients (*20%*), reported a positive SS, *91%* of them had CSI compared to *10%* without a SS (*P<.001*). The SS predictor of CSI showed a sensitivity result of 0.7 and specificity of 0.98, which showed a PPV of 0.91 and a NPV of 0.9. Interestingly, *30%* of the positive SS patients did not experience immediate TSS remission, in comparison with *3.3%* without a SS (*P< .001*). The conclusion to this study was that if a positive SS is present in Cushing's adenomas adjacent to the CSI this provides, "strong PPV, specificity, and positive likelihood ratio for the prediction of CSI." [158] According to Mastorakos et al, this is proving to be a useful method of preoperative planning.[158]

As previously noted, within several similar papers, this information gives the neurosurgery team an aid to predict the likelihood of long-term biochemical remission and the need for adjuvant radiosurgery.

3.3 Pituitary Microadenomas

Chatain et al, (*2017*), as previously mentioned, in their studies reported that postcontrast fluid-attenuated inversion-recovery (*FLAIR*), scans may be useful for the detection of MRI-negative pituitary microadenomas and recommended that post contrast FLAIR sequences should be included to complement 3D-GRE when planning TSS for patients with CD.[154]

According to Fukhara et al (*2019*), MRI only detects *36%-63%* of pituitary adenomas in patients with CD, which is less than quoted in some of the other previous publications of this nature. 3T MRI is now said to provide higher resolution than ≥1.5T MRI. [161] Fukhara et als' research aim therefore, was to investigate the problems and reasons for the outcomes associated with the use of 3T MRI in identifying pituitary tumours and conducted a study of 115 patients who had initially been diagnosed with CD. Prior to their surgery 31 patients with macroadenomas (*27%*), and 54 (*47%*), patients with microadenomas had pituitary 3T MRI scans which were subsequently reported. Interestingly, pituitary adenomas in 30 cases (*25%*), were unidentified, the smallest tumour diameter amenable to a definitive diagnosis was 2mm. SGE was therefore found to be superior for diagnosing microadenomas.[161] Notably, this agrees with. the Grober et al, 2018 study as previously mentioned.[68] The Fukhara et al results revealed that the introduction of 3TMRI showed a sensitivity of *80%* and specificity of *100%* for identification of pituitary adenomas. The authors also however, found that there was a marked decrease (*72%*), in sensitivity when macroadenomas were excluded. 3TMRI in some cases of microadenomas therefore remained undetectable. This was thought to be due to tumour size, location, and intensity. The authors recommended that improvement in sensitivity can be achieved by monitoring the tumours which develop outside the gland.[160]

3.4 The Use of 7Tesla MRI in Pituitary Imaging.

The introduction of 7T MRI for pituitary adenomas is creating a growing interest from both researchers and clinicians in pituitary diseases. Several studies have highlighted the benefits of using this type of ultra-high field scanner. 7T MRI is proving, according to Rotte et al, (*2016*), to be a powerful tool in research and in the clinical diagnosis of patients, as previously mentioned in *Chapter 1, Section 2.7. Pages 33.*[61] The high increase in signal-to noise ratio and higher spatial resolution identifies minor changes in the anatomical and pathological structures, this being vital in establishing neurological changes in the brain structures and in identifying pituitary adenomas, pre-and post-surgery.[61] The authors, however, admit that there are some technical issues which need to be resolved. One of the major problems is the lack of access to 7T MRI scanners. The reason being that they are mainly only available in large neuroradiology and research centres and are extremely expensive.

An interesting article by Law et al, (*2019*), discusses the value of pituitary gland 7T MRI in CD and its relationship to IPSS. This article discusses a case report related to the findings for a patient with CD post TSS.[162] Histopathology specimens identified a Crook's hyaline change with ACTH positive cells suggestive of an adenoma using 7T MRI. The conclusion was that for diagnosing microadenomas, 7T MRI, "may pre-empt IPSS." [162] This suggests that 7T MRI may help in cases where standard and dynamic contrast 1.5T and 3T MRI shows negative CD and could also be a safer imaging examination for the patient than BIPSS. This form of testing is still currently debatable and continues to be compared with BIPSS.

Andreggen et al (*2019*), discussed in their paper the lack of data as to BIPSS symmetry being a more successful predictor of adenoma side in patients with ACTH-dependent CS. Interestingly, the findings from their study showed that during BIPSS, asymmetric inferior petrosal sinus drainage was frequently shown and that the asymmetric venous outflow did not influence the remission rate for CS. [163]

The purpose of Bekci et als (*2019*), retrospective study of 31 patients compared the efficiency of IPSS for the diagnosis of ACTH-dependent CD to that of MRI imaging.[164.] Thirty of their patients had successful IPSS. The sensitivity, specificity, PPV, NPV and IPSS accuracy of differentiating between central and ectopic CS prior to CRH stimulation was: *93.3%, 100%, 100%, 33.3%* and *93%* respectively.

Comparing these results with their MRI reports, Bekci et al reported that the IPSS method had the highest efficiency in differentiating central CD from ectopic CD.[164.] The limitation to this study could be suggested that no indication was given as to the type of MRI scanner used i.e., Tesla strength.

Cristante et al (*2019*), conducted a retrospective study to question why TSS should be a Neurosurgeons' choice for treating CS based on normal or inconclusive MRI results. The objective of their study was to evaluate the

performances of the MRI evolutionary changes over time and its performances following surgery in 195 CD patients with a typical image of adenoma vs inconclusive or normal MRI. [165] During the period 1992-2018, the CD patients had been treated initially using a translabial microscope and then a transnasal endoscopic approach. The patients whose MRI scans had been reported as inconclusive or normal were referred for BIPSS. The researchers found that MRI identified microadenomas in 89 patients, 18 macroadenomas, 44 inconclusive MRI scans and 44 normal scans. The findings revealed that over a period (*1992-1996*), the proportion of inconclusive/normal MRI decreased from *60%* to *27%* (*2012-2018*). On analysing the results of the 4 MRI groups, pre-operatory adenoma visualization rate was only slightly lower when MRI was normal (*95%;100%;86%;79%; P>.012*), and postoperative remission rates were not significantly different (*85%;94%;73;75%; P>.11*).[165.] Interestingly the MRI scanners used from 1993 to 2019 for this study ranged from 0.5T to 3T. These statistics showed that over the study period, MRI scanning had improved due to magnet strength, and this had improved specificity and sensitivity when diagnosing microadenomas. The recommendation from this study, was that patients reported with MRI inconclusive or normal scans and a pituitary ACTH gradient at BIPSS should still be, "directed to an expert Neurosurgeon for TSS rather than medically treated." [165]

A quantitative assessment study of secondary white matter injury in the visual pathway by pituitary adenomas was undertaken by Rutland et al in 2019 using 7T MRI.[166] The prime objective was to study the microstructural damage by pituitary adenomas. This was conducted by performing probabilistic tractography of the optic tracts and radiations using 7T diffusion-weighted MRI (*DWI*).[166] The results of 18 patients with pituitary adenomas were compared with 16 healthy volunteers and their MRI findings were correlated with their neuro-ophthalmological results to assess the utility of ultra-high field MRI for objective evaluation of the damage to the anterior and posterior visual pathways in the 34 patients. Probabilistic tractography is used, "to obtain a connectivity index along a white matter pathway, that reflects fibre organization and is sensitive to pathological abnormalities contributing to disability." [166] The main results of the Rutland et al study, was that optic chiasm compression was found in *66.7%* of the pituitary adenoma patients and visual defects in *61.1%* of them compared with the healthy volunteers. The probabilistic tractography results were compared with their 7T MRI results. The diffusion indices were calculated along the projections and correlated with tumour volumes and compared with the results from their neuro-ophthalmological examinations.[166] The results significantly demonstrated that imaging-based quantification of secondary neural damage from adenomas are strongly correlated with the neuro-ophthalmological findings. The conclusion being that the diffusion characteristics of ultra-high-field DWI in all

probability enables the preoperative characterization of visual pathway damage with chiasmatic compression and the authors concluded it may be a way of predictive value for vision recoverability.[166]

3.5. Imaging in the pre-planning of treatment for pituitary adenomas.

Brain imaging in pituitary disease is highly dependent on the production of high-quality images of the sella and parasellar region of the brain. Prior to surgery, RT and/or medical therapy CS patients require MRI investigation. Bashari et al (*2019*), recommend that T1 and T2 weighted sequences provides information for pre-surgical planning, RT and/or medical therapy and long-term follow-up.[167]

Previous publications quoted in this thesis discussed that in some cases, the standard clinical MR sequences can be indeterminate and therefore additional information is required to aid the choice of therapy for pituitary adenomas. Christante et al as previously mentioned, emphasized the need for Neurosurgeons to fully explore the radiological MRI findings prior to surgery and this should be part of the overall clinical investigations, while Bashari.et al's article, reviewed the current recommendations for imaging of pituitary adenomas and explored the potential value MR sequences and/or CT can offer for pre-planning RT treatments. [165] [167] The latter article also described the use of functional/molecular imaging and how this form of imaging if recommended, may define the treatment, which is particularly useful as some patients may not be deemed suitable for surgery or RT.[167]

Modern technological advancements in brain imaging have enabled Radiologists, Neurosurgeons, and Physicians to identify pituitary incidentalomas more efficiently, and as suggested by Boguszewski et al (*2019*), this is due to the advanced technologies and easier access to scanning facitilies.[168] Pituitary incidentalomas are often diagnosed for non-pituitary disease. The anatomical variations, pituitary hyperplasia and technical artefacts can play a part in image reporting and create challenges for those who report the images. Incidental adenomas are those that fulfil the radiological criteria for a pituitary adenoma in asymptomatic patients in the presence of subclinical diseases.[168] The majority of pituitary lesions are <10mm in size and are normally benign. Macroincidentalomas ($\geq$ *10mm*) are a more serious finding and require intervention as there is a likelihood of hormonal abnormalities and malignancy. The Boguszeewski et al publication discusses the diagnosis and therapeutic management of pituitary adenomas and how the aetiological history of pituitary incidentalomas is relatively unknown. However, according to these authors, the wealth of radiological evidence indicates the differences between micro and macroadenomas and in turn aids diagnosis and subsequent treatments.[168]

3.6 High Resolution multispectral imaging in identifying remission in Cushing syndrome- A novel approach.

A 2018 USA conference presentation discussed the successful use of a handheld high-resolution multispectral imaging device. This was presented as a novel method of studying CS patients, particularly those in remission. Khare et al (*2018*), presented this form of imaging to delegates at the Smart Biomedical and Physiological Sensor Technology conference and highlighted that, "point-of-care technologies have become increasingly important in diagnostic applications." [169]

The use of wireless technology has enabled a method of easy storage and analysis of data at the point of clinical delivery. Using iPads for example have enabled Radiologists and medical doctors to view medical images in remote areas of the hospital. Hand-held near-infrared imaging spectroscopy (*NIR*), systems are now available which can determine blood volume fraction and water content in skin. Khare et al during this conference discussed how the hand-held NIR device enabled the research team during their study, to successfully identify remission of disease after treatment of patients with CD.

The design of this device provides 8 NIR filters with a wavelength range of 700nm to 980nm which means it can provide a flexibility of detecting multiple chromophores in the skin such as oxy and deoxyhaemoglobin, melanin as well as water, thus providing high resolution and information about spatial variations. The latter being an important factor for diagnosing blood volume and water content in the skin. This is indeed an exciting development as it could provide a rapid method of diagnosing remission, reduce MRI waiting lists and be a cost-effective imaging tool.

3.7 Optical Coherence Tomography and Octreotide Scintigraphy in Cushing disease.

In *Chapter 1, Section 2.10*, *Pages 33-34,* the use of OCT was discussed and its role in assessing the thickness of the retinal nerve fibre layer in the optic nerve due to compression caused by a pituitary adenoma. As quoted in *Chapter 1*, the results of the Abalem et al, 2016 study found that *18.8%* of patients had macular changes and it was suggested that this was secondary to choroidal thickening.[73]

Two percent of all pituitary adenomas are due to the thyroid-stimulating hormone (*TSH*) and are usually benign. According to Fukuhara et al (*2015*), "these tumours provoke central hyperthyroidism through releasing inappropriate TSH secretion."[170] Patients experience hyperthyroidism symptoms which are usually mild and can be induced by anxiety.

Okuyucu et al (*2016*), conducted a study of a female patient who had a TSH pituitary adenoma with Grave's disease during and post pregnancy using Indium-111 Octreotide scintigraphy (*OS*), in parallel with investigating

the patient's symptoms of hyperthyroidism. Graves' disease is an immune system disorder that results in producing excess thyroid hormones. The authors findings suggested, that those type of pituitary lesions should be confirmed using functional imaging modalities and OS imaging was in this case useful in illuminating such masses in the pituitary gland, particularly on patients with Graves' disease.[171]

The use and choice of multi-modality imaging modalities for the pituitary gland are proving to be exponential in their growth and significant for the early detection of pituitary adenomas. By increasing visualization for example using fMRI, PET/CT images enables the changes to brain structures created by pituitary diseases, to be fully assessed pre- and post TSS.

According to most researchers however, radiological imaging should be performed alongside biochemical testing which may include BIPSS prior to any surgical or therapeutic intervention.

4.0 Adrenal Imaging

The management of patients with CS is said to be medically challenging and this is clear on reviewing the literature and by interviewing Health Professionals and endocrine experts during the present study. Patients with bilateral adrenal masses and ACTH-independent CS are particularly challenging to diagnose and treat, as it creates a lifelong risk of adrenal crisis. In *Chapter 1, Section 1.8.1d)*, *Page 24,* AVS was discussed and its methodology in facilitating the lateralization of guiding adrenalectomy surgery. Rossi et al in *2015*, interestingly reported that there is no set AVS technique or standardized protocol.[39]

However, Acharya et al in 2018, investigated the utility of AVS using a protocol which had been previously used in a study by Young et al (*2007*).[172] [173] The Young et al study's aim was to establish how to manage patients who had been diagnosed with bilateral adrenal masses and ACTH-dependent CS.[173] In comparison, the Acharya's et al retrospective review unfortunately had a small study population (*n= 9*). However, they did find that AVS was useful in excluding unilateral adenomas as the source of ACTH-CS when studying bilateral adrenal masses in those 9 patients. AVS was successful in 8 of these patients indicating that they had bilateral cortisol hypersecretion. This form of testing, however, requires further data to advocate its use as a being a robust method for the management of ACTH-CS patients with bilateral adrenal masses.[172]

Bansal et al (*2019*), conducted a retrospective study using the CT data of 80 patients who had at least 1 intact adrenal gland, and had an abdominal or adrenal CT scan prior to surgery. Patients age range was 17-81 years. The radiology reports reviewed patients with non-adrenal causes of CS to identify adrenal lesions (*incidence and characteristics*).[174] According to these authors, between *1%-5%* of the general population who have undergone

CT abdominal investigations have been reported as having adrenal masses. Older patients are found to have a higher incidence of adrenal masses which are mostly benign. Notably, the authors in their published findings, mentioned that few adrenal CS patients present with masses and therefore there is little CD or EAS data.[174]
The results of the patients CT scans showed that the prevalence of adrenal nodules in CD and the EAS patients was higher than in the general population. The authors however, admitted that further studies are necessary using a larger population which would enable them to study trends which could be beneficial in the differential diagnosis of ACTH-dependent CS.[174] A study conducted by Bansal et al in 2019, found that nodules >1.3cm confirmed a definitive diagnosis of CS however, in EAS, simple hyperplasia was more likely.[174] Notably, in the older patients, an increase in nodularity could suggest that pre-existing nodules may not be an effect caused by CS.

4.1 Adrenal Incidentalomas

Adrenal incidentalomas are defined as adrenal masses measuring 10mm or more in diameter. Cunha et al (*2019*), conducted an observational retrospective study of the diagnostic imaging findings of 223 patients who were reported as having adrenal incidentalomas. This study period spanned 10 years (*2008-2018*).[175] The radiology reporting of these adrenal incidentalomas showed that they were reported in CT abdominal scans in *75.5%* of the patients, chest CT in *6.7%,* abdominal US in *6.3%, 2.2%* kidney US scans and *1.3%* in lumbar spine CT patients. This was a comprehensive study which identified that most adrenal incidentalomas are benign and non-secretory and malignancy is found to be rare. Notably, abdominal CT was shown to identify the highest number of adrenal incidentalomas (*75.5%*), the image patterns were recognized by, "adrenal size and radiological phenotype." [175] The authors recommended that adrenal incidentalomas should be closely investigated by the endocrinology team to generate a fuller increase in understanding of this prevalent condition.
Previously Sharma et al (*2015*), also reported the increase in referral for CT and MRI imaging for other medical conditions, which led to an increase in adrenal incidental adenomas, this being similar to brain imaging, as previously discussed. The prevalence of these, increases from *0.2%* to *7%* with age, "subclinical," or, "subtle," CS, and has been reported in *5%-10%* of these patients in a study population where CS is more likely to be common.[176] The Sharma et al publication focusses on the epidemiology and the developments related to the clinical management of CS and the modern methods of diagnosing and treating this condition. Previous authors have tended to focus on the underlying causes of CS and often refer to exogenous GCs, which is said to be the most common cause in childhood, adolescence and in adults. Endogenous CS being similar in children as in adults. Some differences however, in infancy are commonly associated with McCune-Albright Syndrome. This

endocrine syndrome affects the skin, skeletal system and several hormone-producing tissues and is more prevalent in girls than boys. Adrenocortical tumours are often diagnosed in children with this condition less than 5-7 years of age. Seven years or over, CD is the most common cause ectopic, EAS is rare.[176] Notably, the Sharma et al article gives a clear account of the statistical prevalence of CS and the human development processes and epidemiological changes which can ultimately affect the human circulatory system resulting in CS. The article contained an informative Table (1) as shown below, which enables the reader to appreciate the statistical prevalence of the varying signs and symptoms of CS, although it should be noted that some of the figures quoted are from older sources (*1961-2007*).

Table 1 ***Sharma et al, 2015[176]. Frequency Table of the Clinical Features of Cushing's Syndrome***

Signs/symptoms	Prevalence (%)
General	
Obesity or weight gain	70-90%
Rounded Face (moon face).	81-90%
Supraclavicular/dorsocervical fat pads (buffalo hump).	50%
Skin	
Hirsutism/alopecia	75%
Facial plethora	70-90%
Violaceous striae	44-50%
Acne	20-35%
Easy bruising	35-65%
Gonads	
Menstrual irregularity	70-80%
Decreased libido	24-80%
Neuropsychiatric	70-85%
Emotional lability/depression Psychosis/mania Cognitive dysfunction/short-term memory loss	
Musculoskeletal	Unknown

- *Please note that the musculo-skeletal prevalence figures unfortunately during this study were unknown.*

Although *Table1* lacked some current figures, it clearly identifies that there are frequency variables related to the clinical presentation of patients. These can be influenced by sex, age, and the long-term effects of CS. The *Table* limitations included a failure to show the prevalence of DM which is currently around *20-47%* of patients and *75%* of patients with CS have insulin or glucose intolerance.

Figure 1 displays the typical Cushingoid features, Page 26.

4.2 Neuropsychiatric disorders induced by Cushing syndrome.

In 2018, Sharma et al continued their studies concentrating on the neuropsychiatric disorders induced by CS. The authors subsequently produced a paper in which they reported their study on psychiatric disorders, body image disturbances, and self-esteem in patients with CD.[177]

Sharma et al in their previous research had identified that between *75%-85%* CS patients experienced neuropsychiatric problems (*Table 1, Page 81)*.[176]

Sharma et al therefore focused their studies on the prevalence of psychiatric disorders in CD patients. The methodology of this study was in the form of a structured clinical review using the Diagnostic and Statistical Manual of Mental Disorders *(*DSM-IV*), BDI, the Rosenberg Self-Esteem Scale and Body Image Concern Inventory (*BICI*), in a study population consisting of 35 patients with clinically confirmed CD.[177]

> **Please note that the DSM-IV refers to a clinically significant behavioural or psychological syndrome or pattern that occurs in an individual.*

A breakdown of their results showed that, *65%* of patients had psychopathology, *21%* major depressive disorder and *28%* moderate depression on the BDI. The authors also found that *50%* of patients had body image disturbances and *60%* low esteem. Depression was found to have a negative correlation with self-esteem, and a positive correlation with body image disturbances. The conclusion to this study being that the prevalence of psychopathology in CD patients is high and according to the authors, "may go undetected." [177] The authors' recommendations underlined the need for the endocrinology team to ensure that patients who reported body image disturbances and self-esteem should be offered the appropriate support.[177.]

Reviewing other publications of this nature which have concentrated on the neuropsychiatric disorders, they all suggest that major depression is found in up to *70%* of CS patients', and *50%-62%* experience mood disorders. [103 108 109 113 120 126 127 128 131 141]

CS has, according to Santos et al, "been related to higher psychopathology." [178] The Santos et al 2016 study of 36 CS patients in remission were compared with 36 matched control groups i.e., age, sex and education and the origin of their CS (*Adrenal or Pituitary*). The results showed that the CS patients showed more psychopathology in all items of the Symptom Checklist-90R *(SCL-90R*), questionnaire variables. The SCL-90R questionnaire is a short self-report psychometric instrument designed to evaluate a broad range of psychological problems and symptoms of psychopathology and is widely used in clinical practice and research. The items of the SCL-90R questionnaire are, somatization, obsessive-compulsive, interpersonal sensitivity, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism, global severity index, positive symptom distress index and positive symptom total, in

comparison with the control groups (*P<.01*).[178] The psychopathology showed no correlation with memory performance, QoL or symptoms. The CS participants in the Santos study also showed poor long-term memory when compared with the control group (*P< .024*), and "higher severity of symptoms," (*P<.01*).[178] In this study, blood tests were taken on both groups. The hostility subscale (*Ho*), of the SCL-90R was positively correlated to the blood cortisol level in the CS patients (*r=.45, P<.005*). The Ho scale was devised by Cook & Medley in 1954 and is a 50-item scale which measures a variety of health-related variables, which includes, insulin resistance, alcohol consumptions and waist-to-hip ratio.[178] [179]

According to Miller et al (*1996*), these Ho scales are predictive of coronary artery disease, which subsequently causes mortality, even if the other health risk factors are controlled. [180] Studies since 1954 have questioned the reliability of using the Ho scale. Currently however, the relationship between the autonomic nervous system, (*ANS*), Ho scale and generalized anxiety disorder (*GAD*), in the long-term treatment outcome, has still been rarely studied, according to Tsung-Hua Lu et al (*2019*).[181] In the their study, the authors' explored whether ANS index and Ho scale at baseline are predictors of long-term outcome in GAD.[181] This was a small study involving only 9 patients with GAD and the findings were that the aggressive response subscale of the Ho scale was significantly negatively correlated with the Hamilton Anxiety Rating Scale (*HARS-HAM-A*) change ratio in both the short and long term, while the mean heart range change, (*MHRR*), which was taken at baseline (*Week 0*) of this study, was significantly positively correlated with these change ratios.[181]

The HARS scale was designed by Clark et al (*1994*), to generally measure anxiety and they found in their studies, that it was a reliable and a valid method of measuring and assessing global anxiety in the adult population.[182] This type of scale was originally designed by Max Hamilton in 1960 to measure the different elements for patients suffering from depression.[183.] Notably, the Tsung-Hua Lu et al results suggest that MHRR and aggressive response subscale (*Ho*) could be used as a method of predicting long-term outcome in GAD.[181]

5.0 The use of PET/CT in Adrenal Imaging

Another retrospective study of 28 patients conducted by Wannachalee et al, (*Nov. 2016-Oct. 2018*), from 3 referral centres and published in 2019 discussed the radiological difficulties of diagnosing EAS caused by CS.[184] The authors acknowledged the need to use a Food and Drug Administration (*FDA*)-approved high- resolution form of imaging but found little evidence that the clinical utility of [^{68}GA]-DOTATATE PET/CT ([^{68}Ga]-DOTA-(Tyr^{3})-octreotide), was being used to diagnose EAS. The objectives of their study were, *a)* determine the efficacy for EAS localization and *b)* the clinical benefit of using this form of diagnostic imaging.[184] The Wannachalee et al

study population was small, but the results did show that [68Ga]-DOTATATE is a sensitive imaging modality for the detection of primary and metastatic EAS, and often identifies occult tumours after conventional imaging, and this impacts therefore on the management and care in most patients.[184]

Varalamov et al conducted a 2019 systematic literature review of patients who had undergone [^{68}Ga] DOTATE, DOTATOC and DOTANOC PET/CT [68Ga-SSTR] PET/CT and conventional imaging found that greater sensitivity in reporting EAS source is limited due to the case reports and few small retrospective studies.[185] Thirty articles were reviewed of [68Ga-SSTR] PET/CT scans in 69 EAS patients and found that the sensitivity was *64%*, biochemical testing confirming that there were 67 lesions (*76.1% -sensitivity*). No false-positive results were found in both adrenal glands.[185] Varalmov et al found that their EAS imaging reviews showed that the sensitivity of [^{68}Ga-SSTR] PET/CT is similar to conventional CT (*81.8%*), in biochemical-proven case studies and is *100%* in covert-cases. These authors acknowledged that the limitations in previous studies were that they were small, and no occult cases were found. However, Wannachalee et al did report that the PET/CT modality can identify occult cases and their findings were published 1 month prior to the Varalmov et al publication. The latter to date is the largest study of its kind.[185]

According to Neiman et al (*2018*), there are 4 challenges which make it complicated when evaluating CS.[186] The increase globally of DM, obesity, increasing use of exogenous GCs all cause CS phenotype. Identifying no pathologic hypercortisolism not associated with CS creates an even greater medical challenge as the symptoms maybe typical of CS, but these symptoms may be extremely mild or cyclic or in renal failure, incidental adrenal masses, and pregnancy. Nieman et al therefore advises that careful choice of biochemical testing is essential for accuracy of diagnosis, while considering the confounding conditions and testing may have to be repeated if the results are ambiguous.[185]

6.0 Epidemiology and the Development in the Management of Cushing syndrome and disease.

6.1 Autoimmune Disease in patients with Cushing syndrome.

Petramala et al published a paper in 2018, which discussed the autoimmune diseases in patients with CS after resolution of hypercortisolism.[187] This retrospective study was in the form of a literature review and case report, (*2001-2017*), of 147 CS patients (*female=109, male= 38, mean age = 52years*). The findings revealed that after surgery and follow-up tests, (*6,12,24 months*), 9 patients presented with clinical signs and symptoms of autoimmune diseases which, they previously had not experienced. The female patients had a higher ratio (*8:1*)

compared to the males in the development of autoimmune diseases. These conditions ranged from RA (1), systemic lupus erythematosus (1), thyroid disease (4), psoriasis, myasthenia gravis (1) and giant cell arteritis (1). The group of patients who developed the autoimmune diseases on testing, post-surgery and medical therapy, all experienced higher levels of endogen overproduction of cortisol, higher levels of total cholesterol, low density lipoprotein (*LDL*), and triglycerides. These results confirmed that all patients had, "metabolic effects of hypercortisolism, especially on the lipid pattern." [187]

6.2 Cardiovascular Risk and other complex medical conditions as a result of Cushing syndrome.

The cardiovascular risk from persistent high levels of cortisol is well documented. In a study conducted by Calao et al in 2000, the authors described how heart disease can develop post cure.[188] Petramala et al who cited the Calao et al publication in their 2018 article, agreed with their study findings, that although CS patients can be successfully cured, there is an increased prevalence of heart disease, thyroid autoimmunity as in Hashimoto's disease and autoimmune thyroiditis and abnormalities associated with immune function.[187] [188]

Interestingly, there are very few literature sources which discuss some of the extremely rare medical consequences induced by CS. One example of a rare conditions is sarcoidosis.

Diernaes et al (*2016*), described a case study of a 46year old, Caucasian woman who presented with the classic Cushingoid appearances and symptoms of hypercortisolism.[189] Following surgery, she developed multiple erythematous painful nodules which developed on her arms. Erythema nodosum was diagnosed and a suspicion of underlying sarcoidosis, which was confirmed in her chest x-rays and elevated plasma interleukin (IL)-2 receptor. Following GC replacements, the lesions spontaneously disappeared which led to the authors recommending Physicians to be mindful when a CS patient is successfully treated that they may have a flare-up or emergence of corticosteroid-response disease. [189]

6.3 Ectopic secretion of ACTH.

The ectopic secretion of ACTH is said, according to Serra et al (*2013*) to be, "an infrequent cause of CS."[190] Ectopic CS accounts for only *10%* of CS etiologies. Serra et als paper describes an unusual case of a 68year old woman with Cushingoid features, serious hypokalaemia and on being referred for an MRI cranial scan, a 46mm mass on her right paranasal sinuses was identified. The immunohistochemical results confirmed the diagnosis of ectopic ACTH production. Resection of the tumour normalised the ACTH and cortisol secretion. Laboratory analysis showed the tumour to be a paraganglioma, most of which do not present as being hormonally active. A

nasal paraganglioma is a rare neuroendocrine neoplasm and the symptoms usually present themselves as headaches, hypertension, excessive sweating, and anxiety.[190]

Previously, according to Pasini et al in 2009, there is mutation of the succinate dehydrogenase SDH enzyme, in patients who present with a paraganglioma and therefore are required to have genetic testing, as discussed in the Serra et al case study.[191] The first line of this testing being for SDHC which is the encode subunits of mitochondrial complex 11, these being responsible for the majority of familial paragangliomas and also for a significant fraction of non-familial tumours, according to Baysal et al 2002.[192]

6.4 "The Adrenal Gland: Central Relay in Health and Disease-Current Challenges: A Perspectives 2018"- Cushing's Disease.

The clinical burden of CD is exacerbated by the comorbidities which persist post-cure. To assess the current challenges, including the diagnostic testing and treatments, a systematic literature review was undertaken by Gunter et al in 2019.[193] By accessing the databases of PubMed and Medline over a period of 5 years the results revealed an increase in mortality despite disease remission. The reviewers found that the increase for example in cases of OB and metabolic syndrome required new diagnostic testing to differentiate between conditions and was discussed earlier in this *Chapter 2*, *Section 2.5, Pages 55-57.*

The evidence that UFC, LNST and the DEXA test are valid diagnostic tools, is confirmed by a plethora of publications which report successful outcomes. TSS remains the treatment of choice for CD patients who experience variable remission and reoccurrences. The most common prescribed medical therapies being adrenal-targeted drugs (*metyrapone, etomidate, mitotane and ketoconazole*), and the pituitary-targeted therapy being, pasireotide, cabergoline and retinoic acid.[193]

6.5 Cushing syndrome in Pregnancy.

Cushing Syndrome during pregnancy is rare. Affinati et al, in 2019 prior to their study, conducted a literature search which identified less than 200 cases of CS during pregnancy. [194] Affinati et als study was in the form of a case report of a patient after biochemical testing who was diagnosed as having pregnancy-induced ACTH-independent CS. Affinati et al suggested that CS may have been induced by aberrant expression of ectopic luteinizing hormone/chorionic gonadotropin receptors (*LHCGR*), in the adrenal cortex which resulted in an increased steroidogenesis and cortisol excess due to high human choriogonadotropin (*hCG*), levels which are produced during pregnancy. This was an interesting case of a pregnant woman who presented with a rapid weight

gain at 17weeks gestation, DM, hypertension, proximal muscle weakness, violaceous abdominal and arm stria, and facial swelling. The biochemical tests suggested ACTH-independent CS, but her MRI scan did not identify the presence of adrenal adenomas. However due to the severity of her condition, she underwent bilateral adrenalectomy at 20weeks gestation. The DM, Cushingoid features disappeared, and her general health improved. This patient, due to her condition was given an urgent Caesarean section. The reason for this intervention was due to, "non-reassuring foetal heart tones at 29weeks." [194] A further kidney scan revealed that her adrenal tissue demonstrated unpigmented 2-16mm nodules, with biochemical testing showing an increase in expression of steroidogenic enzymes, throughout the nodular tissue with suppressed expression in the non-nodular tissue. These results suggested that her pregnancy may have mediated the CS through stimulation of aberrantly expressed LHCGR in her adrenal glands.

CS is undoubtedly challenging to diagnose, but arguably more challenging in pregnancy as many of the signs and symptoms are similar including high cortisol levels. Active Cushing's can cause complications in pregnancy which should be avoided.[195]

7.0 Health-Related Quality of Life

7.1 Worse Health-Related Quality of Life at long-term follow-up in patients with Cushing's disease than patients with cortisol producing adenoma. Data from the ERCUSYN.

The ERCUSYN have conducted many contrasting surveys into the HRQoL using their CS and CD database over the past few decades. One recent survey in 2018, of CD patients was conducted by Valassi et al to provide an up-to-date evaluation of their HRQoL before and after treatment. [196]

The PIT-CS patients (*n=293*), results were compared with those of ADR-CS (*n=120*), patients.

The participants completed the CushingQoL questionnaire and/or EQ-5D questionnaires at baseline and/or following treatment. The results at baseline showed no difference between the pituitary and adrenal patients in both questionnaires. However, at long-term follow-up, i.e., after 1 year of treatment, the total CushingQoL score was significantly lower in the pituitary group ($P<.045$). Interestingly, no aetiology was observed with that of HRQoL. However, patients in remission were found to have a better total CushingQoL score ($P<.001$), but older patients were recorded as having a worse total CushingQoL score ($P<.01$). Depression was also associated with a worse total CushingQoL score measured at their last follow-up appointment ($P<.001$). Age therefore and the presence of depression at the onset of a CS diagnosis, were said to be, "potential predictors of worse HRQoL, regardless of CS aetiology." [196]

7.2 Quality of Life: A Long-Term Issue?

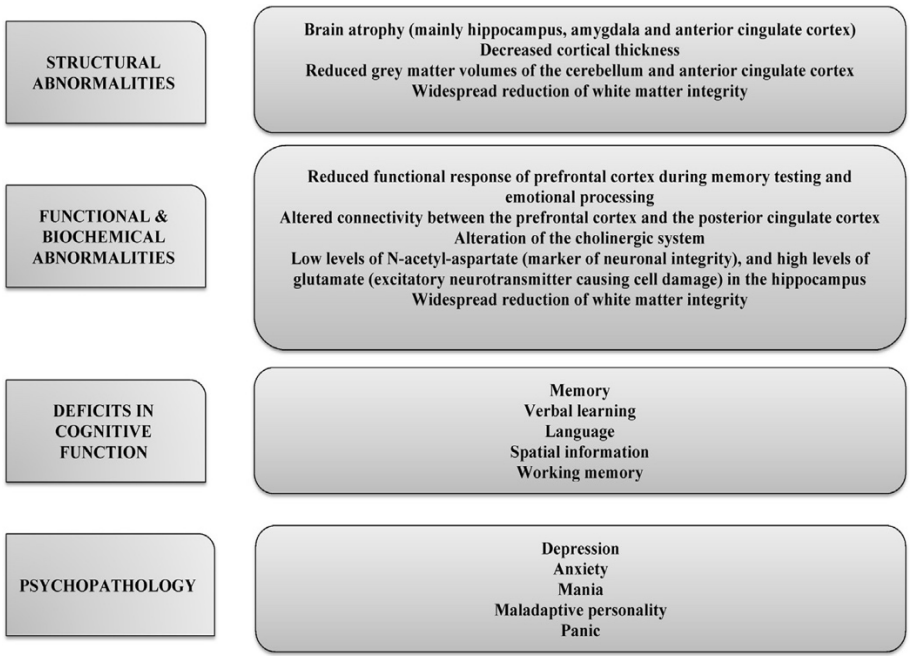
The complex mixture of signs and symptoms caused by active hypercortisolism, do not always recede in patients in remission. According to Webb et al (*2018*), although surgery and medical therapy can control hypercortisolism, many of the signs and symptoms remain.[197] This, as previously discussed, is associated with an increase in morbidity and mortality which are directly a consequence of the metabolic syndrome and cause medical challenges. A recent survey conducted by the Webb et al sought to establish a way to improve CS patients' outcomes and discussed in their paper, the concept of HRQoL defining it as being a patient-reported outcome measure, which can be evaluated with generic or disease-generated or specific questionnaires. The CushingQoL which was designed by Webb et al in 2008 as previously discussed, is a sensitive questionnaire, which identifies specific aspects of CS.[108] The generic questionnaire can be used in any population and allows a comparison to be made of QoL in different diseases or with healthy normal patients. The domain-specific questionnaire being to evaluate a determined problem, examples being fatigue, pain, or loss of libido. The QoL scoring system has proved to be a unique way to measure the patients' impression of their health which is not always identified during a clinical consultation and Webb et al suggested it could routinely form part of the overall clinical assessment used in patient's follow-up. [108]

The Tiesmana et al study previously referred to, also proved, that the CushingQoL questionnaire, regardless of the scoring solution suggested by these authors, was proven to be a valuable resource for assessing HRQoL in patients with CS.[133]

The Webb et al 2018 publication provides clinicians with information as to the long-term effects of CS and how structural brain abnormalities and neuropsychiatric conditions, which had in 2017, been the subject of their QoL research, for a range of physical, psychological, emotional, and social issues for CS patients.[198] [197]

Figure 8, Page 89, describes these physical and psychological issues as referred to in their article.

Figure 8 ***Structural Brain Abnormalities and Neuropsychiatric disorders described in Cushing syndrome.***



Courtesy of S.M. Webb et al. / Annales d' Endocrinologie (2017 [198]).

Worth noting is that organisations such as the ERUCSYN, CRSF and the PF, UK strongly believe that patient awareness and understanding of their signs and symptoms does help them to conform, giving them the hope for final improvement. The stress induced in CS patients from the fear of recurrences and the time between follow-up appointments creates extra anxiety, resulting in psychological issues.

A prospective, randomized study conducted by Martinez-Momblan et al in 2015, was conducted in 2 reference hospitals. The aim of the study was to assess how successful an educational nursing programme in HRQoL was for CS patients. Topics included the clinical parameters, level of pain and physical activity, patterns of rest and the use of health resources.[199] This study of 61 patients, *83.6%* being females was divided into 2 groups. Group 1 was an intervention group which were given educational sessions performed over a period of 9 months and Group 2 was a control group which did not have the educational sessions. The CushingQoL questionnaire post-sessions showed that the intervention group had a higher score compared to the healthy group in all items of the questionnaire. This study revealed that the intervention group had improved physical activity ($r=0.89, P<.01$), and reduced pain ($r=0.46\ P<.05$), and improved sleep ($r=0.53, P>.01$). Although this was a brief study, these findings confirmed that an educational program can improve HRQoL for CS patients and should be recommended as part of their treatment regime. Once again, the CushingQoL questionnaire proved within the context of

longitudinal design, to be a reliable, valid, and responsive test tool in identifying the signs and symptoms matched with the biochemical testing. These findings concurred with previous studies, an example being the Nelson et al (*2013*), psychometric evaluation of the CushingQoL questionnaire, and how they found this to be an ideal tool, which is in accordance with recommendations set forth by regulatory agencies in the USA and Europe and allows comparison of different treatments on the patients' outcomes.[200]

7.3 Affective alterations in patients with Cushing syndrome in remission are associated with decreased Brain Derived Neurotrophic Factor and cortisone levels.

Many of the studies reviewed in this *Chapter*, report on the significant changes physically and psychologically which CS patients experience, thus affecting their HRQoL. Brain-derived neurotrophic factor (*BDNF*), is known to regulate the HPA and this according to Valassi et al (*2019*) is, "highly expressed in brain areas controlling mood and response to stress." [201] These authors study of 36 CS patients in long-term remission aimed, "to assess affective alteration," created by long-term remission of CS and to evaluate whether they are associated with serum BDNF, salivary control and/or cortisone concentrations.[201] The BDI-11 questionnaire, the Center for Epidemiological Studies Depression Scale (*CES-D*), Positive Affect Negative Affect Scale (*PANAS*), State-Trait Anxiety Inventory (*STAI)*, Perceived Stress Scale (*PSS*) and the EuroQoL and CushingQoL questionnaires, were all used in their study. These questionnaires were analysed to evaluate anxiety levels, depression, stress perception and QoL respectively. Biochemical testing was conducted using the LNST. The main results indicated that in all items of each questionnaire, those in remission showed worse scores, and demonstrated that low BDNF levels, "are associated with affective alterations in, 'cured', CS patients," including depression, anxiety, and impaired stress perception.[201] The biochemical testing confirmed that it might also be related inversely with associated trait anxiety ($r=0.377, P<.040$). The latter condition according to Gidron (*2013*), "refers to the stable tendency to experience and report negative emotions such as fears, worries and anxiety across many situation." [202] Chronic hypercortisolism in CD has in previous studies, acknowledged that patients tend to develop alterations in their, "personality profile." [200] Dimpulou et al (*2013*), in their cross-sectional study into the increased prevalence of anxiety-associated personality traits in patients with CS found definite personality traits associated with high anxiety combined with traits of low externalizing behaviour. These authors suggested that changes in levels of anxiety and personality should be considered when treating and diagnosing patients with CS.[203]

7.4 Clinical score system in the treatment of Cushing disease: failure to identify discriminative variables from the German Cushing's Registry.

In 2019, Stieg et al published a paper which reported on their study of using a clinical score system in the treatment of CD.[204] The aim of the study was to develop a multidimensional and integrated scoring instrument that would assess 42 variable CD symptoms, including physical and psychological (*trait-anxiety*) with biochemical testing over a 12-month period. This study proved to be inconclusive as it failed to provide clinical key parameters in the study population with CD in discriminating the biochemical cured CD patients with the non-cured CD patients following their treatment. This resulted in a failure to construct a clinical scoring system which could reflect the benefits of the clinical treatment.[204]

7.5 Preoperative medical treatment in Cushing syndrome. Frequency of use and its impact on postoperative assessment. Data from ERCUSYN.

In 2018, the ERUCSYN group published a paper which discussed their study into the pre-operative medical treatment *(PMT*), in CS patients, the treatment being cortisol-lowering medications.[205]

Examples of these being steroidogenesis inhibitors such as ketoconazole, metyrapone and mitotane. Using the ERUCSYN CS database, the authors accessed information from 57 centres in 26 European countries. *Objective 1)* of this study was to evaluate how frequently PMT is administered to CS patients across Europe. *Objective 2)* was to examine any difference in preoperative characteristics of patients who receive PMT and those who undergo primary surgery, and *Objective 3)* was to determine if PMT influences postoperative outcome in PIT- CS. A total of *21%* of the patients were found to be taking PMT. The results showed that the ectopic-source and pituitary source CS patients, were found to be significantly more likely to have taken PMT compared with ADR-CS patients ($P<.001$). Interestingly, the patients with PIT-CS were found to have more at the point of diagnosis, severe clinical features and a poorer QoL than those who were undergoing primary surgery, ($P<.05$). However, the pituitary patients who were treated with PMT, initial post TSS, were found to be more likely to have normal cortisol levels ($P<.01$), but a lower remission rate ($P<.01$). The results, therefore demonstrated that within 6 months post-surgery, there were no differences reported in the remission and mortality rates between the surgery and PMT groups.[205] The ERCUSYN database presently shows that within Europe a ratio of 1:5 CS patients have PMT before their surgery. The authors found that the type of medication varies throughout the European centres and often Physicians prescribed PMT if there is a long period of time to wait for surgery. Presently there are differences in opinions regarding postoperative normalization of cortisol levels and, "this can generally be

considered a marker of persistent disease and a possible predictor of possible recurrence," according to Valassi et al who conducted this study.[205]

7.6 Cyclical Cushing's Syndrome: A Multidisciplinary Approach to Diagnosis and Management.

Cyclical Cushing's syndrome (*CCS*), is said to be an uncommon disorder which is caused by intermittent hypercortisolism, thus creating a diagnostic challenge. This form of CS is found in patients with PIT-CS, adrenal and ectopic ACTH secretion including bronchial and thymic carcinoid tumours as well as ectopic ACTH secreting pituitary adenomas. A diagnosis of cyclical CS is made through biochemical testing.

Habboub et al in their 2019 publication described CCS as being diagnosed after biochemical testing which demonstrated at least 3 peaks and 2 troughs in cortisol production with similar distance between peaks. [206] The authors in their publication, reported on a single case of a 39year old male who was ultimately diagnosed with CCS. This patient presented with Cushingoid features which included weight gain, bruising, moon face, prominent dorsal cervical fat pad and muscle weakness. His DEXA test revealed an abnormal cortisol level (*19µg/dL*), with elevated 24-hour UFC x 2 (*282µg/24 hour and 119µg/24 hour, normal <100*). The morning ACTH of 61 (*normal 6-48*), midnight salivary cortisol level was also found to be elevated at 1,500 ng/dL. The DEXA-CRH suppression test was also high and therefore suggested the presence of CCS.[203.]

This is an interesting observation in that the number of tests required for a diagnosis of CCS is very dependent on the accuracy and timing of the biochemical testing.

8.0 Narrative Review Summary

This narrative review revealed that the HRQoL in patients, even in remission can be poor due to multifactorial reasons. The complexities of diagnosis, treatment, and patient outcomes cause medical challenges, and this is the reason why more endocrinology teams continue to attempt to find answers as to how to improve HRQoL in CS and CD patients. Since Harvey Cushing in 1912, first described CS the approach to diagnosis and management has significantly advanced yet remains challenging. CS is still rarely considered as a differential diagnosis.

The progress in knowledge to date gained by the multi-disciplinary medical team has created an on-going thirst and quest to find better, quicker solutions for diagnosing CS and CD. The evidence presented within the range of publications confirm many of the theories, and the knowledge gained since Harvey Cushing's first CS patient. This knowledge has been exponential but also prompted the desire to develop less complex but more efficient

methods and tools to measure a patient's HRQoL both pre and post diagnosis and how to reduce the length of time for a diagnosis.

This narrative review informed the author as to the past and present studies of HRQoL and gave the opportunity to critically appraise the relevant material to study current clinical practices and identify if there are, 'gaps,' in the knowledge and if CS patients could be better managed through support mechanisms and raised awareness.

