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Health Technology Assessment Of Continuous Positive Airway Pressure devices in Sleep Apnoea Hypopnoea Syndrome

By

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CONTENTS

ILLUSTRATIONS

TABLES

ABBREVIATIONS

5-HT	5 hydroxy-tryptamine
ACE-I	Angiotensin converting enzyme inhibitor
AHI	Apnoea hypopnoea index
AI	3 second arousal index
BMI	Body mass index
BP	Bodily pain subscale of SF36
CAD	Coronary Artery Disease
CBA	Cost-Benefit Analysis
CEA	Cost-Effectiveness Analysis
CI	95% Confidence interval
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous Positive Airway Pressure
CPK-MB	Creatinine Phosphokinase-MB
CUA	Cost Utility Analysis
CVA	Cerebrovascular Accident
DBP	Diastolic blood pressure
DGH	District General Hospital
DM	Diabetes Mellitus
DOH	Department of Health, United Kingdom
EDS	Excessive Daytime Sleepiness
EEG	Electro-encephalogram
EMG	Electromyogram
ENT	Ear, Nose & Throat Specialists
EOG	Electrooculogram
ESS	Epworth Sleepiness Scale
EuroQol	European Quality of Life Index
EuroQol-HT	European quality of life –health thermometer
FLP	Functional Limitations Profile
GABA	Gamma-aminobutyric acid
GH	General Health subscale of SF36
GHQ	General Health Questionnaire
GP	General Practitioner
HADS	Hospital Anxiety & Depression Scale
HRQL	Health related quality of life
HTA	Health Technology Assessment
HTN	Systemic hypertension
ICD	International Classification of Diseases
IHD	Ischaemic Heart Disease
IRQ	Inter-quartile range
MCS	Mental component summary
MH	Mental health subscale of SF36
MSLT	Multiple Sleep Latency Test
MWT	Multiple Wakefulness Test
NHP	Nottingham Health Profile
NHS	National Health Service

NICE	National Institute of Clinical Excellence
NIDDM	Non-Insulin Dependent Diabetes Mellitus
NREM	Non-Rapid Eye Movement Sleep
ODI	4% arterial oxygen desaturation index
OR	Odds Ratio
PaO_2	Partial pressure of Oxygen
$Paco_2$	Partial pressure of Carbon dioxide
PCS	Physical component summary of SF6
PCT	Primary care trust
PF	Physical functioning subscale of SF36
PGI	Patient Generated Index
POMS	Profile of Mental States
PRV	Pulse rate variability (6 beats per minute)
PSG	Polysomnography
QALY	Quality adjusted life year
RCPUK	Royal College of Physicians, United Kingdom
RCT	Randomised controlled trial
RE	Emotional role limitation of SF36
REM	Rapid Eye Movement sleep
RP	Physical role limitation subscale of SF36
RTA	Road traffic accident
SAHS	Sleep Apnoea Hypopnoea Syndrome
Sao_2	Arterial pulse oxygen saturation
SAQLI	Sleep Apnoea Quality of Life Index (Calgary)
SBP	Systolic blood pressure
SCL-90	Symptom Check List -90
SD	Standard Deviation
SEM	Standard error of Mean
SF	Social functioning subscale of SF36
SF36	Short Form 36 questionnaire
SG	Standard Gamble method
SIP	Sickness Impact Profile
SSS	Stanford Sleepiness Scale
SWS	Slow Wave Sleep
TTO	Time trade off method
UARS	Upper Airway Resistance Syndrome
U_{eq}	Utility derived by the European quality of life index
UK	United Kingdom
UPPP	Uvulopalatopharyngoplasty
USA	United States of America
U_{sg}	Utility derived by the Standard Gamble method
U_{tto}	Utility derived by the Time trade off method
VAS-P	Visual Analogue Scale-Performance
VAS-T	Visual Analogue Scale-Tiredness
VLCD	Very low calorie diet
VT	Energy vitality subscale of SF36

WHO	World Health Organisation
WHR	Waist to hip ratio

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One has to begin traditionally where time began, at least time as far as I am concerned. I am certain that I must have imbibed my passion for healing from my mother's inherent instinct for coming to the right diagnosis by her perceptiveness which reaches almost psychic levels. From a very early age she has coaxed, cajoled and inspired me (along with my brother and sister) untiringly through almost three decades of life. Having gladly sacrificed her own career in music, she has stood behind me like a rock through hail and high water, smiled through my often unkind ranting and raving, while inspiring me on like a shining star. Even to this day although I am immersed in my own world thousands of miles away, she remains omnipresent and ever-inspiring in her courage to believe in the abilities and the destiny of her children.

Emerging from the cocooned existence under my mother's bosom late in childhood, I discovered the Gandhian personality of my father and his incredible scientific genius. Immersed in his work he has perhaps regretted missing out on his children's early development except through his passion for photography. I owe him my interest in science, the art of asking questions and gathering knowledge through the medium of experiments. More than as a perfectionist and a scientist, I admire him for his composure, self-respect and his infectious optimism. He has always taught us to aim high and to believe in our own abilities in the most difficult of circumstances.

My grandmother (*Monimala*) holds a special place in my life as she is the nearest I have come to knowing that human beings even in the most common of circumstances often exhibit superhuman qualities and create their own haven. She has constantly inspired me to look beyond the present in the quest for the 'greater good' and a unifying purpose of my life.

To come from a small town with a burning ambition, perseverance combined with personal ability and the courage to make it big in life is a personal example by which my Uncle (*Smarajit*) and my brother (*Anindya*) have shown me that one can indeed make ones dreams come true. On many long and lonely nights in my flat in the north of the country (S Cleveland) away from the human touch of friends and family and the heat and dust of India, one has often started to question the futility of this somewhat painful phase

of my life. It is then that I have taken solace from the tales of how my Uncle has coped with life in the biting cold of Aberdeen with a young family and kept his sight on his fellowship.

It is at such a moment fresh after my membership as I was strolling around thirsty for some scientific experimentation before embarking on specialist training that I met Ruth who had the courage to take me on. She has remained my philosopher and guide but has never allowed me even for a moment to bask in the comforting thought that I had attained her exacting standards. I have always approached her sessions with apprehension, feeling low where my well-thought out scientific logic has frequently faltered under her gaze but I have always left her presence with a burning desire to achieve perfection. While Ala has been a friend and guide, balancing the rough with the smooth, while providing a shoulder to rest my head on. She has guided the unsuspecting me through the often daunting areas of health economics in the corner in her office over long cups of coffee, almost effortlessly, till I have woken up on the motorway discovering a throbbing in my weary head.

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I have always acknowledged that I am a man whose life and destiny has been shaped by the love and contribution of the most incredible women. One has to mention at this critical juncture my wife (*Subarna*) whose beauty, love and natural exuberance has not only challenged me to stand up and be counted, but at the same time with her superhuman multi-tasking ability (perhaps only available to women) supported me through highest and lowest periods in my life. How she manages to maintain the fabulous

pace of her own life and career, in spite of the often ridiculous demands that I have so selfishly made on her, over nearly a decade will always remain a mystery to me.

My lovely sister (*Sohini*) and my beautiful daughters (*Triya Anushka & Aria Oindrila*) are an integral part of me and are the most effortlessly intelligent and naturally talented women that I have ever come across. They have given me a purpose in life and have encouraged me to continue with my writing whenever I have strayed, even when a lot of water has passed under the bridge. Perhaps when Triya & Aria are a lot older they will forgive me for the broken promises and endless hours that they have spent indoors, entertaining themselves with their dolls, whilst their absent-minded father either tapped at a keyboard or merely stared at his computer screen.

Well, like birth, marriage and parenthood bringing this mammoth chapter of my life to a close will perhaps be put down in history as another 'life changing' experience, from which I hope to emerge a better human being.

DECLARATION

I declare that the research conducted and presented through this thesis is entirely original and my own work and has not been submitted to any other university or institution for a degree.

Early results have been published as a paper in a peer reviewed journal and is appended to this thesis.

ABSTRACT

A.1 Background

The need to assess safety as well as clinical and economic effectiveness of health care innovations and thus prioritise health care provision, created the need for structured health technology assessment (HTA) programs [Gafni *et al.* 1993b;Henshall *et al.* 1997;Stevens *et al.* 2004]. Sleep apnoea hypopnoea syndrome (SAHS) affects 2-4% of the adult population[Young *et al.* 1993] who are disabled by daytime dysfunction [Hardinge *et al.* 1995;Johns 1993b;Mitler 1993;Sauter *et al.* 2000] and a heightened mortality and morbidity [Greenberg *et al.* 1995;Kiely *et al.* 2000;Peker *et al.* 1999;Sanner *et al.* 1997;Tremel *et al.* 1999;Wilcox *et al.* 1998; Moruzzi et al 1999; Malone *et al.* 1991]. The advent of continuous positive airway pressure devices (CPAP) [Sullivan *et al* 1981] made it possible to treat safely, patients over a wider spectrum of disease severity [Borak *et al.* 1996;Mar *et al.* 2003; Engleman *et al* 1997a], yet its diffusion and adoption appears to follow a heterogenous pattern.

A.2 Study design

A retrospective case-control study of 603 SAHS patients was followed by a prospective, randomised, parallel group trial (RCT) of CPAP compared to lifestyle intervention (including weight reduction and sleep hygiene strategy) comparing clinical, health related quality of life (HRQL) and cost-utility ratios (CUR). The final study is a qualitative survey assessing the factors influencing the diffusion and adoption of CPAP among 303 Primary care trusts (PCT) and 261 Respiratory physicians in the UK.

A.3 Results

SAHS patients had a (5x) higher risk of death and (2x) of hypertension, compared to controls. Among 71 SAHS patients in the RCT, those on CPAP demonstrated greater clinical effectiveness (*sleep latency, apnoea hypopnoea index, excessive daytime sleepiness & neuropsychiatric function)* and HRQL *(social functioning, mental health & energy/vitality)* compared to lifestyle intervention. Utilities improved on CPAP and the CUR were lower (£1716-£2027 vs. £3264-£4243).

The diffusion survey demonstrated that the characteristics of CPAP as an innovation, would favour its adoption compared to alternative therapies, except in patient tolerability (*PCT respondents*). However there appeared to be no regular system for the diffusion of innovation knowledge within the NHS and hindrances in SAHS management due to deficiencies in resources, specialists and facilities.

A.4 Conclusions

The results presented in this thesis provide a logical framework for the assessment of the progression of an innovation from the stage of establishing the clinical burden of disease and treatment needs, to its adoption and may help identify potentially modifiable factors in slow diffusion scenarios.

CHAPTER I

BACKGROUND

1.1 OVERVIEW

Evolution of universal provision of healthcare by governments to their people [World Health Organization 1999] was made possible not only by a combination of scientific discovery with technological advancement but also by the impact of global education and efforts to expand health services [World Health Organization 1999]. The result of this combined strategy is reflected in the changes in life-expectancy [World Health Organization 1999] seen among industrialized nations between 1910 and 1998. Even among the developing countries, the average life-expectancy had improved from 40 years in 1950 to 63 years in 1990. These improvements in population health not only translated into gains in well-being but also alleviated the economic burden posed by reduced productivity from unhealthy workers [Subramanian *et al.* 2002].

The goal of healthcare provision was visualized, in the declaration of the 1978 World Health Assembly in Alma-Ata, *'Health for All by 2000'* which envisaged, the attainment by all peoples of the world, a level of health that will allow them to lead a socially and economically productive life [32 WORLD HEALTH ASSEMBLY 1979]. The primary purpose of any health care system or technology was thus to promote, preserve and restore health [WHO 1946].

Patients' preferences and expectations from their health assume a paramount role in assessment of health and health care provision in the present day environment [Anonymous 1998c]. Such are the complexities of measuring a dynamic and multi-faceted state that any health technology assessment (HTA) method has not only to evolve scientific and reproducible mechanisms but also to evaluate the interaction of the various tiers of factors responsible for its promotion, restoration and preservation [Maynard *et al.* 2003].

1.1.1 Health technology assessment (HTA)

Although the advancement in health care technologies allowed the possibility for the emancipation of large sections of humanity of many of its scourges, there were newer problems emerging. These were mainly in the form of the harmful effects of hitherto

unknown or little known technology and the burgeoning costs of their provision to the masses [Pelletier-Fleury *et al.* 1999].

The experience with the adverse effects of many of the industrial, agricultural and chemical processes created the understanding of the potential for similar effects of health care developments. There were some tragedies which fuelled the increasing regulation of the drugs sector like the Thalidomide related birth defects [Annas *et al.* 1999]. The intention of technology assessment in the 1970's was not only to quantify the first-order desirable effects of a new technology but also the unintended and undesirable higher order effects on social, economic and environmental systems [Morton *et al.* 2003].

The rapid expansion of healthcare technologies had been fuelled by a common interest of clinicians and patients alike to take the advantage of what was and still is widely perceived as state-of-the-art in healthcare benefit, regardless of cost. The flow of technology has been increasingly modulated by a widening group of health care policy makers which include researchers, manufacturers, regulators, clinicians, patients, government leaders and politicians [McDaid 2003]. Thus giving rise to a need for well-founded information to support decisions on how to develop and adopt new technology, pay for it, and to regulate it. Since its early years, HTA has been fuelled in part by the emergence and diffusion of technologies that have evoked social, ethical, legal, and political concerns. Some examples are contraceptives [Kohler 1997], organ transplantation [Rublee 1994], in vitro fertilisation, artificial organs, life-sustaining technologies for critically or terminally ill patients [Rettig 1991] and, more recently, genetic testing and genetic therapy [Mowatt *et al.* 1997a]. These technologies have challenged societal institutions, codes, and other norms regarding fundamental aspects of human life such as parenthood, heredity, birth, bodily sovereignty, freedom and control of human behaviour, and death.

Although the ideal HTA conceptually encompasses the direct and indirect effects of a new technology, in practice often the need for speed and resource constraints has restricted the assessment to mainly safety, direct beneficial/ desirable effect quantification and economic impact studies [Goodman 1992].

The outcome of any new HTA can be measured by a change in a health status measure or variable also known as the 'treatment effect' [Gafni *et al.* 1993a]. Such treatment effects can then be compared between old (or existing) treatment options and the new to assess

effectiveness of the new technology. The case of the continuous positive airway pressure devices (CPAP) [Sullivan *et al.* 1981] for the treatment of Sleep apnoea hypopnoea syndrome (SAHS) [American Academy of Sleep Medicine 1999] is an example where a relatively inexpensive technology was developed to alleviate the disability of chronic sleep deprivation in SAHS patients [Wright and White 2000].

1.1.2 SAHS & HTA

The Oxford English Dictionary defines 'sleep' as, 'the condition of body and mind which normally recurs for several hours every night, in which the nervous system is inactive, the eyes closed, the postural muscles relaxed and consciousness practically suspended'[Anon.1996]. Sleep is recognised as two distinct and essential states of existence, namely rapid eye movement (REM) and non- rapid eye movement sleep (NREM) [Rechtschaffen *et al.* 1968].

The role of sleep in normal human life and performance is borne out by consequences of sleep deprivation [Leproult *et al.* 1997]. Sleep deprivation is known to be the cause of at least 56000 accidents annually on American roads directly as a result of driver fatigue/ sleepiness, leading to 1550 fatalities and is estimated to have cost just under 40 billion United States dollars (USD) in 1988, and 720 billion USD for public transportation accidents [Leger 1994]. In 1990, there were 2.5 million injuries with a loss of 52 million work days [Leger 1994]. In the UK, up to a third of serious road traffic accidents are related to sleep [Horne & Reyner, 1995]. Although these estimated figures are indicative but the full economic and societal impact of nocturnal sleep fragmentation or deprivation is difficult to investigate and quantify [Sleep Alliance. 2004].

Sleep deprivation, whether it be a result of a deliberate lack of sleep, sleep restriction due to shift work or due to sleep disorders, has a common pathway in producing excessive daytime sleepiness (EDS) [Johns 1994], poor concentration, neuro-cognitive dysfunction [Engleman and Douglas 1993b] and an increased propensity for accidents [Lloberes *et al.* 2000]. Apart from sleep deprivation and insomnia the predominant pathological cause of EDS is SAHS. Although the prevalence of nocturnal apnoeic or hypopnoeic events is high in the general population, the existence of the clinical syndrome is estimated at 2-4% among middle aged adults [Young *et al.* 1993].

SAHS is characterised by an episodic and repetitive closure/ collapse or narrowing of the naso-pharyngeal airway leading to arterial oxygen desaturation, hypercapnoea and an increased work of breathing [American Academy of Sleep Medicine 1999]. This in turn causes interruption of continuous sleep in the form of arousals leading to sleep fragmentation and EDS [American Academy of Sleep Medicine 1999].

SAHS is intimately associated with obesity [Kopelman 1984;Lindberg *et al.* 2000;Shneerson *et al.* 2001] and lifestyle features (such as alcohol consumption, smoking, poor sleep hygiene, shift-work [Knutsson 2003]) which are known to have an adverse effect on health. Early research has been plagued by a difficulty in extracting the effect of sleep fragmentation from the influence of these lifestyle factors on the individual. There is an observed increased prevalence of hypertension (HTN), Ischaemic heart disease (IHD), Cerebrovascular disease (CVA)[Lattimore *et al.* 2003], mortality and diabetes (DM) [Punjabi *et al.* 2003] among SAHS sufferers. Current research in SAHS has begun establishing the decline in health related quality of life (HRQL) in untreated patients which can be reversed with continuous positive airways pressure (CPAP) therapy compared to placebo [Bolitschek *et al.* 1998;Flemons 2004;Lacasse, *et al.* 2002a;Moyer *et al.* 2001;Stradling *et al.* 1996] or ineffective CPAP [Hein 2002;Jenkinson *et al.* 1999], there is still a considerable variability in the effects measured with varying range of HRQL tools [Jenkinson *et al.* 1997c] and little evidence on the effect of intervention in the adverse lifestyle features associated with SAHS [Wright and White 2000].

The advent of new technology usually brings with it increased cost of diagnostic and treatment procedures and demands increased healthcare resource allotment [Banta 1994;Maynard 1989;Neumann *et al.* 1991]. It is estimated that diagnosis and treatment of SAHS in the USA in 1990 cost 275 million USD and affecting 20 million Americans the estimated cost may reach 60 billion USD by the year 2000 [National Commission on Sleep Disorders Research 1993].