The following *Chapter (3)* explains the research methods adopted to conduct a HRQoL survey of CS and CD members of Pituitary Foundation UK and Associations (*Objective3*) and the Health Professionals semi-structured interviews (*Objective 4*).

Chapter 3

Research Methodology

1.0 Introduction

1.1 Literature Review.

A comprehensive narrative review of current methods of diagnosing and treating patients (*Objective 1*), and the consequences of being diagnosed with CS and methods of measuring the impact of these on their HRQoL. (O*bjective 2*), was conducted.

The narrative review systematically produced results of relevant:

a) diagnostic, prognostic, treatments and the HRQoL challenges for patients in the active and non-active phases of CS and CD.

b) qualitative and quantitative studies reported in books, journals and at conferences enabled a critical appraisal of the strengths and weaknesses of current practices and provided the raw materials which provoked reflection and debate.

Experts in the field of endocrinology and radiology were consulted and their individual ideas, insights and experiences helped to facilitate this research and yielded a deeper understanding of the disease processes and the comorbidities which affects CS and CD patients HRQoL.

Interpreting the results of previous studies which included linkages to the researchers' findings, and observations, and the inferences drawn from other studies, was essential in judging whether the results were relevant and methodologically sound. Comparing the research with this author's personal experience of these medical conditions helped to focus on designing the theoretical format which underpinned the design of the HRQoL Cushing survey questionnaire for this study, (*Appendix 3, Pages 228-242).*

1.2 Defining *Health-Related Quality of Life*

"The aim of measuring HRQoL is to assess a patient's perspectives on the impact of health on their lives as a result of medical interventions." [141] Prior to designing the methodology for this research, the importance of studying the variations in the definitions of QoL was crucial in order to understand why there are these variations

in the definitions and what influence if any that this would have on designing a newer method of measuring HRQoL in CS and CD patients.

Quality of life has been described recently, "as the degree to which an individual is healthy, comfortable and able to participate in or enjoy life events," the concept being that QoL encompasses general wellbeing and happiness in individuals but also includes their physical and mental health.[207]

Health-related quality of life and QoL are said to be used interchangeably, according to Karimi and Brazier. In their 2016 paper they, "concluded that the concepts of HRQoL as used now, are confusing and requires to define HRQoL as the way Health is empirically estimated to affect QoL or use the term to only signify the utility associated with a Health State." [208] Since the 1980s, the concepts of HRQoL have evolved, and although health is one of the important domains of overall QoL, other domains have emerged for example, cultural, social aspects of life, work status and spirituality. These domains have added complexity when measuring QoL and researchers continue to seek new techniques in which to conceptualize and measure these multiple domains in parallel with physical and mental health, (*The WHOQOL Group, 1993*).[209]

The WHO (*2014*), definition of Health is: "the state of complete physical, mental and social well-being, which is marked, not only by the absence of disease or infirmity."[210] This definition remains unchanged on their 2020 website.

Although QoL and HRQoL have been used interchangeably, the latter is preferred when specific effects of a given condition on QoL are analysed. HRQoL provides an unambiguous measure of health status which merges a patient's perspective with clinical parameters, thus allowing an objective assessment of the impact of a disease or the efficacy of a medical intervention on a subject.[141]

1.3 Healthcare Professionals Semi-Structured Interviews.

Objective 4 of this study was to conduct semi-structured interviews with a range of Health Professionals, the objective being to establish their awareness of the signs and symptoms of CS and CD and their knowledge of the diagnostic processes and treatment regimes.

1.3.1 Health-Related Quality of Life Survey- Personal Contribution

As part of the review of literature, the author found it not only useful to study previous HRQoL CS/CD surveys but also to take advice from a Consultant Endocrinologist Dr Elena Valassi, who had assisted in developing the Webb et al, 2008 CushingQoL questionnaire, and was proactive in developing the ERCUSYN guidelines.

Meetings with this Endocrinologist assisted in the process of gaining a fuller understanding of why a disease-specific questionnaire was the most efficient method of measuring QoL in CS patients.

However, based on the author's personal experience of having been diagnosed with Cushing's also helped in designing additional survey questions, to allow the members the chance to provide responses in their own words. Using this personal experience during the design of this questionnaire afforded a unique opportunity to modify and extend existing methods of analysing HRQoL for future studies.

The use of thematic analysis was adopted to integrate the findings and produced compelling insights into the members diagnostic and treatment journeys and their personal lives which in turn, yielded rich information. This method being complimentary to the quantitative results, and seldom if ever, practiced as comprehensively within previous Cushing's HRQoL surveys.

In summary: to achieve this study's objective (*3)*, the author designed a questionnaire, which sought to establish the reasons why CS and CD remain elusive, and complex medical conditions which are often miss or undiagnosed for many years and in addition, find out how aware and informed Health Professionals are of CS when diagnosing and treating these medical conditions (*Objective 4*).

2.0 Pituitary Foundation UK.

Being a member of the PF UK enabled the author to work with them in allowing permission for other Cushing's members to participate in this survey and this included gaining access to other endocrine associations which enabled 12 countries including the UK to participate.

Health-Related Quality of Life Survey.

2.1 Ethics Permission

To conduct a HRQoL survey (*Objective 3*), permission was sought from the PF UK* and the University of Cumbria Ethics Committee (*Appendix 1, Page 226**,** and Appendix 2, Page 227).* The scientific merits of this survey were outlined on the university's ethics form. Information included: the aim of the survey, potential benefits to patients, expected contribution to the existing body of knowledge and the research framework and a copy of the survey questionnaire, (*Appendix 3, Pages 228-242*).

Prior to completing the survey questionnaire, permission to participate in the study from each member was requested. The PF administration staff were responsible for contacting their Cushing's members to gain their permission to take part in the survey and distributing the questionnaires by email to those who accepted the

invitation. The members were also asked for their informed consent on the Information and Instruction form. To comply with the Data Protection Act (*2018*), a numerical code system as described in *Section 2.6*, was applied to each questionnaire to ensure that no individual participant could be personally identified.[211] No GP or hospital medical records were requested or accessed during this study.

*In *Chapter 1, Section 1.3*, *Page 16,* a description is given as to the role of the PF in the UK.

2.2 Inclusion/Exclusion Criteria

The study population was recruited from Cushing's members of the PF, UK, the Pituitary Associations and the CSRF. These members were in the active or non-active phase of CS and/or CD.

These organisations' main role is to give support and advice to patients with endocrine diseases, as previously discussed, and therefore presented an ideal, reliable primary source in which to obtain HRQoL data related to these medical conditions. Excluded from the study were members under 16 years old.

2.3 Pilot Study

The pilot study commenced on the 1st of September 2019 and 12 Cushing's members of the PF UK, were given until the 30th of September 2019 to complete the on-line questionnaire. The quantitative results of the pilot study were analysed, and a minor change was made to Question 1, (*Age replaced Date of Birth*). The response rate was *91.6%,* (*n=11*). A descriptive analysis was conducted, but no inferential statistics were performed on the resultant data. The reason for the latter, was that the study population was considered too small to achieve any meaningful results.

2.4 Main Study

The main study survey commenced in February 2020 and was completed in April 2020. A total of 100 invitations were circulated online to Cushing's members of the PF, UK, the PF Association and the CSRF. Members from other global Pituitary organisations in the world, allowed an inter-individual and inter-country cultural perspective, (*Total of 12 countries*).

**Please note that the survey was conducted during the onset of COVID-19.*

2.5 Study Design

Prior to planning the survey, the narrative review of previous HRQoL studies revealed that the validated CushingQoL disease-specific questionnaire, and the Tuebingen CD-25 contained the major clinically important questions related to the physical, psychological, and cognitive conditions related to CS and CD. [108 118 122]

Using these researchers experiences of measuring HRQoL in Cushing's patients, (*CushingQoL and Tuebingen CD-25*), the design of the present study's questionnaire was disease-specific and contained the main components, based on the fore-mentioned questionnaires standard format design. The latter being essential to compare the present study results with those of past studies. Additional detailed questions were devised to generate more comprehensive information from each member and based on the author's personal experience of CS and CD. This was a cross-sectional study questionnaire which consisted of 76 questions consisting of sub-questions (*open and closed*).

The questionnaire comprised of 4 Sections which contained questions related to: the point of diagnosis, including baseline demographics, aetiology of CS, the length of time between onset of symptoms to final diagnosis, number of Healthcare Professionals consulted, clinical features, comorbidities, diagnostic work-up including medical imaging and biochemical testing, treatments (*surgery and medical therapy*), and the support mechanisms. The latter questions were particularly related to each member's general well-being and their families' and healthcare teams' perceptions of disease awareness,

The final sections of the questionnaire afforded the members an opportunity to rate their QoL and comment on any other personal experiences of their Cushing's illness which would be of benefit to this study.

2.6 Statistical Analysis

An IBM Statistical Package for Social Services version 26 (*SPSS-26*), was used to analysis the data. The analytical methods were both quantitative and qualitative. A simple coding system commencing numerically at F1, (*F=female*), and M1 (*M= male*), was established to categorize the data for each of the questionnaires. The results, including the Tabular and Graphic displays are reported in *Chapters 4, Pages 102-156.*

Please note that a statistician was consulted prior to circulating the questionnaire, to ensure that the chosen methods of analysis were appropriate.

2.6.1 Descriptive analysis was conducted for the socio-demographic and Cushing's variables, (*e.g., age, gender, work/educational status, clinical characteristics, types of biochemical and diagnostic imaging examinations/procedures, treatments including medical and surgical therapies, hospitalisations, remission,*

recurrences, number of Physicians consulted), and were reported using numerical values (*median, mean, min., max., SD*), confidence intervals (*CI),* and frequency ranges (*%*). The Question Response Rate (*QRR=%*), was also included in each of the question results.

2.6.2 Qualitative Analysis. A thematic analysis of the textural content given in the answers to *Questions 8a)*, *9a*), was used to ascertain patterns (*themes*) which were based on the members perceived changes in their social and personal lives and any further information (*Question 40*), which they experienced, negative or positive as a consequence of their Cushing's illness. Using the frequency results for the reasons given for a change, the emerging responses were coded in hieratical order to categorize the data. This process enabled the analysis of the common themes which emerged from the members responses. The frequency (*%*), of responses are displayed in Graphs. The thematic analysis is reported in themes and examples of quotes are given in the narrative analysis,

Question 20 was designed to establish the physical, psychological, and cognitive impairments which each member had experienced *prior to their diagnosis* and whether at the time of completing the questionnaire they were continuing to be experiencing less, the same or more of these conditions, (*current status*). A scoring point system was used for the listed items. One point was given for each condition, using a tick box. *Box A* was *prior to diagnosis* and *Box B current status*. The sum of the scores for each member, for each Box was calculated.

To establish the existence of a significant change in the signs and symptoms scores between *Box A* and *B,* descriptive statistics were calculated and reported in the mean, min., max., and SD values. Paired *t* tests were performed on the data to assess any differences in scores i.e., the 24 items relating to physical signs and symptoms *prior to diagnosis* compared to the *current status*. This test was repeated for the 6 items related to the psychological and cognitive impairment signs and symptoms. The *P* values and *CIs* were reported for the results of the paired *t* tests. The Cronbach's alpha was also applied to the data to measure internal consistency of the test items and the coefficient alpha reported. *A statistically significant level result for the *P* value was set at $P \leq .05$ and *95%* for the CI.

2.6.3. Age Group Analysis: Physical, Psychological and Cognitive Impairments signs and symptoms, (Question 20, Current Status).

To establish if there was an age group of members who had higher scores in *Question 20* (*current status*), the ages of the study population were placed into age groups as follows:

Age Groups: *19-29*, *30-40*, *41-51*, *52-62*, *63-73*.

The mean, min. max. values, including the SD, for the physical signs and symptoms *current_status* and the psychological and cognitive impairment signs and symptoms (*current status*), were calculated for each of the age groups.

An Independent sample *t test* was then applied to compare the mean values of the age groups who had the highest number of scores for Box B (*current status*). The Hartley test for equal variance was also applied to the data and the F and *P* value and CI results reported, to indicate if there was a likelihood of a significant difference in the number of physical signs and symptoms (*current status*), between these age groups and for the psychological and cognitive impairment signs and symptoms (*current status*).

2.6.4 Measurement of Self-rated Quality of Life, prior to diagnosis, during treatment and current HRQoL status was based on Likert scales with five response categories: and was rated on a scale 1-5, where 1 corresponds to Very Poor Health, 2-Poor Health, 3-Fair Health, 4.-Good Health, and 5-Very Good Health. The lower the score representing the greater the impact on perceived HRQoL, (*Questions 39 a*), *b*), *c*). The descriptive analysis was reported using frequency values (*%*), the median, min., max and SD results, The Kruskal-Wallis H test (*KWH*) was applied to the data to examine potential differences between each of the 3 measured categories, i.e., prior to diagnosis, during treatment and *current status.* The results were reported by giving the KWH test value and the *P* values.

2.6.5 Additional Qualitative Analysis.

Assessment for normality in the distribution of the variables was performed using histograms. Two sample *t* tests were performed to compare the differences in the Likert QoL scores for the variables: age, length of time for a diagnosis, recurrence, remission, type of treatments, including surgery, multiple surgeries and use of GCs and RT. The Pearson correlation coefficients were then calculated to assess for linear associations between QoL and age, number of years in remission, number of Physicians consulted prior to a diagnosis and length of time for a diagnosis. Bivariate regression analysis was performed with the predictor values of age, gender, remission status, RT, GC usage, length of time for a diagnosis and aetiology of CS.

The Goodness of fit (*Pearson's chi-square test*), was also applied to the data and the Mallows 'Cp criterion and adjusted R-squared values to quantify *(%)* the main variables affecting their HRQoL.

***In summary*:** These tests were applied to the data to assess the possibility of an association between their HRQoL scores and the variables which could have influenced their response.

2.6.6 Limitations

It is acknowledged that a limitation in the accuracy of the results may be present in *Question 20a)* where the members were requested to *recall their medical conditions prior to their CS/CD diagnosis and in *Questions 39a), 39b),* to rate their QoL prior to their diagnosis and during their treatments. For *Question 20b)*, there is the also an opportunity to answer if their medical conditions, both physical and psychological have improved (*current status*) and in *Questions 39c),* an opportunity to rate their QoL *current status.* The inclusion of *current status* therefore allows the members a chance to reflect and answer more accurately on how their conditions have improved or deteriorated over time.

*Recall bias was taken into consideration when analysing the results, particularly for *Question 20b)* and *Question 39a)* where the ability of the members to recall their past may have resulted in inaccurate responses.

Chapter 4

Results

The following *Chapter* contains the results of the HRQoL survey (*PART 1*), and the interviews with Health Professionals (*PART 2*). The related Graphs and Tables are displayed within the textural content of *Chapter 4, Results, Pages 102-156.*

PART 1

1.0 Health-Related Quality of Life Survey Questionnaire Results

The results of the answers to the questions for the 4 Sections of the questionnaire are presented in the first part of this *Chapter.* A fuller analysis is discussed in *Chapter 5, Discussion*, *Pages 157-196.*

Questionnaire Results Section 1

**Please note that QRR= Question Response Rate * Copy of Questionnaire is in Appendix 3. Pages 228-242.*

Study Demographics, Work and Education Status.

The survey study population was 71 Females and 15 Males, overall *Questionnaire* response rate= *86%.*

***1.1* The following *Table (2*), displays the demographic results (*Questions 1-3*).**

Table 2

SECTION 1	FEMALE	QRR	MALE	QRR
Age Range (Years)	Median ± SD 42 ± 11.2 years (19-70 years)	100%	Median ± SD 39.0 ± 8yrs (28-50 years)	100%
Gender	FEMALE (n =71)	100%	MALE (n= 15)	100%
Country of Residence: (Number of Female & Male Participants) *Total participating Countries=12*	Australia = 1, Canada = 1 England = 37 Guatemala = 1 Kenya = 3 Malta = 2, New Zealand = 3, Northern Ireland = 6 Southern Ireland = 3 Scotland = 12 USA=15 Wales = 2.			100%

1.2 Study Demographic Results

***Main Observations*:** Most of the study population were females (*82.*5%) and resided in England. The youngest member was 19 and the oldest 70 years old, (*Both females*), (*Female median age= 42, years, Male median age=*

39.4 years). A total of 12 nations took part in this survey. Participants (*members*) were recruited from the Pituitary Foundation UK, Pituitary Association and the CSRF.

The following results in 1.3 are the answers to Questions 4-7, which asked the members if and why their Cushing's diagnosis had impacted on their work and/or education.

***1.3*. Impact on Work and Education Status due to Cushing's Illness.**

Question 4 The study population response rate for was *89.5%.* (*Female and Male, n= 77*). Prior to being diagnosed with Cushing's the number of full-time employed was 43 (*64.1%*), part-time employed, 21 (*27.2%*), retired 10 (*14.9%*), and 3 (*4.4%*), were semi-retired but worked part-time. The work status and range of occupations for the study population are displayed in *Table 3 below.*

Question 5. Twelve (*QRR=13.9%*) of the study population answered Prior to their diagnosis, 9 (*75%*), were full-time students and 3 (*25%)* of those were part-time students. ***Question 6*:** was answered by all members. Twenty-nine (*40.8%)* of the 71 females had to give up work permanently from full-time employment although they had named their occupation in *Question 4*, 42 (*59%*), did not give up work or their studies permanently although 13 (*18.3%*) of those members chose to work part-time or take semi-retirement. Two (*13.3%*), males had to give up work permanently prior to their diagnosis, 1 (*6.6%*), had to give up their studies completely and 12 (*80%*), did not have to give up work. However, 1 (*6.6%*) of them now works part-time. ***Question 7*** sought to establish the reason(s) if and why the members had to either give up work, take on part-time work, retire or give up their studies due to their Cushing's illness.

Forty-two females (*59.1%*), who answered YES named their physical and psychological conditions which had caused them to have to change their work or education status.

Table 3 *Female & Male Work or Retired Status.*

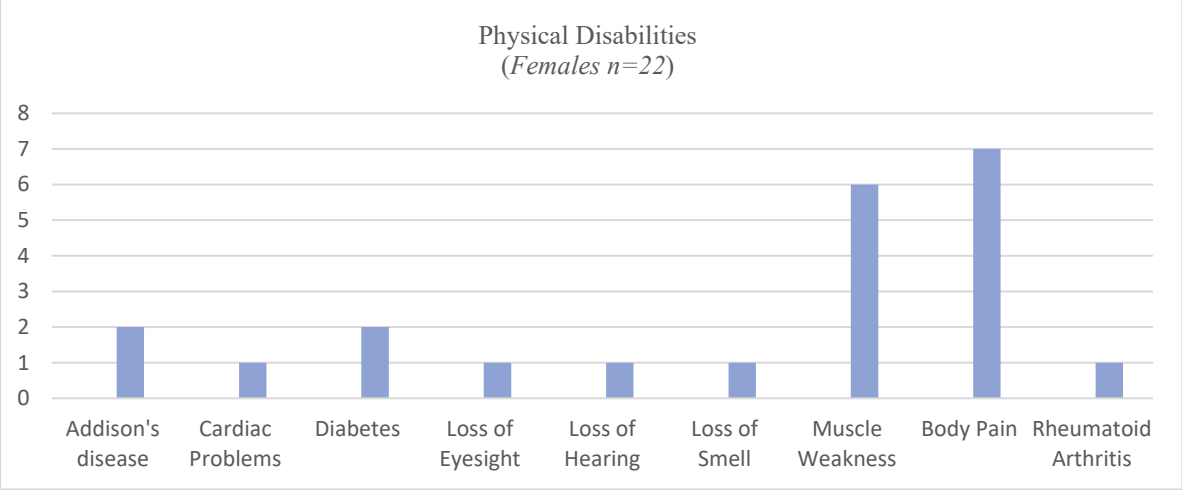
Occupation/Retired	*No*
Managers & Company Directors	**6**
Professional & Technical Occupations	**17**
Administration/Secretarial	**4**
Leisure & Other Services	**6**
Sales & Customer Services	**12**
Elementary Occupations	**3**
Creative Arts & Travel	**7**
Health Care Services	**6**
Retired	**10**
Semi-Retired with Part-time work	**3**
Housewives	**2**
Unemployed	**1**

QRR= 89.5%

Figure 9 displays the range of physical disabilities reported by 22 (*30.9%*) of these females *(Mean number of illnesses=3*).

Impact on Work and Education Status due to Cushing's Illness

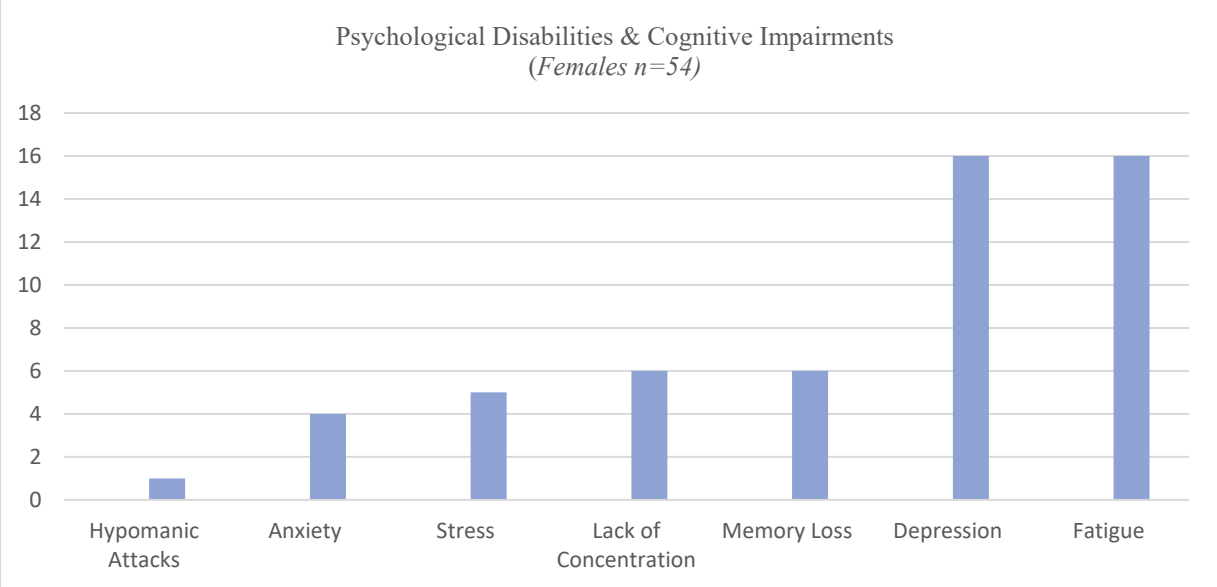
Figure 9.



QRR=30.9% Figure 9 displays the range of physical disabilities reported by the female study population in answer to Question 7. (Mean number of illnesses=3).

Fifty-four (*76%*), females reported that they had experienced psychological conditions and cognitive impairments, [and this had impacted on their ability to work effectively. Twelve (*22.2%*), of the 54 answered this part of the question despite not having to give up work, *(Figure 10),*

Figure 10

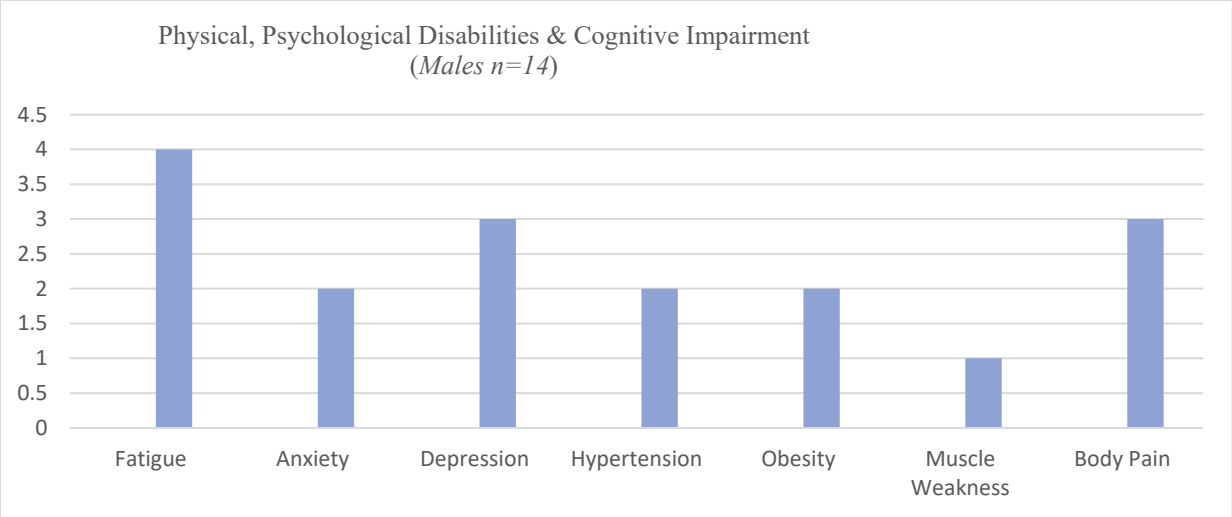


QRR= 76%. Figure 10 displays the range of reported psychological disabilities and cognitive impairments reported by the female study population in answer to Question 7. (*Mean number of illnesses= 4*).

Ten (*14%*) of these females reported that they had experienced both physical and psychological disabilities.

The *QRR* for the males was *93.3%* (*n=14*). Although only 2 males had to give up work permanently and 1 their studies, 14 of them reported physical and psychological conditions which had affected their ability to work effectively. All 14 reported that they had experienced physical illnesses as a result of their Cushing's, (*mean=1 illness*). Nine (*60%)* of them also reported that they had experienced psychological disabilities and cognitive impairments, (*mean=2 illnesses*). Three (*20%*) of the males reported that they had experienced both physical and psychological illnesses (*Figure 11)*.

Figure 11 *Range of Reported Physical, Psychological Disabilities & Cognitive Impairment*



QRR= 88.7%. Figure11 displays the collective results of the physical, psychological disabilities and cognitive impairment for the male study population reported in Question 7.

The following sections 2.0 and 3.0 reports the results of Questions 8, 8a) 9, and 9a). These questions were designed to ascertain if their Cushing's illness had changed their social lives and personal relationships.

Impact of Cushing's on Social life, Personal and Family Relationships.

2.0 Social Life

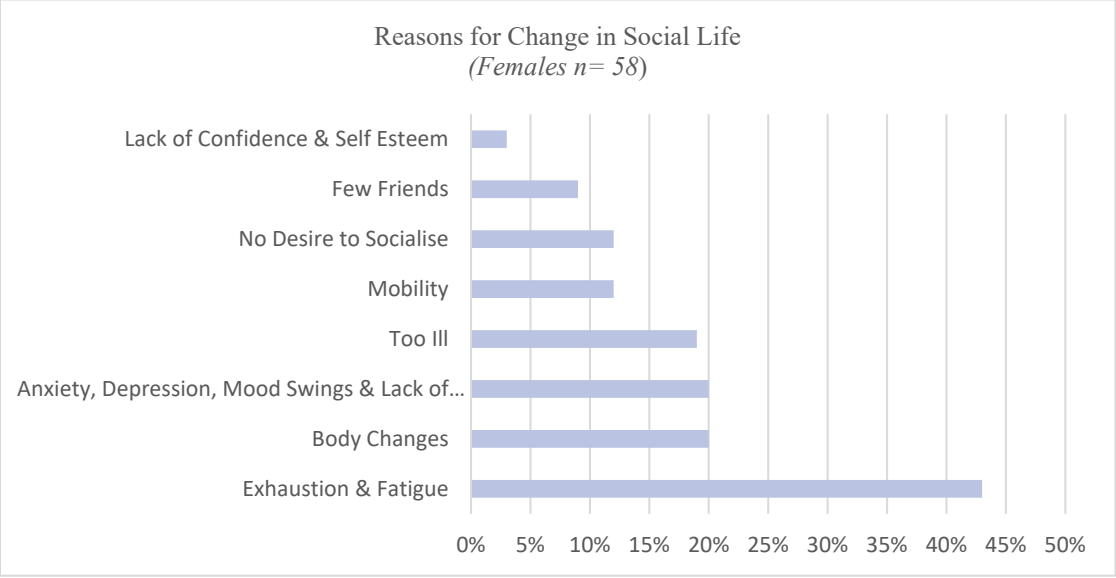
2.1 Descriptive Analysis

Question 8: The *QRR* was *100%.* Fifty-eight (*81.6%*) of the females found that their Cushing's illness had impacted on their social life, and 12 (*80%*), of the males also found this to be the case. The same 58 females and 12 males gave their reasons why their social life had changed in *Question 8a)*. The mean number of reasons for the females was 2 (*min.=1, max=4*), and for the 12 males the mean was also 2 (*min =1, max.=3*).

Figures 12 and 13), displays the study populations reasons why their Cushing's illness had impacted on their social lives.

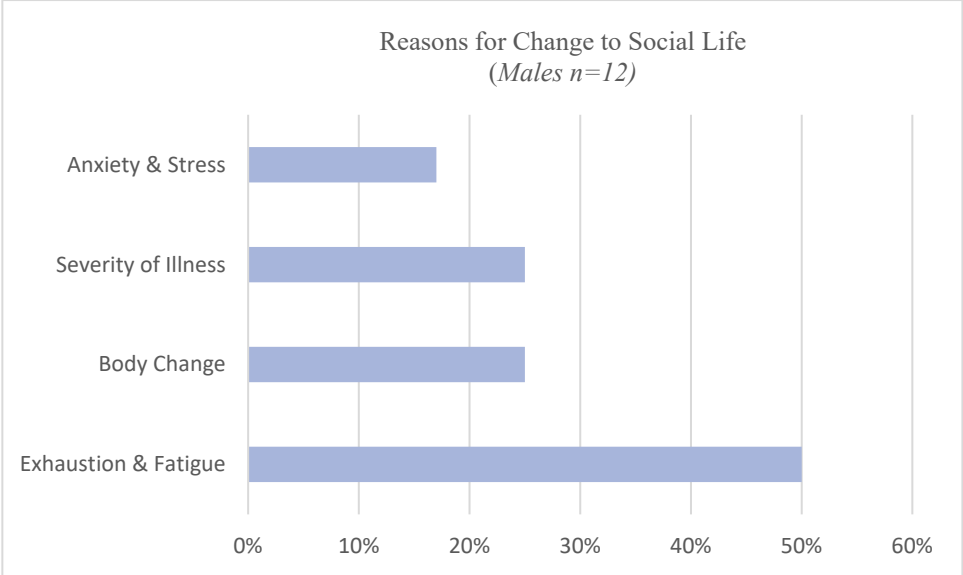
Impact of Cushing's illness, Social Life, Personal and Family Relationships.

Figure 12 Social Life (*Females, n= 58*).



QRR= 81.6%. Figure 12 displays the results of the reasons given by the 58 female members. Details are discussed in Question 8.

Figure 13 Social Life (*Males*, *n=12*).



QRR= 80%. Figure 13 displays the results of the reasons given by the 12 male members. Details are discussed in Question 8.

2.2 Qualitative Analysis.

A narrative-based inductive approach was adopted to combine the descriptive statistics with the textural responses of how Cushing's had changed their social lives and personal relationships.

The sequential responses from these questions assisted with this approach and enabled the analysis of the qualitative data, with the aim of formulating a level of patterned responses within each of the data sets.

2.2.1 **Social Life Changes (*Female Results, Question 8a*)**

Qualitative Analysis

Using the frequency results for the reasons given for a change in their social life, the emerging responses were coded in hieratical order to categorize the data. This process then enabled the analysis of the common patterns which emerged from the members responses. The following are examples of quotes taken from the female responses which are representative of the sample and are reported in the emergent themes 1 to 8.

Theme 1 Exhaustion and fatigue was mentioned by *43%* of the females, highlighting their inability to be able to engage in social activities due to being constantly tired and physically weak.

Example Quotes:

"I have young children but don't go out at all as I am very tired all the time".
"Having to rest before and after work, too tired to socialise".
"Really ill some days and experience fatigue and very tired and sleepy".
"Due to fatigue, I do not even go out with my husband".

Theme 2: Body Changes: These changes were described by *20%* of the members as a reason for not wanting to socialise. This was often due to embarrassment, physical disabilities and psychological conditions which culminated in a lack of self-confidence.

Example Quotes:

"Prefer not to go out or meet people I haven't seen in a long time due to the changes in my body (central obesity, thinning hair, hirsutism) plus I now have to use crutches due to muscle weakness. Conversation is exhausting and I struggle to follow a thread or find words to reply with lots of pauses in the middle of sentences and I will feel mentally and physically drained for a couple of days after social gatherings, even just a couple of people visiting me."
"I used to be a very sociable person. I now spend most days at home. I live with severe hyperhidrosis (excessive sweating) in my scalp, which is very embarrassing when trying to socialise. Severely obese, my weight affects me when I am out as I get short of breath quickly. I avoid being in areas that don't have seats as I cannot stand for long periods. I also have to be close to the toilet as I urinate often and sometimes have sudden release of my bowels."
"I am often too tired or in pain to participate in social functions. I also struggle with brain overload…I struggle to process if things are too busy, and I get overwhelmed. It's also extremely disheartening to be social when your body has changed SO drastically in such a short period of time."

Theme 3: Anxiety, Depression, Mood Swings and Lack of Concentration. Twenty-per cent of the members found themselves, often due to exhaustion and social anxiety, experienced mood swings and a general feeling of negativity associated with these conditions.

Example Quotes:

"After the initial diagnosis my friends felt I should get over it. They are unaware of the daily struggles and the depression that goes with it. They are also unaware of the other illnesses that are a knock-on effect. I have become less social as a result and more paranoid about how people view me. I tire easily and generally cannot be bothered to go out."

"My husband could not 'deal with' my disease, so he divorced me. The main reason that he couldn't deal with it was the mood swings from the hormonal imbalances, and the sudden drop in cortisol levels after the first unsuccessful surgery (Transsphenoidal Hypophysectomy). The adenoma grew back 3 years later, so I had to have Gamma Knife Radiation."

Theme 4*:* Severity of illness: Nineteen- percent found the debilitating effects of their Cushing's illness had caused an impact on their ability to socialise.

Example Quotes:

"I work part-time as I am quite ill."

"I cannot go out without a carer nearby – if I don't have one, I can't see anyone."

"Unable to socialise due to being very ill and therefore no friends."

Theme 5*:* Mobility A lack of general fitness due to a range of physical disabilities created difficulties in mobility for *12%* of the female members and this in turn reduced their ability to socialise, particularly outdoor activities.

Example Quotes:

"Due to mobility issues and fatigue, I am not able to do as much as I used to do. I used to be very fit & active but now I struggle to do much at all."

"I find difficulty in walking due to my spinal problems and therefore rarely go out."

"My social circle has reduced because I can't cope with everything I used to do, I get so exhausted and have developed some social anxiety. Some friends have not understood so have fallen away, over my journey, as I have had to cancel social events at the last minute. My journey started in 2003, so it has been a long road to remission. I can't cope any longer with the physical demands. I have Spinal Stenosis, along with Spondylitis & Arthritis in my lumbar and cervical spine areas. I am reliant on a walking stick, mobility scooter or wheelchair now. This has impacted where I go and what I do."

***Theme 6**:* Lack of Desire to Socialise was given as the reason for not wanting to engage in social activities by *12%* of the females. This was often due to a lack of confidence, sexual desire, and fatigue.

Example Quotes:

"Can't enjoy all the physical pursuits that I once had therefore I do not go out very often. I have no sexual drive."

"Yes, I have a lot of anxiety, for no specific reason. So, I am less social than I was before. I am less tolerant of people and interactions, and don't feel like going out."

"I no longer want to go out with friends in the evenings for dinners or happy hour. My body physically gets too tired. I also cannot handle alcohol in my system. It makes me feel like my cortisol is going way too low."

***Theme 7**:* Friendships: *9%* of the members said that they had difficulty making friends, had lost friends often due to giving up their work or educational pursuits and others found they were too tired to go out and make friends.

Example Quotes:

"Giving up university has meant that I have very few friends now."

"Not well enough to venture out, therefore previous friendships have ended.

"Having to rest before and after work, therefore not able to make friends due to lack of energy."

***Theme 8**:* Lack of Confidence and Self-esteem. Although only *3%* of the members mentioned these feelings in their quotes as being the main reason for not socialising, many of them mentioned their anxiety levels, body changes and this could be suggested as anxiety disorder. This suggestion is also based on their account of their lack of confidence in themselves.

Example Quotes:

"Significantly less self-esteem, do not go out unless it was work or family."

"Can't face going out, lack confidence. Very little friends except at work."

"Giving up work meant that I lost contact with my friends. My husband is not a socialiser, so we very rarely go out."

2.2.2 Male Results (Question 8a).

Four common themes emerged from the male responses and the following quotes are representative of the sample population.

Theme 1*:* Exhaustion and Fatigue. Six (*50%*) of the 12 males who answered YES for *Question 8a*), wrote that they were constantly tired and working exhausted them.

Example Quote

"So tired can't go out."

"Tired after work so mainly sleep after and weekend in bed resting and not happy with people around me."

"Too tired and weary to cope with life."

Theme 2: Body Changes: Three (*25%*) of the males found that their body changes, particularly their weight gain created embarrassment which affected their confidence.

Example Quotes:

"I tend not to go out apart from work as I have put so much weight on and lost all of my hair."

"I find that I am a bit embarrassed about my weight and put off going out because of this."

"Due to my excess weight gain I rarely go out. Cannot also afford much as I am now forced to work part time."

Theme 3*:* Severity of Illness: Three (*25%*) of the males described their physical and psychological conditions which had affected their social activities.

Example Quotes:

"Just really don't understand why, but find it hard to keep a job as I am always feeling ill and have extreme headaches,"

"No social life. Found work and home life extremely hard work, lack of concentration, mood swings and generally feeling unwell."

Theme 4**:** Anxiety and Stress: Two (*16.6%*) of the males described their reason for a change in their social life as being mainly due to anxiety and stress.

Example Quote:

"*Limited amount of outgoings as I find it hard to even go to work at times because I feel so ill with anxiety and stress."*

3.0 Personal Relationship Changes

3.1 Descriptive Statistics (Question 9)

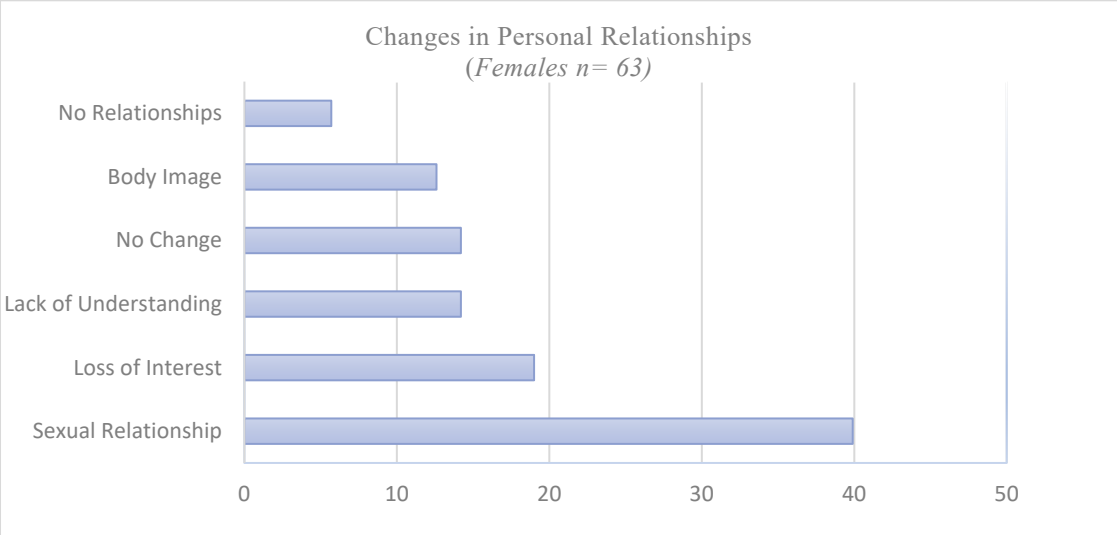
Question 9*:* Sixty-eight (*95.7 %*) of the females and 14 (*93.3%*), males answered this question, and all gave reasons why their personal relationships had either changed or remained the same. Fifty-three (*84.1%*) of the 68 females experienced a negative change in their personal relationships, only 1 (*1.5%*) female found that her relationship with her husband had become closer and 10 (*14.7%*), described their relationships as unchanged. Twelve (*85.7%*) of the 14 males who answered this question experienced a negative change, the remaining 2 (*14.2%*), males found no change.

The mean number of reasons for the females were 2 (*min.=1, max.=4*) and for the males, a *min= 1, max.=2.*

Figures 14 and 15, below displays the frequency results (%) of the reasons why the study populations experienced a change in their personal relationships.

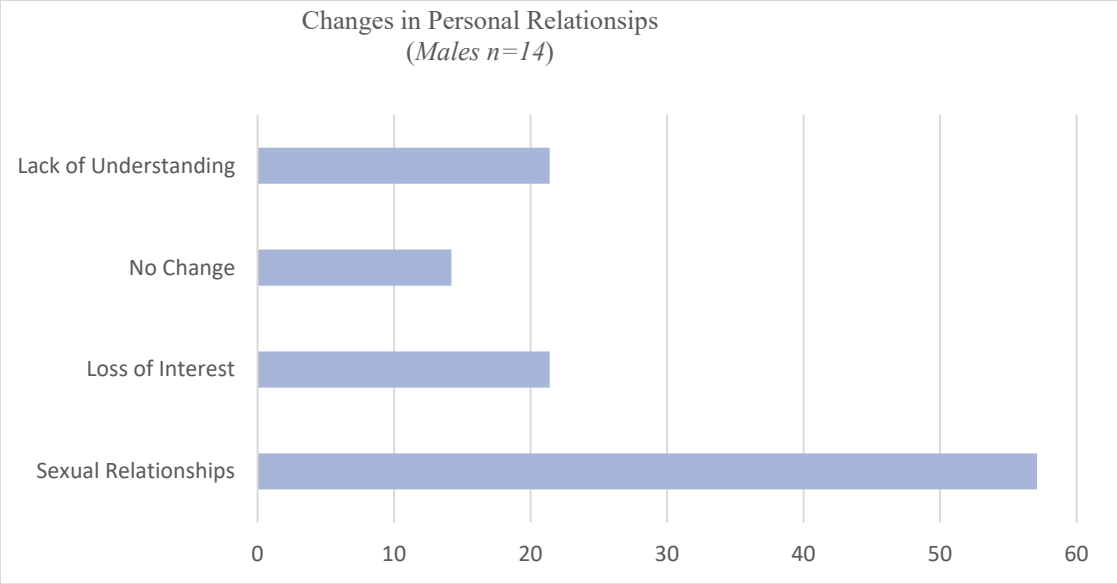
**Please note: Figure 15, Page 112, graph also includes the 14.2% of males who experienced no change.*

Figure 14 Personal Relationships *(Females*).



QRR=95.7%. Figure 14 displays the results (%), of the reasons why their personal relationships had changed for the 63 female members. Details of the results are discussed in Question 9.

Figure 15 Personal Relationships. (*Males*).



QRR= 93.3%. Figure 15 displays the results (%), of the reasons why their personal relationships had changed for the 14 male members. Details of the results are discussed in Question 8.

3.2.1 Qualitative Analysis (Question 9a)

The following are examples of quotes taken from the female responses which are representative of the female sample and are reported in the emergent Themes 1 to 8.

3.2.2. Female Results:

The thematic analysis of the textual content given in the answers to *Question 9a)* are reported in this *Section*, using quotations from the emergent 5 themes, based on the 68 females perceived changes in their personal relationships.

Theme 1 Sexual Relationship: Twenty-five (*39.9%*) of the 68 females who answered this question, wrote intimate details of how their reduced libido had affected their relationships with their partners/husbands. Eighteen (*72%*) of these 25 females split from their partners as a result of this, 9 (*50%*), of them divorced.

Example Quotes:

"My husband is very supportive, but we have been through hell and back. I have been irrational, short tempered and less affectionate *Our physical relationship has changed as well."*

"My husband left me as I did not want sex with him, my children have left home, so I now live on my own. I only have a few friends who worked in the local hospital with me."

"My marriage broke down shortly after I was given my Cushing's diagnosis. This was probably due to my inability to have sex and get pregnant."

Theme 2 Relationship Breakdown: As previously mentioned, 18 (*72%*), of the 25 females who had experienced a lack of libido, due to their Cushing's, split with their partner/husband also gave additional reasons. The overall *%* therefore out of the 63 was *28.5%.* of whom had no relationships of a personal nature.

Example Quotes.

"What few friends are left, I rely on them to come to me. I lost my self-confidence and have become a shadow of who I once was. I'm now post op and embarrassed by how much I rely on tablets and how much I rely on the support and patience of others. My partner resents me having been so ill for so long and there is nowhere I can go as I has little money now and am scared of becoming homeless and ill on my own if I leave."

"Little desire for intimacy with my boyfriend, get irritated by small things and can get moody when I've always been very laid back, plus inability to go out means less variety of activities together."

"Due to the mobility & fatigue issues I'm not able to meet up with friends as much as I used to. I have become more withdrawn from my husband even though he is very supportive, this is due to fatigue, body image. Everything takes so much effort. Intimate relationship is difficult due to lack of libido & tiredness. We don't sleep in the same room now as I need more sleep than he does, plus he snores & fidgets & that makes sleep harder for me. Plus, it's complicated as he suffers with erectile dysfunction due to type 1 diabetes."

"Divorced, my husband stated I wasn't the person he married."

"My last boyfriend said he didn't want my medical history inherited by children."

Theme 3 Loss of interest in Personal Relationships. Twelve (*19%*) females gave reasons why they had lost interest in forming personal relationships. The main reasons were lack of sexual desire, embarrassment because of their body changes, loss of interest in living, self-esteem, confidence, mood swings, widowhood and generally feeling negative.

Example Quotes:

"I am not so out-going as I used to be and don't really want to mix with my fellow students and form a personal relationship with anyone."

"No partner or boyfriend due to my inability to feel confident enough to go out and therefore I have lost interest in forming relationships."

"No interest in pursuing any relationships and find that I am become more and more isolated due to the virus."

Theme 4 Lack of Understanding: Nine (*14.2%*), females gave detailed accounts of how their husbands/partners and close friends did not understand the reasons for their personality changes, mood swings, psychological and physical changes. This in turn created a dissatisfaction within relationships, a mistrust and in some cases a resentment.

Example Quotes:

"Friends didn't get me, maybe even thought I made everything up. They became people I felt I couldn't count on for support and so, they stopped being friends. For those who stood by me, the opposite happened. I now know my true friends. There's also, me pushing people away. Wanting some peace, not wanting to be reminded about my body. So, some friendships ended."

"Lost my friends as I seem to have lost interest in life, friend don't understand."

"My husband and I had a great sex life but now I have lost interest and he get very frustrated to the point of having an affair. He simply doesn't understand."

"Due to my severe psychological changes my husband and family found it difficult to accept and understand the changes."

"Mood swings. I feel people close to me find it very difficult to understand the sudden change in moods. I often have to say no to things, because I tend to have a lot of off days. Having to rely on others more now, to do things. Like help with cooking, cleaning, going to appointments. I need more emotional and moral support."

Theme 5 Body Image: Five (*7.9%*), females said that their body changes were the main reasons which led to breakdowns in their personal relationships and their sexual desire. Three (*5.6%*) others said that they disliked themselves due to their body image as a result of their Cushing's and it was preventing them from engaging in social activities and hence, forming personal relationships.

Example Quotes:

"People don't understand. We look relatively normal, even as our appearance changes…we don't look "sick". But we cannot function as we normally would and participate in social things…that creates distance naturally. Then you have others who think you are making things up or just being lazy."

"None of my friends, nor acquaintances understand the symptoms of Cushing's, and many of them blamed me for the obesity, saying things like, "You're making your own self fat. Just watch what you eat." Though I told them, "I cannot eat half the time, because I become too bloated and uncomfortable that if I eat an apple, it affects me as if I had eaten a 10-course meal." They just don't understand. I had one friend who was consistently trying to convince me to have Gastric Bypass, because it worked for her. However, SHE did NOT have Cushing's. I even went to her Gastric Surgeon and sat through the Seminar. The surgeon himself told me I would NOT be a good candidate for Gastric Bypass due to my Cushing's. It most likely would NOT work."

"I have lost interest in my appearance and have no desire to make love. My children seem to be disgusted with me due to my appearance."

3.2.3. Male Results (Question 9a).

Three common themes emerged from the 14 male responses to *Question 9a)* and are reported below:

Theme 1 Sexual Relationships: Eight (*57.1%*) of the 14 males described how their lack of libido had a negative effect on their personal relationships. Subsequently, 3 (*37.5%*) of them divorced.

Example Quotes:

"Yes, it has -staying at home has meant that I have not been meeting people, I am gay and do not seem to attract any new acquaintances. I have also lost my desire to make love,"

"We hardly ever have sex as I am too tired and have no sexual drive,"

"I am divorced, and I blame this on my illness as I found it difficult to be emotional and lack any sex drive. I also find that I sweat heavily, and I am losing my hair,"

"I have just got divorced after 25 years of marriage. The main reason was that I couldn't make love,"

Theme 2 No Interest: Three (*21.4%),* males admitted that they had no interest in forming personal relationships and they blamed this on their Cushing's illness.

Example Quotes:

"Less tolerance. I get frustrated easily. Prefer to be alone. I worry that things won't work out, so I don't wish to have any personal relationships,"

"Had no desire for relationships,"

"I am married but lost interest in my personal and intimate relationships,"

Theme 3 Lack of Understanding Three (*21.4%*) of the male members wrote of their partners and friends lack of understanding as to the nature of their illness and how this impacted on their ability, desire to have sex and their lack of energy and interest in socialising.

Example Quotes:

"Erectile dysfunction so I lose a lot of fun time and my wife just thinks I am making it up and does not understand this is due to my Cushing's. Energy to do anything together is none after work."

"My girlfriend has left me as I don't want to go out and she doesn't understand and thinks I don't want to be with her,"

Main Observations: Both female and male responses had common themes which identified the interrelationship of social factors with their individual thoughts and resultant behavioural patterns. The body changes, mood swings, anxiety, cognitive dysfunction, and physical disabilities are examples which created negative impacts on their lives and in turn, a lack of desire to socialise, inability to socially adjust and in some cases form personal relationships.

The impact of the psychosomatic aspects of endocrine disease and QoL is well-documented and will be discussed further in *Chapter 5, Discussion, Section 16, Pages 178-180.* where comparisons will be made with other similar findings.

Question 10 sought to establish if friends and family understood the nature of their Cushing's illness. The female *QRR* for this question was *95.7%.* Twenty-nine (*42.6%*) of the 68 members who answered YES, agreed that their family and friends did understand their Cushing's illness, 28 (*41.1%*), of the members answered NO. Eleven (*16.1%*) participants felt that their husband and/or friends partially understand their Cushing's illness.

Four (*28.5%*) of the males answered YES, their family and friends did understand the nature of their illness. Seven (*50%*), answered NO. Three (*21.4%*), of the members suggested that their family/friends partially understand. The male *QRR* was *93.3.%.*

4.0 Endocrine Team Support

The following results are presented for Questions 11, 11a) and 11b). These questions were designed to find out if the endocrine team involved their family during their diagnostic and treatment journeys and how improvements could be made.

4.1 Question 11 had a *QRR* of *98.5%* for the females and *100%* for the males.

Female Results:

Thirty-nine (*55.7%*), females answered YES, the endocrine team had involved their family during consultations, 31(*44.2%*), did not. The male results showed that 7 (*46.6%*), answered YES, the endocrine team had involved their family during consultations, however, 8 (*53.3%*), did not agree.

Thirty-eight (*97.4%*), of the 39 females, who answered YES in ***Question 11a)***, took the opportunity to describe how they found the endocrine team to be very supportive, although 2 (*5.2%*) of them gave some negative comments.

One (*2.6%*) member wrote: "*I always attend on my own. I feel like my mum would get to upset if she came in so trying to manage her feelings while trying to understand what I'm being told would have been tough; and my*

Male Results:

Question 11a): Only 3 males answered this *Question.* One (*33.3%*), found that there was very, *"little information,"* given to them about their illness, while another (*33.3%*), reported that the endocrine team, "*did not seem to understand the full nature of their illness.*" One other member found, "the *endocrine team to be very helpful in answering their questions*."

Question 11b), asked the members for suggestions as to how their endocrine team could improve including involving their families during consultations. The female *QRR* was *60%* and the males *73.3%.*

Table 4 and Table 5, below displays the responses for the study population who answered *Questions l1b).* These *Tables* demonstrate how those who answered these questions felt about their endocrine team support and the suggested methods which could help increase communication and support mechanisms.

Table 4 **Endocrine Team Support (*Male Responses)***

Frequency of Responses (n=11)	***Responses (Question 11b)***
27.2%	Information/Explanation and more advice would be helpful with family present at consultations.
27.2%	Family not asked to attend consultations.
18.1%	Psychological support would help.
9.5%	Consultations to, "rushed".
9%	Would be helpful to have family or friends attend consultations.
9%	More sympathetic and caring approach.

Table 4 displays the results for the male study population who answered Question 11b). which focused on how they felt about their support from their endocrine team, and how it could be improved,

Table 5 Endocrine Team Support (*Female Responses).*

Frequency of Responses (n=42)	***Responses (Question 11b)***
52.6%	Information/Explanation and more Advice would be helpful and better communication skills, caring approach. with their family present at consultations and more time during consultations to ask questions.
21.4%	Helped to have family, friend, or carer during consultations for support and guidance.
9.5%	Don't know how to improve/or does not need to be improved.
9.4%	"Speedier Diagnosis", by listening more, "some endocrinologists are better at diagnosing than others."
7.1%	Counselling and psychological help for both themselves and their family.

Table 5 displays the results for the female study population who answered Question 11b). which focused on how they felt about their support from their endocrine team, and how it could be improved.

The results of Section 2 of the Cushing's Quality of Life survey questionnaire are presented in the following Sections 5 to 7.

5.0 Diagnosis of Cushing's syndrome & disease.

Questions 12 to 19 were designed to ascertain details of the members diagnostic journeys and their length of time in remission and recurrences.

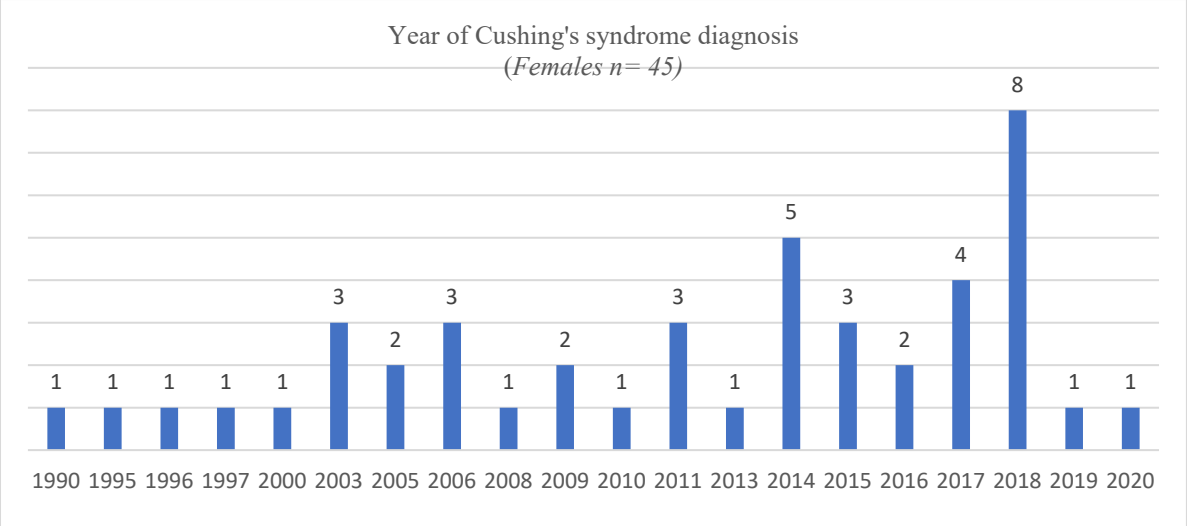
5.1 Year and Length of Time for Diagnosis of CS and CD

Question 12 had a *QRR* of *63.3%* for the females and a *QRR* of *86.6%* for the males. The year of diagnosis for 45 (*63.3%*) of the females who were diagnosed with CS was between 1990 to 2020. One (*1.4%*), female reported that she had been diagnosed with CS but could not remember which year. The year of CS diagnosis is displayed in *Figure 16, Page 118,* along with the numbers of members/year. The number of males diagnosed with CS was 13 (*86.6%*). *Figure 17, Page 119,* displays each year of diagnosis for the 13 males who were diagnosed between 1999 to 2019.

Question 13/14: Forty-four (*61.9%*) of the females were diagnosed with CD between 1993 and 2020 (*Figure 18, Page 119*). Twenty-one (*47.7%*), of the 44 had also been diagnosed with CS. The male results revealed that 6 (*40%*), were diagnosed with CD, 4 (*66.6%*), of them had also been diagnosed with CS. *Figure 19, Page 120*, displays each year of CD diagnosis for the male population, which was between 1999 and 2019. Notable, was that 1 male had been diagnosed in 1999 aged 14.

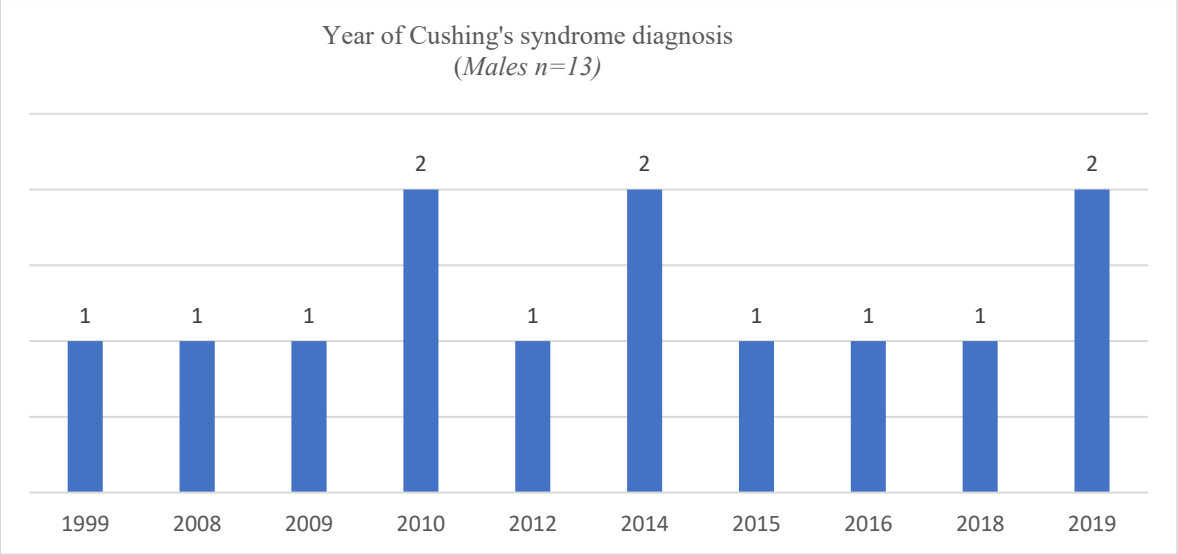
Questionnaire: SECTION 2

Figure 16



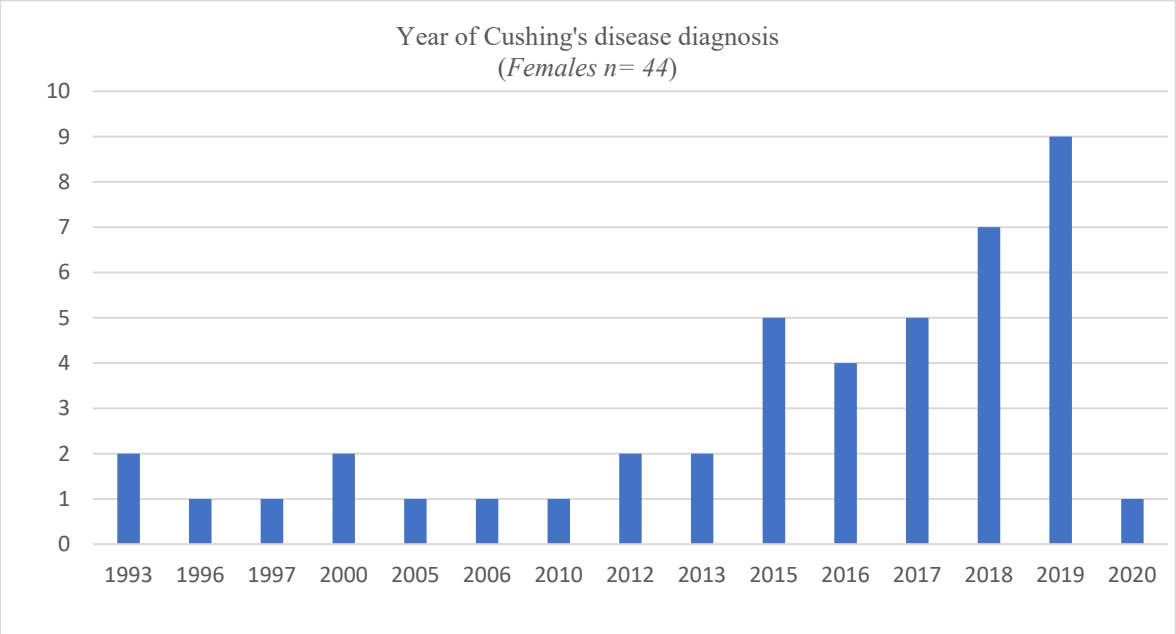
QRR= 63.3%.

Figure 17



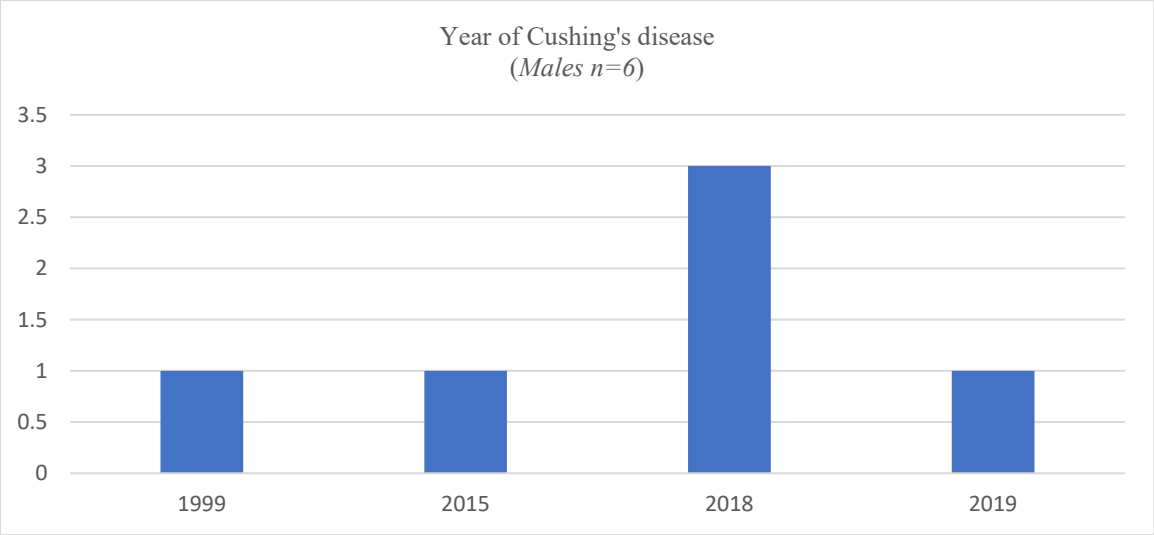
QRR=86.6%
Figures 16 and 17 displays the year in which the study population were diagnosed with CS.

Figure 18



QRR=61.9%.

Figure 19



QRR= 40%

.

Question 15*:* All females answered this question who were diagnosed with CS (*n=45*). Median length of time for a diagnosis of CS was 5.4 years, (*min= 4 days, max.=10 years*).

Eleven (*84.6%*) of the 13 males diagnosed with CS also answered this question. Median length of time for a diagnosis was 3.7 years, (*min. =6 months, max. = 7 years*).

Question 15a). For the 44 females who were diagnosed with CD, the median number of years for a diagnosis of CD was 5.1 years, (*min. =1.6 months, max.=10 years*).

For the 6 males who were diagnosed with CD, the median number of years for diagnosis of CD was 2.2 years, (*min.=3 months. max.=4 years*).

** Total number of members diagnosed with CS= 56 and CD=50 and both CS and CD= 25. Figures based on QRRs (CS=68.6%, CD=58.1%, Both= 29%).*

5.2 Remission and Recurrence

Question 16a) The *QRR* for the females was *98.5%* and for the males *100%.* 52 (*74.2%*) of the females were in remission, *25.7%,* (*n=18*), were not. Eighty percent (*n=12*), of the 15 males were in remission and *20%* (*n=3*), were not.

Question 16b) The *QRR* for the females was *69.2%* and the males *50%.* The length of time in remission of 36 (*69.2%*), of the females out of the 52 in remission, varied from 6 weeks to 19 years (*Median time= 6.1 years*).

For 6 (*50%*) of the 12 males who were in remission, the median length of time in remission was 5.6 years (*min.=1year, max.=12 years*).

Question 16c) Twenty (*31.2%*) of the 64 females who answered this question, had a recurrence and *68.7%* (*n=44*), had not, (*QRR= 90.1%*).

Three (*21.4%*) males did have a recurrence, *78.5%* (*n=11*) have had no recurrence of their Cushing's, (*QRR= 93.3%*).

Question 16d) Nineteen (*95%*), females answered this question out of the 20 who have had a recurrence. Median time for a recurrence was 1.8 years (*min= 6 months, max. =4 years*). The number of recurrences ranged from 1 to 5, the mean number of recurrences was 2.

All 3 males who have had a recurrence answered this question. One of the males had 1 recurrence, 1 had 2 recurrences, and 1 answered 3 recurrences. The median length of time for a recurrence was 1.5 years. (*min.= 13 months, max.= 2 years).*

5.3 Who made the diagnosis and how long did it take?

Question 17 a)-g) sought to establish who diagnosed their CS and CD. The *QRR=100%.*

Tables 6 and 7 below, displays who made the initial diagnosis of CS and CD for the study population. Notable, was that 32 (*45%*) of the females were diagnosed by other Health Professionals, prior to confirmation of a definitive diagnosis by their endocrine team, and only 12 (*16.9%*) by their GP.

All 15 males answered this question. Notable, also was that 8 (*53.3%*) of them were diagnosed by other Health Professionals and 3 (*20%*), by their GP prior to a definitive diagnosis being confirmed by their endocrine team,

Table 6 (*Female Results, Questions 17a-g).*

Who Diagnosed your Cushing's? (Females)	*Number*
General Practitioner	12
Neurosurgeon (*CD*)	11
Other Health Professionals	32
Self-diagnosed/Family/Friends	16

QRR= 100%

Table 7 (*Male Results, Question 17b-g*).

Who Diagnosed your Cushing's? (Males)	*Number.*
General Practitioner	3
Other Health Professionals	8
Self-diagnosed/Family	4

QRR= 100%

Question 17h) Thirty-two (*45%*) of the females and 8 (*53.3%*) of the males named the discipline of the Health Professional who had initially diagnosed their Cushing's. The female participants named 16 healthcare disciplines and the males, 6. The unnamed consultants were reported to be working in orthopaedics, (*Tables 8 and 9*).

Table 8 (*Female Results, Question 17h*).

Which other Health Professional diagnosed your Cushing's? (*Females*)	*Number.*
Orthopaedic Consultant	5
Gynaecologist	5
Psychologist	4
Psychiatrist	3
Urologist	3
Dietician	2
Cardiologist	1
Dermatologist	1
Fertility Clinic	1
Neurologist	1
Obstetrician	1
General Physician	1
Radiologist	1
Rheumatoid Consultant	1
Neuro-endocrinologist	1
Nurse	1

QRR= 45% The results are reported in Chapter 4, Question 17a)-g).

Table 9 (*Male Results, Question 17h*).

Which Health Professional or another person diagnosed your Cushing's? (*Males*)	*Number*
Unnamed Consultants	2
Psychologists	2
Urologist	1
Paediatrician	1
Medical Intern	1
General Physician via Internet	1

QRR=53.3%. The results are reported in Question 17a).

Question 18 invited the members to quantify the number of Physicians and/or member of the healthcare team who they had consulted prior to their diagnosis.

The *QRR* of the females was *92.9%* and for the males, *93.3%.* Two (*3.1%*) of the 64 females answered, 'many.' The median number of Physicians/healthcare staff consulted prior to their diagnosis was 3 Physicians (*min.= 1, max.=18*), for the females and for the males, the median number was 2, (*min.=1, max.= 4*).

Question 19 results reported the length of time for a referral to the endocrine team. The *QRR* for the females was *92.9%* and for the males *86.6%.*

The median length of time for referral to the endocrine team for the 66 females was 3.6 years, (*min.= 1 day, max.= 9.5 years*).

The median length of time to be referred to the endocrine team for the 13 males was 1year, (*min.= 2 months, max = 7 year*s).

6.0 Prior to and Post Diagnosis Signs & Symptoms.

6.1 Signs & Symptoms.

Question 20 A scoring point system was used for the physical, psychological, and cognitive impairment signs and symptoms in the tick boxes provided in the questionnaire. The score was calculated by adding up separately the sum of the number of crosses placed in each of the A and B Boxes, (*1 point for each X*).

Question 20, Box A was composed of 24 physical signs and symptoms questions and 6 psychological and cognitive impairment questions, which asked if the members had experienced any of the listed items prior to their diagnosis. *Box B* asked the same 30 questions to ascertain whether the members were still currently experiencing them.

6.2 Analysis of the physical signs and symptoms *Prior to diagnosis* ***and*** *Current Status.*

a) Female Results.

Table 10, Page 124, displays the results of the Mean, Max., Min and SD results for the physical signs and symptom Prior to and Current Status for the female study population.

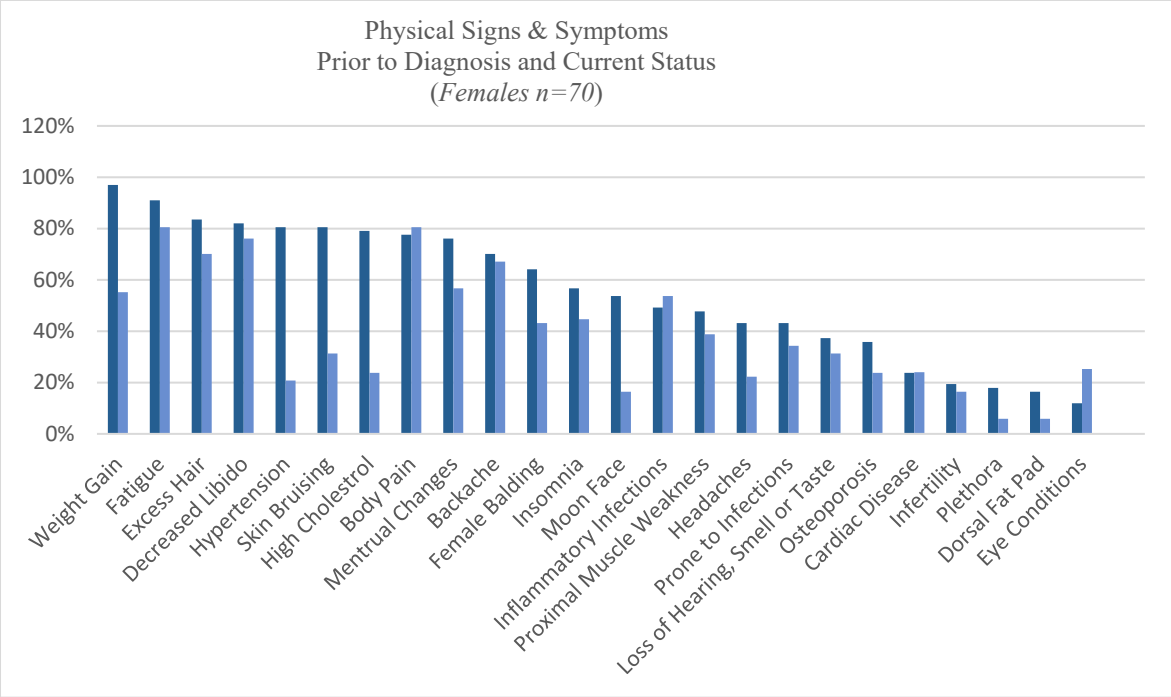
Figure 20, Page 124, displays the frequency results (%), of the collective female physical signs and symptoms prior to diagnosis as answered in Box A and the current status, Box B.

Table 10 (*Female Results, Question 20*).

Question 20 ***Physical Signs & Symptoms***	***Prior to Diagnosis (Box A).***
Mean number items = 13.7	*Min.=0, Max=22, SD= 4.7*
Physical Signs & Symptoms	***Current Status (Box B).***
Mean number items= 9.3	*Min.=0, Max= 20, SD= 4.4.*

QRR= 100%. Total Number of Questions =24, Maximum Achievable Score=24.
Table 10 displays the Mean, Max., Min and SD results for the physical signs and symptom Prior to (Box A), and Current Status (Box B), as reported in, Question 20.

Figure 20



QRR= 98.5%. Figure 20 displays the frequency results of the female physical signs and symptoms prior to diagnosis and current status as answered in Question 20 Box A and current status, Box B.

The mean score differences were 4.4 items (*Box A and B signs and symptoms*). One member's score remained the same, 3 others had an increase in their signs and symptoms post diagnosis and 1 member did not experience any signs or symptoms before or after diagnosis (*current status*).

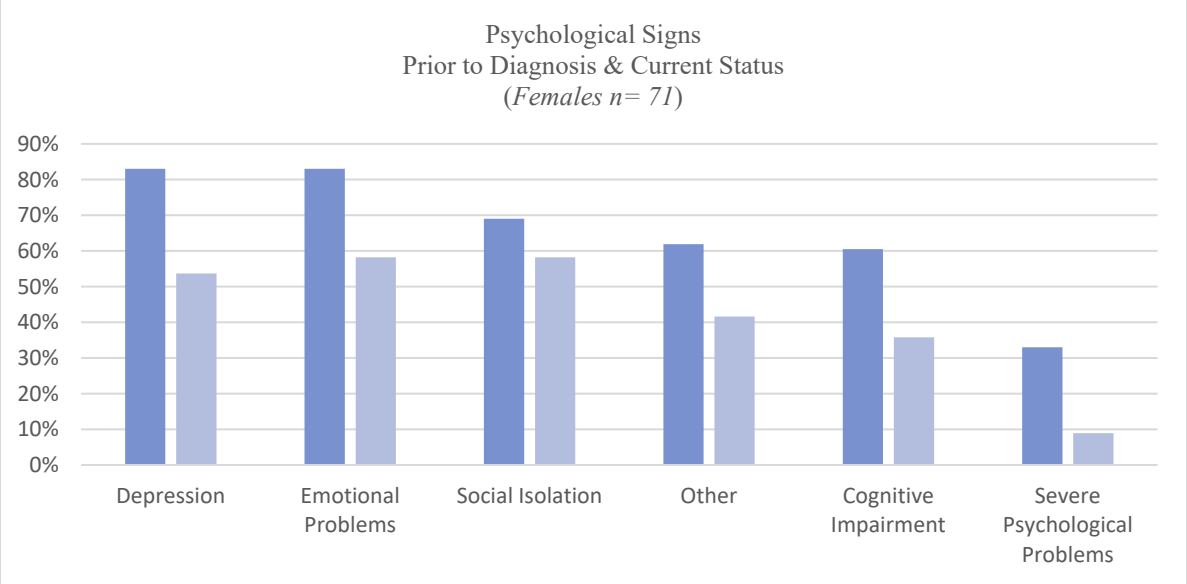
To establish the existence of a significant change in the signs and symptoms scores (*Box A and Box B*), a Paired *t* test were performed on the data to assess any differences in the scores i.e., physical signs and symptoms experienced prior to diagnosis compared with the current status. The results indicated a significant difference, *P*<.0001, which suggested that most of the females were currently. experiencing fewer physical signs and symptoms than they had prior to their diagnosis.

The Cronbach's alpha was used to measure the internal consistency of the test items and refers to the extent to which each item measured different aspects of the same concept: this coefficient was 0.795, which is above the accepted 0.7 level of reliability, therefore reflecting a fair, acceptable level of internal consistency of the unidimensional items within the questionnaire.

6.3 Analysis of psychological and cognitive impairment signs and symptoms for Prior to diagnosis and Current status.

Figure 21, displays the results (%) of the female psychological conditions and cognitive impairments signs and symptoms prior to diagnosis as answered in Box A and the current status, Box B.

Figure 21



QRR=100%. Figure 21 displays the results of the female psychological and cognitive impairments signs and symptoms prior to diagnosis as answered in Question 20, Box A, and current status, (Box B).

Table 11 (*Female Results, Question 20*).

Question 20 ***Psychological & Cognitive Impairments*** ***Signs & Symptoms.***	***Prior to Diagnosis (Box A)***
Mean number = 3.26	*Min.=0, Max=5, SD= 1.3*
Physical Signs & Symptoms	***Current Status (Box B)***
Mean number= 2.42	*Min.=0, Max= 5 SD= 1.35.*

QRR= 100%. Total Number of Questions=6, Maximum Achievable Score=6.
Table 11 displays the female results of the psychological and cognitive impairments signs and symptoms Prior to (Box A), and Current Status (Box B).

The mean difference was = 0.84 items (*Box A and B signs and symptoms*). The Paired *t* test result to compare the means was *P*<.0001. These results suggested a significant difference in the number of signs and symptoms prior to and current status. This result therefore suggested that these female members, at the time of completing the questionnaire were experiencing fewer signs and symptoms.

The Cronbach's alpha was used to measure the internal consistency of the test items: this coefficient was 0.663, reflecting an acceptable level of internal consistency of the unidimensional items. However, the number of items was small (*n=6*) in *Box A and B,* and this may have influenced the results.

6.4 Female Age Group Analysis (physical signs and symptoms).

To establish if there was an age group of females who had a higher score, the 71 females who answered this question were placed into age groups as follows:

Age Groups= 19-29 (n= 6), 30-40 (n=25), 41-51 (n=20),52-62 (n=14), 63-73(n=3).

The median age of the female study population was 42, and the age group who had the most members was the 30-40year age group, (*n=25*). The mean, min. max. values, including the SD, for the physical signs and symptoms *current status* for each of the age groups are displayed in *Table 12, Page 127.*

An independent samples *t* test was applied to compare the mean values of the two age groups who had the highest number of scores for *Boxes A* and *B,* i.e., Age groups 30-40 and 41-51. The Hartley test for equal variance result was F=1.743, the *P* value was .09 (*CI= 95%*), which indicated that there is a likelihood of a slightly significant difference in the number of physical signs and symptoms prior to diagnosis and current status between these age groups. The 30-40 age group, showing more signs and symptoms compared with the age group 41-51. However, it should be noted from *Table 12*, that the sample sizes are unmatched.

For the age groups 19-29 and 63-73 due to the small numbers in each group, no inferential statistics were performed.

Table 12 (*Female Results -Question 20*).

Female Age Groups					
		Mean	Minimum	Maximum	SD
19-29	n= 6	4.60	4.0	6.0	.89
30-40	n= 25	3.96	0	6.0	1.64
41-51	n= 20	3.65	0	6.0	1.74
52-62	n= 14	3.07	0	6.0	1.75
63-73	n= 3	4.40	2.0	6.0	1.67

Table 12 displays the mean, min., max. and SD values for the female psychological and cognitive impairments, current status scores (Box B), for each of the age groups. Total Number of Questions=6 Maximum Achievable Score=6.

6.5 Female Age Groups Analysis (psychological and cognitive impairments signs and symptoms).

Table 13 (Female Results- *Question 20*)

Female Age Groups					
		Mean	Minimum	Maximum	SD
19-29	n= 6	13.1	7	19	4.57
30-40	n= 25	13.4	0	23	4.45
41-51	n= 23	12.8	0	22	5.88
52-62	n= 14	14.0	10	21	3.38
63-73	n= 3	14.1	1	19	6.85

Table 13 displays the male score results of the mean, min, max. and SD number of physical signs and symptoms Prior to diagnosis, (Box A), and Current status (Box B).
QRR- 100% Total Number of Questions= 24, Maximum Achievable Score=24

An independent samples *t* test was applied to compare the mean values of the two age groups who had the highest number of members, i.e., in the age groups 30-40 and 41-51 years old. The *P* value was .38 (*CI= 95%*). On applying the Hartley test for equal variance, the result was: F=1.129. This result therefore indicated that there is no significant difference in the number of psychological conditions and cognitive impairments signs and symptom*s* current status, between these age groups.

6.6 Male Age Group Analysis (physical signs and symptoms)

Table 14, Page 128, displays the male physical signs and symptoms score results for the mean, min, max. and SD number of signs and symptoms prior to as answered in *Box A* and the current status, *Box B.*

The mean difference was 4.3 signs and symptoms for all age groups. The Paired *t* test was performed, and the result was *P*>.0001, indicating that there was evidence of a significant difference, i.e., the male population are currently experiencing fewer physical signs and symptoms.

The Cronbach's alpha was used to measure the internal consistency of these test items: the coefficient result of 0.504, was found to be acceptable but weak in its level of consistency of the unidimensional items.

Table 14 (*Male Results, Question 20*).

Question 20 ***BOX B*** ***Physical Signs & Symptoms.***	***Prior to Diagnosis (Box A).***
Mean number = 9.3	***Min.=5, Max=12, SD= 2.0***
BOX B ***Physical Signs & Symptoms***	***Current Status (Box B).***
Mean number= 5.0	***Min.=0, Max= 12, SD=3.0.***

QRR- 100%Total Number of Questions= 24, Maximum Achievable Score=24
Table 14 displays the male score results of the mean, min, max. and SD number of signs and symptoms Prior to diagnosis, (Box A), and Current status (Box B).

***Question 20*: (*Box A and Box B*).** The following results are the psychological conditions and cognitive impairments signs and symptoms. experienced by the male participants.

Table 15

Question 20 ***BOX A*** ***Psychological & Cognitive Impairments Signs & Symptoms***	***Prior to Diagnosis (Box A).***
Mean number = 4.0	*Min.=2, Max=6, SD=1.3*
BOX B ***Psychological & Cognitive Signs & Symptoms***	***Current Status (Box B).***
Mean number= 2.4	*Min.=0, Max= 4, SD= 1.35*

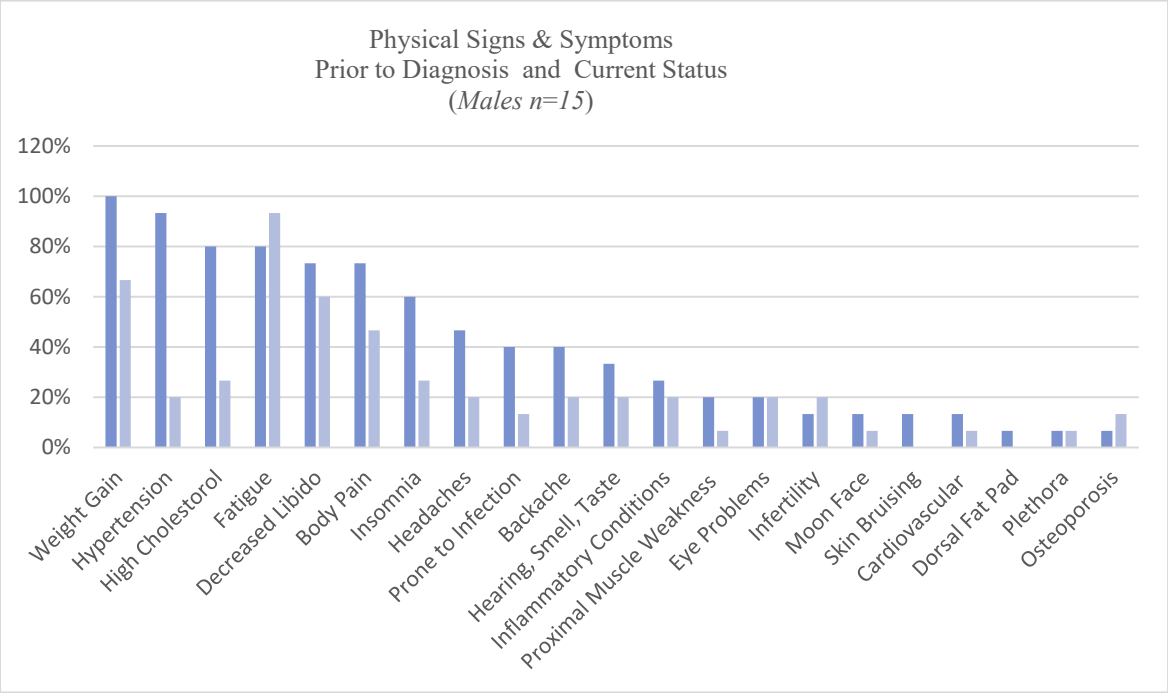
QRR= 100%. Table 14 displays the male results of the mean, min., max. and SD for the psychological and cognitive impairments signs and symptoms Prior to diagnosis (Box A), and Current status (Box B).

The mean difference was = 2.0. The Paired *t* test result was *P*<.004, suggesting that the male members were currently experiencing less psychological and cognitive impairment signs and symptoms.

The Cronbach's alpha was used to measure the internal consistency of these test items: this coefficient was 0.609, reflecting an acceptable level of internal consistency of the unidimensional items. However, the number of items was small and therefore could have influenced this result.

Figures 22, and Figure 23, Page 129, displays the results (%) of the male physical and psychological and cognitive impairments signs and symptoms prior to diagnosis and current status as answered in Box A and the current status, Box B.

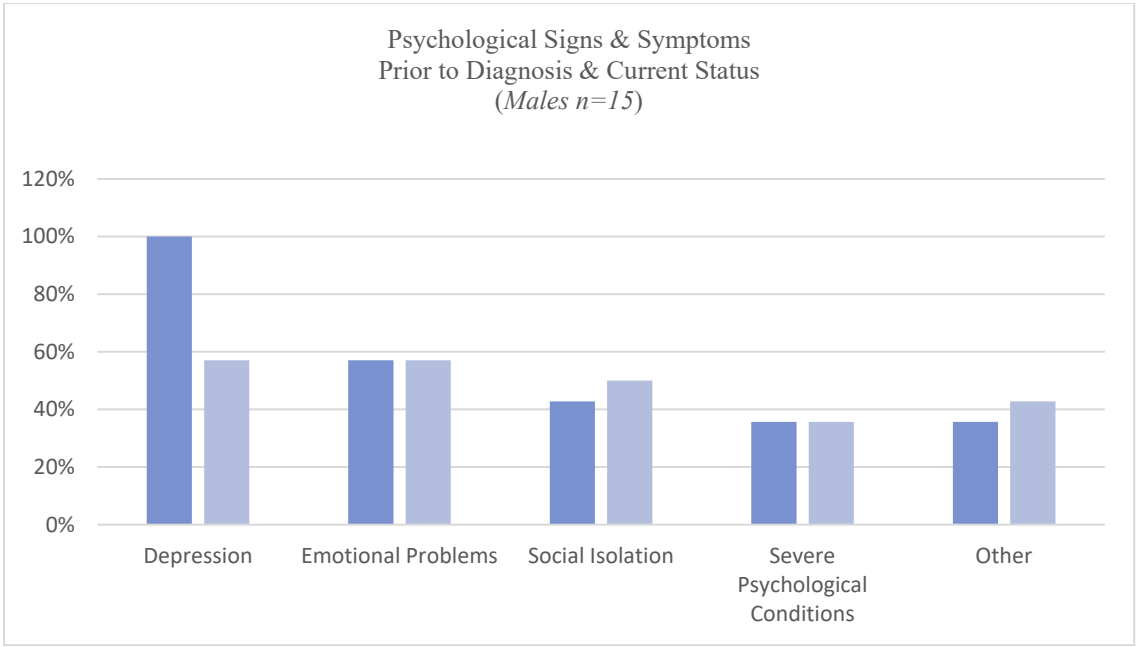
Figure 22



QRR=100%. Figure 22 displays the results of the male physical signs and symptoms Prior to diagnosis (Box A), as answered in Question 20 Box A and Current status, (Box B).

Prior to Diagnosis Current Status

Figure 23



QRR=100%. Figure 23 displays the results of the male psychological and cognitive impairments signs and symptoms prior to diagnosis and current status as answered in Question 20, (Box A,) and the current status in (Box B).

Prior to Diagnosis Current Status

6.7 Male Age Group Analysis (physical signs and symptoms).

Table 16 below displays the male age groups mean, min, max and SD score results (*Current status*). No male members were in the 63-73 age group.

The mean age of the male study population was 39.4. The descriptive statistics showed that the age group 30-40 had the highest number of members (*n=9*), with the *max.* item score being 12, (*min=.8.6, mean value=5.0, SD= 2.29*).

Due to the small study population in each of the age groups, inferential statistics were not performed.

Table 16 (*Male Results Question 20*).

Male Age Groups					
		Mean	Maximum	Minimum	SD
19-29	n= 1	3.0	3.0	3.0	
30-40	n= 9	5.0	12.0	8.6	2.29
41-51	n= 3	7.0	12.0	10.3	2.88
52-62	n= 2	7.0	10.0	8.5	2.12
63-73	n= 0				

Total Number of Questions=24, Maximum Achievable Score=24
Table 16 displays the mean, min., max., and SD values for the male physical Current status results for each of the age groups as reported in Question 20, Box B.

6.8 Male Age Group Analysis (psychological conditions and cognitive impairments signs and symptoms).

Table 17, below displays the number of responses from each of the male age groups along with the mean, min, max, and SD values for each age group score (*Current status*).

Table 17

Male Age Groups					
		Mean	Minimum	Maximum	SD
19-29	n= 1	1.00	1.0	1.0	
30-40	n= 11	2.63	0	4.0	1.20
41-51	n= 3	1.66	1.0	2.0	.577
52-62	n= 0	0	0	0	0
63-73	n= 0	0	0	0	0

Total Number of Questions=6 Maximum Achievable Score=6
Table 17 displays the mean, min., max., and SD values for the male psychological and cognitive impairments Current status results for each of the age groups as reported in Question 20, Box B.

The 30-40year old group had the highest number of males (*n11),* and had the highest items scores, the mean value being 2.63, (*max= 4.0, min.= 0, SD= 1.20*). Notably, none of the other male age group max. scores were above 4.0.

- *Comparing the quantitative results for the female with the male population, the 30-40 age group for both genders had the highest responses, and item scores for both the physical, psychological conditions and*

cognitive impairments, (Question 20.) However, although the female population appears to have considerably higher scores in all the dimension of health, gender comparison. These results could not be qualitatively analysed, due to the smaller male study population in all age groups.

- *The effects of the variations in group sizes therefore unfortunately, limited the power of analysis. It should also be noted that recall bias may also have influenced the results, particularly for the Box A scores (Prior to diagnosis). The consequences of this are acknowledged in Chapter 3, Section 2.6.6, Page 101 and in Chapter 7, Study Limitations, Page 207.*

Section 7 reports the answers given in Questions 25 and 25a). These questions were designed to ascertain if any of the participants had been diagnosed with other conditions associated with CS.