Resource allocation is finite and determined largely by socio-economic, political and market forces [Freemantle 1995;Hurley *et al.* 1997;McKneally *et al.* 1997] and is constantly in need of prioritisation especially in the 'free at the point of delivery' system like the National Health Service (NHS) [Weale 1998] in the United Kingdom (UK) or Medicare health insurance system in the USA [Kinney 1989]. Allocation of resources to

competing technologies is facilitated by measuring the clinical and economic effectiveness using generic outcome variables [Gafni and Birch 1993a;Levine *et al.* 2002;Mehrez *et al.* 1991;Pinto Prades 1997].

SAHS patients report a variable degree of EDS and daytime dysfunction which does not often show a clear relationship with the severity of physiological sleep fragmentation [Punjabi *et al.* 2002]. Hence there exists a perceived need for more generic and comparable measures of effectiveness. These include generic quality of life measures, disease specific measures and health status outcomes, which assess the net effect of an intervention on the patient and allow for comparison between different populations and different disease groups [Flemons 2000].

Over the last three decades, various techniques have been developed to treat patients with SAHS; lifestyle strategies of weight reduction and sleep hygiene improvement [Shneerson and Wright 2001], oral/ mandibular advancement devices [Marklund *et al.* 2004;Smith *et al.* 2002a], laser/ surgical approaches [Friedman *et al.* 2004;Littner *et al.* 2001] to modifying the naso-pharyngeal airway and CPAP [American Thoracic Society 1994;Ballester *et al.* 1999;Scottish Intercollegiate Guidelines Network 2003].

Since 1990, CPAP has been commercially available as a treatment option for SAHS sufferers [American Academy of Sleep Medicine 1999]. A study by the Royal College of Physicians of UK (RCPUK) estimated that only a small proportion of potential patients with SAHS were being diagnosed and treated in the UK, demonstrating a mismatch in the patient needs and facilities available [Stradling *et al.* 1993]. This report also identified the existence of a wide variation in the availability of diagnostic and treatment facilities within the UK and a lack of homogeneity in adoption of CPAP therapy [Gibson *et al.* 1998] This assessment was further supported and updated with the Sleep: Impact on Society report by the Sleep Alliance in 2004 [Sleep Alliance. 2004] which demonstrated the heterogeneity in availability within the framework of health service (which is designed to deliver an equitable distribution of healthcare resources).

The issues which may be influencing the variable availability of CPAP and its slower adoption in the UK maybe manifold;

1. The lack of randomised studies establishing the clinical effectiveness prior to 1997 [Wright *et al.* 1997b].

2. The absence of an objective and universal outcome measure preventing comparability with competing technologies [Jenkinson *et al.*1997c]
3. The absence of a predictable, linear relationship between the pathophysiological measures of SAHS and sleep fragmentation with the (outcome) HRQL measures [Ballester *et al.*1999].
4. The dearth of economic evaluation data [Anonymous 1998a; Moyer *et al.*2001] in SAHS.
5. The possible lack of widespread dissemination of research evidence and knowledge utilisation among secondary and primary care[Gibson *et al.* 1998;Semple and Gibson 1993;Sleep Alliance. 2004].
6. The inactivity of active patient self-help groups and professional champions and hence relative public apathy towards sleep disorders [Sleep Alliance. 2004].
7. The absence of political and policy imperatives and national plan framework for SAHS [Sleep Alliance. 2004] compared to cancer diseases [Holmberg *et al.* 1998;Waller *et al.* 1995].
8. The innovation characteristics i.e. comfort [Beecroft *et al.* 2003;Pepin *et al.* 1995], complexity and user perceptions [Zozula *et al.* 2001b] for CPAP.

Using the case of CPAP use in SAHS, this thesis explores the HTA of a health care innovation and the factors influencing its diffusion and adoption in a managed care setting. It examines the clinical experience from the introduction of CPAP in 1990 in a typical UK district general hospital (DGH), through a retrospective case control study of 603 patients seen over 7 years, investigating their anthropometrics, clinical features, diagnostic modalities, mortality and morbidity as well as referral patterns and growth in numbers of patients and CPAP prescriptions. This then leads to the design and execution of a randomised, controlled trial (RCT) to assess the clinical effectiveness of CPAP therapy in SAHS compared to structured lifestyle intervention. This study also provided the opportunity to assess the sensitivity and reliability of different clinical, HRQL and health status outcome measures.

This is then followed by an exploration of the techniques of economic evaluation of CPAP in the treatment of SAHS, measuring health status or utilities in order to produce a

generic outcome measure; the quality adjusted life year (QALY) which would allow the comparison of clinical and cost effectiveness of competing technologies. The final phase of this research explores the different factors influencing the diffusion and adoption of CPAP as an innovation and the processes of knowledge utilisation in this area. Results from this research may help recommend a logical framework for the assessment and adoption of health care innovations by a managed care sector in the future.

1.2 HEALTH TECHNOLOGY ASSESSMENT

1.2.1 Introduction

The technological advancements in diagnosing diseases and measures to prolong life and restore health have fuelled public expectation for better health care provision, which in turn has resulted in a rise in the economic burden on nation states [Neumann and Weinstein 1991]. Most countries, especially in the developing world, are increasingly forced to choose between infrastructural development for social, educational and economic growth, against improving the diagnostic facilities and treatment of diseases with newer technology [Reich 1988]. This paradigm may sometimes lead to a pressure for the adoption of less effective therapies at high cost before a complete evaluation. The pressure on finite economic resources leads to the emergence of rationing or priority setting in medical care provision, as the next logical step [Maynard *et al.* 1995;Weale 1998]. Medical practice has varied locally, regionally, and internationally, e.g., patients with similar age and stage of cancer can receive very different levels of radiotherapy across Europe [Maynard and Bloor 1998]. For most interventions, the appropriate level of treatment may be asserted on 'clinical need' but is usually not based on cost effectiveness knowledge. Health policy analysts, like clinicians, tend to make assertions about competition and other health care reforms which are value- rather than knowledge-based [Maynard and Bloor 1998].

There has been a need not only to answer the questions of safety, and quality for emerging technologies but also to establish the efficacy and effectiveness of

currently available technological advances [Angus 1994]. HTA was developed to provide this crucial information and has been evolving since [Battista 1992].

HTA is designed to provide information to various agencies with varying perspectives on healthcare provision; i.e. Hospitals and health care providers are concerned with the safety and clinical effectiveness of new and evolving practices/ treatments; while to health care purchasers and medical insurers, HTA provides information on economic evaluation of clinical strategies; and for governmental agencies, it is a tool for the assessment of the public impact of existing and new technologies [Rutten *et al.* 1994].

1.2.2 Definitions

The Office of Technology Assessment was created in 1972 by the U.S. Congress to "provide early indications of the probable beneficial and adverse impacts of the applications of technology [Blair 1994]". HTA was defined as 'the drugs, devices, and medical and surgical procedures used in medical care, and the organizational and support systems within which such care is delivered.'

However recent definitions of HTA have evolved to include, 'all the methods used by health professionals to promote health, to prevent and treat disease, and to improve rehabilitation and long term care [NHS 1992].'

Thus HTA is 'the systematic process by which the direct and indirect consequences of a particular technology are assessed: it is concerned with evaluating the safety, effectiveness, and cost- effectiveness, and (where appropriate) the social, ethical, and legal impact of a technology' [Szczepura *et al.* 1994].

1.2.3 History & evolution of HTA

The concept of controlling for bias dates back to 1898 [Cheng 2004], the RCT, introduced in the late 1930's [Hammerschmidt 2004], was a landmark

development in the history of medicine [Jadad AR *et al.* 1998]. It paved the way for the scientific approach to evaluating the safety and effectiveness of health care interventions and provided the most secure basis for valid causal inferences about the effects of treatments [Office of Technology Assessment 1983].

This was followed by the rapid expansion of the pharmaceutical industry [Bloor *et al.* 1996;Maynard *et al.* 1997] and the rapid introduction of a great number of drugs being developed for treatment, with their potential for both beneficial and adverse effects. Many governments introduced tight controls with the requirement to prove the safety and efficacy of all new drugs prior to their licensing for public use [Maynard and Bloor 1997]. This control regime not only introduced a cost burden on the pharmaceutical industry which pushed up the cost of newer drugs or devices [Dimasi *et al.* 1991] it was also discovered that the efficacy of new drugs or new treatment protocols established in tightly controlled trial settings did not always translate to the same levels of efficacy when in general use. This may be due to lack of motivation, reduced compliance, co-morbidities and less adherence to protocol than in an RCT setting with motivated and supported trial participants.

This led to the introduction of the concept of *'Effectiveness and efficiency'* in 1972 by Archie Cochrane [Cochrane 1972]. By this time cost-benefit analysis (CBA) was established alongside clinical or physiological data in trials assessing health care interventions [Levine *et al.* 2002;Nixon *et al.* 2000]. The economic appraisal of health care technologies evolved and expanded in the 1980's to encompass; cost of illness, cost-effectiveness and cost-utility studies [Torrance 1986a].

In 1972, the US Congress established the Office of Technology Assessment in order to gather information on all forms of technology and to inform policy making at government level [Blair 1994]. The Health Program was established a year later, to synthesise existing knowledge from research evidence [Martin 1981].

Governments in Europe followed a decade later, with the World Health Organisation '*Health for All*' strategy urging member states to establish a mechanism for the systematic assessment of the effectiveness, efficiency, safety and acceptability of health care technologies. It is only in the last decade of the last millennium that countries and their governments began acknowledging the need for a uniform, scientific and systematic approach to health policy decision making about the adoption of new and existing technologies [Davies *et al.* 1994]. However there is still evidence of a reluctance for the utilisation of such assessments in decision making [Maynard and McDaid 2003] except in the case of pharmaceutical companies (where the culture of increasing regulation is well established) who now have to provide evidence of cost-effectiveness along with clinical effectiveness [Maynard and Bloor 1997]. Acceptance of economic appraisal information in decision making is also shown to be far slower and more reluctant in the devices and medical procedural sector [Maynard and McDaid 2003].

Public health establishments like the UK NHS are now widening the HTA horizons by establishing mechanisms to assess the influence of organizational structure and support systems [Woolf *et al.* 2000b; NHS 1992]. The NHS HTA Group now undertakes annual white paper consultations from the NHS, the health care industry and the public on health technology issues and commissioning studies of safety, effectiveness and economic analysis [NHS 1992;Woolf and Henshall 2000b]. The data from such studies are intended to be fed back to the health care industry and the public to help diffusion and policy making [Woolf *et al.* 2000a].

In the UK, a new body with the responsibility of recommending to the NHS on the clinical and cost effectiveness of new drugs and medical devices called the National Institute of Clinical Excellence (NICE), was established in 1999 [Taylor 2002]. A review looking at 32 appraisals conducted by NICE found that around

two-thirds of NICE appraisals had been of pharmaceuticals [Salazar 2002]. There was clear evidence of the use of cost-effectiveness criteria to restrict or reject technologies, although these were not the only criteria used in decision making [Salazar 2002]. Although definitely considered to be a step in the right direction by most health care professionals, the opinion of the both manufacturers and NHS agencies remained mixed as the impact of NICE recommendations are continually scrutinised [Sitzia 2002]. Manufacturers remained concerned about the timing of referrals in the product life cycle and about the quality and consistency of the reviews of evidence undertaken by the academic groups for NICE. Within NHS there were concerns on whether the right technologies were being referred to NICE and also on the opportunity cost of positive NICE recommendations [Davies *et al.* 2002]. In a survey carried out among the Directors of Public Health in the UK, the majority were positive about NICE's role of providing high-quality appraisal and central guidance but negative about its influence on local priority setting. Major concerns remained about the affordability of competing national demands often by the lay public or politicians with a potential for creating difficulties in local priority setting [Sitzia 2002].

Given the global budget constraints and the difficulty of withdrawing services, the NICE recommendations based on economic evaluation may pre-empt growth money that could be better used for more cost-effective purposes [Rosen *et al.* 1998]. NICE also has a defined role in appraising established technologies that may not be cost effective and whose discontinuance could therefore release resources for other more cost-effective treatments [Rawlins 1999]. As the political, economic and social cost of health policy decision making can be immense and largely uncertain, there is still a perceived need for wider understanding, multidimensional participation in a more widespread structured strategy of HTA [Davies *et al.* 2000b].

1.2.4 Purpose of HTA

HTA is the systematic evaluation of properties, effects and/or other impacts of health care technology. The main purpose of HTA is to inform technology-related policymaking in health care at institutional, regional, national and international levels. HTA addresses the direct and intended consequences of technologies as well as their indirect and unintended consequences.

HTA may be used to advise regulatory agencies whether or not to permit the commercial use (e.g., marketing) of a drug, device or other technology [Taylor 2002].

HTA may help health care payers and providers to determine which technologies should be included within the managed care framework or private health plans, addressing coverage (whether or not to pay) and/or reimbursement (how much to pay) policies [Taylor 2002].

HTA may be used to advise clinicians, providers and patients about the proper use of health care interventions for particular health problems (e.g., practice guidelines, disease management programs) [Perleth *et al.* 2001].

Information from HTA may help managers of hospitals, health care networks and other health care organizations to make decisions regarding technology acquisition and management [Lee *et al.* 2003].

HTA is used by governmental health departments in undertaking and commissioning public health programs (e.g., vaccination, screening and environmental protection programs) [Banta 2001].

HTA information supports health care product company decisions about product development and marketing [Siebert *et al.* 2002] [Schubert 2002].

HTA helps to set voluntary or mandatory standards regarding the manufacture, use, maintenance, reuse and other aspects of health care technologies, components and materials [Siebert *et al.*2002].

Data analysis from HTA is used to advise state and national leaders about policies concerning technological innovation, research and development, regulation, payment and delivery of health care [Papatheofanis 2000].

HTA may also include user feedback, public and professional priorities [Johannesson *et al.* 2002] and socio-political aspects of new technologies in a more comprehensive assessment [Lehoux *et al.* 2000].

1.2.5 Factors affecting the timing of HTA

The pace of new technology development and the speed of widespread diffusion and application of a recently introduced instrument or method, determine how and when an HTA exercise needs to be undertaken to play a role in its adoption [Mowatt *et al.* 1998]. This is especially true for new and fast-changing technologies. The factors that may influence the diffusion of unevaluated medical technologies are cost, the presence of enthusiasts, lack of resistance, meeting perceived needs and ease of use [Rogers 1984]. However there may be pressures on the evaluation process from rapid developments in a non-medical field, which may influence adoption through media and pressure groups [Stocking 1986].

The life cycle of a new technology is considered to evolve through five different stages [Banta 1992].

'Future' is the anticipated or conceptual stage of development, when feasibility studies may be undertaken to assess potential benefit and risk.

'Experimental/ emerging' stage usually involves laboratory testing or animal models for benefit / risk assessment.

'Investigational/ new' is the stage when clinical evaluation is conducted in human volunteers before applying for general licensing (e.g. A third phase drug trial).

A technology is considered to be 'established/ accepted' when it is licensed for general use.

Technology becomes 'obsolete', when it is superseded by later developments or considered ineffective or where risks outweigh benefits.

Although technologies may evolve along the simplistic pathways, the real process can be very complex with no clear transition points. The rate of diffusion in this linear model was described by an S-shaped curve with an initial slow diffusion followed by a rapid acceptance till saturation is reached [Feeny 1985]. Except for the highly restrictive world of ethical pharmaceuticals, medical technology rarely followed this orderly progression [Gelijns *et al.* 1994]. Different centres modifying an emerging technology without evaluation may lead to projects becoming established procedures, despite the absence of formal evaluation [Deber 1992]. Timing of an HTA is further complicated by the fact that the stages of the development process are not only influenced by 'technology-push' from research but also by the 'demand-pull' i.e. market forces [Neumann and Weinstein 1991].

Parallel, rapid and non-medical development of a technology which is at an appropriate point transferred for medical use makes it difficult to institute appropriate assessment [Gelijns and Rosenberg 1994]. There is also now diversity in the constitution of technology users beyond enthusiastic clinicians, as health planners, hospital managers and patient-bodies play an increasing role in exercising health-care choices [Mowatt *et al.* 1997b].

A further complexity in the timing of HTA is due to the changes occurring in the early stages of adoption often in an uncontrolled public setting, generating an essential real-world feedback which then helps to reshape and develop it further. A cross-sectional HTA exercise in such cases may be inadequate and sometimes irrelevant to further diffusion and adoption [Gelijns and Rosenberg 1994].

1.2.6 Cost of HTA

In its most well designed and regulatory form, the process of evaluating a new pharmaceutical product for clinical use may cost up to £190 million [Dimasi, *et. al.* 1991]. Though it is reasonably argued, that the societal costs of under-evaluated technologies adopted for common use and subsequently found to be unsafe or ineffective, can far outweigh the initial outlay on assessment and also protect the public from iatrogenic insults (e.g. the thalidomide example) [Annas and Elias 1999].

Interestingly surgical procedures, which involve some of the highest costs, were often found to have the most inadequate forms of systematic evaluation [Love 1975]. Love et al argued that parallels could not be drawn easily between the regulatory mechanism available for drugs and for surgical procedures, as typically surgical procedures evolved with experience and the attainment of manual skills. Thus such evaluation had traditionally taken place in the arena of clinicians' autonomy and evolved through clinical practice [Neumann and Weinstein 1991]. This lack of a systematic evaluation of clinical or surgical procedures perhaps more recently exposed the public to potential risks and the clinicians to libel action and a loss of confidence [Teasdale 2002].

The public perspective of new health care technology is in turn influenced by the media and patient self-help groups. Rigorous evaluation mechanisms impose restrictions on the wider availability of new technology for considerable periods of time. When a major new advance is contemplated over present practice the pressures for its rapid adoption from both the public and professionals can be immense, thus restricting the scope of evaluation. In the 'Viagra' versus the Health secretary case, public pressures for a cure for male impotence were so great that fearing a bankruptcy of the fragile NHS economics, the Health secretary introduced sweeping restrictions on its prescription and use [Klein *et al.* 2002]. This led to animated debates, both in the public and professional domain, as the hastily drawn up restrictions infringed on the clinicians right to seek the

best treatment for their patients. This is a classic example of the importance of the potential role of an early HTA exercise, in both making new advances rapidly available and also to have in place instruments for continual evaluation during and after the adoption and diffusion.

1.2.7 Methods of assessment

1.2.7.1 Categories of HTA

HTA may either be 'primary' involving a direct collection of clinical and cost data from or about patients (usually involves RCTs and epidemiological observation studies) or 'secondary' when it makes use of existing data in the literature (involves systematic reviews and meta-analyses). While economic evaluation (cost-effectiveness or cost-benefit analysis) and ethical, social and legal assessments are carried out in both forms [Donaldson *et al.* 1992].

1.2.7.2 Assessment of clinical effects

1.2.7.2.1 Population health & health care provision

Life is a primary determinant of health; hence the oldest measures of health included a measurement of the length of life. An intervention which prevents the mortality associated with certain diseases can thus be measured by the length of additional survival achieved. On a larger scale, the mortality rate from a certain disease or infirmity provided a measure of the health of a population group and the alteration of this rate by an intervention thus measured its effectiveness. Population health may be assessed in generic terms by measuring the overall mortality rate and hence the life expectancy. Some of the other determinants of health of populations are infant mortality rate, maternal mortality rate and the fertility rate. On the other hand healthcare provision can be assessed at various levels as shown in table 1.1.

Table 1.1: The three main tiers of health care measurement

Tier		Measures
Structure of health care delivery	Administrative, organizational and physical facilities	per capita, advanced equipment, physician to population ratio etc.
Process	Content of healthcare	Bed utilization rates, length of hospital stay, adherence to guidelines
Health status and well-being of patients		Mortality rate, quality of life, morbidity

1.2.7.2.2 Individual health

The health of an individual has been traditionally assessed by measures such as life expectancy, the presence or absence of disease, physiological determinants (like systemic blood pressure), biochemical and haematological markers (blood haemoglobin, serum cholesterol levels) and pain. With a reduction in mortality from diseases such as microbial infections or parasite infestations achieved in the mid-twentieth century in some parts of the world, mortality as an endpoint became insensitive to the subsequent changes in the health states achieved by health care interventions. Hence the impact of chronic conditions on functioning became increasingly important [World Health Organization 1999] [Byrne 1992].

The focus of health provision and its measurement then shifted from laboratory or clinical endpoints to patient-orientated outcomes, like quality of life, relief from pain, absence of anxiety or depression, mental health, physical and social functional capacity and general health status [Slevin *et al.* 1988]. As there were tools developed to measure these specific aspects affecting patients with cancer, chronic arthritis or lung diseases, others measured the overall impact of disease and infirmity on general health, physical, mental or both. An analysis of twenty three studies published between 1975 and 1979 measuring the effectiveness of new health technology using quality of life outcomes, was found to lack seriously in methodology (i.e. failing to represent subjective responses and hence only the professionals' assessment of the impact of treatment on the patient's quality of life)

[Najman *et al.* 1981]. Thus historically the art of measuring individual health has shifted from clinical or laboratory data through professional assessment of impact on patients quality of life to finally patient-based preferences or outcomes, without any influence from the provider of such healthcare.

The inherently subjective nature of such data has been an issue of concern among medical scientists but as the fields of psychometric testing and clinimetrics developed simultaneously, rigorous methods for the development and testing of these quality of life tools have evolved at the same pace [Deyo *et al.* 1991]. There were 1000 articles measuring quality of life in 1995, as health professionals gave increasing attention to the preferences and wishes of patients towards their own healthcare [Rosenberg 1995].

In the current environment of transparency and accountability of medical professionals, health planners and ultimately of government policies to the public, patients rightfully expect to be involved not only in decisions about their individual care, but in formulating priorities and assessment of health care interventions [Siegrist *et al.* 1989].

1.2.7.3 Health Related Quality of Life

Defining quality of life in a form, which offers itself to scientific scrutiny and demonstrates qualities of consistency and reproducibility, is a challenging task. It also needs to encompass the full spectrum of the desirable aspects of life and well-being of all people. In the post World War II era, The Commission of National Goals set up by President Eisenhower of the United States included education, health and welfare, economic and industrial growth and the defence of the free world among the qualities of 'good life' to material affluence and leisure [Anon.1961].

Among all the attributes of a 'good life', health commands a paramount position and is a complex amalgam of satisfactory functioning in all almost all core domains of life, which include psychological, social, occupational and physical. Health technology, which improves quality of life, but has no direct influence on survival, is evaluated by measuring the change in quality of life. There are various tools developed for assessment of health related quality of life (HRQL) as illustrated in table 1.2. The various methods for assessing

quality of life are broadly classified as 'disease specific' or 'generic' allowing for comparisons between patient and disease groups.

Table 1.2 Quality of life assessment tools [Fallowfield 1990]

Type	Description	Example
Performance index	Observation scales usually completed by carer/ physician	Karnofsky Performance Index, WHO Performance status
Self-assessment questionnaires	Visual Analogue Scale Questionnaire	Linear Analogue Self Assessment Nottingham Health Profile, Short Form 36
Scales for Mood States	Assessment of emotional, mental and social well-being	Profile of mood states, Hospital Anxiety & Depression Scale

In recent years, advances have been made in developing and validating measures of HRQL. These combine assessment of various facets of quality of life affected by health and produce aggregate scores allowing comparison and providing along with physiological measures of health a holistic picture [Bergner, 1989].

1.2.7.4 Utility and health status

Advances in medical technology have also created the problem of infinite health needs competing for finite financial resources. There was a need for creating a method of valuing life which combined both the qualitative and quantitative dimensions. Thus the origin of utilitarian theory of health and the delivery of health care is set within the economic limitations; a topic of extensive political, moral and ethical debate. Such an approach might result in the majority of the population being better off but demands that the some may be considerably worse off [Fallowfield 1990].

The Expected Utilitarian Theory was first published in 1944 as a way of rational decision making under uncertainty, included in a theory of games [von Neumann *et al.* 1944]. This theory proposed how an individual ought to make a decision when faced with uncertain

outcomes based on certain axioms which have been rigorously debated over five decades and form the foundation of modern decision theory [Drummond *et al.* 1997].

Axioms for the von Neumann and Morgenstern utility theory

1. Preferences exist and are transitive

For 2 risky prospects y and y'; the individual may either prefer y to y' or y' to y or may be indifferent to both. In the case of 3 choices- y, y' and y"; the individual may prefer y to y' and y' is preferred to y" then y is preferred to y". If the individual is indifferent to y and y' and y' to y" then y is indifferent to y".

2. Independence

This axiom suggests that an individual should be indifferent between a 2 stage risky prospect and its probabilistic one stage equivalent.

3. Continuity of preferences

This axiom suggests that if an individual prefers an outcome x_1 to x_2 and x_3 to x_2, there is a probability p where he/ she becomes indifferent between outcome x_2 with certainty or receiving the risky prospect made up of outcome x_1 with probability p and outcome x_3 with probability (1-p).

There exist basic differences between the normative model to decision making as proposed by the utility theory and observed human behaviour which describes real human behaviour. Utility is a general concept for assessing the value a given individual might place on the consequences of different courses of action. This approach when applied to HRQL provides a numerical value (usually between 0=death and 1=perfect health) to represent the quality or value of an individual's health at a given point in time.

Table 1.3 Methods of utility assessment [Torrance *et al.* 1972b]

Method	Description
Standard Gamble	Requires patients choosing treatment options with varying success to failure risks
Time trade off/ Healthy year equivalents	Trading off years in the present state for years at a better health state
Health & Illness matrix	Rosser & Kind,
EuroQol	were health states valued according to a population derived matrix

The utility values yielded from the above methods combined with the life expectancy of each individual produced the quality adjusted life years (QALY). Hence, the effect of a healthcare intervention would be expressed by the number of QALYs gained. Although the current state of art in QALY measurement does not allow its unequivocal acceptance, it has rapidly become the crucial health measurement in health policy making and resource allocation circles. Unfortunately, even a huge amount of carefully conducted research in to the derivation of QALYs will still not have any relevance at individual level of health care need, specially in the life-saving emergency sector. QALYs may be inconsistent, biased for curative treatments, against the elderly and have different values depending on methods used to generate the utilities [Gafni 1989]. There is also the fear of misapplication of QALY data to rationing of health care [Loomes *et al.* 1989]. Even evidence from different economic scenarios like North America may be used inappropriately in the NHS in the UK [Neumann *et al.* 1997]. Used for its original purpose to help evaluate the effectiveness of treatment or a new technology, utility measurement has a vital role to play, especially with subjective but structured input from patients [Johannesson *et al.* 1994].

1.2.7.5 Economics of health

1.2.7.5.1 Introduction

In its simplest form, health economics is a logical and explicit framework to aid health care workers, decision-makers, governments, or society at large to make choices about how best to use resources [Drummond 1994]. Although the health service is envisaged to provide an equal and universal access to the best possible healthcare, the first real-world situation is that like other resources in society, health care is distributed equitably. It is often a population's view that nearly all health care needs must be provided for, no matter what the costs are. Health planners and purchasers often have to face the dilemma of which technology should be preferred and up to what point health needs can be met, with a majority perspective. Hence it is critical to have a system whereby all dimensions of evaluation are taken in to account in a multi-dimensional approach which includes equity and humanity, as well as effectiveness and economic efficiency [Drummond *et al.* 1996]. Economic appraisal of health technology forms an essential part of this theory. A microeconomic evaluation helps compare the resource implications of alternative health technologies to help assess the most effective solution for the benefit of the maximum number people. Hence, health economics involves a dynamic interaction between medical ethics, humanity and limited resources in a community care scenario [Johannesson *et al.* 1996b].

1.2.7.5.2 Types of economic analyses

At the end of the seventeenth century, Sir William Petty estimated the value of human life to be between £60 and £90 [Petty 1662]. Nearly two centuries later, the value of 'human capital' was estimated as the present value of future earnings minus the maintenance costs to calculate the benefits of therapy [Fitz-enz 2000]. In the mid-twentieth century, the concept of calculating the cost-of-illness emerged followed by cost-benefit analysis (CBA) and cost-effectiveness analysis (CEA) which were developed as applications of classical economic theory to health care [Drummond and Jefferson 1996].

Table 1.4 Methods of economic evaluation [Drummond et al 1997]

Cost-minimisation	Treatments with equal effectiveness, to find the cheapest option	Cheapest treatment option
Cost-effectiveness	Cost of treatment assessed per each unit of health gained	Cost per QALY, days off work, days out of hospital etc.
Cost-utility	Cost of treatment in relation to each year of life gained, adjusted for quality	Cost per QALY
Cost-benefit	Cost of treatment in relation to benefits to patient or society	Monetary units

All methods of economic evaluation value inputs and consequences following the same three step approach of (i) identify inputs and consequences, (ii) measure them in physical units and (iii) and value them.

The importance of conducting economic evaluation is increasing as patients clinicians and healthcare purchasers are rapidly realizing the need for optimizing treatment options in an increasingly cost-conscious environment and scarce resources. Of over 50,000 trials published between 1966 and 1988 only 121 (0.2%) included economic analyses [Adams *et al.* 1992]. This recognition to carry out economic analyses in almost all cases of new HTA development has only recently emerged.

Although the demand for integrating economic evaluation techniques within RCTs is growing as part of healthcare research development, the best model for incorporating this into study design is yet to be established [Sculpher *et al.* 1997]. There is an early introduction of economic analysis in the lifecycle of a new technology development and prior to its diffusion, hence in any carefully designed RCT, economic data is collected from an early stage.

Estimating hidden costs, value of expertise and opportunity costs pose various difficulties in economic evaluation exercises [McNeil 2001]. Especially controversial is the concept of 'discounting', which exists to allow a comparison of immediate costs with future potential benefits [Johannesson *et al.* 1994]. This is based on the premise that an individual would agree to forgo a part of the future benefits if they are accrued now rather than in the uncertain future. Moreover all comparisons made in economic evaluation are based on

'marginal utility' who assumes that costs vary according to the variation in the volume of services or units available and hence comparisons are only valid at a certain set level of variation.

As outcomes are measured in disease specific parameters and usually differ from programme to programme, they cannot be used to make CEA comparisons [Neumann *et al.* 1994]. There may be more than one parameter of interest to different groups of analysts. In order to standardise this approach the CUA was developed by integrating the net effect of various outcomes on the individual into a generic outcome measure. Thus named the 'generalized cost effectiveness analysis' or the 'utility maximization model'. The first coining of the term CUA was established in 1981 in the UK [Drummond *et al.*1997] as the primary method of arriving at the individual preference weights is the utility (as defined by the Utility theory) and in Europe but is still referred to as CEA in the USA [Russell *et al.* 1996].

Randomised controlled trials are regarded as the cornerstone of clinical research [Drummond *et al.* 1991]. Since randomisation not only adjusts for the effects of known biases but also for the unknown. Hence any efficacy claims generated from non-RCT research are currently viewed with caution. RCTs help distinguish between interventions providing moderate clinical benefits with mild deleterious effects (which is the commonest profile of most modern technological advances). However organizing RCTs can be a very difficult logistical task involving huge time and resource allocation. In situations where technology advances rapidly a result from an elaborate RCT may become irrelevant by the time it is reported. Again RCTs are usually carried out on highly motivated and compliant patients in a highly specialized centre hence the results are difficult to generalize in a District General Hospital (DGH) setting, where patient motivation and compliance can vary considerably [Drummond *et al.* 1993]. RCTs provide data on efficacy rather than effectiveness because often the results obtained in tightly controlled research protocols are not readily generisable to real life health care delivery scenarios.

Critics of the RCT argue that in certain situations they may be unnecessary, inappropriate, impossible to implement or inadequate and their faults originate from their origin in the strict scientific methods required in pharmaceutical research. At best, RCTs can form part

of an evaluative inventory which utilizes observational methods like case-control studies, cohort studies and retrospective analyses as appropriate. This concept was supported by Franklin in 1993 [Franklin 1993], who argued that neither RCT nor observational studies can address the complexities of HTA independently; hence they should be regarded as complementary and not competitive. In rapidly changing scenarios, where only a small window of opportunity exists, early observational studies may provide vital evidence to influence diffusion and identify possible implications of adoption [Stocking 1986]. Stocking's model suggests a pattern of clinical evaluation starting at the point when opinion leaders are becoming interested but not yet committed, with a quick inexpensive assessment to determine what potential benefits a new technology may have to offer, followed by observational studies and RCTs as appropriate [Stocking 1986].

1.2.7.6 Non-clinical assessments

In addition to clinical assessments, there is a need for evaluating the economic, legal, ethical and social issues accompanying the adoption of a new healthcare technology [Dolan *et al.* 1993]. This involves a different toolkit and skills compared to clinical assessment. The legal, ethical and social assessment of a new technology may involve interviews with clinicians, public, patients, judiciary and the synthesis of such information in a qualitative analysis. There is an absence of rigorous models for such evaluation as the debate may involve the media, users of the technology and the regulatory authorities. This is especially true in cases for the use of genetic testing for disease potential [Blanck *et al.* 1996], genetic modification of food stuff [Uzogara 2000], pre-natal diagnosis [Bassett *et al.* 2004], organ transplantation [Southern 1989] and human cloning technology [Gilbert 2004]. The Catholic Church has opposed human embryonic stem cell research and any kind of human cloning because they are contrary to the dignity of procreation, of conjugal union and of human embryos [Ohara 2003] arguing on moral implications of health technology. The assessment process may involve discussion and debate [Curtis 2003] with the public and non-governmental agencies [Jin 2000] on moral and ethical implications [Lyngstadaas 2002b] before such technology is widely adopted.

1.2.7.7 Assessing different types of technology

Rigorous methods for assessing clinical efficacy through the RCT evolved within the strict regulatory atmosphere of pharmaceutical development and this approach has been professed in other types of health technology including surgical or clinical procedures, medical informatics and diagnostic techniques. However, this is not widely accepted and there are various guidelines proposed for the evaluation of diagnostic technologies, [Guyatt *et al.* 1986]medical imaging, surgical procedures, picture archiving and communication systems [Banta *et al.* 1994].

1.2.7.8 Summary of HTA

Governments are now faced with the impact of technology push with newer and more effective and inevitably expensive innovations for the purpose of improving health care. This is combined with the demand pull from public and professionals expecting the rapid and widespread implementation of innovative healthcare products. The balance with other competing priorities for public expenditure such as defence, education and infrastructure building tends to introduce the angle of societal and political imperatives on clinical and cost-effectiveness. Hence HTA programs are designed and implemented not only to identify new and emerging technologies with a potential of delivering improved health care to the general public, but also to ensure their safety and effectiveness and finally to ensure a 'value for money' for public expenditure. In times when the focus of health care provision has largely shifted from reducing mortality from infectious diseases to health promotion and primary prevention and the improvement in quality of life; the HTA of CPAP in SAHS patients gives an opportunity to formulate a generic pathway for assessment of similar technologies designed to improve primarily quality of life parameters in a large section of the adult public afflicted by chronic disease.

1.3 SLEEP APNOEA HYPOPNOEA SYNDROME

1.3.1 Introduction

This section reviews the various aspects of the SAHS covering the epidemiological, pathophysiological, and clinical, HRQL and economic issues. This will be followed by an analysis of the treatment pathways for patients and review the evidence available to date on the efficacy and effectiveness of various options, introducing the case of CPAP as a technological innovation. This will then set the scene for the HTA of CPAP in SAHS patients as has been researched and presented through this thesis.

1.3.2 History of sleep apnoea research

SAHS is characterised by repetitive partial or complete obstruction of the upper airway during sleep, leading to daytime consequences of hyper somnolence, an increased risk of accidents and impairment of general health status. The syndrome definition has evolved and expanded since the latter part of the nineteenth century. Sir Charles Dickens is credited with the most well-known and picturesque description of some of the features associated with this syndrome in the English language, in his sleepy red-faced boy Joe, in the novel *'The Posthumous papers of the Pickwickian Club'* published in 1837 [Dickens 1837].