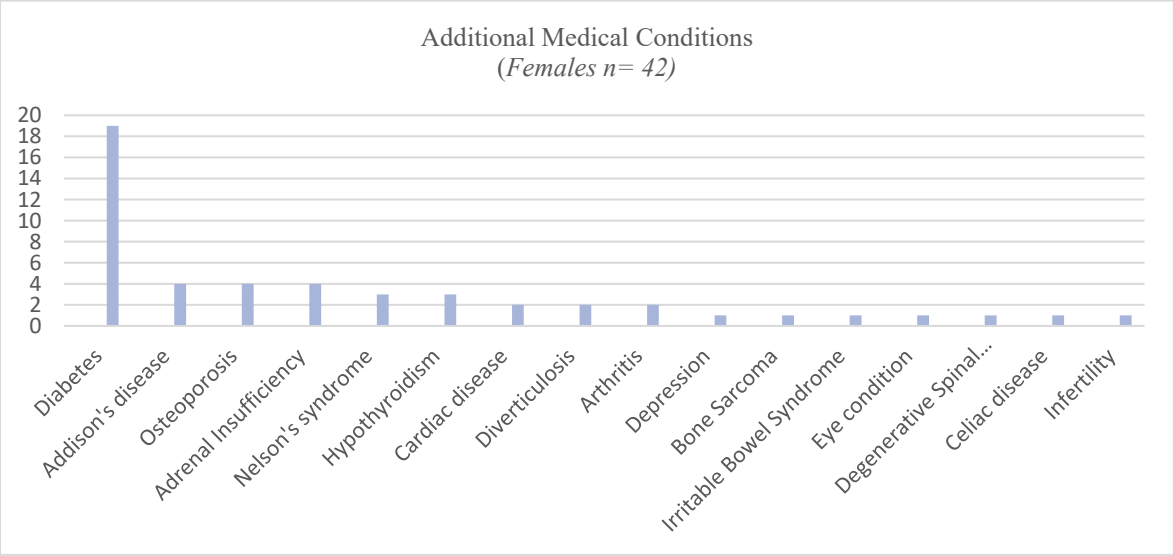
***7.0 Other* Conditions Associated with a Cushing's Diagnosis**

Question 25 Forty-two (*60%*) of the females answered YES, 28 (*40%*), answered NO. Eight (*53.3%*), males answered YES, 7 (*46.6%*), answered NO.

Question 25a) The 42 (*60%*), females who had answered YES in Question 25 named the range of medical conditions which were associated with their diagnosis of their Cushing's illness. (*Range of female named medical conditions=16 as displayed below in Figure 24).*

Four (*50%*) of the 8 males who answered YES named their other medical conditions associated with their Cushing's illness. Two (*25%*), members had developed diabetes, 2 (*25%*), Addison's disease following their adrenal surgery.

Figure 24



QRR= 59.1% Figure 24 displays the additional medical conditions experienced by the 42 females and reported in Question 25a).

Section 8 reports the results of Questions 21 to 24a). These questions were designed to establish hospitalisations and the diagnostic tests, including medical imaging which each member had prior to their diagnosis.

8.0 Hospitalisation & Diagnostic Tests.

8.1 Hospitalisations

Question 21*:* sought to establish if any of the study population had been hospitalised due to their Cushing's or any other associated medical conditions which they had identified in *Question 25a).*

The *QRR* was 98.5% for the females and *100%* for the males.

a) ***Female Results:***

Fifty-six *(80%*) of the females had hospital confinements.

b) ***Male Results:***

Fourteen (*93.3%*), males were hospitalised due to their Cushing's illness.

Question 21a): established the number of hospital confinements and were answered by all the study population who had answered the previous question. The mean number of confinements = 4 (*min= 1, max= 9*), for the 56 females and the mean number of confinements for the 14 males was= 2 (*min.=1, max.=5*).

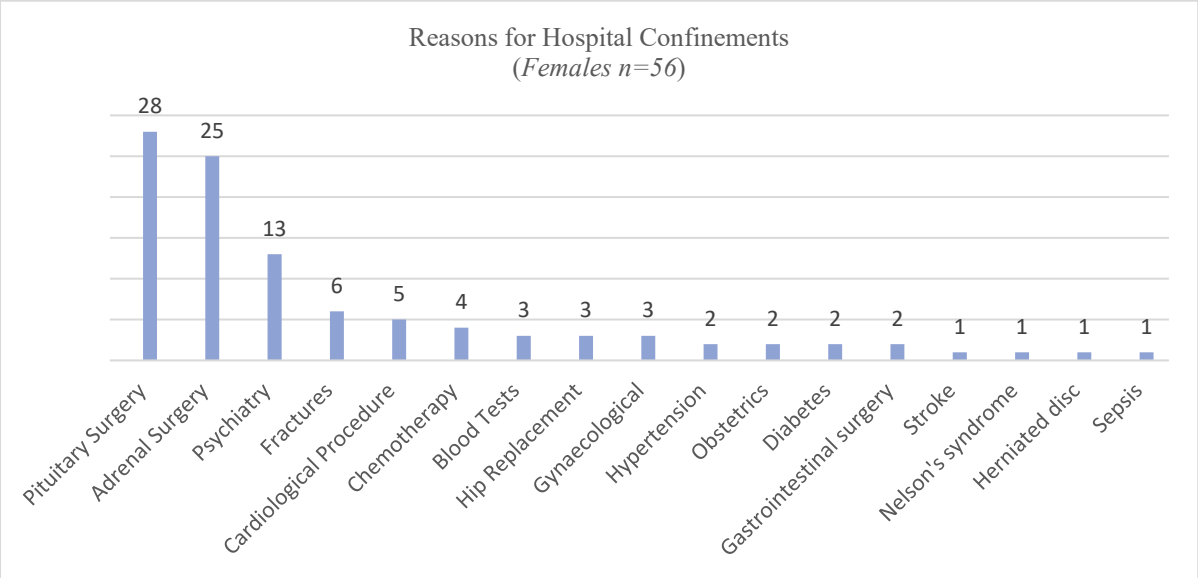
Question 21b): was also answered by the same 56 females.

Main Observations: A large proportion of the females were admitted to hospital for adrenal (*44.6%*), or pituitary (*50%*), surgery, in some cases as earlier reported, for both.

Figure 25, Page 133 and Figure 26, Page 133, displays the types of medical conditions which were the reasons for the 56 female participants hospitalisations and the 11 males.

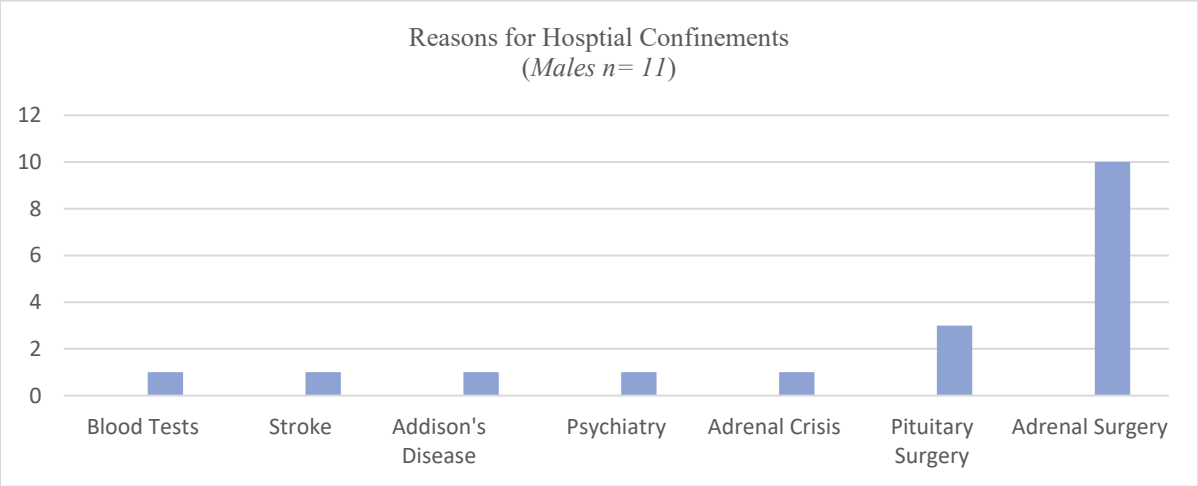
This question was also answered by 11 (*78.5%)* of the males who were hospitalised. Similar to the females, adrenal surgery (*90.9%*), and pituitary surgery (*27.2%*) were the main reasons for hospitalisation.

Figure 25



QRR=80%. Figure 25 displays the female results of Question 21b) which gives the number of responses to for each of the reasons for their hospital confinements. Details of the results are discussed in Chapter 4.

Figure 26



QRR= 78.5%. Figure 26 displays the male results of Question 21b) which gives the number of responses to for each of the reasons for hospital confinements.

8.2 Diagnostic Tests

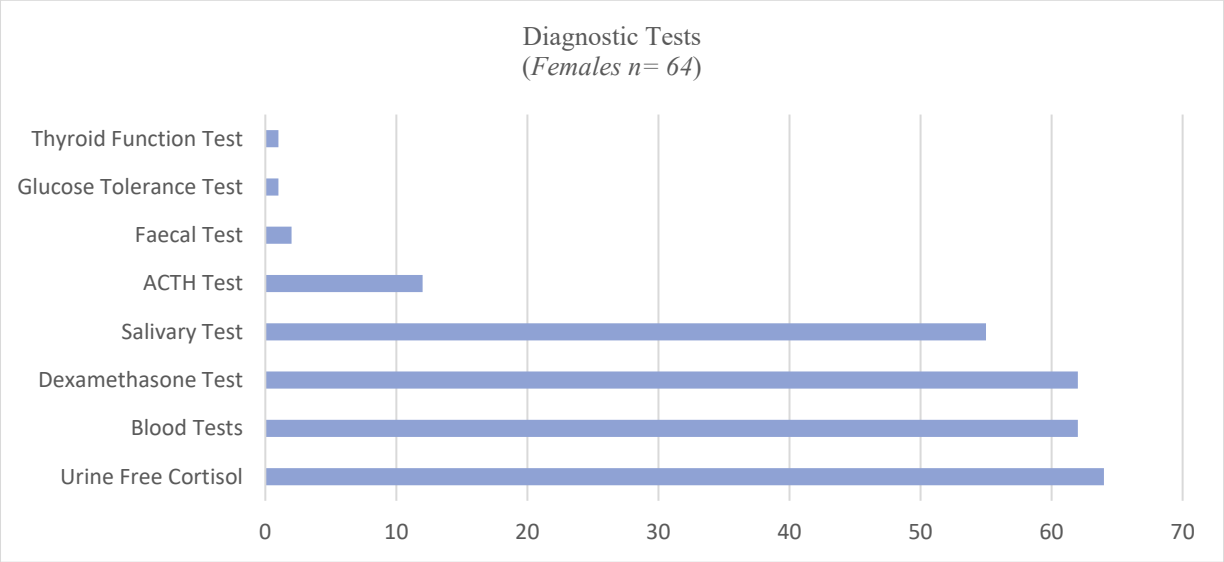
Question 22) All 86 members of the study population answered this question, and all reported that they had a series of blood tests, urine, and salivary tests.

Question 22a) sought to establish which type of tests were conducted and although all answered *Question 22*, the female *QRR* for this part of the question, was *90.1%* and the male, *86.6%*. The mean number of tests for the females was= 4 (*min=2, max=6*), and the males was also 4 tests (*min=3, max.=5).*

Figure 27 and Figure 28, below displays the full range of tests for the study population.

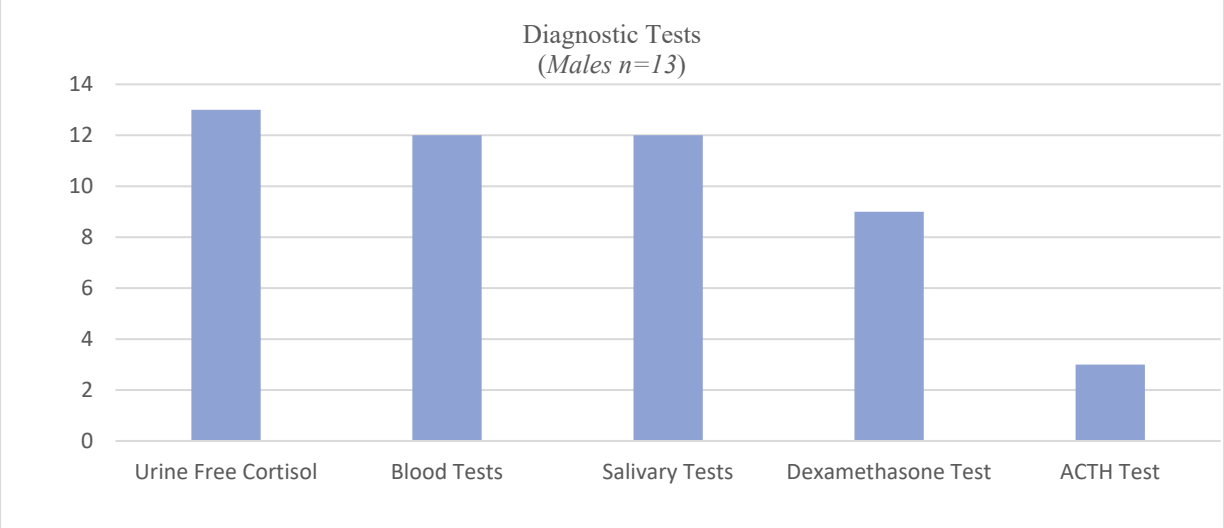
** Please note that many of these tests are repeated throughout the diagnostic assessment, during treatment and post treatment as reported by the members.*

Figure 27



QRR= 90.1%. Figure 27 shows the results of the type of diagnostic tests for the female population who answered Question 22a).

Figure 28



QRR= 86.6%. Figure 28 graph shows the results of the types of diagnostic tests for the male population who answered Question 22a).

8.3 Diagnostic Medical Imaging

Question 23 The *QRR* for the female population was *63.3%*, (*n=45*), all of whom had a CT abdominal scan of their adrenal glands, prior to their diagnosis. Twelve (*80%*) of the males also had a CT scan of their adrenal glands.

Question 24 This question sought to establish whether any of the members had an MRI pituitary scan prior to their diagnosis.

Forty-nine (*QRR=69%*), of the females had an MRI scan and 38 (*53.5%*), of them also had both a CT of their adrenal gland and an MRI pituitary scan.

Four (*26.6%*) of the males also had an MRI pituitary scan, 3 (*20%*) other males had both a CT and MRI scans (*QRR= 100%*).

Question 24a) asked the members if they had been referred for any other type of diagnostic imaging examination or procedure during their diagnostic journey.

Fifty-eight (*QRR=81.6%*), females reported that they had other medical imaging examinations/procedures. The mean number of additional examinations/procedures was 2 (*min.=1, max.=6*).

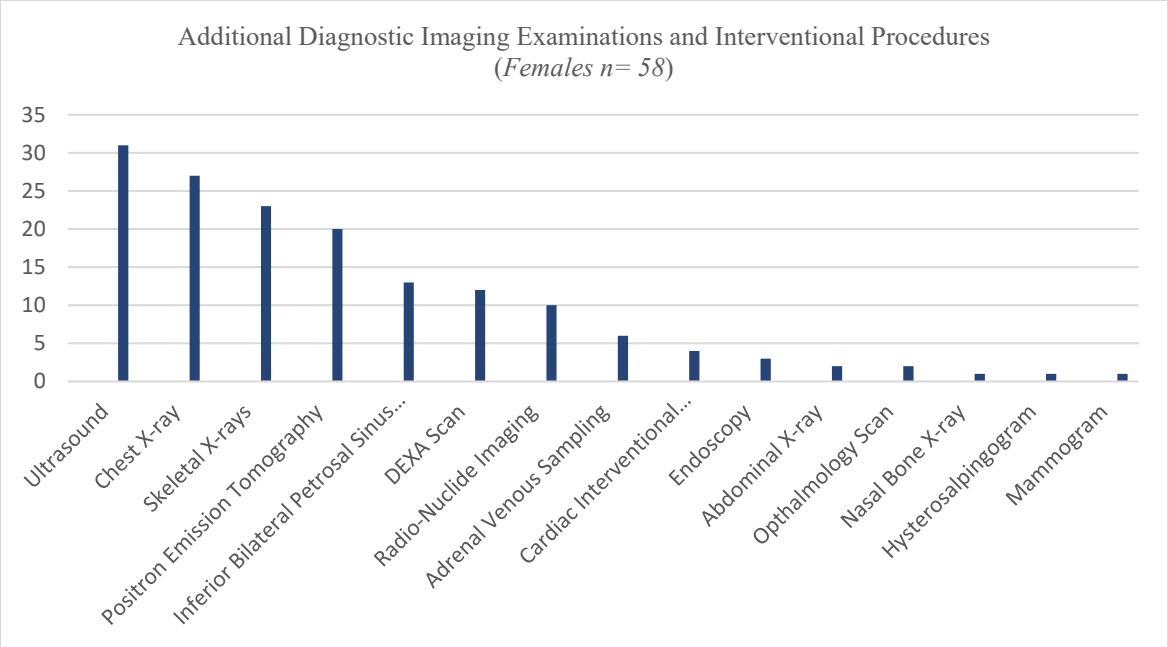
The *QRR* for the male results for this question was *93.3%.* Fourteen males answered giving details of their additional examination(s)/procedures. Eight (*57.1%*) of them had more than 1 additional examination/procedure, the mean number being 2 (*min=1, max-3*).

The mean number of additional examinations/procedures for 40 (*46.5%*) of the study population who were diagnosed with both CS and CD, was 3 (*min.=1, max.=8*).

Interestingly, the collective total of additional examination/procedures for all members was 182. The range of imaging examinations/procedures for the females was 15 and the males, 7.

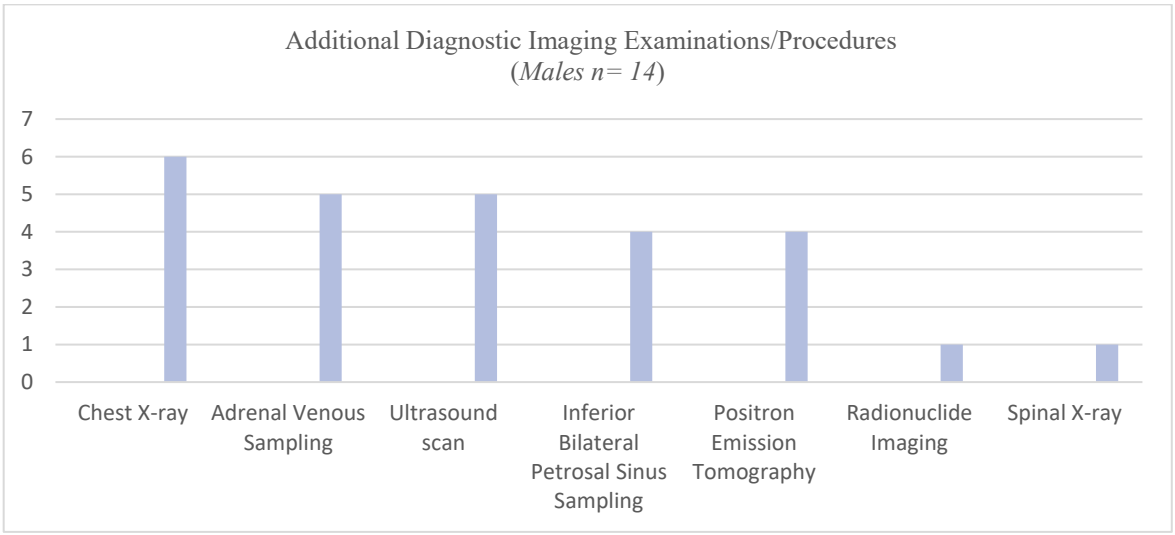
Figure 29, and Figure 30, Page 136, displays the range of additional radiological examinations/ procedures for the study population.

Figure 29



QRR= 81.6% Figure 29 displays the additional medical diagnostic examinations/procedures reported by the 58 females who answered Question 24a).

Figure 30



QRR= 93.3%. Figure 30 displays the additional medical diagnostic imaging examinations/ procedure reported by the 14 male participants in Question 24a).

The results of the questions in Section 3 of the Cushing's QoL survey questionnaire are presented in the following sections.

Sections 9 to 12 reports the answers to Questions 26, to Question 36c. These questions are related to the types of surgical procedures and the range of therapies which each of the members received post diagnosis.

9.0 Surgical Procedures and Therapeutic Treatments

9.1 Surgical Interventions

9.1.1 Adrenal Surgery

Question 26: asked the members if they had adrenal surgery. Fifty-four (*76%*) of the females answered this question, 34 (*62.9%*), of them had adrenal surgery for their CS. One female was awaiting surgery. The male *QRR* was *100%,* 13 (*86.6%*), of them also had adrenal surgery for their CS.

The follow-up questions (*26a*) asked the members what type of surgical procedure had been carried out. All 34 females who had surgery answered this question. Ten (*76.9%*), out of the 13 males who had adrenal surgery also answered this question.

Question 20bi), and 26bii): were follow-up questions which were designed to ascertain the techniques performed during their surgery.

All 34 females who had surgery answered this question. Twenty-one (*61.7%*) of the females had laparoscopic surgery and 13 (*38.2%*), had open surgery.

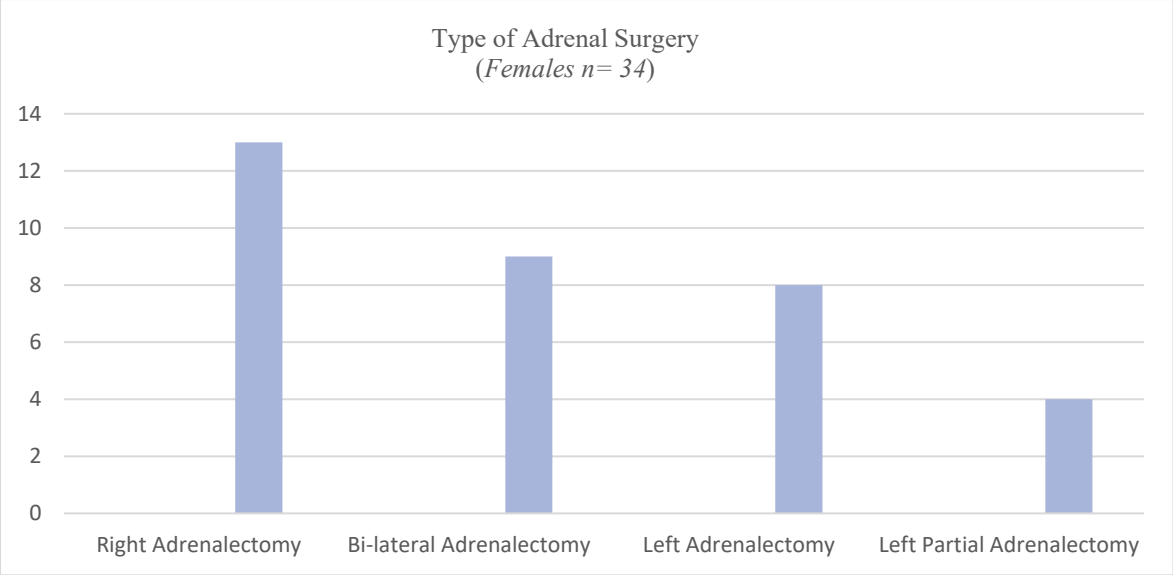
Only 10 (*76.9%*) of the 13 males who had adrenal surgery also answered this question Six (*60%*), had laparoscopic surgery, 4 (*40%*), had open surgery.

Figure 31 displays the type of adrenal surgery for the 34 females and Figure 32, for the 10 males, displayed in Page 138.

Questionnaire: Section 3

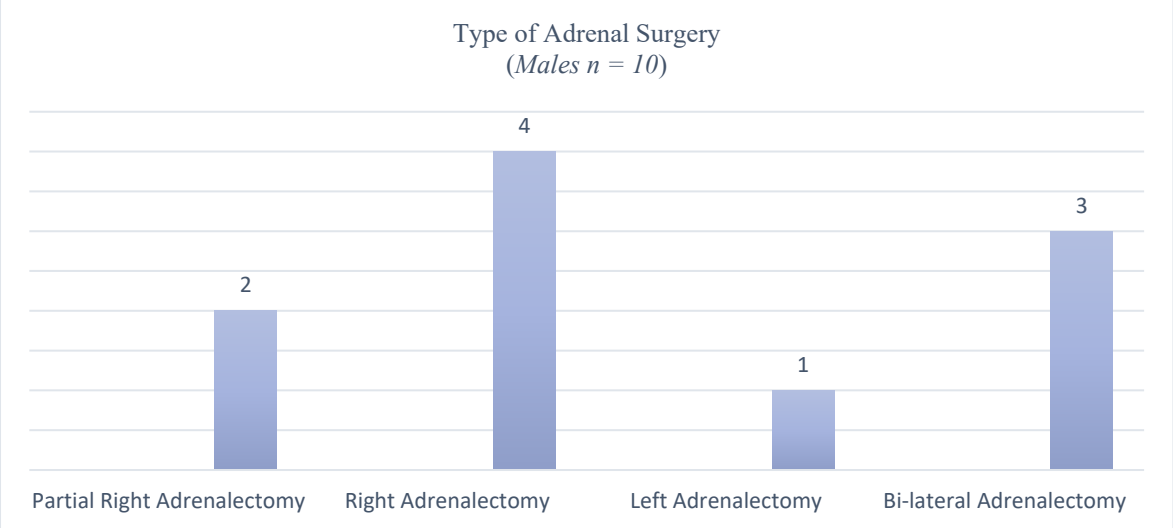
Results Surgical Procedures

Figure 31



QRR= 47.8% Figure 31 displays the results for Question 26,

Figure 32



QRR= 66.6%. Figure 32 displays the male results for Question 26,

Question 26biii): sought to establish if those members who had surgery were cured (*in remission*), of their CS. The *QRR* was *46.2%* for the females who had adrenal surgery. Twenty (*58.8%*) of them answered YES, adrenal surgery had cured their Cushing's. All the males who had adrenal surgery, answered this question. Five (*38.4%*) of them reported that surgery had not cured their Cushing's.

9.1.2 Pituitary Surgery

Question 34: asked the members if they had pituitary surgery for their CD. Both the female and male *QRR* was *100%* for this question. Forty-three (*97.7%*) of the 44 females who were diagnosed with CD had pituitary surgery. Thirty-six (*83.7%*) of them out of the 43 answered ***Question 34a*).** This question asked the year they had their surgery. The years ranged between 1988 and 2020, 2 (*5.5%*), of them as recent as 2020. Fourteen (*32.5%*), out of the 43 answered YES to ***Question 34b*),** which asked if they had repeat surgery. Eleven (*78.5%*) of the 14 females answered YES to ***Question 34c)*** which asked how many times, did they have pituitary surgery: (*min=2, max= 5, mean= 2*).

Six males also had pituitary surgery for their CD. Four (*66.6%*) of them answered ***Question 34a)*** giving the year ranges between 1999-2019 and 3 (*50%*), of them had repeat surgery **(*Question 34b*).** One (*33.3%*) of these males had 1 repeat surgery, and 2 others had 2 repeat surgeries **(*Question 34c*).**

10.0 Medical Therapy, Radiotherapy and Chemotherapy

10.1 Medical Therapy Treatment

Question 27*:* asked the members if they were currently taking hormone replacements in the form of steroid/GCs for their Cushing's illness. The female *QRR* was *97.1%,* 50 (*72.4%*), of the 69 answered YES, while 19 (*27.5%*), answered NO. All males answered this Question, 10 (*66.6%*), stated that currently they were taking hormone replacements, while 5 (*33.3%*), were not.

Question 28*:* focused on when these members commenced taking their medication. The female *QRR* was *85.9%.* Twenty-seven (*44.2%*) of the females commenced taking their steroids/GCs post-surgery, 21 (*34.4%*), as soon as they were diagnosed and 13 (*21.3%*), prior to their surgery.

The male *QRR* was *100%.* Eight (*53.3%*), males were recommended to take hormone replacements post-surgery. One (*6.6%*), male started hormone therapy prior to their surgery and 1 (*6.6%*), was unsure when they commenced their hormone therapy. Five (*33.3%*), males reported that they had taken steroids but are not currently taking hormone replacements, as reported in *Question 27.*

Question 29*:* was a follow-up answer from *Question 27* in that the members were asked which GCs or hormone replacements that they are currently taking. The *QRR* was lower for the females than in *Question 27,* i.e., 57 females (*82.6%*).

Fifty-one (*89.4%*), females reported that they were prescribed Hydrocortisone, 2 (*3.5%*), Prednisone, 1 (*1.7%*), female is taking a combination of Hydrocortisone and Fludrocortisone, 1 (*1.7%*), takes Metyrapone and Hydrocortisone and 1 (*1.7%*), Metyrapone only. One (*1.7%*), female was taking Hormone Replacement Therapy (*HRT*).

The 10 males who answered *Question 27*, also answered this question. Nine (*90%*) of the males named Hydrocortisone as their prescribed GCs and 1 (*10%*), male answered Prednisone.

Question 30: This question sought to establish the information/advice given to them by their endocrine team regarding the length of time that they would be required to take steroids/GCs for their Cushing's illness.

Sixty-seven (*94.3%*), females answered this Question. Twenty-six (*38.8%*) of them answered that they have been advised by their endocrine team that they will always require to take steroid medication, 18 (*26.8%*), no longer take steroids. Ten (*14.9%,)* of the females reported that they are attempting to reduce and stop taking their steroids, 6 (*8.9%*), were unsure. Seven (*10.4%*) of the females answered N/A as they had not been prescribed steroid medication.

All males answered this question. Seven (*46.6%*) of the males are no longer taking GCs, 3 (*20%*), are attempting to reduce but did not know how long they would be required to take them. Five (*33.3%*) of the males have been advised that they will always require to take GCs.

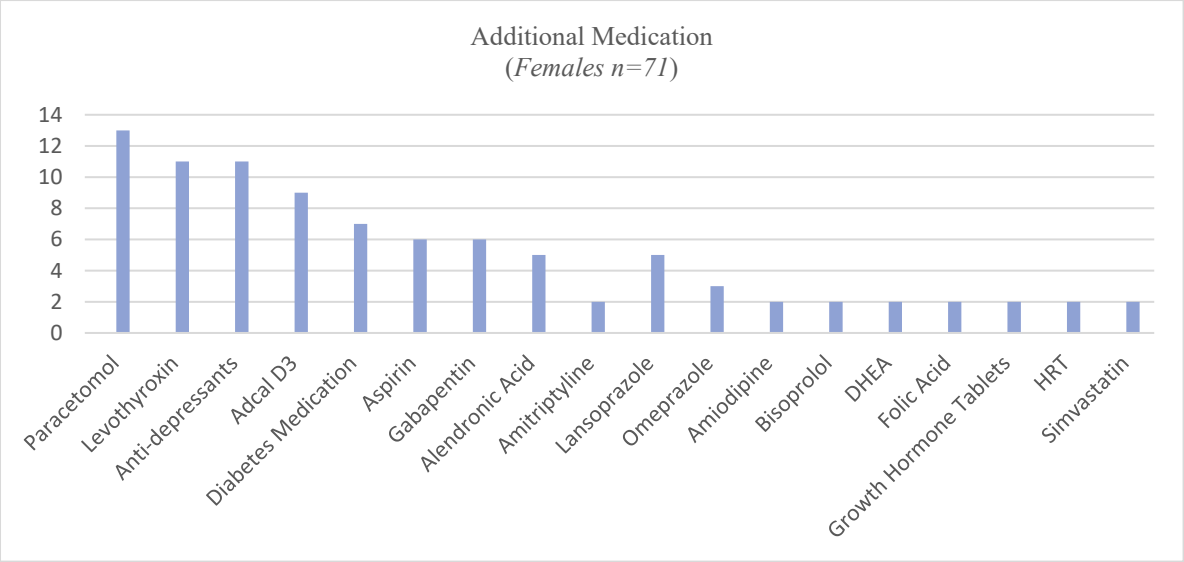
Question 31: asked the members if they were also prescribed other types of medication because of their Cushing's illness. All 71 females have been prescribed additional medications since being diagnosed with their Cushing's illnesses. However, 19 (*26.7%*) of them currently do not take additional medication.

Similar to the female response, *100%* of the males answered this question. Nine (*60%*), males reported YES, they were prescribed other medications in relation to their Cushing's illness.

Question 31a):

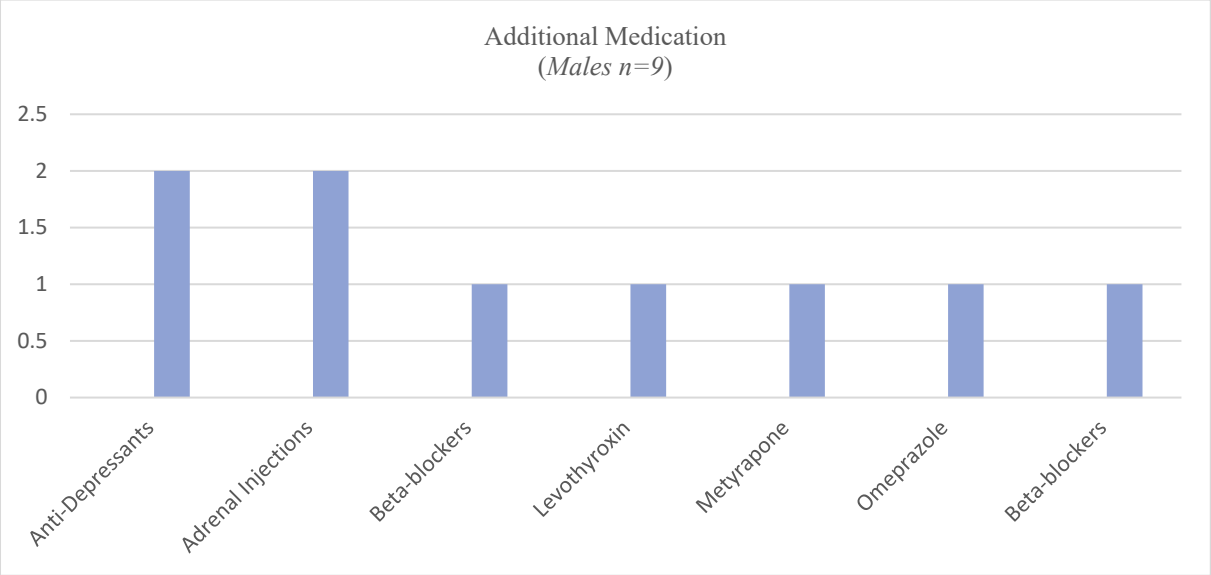
Figure 33 and Figure 34, Page 141, displays the range of additional medications prescribed for the study population. A range of 18 types of medications were reported for the females and 7 for the males.

Figure 33



QRR= 100%. Figure 33 displays the additional medications which were prescribed for the female participants due to their Cushing's illness. (Range of prescribed medications= 18). Details of the results are discussed in Question 31.

Figure 34



QRR= 60%. Figure 34 displays the results of the nine male participants who answered this question. (Range of additional medications = 7). Details of the results are discussed in, Question 31.

Female Main Observations: The highest number of females who were taking additional medication for body pain was 13 (*18.3%*), (*Paracetamol*), 11 (*15.4%*), (*Levothyroxine*), for their hypothyroidism, 11 (*15.4%*), taking unnamed medicine for anxiety and depression, 9 (*12.6%*), (*Adcal D3*), and Vitamin D for osteoporosis and 5 (*7%),* also were taking Alendronic Acid-bisphosphonate for osteoporosis. Seven (*9.8%*), females were taking a range of medicines for their Diabetes, and 6 (*8.4%*), were taking Aspirin regularly for pain and inflammatory conditions. Eight (*11.2%*), females were taking Proton Pump Inhibitors (PPI), (*Omeprazole=n=3, Lansoprazole n=5*), for gastric reflux.

The calculation of the mean for additional medications (*Physical and Psychological*), = 3, (*min.=1, max.=6*).

Male Main Observations: Seven (*77.7%*) of the 9 males who answered, were prescribed additional medication for physical illnesses and 2 (*22.2%*), were prescribed anti-depressants for psychological issues. Only 1 (*11.1%*) of them was taking 2 types of medicine, 1 (*11.1%),* for thyroid reasons (*Levothyroxine*), and anti-depressants for psychological conditions.

11.0 ***Radiotherapy Treatment***

Question 35/35a): sought to establish if any of the study population had received RT following their adrenal or pituitary surgery. The study population *QRR* was *100*%.

Sixteen (*37.2%*) of the 43 females had RT following their pituitary surgery. Three (*20%*), males had RT for their pituitary gland and 1 (*6.6%*), had RT following their adrenal surgery.

***Question 35*bi), *35b*ii):** were follow up questions asking which type of RT treatment they had and how many treatments. Fourteen (*87.5%*) of the 16 females who had RT were treated with GK-RS, 2 (*12.5%*), participants had RT treatment using LINAC. Thirteen (*81.2%*), out of the 16 females who had answered ***Question 35*bii),** gave their number of treatments which ranged between 1 set of treatments and 12, (*mean=4*). Surprisingly, many of them admitted that they were unsure as to the exact number of RT sessions.

Thirteen (*81.2%*) of the 16 females who answered ***Question 35bii*),** reported a range of 9 types of side effects as a result of their RT treatment **(*Question 35biii*).** Nine (*69.2%*) of them reported that they experienced sickness following treatment, 3 (*23%*), fatigue, 2 (*15.3%*), nausea, 2 (*15.3%*), diarrhoea, 1 (*7.6%*), reported migraine headaches and 1 hypothyroidism. One (*7.6%*), participant also reported visual impairment, 1 (*7.6%*), dizziness and 2 (*15.3%*), reported that their skin became red with blisters. Mean number of side effects= 2, (*min= 1, max =3*).

Two (*50%*) of the 4 males answered GK-RS for their pituitary gland and the 2 (*50%*), others were unsure what type of RT they received. Two (*50%*), males answered that they had 6 treatments sessions.

Three out of the 4 males who had RT answered ***Question 35biii).*** Two (*50%*) of them reported nausea and sickness post treatment, the other reported nerve damage to their eyes following GK-RS.

12.0 ***Chemotherapy Treatment***

Question 36a)**:** asked if any of the members had chemotherapy treatment and if this had followed their surgical procedure **(*Question 36b*):** The *QRR* was *100%.* Four (*5.6%*), females answered YES, that they had chemotherapy treatment following their pituitary gland surgery. A range of 7 side effects were reported by these participants **(*Question 36c)*:** Side effects included sickness (*n=4*), hair loss (*n=3*), weight loss (*n=2*), loss of taste (*n=1*), loss of smell (*n=1*), 1 participant reported blurred vision and 1 participant reported extreme fatigue. Mean number of side effects= 3 (*min= 2, max= 4*).

Two males were awaiting consultation with an Oncologist, none of the other 13 had chemotherapy.

The following Sections 13.0 to 14.0 reports the answers to Question 32, 32a), 37 to 38b), which focuses on the provision of support groups and the Health Professionals and the public awareness of CS.

13.0 Endocrine Support Groups & Health Professions & Public Awareness

13.1 Endocrine Support Groups.

Question 32*:* asked the members if they were meeting regularly with their endocrine team for check-ups. The *QRR* was *100%*, 62 (*87.3%*), of the females answered YES. The *QRR* was *100%* for the males, 93% of them answered YES.

Question 32a) The *QRR* for the study population was *100%*. The mean time between consultations for the females was 8 months (*min. =3 months, max.= 3 years*). The male result was a mean time of 1.2 years (*min.= 2 months, max.= 2 years*).

Question 37**:** asked if their endocrine team suggested joining a support group?

The *QRR* for the study population was *100%***.** Thirty-one (*43.6%*), females answered YES, their endocrine team suggested joining a support group and 7 (*46.6%*), males also were given this suggestion from their endocrine team.

Question 37a): asked the members if they found joining a support group to be helpful? Thirty (*96.7%*), females who had answered YES in the previous question, found joining a support group was helpful, 1 (*1.4%*), participant did not. All 15 males answered this question which included the 7 (*46.6%*), who had answered YES to *Question 37*. All of whom found joining a support group to be helpful.

Question 37b): sought to establish the reasons why joining a support group had made a difference to their lives. The female *QRR* was *71.8%, (n=51).*

Seventeen (*33.3%*) of the female participants who answered this question, found that by joining a support group was helpful due to the information and advice which was provided. Fourteen (*27.4%*), participants discussed how it provided a support mechanism. Ten (*19.6%*) of the participants felt that by joining a group it provided the opportunity to exchange views, particularly through the social-media platforms giving, "pan-network support," and participating in conferences and online instant information. Eight (*15.6%*), explained the importance of the PF due to the benefits that it provides for them, particularly in discussing their illness and treatment regimens with endocrine experts. The remaining 2 (*3.9%*), who answered this question discussed the benefits of sharing their anxieties and problems. Twenty-one (*41.1%*), of the 51 responses were those who had not been given advice by the endocrine team to join a support group but included in their answers, who had suggested that they join a support group. These were friends (*4*), family (*6*), GPs (*2*) Gynaecologist (*1*), Psychologist (*1*), Gastroenterologist

(*1*), Haematologist (*1*), Psychologists (*2*), Orthopaedic Surgeons (*2*) and 1 member joined via the internet PF site on the advice of their psychiatrist.

The male *QRR* was 93.3% (*n= 14*). Eight (*57.1%*) of the males were not given the suggestion of joining a support group by their endocrine team but 6 (*75%*), of them named who had suggested that they join a support group. These were friends (*3*), their psychologist (*1*), their father (*1*), and a CSRF endocrine nurse.

Six (*42.8%*), other males said that they found that by joining a group it was an opportunity to talk to, "someone that understands," "share stories," experiences and, "helps the loneliness." Two (*14.2%*) of them found it was not only particularly helpful but alleviated their anxiety and was informative.

Forty-two (*48.8%*), members also discussed how they could access psychological support via support organisations and during their contact with their fellow members. However, they did feel that this should be offered by the endocrine team as part of their treatment options and encourage those who were not interested to join a support group.

Question 37b)

Table 18 below highlights further improvements which could be made by the endocrine team as suggested by 73 (84.8%), members of the study population.

Results Endocrine Support Groups & Health Professions and Public Awareness.

Table 18 highlights the improvements which could be made by the endocrine team, suggested by 73 of the participants (*Question 37b*).

Improvements	*Frequency*
Adequate time to discuss condition and advise.	100%
More understanding by the endocrine team of the psychological effects of the disease processes.	89%
More opportunities for psychological support.	92%
A more caring approach and interpersonal skills.	76%
Helpful to have a friend/or family member during consultations	46%

QRR= 84.5%

14.0 Health Professions & Public Awareness.

Question 38): was answered by *89.5%* of the study population. Sixty-four (*74.4%*), females answered NO, there is insufficient public awareness, 13 males (*15.1%*), had similar thoughts.

Question 38a): *Table 19, Page Appendix 2, displays the reasons given as to why public awareness is thought to be insufficient as reported by the 86 participants.*

** Notably, most of the study population included the need to raise awareness of CS for Healthcare Professionals which is also reported in Table 18, Page 145.*

Table 19 below displays the reasons given in *Question 38a),* as to why Health Professionals and Public Awareness is thought to be insufficient as reported by the 86 participants (*Question 38a*).

Perceptions	*Frequency*
Insufficient Health Professions & Public Awareness.	95%
Doctors, particularly GPS failure to recognize the signs/symptoms.	44%
Lack of Education & Training for medical staff.	42%
General lack of public awareness, particularly employers.	56%
Little information and promotion to create awareness.	15%

QRR= 100%

Question 38b*): Table 20, below displays the suggestions made by the 86 members which gave methods of increasing awareness, many of the answers included education and training for all Health Professionals.*

Table 20 displays the suggestions made by 86 participants which gave methods which could assist in increasing public awareness and knowledge and skills for Healthcare Professionals (*Question 38b*).

Training Needs	*Frequency*
Education & Training for all Healthcare Professionals & students.	66%
Raise Awareness via social media platforms.	30%
Post leaflets, brochures in GP surgeries and hospital clinics.	14%

QRR= 100%.

The results of the questions in Section 4 of the Cushing's QoL survey questionnaire are presented in in the following Sections.

The following Section (15) reports the answers to Question 39a) 39b), 39c) which focuses how the members rate their QoL

15.0 Health-related Quality of Life.

15.1 Survey Results for Measurement of Quality of Life (*Both Genders*)

15.2 Female Results

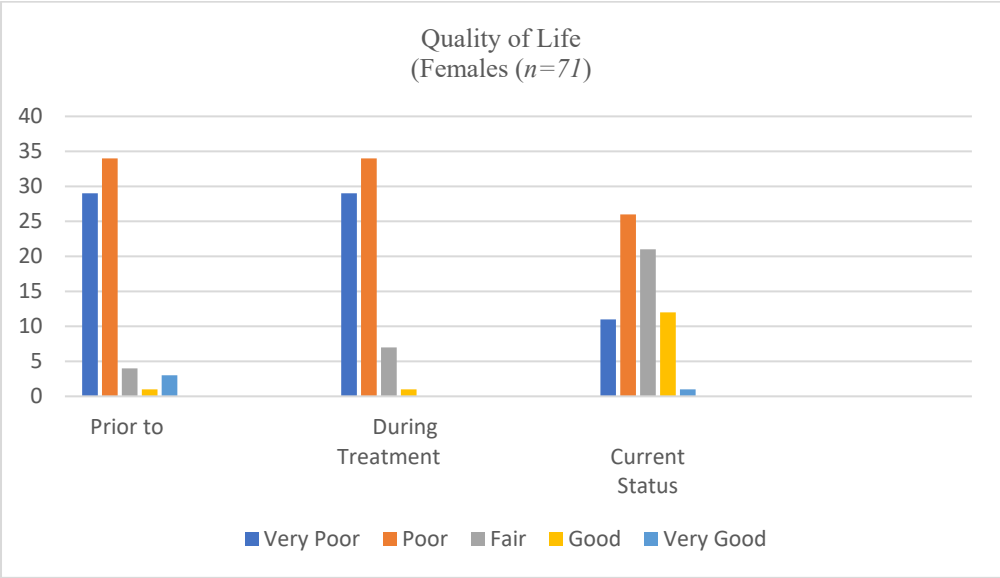
Question 39a), 39b), 39c).: This question was included in this survey to give the members the opportunity to respond to how they rated their QoL prior to their diagnosis, during their treatment and their current health status. The members responded on a Likert scale with 5 response categories. The responses were scored on a scale of 1-5, where 1 corresponds to Very Poor Health, 2-Poor Health, 3-Fair Health, 4- Good Health and 5 -Very Good Health. Each member's response for ***Questions 39a), b)*** **and** ***c),*** were added to the overall score for each individual part of this question. Descriptive statistics were used to summarise the quantitative data and inferential statistics to ascertain if there was a significant difference between each of the 3 categories i.e. ***Questions 39a) b)*** **and** ***c).***

Figures 35, below displays the female results of the Likert scale responses for Questions 39 a), b) and c).