The earliest scientific account of apnoeas during sleep dates back to W. H. Broadbent in 1877 when he recognized and described a case of snoring and periodic breathing in a sleeping patient (Cheyne-Stokes respiration) following cerebral haemorrhage [Broadbent 1877]. It was eleven years later that Richard Caton presented a classical case-report of a 37 year-old patient with daytime sleepiness, obesity and apnoeas in sleep, observed by the night nurse [Caton 1889]. In the same year, Morison reported chronic daytime sleepiness in a 63 year-old man, with his own observation of apnoeic events during sleep, disagreeing with Caton's diagnosis of narcolepsy for his patient [Morison 1889].

Even in 1889, Christopher Heath the president of the Clinical Society of London, recognized the characteristic similarity to sleepy Joe in the Dickens' novel with the case described by Richard Caton [Caton 1889;Lavie 1984]. The term *'Pickwickian'* was coined

by Osler in 1918 in association with obesity. Another early reference to the Dickensonian fat-boy Joe comes from the writing of Bramwell in 1909, when he describes a fat, somnolent postal delivery boy who tends to fall asleep on the box, raising the possibility of an accident and the grounds for a medico-legal dispute with the insurers, knowing of the boy's condition [Bramwell 1909]. Thus by the turn of the twentieth century, the association of obesity, snoring, nocturnal respiratory disturbance and daytime somnolence was increasingly recognized.

However considerable confusion and overlap existed for the next few decades with obesity related hypoventilation, Cheyne-stokes breathing, respiratory failure during sleep and narcolepsy. While Caton in 1889 mislabelled his patient with probable sleep apnoea as narcolepsy and Spitz in 1937, reported features of obesity, cyanosis, excessive daytime sleepiness and right-sided heart failure in 3 patients, who were also incorrectly labelled as 'narcoleptics' [Spitz 1937]. Burwell et al in 1956, reported an obese, somnolent, polycythaemic patient as resembling the character Joe and hence having the '*Pickwickian syndrome'* but without citing any nocturnal breathing disturbance [Burwell *et al.* 1956].

Thus the hypothesis in the mid-twentieth century centred around obesity which increased the mechanical load on the respiratory system, which in turn blunted the respiratory centre resulting in hypoventilation. The hypercapnoea and hypoxaemia caused by hypoventilation in turn explained the consequences of daytime somnolence, cyanosis, periodic respiration, and polycythaemia and right-heart failure [Kryger 1983].

The first scientific team to identify and record repeated apnoeas in sleep among patients labelled as having the *'Pickwickian syndrome'* were Gastaut et al in 1966 [Gastaut *et al.* 1966], who postulated the causative link with daytime consequences. They were also perhaps the first to suggest that obesity related cardio-respiratory syndrome was probably responsible for the cyanosis, polycythaemia and right-ventricular failure seen in the Pickwickian syndrome described by Burwell et al and was unrelated to apnoeas in sleep. Thus SAHS was established as a distinct physiological entity from obesity-related alveolar hypoventilation (or 'Pickwickian syndrome').

In Hindu mythology, when *Ravana* wanted his brother *Kumbhakarna's* help in his epic battle against *Rama*, it required the beating drums, piercing with sharp instruments and then finally a thousand elephants marching across his chest to wake him [Dharma 2000].

The earliest recorded form of treatment for daytime somnolence, which was the most striking feature of patients with the sleep disordered breathing, dates back to the needles of *Dionysius,* the Heracleote, born in 360BC. His physicians ordered a novel remedy to awake him from sleep and thus rid him of his shortness of breath and choking, by piercing his belly with very long and small needles till they had passed through the fat and reached firm flesh, and thus he felt it and awakened [Aelianus 1666].

Since the nineteenth century, extreme obesity has been linked with disease and death, hence weight loss was advocated and reportedly improved symptoms, in patients as far back as 1816, as reported by William Wadd in his '*Cursory remarks on Corpulence*' [Wadd 1822]. Caton in 1889 treated his patient with considerable doses of naphthalene, iodoform and charcoal, which reduced drowsiness and his weight much to the delight of the patient who could then read a newspaper for half-an-hour at a time [Caton 1889].

Wells in 1898, identifying the link between obstructed nasal breathing and daytime somnolence, treated 10 patients surgically removing the nasal obstruction with a relief of somnolence in each and everyone of them [Wells 1898].

1.3.3 Definition

Earlier definitions relied on the unmistakable apnoea caused by the upper airway collapse for the definition of 'Obstructive sleep apnoea' [Guilleminault *et al.* 1976]. The recognition of partial closures or hypopnoeas causing arousals or sleep disruption led to their incorporation in the definition of the SAHS. Hypopnoeas are defined as a 50% reduction in oro-nasal airflow (or frequently estimated using surrogate measures such as change in temperature across oro-nasal thermistors, chest or abdominal excursions etc) from baseline lasting more than ten seconds. They may or may not be accompanied by a 3-4% desaturation of arterial oxygenation and electroencephalographic evidence of arousal [Gould *et al.* 1988].

The net result of such compromise of the upper airway patency during sleep or significant increase in the upper airway resistance leads to repetitive disruption in the continuity of nocturnal sleep. This is manifest by a well-recognized alteration in the electroencephalogram recording known as arousals. Again, variation exists in the

definition of arousals based on their duration ranging from 1.5 to 10 seconds [Bonnet *et al.* 1992]. In turn nocturnal sleep disruption leads to daytime consequences primarily manifest as hyper somnolence.

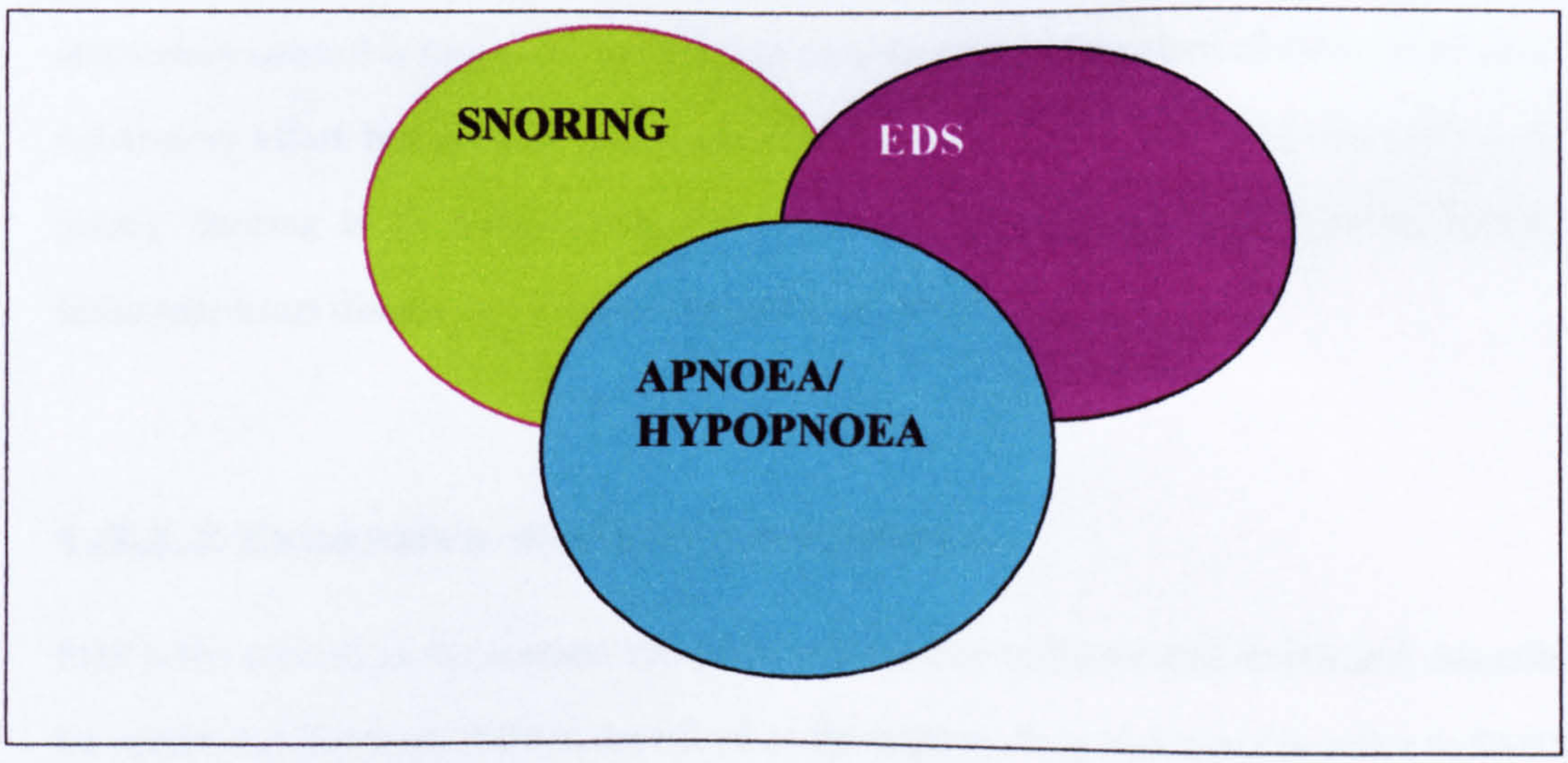
The most recent consensus document trying to define the syndrome is from the American Academy of Sleep Medicine published in 1999 which (detailed in Chapter III) defines SAHS as combination of the symptoms of sleep fragmentation (snoring and / EDS) in the presence of apnoeas / hypopnoeas of at least 5 $hour^{-1}$ during sleep [American Academy of Sleep Medicine 1999].

1.3.4 Epidemiology

1.3.4.1 Prevalence of snoring, EDS and SAHS

Population based studies of the prevalence of SAHS are closely interlinked with associated snoring and EDS as these are essential components of the syndrome definition. Habitual snoring is reported by 19-35%of men and almost half of that in women. An AHI ≥ 5 $hour^{-1}$ was found in 11-24% of men and in 6-9% of women. Thus the prevalence of SAHS (EDS + AHI ≥ 5 $hour^{-1}$) was 1-2% in women, 2-4% in men [Duran *et al.* 2001;Jennum *et al.* 1992;Ohayon *et al.* 1997;Young *et al.*1993]. The percentage of subjects with EDS increased from 21% in subjects with AHI < 5 to 35% in those with AHI ≥ 30 [Gottlieb *et al.* 1999].

Figure: 1.1 Venn diagram showing the overlap of EDS, Snoring and nocturnal breathing disturbance constituting SAHS



1.3.4.2 Under-diagnosis

It is estimated that a large proportion of patients with clinically significant SAHS remain undiagnosed. In a sample of 4,925 employed adults, questionnaire data on doctor-diagnosed SAHS was followed up to ascertain the prevalence of diagnosed SAHS with in-laboratory polysomnography on a subset of 1,090 participants. In this population, without obvious barriers to health care for sleep disorders, it was estimated that 93% of women and 82% of men with moderate to severe SAHS were not clinically diagnosed [Young *et al.* 1997c].

1.3.5 Clinical presentation

1.3.5.1 Snoring

The two most frequently reported symptom of SAHS are loud habitual snoring and EDS and hence often constitute the main reason for a patient seeking medical advice. Snoring is often described as a coarse, harsh respiratory sound typically caused by vibration of the uvula and the soft palate [American Thoracic Society 1989]. Snoring represents a mechanical loading of the upper respiratory system that can produce sleep disruption. Snoring has been further categorised into mild, moderate and severe depending on frequency, intensity, body position and disturbance to others.

Snoring is a common symptom in the community and increases in prevalence with male sex, age and a high body mass index (BMI), smoking, caffeine and the consumption of alcohol [Ohayon, *et al.*1997; Stradling *et al.* 1989]. In later stages of SAHS, when respiratory control is impaired, the drive to breathe may be impaired allowing little or no respiratory effort being made and hence snoring is no longer produced [Gottlieb *et al.* 2000]. Snoring is an independent risk factor for hypertension [Young *et al.* 1996a], Ischaemic heart disease and strokes [Shepard, Jr. 1992].

1.3.5.2 Excessive daytime sleepiness

EDS is the second most common symptom reported by patients with SAHS and essential for syndrome diagnosis. EDS is described as the urge to sleep and is not peculiar to SAHS

but a common phenomenon related to poor nocturnal sleep or sleep deprivation. Studies of sleep disruption induced by auditory tones in normal volunteers have indicated that minimal arousals reflected in electroencephalographic (EEG) criteria even without true awakening can impair daytime performance and cause daytime sleepiness.

The pathophysiology of EDS in SAHS patients was initially thought to be a function of hypoxia and hypercapnoea which occurred as a result of upper airway occlusion via receptors in the medulla, carotid body and the nasopharynx. Arousal is thought to be caused by activation of the reticular activating system through neuronal inter-connections, however these postulates have been difficult to prove [Berry *et al.* 1997]. Later studies have shown evidence that large intra-thoracic pressure swings generated when an apnoeic subject strains to breathe against a nearly closed gullet causes sleep fragmentation and EEG arousals [Wiegand *et al.* 1989]. This concept has now been extended to show that upper airway resistance (UAR) leading to an increased ventilatory effort during sleep is also associated with sleep fragmentation and hence daytime consequences on function and EDS similar to patients with SAHS [Montserrat *et al.* 2001].

Unlike objective measures of EDS (i.e. multiple wakefulness test, multiple sleep latency test and less slow wave sleep) the severity of self-reported EDS is not linearly related to the degree of physiological SAHS (AHI) [Sauter *et al.* 2000] and may fail to discriminate between snorers and SAHS patients [Osman *et al.* 1999]. Thus aetiology of EDS in patients with SAHS is not well established although sleep fragmentation and reduction in SWS are the most likely mechanisms [Punjabi *et al.* 1999]. Although poorly understood, there is some evidence that nocturnal sleep apnoea without daytime symptoms or deterioration in HRQL may not respond to treatment, strengthening the need for EDS in the syndrome definition [Barbe *et al.* 2001].

Table 1.5: Presenting symptoms of SAHS [Stradling 1995a]

Most common	Less common	Rare
Loud snoring	Nocturnal choking	Enuresis
Excessive daytime sleepiness	Reduced libido	Recurrent arousals/ insomnia
Restless sleep	Nocturnal sweating	Nocturnal cough
Un-refreshing sleep	Morning headaches	Gastro-oesophageal reflux disease
Nocturia		
Personality changes		
Witnessed apnoeas		

1.3.6 SAHS & Co morbidity

1.3.6.1 Obesity

Overweight and obesity represent a rapidly growing threat to the health of nations replacing more traditional problems such as under-nutrition and infectious diseases as the most significant causes of ill-health. Obesity is associated with coronary artery disease (CAD), hypertension and stroke, types of cancer, non-insulin-dependent diabetes mellitus (NIDDM), gallbladder disease, dyslipidaemia, osteoarthritis and gout, and pulmonary diseases, including SAHS. A WHO sponsored international consultation exercise concluded; that the fundamental causes of the obesity epidemic were sedentary lifestyles and high-fat energy-dense diets [Anon.2000].

Obesity and SAHS have been historically linked closely together and in turn are considered to be contributing to increased prevalence of hypertension, IHD and Insulin resistance in diabetes mellitus. In obese patients, upper airway soft tissue enlargement may play a more important role in the development of obstructive SAHS [Whittle *et al.* 1999], whereas in non-obese patients, bony structure discrepancies may be the dominant contributing factors for SAHS [Sakakibara *et al.* 1999].

1.3.6.2 Systemic hypertension

SAHS is an independent risk factor for the development of hypertension. Data from cross-sectional studies show a progressive increase in mean blood pressure with an increase in AHI suggesting a dose response link [Grote *et al.* 2001]. AHI has been shown to predict

daytime ambulatory diastolic blood pressure (DBP), nocturnal ambulatory systolic blood pressure (SBP) and DBP [Lavie *et al.* 2000]. SAHS is also a risk factor for drug resistant hypertension, independent of obesity and age [Lavie *et al.* 2001]. In the Sleep Heart Health Study with 6132 subjects the odds ratio for hypertension, comparing the highest category (of AHI ≥ 30 hour^{-1}) with the lowest category (AHI < 1.5 hour^{-1}), was 1.4 [Nieto *et al.* 2000].

Although age, obesity, smoking and alcohol consumption are known to confound the link between SAHS and hypertension in primary care based studies [Stradling *et al.* 1990], there is prospective randomised trial evidence linking SAHS with development of systemic hypertension, in normotensive patients with SAHS over 4-5 years [Wright, Jr. *et al.* 2001] [Peppard *et al.* 2000].

1.3.6.3 Cerebrovascular disease

SAHS is more frequently reported in association with strokes and transient ischaemic attacks (TIA) [Bassetti *et al.* 1996]. SAHS is known to be frequent during the first night after cerebral infarction (62%) and is associated with early neurological worsening [Iranzo *et al.* 2002]. Cerebral infarction onset during sleep is also associated with the presence of moderate to severe SAHS (AHI ≥25 hour^{-1}) [Bassetti *et al.* 1999].

SAHS is a well-established complication of stroke involving the brainstem. Diffuse cerebral symptoms such as cognitive deficits, depression or fatigue after a hemispheric stroke may mimic SAHS symptoms. Sleep is fragmented because of the presence of increased AHI (>50 hour^{-1}) majority being obstructive apnoeas and associated with arterial oxygen desaturations (Sao_2) and arousals [Mohesenin, 1995]. In the Sleep Heart Health Study the risk of stroke was 1.6 times higher in SAHS (AHI>5 hour-1) then normal subjects [Shahar *et al.* 2001] although there is as yet no prospective evidence to suggest that SAHS is causally linked to strokes [Neau *et al.* 2002].

1.3.7 Consequences of SAHS

1.3.7.1 SAHS & Driving

Sleepiness is recognised as a common cause of road traffic accidents (RTA) with a consequent human and economic cost to the individual and society. Sleepiness while driving maybe a manifestation of EDS and has a multi-factorial aetiology from sleep debt or deprivation and insomnia to sleep disorders causing sleep fragmentation [Aldrich 1989; Horne & Reyner 1995]. Sleep related accidents are considered when there is no sign of avoidance or braking and are more commonly high speed, single-vehicle accidents. The proportion of patients with severe SAHS who had sleep-related accidents was almost 2-7 times that of patients with mild or moderate SAHS, although MSLT sleep latency did not differ significantly in patients with accidents and those without [Haraldsson *et al.* 1990;Teran-Santos *et al.* 1999].