Questionnaire: Section 4

Results Quality of Life Score Results.

Figure 35



QRR=100%. Figure 35 displays the female results of the Likert scale responses for Questions 39a), b) and c). The numerical values are displayed in the left- hand column.

The results revealed that *88.6%* of the females who answered *Question 39a),* rated their health as being either very poor or poor prior to their diagnosis. The responses to *Question 39b)* also showed that *88.6%* continued to have very poor and poor health. However,

Question 39c) results showed higher QoL scores at the time of completing the questionnaire. The responses to this Question resulted in *36.6%* less, in the categories Very Poor or Poor health, with *16.9%* being in Good health, *1.4%* in Very Good Health, *29.5%* in Fair health. However, it should be noted that *7.9%* of the latter had been in the Fair category prior to and during their treatment.

To establish if there was a significant difference between the health status responses for ***Questions 39a), 39b), 39c),*** the Likert scales which had produced ordinal data from each of the responses enabled the mean, median and inter quartile ranges (*IQR*) to be calculated for each category.

Applying the Kruskal-Wallis H test to examine the potential differences between the responses to all 3 questions, no significant difference was found, (KWH test= 4.000, df=4, *P*=.406).

This result therefore suggested that there was insufficient evidence that there was a significant improvement in health status (*QoL*), from prior to diagnosis, during treatment, to current status, despite the descriptive statistics suggesting an improvement in the members QoL prior to diagnosis, during treatment to current status.

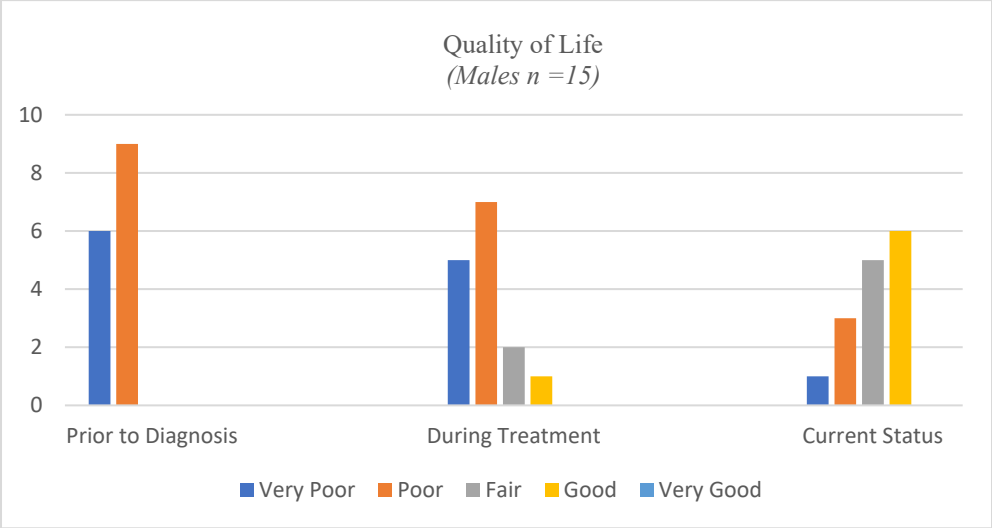
Further Analysis:

- *The difference in these results may have been due to a systematic error as the study population may not have been able to recall their QoL prior to their diagnosis. This is often referred as previously mentioned in Question 20 results, as recall bias. This may be one of the reasons why Question 39a) and 39b) results were very similar. Regarding Question 39 c), although the results showed no significant difference compared with Questions a) and b), when the Kruskal-Wallis test was applied to the data, this may have been due to a Type II error caused by the power of the study, this being a small study population, for each of the 5 categories.*

16.0 Male Results:

Figure 36 below displays the male results of the Likert scale responses in each category for Questions 39 a), b), c).

Figure 36



QRR= 100%. Figure 36 displays the male results of the Likert scale responses for Questions 39a), b) and c).

All 15 males prior to diagnosis were either in the Very poor or Poor health categories, although *20%* (*n=3*), less males responded to these QoL categories for ***Question 39b).*** Four (*26.6%*) males are currently in Poor health or Very Poor Health, **(*Question 39c*).** However, the responses in the latter question**,** did show a marked improvement for 11 of the males, i.e. they were currently experiencing, Fair or Good health, although 3 of them had reported Fair and Good Health for *answer 39b*). Applying the Kruskal-Wallis test, the result showed no significant difference in health improvement between the 3 questions, (KWH test= 3.000, df=3, *P*=.392).

A similar argument can therefore be suggested as previously mentioned, i.e., the power of this test was small in each of the categories.

17.0 Additional Analysis

This section reports the results of the qualitative analysis which was performed to assess if the variables of age, length of time for a diagnosis, origin of CS (*Pituitary or Adrenal*), disease factors (*remission, recurrence, hospitalisations*, *endocrinology. follow-up*), type of treatments (*including surgery, multiple surgeries, the use of steroids and RT*), had impacted on how the members had self-rated their QoL in ***Question 39c*****,** (*current status*). The methodology of analysis is outlined in *Chapter 3, Research Methods*, *Section 2.6.4, Page 100.*

17.1 Qualitative Result: Influencing Factors on Quality of Life (Female Results)

The results of the Pearson's correlation coefficient between the QoL scores (*current status*) and the length of time for a diagnosis of CS and CD showed a very good correlation (*r=0.79),* and a *P<.07*), suggesting that this was a significant result, (*Table 21).*

Table 21 Correlation Between QoL score and Length of time for a Diagnosis of CS and CD, (*Female & Male Results*).

Cushing Syndrome and Cushing Disease	*N*	*Years/Months*	*Correlation coefficient*	*P value*
Years to Diagnose Median	*109	4.6	.79	<.007

- *This result is the combined CS and CD median value for all the members who were diagnosed with both CS and CD. * The number of females and males who were diagnosed with both CS and CD. (59 members diagnosed with CS and 50 members with CD).*

The Pearson's correlation coefficient was calculated to ascertain if there was a relationship between the QoL (*current status*) scores and the origin of disease i.e., Adrenal or Pituitary. The result showed a strong negative correlation for the adrenal origin, (*r = -1, P < .20*) and for pituitary origin, the *r* = 0.30, *P* <.05, indicating a moderate correlation, (*Table 22*).

Table 22 Correlation between QoL Scores and origin of CS, (*Female Results*).

Cushing Syndrome	*N*	*Corelation coefficient*	*P value*
	46	-.1	< .20
Cushing Disease			
	44	.3	<.05

.

On applying the Pearson's test to age and QoL (*current status*) scores, the *r* value was 1, the *P* <.03. This result is thought to be significant and suggests a strong correlation, (*Table 23*).

The Pearson's was also applied to the years in remission to establish if this had affected the members QoL (*current status*) scores. The *r* value was -.92, the *P* < .05, therefore suggesting a strong negative correlation, (*Table 23)*.

Table 23 Correlation Between. QoL Scores and Disease Factors, (*Female Results*).

	N		*Correlation Coefficient*	*P value*
Age Mean ± SD	71	44 ± 26	.1	< .03
Years in remission Mean	36	6 years (6weeks–19years)	-0.92	< .05
ADR-CS v PIT-CD Remission	64		-1	>56
Recurrence Mean Number	19 2 (min=1, max.=5)		- 0.22	< .36
Hospitalisations Mean	56 4 (min= 1, max= 9)		0.48	< .001
Endo. Follow-up Mean	62 8 months (min= 3 months- max.= 3 years)		0.8	< .0001

The test to ascertain if the ADR-CS and PIT- CD patients in remission had similar QoL scores, the result showed a negative correlation, indicating that there was no difference in their QoL scores due to the origin of their CS (*r= -1, P. >*56), (*Table 23*).

The test results for the members who had a recurrence when measured with their QoL (*current status*) scores the *r = -0.22*, *P*<.85. which also indicated a negative correlation, (*Table 23*).

The number of hospitalisations were also compared with the QoL (*current status*) scores. The *r*= 0.46, *P*<.003. This result therefore suggested a moderate correlation, (*Table 23*).

To ascertain if regular endocrinology follow-up appointments, had an impact on their QoL (*current status*) scores, the Pearson's result *r* value = 0.8, *P*<.001, thus indicating a strong correlation between the 2 variables, (*Table 23*).

The Pearson's results displayed in *Table 24, Page 152,* shows that the QoL (*current status*) scores with those who had adrenal surgery (*laparoscopic or single incision*), and who had either, 1 adrenal gland removed or partial removal, the Pearson's *r* was -1, *P*>.003, indicating a negative relationship. However, although there were only 9 members who had received a bi-lateral adrenalectomy, the result showed a strong correlation, on applying the Pearson's test, which was reflected in their QoL (*current status*) poor scores, (*r=0.8, P<.02*).

The Pearson's was also applied to the members who had pituitary surgery with their QoL (*current status*) scores. The results showed a moderate correlation (*r*=0.5, *P value .02*), (*Table 24*). Those who had 1 repeat surgery, the results showed a negative correlation, *(r= -1, P >.03*), and those who had more than 2 repeat surgeries had an *r* value of 0.7, *P* value of <.05. indicating a strong correlation, (*Table 24,*).

Table 24 Correlation between QoL Scores and Treatment Factors (Surgery, Medical Therapy, Radiotherapy), (*Female Results*).

Table 24

	N	*Correlation coefficient*	*P value*
Adrenal Surgery	25	.1	<.001
Bi-lateral Adrenal	9	.8	<.009
Pituitary Surgery	44	.5	< .005
Repeat Surgery (1) Repeat Surgery (2-5)	14 11	.1 .7	< .01 < .05
Glucocorticoids (Always use)	26	-.1	>.05
Additional Medications.	70	.5	< .0001
Radiotherapy	14	.5	<.06

The effects of long-term use of GCs were also measured using the Pearson's test with their QoL scores (*current status*), to ascertain if taking steroids impacted on their QoL. The results showed a negative correlation (*r*=-1, *P*>.05), (*Table 24*).

The same test was applied to the members who were taking additional medication, the results showed a moderate correlation (*r*=0.5, *P* <.02), (*Table 24*).

To establish a relationship between the members who had received RT and their QoL (*current status*), scores, the Pearson's coefficient *r* was 0.5, *P*<.001), thus suggesting a moderate correlation, (*Table 24*).

Finally, the Pearson's correlation coefficient was applied to ascertain if the number of Physicians consulted prior to diagnosis had affected their QoL (*current status*) scores. The *r* was 0.78, the P<.05, which indicated that there was a strong correlation, (*Table 25)*.

Table 25 Correlation between QoL Scores and number of Physicians prior to Diagnosis, (*Female Results*).

Number of Physicians Prior to a Diagnosis	*N= 64*	*Correlation Coefficient*	*P value*
Mean ± SD	3 ± 2.5	.78	< .05

The length of time for a diagnosis, endocrinology regular follow-ups, bi-lateral adrenalectomy, number of physicians consulted prior to diagnosis and repeat surgeries all had strong correlations and significant *P* values and this concurred with their QoL (*current status*) very poor/poor scores. Pituitary origin of disease, combined with surgery and hospitalisations showed moderate correlations for those with lower QoL scores, and similar results were recorded for the members ages, those taking additional medications and RT treatment. It should be noted that due to the small number of those members who had chemotherapy (*n=4*), no inferential analysis was conducted.

18.0. Qualitative Analysis of Quality of Life

Question 40: Female Results:

18.1 Descriptive Analysis

The *QRR* female was *91.5%.* The 65 females who responded to this question gave detailed accounts of their experiences of being diagnosed and living with CS and CD. Many of the responses were similar to those which were reported in Questions 8 and 9.

The resultant patterns within the responses emerged as themes and are representative of the sample and are presented in the sections below:

18.2 Qualitative Analysis.

The following are examples of quotes taken from the female responses and are reported in the emergent themes.

Theme 1 Change of Life Thirty-one (*47.6%*) of the females discussed their change in their life's due to their CS illness. These changes included, mobility, physical pain, fatigue, living with fear of reoccurrences, less active and generally feeling unwell. Three (*9.6%*) of them mentioned their financial problems due to long-term sickness and inability to work and the subsequent anxiety and depression this creates.

Example Quote:

"*Although I have said that my health is fair it does fluctuate. I can have good days when I feel like my old self- but unfortunately these are few and far between. The lack of sleep, night sweats and generally looking older than my years depresses me to the point that I don't want to face life. I am fearful of recurrence and presently petrified that I contract the Covid-19 virus as I think it would kill me. The lockdown means that I am not able to work, and this is causing me to be depressed. I have so much time to think about myself and sometime wish I were dead, and the daily struggles would end. Please help other people to cope by raising awareness with doctors"*

Theme 2 **'**No one seems to understand, including the health care team.' Twenty- nine (*44.6%*), females gave detailed accounts of how they felt that their friends, relatives, and members of the healthcare team did not fully understand the nature of their illness. The answers were similar to those reported in *Question 8.* However, more details were given which explained more clearly their personal feelings.

Example Quote:

"*Each day brings its own challenges for me. The fact that my cortisol levels continue to be high despite my adrenal surgery brings with it an uncertainty that creates anxiety. Being a student and not having the pleasures that student life bring is sad. Researching Cushing's and reading about the mortality rates doesn't help. I think it is appalling that the endocrine team don't contact me during this virus crisis as I label myself as being vulnerable. At least the Pituitary Foundation is comforting in that we can phone up for advice-otherwise there is not support via the NHS. I would have thought to save lives that people like me would be contacted to warn us of the dangers of infection and what to do if we are ill.*
Hope your study goes well and wish you all the best, it really is great that someone cares and takes on the challenge of increasing awareness. Many thanks."

Theme 3 <u>More Awareness.</u> Fourteen (*21.5%*), female members commented on the lack of public and health professional awareness and this was blamed for a delayed diagnosis. Three (*4.6%*), suggested that leaflets for women and employers would help to raise awareness and medical training for health professionals.

Example Quote:

"*My disabilities seem to be getting worse and this impacts on my life in many ways. My only way of relaxing is my studies and watching television although now during this virus scare, I am so worried that if I get the virus I will die as I have little defence to fight it. I am not going out and depending more and more on my neighbours to help.*
Public awareness would certainly help and training for general practitioners so that they can pick up the signs of this illness quickly saving their patients so much anguish and pain. I do hope that your study will improve awareness and this I am sure will save many lives."

Theme 4 <u>Psychological support</u> A need for psychological help and support was mentioned by 11 (*16.9%*) of the females. Depression, mood swings, hypomania and suicide were examples of how their personal anxieties had affected their lives.

Example Quote:

"*The long-lasting effects of having been diagnosed with Cushing's has changed my life and my personal relationships. I continue to feel poorly and do not have the energy to focus on anything, my self-esteem has gone, and my appearance disgusts me, and my family and I don't know how to right it. I really need more psychological help for my wellbeing, but this has not been suggested. The only way I can get this is to go privately but cannot afford it unfortunately.*
Doctors only want to prescribe pills when they should be treating the whole body and assuring their patients that they can be cured. More awareness would certainly help."

18.2.1 ***Additional Observations:*** Twenty-one (*32.3%*) of the study population mentioned their fear of contracting Covid-19 and how delayed treatment appointments may cause them to become even more ill or die.

Example Quote:

"*I need constant help really to get through most days. I don't know if I will require more surgery. I am told that my pituitary tumour is aggressive but over the past few years has now stabilised due to my drug regime. It is a case of getting regular MRI scans but recently my appointments have been cancelled and therefore I am unsure as to the state of play regarding my tumour growth. As you can imagine this is causing me even more stress. I must admit that my endocrinologist has not really kept in touch despite my attempts to contact him. I guess he must be too busy coping with the virus crisis. I know that I am not alone in this as many of my support group*

contacts are also awaiting their out-patient appointments. People with adrenal insufficiency problems should not be ignored.
By raising awareness this may waken up the medical profession to understand more about their patients and how to diagnose them."

Question 40: Male Results:

18.3 Descriptive Analysis:

The male *QRR* was *93.3%.* The comment boxes generated a large amount of data. Similar to the female responses several themes emerged. The following sections report the main themes which are representative of the sample responses.:

18.4 Qualitative Analysis

Themes 1 More Public and Health Professional Awareness. Eight (*57.1%*), males commented on the lack of public and health professional awareness, particularly GPs., leading to a long period of time prior to a diagnosis and subsequent treatment.

Example Quote:

"*I am so glad that someone is taking up the gauntlet of promoting awareness and studying this medical condition. I would not want to wish this illness on anyone and the more people that can be aware of the consequences of long-term cortisol exposure the better. It has ruined my future plans as I am so scared that it comes back. No one seems to give you any warning of what to expect and how I can go onto developing other ailments as a result of my Cushing's.*
Good luck with your studies and hope you can help save lives."

Theme 2 Psychological support and advice. The depressive manifestations of the Cushing's were discussed in detail from 5 (*35.7%*) of the males. Two of them mentioned their lack of interest in life, which had led them to suicidal ideation, one of them had been sectioned.

Example Quote:

- "*My surgery was a failure in Sept 2015 and was put on metyrapone which gave me some of my life back to me in the walking and energy to work but my mind was running fast and not helping my sanity as I do believe if my parents were not alive, I would have ended it years ago, but I couldn't die before my mother.so, I was on tablets since then as in May 2017 an MRI found my tumour but in a dangerous place, so surgery was out and had gamma knife august 2017 and waiting for it to work as now May 2020 waiting for Covid-19 to stop and allow me to go for day curve test to check cortisol levels."*

Theme 3 Change of Life. Five (*35.7%*), males commented on how Cushing's had changed their lives, mentioning personal and social life and their work status, in some cases personal financial hardship.

Example Quote:

"*I would like to x very good health and some days I can probably tick this box. I am finding as I get older that somehow the after-effect of my Cushing's is taking its toll as I seem to have bouts of extreme fatigue.*

I also find that my concentration reduces, particularly after I have finished my work and it takes me so long to make a meal. My weight is slowly reducing but I feel 20 years older than I am which is rather boring for the odd friend I have.
This type of study may help others in getting a quicker diagnosis and this may increase their chances of an improved quality of life. Hope it all goes well."
Further Observations: Eleven (*78.5%*) of the male responses mentioned their fear of Covid-19 and 5 (*45.4%*) of them mentioned that they had not been given support or advice from their endocrine team as to how this illness would affect them. All of them mentioned, that their diagnostic and treatment appointments had been cancelled and this had caused them a great deal of anxiety Six (*42.8%*), also wrote about their fears of reoccurrence and four (*28.5%*), other males discussed their dissatisfaction with the NHS.

Example Quote:

"*I was supposed to be going to hospital for cardiac surgery, but this has been postponed due to the virus and each day I experience more breathlessness. I also continue to have headaches and severe fatigue. For many years I thought that I would never have a definitive diagnosis. The transsphenoidal surgery left me very weak and I have lost my ability to taste food or smell. My tumour was not removed during my first surgery and therefore I had to have another operation followed by radiotherapy. This has affected to a certain extent my eyesight.*
Do hope more awareness is increased to have faster diagnosis. I might not have needed to go through this if I had been diagnosed earlier."

PART 2

Health Professionals Interviews.

A total of 21 Health Professionals including experts in the field of Endocrinology were interviewed and gave advice and information during this study (*Objective 4*). The Health Professionals included 2 Radiologists, 5 Radiographers, 5 Endocrinologists, 1 Orthopaedic Consultant, 1 Ultrasonographer, 1 Rheumatologist, 1 Dermatologist, 1 GP, 1 Ophthalmologist, 1Neurosurgeon, 1 Clinical Psychologist and 1 Social Psychologist.

Main Observations: 5 of the interviewees had not heard of CS or CD. The GP had never diagnosed CS and was unsure as to the signs and symptoms and all the other Health Professionals except for the Clinical Psychologist, Endocrinologists and Neurosurgeon had only seen a few patients during their careers. Interesting 1 Endocrinologist could not say how many Cushing's patients he treated in his Health Board. Surprisingly both the Orthopaedic surgeon and the Rheumatologist admitted that they knew very little about Cushing's despite regularly treating patients referred for osteoporosis and skeletal abnormalities. *Chapter 5*, *Discussion, Pages, 157-196, and Chapter 6, Conclusion, Pages 197-206***,** fully discusses the main findings from these interviews.

Chapter 5

Discussion

The following Chapter discusses the findings of the present study.

1.0 Introduction

Undoubtedly, chronic hypercortisolism during the active phase of CS and CD causes severe physical and psychological illnesses resulting in long term comorbidities. Evidence from the author's personal experience of having been diagnosed with Cushing's along with reviewing past and current HRQoL studies, consulting with leading authorities, support organisations and other healthcare disciplines, all served to map the direction of this study.

In *Chapter 4, Pages 102-156,* the results of the HRQoL survey were reported and this *Chapter (5),* discusses the main results and reprises the important findings which have emerged from this study. This includes a comparison with current HRQoL studies for CS and CD and highlights how the findings can influence new ideologies and advances to change the roadmap in which the endocrinology medical discipline consults and treats patients, combined with cross-boundary working to raise awareness of the signs and symptoms for other healthcare disciplines to consider CS as the differential diagnosis.

2.0 *Narrative Literature Review Analysis.*

By conducting a review of the literature at the onset of this study, enabled the historical progress of diagnostic testing, treatments, associated conditions, and the past and current evaluative processes of measuring HRQoL. By studying the subject matter, it became clear, that the measurement of HRQoL is indeed a complex but important concept in the fields of health, well-being, and medicine.

From the onset of conducting the review of literature, which focused not only on the disease processes but the consequential changes to the body and mind, assisted the author of this thesis, in recognising the complex reasons for the deterioration in a patient's health and wellbeing. The textural content of books and journals informed the author to further appreciate the physical and mental disease factors which create a change in the way CS patients live and in turn can have a detrimental effect on their work, education, personal and social lives, (*Objective 1and 2*).

3.0 The Health-Related Quality of Life- The Present Study

Since the initial review of literature, over the past 2 years there has been many new publications related to the diagnostic processes, treatments and HRQoL studies of CS and CD.

This *Section* compares some of the most recent HRQoL studies with the results of the present study's HRQoL survey, (*Objective 3*), and discusses the main survey findings.

A 2019 systematic review for example of QoL research in medicine and health sciences found that when interpretating and defining QoL there were differences in opinions within and between the medical disciplines and suggested that this could be due to the complex nature related to the different fields of health and medicine. The overall view being, that traditionally, the evaluation of a patient's health was the biochemical clinical, "endpoint," in most fields of health, medicine, and research. This review highlighted the need for clinicians to understand the consequences of illnesses and treatments prior to making decisions and that age and culture must be taken into consideration and reflected within the design of QoL studies. [212]

In the present study, the design of the self-reported QoL survey, took the form of a disease-specific questionnaire with additional modifications. This enabled a more unique, personalised approach which was produced in the textural responses and helped to identify the range of challenges and issues which had affected the participating members, including those who had long-term comorbidities. Similarities emerged in the narratives and produced recurring themes which allowed a better insight into the personal and socials aspect of their lives, beyond just the descriptive data.

A good example of this was where the members felt that although many Physicians wish to adopt a more patient-centred approach, the pressures of heavy workloads create a challenge to adopt strategic healthcare policies. This was reflected in *61.6%* of the members who relied on their support groups and endocrine associations to share their experiences, seek advice and information by accessing communication networks, (*formal and informal*), and helplines. Feelings of frustration and dismay were experienced by a high percentage (*43.3%*), of the members who answered *Question 11b*) expressing that they felt their appointments were, "rushed," with very little information, advice and what to expect regarding the long-term effects of Cushing's. Families were often not invited to attend their consultations and therefore in many cases this led to a lack of understanding by their families as to the true nature of their illness., and how they could support them, often believing that they were, "faking," their illnesses.

The impact of the disease on patients is measured using HRQoL research but the impact can equally have a negative effect on families and friends.[213]

Kazak et al, commented in their 2002 publication that the lack of communication between medical specialities can be problematic for patients which in turn can obscure commonalities in different dimensions of health**.**[214] This was observed within the present study and emerged as a serious problem, as many of the members reported a lack of continuity and progress during their diagnostic journey, which resulted in long waits between appointments, therefore lengthening the time for a definitive diagnosis.

Interviewing NHS staff during this study enlightened the author to the fact, that when consulting patients, due to the overwhelming workloads, their main aim is to clinically assess, prescribe treatment and in the case of endocrine patients, ensure that regular follow-up appointments are made. However, the average consultation time being 10-20 minutes could be suggested as too short a time to fully explain the consequences and likelihood of developing comorbidities, particularly in rare diseases and how they can access support and give further guidance. This quoted average figure is debatable as appointment scheduling for outpatient clinics can vary depending on the practical implications and the medical speciality. According to a recent study of appointment scheduling, the results found, "that there was an enormous gap between scheduling theory, which offers a rich edifice of formal mathematical optimisation approaches and practice." [215] The main recommendation from this 2019 study was that clinics should run at utilisation levels, introducing modern technology to increase efficiency and this would allow planned consultation time to increase.

For several years clinicians and healthcare organisations have acknowledged the need to adopt a more patient-centred approach to ensure that individuals are correctly diagnosed and treated but are also given emotional support involving their friends and family and are therefore given the appropriate time and care during consultations. For example, the Healthcare Quality Strategy for NHS Scotland for, "person-centred care," is described as, "Mutually beneficial partnerships between patients, their families and those delivering healthcare services which respect individual needs and values, and which demonstrates compassion, continuity of care, clear communication and shared decision-making." [216]

Study Results, Finding & Observations.

4.0 Demographics (Questions 1-3).

The survey Questionnaire, which contained 4 *Sections* was designed to encompass a range of questions which would span the dimensions of health not only in terms of physical and psychological conditions but how being diagnosed with Cushing's impacted upon their daily lives. Seventy-one females and 15 males agreed to participate in the survey, the median female age was 42 and for the males, 39.4 years.

The study population was either in the active or non-active phase of their Cushing's illness. One member had been diagnosed within the same year that the questionnaire was distributed (*2020*), and 1 member over 30 years since their diagnosis, (*range of years when diagnosis was confirmed, 1990-2020*). The result showed a strong correlation between age and QoL (*status*), scores for the study population ($r<1, P < .03$), which is a result reported in most CS QoL studies. Older patients are more likely to develop comorbidities and general poor health.

***5.0 Perceptions of the Disease Burden* (*Questions 4,5,6,7,8,9,10,11,11a),11b)*).**

Over *81% of the females* and *80%* of the male members found that their social lives had changed and *95.7%* of the females and *93.3%* of the males their personal lives had also changed since being diagnosed with Cushing's and this had created not only a physical but an emotional impact. The main reasons given were their lack of sexual desire, the body changes, anxiety, depression, mood swings and personality changes, combined with the exhaustion and fatigue caused by the physical conditions (*Results, Figures 9, 10,11,12,13, Pages 104-107. Figures14,15, Pages 111 and 112,*

Financial hardship due to having had to give up work (*57%*), combined with relationship breakdowns and loneliness (*50%*), contributed to the way in which the members viewed their QoL. The human challenges and concerns revealed in the thematic analysis was compelling to read and could only be captured in a narrative response by those who had truly suffered from the consequences of having been diagnosed with CS.

Family support was found to be crucial in reducing distress, isolation, and loneliness, particularly when facing the consequences of being diagnosed with Cushing's. Thirty-nine (*55.7%*) of the females and *46.6%* (*n=7*), of the males had the opportunity to involve their family during endocrine team consultations, reported in *Question 11*. The remaining *43%* of the study population did not have this opportunity, the main reason being that it was simply not suggested by their endocrine team. This result was based on the *QRR* (*Female=98.5%, Male= 53.3%*).

The need to involve them in consultations with their endocrine team was suggested by *61.6%* of the members (*Results, Table 4,5).* Thirty-eight (*97.4%*) of the females who answered *Question 11*a), described how helpful it

was to have their family present during consultations, while 2 (*5.2%*), males also agreed. However, in *Question 11a)*, disappointment was also expressed by *36%* of the members that their family was not invited to join them for their consultations, and some reported that, "*little information was given to me about my illness*," and, "*the endocrine team did not seem to understand the full nature of my illness*," and, "*if my family were in attendance, they could have helped to ask questions."*

5.1 Length of time for a Diagnosis (Questions 12.13,14,15,15a,19).

A recent 2019 meta-analysis, reviewed 5367, patients and found that the length of time for a definitive diagnosis was almost 3 years for CS and CD was over 3 years, and was not influenced by gender, age or year of diagnosis.[217] However, Papoian et al, in their 2016 study found a median of 5 years and as long as 30 years to diagnose, while Flitsch et al (*2000*), reported a mean delay of diagnosis of 5.4 years for CS patients and Kreitschmann-Andermahr et al, 2015, 3 years for CS.[21] [218] [123]

In comparison, the present study results for *Questions 12 and 15.* related to the length of time for a diagnosis, reported that a total of 59 members were diagnosed with CS and 50 members with CD, diagnosed between 1990 to 2020. In the present study, the median time for the females who were diagnosed with CS was 5.4 years (*n=46*), and 5.1 years for CD (*n=50*). The male results for a diagnosis of CS were 3.7 years *(n=11*), and for CD 2.2 years. (*n=6*). Twenty-five members (*29%*) were diagnosed with both CS and CD, as reported in *Chapter 4, Section 5.0, Page 118.* The difference in the length of time for a diagnosis when comparing both genders, is likely due to the smaller male population which did not allow for an equal comparison. However, often males who have erectile dysfunction and are infertile tend to consult their doctor more regularly, which was highlighted in some of their responses within the thematic analysis relating to their social and personal relationships.

The results for the combined length of time for a diagnosis of CS and CD for all members who had been diagnosed with both CS and CD when compared with their QoL scores showed a very good correlation *(r .79, P <.007)*. The study population median time for a diagnosis of either condition was 4.6 years. This result was therefore significant in that the longer time for a definitive diagnosis adversely affected their QoL.

Question 19 reported the results of the length of time for a referral to the endocrine team, which is a question that is rarely, if ever asked in CS HRQoL surveys. This question was answered by *92.9%* of the female population and *86.6%* of the males. The length of time for the study population varied from 1 day to 9.5 years. The latter result (*9.5 years*) was a female who had consulted with 18 physicians prior to being referred to the endocrinology team.

5.2 Remission, Recurrence and Hospitalisations, (Questions 16a), 16b), 16c),16d), 21,21a),21b, 25a),25a).

Question (16a) asked the members if they were in remission and was answered by *98.5%* of the female population and *100%* by the males. Fifty-two females were in remission and 12 males.

Thirty-six female members who answered *Question 16 (b*), reported that they were in remission for between 6 weeks and 19 years (*Median time= 6.1 years*), and for the 6 males who answered, they reported a min of 1 year, and a maximum of 12 years (*Median =5.6 years*). These members showed higher QoL scores in this study, suggesting that remission was the strongest determinant of QoL improvement, (*r=.92*, *P < .05*), *(Results, Table 23).* However, in *Question 25*, 42 females (*60%*), and 8 (*53.3%*), males reported additional medical conditions which had evolved post diagnosis. Notably, these members were found to have low to moderate QoL scores **(***Very Poor, Poor, Fair***).**

These additional conditions were named in *Question 25a),* and included: Addison's and Nelson's syndrome, cardiac diseases, diabetes, hypothyroidism, infertility, and skeletal abnormalities (*including osteoporosis*), (*Results, Figure 24, displays the female results*). The range of female additional medical condition was 16 and 2 for the male members.

The systematic review of CD patients conducted by Andela et al in 2015, as previously discussed, reported a worse QoL score at diagnosis, and the smallest improvement after remission, as compared with patients with non-functioning pituitary adenoma and prolactinoma.[220]

The risk of recurrence from TSS for CD is well documented.[241] Although the results of the prevalence of recurrence in different studies varies greatly, between *0* and *47%*, according to a 2016 meta-analysis study. The "overall rate," of patients with CD, who have received TSS was *10%* (*CI=95%, 6-16%*) at the longest period of follow-up. This study also found that higher rates of remission after surgery were observed in those with smaller adenoma size, i.e., microadenoma versus macroadenoma; 0.83 versus 0.63; (*P<. 001*).

Dabrh et al published these figures in 2016, as previously discussed, and commented that, "overall, the biochemical remission rate after TSS was *76%* (*95% CI, 72 to 79%*) and the failure rate was *23%.*" [74]

In the present PhD study, recurrence(s) also impacted on QoL scores, and the overall results indicated a negative correlation between number of recurrences and QoL scores in 19 of the female members, (*r -0.22, P <0.36*), (*Results, Table 23)*. The 44 female members who had received pituitary surgery however, had lower QoL scores than those who had adrenal surgery. A moderate correlation was indicated for the pituitary surgery results (*r 0.30, P <.05*), (*Results, Table 24*), compared with a negative correlation for those with adrenal surgery, except for those

who had bi-lateral adrenalectomies, as previously discussed. Of the 44 female members who had pituitary surgeries, 14 had repeat TSS (*mean= 2*), and 3 males also had repeat TSS, one of them had 2 repeat surgeries. According to a 2021 retrospective study, "the outcome for pituitary endocrine function endoscopic TSS remains unclear." [242] The authors, Galloway et al recommendations were also similar to other studies, i.e., advise counselling pre-surgery so that patients are made aware that they may have to have HRT permanently and this may have an impact on their QoL. These authors also suggested that long-term robust collaborative studies of TSS outcomes should be conducted.[242]

It is well documented that, surgery is the best method of controlling excess cortisol and if unsuccessful can lead to a range of comorbidities including metabolic syndrome, cardiovascular and morbidity.[243]

The present study results found that *80%* of the females and *93.3%* of the males had hospital confinements, (*Question 21a*): *Study Population*: *mean= 4*, *min=1, max=9*). The main reasons for the study population's confinements were adrenal surgery (*52.2%*), pituitary surgery (*46.2%*) and psychiatric conditions (*20.8%*). The test of association when comparing the QoL scores with hospitalisations indicated a strong correlation (*r .8, P < .001*), (*Results, Table 23, Page 151*).

5.3 Number of Physicians Consulted and Who made the diagnosis? (Question 17a)-g), 18,19).

It is unsurprising that the median number of Physicians consulted prior to diagnosis and before being referred to an Endocrinologist, in the present study was 3 Physicians (*Question 18*: *Females (range=1-18*) and 2 Physicians for the males (*range =1-4*). This result however, being lower compared with some of the other Cushing's studies. Kreischmann-Ander in 2015[123] as previously mentioned, quoted 4 Physicians, and previously Flistch et al in their 2000 study was 4.6 Physicians.[218]

For the present study, the test for association between the number of Physicians consulted prior to diagnosis and the QoL scores, indicated the existence of a strong correlation (*r .78, P < .05*), (*Results, Table 25, Page 152).*

The reasons for a delay in diagnosis could be said to be multifactorial, particularly due to the range of signs and symptoms that a patient presents with, on initial consultation. The Cushingoid features are not always obvious during clinical assessment. The range of ailments can be extensive and can range from spinal abnormalities, skin infections, central obesity, diabetes, depressive and cognitive disorders, thus presenting a medical dilemma. Kreitchman-Andermahr et al in their 2015 study also found that in CD patients, who had nonspecific features of hypercortisolism for 0.9 years prior to seeking medical advice, consulted many Physicians before a definitive diagnosis was made. In the Kreitchman-Andermahr et al study, the patients were asked if there was an aspect of

their condition which affected them the most. A, "*fight for diagnosis*," was found to be one of the "most bothersome along with hypercortisolism-related symptoms." [123]

Question 17a)-g) gave the members the opportunity to name the Physician who had made the initial diagnosis. These set of questions were answered by *100%* of the study population and notably only 15 (*17.4%*), reported that their GP had diagnosed their CS. *Results, Tables 6-7, Page 121,* displays who diagnosed their Cushing's, other Health Professionals being the highest number (*46.5%*), for the study population and interestingly, *23.2%* either self- diagnosed or their families.

The present study results confirmed that both the length of diagnosis and number of Physicians consulted prior to diagnosis impacted on the members HRQoL and notably in many cases even when a suspicion or confirmation of a CS diagnosis was made and as reported in *5.2* of this *Chapter*, it took a median of 3.6 years for the female population and 1 year for the males to be referred to the endocrine team (*Question 19*).

5.4 Prior to and Post Diagnosis Signs and Symptoms (*Question 20A/B*).

One of the questions, (*Question 20A/B)*, gave the opportunity for the members to reflect on their signs and symptoms *prior to their diagnosis* and how these had deteriorated or improved over time (*current status*).

The results for the study population, showed that currently when compared with their, *prior to diagnosis* scores, a significant reduction in the number of items for the physical signs and symptoms scores, suggested that the members were experiencing less signs and symptoms (*P <.0001*). There was also a similar result for the psychological and cognitive impairments signs and symptoms for both genders, (*Females=P <.0001, Males= P <.004*).

The study population for the females was high (*82.5%*) compared to the male population (*17.4%*). These figures are similar in proportion to previous HRQoL studies and reflect that CS is more prevalent in women than in men. [108 141.] Notably this question was quite unique to other CS questionnaires, i.e., *Question 20* contains 30 items which allowed each member to have the opportunity to identify a wide range of signs and symptoms. In comparison, for example, the Webb et al CushingQoL questionnaire only contains 12 items.

5.5 Age and Health Related Quality of Life.

The highest number of female members who had the highest scores were the age groups, 30-40 (*n=25*) and 41-51 years (*n=20*), The higher score being the number of Xs placed in *Question 20, box B, current status*). The 30-40 age group were found to have more physical signs and symptoms (*current status*) than the age group 41-51 (*P<.09*). However, there was no significant difference found between these age groups for the psychological and

cognitive impairments (*current status*), (*P >.38*). These results concur with other studies, in terms of age-related signs and symptoms. The physical (*n=24)*, and the psychological and cognitive impairments (*n=6)*, questions included all items relative to common CS and CD signs and symptoms of which can be caused by the ubiquitous effects of excess cortisol. This question therefore gave the members an opportunity to reflect on the variety of signs and symptoms that they may have previously and/or currently experienced (*Question 20A and B).*

A further opportunity in *Question 21*), gave the chance to record other medical conditions associated with their Cushing's illness which were not listed but of equal importance in evaluating the full impact on their physical, mental health status and HRQoL. One must of course acknowledge that recall bias could have influenced these results, particularly the length of time for many of the members to recall their signs and symptoms prior to their diagnosis. That said, *Question 20B),* did enable a current perspective of the types of illnesses they were experiencing and if any improvement during and post treatment or time had made a difference to their overall scores, many of whom were in the non-active phase of their illness. This was further evidenced in their detailed, linear narrative which delved into the personalised, characteristics of both the physical and mental detrimental effects of their Cushing's, which had changed their lives and their relationships with those who cared for them.

It was notable, that the males in the age group 30-40 (*n=9*), had the highest number of members and the highest scores for this question, the mean value for the physical signs and symptoms being 5.0 (*min.=8.6, max=12)*, and the psychological mean value being 2.63 (*min= 0, max=4.0*). These results were remarkably smaller in both the physical and psychological dimensions of health compared with the females in this age group. On observing their narrative accounts, they experienced more psychological problems, mainly due to their fertility, lack of libido and self-esteem which had created anxiety, depression leading to relationship breakdowns. Due to the small male population, no inferential statistics were performed on the age group data, as previously stated.

*5.6 Other Observations from Question 20*A/B

The ratio between genders in this study, showed a higher ratio 3.5:1 for CS and 7.3:1 for CD for the females compared to the males. On studying the differences in the *current status* scores in *Question 20B,* and the frequency charts which displays, the frequency responses for each of the named physical and psychological conditions, it could be argued that many of the common dimensions of physical impairments were similar for both genders, (*Results, Figure 20, Page 124 and Figure 22, Page 129)*.

The male results showed that the frequency response rate for many of the items listed in the questionnaire had minor frequency differences for example in weight gain, fatigue, higher cholesterol, and infertility. Although inferential statics for gender comparisons could not be conducted due to the small number of males, the overall

physical signs and symptoms per member*, current status*, did show medium to high prevalence when the total for both genders were computed. It is interesting to note, when the combined gender frequency scores were calculated, the results below give an overview of how the following items continue to have a detrimental effect on the physical well-being of the members.

The number of item responses (*current status*), were for body pain (*74.5%*), decrease in libido (*73.3%*), weight gain (*48.4%*), skin bruising (*28%)*, fatigue (*56.3%*), backache (*58.7%*), inflammatory infections (*47.7%*), raised cholesterol (*23.8%*), insomnia (*59.5%*), hypertension (*20.6%*), proximal muscle weakness (*68%*), prone to infections (*57.1%*) and loss of hearing smell or taste (*56.1%*), eye conditions (*23.4%*), and infertility (*16.9%*). A lower prevalence was found in osteoporosis for the males (*n=13.3%*), compared with the females (*23.8%*) and for cardiovascular disease, (*Females=24%, Males= 6.6%*).

The loss of hearing, smell, taste, and eye conditions occurred in those members who had undergone pituitary surgery.

Most of these results are therefore comparable with the ERCUSYN Registry database (*2018*), and other CS studies, for example weight gain being a common feature, hypertension, skin bruising, cardiovascular and prone to infections. [205]

- *As suggested in Chapters 3 and 4, the accuracy of Question 20a) result may have been compromised by recall bias.*

6.0 Disease Processes

Until the 20th century, little was known as to the true function of the pituitary gland sometimes referred to as the 'master gland,' The primary reason for this is said to be the due to limited knowledge of endocrinology prior to this time.[18] This gland as previously discussed in *Chapter 1,* controls several other hormone glands, including the thyroid, adrenals, ovaries, and testicles. Cortisol is arguably the most vital hormone regulated by the pituitary gland. Interestingly, the present survey identified that the members who were diagnosed with PIT-CS had lower QoL scores than those with adrenal origin CS. The results for PIT-CS v ARD-CS suggested a strong negative correlation (*Results, Table 22, Page 129).*

The adrenal glands release cortisol minute by minute and therefore the complexity of establishing the source of hypercortisolism often creates challenges, CS and CD both being cortisol driven. Hypercortisolism without CS can therefore be confirmed in some of the clinical features such as pregnancy, depression and other psychiatric conditions, alcohol dependence, GC resistance, morbid OB, and poorly controlled DM.

Those unlikely to have the clinical features of CS include patients presenting with for example, anorexia nervosa/malnutrition, stress, pain, hypothalamic amenorrhea, and CBG, excess (*increased serum but not urine cortisol*). These being the reasons why many additional forms of testing are required. One example, as part of the diagnostic work up of primary aldosteronism, patients undergo CT scanning, and often US examinations. However, in some cases patients are referred for AVS which is also discussed in *Chapter 1, Section 1.8.1, Page 24b).* Six (*10.3%*) of the females and 5 (*41.6%*) of the males in the present study were referred for this procedure, prior to their adrenal surgery, (*Results, Figures 29, Figure 30, Page 136*).

Wolley et al, in their 2020 publication on AVS agreed that this procedure albeit is well-established but it, "remains controversial." [222] The reason given by these authors, was that it was dependent on patient selection and how precision and skill are required to successfully perform AVS.

7.0 Cushing syndrome and disease: The Diagnostic Challenge.

The diagnostic challenges related to CS and CD since the Harvey Cushing era remains the same. However, even with more efficient methods of biochemical testing which is the essential first-line method of establishing a diagnosis and diagnostic imaging advancements, a CS/CD diagnosis continues to create challenges.

As previously mentioned, the clinical features are not always a reliable method of identifying CS. The guidance for testing recommends a minimum of 2-3 tests, which rely on the technical assay and cyclic hypercortisolism. Patients with the latter, find themselves having to be tested over a period of intervals, as they may have normal responses to any of the tests during the non-active eucortisolemic period and therefore require repeat testing. This may require hospitalisations for 1-3 days, which was reported by 8 of the members.

As previously discussed, "the diagnosis of CS is one of the most challenging tasks of clinical neurology." [244 195]

This present study suggests that it remains the same today.

Why is a diagnosis so challenging? The main challenge is identifying the underlying cause of hypercortisolism. The second method for diagnosing CD is MRI using a scanner of at least 1.5 Tesla (*Chapter 1, Section 2.7, Page 32-33.* Forty-nine females and 4 males in the present study were referred for MRI. (*Question 24*). All members had been referred for diagnostic imaging using at least 1 imaging modality, the mean number for the study population was 2, (*min=1, max.=6,).* The importance of diagnostic imaging was reflected in the members answers, that after the total collection of examinations. i.e., additional to their initial diagnostic imaging referral, was 182 for the study population and the range of examinations being 15 for the females and 7 for the male members (*mean*= 3, *min.=1, max.=8, Question 24a*).

According to Tortora et al, "identification of the secreting ACTH-pituitary adenomas is still very difficult," to identify.[245.] If pituitary lesions less than 5mm are identified, this does not necessarily mean than adenoma is responsible for the clinical symptomatology, as between *3%* to *27%* of pituitary incidentalomas are found in the general population.[246]. High quality imaging is therefore paramount in identifying key structures such as the sella and paraseller regions prior to surgical removal for cure or reduction of tumour size or RT.[247] 3T or 7T MRI, however, are the preferred modalities, as for example in CD, a microadenoma may not be detected if a lower field strength is used i.e., 1.5T. [61 151 161 162 166 2248 250]

Several members in the present study, volunteered information on how they had a yearly MRI examination following their CD diagnosis and TSS, along with biochemical tests as part of their clinical check-up.

8.0 Other Medical Imaging Modalities (Question 24a).

The exponential advancements in diagnostic medical imaging over the past 30 years, have enabled Physicians and Surgeons from all branches of medicine to further evaluate the consequences of the disease processes.[141]

In this study, a range of 15 additional imaging examinations and interventional procedures were reported by 72 members who answered *Question 24a*) and the full range of imaging modalities are displayed in *Results*, *Figure 29, Figure 30, Page 136).* This Question sought to ascertain how many examinations/procedures were conducted prior to their diagnosis. The number of the additional examinations prior to diagnosis was 172 (*Females= 156, males= 26*, *mean= 2.5*). ** This figure does not include <u>initial</u> MRI pituitary or CT abdominal scans.*

One can therefore extrapolate from these figures and the range of biochemical tests that patients undergo prior to diagnosis, that it is not only costly in terms of the use of healthcare services, but also there is a cost to patients, in terms of the risk of drug reactions and IR from the imaging modalities using x-ray sources., the latter was discussed in *Chapter 1, Sections 1.8.1, Pages 22-25, Section 2.2 Pages 27-28 , and Section 2.3, Pages 28-29.*

The benefits of course can be argued as justifiable in the use of IR and undoubtedly when appropriate non-ionising radiation such as MRI and US are used. Importantly, if a CS and CD were diagnosed sooner this could have an overall bearing on an individual's accumulative dose over time and may reduce the risk of a cancer induced by overexposure to radiation. Referral for US for adrenal gland imaging varies but can be beneficial as a non-ionising radiation before considering CT. A total of 36 members had an US examination. *Appendix 5 Figures 44,45,46, Pages 250-251***,** displays US images of the adrenal gland including a case study.

8.1 Endocrine Referral

Reflecting on this, it is also not surprising that even when a patient is referred for endocrine assessment it can take months and often over a year to reach a definitive diagnosis. By this time a patient's health deteriorates, patients have mixed emotions, they can become angry, some are happy that at last a diagnosis has been reached but sadly by this time many of the deleterious effects have impacted on their health, and the illness becomes life-threatening,[18] There is therefore a risk of increased mortality primarily due to cardiac disease, which is created by prolonged hypercortisolism, GC-excess which induces metabolic changes.[253]

Four of the female members had interventional cardiac angiography prior to their diagnosis, *24%* out of 70 females reported cardiovascular conditions prior to their diagnosis and 1 *(6.6%*) of the 15 males also reported having cardiovascular conditions, and 1 was awaiting surgery. It is well documented, that a higher ratio of females when compared to males who are diagnosed with CS often develop cardiac disease., also previously mentioned.

However, independent of age or sex, hypertension which is caused by cortisol excess, is found in approximately *80%* of patients with CS, and post treatment persists in approximately *30%* of them. There is therefore a high risk of developing cardiac disease in CS patients with hypertension.[254]

Eighty-one percent of the females and *93%* of the male members in the present survey, reported that they had hypertension prior to their diagnosis. After treatment (*current status*), a significant change was observed, whereby only *20.8%* of the females and *20%* males reported hypertension in *Question 20A and B*, (*P <.05*). For these members who continued to have high blood pressure, antihypertensive drugs were prescribed.

In the present study, 24 (*33.3%*), out of 72 members who answered *Question 24a)*, were referred for a PET scan. PET/MRI imaging is said to provide and ideal modality for the detection of small hormone-producing adenomas. However, those members did not identify whether their PET scan was for pituitary or adrenal conditions. It may be likely that it was for pituitary as normally CT and US are the preferred modalities for adrenal gland micro and macroadenomas and in some cases AVS. Radionuclide Imaging, however, may also be used in adrenal gland studies to assess possible metastases of other organs, and this can include integrated- PET-CT for the characterization of the adrenal gland. Eleven (*15.2%*) members reported that they had an RNI scan.

Results, Figures 29, Figure 30, *Page 136, displays the additional diagnostic imaging examinations/procedures.*

2019 study, conducted by Akkus et al, was to assess the standard uptake values (SUVmax) in different adrenal masses including CS, pheochromocytoma, primary hyperaldosteronism and non-functional adrenal adenomas using ^{18}F-FDG PET/CT scan. The limitation of this study was the low number of patients (*n=9*). However, the authors found their results to be consistent with other similar studies in that non-functional adrenal adenomas did

not typically identify an increased FDG uptake, but a certain form of functional adenoma could present various FDG uptake in FDG PET/CT. This was particularly identified in cortisol-secreting adrenal adenomas.

The authors recommended that ^{18}F-FDG PEET/CT screening, "may be helpful in searching for functional characteristics of adenomas in patient with cortisol-secreting adenomas." [251]

In several case series involving adult patients, only *40%-50%* of pituitary adenomas were detected with MRI due to CS being a complex condition to diagnose, as previously described. If a definitive diagnosis is not achieved, through clinical, biochemical and MRI investigation (*equivocal or discordant*), then patients are referred for IPSS.[164.]

Seventeen (*23.6%*), out of the 72 members who answered this question, reported that they had BIPSS. This procedure is performed to distinguish a pituitary from an ectopic source of ACTH and is often referred to as the 'gold standard,' method to confirm the causes of ACTH-dependent CS. The sensitivity and specificity being approximately between *95%-99%.*

A comprehensive review of IPSS from 1977-2020, was performed by Periman et al, to establish, the pitfalls in performing and interpreting BIPSS from a personal experience and a literature review. The authors findings concluded that, "IPSS cannot be used to confirm the diagnosis of ACTH-dependent CS," and recommended that it is essential to establish ACTH-dependent hypercortisolism prior to performing IPSS and requires to have further evaluation of the value of the inter-sinus ACTH ratio to predict a tumour. [252] It was suggested that lateralisation may be improved using a prolactin-adjusted ACTH ratio. The authors recommended that a stepwise approach to performing and interpreting IPSS will provide clinicians with the "best information from this important but delicate procedure." [252]

A 2020 meta-analysis conducted by Wang et al included a total of 23 studies taken from 1642 patients radiological records and studied the use of BIPSS in CS differential diagnosis. The findings indicated that BIPSS had a higher diagnostic value for detecting ACTH in patients with ACTH-dependent CS than MRI. The authors therefore recommended that the most effective method of identifying ACTH-secreting sources was BIPSS.[34]

9.0 *Semi-Structured Radiographers and Radiologists Interviews*

9.1. Introduction

Undoubtedly medical imaging plays a major role in diagnosing both CS and CD. An important part of this study was to discuss with Radiographers and Radiologists who are responsible for the production and reporting of images, the range of imaging examinations and procedures for patients who were in the process of being or had

been diagnosed with Cushing's. (*Objective 4*). To achieve this, semi-structured interviews were arranged with radiology personnel and imaging centres visited. This gave an opportunity to interview radiology personnel working within large radiology departments which have the type of equipment used for diagnosing pituitary and adrenal adenomas and establish how aware they were of these medical conditions (*Objective 4*).

9.2 Radiology Semi-structured interviews

During the semi-structured interviews, 2 Neuroradiologists in a large University teaching hospital, when asked if the use of 3 Tesla or 7 Tesla made a difference when imaging small pituitary adenomas, they both agreed that it can have an impact on diagnosis, and they also discussed the benefits of using PET for its' potential superiority for the investigation of NETs.

The use of RNI was also discussed with the Radiologists, regarding its use in diagnosing metastasis and wide-spread disease processes

During the hospital visit, there was an opportunity to discuss the imaging equipment, scanning protocols and view the resultant images with the Radiographers. Interestingly, only 4 of 6 Radiographers had heard of CS, but regularly examine patients who are referred for pituitary MRI and CT adrenal imaging.

Notably, during the interview held with the 2 Neuroradiologists, the use of BIPSS was discussed and the benefits in confirming CS. Interestingly, 1 of the Radiologists interviewed, had performed 5 BIPSS procedures during his 15 years career in neuroradiology, the other Radiologist had not. It is widely accepted that BIPSS should only be performed by experienced Interventional Neuroradiologists due to their skill of successful sinus cannulation which relies on operator experience. The Radiologist did admit that it was difficult to teach other Radiologists this technique as there are very few referrals for BIPSS. This procedure is normally performed mainly in large, teaching hospitals and therefore is not always readily available. Some patients require to travel long distances if BIPSS is requested. An example was that 1 of the survey members travelled from Malta to mainland Spain for this procedure.

10.0 Additional Medical Conditions. (Question 25a).

It was important to afford the opportunity for the members to report any additional medical conditions which were associated with their Cushing's illness. A total of 16 additional medical conditions were recorded by 42 (*60%*) of the female members (*Question 25a), Results, Figure 24*). Eight (*53.3%*), males also reported additional conditions, 4 named their condition (*Diabetes= 2, Addison's disease= 2*).

However, it should be noted that osteoporosis, eye conditions, cardiac disease, and infertility were also reported by the same female members who had reported them in *Question 20A/B*. The additional female conditions therefore were DM (*42.5%*), AI (*9.5%*), Addison's disease (*9.5%*), Nelson's syndrome (*7.1%*), hypothyroidism (*7.1%*), diverticulosis (*4.7%*), arthritis (*4.7%*), bone sarcoma (*2.3%*), cardiac disease (*2.3%*), irritable bowel syndrome (*2.3%*), degenerative spinal changes (*2.3%*), eye conditions (*2.3%*), celiac disease (*2.3%*), depression (*2.3%*), infertility (*2.3%*). These conditions will be discussed in the concluding *Chapter 6, Conclusion, Pages 197-206.*

11.0 Surgical Intervention.

11.1 Adrenal Surgery (Questions 26) 26a) 26bi) 26bii)

For those in the present study who received partial or the removal of 1 gland the result also showed a negative relationship (*r -1, P>.001)*, with QoL scores. Interestingly, 21 (*61.7%*) of the females had laparoscopic surgery with 13 (*38.2%*), having open surgery. No difference was found i.e. (*open surgery versus laparoscopic surgery*) in their QoL scores, (*P <.05*), (*Table 24, Page 131)*. However, 1 observation was, that 6 of the members who had open surgery, had more hospitalisations, and 4 were not in remission. The present, 'gold standard,' approach to remove adrenal masses is laparoscopic adrenalectomy. In the past, literature has suggested that open surgery should be conducted in cases of malignancy, recurrent cases and larger masses, laparoscopic surgery being contraindicated for such cases (*masses >6cm*.). Surgeons require to balance the risk factors, affecting an operative approach for open adrenalectomy, including the likelihood of conversion and the clinical variables that are important in selecting patients for open surgery and the perioperative morbidity. Patients for adrenalectomy must therefore be fully assessed to decide the type of surgery required and the risks involved. [223]

A retrospective 5-year study conducted in 2020 of the laparoscopic approach to removing adrenal masses assessed the postoperative results of 76 patients who had this type of surgery. While adrenalectomy is considered a serious operation, a strategic approach requires to be adopted in patients with complications. The authors concluded that laparoscopic techniques should be applied following careful selection and when necessary, conversion to open surgery should be applied.[224]

In several other previous studies, the surgical approach was found often to be associated with longer recovery times, hospitalisations and postoperative morbidity, mortality, and pain. [21 219 226]

In the present study, 9 members who had bi-lateral adrenalectomies and subsequently developed AI, had lower QoL scores and. the result showed a strong correlation (*r= 0.8, P<.009*), (*Table 23, Page 151).* This result is similar to a study conducted in 2019, which concluded that despite clinical remission, patients who had bi-lateral

adrenalectomies are more likely to have a poorer QoL.[227] This is due to a more prolonged period of uncontrolled hypercortisolism combined with continuous AI.

In the present study, 5 members were hospitalised for having experienced an adrenal crisis, 4 females for Addison's disease, 3 for Nelson's syndrome and 2 males for Addison's disease. Notably, these members all had low QoL scores (*very poor, poor*).

11.2 Pituitary Surgery (Questions 34,34a),34b),34c).

For those who were diagnosed with PIT-CS, a moderate correlation was found, suggesting that members who developed PIT-CS had a poorer QoL compared to those with adrenal CS, (*r .1, P <.02*), as previously mentioned. In 2018, Valassi et al, published a paper which identified from the ERCUSYN database, that after a median of 38 months post treatment, patients with CD also had lower QoL questionnaire scores (*CushingQoL*), than patients with adrenal-dependent CS.[205] The ERCUSYN database also however, identified that patients who were in remission from both adrenal and pituitary origin, showed no difference between their QoL score. The present study results also reported similar findings (*r-1, P >.4), (Table 24, Page 131).*

11.3 Transsphenoidal Surgery

The first-line treatment for CD is TSS and a recent meta-analysis review conducted by Stroud et al, 2020 studied the remission and recurrence rates in patients who had undergone TSS and sought to identify predictors for the surgical outcomes.[229] The study excluded patients who had prior GK-RS and RT, mixed pathologies, or interventions without separated data, follow-ups not reported or population size >20. The conclusion to their study was that in cases of primary microadenomas, TSS was found to be the preferred surgical option. This was evidenced using a comparative approach, i.e., preoperative imaging and without CS invasion, biochemical testing with postoperative results. [229]

A total of 49 members in the present study had pituitary surgery. Twenty-five females, and 2 males had repeat surgery (*mean =2, min.= 1, max=5*). On viewing the female QoL scores, 14 of the 25 had 1 repeat surgery and poor QoL scores, (*r =.1, P<.01*). The 11 others who had between 2-5 repeat surgeries had very poor QoL scores. The test of association showed that repeat surgery significantly decreased their QoL (*r= .7, P<.05*), (*Table 24, Page 131*). It was also noted that most of these members had additional medical conditions due to their Cushing's illness, including 1 who had hypothyroidism. The latter condition was studied recently by Xiang et al, in 2019 before and after remission of endogenous CS. These authors felt that there was a lack of knowledge about this

condition and concluded that thyroid functions may be mistakenly diagnosed as hypo or hyperthyroidism post-surgery which can then result in prescribing antithyroid drugs [230]

According to Professor J Newell-Price, 2021, there are 3 main possible outcomes, post pituitary surgery i.e., success, partial success, or failure.[195] Biopsies are taken during TSS, and biochemical follow-up after 6 weeks is crucial in order to analyse the ACTH levels. The latter test is regularly conducted in the months that follow surgery to confirm that the cortisol levels return to normal. An MRI scan is also performed months later to confirm that the adenoma(s) have been successfully removed and follow-up MRI scans are conducted annually.

12.0 Clinical Presentation and Differential Diagnosis

When patients present with CS/CD the clinical presentation can present a challenge, as previously discussed. This is evidenced by the range of medical conditions and number of Physicians consulted prior to the members in this survey having a definitive diagnosis. This could suggest that the differential diagnosis creates a long diagnostic journey before a definitive decision is made.

The challenge is often in cases with mild or cyclic hypercortisolism, and the "overlap of symptoms in individuals with and without the disorder." [7]

The seriousness of hypercortisolism is that it is strongly associated with increased morbidity and mortality. The impact on QoL, despite remission was clearly demonstrated and reflected in the answers in the present study. Sixty members continued post remission to be reliant on GCs and other steroid medicines and *24%* of the females reported cardiac disease disorders, which had developed gradually prior to their diagnosis and has continued throughout their treatment. Thirteen per cent of the males also reported cardiovascular conditions prior to their diagnosis, and currently 1 member is awaiting surgery. Uncontrolled hypercortisolaemia is associated with high risks of metabolic, cardiovascular, cognitive, and psychological alterations. Unfortunately, these conditions can persist for many years after diagnosis, reducing QoL which is reflected in many studies which show growing evidence of the risks and morbidities of CS.[176]

A recent study for example, was conducted accessing the records of 242 CS patients including benign CS (*PIT-CS= 101, ARD-CS= 99, Ectopic-CS=13*), and 29 with malignant disease. The aim being to look at the morbidity and mortality in CS patients over a period of 1 year from first symptoms of hypercortisolism until biochemical remission. The findings highlighted the whole spectrum of acute and life-threating complications of CS and their high prevalence even prior to diagnosis and after successful surgery. Interesting, the prevalence of infections was *25%* in the study conducted by Scheernthaner-Reiter.[228] Comparing this figure with the present study results, *43%*

of the females had infections prior to their diagnosis and an increase was noted in the percentage (*50%*), *current status*, (*Question 20b*). While the male results for infections was *40%* and reduced to *13.3.%,* (*current status)*. For the Scheernthaner-Reiter's study cardiac complications were, *19.7%* compared with *24%* for the female members, which notably did not change over time. However, the results for the males showed an improvement from *13%* prior to their diagnosis to 6.6% *(current status).*

In Scheernthaner-Reiters's study, the mortality during the observation period was *2.8%* for benign CS and *59%* for those patients with malignant CS.[228]

13.0 Medical Therapies (Questions 27,28,29,30,31).

Some patients are unable to have surgical intervention. This may be due for example, to underlying serious medical conditions or where surgery has failed. In these cases, medical therapy for any cause of CS is considered. Wagenmaker et al, (*2012*), found on studying the HRQoL dimensions in several questionnaires, when compared with healthy subjects, regardless of the aetiology of previous hypercortisolism, pituitary hormone deficiencies and treatments received, CS patients scored worse QoL on most of the dimensions compared with the healthy subjects. In these cases, medical therapy was prescribed.[109]

Medical therapy is used extensively in CS and CD to improve the associated conditions, QoL and to reduce mortality.[20] Adjunct therapy is used regularly during the active phase of CS and for the comorbidities, prior to and following surgery, the latter being the first-line approach to resect causal lesion(s). A variety of pharmacological treatments are available, and the choice of treatment is individualised for each patient, normally prescribed by their endocrine team.

The use of hormone replacements prescribed for the members in the present study is fully reported in *Chapter 4, Results, Section 10, Pages 139-142.* Notably,*72.4%* (*n=50*), of the females and *66.6%* (*n= 10*), of the males were currently taking steroid/GCs medication. As previously reported, most of them, *44.2%* (*females*, *n=27*) and *53.3%* (*males, n=8)*, were advised to take these, post-surgery and *38.8%* (*n=26*) females and *33.3%* (*n=5*), males were advised by their Endocrinologist that they would always have to take steroid medicine. As previously reported, the majority of these members were taking hydrocortisone (*89.4%, n=51 females, 90%, n=10 males* figures based on QRR*). Most of them had high physical signs and symptoms scores (*>15*), and high psychological and cognitive signs and symptoms scores (*>3*), (*Question 20 B, current status*), thus indicating a poor physical and mental state, at the time of completing the survey questionnaire. However, with regards to the effects of the 26 members who were on long-term use of GCs when measured with their QoL scores, the results showed a negative correlation (*r-1, P >05*), (*Table 2, 129*).

This result suggests that the use of medication can and should help to alleviate some of the symptoms, despite being diagnosed with other associated medical conditions. Or was this result simply due to many of them having just had surgery and the long-term effects of GCs had not yet impacted on their physical, mental health and QoL? Tiesma et al showed in their 2011 study, that CS patients in long-term remission who had some form of hypopituitarism scored lower CushingQoL in the physical and psychosocial dimensions when compared with pituitary insufficiency.[110] It was also noted in their study, that those who had GC replacements also had lower CushingQoL scores in the same physical and psychosocial parameters. Contrary to this, other large studies did not find any significant association with GC replacements on HRQoL except patients with AI. [117] [108] Interestingly, De Bucy et al, 2017, found that over a period of 3 years, a progressive deterioration of mental health in CS patients with concomitant cortisol deficiency.[238]

Health Related Quality of Life was significantly impaired in women treated for GHD than those with GHD due to other diseases, in a study conducted by Feldt-Rasmusseen et al in 2002. The findings suggested that prior exposure to GC excess is a stronger determinant of HRQoL.[239]

For those members in the present study, who reported AI, the lifelong need to take GCs and mineralocorticoid replacement therapy reflected in their lower QoL scores. Nine members as previously reported, had bi-lateral adrenalectomies. The 10-year mortality after this type of surgery is approx. *3%*, but notably approximately *50%* of deaths occurs within the first year of surgery. The risk of CD recurrence is estimated around *2%* (*range=0-12%*). However, 1-2% of patients develop clinically evident hypercortisolism.[131]

Ninety-three percent of the members who were diagnosed with other medical conditions named the types of medication they had been prescribed. *(Figure 33, Figure 34, Page141*). Notably, those with AI, who answered *Question 31* were prescribed Metyrapone and for those with hypothyroidism, Levothyroxine. *Both these can have similar side effects and can cause sweating, chest pain, headaches, vomiting and diarrhoea.

14.0 Radiotherapy Treatment (Questions 35,35a), 35bi),35bii).

Fourteen (*87.5%*) of the 16 females in the present study who had RT, were treated with GK-RS and 2 (*50%*), of the 4 males who had RT also had GK-RS. A range of 9 side effects were reported including nerve damage to the eyes resulting in vision impairments (*n=3*) and 1 with hypothyroidism.

Stereotactic- radiosurgery (*SRS*), is used for the management of residual or recurrent CD. Since the introduction of a GK-RS unit in 1969, it has been the modality of choice for intracranial RS, and is the first line treatment in CD, used in cases where residual disease is present and not amenable to surgical resection. [231]

With the increase in technological advancements and experience of using GK-RS, clinical outcomes have impacted on CD patients according to Bunevicius et al, in their 2021 publication.[232] These authors advised Physicians to consider during the planning and subsequent reporting and treatment that patients' pre-treatment, should be fully advised and counselling made available prior to proceeding with this type of treatment and recommended additional studies in order to explore, "the learning curve of GK-RS." [232]

Another challenge for Neurosurgeons, is the surgical resection of NFPA requiring the invasion of the cavernous sinus and can be a significant factor associated with incomplete resection.

Lee et al, in 2020 aired their concerns that there is little information concerning SRS as an initial treatment for CS-invading NFPA. Hence, they conducted a retrospective, study analysis of 11 patients with CS tumour invasion and found that tumour control was achieved in all these patients, and interestingly, none of them developed hypopituitarism or visual disturbances. However, this study's population was small.[233]

Another 2020 more robust study of the long-term results of GK-RS for postsurgical residual or recurrent NFPA conducted by Deng et al, showed in 148 cases that GK-RS offered high lesion control. In this study, the authors referred to, "new hypothyroidism," which they found occurred in 9 patients, 6 patients developed new or worsening visual dysfunction, while 4 patients developed new cranial neuropathies.[234]

Two female members in the present study, were treated with LINAC RT and had side effects, similar to those who had GK-RS. No difference was found in their QoL scores however, no inferential statistics were performed due to the small study population.

External beam RT is known as an effective treatment modality for pituitary adenomas which have not been cured by TSS or medical therapy. According to Gupta and Chatterjee, (*2020)*, this type of RT provides *>90%* long-term local control but lower and variable rates (*50%-80%*), of biochemical remission in secreting lesions.[235] The recommendations from these authors being that further research is required in PIT-RT in the dose volumes for different subtypes of pituitary adenomas and advised that a careful approach to assessing the risk versus benefit ratio must be conducted by a multidisciplinary neuro-oncology team.[235]

The concerns over PIT-RT for benign tumours prior to the new advancements, are the fear of irreversible damage including hypopituitarism, neurocognitive/neuropsychological dysfunction, optic neuropathy, cerebrovascular accidents, and secondary malignant neoplasms, with a higher risk of morbidity and mortality.

Two of the members who had GK-RS did express their fears of having to have repeat surgery and how it took a long recovery time. These 2 members both had very poor QoL scores (*current status- Question 20B*), and high

signs and symptoms (*current status*) scores for both dimensions of health i.e., physical, and psychological. in these cases, psychological support was given post-surgery.

Advancements in RT are discussed in *Chapter 1, Section 2.11, Pages 34-35.*

15.0 Chemotherapy Treatment (Question 36a), 36b), 36c).

Only 4 female members in the present study received chemotherapy and reported several side effects (*n=7*), (*mean=3, min= 2. max =4*). All 4 members QoL Likert scales showed lower QoL scores (*very poor, poor*) and were advised that they would always require to take GCs. Notably they also had high signs and symptoms scores for both physical and psychological dimensions of health prior to diagnosis and *current status. (Question 20A/B).*

The ESE Clinical Practice Guidelines for the management of aggressive pituitary tumours and carcinomas, suggested that there was a need to define aggressive tumours which related to their clinical orientation.[236] The publication of their Guidelines in 2018, provided important and clinically relevant bases for the management of aggressive tumours. Several new therapies have emerged which have improved the mortality rates for various types of cancers. However, the data for aggressive pituitary tumours remains limited and further studies using multi-centre trials was recommended. [236]

As previously discussed in *Chapter 1*, *Section 4, Pages 39-40***,** the therapeutic options for aggressive pituitary tumours are very limited after failure of surgical intervention and RT. What is emerging however, is the use of TMZ as an oral chemotherapy, with relatively good tolerability. None of the members unfortunately gave details of the type of chemotherapy they had received.

According to Petersenn (*2019*), many questions remain over how long chemotherapy treatment should be continued, combined with RT and are there any reliable markers to predict treatment efficacy and what is the second-line option, if this treatment fails? [237]

Primary treatment is surgical removal of the cause where possible, bi-lateral adrenalectomy is an option if pituitary surgery for CD or ectopic ACTH is not effective or possible. Presently the RT treatment for CD only is pituitary RT (*standard or stereotactic e.g., GK-RS*).[195]

16..0 Psychosomatic Aspects of Cushing syndrome.

Perhaps what is often, 'missed,' during initial consultations either at the primary or even the secondary care stages of diagnosis, is the psychological and cognitive effects of the disease processes which in short consultations can

be unnoticed. Unless the patient has been diagnosed by a Psychiatrist or Psychologist at the onset of their CS, then there is a potential for a patient to have unmet needs.

Previous research has shown that the neuropsychological effects of hypercortisolism may not be reversible. This results in life changes, examples being work and social interactions.[240]

The present HRQoL survey as previously mentioned, revealed that *40.8%* of the females and *13.3%* of the males gave up work and *18.3%* of the females and 1 (*6.6%*), male chose to work part-time or take semi-retirement due to their Cushing's illness, and 1 male (*6.6%*), also had to give up his studies.

Fifty-eight (*81.6%*), females and 12 (*80%*), males found that their Cushing's illness had severely affected their social life, giving at least 2 reasons why this was the case.

Cushing's had also affected 68 (*95.7%*) of the females' personal relationships and 14 (*93.3%*) of the males, resulting in serious consequences. Examples being self-isolation, depression, anxiety, stress, breakdowns in their marriages and partnerships, and in 3 cases suicidal ideation, 2 of them being males. Fourteen members had to be admitted to a psychiatry hospital for hypomania and psychiatric conditions and 3 were subsequently sectioned. Each of them thought that this could have been avoidable if a diagnosis of CS had not been delayed and if their Physician had recognised the symptoms earlier. For these cases, each had visited between 2-4 Physicians including their GPs prior to their diagnosis.

In *Chapter 1, Section 1.6, Page 19***,** of this thesis, a publication by Pivonello et al in 2015 highlighted that, even after hypercortisolism resolution, "that despite the improvement of the overall prevalence of psychiatric and neurocognitive disorders, the brain volume loss at least partially persists." [22] Sadly, this results in the depressive disorders, panic attacks and cognitive impairments which were given in the textural survey responses as reasons why the members experienced changes to their normal lives.

This evidence reported in the members narrative accounts revealed that their QoL, was seriously compromised and this was further highlighted in those members who had lower QoL scores (*current status-very poor, poor*), many of whom were in the active phase of CS (*not in remission= 25.7% females, 20% males*). Interestingly, these members had higher signs and symptoms scores for both physical and psychological signs and symptoms (*Question 20 B, current status*) and other medical conditions which had been diagnosed as a result of the disease processes created by their Cushing's illness.

Although no medical records were accessed during this study, it could be suggested that many of these members had long-standing hypercortisolism. This was evidenced by their QoL scores, their signs, and symptoms scores (*prior to diagnose versus current status*), dependence on GCs and their individual diagnostic and treatment

journey, including the length of time in remission, recurrences, and repeat surgeries. Notably, *37.9%* reported a lack of psychiatric and/or psychological support which had not been a suggested method of intervention by any of their Endocrinologists. This is thought to be due to wide-spread limited availability of mental healthcare services; private services are expensive and there is a recognised insufficiency of mental health care policies and education. Clearly this lack of psychological support had made an impact on the members lives and families, particularly those who struggled to come to terms with their diagnosis and required help for their mental health, well-being, and unmet needs. This I suggest is a barrier to improving their HRQoL.

Long-standing hypercortisolism is often suggested as being irreversible and therefore the pathological processes creates both physical and psychological detriments which require long-term interventional care.

In *Questions 8-9a),* the study population described exhaustion, fatigue and insomnia (*65.1%*), physical body changes (*31.1%*), which caused embarrassment, physical disabilities, (*e. g. mobility=16.9%*), reduction in self-confidence, lack of sexual desire (*38.3%*), memory loss and the sheer severity of their illness (*19%*), culminated in a lack of desire to socialise and therefore created difficulty in making friends (*17.4%*), maintaining relationships (*30%*), and a lack of concentration and energy to work and study effectively**.**

17.0 Weight Gain.

Another, finding in the present study, was the largest sign indicated by the members in *Question 20A*, which was weight gain prior to their diagnosis (*Females= 97%, Males= 100%*). Weight gain is said to be the first most common sign prior to a CS diagnosis.[97] However, a significant number of members had lost weight during their treatment (*Females= 55.5% and Males= 66%), (P <.03), (Question 20B-current status)*. Interestingly, many of these members mentioned in their social and personal accounts, how it was a causal influence in their depressive state. The main reason being that it caused embarrassment and sometimes humiliation from friends and family. Two of these members had been diagnosed with CS by their Dietitian during an OB clinic. Obesity is now one of the most identified problems in the world, the prevalence has been increasing over the last several decades.[255] In the UK it is now said to have a higher mortality rate than cancer, according to the Public Health Intelligence Network 2020 statistics and the obesity profile.[256.257]

A 2020 study conducted by Atar et al, recommended a screening programme for CD, CS and ACS in patients with stage-1 OB who were older than 50 years with uncontrolled type-2 diabetes and hypertensions.[258] Interestingly, 12 members mentioned in *Question 40*, that it would be helpful to have been referred to a Dietitian early on in their treatment.

Patients with DM often develop cardiac disease. This can be induced by taking medicine such as pasireotide, cabergoline, the latter used to normalise UFC levels in approximately *30%* of patients to reduce blood pressure.[259] In the present PhD study, 19 females and 2 males reported that they had been diagnosed with diabetes. However, they did not specify, whether their diabetes was mellitus or insipidus. Two females had hospital confinements because of their diabetes illness and 1 female had been diagnosed with CS during a consultation with their Cardiologist.

Other conditions reported by the members which were related to cardiac conditions included 1 male who had a stroke which resulted in surgery and 5 females which meant that *8.9%* of the 56 members, who answered *Question 21b*), had cardiac surgical procedures. Notably, these members all had low QoL scores (*very poor to poor*).

Cholesterol levels are assessed as part of the blood tests during a CS diagnostic-work up and after diagnosis as an ongoing investigation to ensure that serum cholesterol levels remain within normal limits.[260]

Seventy-nine percent of the female members reported high level of serum cholesterol prior to their diagnosis, and this condition remained in *23.8%.* of them, (*Question 20B*, *current status*). The males also reported high levels *prior to diagnosis* (*80%*) and currently *26.6.%* of them continue to have high cholesterol levels (*Question 20B*). An overall significant improvement in the cholesterol levels, however, was recorded for the study population, ($P < .001$).

As previously discussed, CS, induces a variety of changes in the immune system and complications regularly lead to severe infections, inflammatory disorders, including sepsis. Two females were hospitalised, 1 due to sepsis and another female also developed coeliac disease which is a condition whereby the immune system attacks its own tissue when gluten is ingested.

The comorbidities of CS include several characteristic clinical changes which alters the shape of the body not only weight gain or occasionally weight loss, but in the round facial appearance (*moon face*), facial plethora, thinning of the skin, bruising and hirsutism (*excess hair growth in women*).[260]

The female members reported high signs and symptoms scores in *Question 20A, (prior to diagnosis)*, for hirsutism (*84%*), skin bruising (*81%*), balding (*64%*), moon face (*54%),* proximal muscle weakness, (*48%*), plethora (*18%*) and dorsal fat pad (*16%*). While the male results showed that *13%* of them had developed a moon-shaped face, *13%* skin bruising, *7%* dorsal fat pad, *7%* plethora and *20%* proximal muscle weakness. The latter condition is often described as an important feature of CS. Proximal muscle myopathy is normally caused by GC induced protein metabolism and affects muscle strength.[261.]

A 2020 study of muscle strength in CS patients conducted by Muller et al, highlighted that due to a breakdown of protein caused by excess cortisol can result in muscle weakness and despite regular exercise, weakness can persist often for months to years.[262]

The further items reported by the female members (*Question 20B*, *current status)*, showed a change in scores for all items i.e., small to medium improvements. A *P* value < *.05*. was thought to be significant, for the items: balding, skin bruising, cholesterol levels, dorsal fat pad, headaches, hypertension, moon face, plethora, weight gain, therefore suggesting a current improvement in these conditions.

Interestingly, 1 of the females had been given the suggestion of CS as a possible causal reason for her plethora and skin bruising, during a consultation with her Dermatologist.

The males also showed improvements in all items except fatigue, infertility, and osteoporosis (*current status).*

Notably, an increase in osteoporosis (*current status*) for both genders was reported in *Question 20B,* (*Results, Figure 20, Page 124, Figure 22, Page 129).*

The benefit of a detailed questionnaire is that it can be embarrassing in a face-to-face interview to discuss these very personal changes to the body in detail, and this was reflected in several of the open questions, in the personal statements regarding how these changes had affected their looks, personality, attitudes towards life and QoL.

18.0 Menstrual Irregularities, Infertility and Libido.

It is well documented that decreased libido and menstrual irregularities are common in CS patients.[7 97] These disorders are often referred to as menstrual cycle disturbances. Decreased libido had affected both genders in this present study, which had caused psychological conditions culminating in depression, anxiety disorders and relationship breakdowns.

Eighty-two percent of the females reported that they had no desire to have sex prior to their diagnosis but this had only improved for 13 of them post treatment.

Seventy-three percent of the 15 males also experienced a lack of libido prior to their diagnosis and this has continued in *60%* of them, (*current status, Question 20B).*). Notably, 3 of these males had been diagnosed with erectile dysfunction by a Urologist.

A high number of the women in this study had experienced menstrual irregularities prior to their diagnosis (*76%*). However, the current scores showed a moderate change, i.e., *56.7%* were still experiencing these irregularities. Interestingly, 5 Gynaecologists and 1 Obstetrician had suggested CS as a possible cause of this and 1 Nurse when she attended a fertility clinic.

Unfortunately, for *19%* of the women and *20%* of the men in this study (*current status*), infertility had impacted on their ability to produce children *prior to their diagnosis*. Currently 2 of the women, have found that their fertility has improved enabling them to conceive, but the male result showed infertility continued in *20%* (*n=3*) of them.

According to Naz et al, (*2020*), this condition is one of the most common clinical features and is reported by the ERCS to be found in *56%* of women diagnosed with CS. [265.]

19.0 Sleep Irregularities and Chronic Pain

Members who reported having insomnia had experienced a difference in their sleep patterns before and after treatment, (*Question A/B*: *Females= 57% prior to diagnosis, 44.7% current status and the males= 60% prior to diagnosis and 26.6% current status*).

A 2020 study conducted by Moyers et al, of 147 CSRF CS patients completed the CushingQoL questionnaire and the Pittsburgh Sleep Quality Index (*PSQI*) and physical activity with the Godin-Sheppard Leisure-Time Physical Activity questionnaire (*GSLTPAQ*). The results reported that sleep quality was significantly associated with both subscales of CushingQoL (*both P <.001*), but physical activity was not significantly associated with either subscale. These results concluded that there was no significant association with the engagement of physical activity and sleep disturbances, and are significantly associated with impaired CS QoL[266]

A few small studies one of which was D'Angelo et al, in *2015*, have called for more research to be conducted to assess sleep alterations in CS patients [267] It is well documented that there is an association between the HPA axis and sleep and that the HPA axis disturbances cause insomnia. D'Angelo et al assessed sleep alterations using wrist actigraphy, with the aim of evaluating sleep quality and duration in 12 CS patients.[264] High GCs, as previously mentioned, are known to have detrimental effects on the brain, causing neurocognitive and psychiatric symptoms, this in turn creates cognitive dysfunction which increase anxiety levels, insomnia, irritability and depression[253 262 263] D'Angelo et al found that hypercortisolism is associated with low sleep quality and can help to lower QoL and increase metabolic comorbidities in CS patients.[267]

Another reason for insomnia can be body pain, arthritic changes, and osteoporosis in CS patients. [268 269]

Prior to diagnosis, *78%* of the females had experienced body pain and this had persisted in *80.5%* (*current status*) of them, the latter figure accounting, for 1 additional female. Notably, 44 of these females were currently in remission. Seventy-three percent of the males also experienced body pain *prior to their diagnosis.* However, a reduction of responses showed that 4 less males were currently not experiencing body pain (*43.3%).* Notably, 10 of them were in remission.

The most widely accepted definition of pain was developed by the International Association for the Study of Pain: "Pain is an unpleasant sensory and emotional experience that is associated with actual or potential tissue damage or described in such terms." Body pain can range from mild, localised discomfort or agony.[270] This definition has been debated since it's conception in 1979, and Treed, commented recently on the Cohen et al, 2018 article which related to the definition of pain. According to Cohen et al, the "cognitive and social dimensions of pain are claimed to be missing in the IASP definition." [271] However, on reviewing this work, Treed, concluded that Cohen's redefinition of pain, "is not useful," and described how verbal cultural differences in language could, "flaw," the translation between languages.[271]

The sensory pain that CS patients experience is often for example caused by headaches (*neuropathic*), bone and muscle atrophy, gastrointestinal inflammatory conditions, skin infections (*including viral*), urinary tract infections and functional pain, which is pain without obvious origin. Acute pain is the short-term pain that comes suddenly normally from a specific cause and chronic pain can last for years and ranges from mild to severe on any given day. Examples of the latter being frequent headaches, nerve damage pain, low back pain, arthritis, and fibromyalgia pain.[272] Chronic pain is recognised as a major public health problem, producing a significant economic and social burden. [273] [274]

During the present study, the author having attended endocrinology conferences, found that one of the main topics focused on functional pain. In the survey results, the high signs and symptoms scores for body pain and other conditions which are related with high levels of pain, were further highlighted in the survey's narrative accounts and in their QoL scores. This was not only compelling evidence of the physical pain that these members were experiencing but also the detrimental effects that it had on their health, work status, studies, mental health, and overall well-being.

According to Stanley, 2020, "Fatigue is one of the most common complaints, particularly adolescents," in CS patients.[275] Stanley discusses in her paper, 'Fatigue or Weakness,' and other reasons why patients experience one or both, which includes underlying diseases such as CS often being the differential diagnosis.

The 2020 Valassi et al, Cushing's collaborative patient survey results, of 250 participants from 26 countries, found the 5 symptoms reported as the most burdensome were obesity/weight gain (*15.5%*), fatigue (*10.7%*), depression/mood problems (*9.5%*), sleep disturbances (*8.7%),* and anxiety (*8.2%*). However, their study showed that post-treatment, *83%* of the participants continued to experience fatigue (*72%*), muscle weakness (*47%*), obesity/weight gain (*43.1%*), memory loss (*41.4%*), and lack of attention/concentration (*38.8%*).[276]

In the present study *43%* of the females and *50%* of the males reported exhaustion and fatigue which had made them in many cases too tired to, quote, "cope with life," and, "work," and reduced their concentration at work and social activities, (*Chapter 4, Results, Section 2.2.1. Theme 1, Page 107.*

Interestingly, the Valassi et al study's conclusion was that a number of these symptoms were left untreated after diagnosis and treatment, recommending that this should be addressed by developing management strategies.[276]

20.0 Osteoporosis and Skeletal Abnormalities.

Glucocorticoid-induced Osteoporosis (*GIOP*), in CS remains the most common form of drug-induced osteoporosis, according to Saag et al, 2021.[277] This health condition creates weaknesses in bones which are then easily fractured and is more prevalent in women than men. As previously mentioned, *36%* of the female members in the present study had been diagnosed with this condition prior to their diagnosis and during their treatment phase of their illnesses. Twelve of them had a DEXA scan to confirm their diagnosis, *23.8%* described how that they had found an improvement in their condition after being prescribed medical therapy. Five of the females were prescribed Alendronic Acid in combination with Adcal D3 and 4 were prescribed Adcal D3 only, which are commonly prescribed for osteoporosis. Bisphosphonates are prescribed as the first-line approach and includes Alendronate and Adcal D3.

One male was diagnosed with osteoporosis prior to his diagnosis and continues to have this condition while 1 other male was diagnosed post treatment. None of these men reported having a DEXA scan or which medication they had been prescribed.

Interestingly, Harvey Cushing first explained the association between excess endogenous GCs and fractures in 1932 and in 1954, a few years after the introduction of prednisone to treat RA, it was then reported that exogenous GCs had deleterious effects on the skeleton.[278]

Osteoporotic fractures are often diagnosed pre-CS, particularly atypical symptoms for specific age groups for example, pre-menopausal and older women and men under 50 years.[278] [279]

According to Braun et al (*2019*), it is important when looking at clinical scoring for QoL that all physical comorbidities should be considered. This should include the screening of patients for osteoporosis.[280]

Four of the women in the present study, reported that an Orthopaedic Surgeon following a spinal x-ray had suggested CS as they had identified incidental adenomas, and this was the probable reason for a loss of bone density on their x-ray images. The ages of these women were between 35 -68 years old, all had low QoL scores (*very poor, poor*), except the 35year old, who had a moderate QoL score (*Fair-current status*).

The 2 male members who were diagnosed with osteoporosis were 43 and 44 years old and both had low QoL scores (*Poor- current status*).

Osteoporosis can cause severe back pain and slow loss of height.

The aim of a 2021 study conducted by Stachowska et al, was to compare the trabecular bone score (*TBS)*, and the fracture risk in patients with endogenous CS to controls i.e., sex and age matched non-CS patients. The methodology of this study was to measure the anthropometric parameters, biochemical and hormonal data between these 2 groups. The TBS values were taken from the DEXA scans. Findings showed that the patients with active CS have altered bone microstructure which was verified by a marked decrease in the TBS. This study concluded that CS patients are more at risk of hip fractures and major osteoporotic fractures compared with non-CS patients.[281]

Interestingly, *91%* of the women in the present study who were diagnosed with osteoporosis had low QoL scores i.e., *very poor-poor*. These women also reported mobility disabilities, 1 is permanently in a wheelchair and 3 of them were regularly attending a fracture clinic. Another observation within the thematic analysis was that mobility disabilities was reported in *12%* of the female members, and their disabilities had, reduced their ability to socialise and work (*Chapter 4, Results, Section 2.2.1, Theme 5, Page 108.*

21.0 Visual Impairment Conditions related to Cushing syndrome

Fifteen percent of the females and *20%* of the males experienced eye problems prior to their diagnosis. Currently *25.3%* of the females are still experiencing eye problems. The male results remain the same.

Visual complaints are often reported pre/post pituitary surgery. The acute changes of cortisol levels following successful surgery can be associated with a transient deterioration of the patients' general condition, which includes insomnia, fatigue, depression, and visual impairments.[20] The adverse effects from drugs for example, mifepristone can cause fatigue and nausea, and second-line treatments as previously mentioned, such as GK-RS can cause serious damage due to the proximity of the optic nerves/chiasm, stereotactic RS being a contraindication.[20]

Multi-modality imaging was discussed in both *Chapters 1 and 2* and highlighted that they play a large role in ophthalmology and the screening of patients with CS, particularly in retinal abnormalities, for example chorioretinopathy (*CSC*), in active endogenous CS and suspected increase in choroidal thickness. According to Eymard et al, 2020, CSC pachychoroid spectrum disease (*PSD*, is more prevalent in CS patients.[282.] The latter disease being described by Ming et al, "as a novel concept describing a phenotype characterised by attenuation of

the choriocapillaris overlying dilated choroidal veins and is associated with progressive retinal pigment epithelium dysfunction and neovascularisation." [283.]

Up to 5% of CS patients have been described as having 1 or more episodes of CSC, experienced during their hypercortisolaemic state.[284] It could however be suggested that this figure may now be greater due to the more advanced imaging techniques. This was the case in 56 CS patients in the Eynard et al study, whereby the PSD was significantly higher in CS patients when compared to a control group (*21% versus 3.6% P<.004*).[282]

In the Brinks et al 2021 study, findings also detected CSC (*subclinical*), and other ocular fundus abnormalities in a large percentage of their CS patients who had not reported visual complaints. [285]

In the present study, none of the members reported the actual medical term(s) for their eye conditions but reported failing eyesight including blurred vision, eye twitching and 2 females reported having an ophthalmology scan due to a deterioration in the sight of both eyes.