None of the clinical or physiological markers commonly used to define disease severity were able to discriminate those patients at higher risk of having an automobile accident [Barbe *et al.* 1998].

1.3.7.2 Health related quality of life

SAHS is a cause of generalized fatigue, poor motivation and HRQL deterioration [D'Ambrosio *et al.* 1999]. In a qualitative analysis using semi-directive interviews with a trained psychologist, patients with severe SAHS spoke mainly of abnormal fatigue and somnolence. Many had problems with obesity, snoring related problems and depression. Patients had problems with relationships and sex and were concerned about loss of memory and the fear of dying [Veale *et al.* 2002]. SAHS has been reported to be an independent predictor of amount of sick leave, impaired work performance and divorce rate [Grunstein *et al.* 1995].

All dimensions of HRQL were found to be significantly impaired when compared with an age- and gender-matched population [Bolitschek et. al. 1998]. SAHS not only affects the individual adversely but also partners who frequently report moderate to severe

disturbance from patient snoring/apnoeas/restlessness and had poor sleep quality and self- reported health status [McArdle *et al.* 2001b].

Participants in the US population- based Sleep Heart Health Study reported poorer HRQL scores on several Short Form 36 (SF-36) scales although energy/ vitality was the only subscale which correlated with AHI [Baldwin *et al.* 2001]. Whereas it is advantageous to demonstrate the HRQL deterioration in SAHS patients utilizing already established generic HRQL instruments like the SF36, the problem lies in different countries using different approaches which have the potential to yield variable results. This in turn would make comparisons of effectiveness difficult due to a lack of consistency between the effect sizes obtained using different instruments. This is illustrated well by a study examining three generic approaches to the measurement of patient-reported health status: the Patient-generated Index (PGI), the European Quality of Life Questionnaire (EuroQol) and the SF36. Of 100 patients with mild to moderate SAHS approached, 86-89% responded with SF-36 summary scale scores being lower than those of the general population at baseline, but had improved to the normative levels after treatment. The EuroQol showed no decrement at baseline and no change with treatment and was considered to lack sensitivity to the type of HRQL decrements expected in SAHS patients [Jenkinson *et al.* 1997b].

When disease specific questionnaires have been used like the Calgary Sleep Apnoea Quality of Life Index (SAQLI), this was found to have a high responsiveness index of 1.9 and an effect size of 1.1, which was much greater than the domains of the generic questionnaires like the SF-36 and the Functional Profile Quality of Life Index [Flemons *et al.* 2002].

HRQL data (whether generic or disease specific) has been now incorporated in assessing the effectiveness of therapy for SAHS, as the main goal of treatment in these patients tends to be symptomatic benefit. However there is no clear relationship demonstrated between the HRQL scores obtained with physiological parameters of nocturnal sleep disturbance, hence the causal mechanism of HRQL deterioration remain to be established [Barbe et. al. 2001]. The large overlap between the poor HRQL suffered by patients with obesity, depression and other co morbid diseases makes the interpretation of the HRQL changes difficult. Different generic measures of HRQL show variable effect sizes

depending on which measure is used and in which population. The therapeutic benefits measured in SAHS are not wholly conducive to comparison with gains obtained with competitive health care intervention strategies. This in turn makes the work of health policy prioritising difficult.

1.3.7.3 Mortality

SAHS has been implicated in epidemiologic studies as an important risk factor for cardiovascular disease which is the primary cause of death in males. There is a greater incidence of hypertension and atherosclerosis related diseases such as stroke, angina, and acute myocardial infarction [Mooe *et al.* 2001]. However, obesity is a common association and is argued by some to be the etiological factor for both SAHS and cardiovascular morbidity. There is shortened longevity seen in patients with untreated or inadequately treated SAHS [Fletcher 1996c] and there are pathophysiological factors thought to account for this early mortality, like sudden death during sleep (arrhythmia) or even fatalities from sleep related automobile accidents. The reason that the association between SAHS and cardiovascular disease remains unclear is that the relationship thus far is demonstrated only by epidemiological association and not yet convincingly by mechanisms showing a cause-effect relationship. Although the overall mortality among SAHS patients is reported to be similar to the general population, a significant excess of cardiovascular deaths and an excess of deaths from accidents and poisonings was found [Veale *et al.* 2000].

The presence of obesity can confound the interpretation of data obtained from un-controlled trials into the association of SAHS and mortality. Autopsy of 34 obese men with sudden death demonstrated that those with a history of SAHS have a high risk of sudden cardiovascular death, despite the absence of other conventional risk factors [Rossner *et al.* 1991]. Cardiovascular cause of death was more common among those who snored habitually or often than among those who snored occasionally or never, while 'habitual' snorers died more often while sleeping or in the early morning [Rajala *et al.* 1991].

There is some evidence that increased mortality may be linked to the severity of nocturnal sleep disturbance, when other confounding variables have been accounted for [He *et al.* 1988].

1.3.7.4 Neuro-cognitive dysfunction

SAHS is most frequently associated with reduced concentration and recent memory (verbal, visual and spatial) loss, along with increased prevalence of mental stress, depression and anxiety [Borak *et. al.*1996]. Patients also have longer reaction times and poor vigilance in driving simulation testing [Munoz *et al.* 2000]. Appropriate treatment is reported to show either improvement in cognitive performance, vigilance, mental flexibility and attention [Henke *et al.* 2001].

As depression and neuro-cognitive dysfunction remain important determinants in SAHS, these are important issues to be addressed in any assessment of the benefits of health care intervention strategies. There are traditional instruments used in neuropsychiatric research as the Hospital Anxiety and Depressions Scale (HADS) [Bjelland *et al.* 2002] and the General Health Questionnaire (GHQ) [Goldberg *et al.* 1988] which may provide a measure of the prevalence of psychiatric disorder and the effect of treatment.

1.3.8 Treatment of SAHS

1.3.8.1 Aims of treatment

The primary goal of treatment in individual patients is to improve their EDS and daytime function [Scottish Intercollegiate Guidelines Network 2003]. Treatment has an impact not only on HRQL [Ballester *et al.* 1999] but on morbidity and mortality associated with accidents both on the road and at work [Cassel *et al.* 1996a], although there is limited RCT evidence of this as yet [Wright and Dye 1995]. Presently there is little evidence for treating otherwise healthy and asymptomatic individuals simply on the basis of a nocturnal sleep breathing disorder [Scottish Intercollegiate Guidelines Network 2003]. However there is an epidemiological risk of developing hypertension [Peppard *et*

*al.*2000] and secondary CAD in patients with SAHS [Peker *et al.* 1999], regardless of symptomatology. Patients already at increased risk with a combination of co-existent obesity, hypertension, cardiovascular and cerebrovascular disease along with diabetes are more likely to benefit from treatment of their concomitant SAHS [Wilcox *et al.* 1998], with improvement not only in HRQL [Flemons *et al.* 1997a] and daytime function [Engleman *et al.* 1994a] but perhaps also in a reduction in mortality [Fletcher 1996a].

1.3.8.2 Surgical treatment

Surgical treatment for SAHS has ranged from early tracheostomy [Cohen *et al.* 2002] with genioglossus mobilisation, maxillo-mandibular advancement [Cohen *et al.* 1998], and nasal surgery [Salib *et al.* 2000] to the more recent laser assisted Uvulopalatopharyngoplasty (UVPPP) [Ikeda *et al.* 1997]. Although there is some evidence of improvement in symptoms and a reduction in AHI seen among these patients the impetus has currently shifted towards minimally invasive techniques. These include radiofrequency ablation of the uvula and soft palate to reduce the inherent collapsibility of the pharyngeal airway [Masood *et al.* 2001]. There are no RCTs comparing surgical treatment in SAHS hence no evidence based recommendations which are free of statistical regression to mean errors [Scottish Intercollegiate Guidelines Network 2003]. A meta-analysis of smaller studies of the effectiveness of UVPPP [Verse *et al.* 2000] concluded that there was possibly a 50% benefit in 50% cases based on subjective measures, hence current best practice guidelines do not recommend routine use of surgical techniques for SAHS patients [Scottish Intercollegiate Guidelines Network 2003]. The techniques and evidence surrounding these surgical treatment options are beyond the scope of this thesis and hence have not been discussed here.

1.3.8.3 CPAP therapy

CPAP therapy was first used in the treatment of SAHS in 1981 in Australia [Sullivan, Issa, Berthon-Jones, and Eves 1981]. CPAP dilates the upper airway using intra-luminal high pressure air during the breathing cycle, counteracting the normal predominantly collapsing forces in the pharynx, thus preventing airway narrowing and collapse. This high pressure is generated via a compressor and delivered to the patient through a tight

fitting nasal/ full face mask, which in the original experiment the nasal mask was fixed with a silicone adhesive each night.

1.3.8.3.1 Benefits of CPAP therapy

1. Sleep & symptoms of SAHS

Sleep architecture in SAHS patients is characterized by a reduction in SWS in the early part of the night and this is correlated with a reduction in sleep latency recorded in the MSLT. After CPAP therapy, SAHS patients significantly increased their mean SWS in the first and second sleep cycles and restored a more physiologic decay of SWS across the night [Heinzer *et al.* 2001]. Patients on CPAP show significant reductions in the symptoms of EDS, restless sleep, heartburn, nocturia, enuresis, headache and nocturnal sweating [Kiely *et al.* 1999] [Tiihonen *et al.* 1998].

Although obesity is closely inter-linked with SAHS, patients on CPAP and conservative weight loss therapy were shown to have a six times higher odds ratio of successful treatment compared with weight loss alone [Ballester *et al.* 1999].

In long term use more than 80% of 3225 respondents in a French population study reported that CPAP treatment had greatly improved their symptoms (based on Nottingham Health Profile scores) [Meslier *et al.* 1998]. Other studies demonstrated improvements in AHI, emotional reactions and energy [Sanner *et al.* 2000] and in HRQL (energy/ vitality, physical and mental component summary dimensions of the SF36 and the sleep and rest dimension of the FLP) [Stradling et. al. 1996].

Asymptomatic patients with significant SAHS [Barbe *et al.*2001] or symptomatic mild SAHS patients are reported not to show any improvement in EDS with treatment [Engleman et. al. 1997a], hence currently treatment is not recommended for asymptomatic patients [Scottish Intercollegiate Guidelines Network 2003].

2. Cardiac Function

Two different studies involving a total of 83 patients with SAHS demonstrated a significant improvement in left ventricular diastolic function and a drop in blood pressure in SAHS patients [Alchanatis *et al.* 2000;Fung *et al.* 2002].

3. Accidents

CPAP treatment has been shown to reduce the rate of RTAs [Young *et al.* 1997b] including both real and near-miss accidents along with a reduction in accident related hospital stay [Kryger 1997].

There are limitations in designing randomized studies to assess the benefit of treatment on real RTAs; hence studies have used surrogate performance measures in driving simulators [George *et al.* 1996]. Untreated SAHS patients, whose baseline performance had been worse than controls in all measures [Turkington *et al.* 2001], improved significantly after CPAP treatment, particularly in 'tracking error' which returned to the level of controls [George *et al.* 1997].

4. Neuro-psychiatric function

CPAP treatment has been shown to improve mood and cognitive performance especially in improved vigilance, mental flexibility (trail-making B time) and attention [Engleman *et al.* 1994b]. Some patients with affective disorders (anxiety & depression) have been shown to improve with CPAP treatment [Yamamoto *et al.* 2000] while others have reported no change in their emotional status [Borak *et al.* 1996]. The cognitive dysfunction is shown to be more closely related to EDS then to underlying AHI [Cohen-Zion *et al.* 2001]. Deductive thinking and verbal attainment were more severely impaired in SAHS when compared to patients with Alzheimer's disease, while impairment in constructive ability and immediate memory were comparable [Antonelli Inc *et al.* 2004].

1.3.8.4 Oral appliances for the treatment of SAHS

Oral appliances present a useful alternative to CPAP, especially for patients with simple snoring and patients with SAHS who may not be able to tolerate CPAP therapy [Scottish Intercollegiate Guidelines Network 2003]. They work on the principle of moving the mandible forward thus stretching open the oro-pharyngeal airway and positioning the tongue forward, preventing its inherent tendency to fall back and obstruct the airway [Marklund *et al.*2004]. This maybe titrated by advancing 1 mm every week until there is a

resolution of the symptoms and a reduction in the oxygen desaturation index (ODI) [Fleury *et al.* 2004].

These tend to be more effective in female [Battagel *et al.* 1999], younger patients with normal BMI presenting with a history of snoring and/or mild hypopnoea [Liu *et al.* 2000;Verse *et al.* 2003]. Although the reduction in AHI was less when compared to CPAP [Barnes *et al.* 2004], patients reported improved EDS and preferred using an oral device over CPAP in a cross-over study [Clark *et al.* 1996].

A Cochrane review of 7 trials involving 177 SAHS patients found that although it was less effective than CPAP, patients strongly preferred the oral appliance to CPAP (odds ratio 9.5) [Wright and White 2000].

When compared with UVPPP, mandibular advancement has been shown to be more effective but with less patient contentment [Wilhelmsson *et al.* 1999].

1.3.8.5 Lifestyle Interventions in SAHS

Sleep and SAHS are closely related to lifestyle influences from sleep opportunity, work, mental stress, jet travel, sleep hygiene factors, obesity, and consumption of alcohol, smoking and drug use. These lifestyle factors tend to cause EDS, generalised fatigability and confound intervention studies in SAHS [Shneerson and Wright 2001] if they are not specifically corrected for in analyses. There is as yet little evidence of the influence of lifestyle intervention in SAHS [Shneerson & Wright, 2001] and hence the next section reviews the current evidence and identifies the key features which may be incorporated into an intervention study.

1.3.8.5.1 Sleep hygiene

The daytime performance, EDS and chronic fatigue are in turn linked with the qualitative and quantitative aspects accompanying nocturnal sleep and the influences on it. Hence conservative measures to improve nocturnal sleep have an important contribution in the treatment of patients with SAHS. The evidence for sleep promotion measures comes from research into behavioural strategies for the treatment of insomnia but are equally applicable in other sleep disorders for promotion [Becker *et al.* 1993;Blake *et al.* 1998]. The factors affecting sleep quality and quantity are;

1.3.8.5.1.1 Psychological Factors

Stress is considered by most sleep experts to be an important cause of short-term sleeping difficulties [Breslau *et al.* 1995]. Common triggers include school or job-related pressures, family or marital problems, and serious illness or death in the family. Usually the sleep problem disappears when the stressful situation passes. However, if short-term sleep problems aren't managed properly right from the beginning, they can persist long after the original stress has passed and are increasingly associated with chronic depression [Breslau *et al.* 1995].

1.3.8.5.1.2 Lifestyle Stressors

These include drinking alcohol or beverages containing caffeine in the afternoon or evening [Taillard *et al.* 1999], exercising close to bedtime, following an irregular morning and night-time schedule [Knutsson 2003], and working or doing other mentally intense activities right before or after getting into bed. Jet lag [Brown *et al.* 2001] and shift work contribute adversely to the quality of sleep and subsequent performance. It is difficult to reset the internal circadian clock and not surprisingly 10- 20% of night shift workers report falling asleep on the job, usually during the second half of the shift [Harma 1996]. They may also find it difficult to sleep during the day, even though they are tired [Phillips *et al.* 1991]. Hence adherence to a sleep routine is shown to help sleep.

1.3.8.5.1.3 Environmental Interferences

A distracting sleep environment such as a room that's too hot or cold, too noisy or too brightly lit [Schnelle *et al.* 1998], the comfort and size of beds [Ancoli-Israel 1997] and the habits of the sleep partner can be a barrier to sound sleep. In a study comparing structured sleep hygiene measures in combination with light therapy and exercise all subjects showed a trend toward improvement, independent of the treatment received [Guilleminault *et al.* 1995].

1.3.8.5.1.4 Physical factors

A number of physical problems can interfere with the ability to fall or stay asleep like arthritis and other conditions that cause pain or discomfort [Bloom *et al.* 2002] and so can breathing disorders such as asthma and Chronic obstructive airways disease (COPD)

[Bohadana *et al.* 2002], hormonal shifts including those that cause premenstrual syndrome [Lee-Chiong, 2004] or menopause [Empson *et al.* 1999] and pregnancy [Maasilta *et al.* 2001].

1.3.8.5.1.5 Drugs & Alcohol

In addition, certain commonly used drugs such as steroids, antihypertensives, bronchodilators and can cause sleeping difficulties [Obermeyer *et al.* 1996]. The effect of alcohol on sleep is dose dependant usually causing central nervous system stimulation and dis-inhibition in smaller quantities leading to a stuporous state in excess [Issa *et al.* 1982]. Typically, these individuals take a longer time to fall asleep and show decreased sleep efficiency, shorter sleep duration and reduced amounts of SWS when compared with healthy controls. Their sleep patterns are fragmented, and the typical time course of EEG delta wave activity is severely disrupted. The amount of REM sleep may be reduced or increased. Sleep changes can persist during months or years of abstinence, and recent studies indicate that certain alterations in sleep architecture, as well as subjective sleep complaints, predict relapse to alcoholism [Landolt & Gillin, 2001]. Long term alcohol consumption causes significant interactions with Stage 1 sleep percentage, SAHS and periodic limb movements, with older subjects having the most disturbances [Brower *et al.* 2001] .

1.3.8.5.1.6 Time for sleep

Eveningness was associated with an irregular sleep/wake habit and greater caffeine consumption. Subjects built up a sleep debt during the week and extended their duration of sleep at the weekend [Taillard *et al.*1999]. A temporal discrepancy between the endogenous sleep-wake cycle and the daily structure of the surrounding social network are characteristic for chronobiological sleep disturbances. Structuring daily activities by paying attention to natural daylight (dawn and dusk) and to the social routine strengthen the synchronizing effect of external timekeepers necessary for the concordance between inner and outer rhythmic phenomena.

Table 1.6: Advice on sleep hygiene adapted from the National Sleep Foundation, USA 1999 [Alward 1995; National Sleep Foundation 1999]

BEDTIME RITUALS

Take a warm bath.

Lower the room temperature (a cool environment improves sleep).

Don't "activate" your brain by balancing a check book, reading a thriller, or doing other stressful activities or watching television in bed.

LIGHT

Light is one of the main sources of stimulus for the inherent chronobiological rhythm and simple measures to darken the bedroom and bathroom helps induce sleep and prevent early awakening.

Install light blocking and sound absorbing curtains or shades.

Wear eye shades.

SOUND

Wear ear plugs.

Gentle soothing music or a white noise source (like a fan) may help to reduce the effect from other noises.

Sound proofing of the bedroom allows less external interference (Install carpeting and drapes to absorb sound).

Avoid interference from telephones etc.

FOOD

Avoid caffeine, nicotine or tannin (which are stimulants for the central nervous system) less than five hours before bedtime.

Avoid alcohol before bedtime as it may help induce sleep but in the long term or in excess affects sleep architecture and worsens snoring and sleep apnoea.

Light snack before bedtime is considered to be better than either extremes of an empty/ full stomach.

EXERCISE

Exercise promotes alertness and raises the body temperature and hence should be avoided for at least 3 hours before bedtime.

Daytime naps usually reduce continuity of nocturnal sleep and should be avoided.

1.3.8.5.2 Impact of weight loss on SAHS

The ideal management for an obese patient is the combination of a suitable calorie-restricted diet with a programme of physical exercise [Kopelman 1984]. There appears to be a lack of consensus among physicians at all levels of care regarding the best approach to managing lifestyle changes including dietary strategies. Most primary care physicians do not treat obesity, citing lack of time, resources, insurance reimbursement, and knowledge of effective interventions as significant barriers. However there is evidence that a brief, physician-directed program with nutritionist support by telephone can be implemented in a busy primary care office [Bowerman *et al.* 2001].

Although weight reduction reduces apnoea severity and improves pulmonary function it is not known to be curative in most obese patients with sleep apnoea [Grunstein *et al.* 1994; Largerstrand & Rossner 1993]. Among morbidly obese patients (BMI ≥40 kg m^{-2}) vertical-banded gastroplasty and an intensified dietary regimen had variable results. Only those with significant reduction in BMI (27%) reported improvement in SAHS symptoms [Rajala et. al. 1991]. Although it is possible for various low calorie diet systems to achieve a reasonable weight loss, there is usually a weight gain in the long term.

Appetite modification with amphetamine related products lead to pulmonary hypertension and valvular heart disease and have been severely restricted [Sobieraj 1997]. Sibutramine is an appetite suppressant with some evidence of sustained weight loss when used up to 2 years with some risk of increased blood pressure [Bray *et al.* 1996].

Orlistat is an inhibitor of pancreatic lipase enzyme when administered with meals it results in a 30% reduction in dietary fat absorption, which equals approximately 200 kcal daily energy deficit [Ballinger 2000]. In the long term, orlistat has been shown to be more effective than placebo in reducing body weight and serum total and low-density lipoprotein cholesterol levels [Foxcroft *et al.* 2000].

1.3.9 Summary

The review of the SAHS literature demonstrates that SAHS is a common condition [Young, et. al. 1993] with patients suffering socially debilitating symptoms of EDS [Johns 1993a], generalised fatigability, lack of motivation, depression [Flemons and Tsai 1997a] and neuro-psychiatric dysfunction [Cheshire *et al.* 1992;Engleman and Douglas 1993b]. Although there is a far wider prevalence of snoring, EDS, obesity and nocturnal apnoeas/ hypopnoea, the syndrome definition includes only patients with both symptoms and nocturnal sleep breathing abnormalities (AHI≥5 hour^{-1}) [American Academy of Sleep Medicine 1999] , who in turn are more likely to derive benefit from therapy [Barbe *et al.*2001]. The recent trial evidence demonstrates significant but variable reduction in HRQL measures associated with this condition [Bolitschek *et al.* 1998;Flemons 2004;Lacasse, *et al.* 2002a;Moyer *et al.* 2001;Sanner *et al.*2000;Stradling *et al.* 1996]; although the tools used vary in their effect sizes and sensitivity in measuring change with treatment [Jenkinson, *et al.*1997c]. There is little correlation seen between disability levels reported by patients compared to the patho-physiological measures of nocturnal sleep apnoea [Barbe *et al.* 2001;Carrera *et al.* 1998;Monasterio *et al.* 2001a]. These in turn create difficulties in validating and comparing the impact of SAHS treatment with other health care interventions competing for scarce economic resources.

The impact of untreated SAHS is considerable both at individual and societal level [Sleep Alliance. 2004]. The economic burden of the disease and its consequences if measured at the societal level, with manpower and RTA implications, may far outweigh the cost of therapy provision[Rodenstein 2000] [Leger 1994] [Douglas *et al.* 2002] [Sassani *et al.* 2004] [Pack *et al.* 2004] [Pelletier-Fleury *et al.* 2004].

Therapy for SAHS includes surgical measures [Lang *et al.* 2004] or oral mandibular advancement devices in specific situations [Bennett *et al.* 1998]. However since 1990, CPAP [Sullivan et. al. 1981] is the most common treatment for the majority of SAHS patients with increasing evidence of success with minimum side effects [Scottish Intercollegiate Guidelines Network 2003].

As a health technology innovation CPAP has certain characteristics and advantages over previously available treatment options for SAHS treatment. There is evidence of the

efficacy of CPAP in preventing the episodic collapse of the pharyngeal airway in SAHS patients, prevent snoring and also reduce the work of breathing in the mild SAHS and UAR patients [American Thoracic Society 1994;Engleman *et al.* 1997a] [Cassel *et al.* 1996b;Stradling *et al.*1996]. However there are difficulties in assessing the clinical effectiveness of CPAP as the common measures of SAHS severity (i.e. AHI, AI, EDS) are not strongly correlated with improvement reported by symptoms [Barbe *et al.*2001]. One of the main shortcomings arises from the lack of a unified outcome measure in these patients which can be reliably used to measure the impact of treatment provision [Jenkinson *et al.*1997c].

The other principal difficulty in assessment of CPAP is the need to adjust for the effect of confounding variables [Wright and Dye 1995]. As almost half of patients with symptomatic SAHS, have either obesity of significant sleep hygiene abnormalities, careful attention to these factors with conservative measures may improve symptomatology in many patients precluding the need for more expensive or invasive strategies [Shneerson and Wright 2001].

1.4 DIFFUSION OF INNOVATIONS

1.4.1 Introduction

The majority of growth in healthcare costs over the last fifty years has been attributable to technological innovations [Newhouse 1992] which have resulted in a net improvement in patient well-being [Cutler *et al.* 1998]. The goal of HTA exercise is to optimise patient outcome, both objective (clinical) and subjective (patient-cantered) [Berwick 1989]. This is achieved by developing consensus recommendations based on scientific evidence of efficacy and effectiveness as well as the tangible and even intangible impact on society [Sultz 1991]. HTA analysis usually provides evidence to support further resource allocations or decisions to restrict them [Feeny *et al.* 1987]. An essential part of completing an HTA is then to help transmit the evidence of clinical and cost-effectiveness to the appropriate forums for incorporation into health policy and planning, by a process of knowledge utilisation [Booth-Clibborn *et al.* 2000] [Hillman 1986].

Unfortunately the assumption that scientific evidence will be seamlessly incorporated into everyday practice and planning appears to be far from true in real life [Omery *et al.* 1999]. The classical example dates back to the slow adoption of evidence on the effectiveness of lemons in treating scurvy which was the scourge of sailors in the British Navy [Cheng 2004]; an innovation which took 264 years to diffuse to widespread use within the merchant naval ships at a great cost of life [Berwick 2003]. More recently, there has been little demonstrable net effect on commissioning of healthcare or planning based on the availability of effectiveness data [Hailey *et al.* 2001]. Thus the mere generation of an evidence based report may not transform practice as would be anticipated in an ideal setting.

The forces which influence the process of the spread of an innovation within a social system play an important part in the final utilisation/ adoption and ensuring benefits reach society at large. This process of *diffusion*, according to the classical diffusion paradigm, may be seen as a linear communication from the innovator to the passive adopter [Rogers 1995]. But this is often found to be far more complex and interactive a simple linear one between a change agent attempting to persuade a client to adopt an

innovation [Rogers 1995]. One of the first to write about diffusion was Gabriel Tarde who in his book '*Laws of imitation*' described the concept that individuals learn of an innovation by copying another individual's adoption behaviour [Tarde 1962]. In any situation where an innovation maybe introduced there are usually certain uncertainties which exist with alternatives which offer a choice, thus adoption is in turn determined by information on technological innovations.

HTA exercise is designed to gather this knowledge and make it available for policy makers. Although it is argued that health services are most inefficient among all sectors in their ability to extract the value of resources consumed [Newhouse 2002], it is still suggested that health policy should be biased to encourage technological progress rather then be restrictive and focus only on avoiding waste by delaying the adoption of new technology [Cutler *et al.* 2001].

1.4.2 Elements of the Diffusion Process

1.4.2.1 Innovation

Innovation is an idea, practice or object which is perceived as new by an individual or other unit of adoption. The newness of an innovation may not involve dealing with objectively new knowledge and the individual may not have formed a favourable/ unfavourable attitude towards it or a decision to adopt [Rogers 1995].

There are three phases within the lifecycle of an innovation;

(i) technology development which includes invention, demonstrations and clinical trials;

(ii) launch including approval by regulatory bodies and reimbursement decisions; and

(iii) Dissemination includes experimentation / reinvention, acceptance, integration and post-launch trials [Coye *et al.* 2003].

Research suggests that perceptions of the attributes of an innovation may account for 49-87% of the variance seen in their rate of diffusion and adoption, while compatibility with current social norms and relative advantage are shown to positively influence diffusion, complexity of an innovation has a negative influence [Tornatzky *et al.* 1982]. The most consistent innovation characteristics which tend to determine rate of diffusion, identified

from diffusion studies, are listed in table 1.7 and are namely; economic advantage, effectiveness, observe ability, trial ability, complexity, compatibility, reliability, application, communality, and radical ness [Rogers 1995].

In an exploratory investigation, Dearing et al suggested that when risky-innovations are disseminated, applicability and reliability are important attributes [Dearing *et al.* 1994]. They also noted that accompanying these predictors was two or more traditional attributes, complexity and compatibility. Their research suggests that while the diffusion model provides a framework with which to study a given innovation, each innovation differs and should be conceptualized based on its specific attributes and the results are likely to be applicable to a specific social system. However, similar innovations could be compared on a set of attributes common to all of them [Dearing and Meyer 1994].

Table 1.7: Characteristics of an innovation

Relative advantage	Is the degree to which an innovation is perceived to be better than the idea it supersedes
Compatibility	The degree to which it is considered to be consistent with the existing values, past experiences and the need for potential adopters
Complexity	The degree to which an innovation is perceived as difficult to understand and use
Trial ability	The degree to which an innovation may be experimented on a limited basis. The more divisible an innovation is the quicker and easier it will be to try it and hence quicker diffusion.
Observe ability	The degree to which the results of an innovation are visible to others. The greater the visibility the quicker the diffusion and adoption occurs.

Adapted from 'Elements of diffusion' chapter in Diffusion of innovations [Rogers 1995]

When chemotherapy for tuberculosis was introduced as an innovation it provided a distinct *advantage* to the then current procedures of sanatorium stay and iatrogenic collapse of the affected lung. Even so, it did not diffuse well as it was viewed to be expensive and required taking unpalatable medication for extended periods of up to two years. Only with the later introduction of Rifampicin and the reduction of the chemotherapy period did this modality of treatment gain widespread acceptance in spite of its high cost [Reekie 1982]. Relative advantage over current therapy has been shown to be a primary factor in the adoption of pharmaceutical innovations like in the case of cardiovascular drugs adoption in Germany [Wieringa *et al.* 2001].

The lack of *compatibility* with current norms prevented the diffusion of the energy efficient compact fluorescent lamps in a market dominated by tungsten lamps. Their delayed start mechanism and cold light was perceived unfavourably by the market to a point where they were nearly withdrawn. Only a significant modification and adaptation to the warmer light helped them gain a market niche [Menanteau *et al.* 2000]. Unlike other health technologies, most of health care innovations are developed as a partnership between users/ academic institutions in combination with industry. This gives them the advantage of being compatible with the intended adopters' needs and hence can allow for accelerated adoption in the absence of expensive marketing and product placement strategies [Tabak *et al.* 1999].

Perceived *complexity* of an innovation may hinder or slow down the rate of diffusion. In a comparison of anticholinesterase inhibitor use in German patients with Alzheimer's disease, research showed only a 9% adoption among primary care physicians compared to 45% among specialists although the drug was targeted equally in primary and secondary care; this was due to the perceived specialist nature of the treatment and the lack of personal knowledge and expertise [Ruof *et al.* 2002]. In a computer based stroke management system set up to improve and standardise care within a hospital, the diffusion was slow until sustained education, round-the-clock support and system refinement was instituted [Lau *et al.* 1998]. A similar computerised physician order entry system was shown to have a slow diffusion although perceived to be beneficial allowing remote access to patient data, decreasing errors and allowing decision support due to complexity compared to paper based systems, lack of flexibility, user interaction and absence of perceived need by the end user [Ash *et al.* 2001].

Findings suggest that relative advantage; compatibility with current practice, its complexity, and *observe ability* were the strongest predictors of likelihood to adopt genomic medicine innovation tasks into primary care practice in Texas [Suther *et al.* 2004].

Both observe ability and trial ability, may affect the diffusion of surgical technique innovations as shown in a Canadian study where areas using laparoscopic gastric surgery recorded an annual rise of 16% in cases compared to only 3% in areas still dependant on

open surgical technique [McMahon *et al.* 2000]. The availability of the new technique encouraged new adopters to observe its use and trial themselves leading to a much greater adoption then in regions without this degree of availability.

1.4.2.2 Innovators & innovativeness

The process of innovation development usually begins with a perception of need or recognition of a problem / deficiency (economic/ institutional model). Innovations developed due to user needs tend to be more focussed and need less dissemination efforts [Roehrich 2004]. On the other hand, in some cases there is a technological push where new products or innovations are seen to drive the diffusion process and create the need [Kaplan 2001] [Prater *et al.* 2002] [Kreps 2002].

The innovativeness of an individual is his/ her attitude towards experimenting with new knowledge and is determined by the rate at which he/ she are likely to adopt a new idea. Innovativeness is based on the assumption that adoption of innovation is desirable and enhances the performance or efficiency of an adopter [Dos Santos *et al.* 1995]. Followers of the *'contingency theory'* believe that the stimulus for adoption emanates from the environmental flux, and rate of diffusion is faster (individuals tend to be more innovative) in unstable environments on order to achieve an advantage over competitors [Lawrence *et al.* 1967] [Robertson *et al.* 1986].

While in stable environments innovativeness may be considered a wasted effort and individuals do not adopt early nor are they consistent in their attitude to innovation [Hambrick 1983]. While traditionally health care provision in the UK has been non-competitive, there have been recent innovations to make individual hospital trusts compete for local priorities and funding, creating a marketplace environment to drive progress [Maynard 1993].

An alternative theory is one of *'strategic decision making'* which suggests that innovativeness is a function of strategic management where decision makers actively choose innovations for improving performance and efficiency [Child 1972] [Dougherty *et al.* 1994]. According to this theory, adopters are classified as 'Prospector', 'Analyzer', 'Defender' and 'Reactor'. Individuals or firms who rapid adopters (prospector) were held

greater market share while slower adopters (defenders) were shown to be more profitable [Miles *et al.* 1978].

Thus the rate of diffusion depends on the relative advantages offered by the innovation over current practice/ technology. 'Innovativeness' has also been defined as a multi-dimensional phenomenon based on the number of innovations adopted, time of adoption and consistency of adoption [Subramanian 1996].

It has been said that 'to create a future different from its past, health care needs leaders who understand innovation and how it spreads, who respect the diversity in change itself and who drawing on the best of social science for guidance, can nurture innovation in all its rich and many costumes' [Rogers 1995]. Innovators are thus characterised by their venturous ness, fascination with novelty and willingness to step out of their systems to learn.

It has been shown that frequent and consistent adopters tend to progress faster along the innovation learning curve and become more efficient than others [Pennings *et al.* 1992], giving them an inherent 'first mover' advantage [Dos Santos and Pfeffer 1995]. The health care sector in the USA is characterized by a similar market based strategy of rapid technological progress fuelled in part by a reimbursement system that generously pays for the use of new and advanced therapies [Weisbrod 1991]. While new technologies such as implantable defibrillators [Greenberg *et al.* 2002], percutaneous coronary stent insertions [Booth-Clibborn, Packer, and Stevens 2000], drug eluding stents, gene therapy [Lyngstadaas 2002a] etc have diffused rapidly there have been others such as magnetic resonance imaging scanners [Baker 2001], neonatal intensive care units [Baker *et al.* 2000] and proliferation of mammography screening units [Bryant 1996] which have been slower as a result of introduction of recent managed care regulatory strategies [Cutler and Sheiner 1998].

In a market driven health care sector changes in financial incentives, reduction in profitability [Reinganum 1989] and regulation have the same effect in slowing diffusion of expensive innovations [Baker 2001].

Socialist economies in the later part of the 20th century lacked market structures hence diffusion of innovations was led by factors such as personal creativity of academicians and

engineers and recognition of societal need and government encouragement [Achilladelis *et al.* 2001].

Similarly in a completely managed health care sector like the NHS in the UK, the dynamics of diffusion are entirely different from the experience in the USA. At an individual level innovation decisions may be made on an optional or collective basis within small groups of individuals (like clinical groups or Primary Care Trusts). However decision making within managed care settings is done at a regional level (like the Regional Health Authorities [Pettigrew *et al.* 1989] and the recently formed Strategic Health Authorities [SHA] in the UK NHS). This is guided by national bodies for assessment of innovations and health care technologies [Rawlins 1999]. Decision making at SHA level is increasingly becoming dependant on formal systems of HTA (assessments and guidance from the National Institute of Clinical Excellence [Taylor 2002] [Davies and Littlejohns 2002]), social-political imperative [Pettigrew, McKee, and Ferlie 1989] and mechanisms of identifying new and emerging technologies for appraisal.