22.0 The Prevalence of Infections in Cushing syndrome Patients.

The prevalence of infections is found to be between *21%-51%* of CS patients in the active phase of their illness.[97]. According to Hassenmajer et al, 2020, few studies have described the epidemiology as they mainly focus on EAS.[261]

Prior to their diagnosis, 43 (*60.5%*), females and *40%* of the males in the present study, reported that they were prone to infections, (*Question 20 A)*. The *current status* results in *Question 20B* however, showed a reduction in both genders scores, (*Females= 34.3%, Males= 13.3%*). Two of the main causes of death in CS patients is cardiovascular and infectious diseases.[286 287 96]

The European database of CS patients shows that as the disease progresses, mortality is *37%* in patients who died within 90 days of their diagnosis, infections being the second cause of death in approximately *31%* of patients.[205]

In the present study, 6 members named the type of infection they had contracted because of their Cushing illness. (*Question 20a)*). One female member developed sepsis which resulted in hospitalisation, and 5 other female members developed intermittent viral infections. CS patients are more susceptible to viral infections due to increased GC exposure, this being due to the neutrophil count which helps to cause a hypercoagulative state resulting in sepsis.[261]

23.0 Neuropsychiatric conditions and Cognitive Impairments.

Undoubtedly, serious illnesses impact on the human body in many complex ways. Cushing's patients report how exhaustion and fatigue can change their lives and was highlighted in the present study in their written accounts of

how work, education, social and their personal lives had changed. This provided substantial evidence that CS patients suffer from a variety of neuropsychiatric and cognitive disorders. Many publications including Vries et al, 2020, warn that even CS patients post remission have long-lasting effects, which include as previously mentioned, structural and function brain abnormalities.[288]

High resolution MRI images have enabled neurocognitive assessment prior to and post treatments. The Vries et als recent investigation into the extent and time-course of restoration of physical and neurocognitive symptoms, as well as functional and structural brain abnormalities in CS patients is still ongoing. Work-in-progress was discussed at the Endocrinology 2020 Congress. This included the use of neurocognitive tests, general and disease-specific QoL questionnaires, and functional task-based and structural MRI performed before treatment and 1 and 2 years after treatment. Early indications show that this type of study will compare treatments with the objective of increasing the remission rates.

It is clear from other Cushing's surveys of this nature, that the psychological and cognitive impairments experienced by those who are diagnosed with CS have a negative effect on their lives. Both genders in the present study prior to their diagnosis, as previously mentioned, experienced depression (*89.9%)*, lack of concentration (*8.8%*), memory loss (*8.8%*), severe psychological problems including hypomanic attacks (*28.8%*), emotional problems (*61.5%*), social isolation (*55.3%*), and other psychological unnamed conditions (*49.4%*), (*Question 20A*). Loss of self-esteem and lack of confidence (*4.2%*), anxiety, depression, mood swings and stress (*25.9%*), were given as reasons for a change in their social life (*Question 8*). Similar psychological reasons were given as reasons for giving up work, education, having to work part time or take early retirement, (*Question 7*).

Lin et al, (*2020*), conducted a systematic search of the literature database using a pre-defined criterion, in order to review the prevalence of psychiatric symptoms in CS and to determine the impact of psychiatric symptoms on morbidity, functioning and QoL, and to analyse the impact of treatment on their symptoms.[28 69] The authors found that most of the literature confirms that psychiatric symptoms can persist post cure, and patients have overall lower HRQoL scores. The recommendation being to monitor CS patients, their long-term effects of neurocognitive and psychiatric symptoms and the impact that it has on their lives. In the Lin et al study, *55-81%* had experienced depression, anxiety (*12%*), hypomania or mania (*3-27%*), and panic disorder (*53%*). The symptoms recorded in the Lin et al study, continued from the prodromal phase to remission.[289]

The analysis of the data produced in the present study, captured the true psychological manifestations which were reflected particularly in their narrative accounts. Three members were diagnosed by a Psychiatrist and 4 Psychologists suggested a CS diagnosis. As previously reported, 13 female members were admitted to a

psychiatric hospital and 1 male. Notably, very little psychological support was given pre and post diagnosis, including after hospital care.

The following Sections discuss some of the additional information collated from the survey questionnaire, including rare conditions, observations from the other participating countries and the impact of COVID-19 on the members lives.

24.0 A Case of Dwarfism

One male member, who was 39 years old had been diagnosed with Dwarfism and CS when he was a child. He reported that his QoL score had been very poor prior to his Cushing's diagnosis and during his treatment but currently reported a Good QoL score. and can work full-time.

This condition is often referred to as short-stature and has been defined, "as height-vertex below 2 standard deviations or in the third percentile for a given age and sex." [290] One of the differential diagnoses for dwarfism is CS and often children diagnosed with this condition have lower bone density associated with osteoporosis, often suffer from sleep apnoea, spinal stenosis, kyphosis, arthritis, and weight gain. This member reported some of these complications and in addition, infertility and prone to infections. He continues however, to have depressive illness, lack of confidence and emotional problems, but quoted has, "*learned to accept my condition and make the most of life while I can."*

25.0 Addison's disease

Four females and 2 male members were diagnosed with Addison's disease (*primary AI*), which is a progressive disorder. According to the National Organisation for Rare Diseases (*NORD*), Addison's effects 1 in 100,000 people, in the USA and the overall prevalence is estimated to be between 40-60 people per million.[291] Primary AI is defined as the insufficient production of cortisol and aldosterone as described in *Chapter 1*. The major symptoms were identified by these 6 members and. included: skin pigmentation and psychological symptoms including mood swings, their QoL scores were *very poor=4, poor=2*. All of them had been advised that they would always require to take GCs, and all had more than 1 adrenal crisis. All had been admitted to hospital to receive treatment for their adrenal crisis. One member reported that this condition had caused him a great deal of stress and lives with the fear of having subsequent adrenal crises, which currently quote, "*prevents me from having a social and personal life."*

26.0 Nelson's Syndrome.

Three females had been diagnosed with Nelson's syndrome, which is also classified as a rare condition as explained in *Chapter 1.* All these members had bilateral adrenalectomies. Nelson's syndrome is said to affect *15-25%* of those who have had both adrenal glands removed.[291] The members who had been diagnosed had experienced some of the classic signs and symptoms which included menstrual irregularities, skin abnormalities (*pigmentation*) and 2 of them reported visual impairments. Two members QoL scores were Poor and the other Fair. All members had high physical, psychological signs, and symptoms scores both *prior to diagnosis* with no change in *current status, >15 physical, >2 psychological and cognitive impairments.*

There are variations in the data of the prevalence of Nelson's syndrome and on the length of time after bilateral adrenalectomy this syndrome takes to develop. This is mainly due to the different diagnostic criteria and on the length of follow-up up in patients' post-surgery.

A 2020 study of 68 patients who were diagnosed with Nelson's syndrome between 1969 and 2018, reported that the median time between their surgery and diagnosis was 3 years.[289] Clearly, in the present study the members diagnosed with this additional condition had resulted in a deterioration in their health, reporting low to moderate HRQoL scores. The management of patients who have shown progression of their Nelson's syndrome presents, according to Fountas et al, 2020, "a challenge, given that there is scarce published literature." [292]

27.0 Bone Sarcoma

One female reported that she had a bone sarcoma which is a rare form of cancer and makes up only *0.2%* of all cancer diagnosed in England and approximately 5,300 people per year. There are approximately 360 bone sarcoma deaths in the UK per year.[293]. This condition had caused her acute pain and swelling in the upper thigh, fatigue, anxiety, and fear. As part of her diagnosis, she had a CT, MRI and RNI scans. No data was given as to the Grade of tumour or treatment regime. This female's QoL score (*Question 38c), current status*) remained Very Poor and her signs and symptoms scores for all dimensions of health, (*Question 20 A and B*) were extremely high (*23/24, 5/6*).

A 2020 UK National Sarcoma Survey found that *25%* of the respondents reported that their diagnosis and treatment of sarcoma had severely negatively affected their overall mental health and *45%* said that they were given insufficient information when they were first diagnosed.[293]

28.0 Main Survey Observations from other participating countries.

In the present study, 26 members including a Psychologist and an Endocrine Nurse from the other 8 participating countries were diagnosed with CS, 8 of them with CD. Most of these members were from the USA, (*57.6%*). Three of them were diagnosed within weeks of presenting themselves to their GPs, and 2 others were diagnosed by an Internist in an Accident and Emergency Department. The median length of time for the 15 USA members for a diagnosis was 2 years, and the number of Physicians consulted prior to a diagnosis was 3 (*mean*). Interestingly, for the members from Guatemala (*n=1*), and Kenya (*n=3*), the length of time for their diagnosis was 4 years and 5 years respectively and >5 Physicians were consulted prior to their diagnosis.

No significant difference was found in the results for the international members physical, psychological, and cognitive impairments scores compared with the UK members or their QoL scores. When comparing their social lives and personal relationships it could be suggested that there was more psychological support, particularly for the USA members who were offered this by their endocrine team. Nine of the USA members and the 1 member from Australia had private Psychologist consultations. All 10 members also reported a better understanding from family members as to the nature of their illness. The reason being was that this had been fully explained by their Endocrinologists and in some cases their Psychologist and discussions with them included the possible consequences of the disease processes.

The support networks for all the other countries also seemed to encourage international participation to share information, encourage networking and some members had formed a, 'Cushie,' club.

On reading their personal statements the impression one was given was that this sharing of experiences helped them to come to terms and cope with their illness. Interestingly, 1 member who was a Psychologist from the USA was proactive in setting up a social media platform to offer advice and counselling.

29.0 The Global Pandemic- Coronovirus-19.

During the present study, the global COVID-19 pandemic in 2020 dramatically changed the way in which hospitals operate. Endocrinologists were required to collaborate with other Physicians which included emergency and internal medicine. Deployment of endocrine staff meant that outpatient clinics were cancelled. Among the high-risk categories of contracting COVID-19 are patients with DM, endocrine disorders, AI, and OB. The virus outbreak prompted the ESE to produce a statement to support their ESE members and the whole endocrine community.[294] The strategy adopted to cope with cancellations was to increase the use of telemedicine which has now been implemented in hospitals throughout the UK and was widely discussed at the Endocrinology International Congress, 2021.

Although this form of consultation is well established in the outpatient setting, several members in the present study survey expressed their concerns that *a)* their Endocrinologist did not contact them, *b)* their surgery had been delayed and *c)* outpatient appointments had been cancelled. This had created a great deal of stress, anxiety, and depressive disorders.

A 2021 paper discusses the importance of implementing virtual coverage in an endocrinology practice: and the lessons learned from the COVID-19 pandemic. The paper explores how the rapid change in the landscape of medical care and healthcare systems needs to continue to provide optimal medical care across medical disciplines and also to hospitalised patients in a safe, efficient, and effective way.[295] For Endocrinologists, the main recommendation which emerged from this paper was to develop inpatient telemedicine endocrine services, based on the success of outpatient virtual clinics, placing safety at the heart of medical practice for both patients and healthcare staff.

In 2021 the author of this thesis discussed in an audio-poster presentation at the Endocrinology Congress, the urgent need to further assess how CS patients have reacted to this pandemic and what mechanisms are in place to support them. Using the data extrapolated from the results of the QoL survey, from the 29 members who discussed their fears of contracting the virus, as reported in *Chapter 4,* the recommendations were to ensure that Cushing's patients have the advice and support they need.[296]

The following Sections discusses Health Professionals Awareness, the need for patient support and training needs and the lessons learnt from the semi-structured interviews.

30.0 Health Professionals Awareness of the Signs & Symptoms of Cushing syndrome and disease.

Health Professionals play key roles, in diagnosing and treating patients. One objective of the present study was to ascertain their awareness of the signs and symptoms of CS and CD, (*Objective 4*).

Many of the members' responses to the open questions in the present study, reflected upon their frustrations that their Health Professionals often failed to recognise their signs and symptoms, particularly GPs. As previously discussed, only *17.4%* of the study population were initially diagnosed by their GPs, the largest percentage (*46.5%*) were diagnosed by other Health Professionals and *23.2%* self-diagnosed or their family or friends had suggested that they may have Cushing's, (*Tables 6,7, Page 121, Tables 8, 9, Page 122*). Notably, none of the members had been initially diagnosed by an Endocrinologist. Papoian, et al, 2016 also found that most patients in their survey were diagnosed by other Physicians (*76%*), and *20%* by self-diagnosis or their family. This study

also found that Endocrinologists, "typically confirmed the diagnosis," which was the case in the present study.[21] Kluger et al, in 2014, interesting discussed the lack of expertise in diagnosing CS.[219]

The bivariate analysis in the present study showed that delay in diagnosis combined with the number of Physicians consulted can have a major impact on QoL, even those in biochemical remission.

The ERCUSYN showed from their 2018 Cushing's database that a large percentage of patients are seen by at least 1 specialist prior to being referred to an Endocrinologist. [196]

There is, however, conflicting data as to the length of time for a CS diagnosis and the number of Physicians consulted prior to a diagnosis. In their defence Physicians argue that the difficulty lies in the signs and symptoms which are common in other medical conditions and the onset can be slow. If it is rapid, to a degree it makes it easier to diagnose. Never-the -less, the common finding is that CS takes a longer time to diagnose than common medical conditions and that more than 1 Physician is normally involved prior to reaching a definitive diagnosis.

In 2014 the NHS Constitutional and 5-year Forward View 3, prioritised partnership working between care providers and by developing partnerships with individual patients and with patient groups. The latter plan was cited as a route through which to enhance service development.[221] According to the PF UK, there are more Endocrine Nurses within hospital and endocrine centres than a few years ago, but patients still rely on peer support, many of them connect through charity's social media channels. During the distribution of the survey questionnaire, several of the members contacted other Pituitary Associations and the CSRF groups. This resulted in an additional 26 members joining in the survey from 8 other countries out-with the UK.

The PK UK relies not only on its membership fees but in its partnership with The Society for Endocrinology and other medical committees which review patient publications via their monthly news magazine, enabling them to listen to patients' views, thus adopting a more patient-centred approach.

During a 2021 virtual PF conference, a Director of the PF, Professor J Newell-Price described the need to, "promote active awareness and education," but explained that this, "remains a big problem."[195]

***31.0 Benefits of Joining a Support Group* (*Question 37, 37a),37b)*).**

Thirty-one (*43.6%*), females and 7 (*46.6%*), males who answered *Question 37*, had been advised by their endocrine team to join a support group.

Only 3 members found joining a support group to be unhelpful (*Question 37a*). One female member gave a reason, "*I find it depressing to hear others talk about their negative experiences and what has happened to them makes me scared."*

Ninety-eight percent of the members in their answers to *Question 37b*), discussed the benefits of having joined an endocrine support group and these are summarised as follows:

- Improved coping skills by sharing experiences.
- Helped in keeping positive and feelings of not being alone.
- Helped to advise and manage treatment regimes.
- Immediate access for advice and information from their endocrine team support group.
- Support group conferences were excellent in meeting experts in the field of endocrinology, psychology, and other Cushing's members.
- Helped family and friends to understand the nature of their illness.

Tables 4, 5 Page 117 results display the improvements which could be made by the endocrine team, suggested by *61.6%* of the study population. Many of the suggestions were echoed within the textural content and highlighted in the thematic analysis. Interestingly, *89%* of these members, wrote compelling statements on how they felt that their endocrine team did not seem to, "*understand fully the psychological impacts that their Cushing's, because of the effects of the disease processes*," and that a, "*more caring approach*," would help to improve their relationships with their healthcare team.

A 2015 Andela et al study found that due to a lack of time during consultations, "*embarrassment over their own feelings,"* and thoughts and concerns about, "*bothering their healthcare provider*," with, "*minor*," problems were some of the reasons why certain psychosocial needs remained unaddressed.[220] Andela et al in their publication discussed how patients often do not share their psychological concerns during their consultations with Physicians. This publication also reported the results of a CS focus group which highlighted the importance of disease-specific aspects of QoL and suggested that they are, "neglected in current available questionnaires." [220]

Andela et al concluded in their follow-up study in 2016 using the Leiden Bother and Needs questionnaire, that the patient's perspective was vitally important when considering how to improve QoL in patients with CS.[138]

The present study therefore sought to address this by including open questions which asked the members about their support from the endocrine team which gave them an opportunity to suggest methods on how to improve their consultation experiences.

"Misconceptions about their short to long term consequences of their condition prevents patients from elaborating adequate strategies of psychological adjustment." [141] The need therefore to discuss the pathophysiology related to the disease processes, treatment options, and the consequences of treatment with their Physicians is prime in

helping patients to understand and come to terms with their illness. One quote from a member was that *"it would be helpful to have my illness explained instead of having to look it up on the internet."*

The many victims of CS find that the strains due to the "psychiatric, cognitive and physical changes wrought by this disease," [18] destroy their relationships. Patients find that they are, "dropped by friends, spouses and partners not only by their change in appearance but also because of personality changes."[18]

Learning to self-manage and the develop coping mechanisms to adapt to their illness is suggested to improve QoL.[141] This was evidenced also in the present study, whereby *48.4%* of the members felt that psychological support, if offered as a treatment, would improve their lives to self-manage their illness, involve their family and friends more and restore their confidence in coping with their illness. These members also felt that some CS patients may not however, be interested in joining a support group.

32.0 Education for Healthcare Professionals, Patients and Training Needs.

The final *objective (5)* of the present study was to identify methods of accelerating the diagnostic processes which may lead to earlier reviews by the multi-disciplinary healthcare team.

Interestingly, Harvey Cushing was the world's leading teacher of Neurosurgeons in the first decades of the 20th century believed in passing his knowledge and skills onto his students, colleagues, and the medical community.[297]

Education and training for all Health Professionals particularly over the past 30 years has changed, medicine has moved on developing new advanced technologies which have enabled an even better understanding of how the body works.

Surprisingly, many Health Professionals have never heard of CS or CD, and this is suggested as the main reason, in many cases why it takes so long to be referred to the endocrine team. Many of the members expressed their disappointment with their Health Professionals, particularly their GPs and suggested that more education was required in their training to identify the signs and symptoms of CS.

A lack of knowledge in recognising the signs and symptoms was apparent in the textural content of the members statements and in the interviews with healthcare staff during the period of this study. In discussions with national and international Endocrinologists, Psychologists, and the PF UK staff, this was also recognised that generally Health Professionals have little knowledge of hormonal medical conditions and endocrine disorders.

It is therefore imperative that the patient's perspective of their illness should be fully recognised, "as a mainstay of CS management which should integrate biochemical and radiological work-up." [141]

Adopting a more patient-centred approach requires education and training to engage with each patient throughout all phases of their HRQoL evaluation to identify their unmet needs, changing concerns and evolving personal situations. The present study suggests that this can only be done by adopting a multi-disciplinary approach. The author of this thesis in her published 2021 paper described how, "individualized educational programmes and focus groups should be promoted, also through the new technologies, to empower patients, increasing self-management, self-confidence and adaptation process to their new situation." [141]

The author of this thesis has found that by joining a support group has provided support, helped in overcoming feelings of isolation and continues to provide a network in which to find out more about the disease processes.

Raising awareness among Health Professionals from a range of disciplines on signs and symptoms of this rare disease appears fundamental to shorten delay to diagnosis, which is strictly associated with the sustained burden of hypercortisolism. In 2020 an audio-poster was presented by the author of this thesis at the Endocrinology Congress, discussed the results of the HRQoL survey on how the members felt about their Health Professionals knowledge of the signs and symptoms of CS. The recommendation being that all healthcare disciplines should be made fully aware of the signs and symptoms of CS and CD and the support organisations for endocrine disorders.[298]

As new chapters of medicine open, the lessons learned are that we should not just consider CS patients as a patient with a medical condition, but a human life with needs beyond her or his medical condition.

Chapter 6

This Chapter concludes this study by providing an overview of Cushing syndrome and disease and reflects on how this fascinating and mysterious illness continues to create a thirst for new knowledge, understanding and awareness.

Conclusion

Prior to and since the onset of this PhD study, a plethora of on-going research has been conducted into the understanding, diagnosis, treatment, and management of CS and CD which continues to challenge Physicians not only in the diagnosis but how to treat their patients.

The learning process during this study has been exponential and led to a clearer understanding as to why it took so long for the author's medical team to make a definitive diagnosis of initially CS and then CD. This personal CS journey of study revealed the reasons for the twists and turns on the 'bumpy,' road to diagnosis, treatment and then remission. It also provided an understanding why patients experience pain, changes in their personality and brain function, a reduction in QoL and in most cases, irreversible comorbidities. During the process of study, the author has endeavoured to use her experience not only by studying the condition but by presenting the findings of her studies during conferences and publications.

During the Scottish Network Imaging Conference in 2019, attended by 150 Health Professionals the authors patient experience was discussed in the form of a keynote lecture thus giving the opportunity to raise awareness.

Cushing syndrome results from a prolonged exposure to excessive amounts of GCs and can significantly impact on QoL and is classified as a rare disease. The estimated incidence of CS reported varies but in 2021 was 0.7-4 new cases per million inhabitants and can occur in any age group but mostly in female adults with a median age of 41 years, this author being in her sixties when diagnosed. [195]

This study has shown that, undoubtedly, early diagnosis and prompt treatment are required to reduce the consequences of CS, and these include HRQoL, morbidity and mortality.

The mortality rate is said to be between 2-4 times higher than the general population due to: PE, stroke, cardiac failure, infectious diseases, sepsis, and suicide. The incidence of venous thromboembolism (*VTE*) in CS in the general population being 1-2 per 1000/year per person i.e., the VTE risk is 10 times higher in CS patients than in the general population.[299]

The diagnostic approach is a 3-step investigative process and includes *a)* a Physician's knowledge to screen the right patients for CS which is crucial to make a confident diagnosis of CS.; *b)* the second step of this process is to

identify the reason for excess cortisol production, and this can be achieved by; *c)* ensuring that the appropriate biological tests and imaging examinations are conducted.

The wide clinical spectrum of CS and CD produces a medical dilemma as patients' symptoms often as previously discussed, can vary. The typical Cushingoid features which are referred to as the classic symptoms are not always obvious when a patient presents. There are population groups which have increased incidence of CS which includes OB (*central type*), DM and osteoporosis diagnosed and disproportionally serious at an early age and includes women with polycystic ovary syndrome. These population groups have a high risk of hypercortisolism therefore early screening for CS is recommended.

The European Society Clinical Practice Guidelines assist clinicians in identifying patients who present with unusual features and includes those with hypertension.[236] Patients can have progressive features such as easy bruising, facial plethora, proximal myopathy, proximal muscle weakness, abdominal and axillary stria especially if reddish purple and more than 1cm. wide. Many studies suggest an association between cortisol excess and several cardio-metabolic diseases. Despite the author having several typical CS features, it was as previously mentioned, a right kidney incidental adrenal adenoma which, 'kick-started,' the diagnostic work-up, which included US, an abdominal CT and AVS. Most patients similar to that of the author require cortisol replacement for approximately 3 months post-surgery, and all require regular biochemical testing.

Adrenal incidentalomas are frequently found in approximately *5%* of the population, most of which are non-secreting. However, *20%-30%* produce cortisol in excess (*autonomous cortisol secretion*), and *25%* of adrenal incidentalomas are bilateral. If adrenalectomy is planned then it is important to establish if the cortisol overproduction is uni- or bilateral, AVS or Cholesterol scintigraphy being the safest and feasible methods to decide laterality. Worth noting is that bi-lateral adrenal nodules are not so rare and according to many surgeons can be 'tricky,' to remove and can cause an adrenal crisis.

It is relatively easy however, to understand how CS is often missed as these patients may find themselves being sent by their GP to other Physicians and Healthcare Professionals**,** CS rarely being considered as the differential diagnosis. The pathway to reach a diagnosis can be a long one. Initial screening where cortisol levels are measured depends on the accuracy of the biochemical tests. Most Endocrinologists will admit that no test is perfect. The biochemical features of acute CS are DM, hypokalaemia, low albumin, and leucocytosis. However, mild, cyclic CS can create difficulties in interpreting the tests. This can cause further delay in reaching a definitive diagnosis. The diagnostic workup and treatment in patients with unexpected hypercortisolism require Physicians to investigate the patient's past medical history; which medications, if any, they have been prescribed; and the

patient's physical presentation to look for Cushingoid features, BMI, weight gain, mood changes, and in some cases failure to thrive whilst being cognizant of the fact that hypercortisolism can occur in many other conditions. These conditions include pregnancy, alcoholic abuse, and morbid OB. Pseudo-CS for example, should be excluded when evaluating patients with hypercortisolism, although it is not always easy to differentiate between PCS and CS. Physicians in this case recommend a full evaluation after 6-12 months in such cases.

Distinguishing between CD and ectopic ACTH-dependent CS must be considered. Ectopic ACTH is said to be clinically and biochemically indistinguishable from CD, the more severe the syndrome the higher the ACTH levels are, lower potassium being a sign of ECS. In this case BIPSS is said to be essential in establishing that there is no obvious mass. In most cases, bilateral adrenal masses represent benign bilateral adrenocortical disease: bilateral adenomas, distinct bilateral nodules with normal or atrophic cortex intervening or macronodular hyperplasia. However, there are pitfalls in the use of BIPSS. These include the care and expertise required for performing this procedure and the correct interpretation of results-false -ve for CD is more commonly found than false +ve. Other pitfalls are the prolactin measurement which may assist if no IPS: i.e., ACTH gradient is found. This is an invasive and highly technical procedure and ECS hypercortisolaemia must be established prior to this procedure. The biochemical pre-test probability in females is however, *90%.*

On a personal level, the severity of the disease itself began to be internalised during the pre-surgical stage of the author's illness. This was experienced on being referred for the more invasive radiological investigations and the warning of the mild to severe side effects of contrast media and the insertion of catheters, albeit familiar to this author.

The modern advancements in diagnostic medical imaging have proved to be invaluable tools in diagnosing CS and CD. The number of medical imaging examinations can be extensive during the diagnostic journey and continues in most cases for life. Imaging in ECS for example is normally CT and MRI as the first line investigation for tumour source. The present study recommends referral for CT/US kidney and pituitary MRI scans as the chosen route of establishing tumour origin, prior to invasive surgery or medical therapy, for the reasons outlined in *Chapter 1, Sections 2.5 to Section 2.9, Pages 31-33.* Undoubtedly, functional imaging has an important part to play a part alongside MRI. The latter the 'gold standard,' for ACTH-secreting pituitary adenomas.

Modifications for both imaging modalities are recommended in the case of small lesions. ^{18}F-FDG PET having a higher sensitivity is recommended for undifferentiated tumours without SS receptors. However, it has poor sensitivity for small lung carcinoids, bowel lesions and pancreatic lesions. While, ^{68}Ga-DOTA(SS1) has the best sensitivity and specificity, interestingly, NMR can detect *80%* of undetected tumours and has better specificity

compared with MRI, an example being bone lesions. CS patients are regularly referred for endoscopic US for undetected lesions which are too small to be identified on CT and can identify multiple lesions with different characteristics.

Patients often find the waiting for appointments and their results and often in the case of CS, the disappointment of the lack of a definitive diagnosis hard to bear.

The fear of malignancy is indescribable and at the same time the presence of hope whilst cognizant of the physical body language and facial expressions of the Health Professionals, indicating good or bad news. One of the main concerns expressed by many of the participating survey members was the lack of information, rushed consultations and advice from the endocrine team. This being compounded by COVID-19 where little or no support was offered. For patients who already report feelings of self-isolation, depression, and anxiety, this indeed created a further step-back in their progress. These factors, for many, do not help their mental state, which in most cases, is already fragile.

The right adrenalectomy, in the author's case did not cure her Cushing's and the diagnostic and treatment journeys seemed unending, compounded by lengthy hospital stays. This perhaps explains why many CS patients are anxious, experience depression and are in some cases suicidal.

When surgery for CS fails then investigation for CD is performed, which includes a pituitary MRI scan. Notably, a negative scan is found in *40%* of CD patients.

Some patients, in the case of macroadenomas which, if shown well-defined on the MRI scan, would be a prime case for RT and in most cases GK-RS. With all surgeries and RT techniques there are side effects which can be severe. For example, the risk of pituitary insufficiency with GK-RS. These patients tend to have longer recovery times, increased hospitalisations, and subsequent depression. With TSS patients' sense of smell, taste and hearing loss can be permanent, but complications are said to be rare. In the author's case a microadenoma was suspected on the MRI scan, confirmed with BIPSS, and removed using TSS and post-surgery, remission was achieved. The author did not have RT or chemotherapy, however, the TSS surgery did cause temporary loss of smell and taste and slight permanent visual impairment. Notably, the memory loss improved, and the temporary neuropsychiatric conditions experienced at the onset of her Cushing's also improved without further invasion or medical therapy.

However, for less fortunate patients whereby revision surgery has failed, or surgery is ruled out, the use of medical therapy is the best and often the only option for the treatment of CS and CD. During the last few years, several newer pharmaceuticals are currently being used in clinical trials. The main aim of medical therapy is normally to reduce tumour volume or reduction of cortisol excess from source with the objective of not compromising QoL

An observation during this study was that due to Cushing's being rare, there is still a great deal of research to be conducted into the potential genetic causes of CD, which is often unknown. There is some work as previously mentioned, studying the mutations in certain genes (*somatic mutations*), which have found to lead to a CS diagnosis and some people may have a tendency to develop a tumour in one or more of the endocrine glands. Comorbidities persist in most CD patients even after apparent biochemical remission and therefore can only be accepted in the context of partly predictive remission. The definition of biochemical remission is hampered by the discrepancies between different HPA-axis parameters, thus creating challenges in the efficacy of results. A prime example is the normalisation of UFC and the comparison with the LNST. The normalisation can mean that the patient is technically in remission but without recovery of cortisol diurnal rhythm which may have an impact on tissue cortisol exposure, having a sustained effect on target gene expression. Persistent comorbidities despite being in remission is found in most patients diagnosed with CS. This may be the result of hydrocortisone over-substitution, irreversible tissue changes due to long-term cortisol exposure, cyclical hypercortisolism or as previously mentioned, absence of recovery of cortisol diurnal rhythm.

As more pharmaceutical trials take places, particularly novel medical therapies, researchers seek to reverse the comorbidities and attempt to support the patients' overall risk of a recurrence by taking a multi-modal management approach. Many CS patients as reported in this PhD survey results, have shown that they are on a lifetime of medication and surveillance. New medical therapies for acromegaly and CS have recently been approved as some tumours can be more aggressive and require a multimodal therapeutic approach, according to Fleseriu et al, 2022.[301]

However, the risks of recurrence, poor HRQoL for CS patients, outweighs the financial burden for health services. Cushing Syndrome and CD are costly medical conditions not only for the patients in terms of health and wellbeing, family, and personal relationships but for health service providers.[300] This author was fortunate that her family, colleagues, and friends supported her throughout her illness but according to this study's survey this is not always the case. As patients struggle with the physical and psychological effects of CS, their families also wrestle with the changes in their relationships and the understanding of the complex disease processes, and this often culminates in lack of belief and support. What does not emerge in many publications related to the psychological effects of CS is that many patients are hospitalised, often sectioned and can be suicidal without CS being considered as a diagnosis, excess cortisol being normally the route source of their condition. If CS is not considered, then this of course is counterproductive in treating the patients due to the wrong choice of medication. Neuropsychological impairment is common in CS patients, as previously discussed and is a disabling concomitant

of depression and has been linked to disturbance of the HPA axis. The HPA plays a central role in regulating a range of physiological functions. Cognitive dysfunction in CS has been linked with the duration of the illness and persists into recovery. Reduction of cortisol levels and effective treatment of depression normally improves in several domains of neuropsychological performance. However, although treatment can ameliorate the impairments, patients are said to be especially vulnerable to cognitive impairment secondary to small disturbances in HPA dysfunction. Patients therefore who suffer from severe CS neuropsychiatric impairments and recover can have reduced tolerance to stress during their lifetime.

Not only the patient themselves, but their families and friends find it difficult to understand the many changes a CS patient experiences. Fundamentally, it is hard to recognise the illness as the facial and body changes can vary from subtle to extreme. The neuropsychiatric effects caused by the elevation of hormones influences brain functioning and causes several psychiatric manifestations, including hypo/hypermania, bi-polar, personality changes and severe depressive illnesses. When patients present with one or more of these manifestations as the predominant complaint, in the early stage of CS, patients are often treated by Psychiatrists and can be treated for several years without identifying the underlying cause. The rarity and overlapping characteristics of CS, can only normally be diagnosed by a Physician trained in recognising the signs and symptoms. Interestingly, patients with hypomania, mania, depression, and psychosis are often prescribed corticosteroids which of course is a contraindication for those who have CS. As earlier discussed, the use of steroids including topical creams can cause exogenous CS. Unfortunately, this is perhaps how this author contracted CS as she was prescribed a corticosteroid-based pharmaceutical for several years for muscle pain prior to her amputation and depression.

The study survey therefore revealed a lack of Health Professionals knowledge and awareness of the signs and symptoms of CS and CD, particularly GPs. Having experienced these medical conditions combined with the HRQoL survey and interviewing healthcare staff and experts in the field of endocrinology, it is clear that very little work has to date been undertaken on how awareness can be increased. The introduction of more robust, informative educational programmes for healthcare staff could dramatically improve this void.

It is encouraging that more research is being focussed on the disease processes of CS, but the energy and drive is mainly concentrated on the diagnosis, treatment and management approaches and the consequences in terms of HRQoL. The main body of research is conducted by specialists in the field of endocrinology, therefore there is little research being undertaken by other health disciplines, many of whom have responsibilities for pre and after care services.

While attending endocrine conferences, it is notable that little time is spent on the patient as an individual, how to support them post diagnosis and their unmet needs. Few patients take part in these events.

Technological advancements are helping to provide more information and clarity as to the presence of the disease processes. There are strong discussions and debates into the methodology of testing including imaging protocols. The technological revolution, however, can only work if awareness of Cushing's is increased. There is undoubtedly as mentioned, a void in education and although during the undergraduate medical programme students have endocrine clinical placements, the rarity of CS and CD means that they have little chance of seeing or interviewing a patient with this illness.

The way to resolve this is to use the new technology in providing webinars, online study of rare diseases which highlight the methodology of diagnosis and treatment and ways of considering CS and/or CD as the differential diagnosis, particularly when some of the symptoms or signs are recognised, albeit physical or psychological.

There is a need for Endocrinologists to take a more active role in educating all healthcare staff who provide the many diagnostics, treatment, and support services for CS patients. These include for example, AHPs, Audiologists, Dermatologists, GPs, Gynaecologists, Obstetricians, Nurses (*other than endocrine*), Ophthalmologists', Psychiatrists, Psychologists, Radiologists, Rheumatologists, Orthopaedic Surgeons, and the future healthcare workforce. The author encountered most of these healthcare disciplines during her diagnostic and treatment journey and very few of them had experience of patients with CS nor heard of CS.

The exponential use of the internet, particularly over the past decade, has given a unique platform for the public to find out about common as well as rare diseases. Admittedly, there are websites featuring CS, but it could be argued that they mainly focus on the disease itself and perhaps do not concentrate enough on the support mechanisms, to ensure that families, friends, colleagues, and the general public have a better understanding of the nature of this illness and the potential consequences, an understanding being the key to caring, support, guidance, and empathy. This study's survey also revealed the importance of support group organisations, providing additional guidance information and speedy advice.

What has also emerged from the process of this study is that patients and Endocrinologists all agree that ideally there should not be a delay in diagnosing CS. However, the time frame in delay can be extensive and Endocrinologists will argue that until a Physician or Surgeon from another discipline recognises that their patient may have an endocrine disorder, they will not be referred for an endocrine consultation.

The evidence within the present study does show the lack of awareness from GPs, Healthcare Professionals, including Consultants in different fields of medicine. This is disappointing so long after Harvey Cushing in 1932

fully described CS, and the collective signs and symptoms he previously presented to medical Physicians and medical students in his 1930 Lister Lecture on pituitary physiology.[297]

The author of this thesis, suggests, in all probability this is the first study of its kind to truly expose the extensive lack of Health Professionals awareness. The *current knowledge* from this study, is that we have the skills, the tools and expertise to speed up the process of diagnosis. The *new knowledge* is that we must use these skills, not only to focus on the disease itself but promote its presence by raising awareness and be patient-centred in our approach to treat each CS patient as an individual with unmet needs. The only way we can do this, is by ensuring that when a patient presents for a medical consultation with certain symptoms and ailments, i.e., with the key CS and CD indicators, then more time should be spent in their diagnostic evaluation which must include potential additional illnesses due to endocrine abnormalities. The extra time could save lives, increase HRQoL for Cushing's patients and reduce the long-term financial burden of this medical condition for healthcare service providers.

The main aim of this study was to appraise the current methodology of diagnosing and treating Cushing's patients and to evaluate the clinical consequences of the disease processes in terms of HRQOL. During this study the literature review and study survey revealed the full extent of how a Cushing's diagnosis affects patients both physically and psychologically. Whilst diagnostic challenges remain, advanced technologies, RT and medical therapies continue to improve. The HRQoL survey revealed how a Cushing's diagnosis impacts on social and personal lives and the importance of interprofessional team strategies for improving the care coordination and communication, whilst aiding the diagnosis of CS and improving patient outcomes. Patients should be educated about the comorbidities and complications which impair their QoL, particularly in the active phase of the disease and when corticosteroids are prescribed, their GP and Pharmacist should discuss how to prevent ulcers, DM, OB, and the possible side effects. The mortality and morbidity of CS is normally due to the long-term effects associated with the disease processes. Examples being autoimmune diseases, cardiac disease, GH deficiency, OB, osteoporosis, hypertension, hypercoagulability, and sudden changes in GC levels can cause an adrenal crisis.

In 2021, the Pituitary Society convened a consensus workshop to discuss evidence collated from 2015-2021 data on the management of CD including the biochemical testing, imaging, and treatments, along with the algorithms for the diagnosis of CS. The guidelines which emerged as a result of the workshop, included recommendations for the use of laboratory tests, imaging and treatments which are similar to those of the Endocrinology guidelines. Notably, the importance of clinical research was identified and included the optimisation of MRI and PET pituitary imaging to improve microadenoma detection. The identification of additional corticotropic adenoma

mutations and develop a comprehensive panel of genomic and proteomic tests for corticotropic adenomas, was also recommended as an important area for future research.[302] The genetic cause of CD is said to be unknown, however mutations in certain genes have been found to lead to a CD diagnosis, as previously mentioned in *Chapter 1, Section 1.4.1, Page 17.* Recognition of the germline and somatic genetic defects behind corticotroph and adrenocortical tumorigenesis could be said to be crucial for the individual management of CS patients. This would aid genetic counselling and clinical screening as routine medical practice and the present study recommends that Geneticists should be more involved in future research.

Objective 5 of this study was to identify methods of accelerating the diagnostic processes, which may lead to earlier reviews by the multi-disciplinary team. This was achieved by identifying the factors which delay diagnosis and was found mainly to be the failure of Health Professionals to recognise the signs and symptoms. This could easily be addressed through educational pathways incorporated into the education and training programmes and through innovative methods such as simulation techniques, AI in diagnosing for example bone density changes and vascular disease, thus leading to CS being the differential diagnosis whilst ensuring that patients and the public are better informed including encouraging them to join support groups.

The voice of the patient is crucial, and Physicians must listen to their challenges and assess fully their psychological and scheduling time early, could help to reduce the effects on their HRQoL leading to better prognostic outcomes.

1.0 *Summary of Study Objectives:*

The aim and objectives of this study were reported and discussed in *Chapters 4, 5, 6* and the recommendations which emerged in *Chapter 7(Section 2).*

The following list is a summary of how the objectives were achieved:

1. *Review the current methods of diagnosis and treatments.* This objective was achieved by conducting a robust current literature review and interviewing researchers and Endocrinologists who diagnose and conduct relevant studies which focus on methods of diagnosing and treating patients. Objective 1 was also achieved in the results of the HRQoL survey questionnaire (*Chapter 4, Results, Sections 8.2 8.3, 9, 10, 11 and 12.*)

2 and 3: *Explore the consequences of being diagnosed with CS and/or CD and 3, Conduct a HRQoL survey.* These objectives were achieved by conducting a HRQoL, which identified the physical and psychological impact on the survey participants *(Chapter 4, Results, Questions 4, 5, 6, 7, 8 and 9, Question 20a), b).* The

literature review also confirmed that CS and CD patients experience many physical, psychological and comorbidities, prior and following their diagnosis.

4. *Establish how aware and informed Health Professionals are when diagnosing and treating a patient with CS and CD.* The semi-structured interviews and meetings with a range of Health Professionals highlighted the lack of awareness of CS and CD, particularly in recognising the signs and symptoms and how patients are diagnosed and treated. (*Chapter 4, Results, Part 2, Page 156 and discussed in Chapters 5 and 6*).

5.*Identify methods of accelerating the diagnostic processes which may lead to earlier reviews by the multi-disciplinary teams.* Increasing awareness and training were both recommended as a result of this study. This is fundamental to ensure that when a patient presents with 1 or more of the Cushing's symptoms, they should be referred for biochemical testing. By listening to the patient's voice would also undoubtedly assist in this process. An increase in public awareness was also recommended and has an important role to play in recognising early signs of the disease processes. (Recommendations are featured in *Chapter 7, Section 2.0, Page 207-208*).

In the words of William Oster, (*1849-1919*), Founding Professor of the John Hopkins Hospital, *"The good physician treats the disease, the great physician treats the patient who has the disease."*

Chapter 7 Study Limitations and Recommendations

1.0 Study Limitations

During the present study, it was acknowledged that there were inherent limitations within areas of the methodology of study. The following is a list of the limitations encountered:

1. The male population sample size (*17.4 %*) may have reduced the reliability of the data.
2. The time frame, which was short could not be considered as a longitudinal study. If therefore this study was conducted over a longer period of time, this may have altered the HRQoL scores as health may improve or deteriorate over time.
3. The study population comprised of members of pituitary support groups and therefore they had a good understanding of CS and CD, and this may have affected their question responses.
4. Although every effort was made to analyse and report the data objectively, researcher bias may have influenced the results due to the researcher having experienced personally both CS and CD.
5. Survey answers were dependent on the members memory, particularly pre-diagnosis information and is highlighted in Chapters 3, 4 and 5 with reference to *Question 20a)* and *Question 39a).* The answers to the survey questions relied on the members goodwill and ability to accurately answer each question. As the pilot study population was small (*n=11*), no test-retest reliability was conducted.
6. A disadvantage of conducting the semi-structured interviews with peers is that despite assurances to the contrary, some may feel the interview is a test of knowledge or competence.
7. No comparison could be made with healthy control groups.
8. No access to medical records, therefore no factual details of health status, biochemical testing, imaging, and treatment regime results.

2.0 Recommendations

1. The use of virtual platforms for education and teaching to inform both undergraduate students and postgraduate healthcare staff on the signs and symptoms of CS and CD.
2. Explore the use of technology such as an extension of the use of Apps for Healthcare Professionals with a view to using a signs and symptoms recognition systems for the diagnosis of CS and CD.
3. Recommend the use of this study's QoL survey questionnaire to the European Society of Endocrinology and other endocrine organisations through publication and promotion.

4. Encourage more extensive use of thematic analysis within HRQoL questionnaires and adopt a more personalised approach in giving patients a platform in which to share their unmet needs.
5. Raise awareness with the public including families and friends of patients who have been diagnosed with CS. This should be done using internet, webinars, leaflets in hospital clinics and advising on support mechanisms.
6. Presentations at conferences which not only focus on endocrine disorders but other conferences examples being, AHP, gynaecology, radiology and oncology, psychology, and psychiatry.
7. Identify target audiences to advise and inform, particularly for women. Examples being fertility and gynaecology clinics.
8. Continue working with other specialists in the field of endocrinology to publish on-going work, particularly the patients experience of Cushing's and the promotion of personalised care, shared decision-making, patient activation and the self-management of their illness.
9. Recommend the use of both CT/US kidney and pituitary MRI scans in parallel with biochemical tests, prior to invasive surgery and medical therapy.
10. AVS and BIPSS only performed when CT and MRI results are inconclusive, and the source of ACTH-secretion requires to be established/confirmed.
11. Highly recommend, that more information/advice is made readily available for CS and CD patients in the event of a medical crisis and a pandemic.
12. Recommend methods of screening OB patients to consider CS as the differential diagnosis, e.g., biochemical testing for CS in OB clinics
13. Promote the importance of research in genetic testing.
14. Development of AI technology for measuring bone health from a single radiographic image. This would have the potential to identify osteoporosis which may in turn lead to an earlier CS diagnosis and reduce the dangers of fragility fractures.

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Appendices

Appendix 1- Ethics Permission (The Pituitary Foundation, UK).).

Pituitary Foundation, UK Letter of Consent

The Pituitary FOUNDATION

25th ANNIVERSARY 1994-2019

86 Colston Street
Bristol BS1 5BB
Admin: 0117 370 1333
enquiries@pituitary.org.uk
www.pituitary.org.uk

To whom it may concern,

The Pituitary Foundation are pleased to support Margot McBride's HRQoL Cushing's survey for her PhD study. Our involvement will be only to help advertise this survey and to inform Cushing's patients who wish to take part.

Kind regards,

Pat McBride
Head of Patient and Family Services

The Pituitary Foundation

0117 370 1315
pat@pituitary.org.uk
www.pituitary.org.uk

Office hours: 9am - 5pm Monday – Friday
86 Colston Street, Bristol, BS1 5BB

University of Cumbria Ethics Approval

Margot McBride Institute of Health Lancaster

15 August 2019

University of Cumbria, Research Office, Lancaster Campus, Bowerham Road, Lancaster, LA1 3JD

01524 590804 Research.office@cumbria.ac.uk www.cumbria.ac.uk

Request for Ethical Clearance – Our Ref: 18/65
Project: Cushing's syndrome and Disease: A Health-Related Quality of Life Survey.

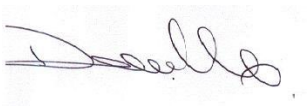
Dear Margot

Thank you for your response to the issues raised and the revised documentation. Approval is granted with no further changes or amendments required.

Kind regards

Professor Diane Cox

Chair
Research Ethics Panel



Quality of Life Questionnaire

Study Code Number.

Consent & Information Form

Cushing's syndrome and disease. A Doctor of Philosophy study.

As part of this PhD study, a survey is being undertaken by a member of the Pituitary Foundation UK who has experienced both *Cushing's syndrome and/or *disease.
The prime aim of this survey is to establish the main challenges which present themselves pre- and post-remission of having been diagnosed with Cushing's.

In order to fully explore these challenges that you have faced due to having been diagnosed with Cushing's and to assess your health-related quality of life during and after the on-set of your Cushing's, the attached questionnaire has been developed.

This is an invitation to participate in this study and contribute to the existing body of knowledge. The research findings will be reported in this PhD thesis and, if accepted, be published in future endocrinology and radiology journals, and presented at appropriate conferences.
Please note that a Code system will be used in order to protect your identity.
Please X YES or NO in response to the following questions.