1.4.2.3 Communication

This involves the transfer of a 'new idea' or innovation between an individual/body who has the knowledge or experience of this innovation, through communication channels to those who do not yet have the knowledge [Rogers 1995]. Although *mass media* channels are usually the quickest way of disseminating knowledge to a large audience, the disadvantage is the lack of individual tailoring/ focus and the diversity of this large audience group [Gupta 1996]. Individuals tend to only take notice of mass media messages which they perceive to be relevant to them and hence a perception of need or prior knowledge is essential for them to be successful [Scullion 2002]. Hence the people in a social system who are likely to be inclined to early adoption and are seeking knowledge about an innovation are likely to be influenced by mass media campaigns rather than the ones with the least knowledge [Scullion 2002].

Contrary to planned mass media communication campaigns, the media coverage of particular individual stories may have a great influence in shaping public perceptions and pressuring public spending policies. This is illustrated by the effect on prescription of

certain drugs like anti-influenza drug 'Zanamivir' [Barnett 2001] and 'Sildenafil' for male sexual impotence [Smith 1998b]. Media may also have an adverse impact on adoption of even well-established technologies. In 1997, when a medical journal published research suggesting the link between a vaccine and the development of autism [Wakefield *et al.* 1998], this was taken up by mass media leading to a sharp decline in the immunisation coverage in the UK, in spite of governmental efforts to reassure the public of its' safety [Ramsay 2001]. This illustrated the impact of quantitative evidence in the absence of qualitative or philosophical insight and suggests the need for a combined approach in policymaking [Roberts *et al.* 2002].

On the other hand, for professionals research suggests that in the diffusion of innovations particularly among new pharmaceutical products, *inter-personal communication* channels are considered far more effective in persuading a potential adopter [Mahler *et al.* 1999]. There is empirical evidence that physicians tend to view information available in professional journals as appearing too late to be useful, as too positive, as providing too little information regarding complications and the transferability of results to their own practice [Greer *et al.* 1977]. Instead they feel that the best source of information concerning the efficacy of new medical procedures or innovations is other physicians with first-hand experience [Stross *et al.* 1979]. The experience of the introduction of Tetracycline is a classical example where the initial innovators only used a few prescriptions while late majority users wrote a much larger number of prescriptions when uncertainties about this new innovation were reduced with directly observed behaviour of peers [Coleman *et al.* 1966]. This dependence on the adoption behaviour of peers suggests that diffusion is a very interactive and social process.

When diffusion of communication technologies is involved they can in turn accelerate the diffusion of newer technologies by boosting the communication infrastructure and the access to knowledge [Redmond 2004].

The adoption process consists of several stages and not merely a function of knowledge acquisition but is shown to require also evaluation and trial. The diffusion of higher technology products may be faster in communities where it has arrived later [Gruber 2001] and especially if many similar products are introduced simultaneously with synergy between the communication methods.

The impact of the *social network* approach on modern contraceptive use was shown to be almost double that of conventional field worker visits to individual homes after controlling for the effects of prior contraceptive use and intention, prior home visits, and selected socio-demographic characteristics [Kincaid 2000]. The same approach may hold true for the diffusion of new technology using 'workshop' based learning methods in the health care sector as in the appropriate use of rapid diagnostic tests for Tuberculosis [Anon.1997a].

Much of the information necessary to support the diffusion of an innovation flows through personal contacts. Although in the diffusion of medical knowledge much emphasis is placed on publication of information about an innovation in scientific journals, research has shown that most physicians depend on a subjective evaluation of an innovation by other physicians who have already adopted this [Elford *et al.* 2002] [Rappolt 2002]. Hence the closer the individuals are to each other in certain attributes, beliefs, education and social status the more effective the communication between them is likely to be (homophily). While in many situations, the heterophily of individuals makes it difficult to establish effective lines of communication, leading to a slower diffusion [Rogers 1995].

Networks of interpersonal communication that link organisations developing new systems with those that are adopting technological innovations thus allowing for a free exchange of ideas and feedback are of considerable importance in the diffusion process [Debresson *et al.* 1991].

Networking appears to be essential for the development of a region's knowledge infrastructure [Tassey 1991] and *network cohesiveness* (defined as direct user-to-user influence) has a positive impact on the diffusion of industrial innovations [Midgley *et al.* 1992].

Pressures from social emulation and a localised competitive environment lead organisations and even individuals to adopt a new technology in order to "stay in the game" [Ebadi *et al.* 1984]. The pharmaceutical industry began with the commercial application of scientific research which was initially born within academic institutions. Since then it has flourished while maintaining a very close link with academic institutions which facilitate learning by use, interaction, credibility building and maintaining market

focus. The close sharing of information within pharmaceutical - academic networks leads to reduction in time to marketing and gives these firms a competitive advantage [Achilladelis and Antonakis 2001].

1.4.2.4 Time

The innovation-decision process is one by which an individual or decision making body passes from first knowledge of an innovation to developing an attitude towards the innovation which in turn determines its adoption. This process is conceptualized by Rogers into 5 steps; 1) knowledge 2) persuasion 3) decision 4) implementation and 5) confirmation [Rogers 1995].

While the knowledge of an innovation is usually transmitted by mass communication channels it is at the persuasion and decision stages that individuals need information on cause-effect, consequences and innovation evaluation information. Inter-personal communication channels provide the information usually at this stage especially regarding applicability in individual microenvironments. Subjective evaluation in such situations has been shown to be very effective in establishment of firm attitudes. The time taken by an innovation to be adopted is known as the *innovation-decision period* [Rogers 1995].

When adoption behaviour is plotted as a histogram it has been shown to take the typical shape of a normal distribution curve. This has been divided according to mean and standard deviation into five different categories. Although individual innovations may demonstrate different variations depending on individual factors, Rogers has generalised these into 5 categories commonly found normal distribution. This was initially reported in a seminal study of the diffusion of hybrid corn among Iowa farmers in 1943 [Ryan *et al.* 1943]. These were innovators (2.5%), early adopters (13.5%), early majority (34%), late majority (34%) and laggards (16%).

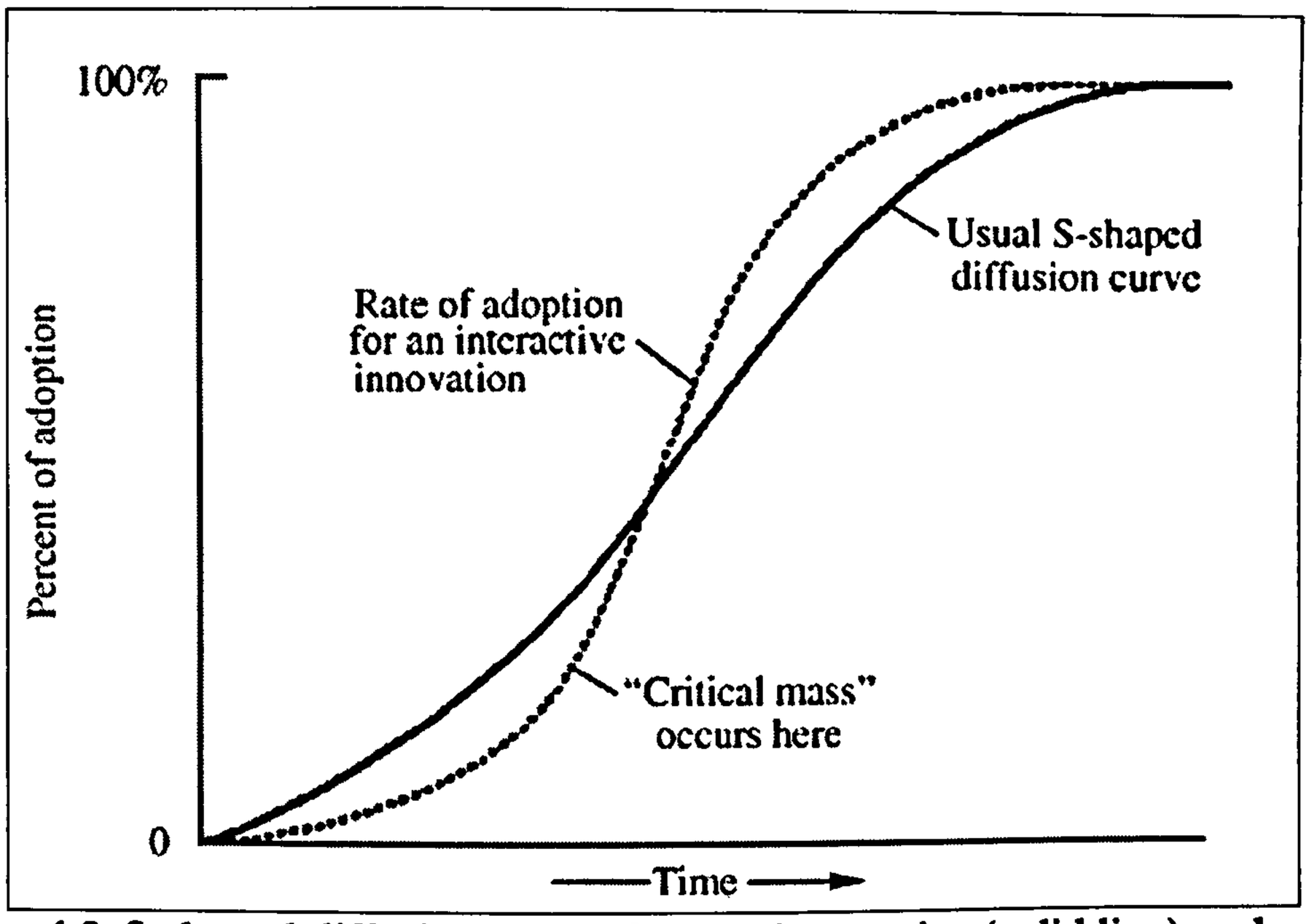


Figure 1.2: S-shaped diffusion curves for non-interactive (solid line) and interactive (broken line) innovations [Mahler and Rogers 1999]

The rate of adoption measures the relative speed with which an innovation is adopted by members of a social system. When the diffusion of most common innovations are plotted in a cumulative graph over time it demonstrates an *'S' shaped curve* [Beal et al. 1960] with an early majority of adopters and a plateau effect late in the diffusion process. The rate of adoption i.e. the rate at which a certain percentage of individuals adopt an innovation is however dependant on many factors.

The *critical mass* is defined as the minimal number of adopters of an interactive innovation for the further rate of adoption to be self-sustaining. The term critical mass comes originally from nuclear physics where it referred to the amount of radioactive material needed for a pile to `go critical' in a self-sustaining reaction. Whether or not such a critical mass problem is involved in the diffusion of a health innovation depends in part on the innovation's degree of interactivity and the existence of social networks. In the early stages of the diffusion of an interactive innovation, when relatively few individuals have adopted, the rate of adoption proceeds extremely slowly. The cumulative rate of adoption is characterized by almost a straight line with a long tail to the left. But eventually enough adopters are reached when many individuals in the system perceive that `everybody's doing it'. At this point enough other individuals have adopted so that an

individual considering adoption of the innovation perceives that the innovation would have sufficient utility to justify its adoption [Mahler and Rogers 1999]. The *critical mass point* in the diffusion process is generally expected to occur approximately between 10 and 20% adoption [Rogers 1995].

The study carried out by Ryan and Gross [Ryan and Gross 1943] about the diffusion of hybrid corn in two Iowa communities is often considered as the starting point of the research on innovation diffusion. Their main problem was to understand why some farmers adopted earlier than others, among all who had an economic interest to adopt the innovation. They tried to capture these differences with variables such as social participation, education, cosmopolitanisms, and media consumption which were more highly correlated with the time to adopt than the size of the farm and the length of farming experience. Moreover, the data of cumulative adoption showed the typical S-shaped curve for the diffusion of innovation.

This type of curve is explained by the risk of innovation adoption, and the uncertainty about the outcome of adoption. The observation of earlier adopters is a means for reducing this uncertainty. Therefore risk tends to force individuals to turn to their peers to gain more information and/or reassurance about the outcome of the adoption. [Rogers, 1984] refers to contagion as the diffusion effect. When the number of adopters increases in the network of peers, the pressure for adoption also increases. However, the capacity to resist to this pressure varies among individuals. This led to the definition of the *threshold models* [Granovetter, 1978]. An individual's threshold is the proportion of adopters in the considered group necessary to convince him to adopt. Originally this model was applied to the case where the group was considered to be seen globally by all individuals (the example of riots).

The network approach led to refine the models and to define the *personal network threshold* models, corresponding to the proportion of adopters in the personal network (also called personal exposure) leading to adoption. The exposure can be calculated for direct links, or for indirect links divided by their length using the flow matrix [Freeman et al 1991]. The exposure at the first level is used to define a *local threshold* for adoption, corresponding to the proportion of adopters in this one step network which led to adoption. The *threshold lag* corresponds to the time necessary for adoption when the

threshold is reached (in general the adoption does not occur right when the threshold is reached). The more formal definition of the threshold is the point at which the perceived benefits exceed the perceived costs [Granovetter, 1978].

The network approach also led to reconsider the critical mass concept, and connect it to the different versions of the personal network threshold. This research shows that the critical mass varies with the threshold distribution of the population and with the social network structure.

A historic example of a rapidly diffusing health technology innovation was the computed tomography (CT) scanner in the USA in the early 1970s. This was adopted at a rapid rate in the USA due to an early realisation and perception among radiologists, administrators and physicians alike of its immense benefits over conventional technology. However the scanners were purchased rapidly at great cost even for well resourced hospitals, when still undergoing rapid changes in development. Hence, most initial scanners became obsolete within 2 years. There was a second spate of purchases by tertiary hospitals so that diffusion reached a peak by four years from the introduction of this technology, before safety and effectiveness were established with traditional research methods. In some states this created a regulatory backlash and diffusion became variable geographically. Thus perhaps there was a need for a proper assessment of efficacy similar to those required for pharmaceutical innovations before being licensed for widespread adoption [Baker 1979]. In a similar case of diffusion of Magnetic Resonance Imaging (MRI) scanners in the USA, the technical and financial uncertainties surrounding MRI had inhibited its diffusion compared with that of CT. Medicare's prospective reimbursement system and certificate-of-need regulation by states had reduced overall MRI diffusion and stimulated purchases of MRI by non-hospital organizations [Hillman *et al.* 1985]. In England, MRI scanners were initially purchased six years after first availability with a subsequently slow rate of diffusion, and are still absent from some hospitals [Booth-Clibborn *et al.*2000] their steep cost being the primary hindrance to adoption.

While coronary stents were initially used six years after first availability, but within two years all responding hospitals in England reported using them, as their diffusion was accelerated by professional champions [Booth-Clibborn *et al.*2000].

1.4.2.5 The social system

A social system is a set of interrelated units that are engaged in joint problem solving to accomplish a common goal [Rogers 1995]. Individuals in a social system are different but usually work towards a common goal. The structure of a social system is the way the individual units are arranged in a system, i.e. primary, secondary and tertiary care health systems where there is usually a diffusion of innovation from the tertiary care establishments engaged in research or early implementation of an innovation through secondary care and finally at the grass roots level among primary care health workers. The advantage of a social structure is some predictability of the way the system might respond to a new idea/ innovation. In addition to a basic social structure there are well established channels of communication which determine how a set of individuals may or may not respond based on their inter-personal channels [Rogers 1995].

Established patterns of behaviour (norms) are instrumental in influencing the variable way an innovation may diffuse in different subsets of the same social system with a homogenous exposure. In 1991, Hofstede suggested possible factors in different social structures which could be related to innovativeness; 1) individualism vs. collectivism or self-orientation, 2) femininity vs. masculinity or achievement orientation and 3) uncertainty avoidance or risk orientation. Social systems or cultures with individualism and masculinity were more likely to be early adopters than those with a conservative and risk aversion outlook [Hofstede 1991].

Social networks of potential users of a service have been used to determine the prioritisation of healthcare interventions and thus may have a role in influencing the diffusion of adoption of health care innovations. The Oregon Plan in the late 1980s and early 1990s was an experiment to prioritise health care spending based on adopting public preferences to a combination of health care interventions ranked according to cost-utility ratios and professional prioritisiation. Although regarded initially as a progressive movement to explicit rationing of healthcare delivery influenced partly by user preferences, compared to the implicit rationing seen in other systems, there were inherent flaws due to factors such as the under-representation of minorities, the disabled and mental health patient groups in such user surveys [Brown 1991]. This led to the removal

of the potential user group influence on prioritising in the revised plan which was adopted later to fund 565/696 condition/treatment pairs [Sipes-Metzler 1994].

The adoption of computers in hospitals demonstrates the flexibility and compatibility influencing its diffusion in two waves, initially as an administrative tool and later in clinical application areas. Hospitals were plagued by rapidly escalating workloads and costs and computers offered a solution for some of the major health-management problems and offered assistance to all individuals involved in health care. With the availability of personal computers, it became feasible for even small hospitals to have access to computer systems. However in the early days of the introduction of computers, diffusion was not being achieved across areas of clinical application. Most of the leading hospitals in the United States used to perceive and use computers only for administrative applications. The use of computers in clinical applications and patient care had not been exploited in the 1970s.

Mahajan identified the need for focussing resources on the diffusion of knowledge on computer-based clinical applications and links with teaching hospitals as change agents through communication networks to implement the diffusion of computers in clinical applications [Mahajan 1979]. Since then in the last two decades the use of personal computers (PCs) in clinical applications, telemedicine, digital imaging, electronic patient records, ordering of investigations, and the use of intra-nets for the dissemination of clinical practice guidelines have become the mainstay of hospital practice and their use has also expanded into primary care [Egan *et al.* 1995] [Majeed 2003].

Systematic barriers are known to slow down the adoption of certain innovations as demonstrated in the slow market penetration of anti-cholinesterase inhibitors in Alzheimer's disease in the UK and in Germany. Although there were positive attitudes regarding the safety and efficacy of these drugs, the negative attitudes regarding the budgetary limitations to prescribing these drugs in particular seemed to inhibit the adoption of the innovation by the majority of General Practitioners (GPs). Budgetary systems such as those in the UK and Germany support short-term cost control behaviour and thus, do not encourage long-term disease management and cost saving strategies [Ruof *et al.* 2002].

1.4.2.6 Opinion leadership

Although the most innovative individuals maybe virtually rejected by society as they are perceived to be mavericks and out of touch with their peers, others who function as opinion leaders have considerable influence on the adoption or rejection of new ideas. Opinion leaders are closer to early adopters then to being innovators themselves. This position is usually earned and maintained by an individual's competence, social accessibility and conformity to the system's norms [Rogers 1995]. Characteristically opinion leaders are; 1) more exposed to all forms of external communication, 2) have a higher social status and 3) are usually more innovative.