1. Have you read and understood the above information? YES. NO

2. Have you been able to ask questions and had sufficient information? YES NO

.

3. Do you understand that you can withdraw from this study anytime and, without giving a reason for your withdrawal? YES NO

4. Your responses will be anonymized. Do you therefore give permission for members of the research team to analyse and quote your anonymous responses? YES NO

5. Do you wish to give consent to take part in this survey? YES NO

If your answer is YES, complete the attached questionnaire

Cushing' Syndrome and Disease Quality of Life Questionnaire

**Please note that the definition of Cushing syndrome is: A metabolic disorder caused by the overproduction of corticosteroid hormones by the adrenal cortex. The definition of Cushing's disease is: a condition in which the pituitary gland releases too much adrenocorticotrophic hormone.*
Distribution and collation of the results: Courtesy of the Pituitary Foundation UK.
Responsibility for the interpretation and reporting of results: Dr M McBride, Lancaster University.

You are asked to answer the questions with an X, N/A or write your answer.

Section 1

1. What is your age? ☐
2. What is your gender? Female ☐ Male ☐ Other ☐
3. Where do you live? (*County/Country*)? ☐

If you cannot answer the following questions, please type N/A.

4. What is your Occupation or are you retired? ☐
5. Are you in full or part-time education? ☐
6. Have you had to give up work or your studies due to your Cushing's?

   YES ☐ NO ☐

If the answer is YES for question 6, please answer question 7 of this section.

7. What type of disability(s) i.e., physical, or mental caused by your Cushing's, has forced you to give up work or your studies?

8. Has your Cushing's impacted on your social life and if YES how?

   YES ☐ NO ☐

8a)

9. Has your illness changed your personal relationships? YES ☐ NO ☐

9a) If so, please state the reasons why.

10. Do you feel that your close family and friends understand the nature of your Cushing's illness and how it has impacted on your QoL?
YES ☐ NO ☐

10a) Please give the reasons for your answers, i.e., whichever answer that you may have chosen.

11. Did you find that your endocrine team involved your family during your diagnostic and treatment journey?

☐ YES ☐ NO

11a) If the answer is NO then please explain the reasons why you feel that this was the case.

11b) If you answered 11a), how do you feel that this could have been improved?

Section 2

The following section asks questions related to your diagnosis of Cushing's syndrome and/or disease.

12. When were you diagnosed with Cushing syndrome?

13. Have you also been diagnosed with Cushing disease? YES NO

14. If you answered YES to question 13, when were you diagnosed?

15. How long did it take to diagnose these condition(s)?

Cushing syndrome?

Cushing disease? ☐

16. a). Are you in remission? YES ☐ NO ☐

b) If your answer is YES, how long? ☐

c) Have you had a recurrence? YES ☐ NO ☐

d) If your answer is YES how long after your treatment did this occur and have you had more than one reoccurrence?

months/ years ☐ *Number* ☐

17. Who diagnosed your Cushing's syndrome/disease? Please X one or more of the boxes provided.

a) General Practitioner ☐ b) Endocrinologist ☐

c) Neurosurgeon ☐ d) Physician(s) ☐

e) Yourself f) ☐ Family or Friend ☐

g) Another, (*Example-nurse*). ☐

h) If you have answered (d or g) please name the discipline of the physician, (*Example GP, endocrinologist),* Health Professional, (*Example, nurse*) or another person.

☐

18. How many physicians did you consult prior to your diagnosis? ☐

19. How long did it take to be referred to the endocrine team? ☐

20. The following list shows many of the signs and symptoms that you may have experienced prior to being diagnosed.

Please **X** any of these that you may have experienced in Box A.

Please **X** Box B if you are still experiencing any of these.

Physical Signs/Symptoms	**A**	**B**
• Round face (*Moon face*).	☐	☐
• Excess of hair (*Excess Facial hair in women*).	☐	☐
• Female Balding.	☐	☐
• Weight gain (*Example-Abdominal region*).	☐	☐
• Skin bruising.	☐	☐
• High Blood Pressure.	☐	☐
• Raised Cholesterol level.	☐	☐
• Headaches.	☐	☐
• Plethora.	☐	☐
• Osteoporosis or fracture	☐	☐
• Proximal muscle weakness.	☐	☐
• Loss of hearing, smell, taste.	☐	☐
• Backache.	☐	☐
• Dorsal fat pad.	☐	☐
• Fatigue.	☐	☐
• Decreased libido.	☐	☐
• Menstrual changes	☐	☐
• Infertility	☐	☐
• Prone to infections.	☐	☐
• Inflammatory conditions (*Example, IBS*).	☐	☐
• Cardiovascular conditions.	☐	☐
	☐	☐

- Eye problems.
- Insomnia.
- Bodily Pain.

Psychological/Psychiatric Symptoms

- Depression.
- Cognitive impairment.
- Severe psychological/psychiatric disorders.

- Emotional problems
- Social Isolation.
- Other.

20a) If you have answered Other, then please name the condition(s) and if you continue to experiencing them.

20b) If you are symptom-free post-treatment for Cushing's, how long has it taken for this to happen? *Months* *Years*

21 Have you been hospitalized, due to Cushing's or any of the medical conditions you have identified in question 20?

YES NO

21a) If your answer is YES, how many hospital confinements?

21b) If your answer is YES in 21a), which medical condition(s)?

22.Did you have a series of blood, urine, salivary tests taken prior to your diagnosis?

YES ☐ NO ☐

22a) If you know which tests(s) you were given please name them below. If not, then please proceed to Question 23. (Examples tests: Dexamethasone tablets, Urine sample, Salivary sample). If you are unsure of which type of tests you received, please write UNSURE.

23. Did you have a CT scan taken prior to your diagnosis for your adrenal glands?

YES ☐ NO ☐

24 Did you have an MRI scan taken prior to your diagnosis for your pituitary gland?

YES ☐ NO ☐

24a) If you know of any other type of diagnostic imaging tests you have received during your diagnostic journey then please explain below. (Examples: Ultrasound, Positron Emission Tomography (PET), Radio-nuclide Imaging, Bilateral Petrosal Sinus Sampling, Adrenal Venous Sampling, X-rays example Chest and skeletal.)

25. Have you ever been diagnosed with any other condition (s) associated with Cushing's syndrome? (*Examples: Addison's Disease, Nelson's Syndrome, Carney Complex, Diabetes Mellitus, Diabetes Insipidus*).

YES ☐ NO ☐

25a) If YES, please name the condition below.

Section 3

This section asks questions which are related to your treatment of Cushing's syndrome. Please answer questions 26, if you have received adrenalectomy surgery. If you have not had surgery, please proceed to question 27.

26. Did you have adrenal surgery to treat your Cushing's syndrome? Please √ the box with your answer.

YES ☐ NO ☐

26a) If your answer is YES, have you had one adrenal gland removed (Left or Right), or both adrenal glands (i.e., bi-lateral adrenalectomy), or just part of one gland removed (i.e., partial adrenalectomy)? If you are unsure of what type of surgery, you received please write UNSURE in the box on the following page.

26b) If you have had adrenal surgery, what type of surgical procedure did you have?

26c) i) Laparoscopic excision ☐

ii) Single surgical incision. ☐

iii) Did this cure your Cushing's syndrome? ☐ YES ☐ NO

27. Do you take hormone replacement steroids/glucocorticoids for your Cushing's?

YES ☐ NO ☐

If your answer to question 27 is YES, please answer the following questions. If NO, then please proceed to question 31.

28. When did you commence taking medication for your Cushing's? ☐

29. Which glucocorticoids are you taking? (*Example-Hydrocortisone*).

30. Please **X** to answer the following statements that you agree with:

- I am no longer on glucocorticoids. ☐
- I am attempting to reduce my glucocorticoid medication. ☐
- I have been advised that I may always have to take glucocorticoids. ☐
- I am unsure as to how long glucocorticoid medication will be prescribed. ☐

31. Are you prescribed other medication in relation to your Cushing's?

YES ☐ NO ☐

31a) If your answer is YES, please give details of your medication below.

32. Are you meeting regularly with the endocrinology team for check-ups?

YES ☐ NO ☐

32a) If so, how regularly? ☐

33. Have you been referred to other physicians due to long-lasting ailments as a result of Cushing's syndrome?

YES ☐ NO ☐

33a) If your answer is YES, please list below.

☐

34. Have you had pituitary surgery for Cushing's disease? YES ☐ NO ☐

a) Which year did you have your surgery? ☐

b) Have you had to have repeat surgery? YES ☐ NO ☐

c) If YES, how many times? ☐

35. Have you had Radiotherapy treatment following your adrenal gland and/or your pituitary gland surgery?

YES ☐ NO ☐

35a) If YES, please specify with a X: Adrenal ☐ Pituitary ☐

Both ☐

35b) Please X if you know the answer to the following question:

i) Which of the following type of Radiotherapy treatment did you receive?

LINAC ☐ Proton Beam ☐ Gamma Knife ☐

ii) How many treatments did you have? ☐

iii) Did you have any side effects? YES ☐ NO ☐

35c) If your answer is YES, please state details below.

36. Did you receive Chemotherapy treatment? YES ☐ NO ☐

36b) If so, specify the reason, i.e., following adrenal and/or pituitary surgery or instead of surgery.

36c) What side effects if any did you experience?

37.Did your endocrine team suggest joining a support group? (*Example-the Pituitary Foundation UK*).

YES ☐ NO ☐

a) If YES, have you found this to be of help in supporting your illness by exchanging views with other Cushing's members and staff?

YES ☐ NO ☐

37b) Please explain your reasons for your answer to 37 a) below.

38.Do you feel that there is sufficient public awareness of Cushing syndrome and disease?

YES ☐ NO ☐

38a) Please give the reason(s) for your answer.

38b) If your answer is NO, can you suggest how public awareness could be improved?

Section 4

39. *Measurement of your Quality of Life (QOL), prior to, during and after the diagnosis of Cushing's syndrome and/or Cushing's disease.*

The final question asks you to rate how your Cushing's syndrome and/or Cushing's disease affects or have affected your QoL. (1-Strongly disagree - 5 Strongly agree).

*On a scale 1-5 please **X** in the box to indicate the degree to which you have found that Cushing's has affected or not affected your QoL.*

Poor Health (1) will indicate that Cushing's DID affect your QoL.
Very Good Health (5) indicates that Cushing's DID NOT affect your QoL
If you have 2,3 or 4, you may feel that your chosen numerical figure indicates the degree to which you feel Cushing's has affected your QoL

39a) This part of the question asks you to rate your QoL, <u>prior</u> to your diagnosis.

1. Very Poor Health	***2. Poor***	***3. Fair***	***4. Good***	***5. Very Good Health***

39b) This part of the question asks you to rate how Cushing's affected your QoL, <u>during</u> your treatment.

1.Very Poor Health	***2. Poor***	***3. Fair***	***4. Good***	***5. Very Good Health***

39c) This part of the question asks you to rate your <u>current</u> QoL.

1.Very Poor Health	***2. Poor***	***3. Fair***	***4. Good***	***5. Very Good Health***

40.If you wish to give additional reason(s) for one or more of your answers, please explain them in the box below and any other comments you wish to include which you feel will be of benefit to this study.

Thank you for completing this survey questionnaire and if you feel that there is further information you would like to share with me, then please do not hesitate to contact me at the following email address: dr.margotmcbride@gmail.com

Thank you also to the Pituitary Foundation UK for their support in this research project.

Imaging Modalities.

Figures 37 Computed Tomography Scanners.

Courtesy of two -view.com

Figure 38 Magnetic Resonance Imaging Scanners

Courtesy of gettyimages.co.uk

Figure 39 Ultrasound imaging modalities.

Portable Ultrasound unit, Courtesy info.co.uk

Anatomical Illustrations, Radiographic Images and Radiology Case Studies.

Figure 40 Illustration of the kidneys including the adrenal Glands.

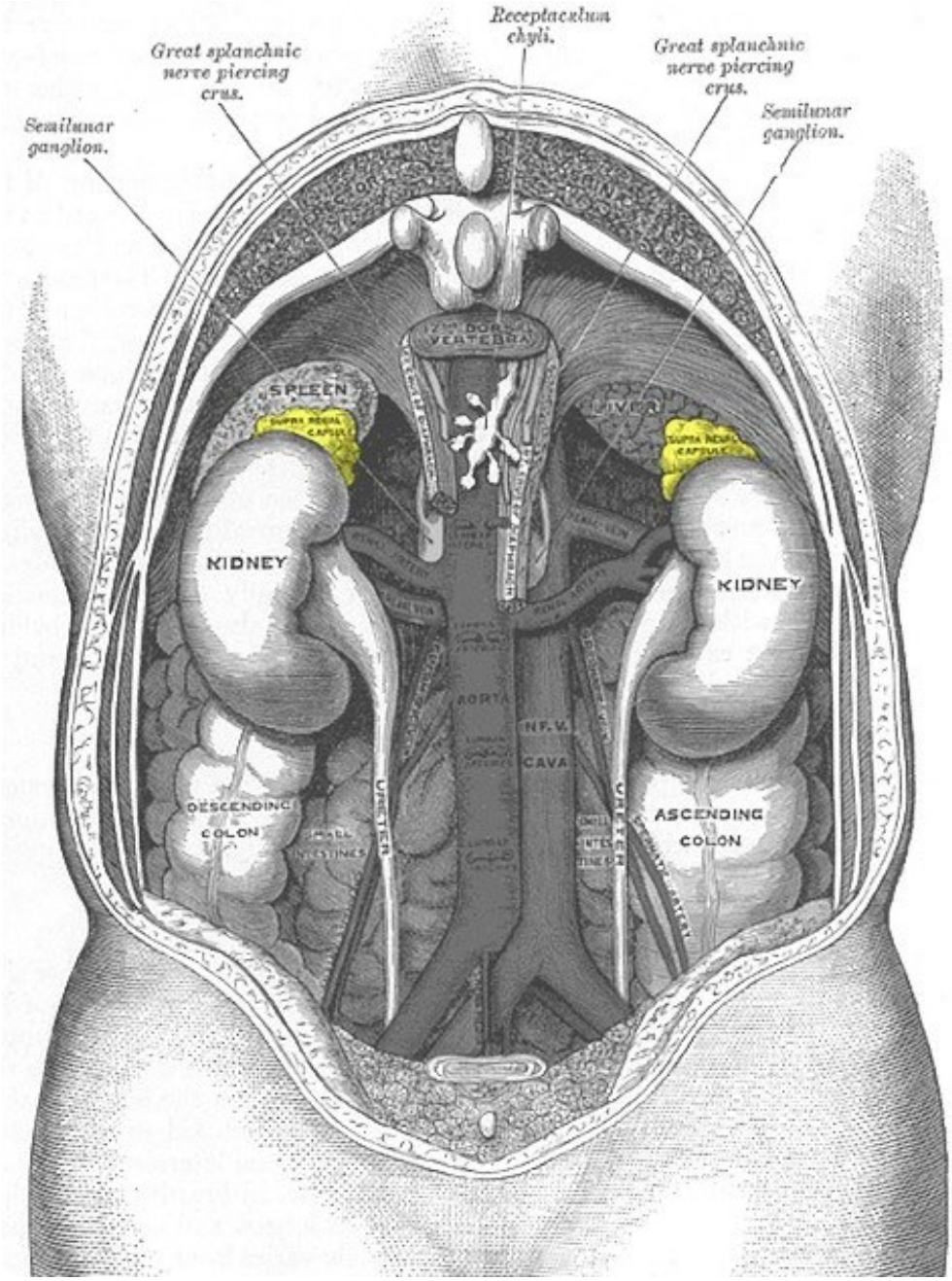


Illustration from Gray's Anatomy, Courtesy of Radiopaedia., adrenal glands highlighted in yellow.

Figure 41 Image 1 CT Right Adrenal Adenoma (*Biopsy found to be benign*). An adrenalectomy of the right adrenal gland was performed.

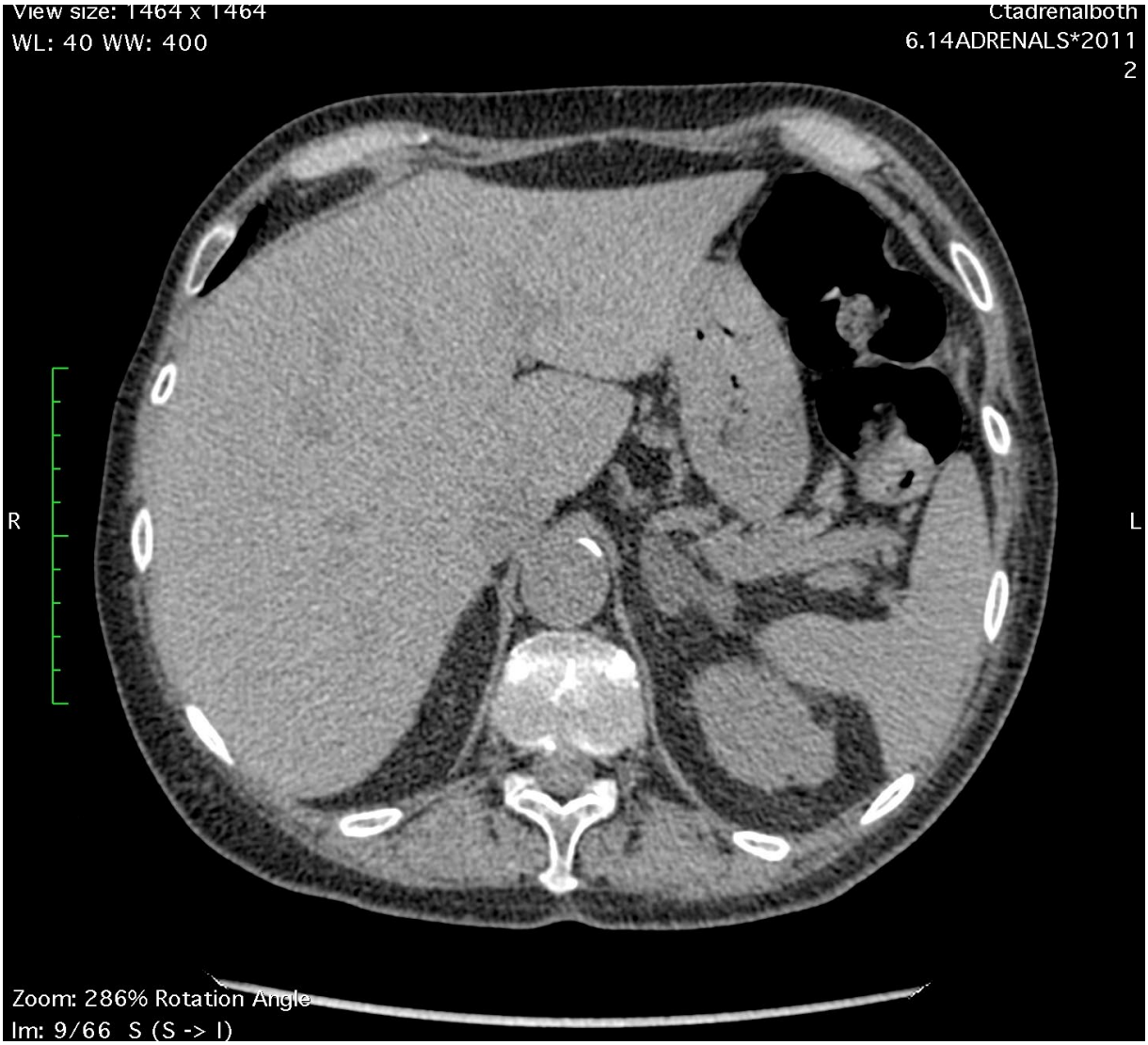


Image 1: Courtesy of Radiopaedia, 2021.

Figure 42 Image 2 CT Adrenal Glands (*Normal CT Anatomy*).

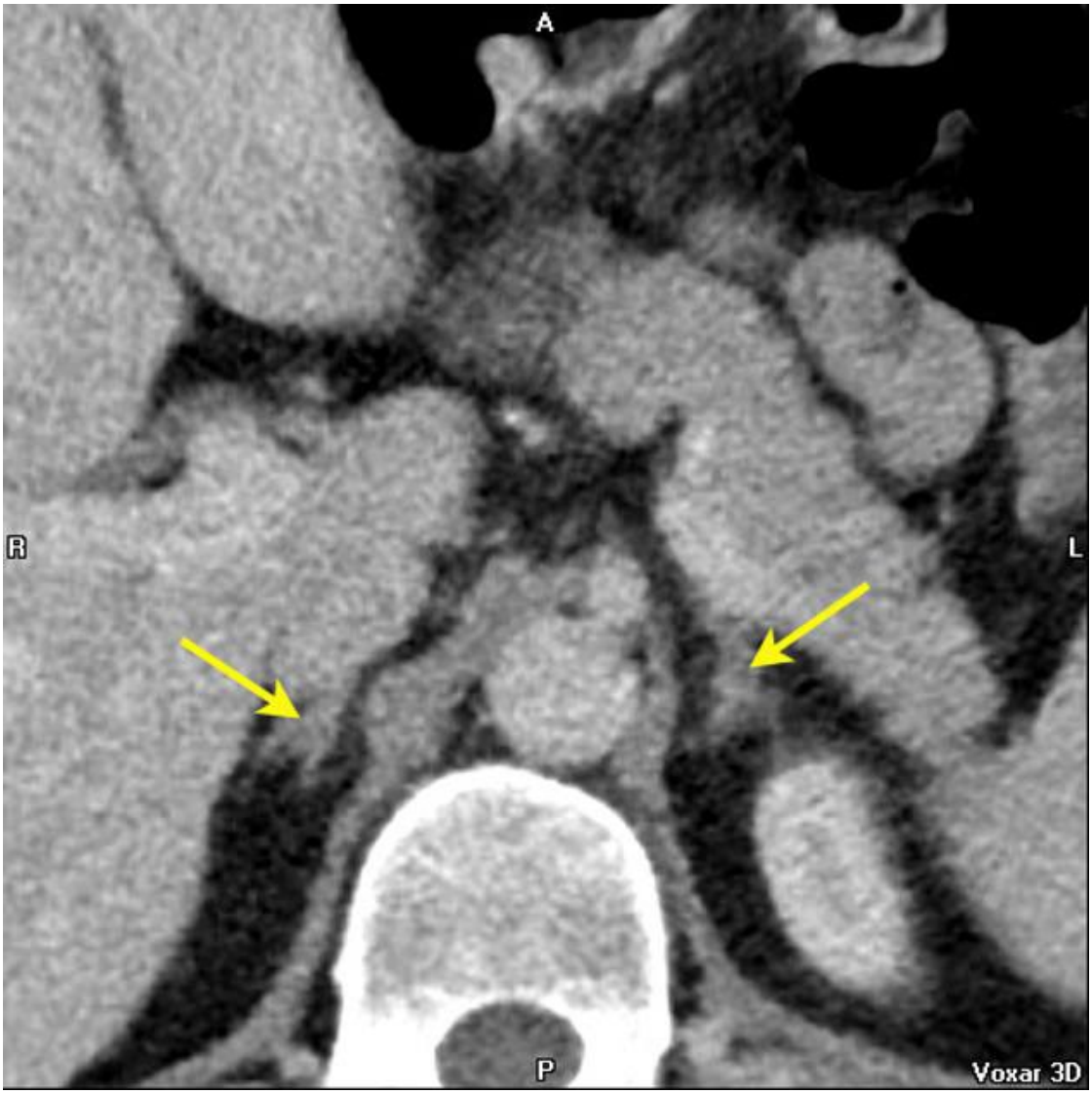


Image 2: Courtesy of Radiopaedia, 2021.

Figure 43 Image 3 CT Adrenal Cortical Carcinoma in female patient aged 65 years, with Cushing syndrome.

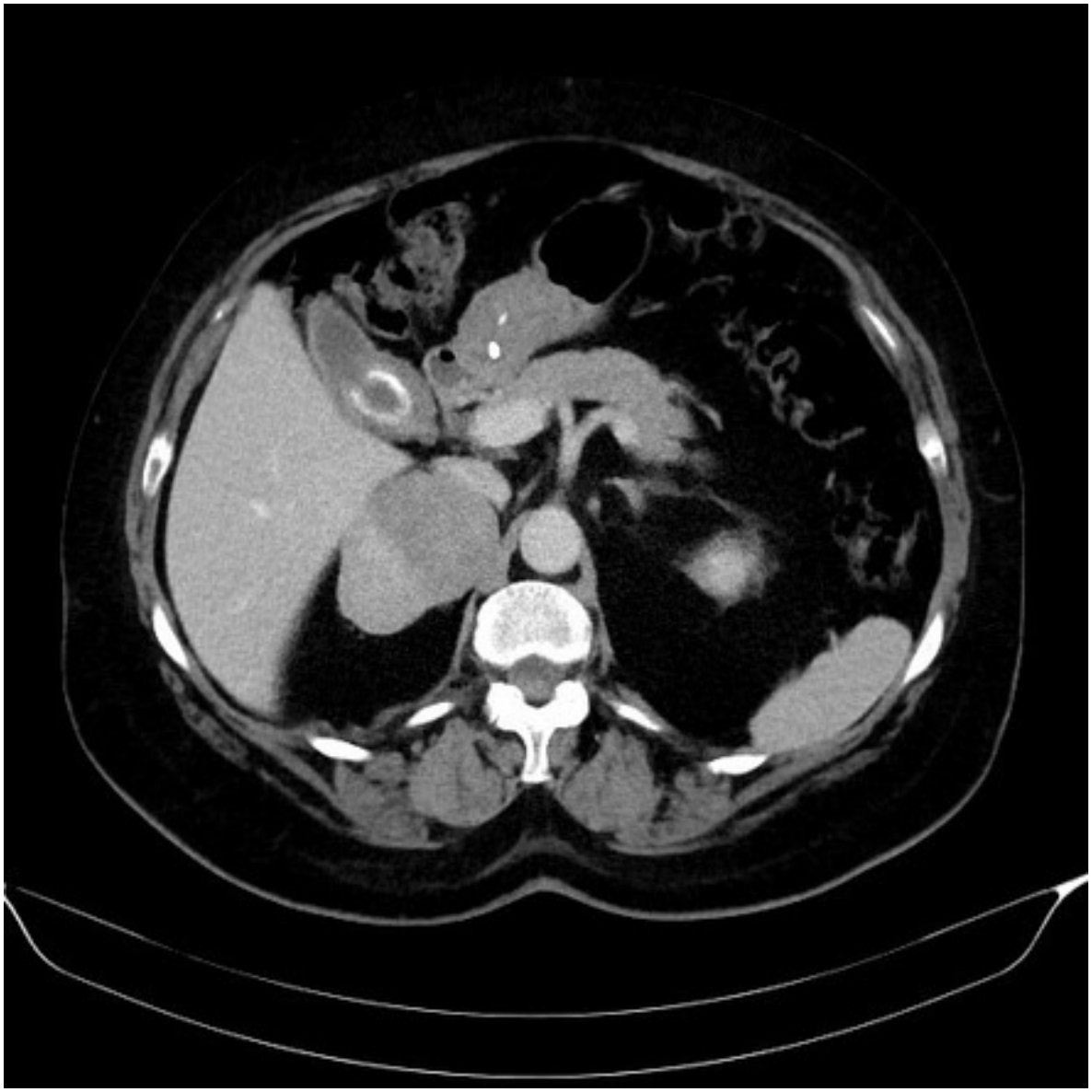


Image 3: Axial non-contrast.

Radiologist CT Report (Diagnosis almost certain).

Large right adrenal mass lesion. This lesion is relatively well demarcated and abuts the posterior margin of the IVC, medial margin of the liver and lateral margin of right hemidiaphragm crura. There is no evidence of local invasion. The more prominently enhancing posterosuperior component measures 29 HU on non-contrast, 84 HU on portal venous and 43 HU on delayed phase - calculating to 74% absolute washout and 49% relative washout. The anterior component has less prominent enhancement and measures 35 HU on non-contrast, 59 HU on portal venous and 43 HU on delayed - calculating to 66% absolute washout and 27% relative washout. Normal left adrenal gland. No hepatic mass and no lymphadenopathy.

CT Report Case Discussion:

The imaging features of this mass are not particularly suspicious for malignancy, although the size (>5 cm) and heterogeneity are worrisome features along with the endocrine abnormality that prompted imaging. Absolute washout is >60% which is compatible with an adenoma, however, the anterior component has a relative washout of <40%, which is indeterminate. MRI shows no fat signal drop-out, which is compatible with a lipid-poor adenoma, however, the restricted diffusion is concerning. The patient proceeded to resection, which demonstrates an adrenal cortical carcinoma.

Radiographic Image and Report Courtesy of Radiopaedia, 2021.

Figure 44 Image 4 Ultrasound of Normal Adrenal glands.

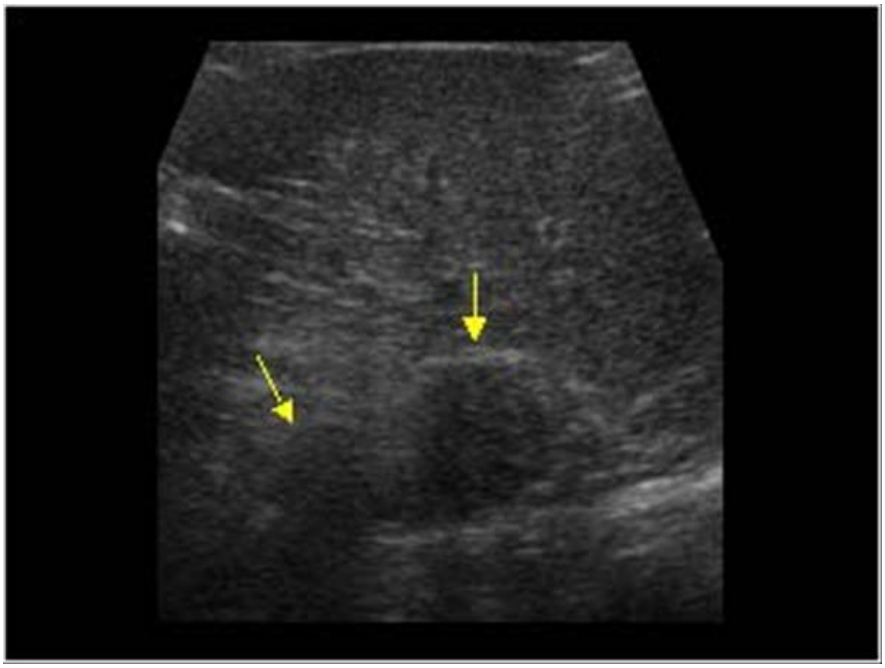
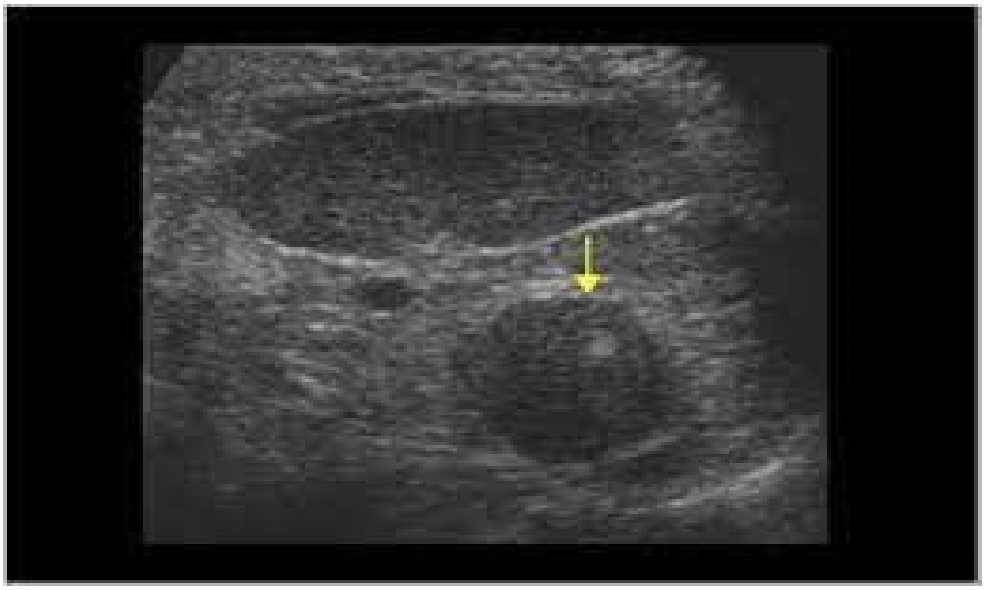
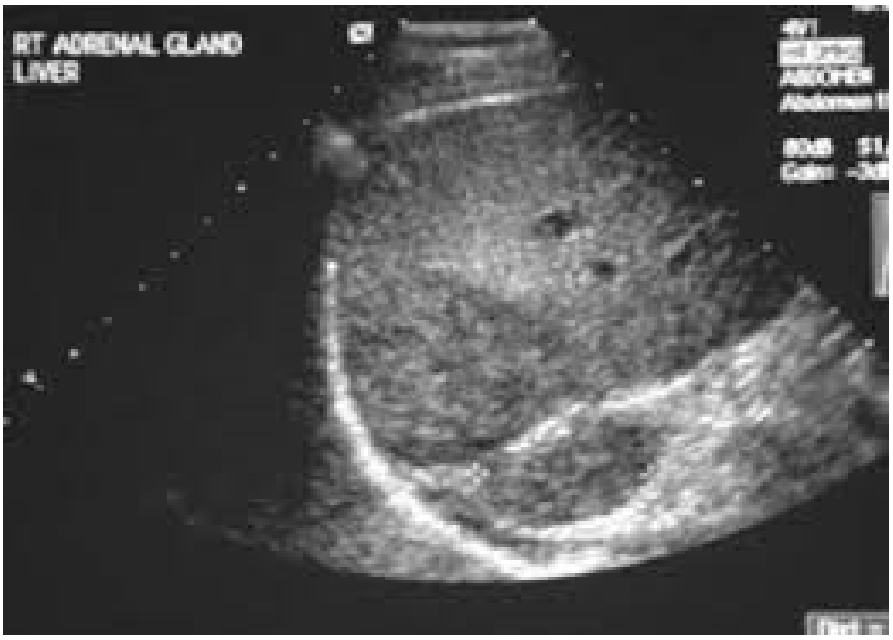


Figure 45 Image 5 Ultrasound Adrenal adenomas.



Ultrasound image: Courtesy of ultrasoundcases.com

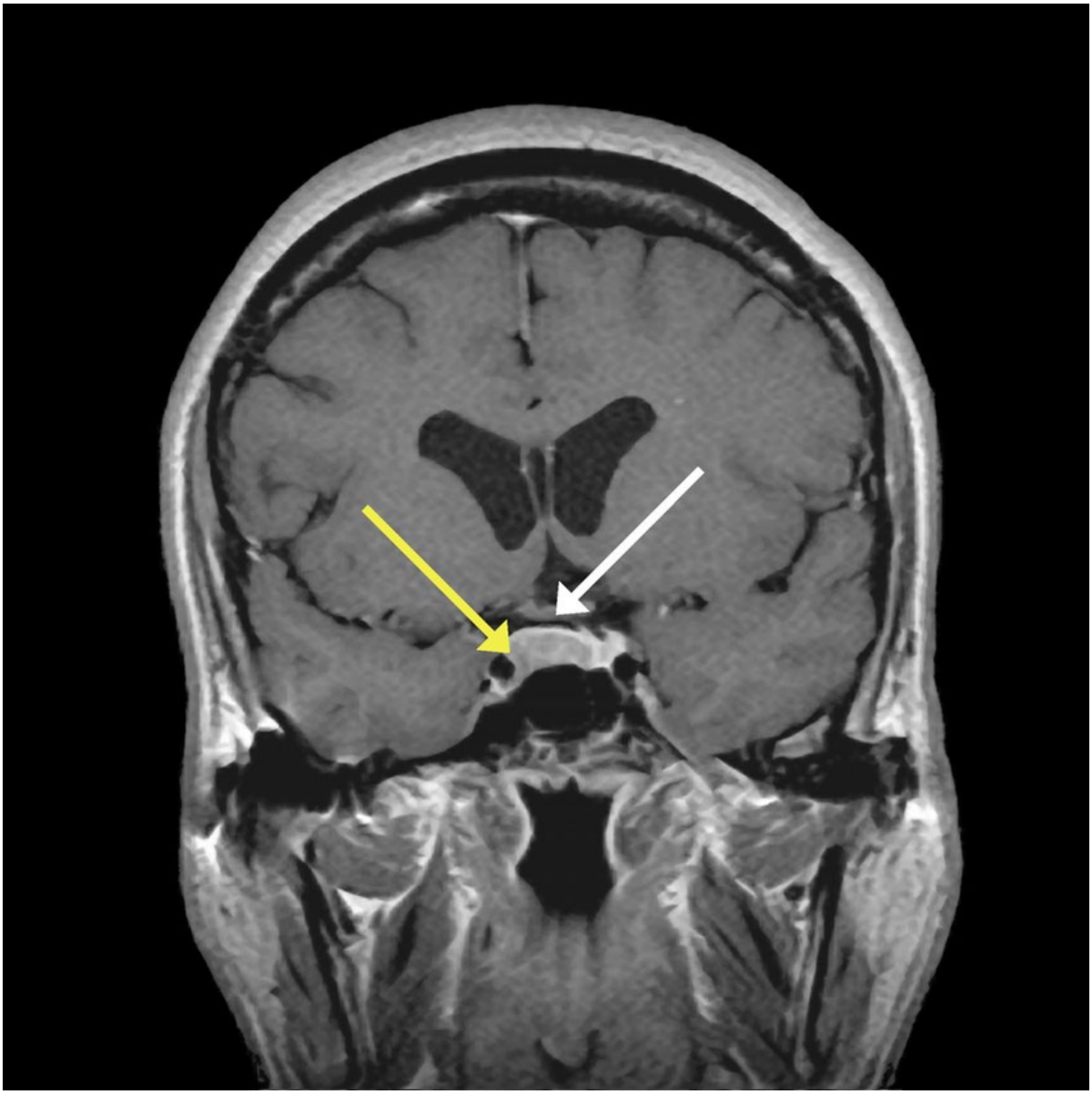
Figure 46 Image 6 Ultrasound Arenal Metastases



Ultrasound: Courtesy of Emedicine.medscape.com

Pituitary Imaging.

Figure 47. Image 7 MRI Pituitary Gland.

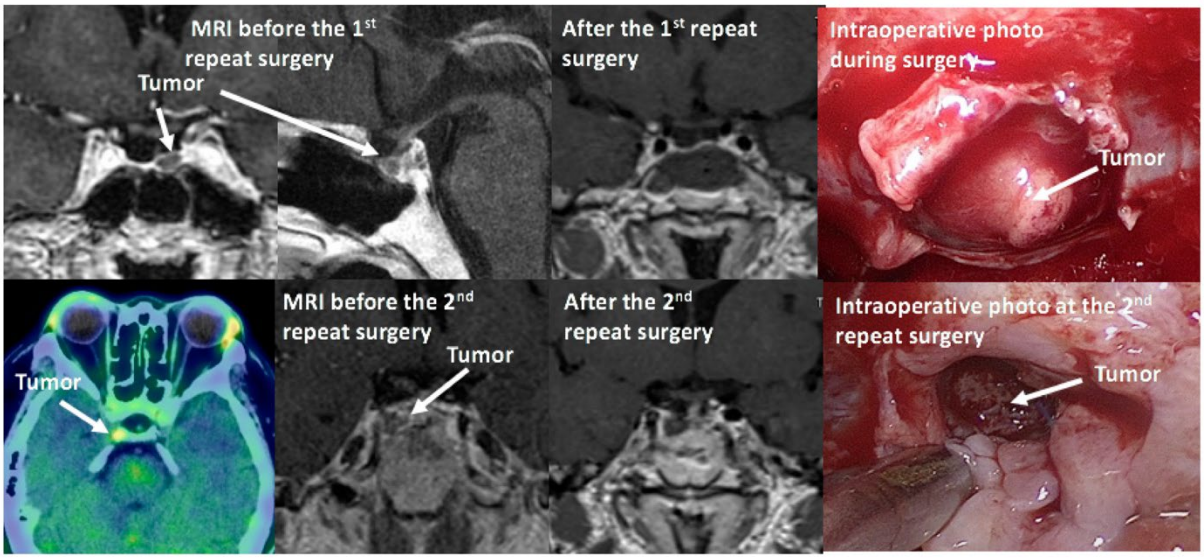


MRI of the Pituitary Gland showing a non-enhancing lesion occupying the bulk of the pituitary fossa (yellow arrow). The remaining normal pituitary is pushed to the left, as is the pituitary stalk. The optic chiasm can be seen just superior to the pituitary gland (white arrow).

Razvi S, Petros P, 2007. A 52-year-old female with a Hoarse Voice and Tingling Hand. PLoS Medicine, March 2007 Vol. 4, Issue 3. Accessed on-line.

Image: Courtesy ResearchGate 2021.

Figure 48 MRI images of the pituitary gland taken prior to surgery and after repeat first and second surgeries.



Case Study.

This 52-year-old lady had undergone transsphenoidal surgery for the treatment of pituitary apoplexy (tumor was large macro-tumor at that time). Several years later she showed Cushing's syndrome and a detailed examination confirmed Cushing's disease due to pituitary tumor located in the left side of pituitary which was removed by the first repeat surgery. However, both ACTH (91.3 pg/mL) and cortisol level (13.8 μg/dL) were still high. 11C-methionine PET-CT confirmed active small tumor still remained at the right posterosuperior sellar region which had been separated in the primary surgery and was removed by the 2nd repeat surgery (ACTH and cortisol levels reduced to 7.4 pg/mL and 2.6 μg/dL, respectively).

Case Study from Nishioka H, Yamada S, 2019. Cushing's Disease, Volume. 8, Issue 11, Journal of Clinical Medicine, Nov. 2019.

Figure 49 Case study of negative MRI

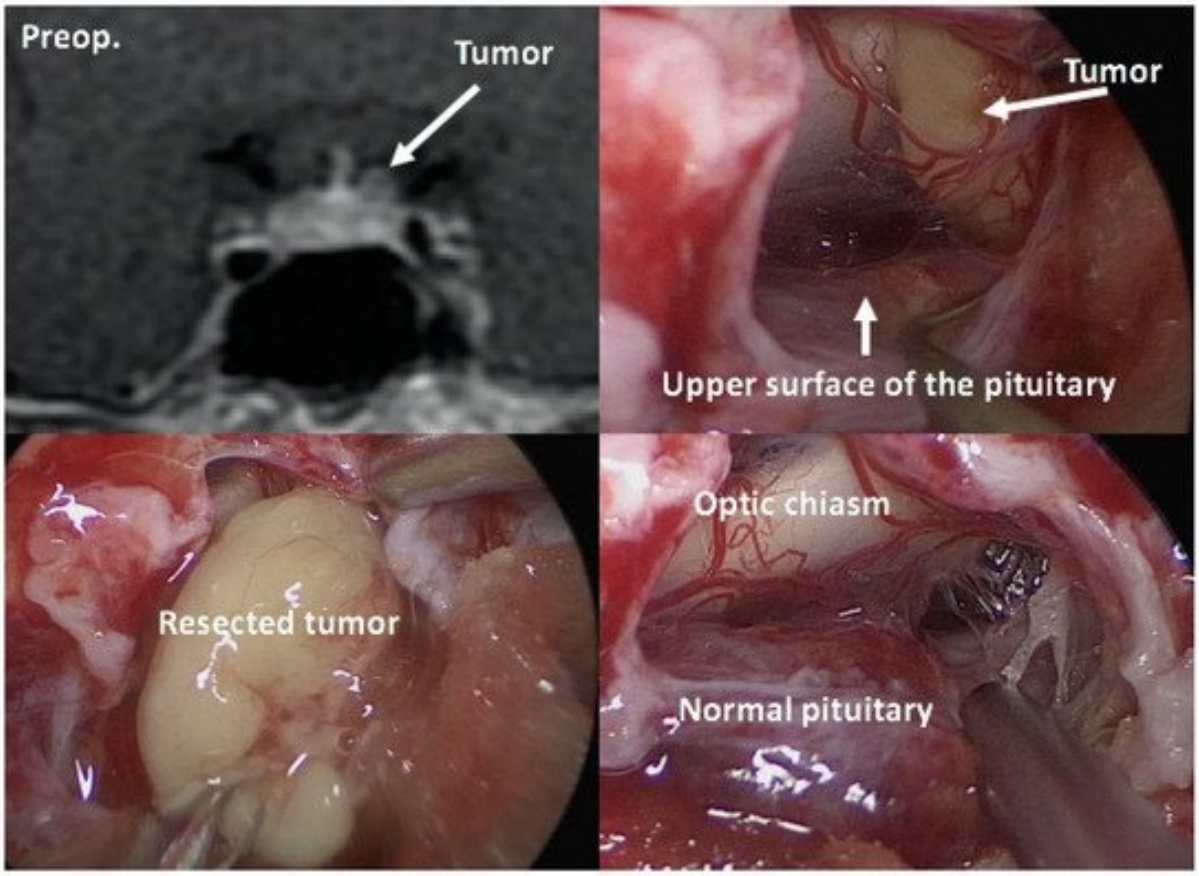


Figure 47. A patient of Cushing's disease with negative-MRI. Extensive MRI studies including 3T MRI failed to demonstrate any findings suggesting tumour, but inferior petrosal sinus sampling (IPSS) suggested pituitary origin of ACTH-dependent CD in a 20-year-old woman. A 3-mm diameter micro-tumour was found on the left side of the pituitary as predicted by IPSS. Selective tumorectomy resulted in complete remission of the disease. No abnormal findings were found in preoperative MRI even after review in MRI scans retrospectively comparing them to postoperative MRI findings.

MRI and illustration of tumour resection extracted from Nishioka H, Yamada S, 2019. Cushing's Disease. Vol. 8, Issue 11, Journal of Clinical Medicine.