Opinion leaders are members of the social system and exemplify the norms of the social system and hence their innovativeness depends on the innovative behaviour of the social system. The behaviour of opinion leaders may influence the rate of adoption of an innovation within a social system and hence may be chosen for individual targeting by agencies seeking to influence adoption. Opinion leaders may be sought out by change agencies in order to learn about public perceptions to assist in removing hurdles and speeding up innovations. In the adoption of environmentally safe alternative energies, i.e. solar energy systems early adopters revealed high education and income levels; professional and executive occupations; economic, energy saving, and environmental concern as the principal purchase motivations; and high satisfaction levels. Their early adoption in turn set the example for further adoption in their communities [Sawyer 1982]. In the early days of adoption of internet based systems in healthcare practices, studies among physician leaders identified six internet-enabled services as "essential" for the future success of their practice and indicated that reduced administrative costs, faster payments, and improved quality of care are the most important benefits derived from internet-enabled applications. Ninety-six percent of survey respondents estimated that internet-enabled technologies will have a significant, positive impact on the practice of medicine in general and will improve the quality of care [Coye *et al.* 2001].

1.4.2.7 Change agents

The external agents or professionals entrusted with the specific task of imparting knowledge about an innovation to members of a social system (e.g. medical representatives bringing news and technical information on new drugs to medical practitioners) are called *'change agents'*. Unlike the rural agricultural sectors or third world family planning programs, in the healthcare sector local implementation activities often capitalise on knowledge primed individuals (who are highly skilled and educated) by enabling and reinforcing the desired behavioural change [Lomas 1993]. Direct marketing with medical representatives continues to be a common route used by pharmaceutical industry where the industry representative may act as a change agent and influence the behaviour and practice of individual clinicians towards more evidence based practice. This raises many potential ethical issues and may leave a danger for non-evidence based practice with increased cost and safety implications [Stryer *et al.* 1996] [Lober 1993] [Lal 2001]. However change agents can be useful as a mechanism for feedback of user perspectives to industry which may help to improve the innovation [Calfee 2002].

When a new technology is introduced in the market place there are several potential hurdles from established technologies such as relatively crudeness of a new technology in its early stages, lacking the benefit of cumulative learning and economies of scale in production. New technologies can be perceived as more expensive, and comparison against the established evaluation criteria may fail to highlight the advantages of the latter. There is also an inherent inertia to change among most adopters which may slow down diffusion significantly [Menanteau and Lefebvre 2000].

1.4.3 Summary (Diffusion & adoption of CPAP)

CPAP as an innovation provided certain advantages over older technologies (i.e. surgery) by having less adverse effects, being safer, reversible, reduced need for hospitalisation and perceived to be more acceptable to patients [American Thoracic Society 1994]. At the same time the perceived advantages of this form of therapy compared to alternative therapies, and the high prevalence of SAHS led to a rapid expansion of demand and provision in some countries.

In a managed care setting like the NHS, where purchasers were faced with the prospect of resource provision for 2-4% of the adult population [Young *et al.* 1993], reviews of the evidence base commissioned by the purchasers showed gaps in the evidence of effectiveness available [Wright and Dye 1995]. This report led to many purchasing authorities seeking to restrict the availability of CPAP treatment and facilities for diagnosis and treatment in various NHS regions in the UK [Gibson *et al.*1998]. Local Physicians were impelled to argue and win resources on a region-by-region basis [Sleep Alliance. 2004].

Although physician bodies such as the British Thoracic Society initially took up the challenge and provided forums for debate and discussion of the controversies [Kryger 1997] [Fleetham 1997;Pack and Young 1997;Shaw 1997;Stradling 1997;Walsworth-Bell 1997], the lack of media interest, patient advocacy and absence of industry influence probably resulted in a lack of large scale national studies and the absence of a national service framework [Sleep Alliance. 2004]. More recently in 2001, consensus guidelines were produced to assist in service provision and guiding research into hitherto unknown aspects of SAHS and CPAP use [Scottish Intercollegiate Guidelines Network 2003].

By contrast in the USA, the existence of the American Academy of Sleep Medicine [American Academy of Sleep Medicine 1999], the National Sleep Foundation [Anon.2004b;National Sleep Foundation 1999], active media interest in the consequences of national sleep habits and sleep related accidents [Leger 1994], governmental bodies such as the National Institute of Health sponsored research [National Commission on Sleep Disorders Research 1993] had created a situation for a much more widespread and rapid adoption of CPAP technology across the nation [Mack 1999].

Although perhaps slower than in the USA, the diffusion of CPAP in Europe has been variable with countries such as Germany, France and Spain taking the lead with national large scale studies and widespread resource provision [Rodenstein 2000] [Fischer *et al.* 1997]. Not much is known about the economic evaluation of CPAP in SAHS [Tousignant *et al.* 1994] [Douglas and George 2002] [Pelletier-Fleury *et al.* 2004] and the state of diffusion other than by unpublished industry estimates in Europe.

Thus CPAP provision in the UK has not kept pace with USA, Germany and Australia due to a variety of reasons. Principal among them are the questions of RCT evidence of effectiveness, influence of confounding variables (i.e. obesity), lack of a uniform outcome measure and economic evaluation. This thesis addresses these issues and explores the factors influencing the diffusion and adoption of this new health technology in the UK NHS.

CHAPTER II

AIMS OF RESEARCH

2.1 Overall aim

The primary aim of the research presented in this thesis was to conduct an HTA case study of an innovation (CPAP), appraising its impact on the course of a chronic disease condition (SAHS) where the outcome is measured not by increased survival but by an improvement in HRQL and health status. The research design includes a clinical review, a prospective RCT of clinical effectiveness and a cost utility analysis.

The secondary aim was to study the process of diffusion of new technology from innovation to it's' adoption by the end user in a managed care setting like the NHS.

Thus this thesis aims to provide a framework for the assessment of future innovations in the treatment of chronic disease states within a managed care setting.

2.2 Clinical review of SAHS in a DGH (Chapter IV)

The aim of the research presented in this chapter was to assess the population demographics and the morbidity and mortality associated with SAHS in a typical DGH Sleep clinic population.

To measure the change in the demand for diagnostic and treatment services over the 7 year review period and to assess the success of CPAP trials and compliance over a medium term follow up.

2.3 Clinical effectiveness (Chapter V- VII)

The aim of the research presented in these chapters was to conduct a prospective RCT to assess the effectiveness of CPAP use in SAHS patients compared to a control group given conservative lifestyle modification advice.

Chapter V presents data on clinical efficacy using EDS, neuro-cognitive function (Trail making B) and polysomnographic variables.

Chapter VI presents comparative data on HRQL using two different generic questionnaires and two mental health assessment tools. Generic HRQL tools not only examine a multi-dimensional profile of health state but by their nature make it

possible to compare the impact of competing technologies, a vital step in health policy and setting of priorities for resource allocation.

The secondary aim in this chapter was to evaluate the validity, sensitivity and reliability of generic HRQL tools (SF36 and EuroQol) in SAHS patients.

In Chapter VII the aim of research presented was to evaluate the traditional measures of utility / health status based on patient preferences generated by the Standard gamble, Time-trade off and EuroQol utility in SAHS patients for use in a cost utility analysis. To measure the QALYs generated by the provision of CPAP vs. lifestyle intervention in these patients and calculating the cost/ QALY ratios. As a universal outcome measure (i.e. QALY) would incorporate patient preferences with the quality and quantity of life and thus facilitating comparison of health technology interventions. The cost/ QALY ratios would then be compared to other health care interventions and use in health policy and planning of services.

The use of a control group (given conservative, written lifestyle intervention advice combined with weight losing advice from NHS dietary services) provided the added opportunity to assess the impact of such lifestyle modification strategy in a population group where such lifestyle factors (i.e. obesity) have been considered to confound both mortality, morbidity and a majority of symptoms of EDS and fatigability identified in previous research.

The secondary aim being to assess the relationship between physiological variables of disease severity with patient reported symptoms, HRQL decline and change in health status.

2.4 Diffusion of Innovation (Chapter VIII)

The aim of the research presented in this chapter was to assess the factors affecting the diffusion of CPAP in the UK by qualitative questionnaire surveys of primary care physicians (entrusted with the screening of individuals in the community and refer them to specialist centres) and respiratory physicians in secondary care; entrusted with provision of facilities for the diagnosis and treatment of SAHS. The

questionnaire survey was designed to assess the characteristics of CPAP as an innovation (safety, effectiveness, advantages when compared to other established therapies, patient acceptability, possibility of providing safe therapeutic trials, ease of use by patients); methods of knowledge utilisation which may impact on the rate of diffusion and adoption of new technologies; innovator categories; factors affecting adoption of new technology within the NHS- infrastructure for diffusion of expert knowledge, communication systems, funding restrictions and finally the future of CPAP.

CHAPTER III

DESIGN & METHODS

3.1 Ethics

The study was approved by the Birmingham Heartlands & Solihull Hospital Research & Ethics Committee.

3.2 Study design

3.2.1 Clinical review

All case notes and physiological data sets from patients referred to the Birmingham Heartlands Hospital Sleep Disorders clinic from 1990 to 1997 were examined.

Subjects were classified into cases or controls based on diagnostic criteria incorporating symptoms of snoring and EDS, combined with evidence of nocturnal respiratory disturbance (i) (either on overnight oximetry with an oxygen desaturation index (ODI) of ≥ 15 $hour^{-1}$, 4% drop in arterial oxygen saturation or (ii) in those undergoing full PSG an AHI ≥ 15 $hour^{-1}$).

Using a retrospective, case-control analysis, the prevalence of co-morbidity (hypertension, stroke, and diabetes and ischaemic heart disease) and mortality were compared between cases and controls.

Secondary outcome variables were the change in the number of referrals, diagnosis based on ODI criteria, success of therapeutic trials of CPAP and compliance with CPAP over the follow up period.

3.2.2 Randomised controlled trial

The trial was conducted in accordance with the best practice standards as set out in the CONSORT agreement (*details in the appendix*).

3.2.2.1 Recruitment

All patients referred by General Practitioners to the Birmingham Heartlands Hospital (BHH) Sleep Clinic between June 1998 and October 1999, with a history of snoring and EDS were invited to participate in the study with an information leaflet (*please see appendix)* mailed with their first clinic appointments.

3.2.2.2 Clinical assessment & investigations

Patients were reviewed in clinic with their partners by a clinician. Patients who reported symptoms suggestive of SAHS then completed the Epworth Sleepiness Scale (ESS) questionnaire [Johns 1991] and were invited to participate in the study and provided further information about the study aims and asked to sign the consent forms (appendix) witnessed by their partners in accordance with the Birmingham Heartlands Research Ethics committee requirements. Domiciliary overnight arterial oximetry was conducted in all patients.

3.2.2.3 Exclusions

Patients with neuromuscular disorders, kyphoscoliosis, hypothyroidism and chronic respiratory diseases were excluded from the trial.

As shown in the flow chart, all patients who gave written consent then underwent an inpatient full polysomnography (PSG). Patients with symptoms of Snoring +/- EDS and an AHI ≥15 hour^{-1} (moderate-severe SAHS) [American Academy of Sleep Medicine 1999] then proceeded to the health status interview.

Patients who declined to participate in the trial progressed along the clinical protocol of the unit.

At the conclusion of the baseline health status interview, **randomisation** was undertaken. A random number sequence was generated by PC using the EPI-INFO software v6 (*CDC, USA*). This random number sequence was kept under the supervision of the chief technician of the laboratory and blinded to the chief investigator. Patients were allotted to CPAP if the random number was even and lifestyle intervention if the number was odd.

Patients randomised to receive **CPAP (Group I)** underwent a home based overnight CPAP titration study using the ResMed Auto-titrating CPAP device, followed by fixed pressure CPAP (95% percentile) set up by experienced technicians. They were given open and ready access to follow up with technicians as needed, for adjustments of masks and pressure if needed during the three months of the study. At the conclusion of the study,

patients underwent a final PSG using their CPAP machine. Compliance data on usage (hours/ night) was downloaded from the machine and recorded in a PC database using the ResMed autoscan software v1.1 (ResMed Inc, USA).

Patients randomised to receive **lifestyle intervention (Group II)** were given written and verbal guidance on sleep hygiene measures and formal dietary assessment by a clinic dietician. They were then given further reinforcement of the dietary and sleep hygiene advice after 4 and 8 weeks of initiation with repeat hospital visits. At the conclusion of the trial they underwent a final PSG at the end of the three month study period.

The final step in the trial was a **health status interview** in the same format of the baseline assessment undertaken by the principal investigator. The principal investigator was not blinded to the form of treatment given to patients as the health status assessment methods had to be standardised.

Patients were then returned to normal clinical follow up protocol. Those who were randomised to receive lifestyle intervention were offered a CPAP trial as appropriate on clinical decision.

3.2.3 Diffusion study

The diffusion of innovation phase of the research was divided into two questionnaire surveys. Both the questionnaires were designed to assess the following (*please see appendix*);

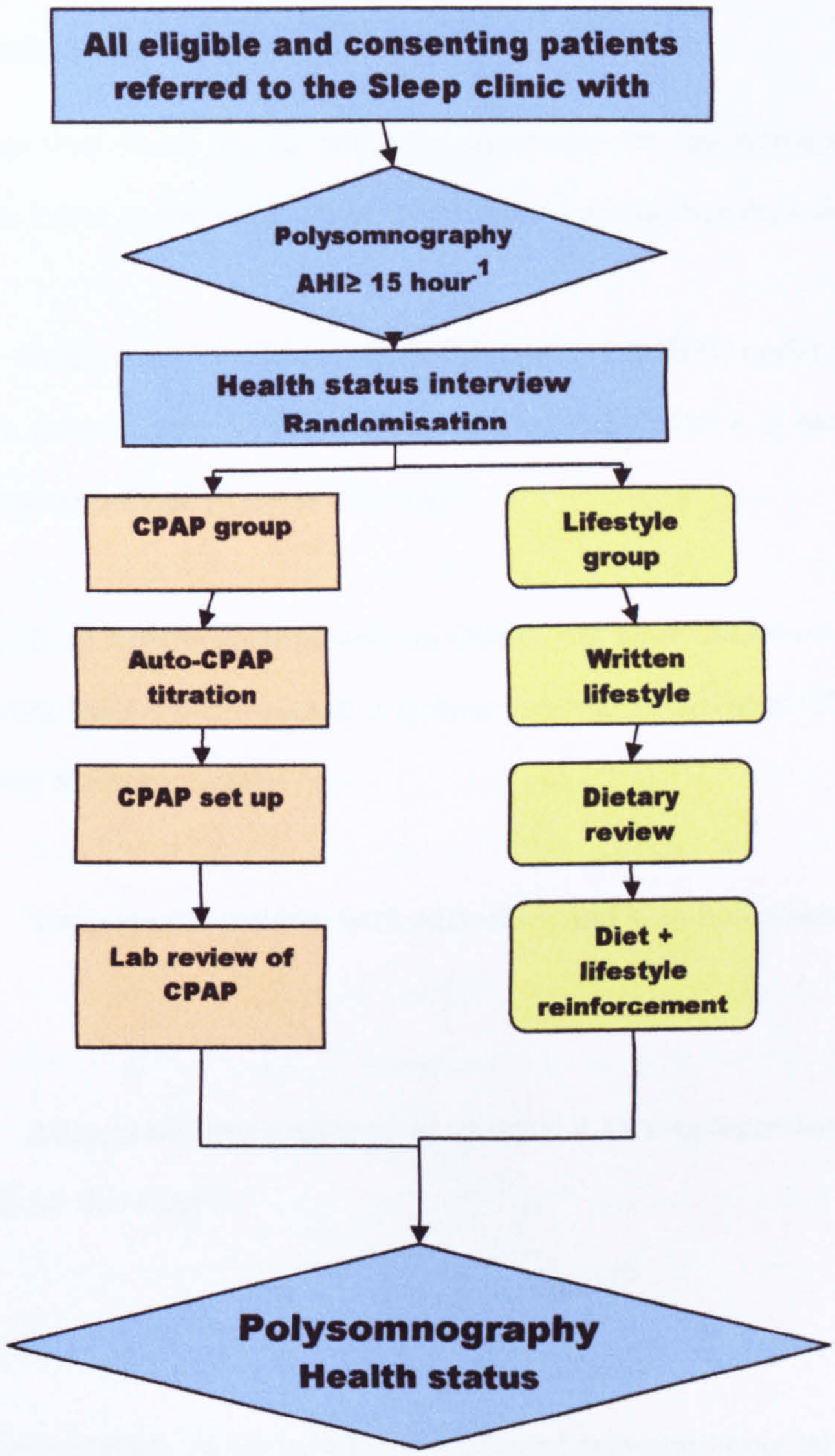
- Innovator categorisation of respondents
- Innovation characteristics for CPAP
- Communication networks for knowledge diffusion
- Factors influencing diffusion
- Secondary data on patient referral patterns, number of patients and size of the service need.

The primary care questionnaire survey was mailed to the chief executives of 303 primary care trusts in England & Wales requesting them to be forwarded to GPs interested in sleep disorders or new technologies.

The secondary care survey was mailed to one individual Respiratory Consultant in each Respiratory Medicine department in all NHS hospitals in England & Wales.

Both the questionnaires were followed up with a second mailing after 6 weeks for non-responders.

3.2.2.4 Flow chart of the sequence of events



3.3 Methods

3.3.1 Diagnosis of SAHS

3.3.1.1 Clinical review

SAHS was diagnosed based on the following algorithm for the retrospective clinical review. This was based on the clinic protocol which had evolved over the study period.

Step I: Patients with symptoms of SAHS (snoring & EDS) under went a home-based overnight pulse oximetry. Patients with a 4% arterial ODI of ≥ 15 hour^{-1} were given a therapeutic trial with CPAP [Ryan *et al.* 1995b].

Step II: Symptomatic patients with an ODI of <15 hour^{-1} underwent an inpatient overnight full PSG. Patients with an AHI ≥ 15 hour^{-1} were given a trial of CPAP [American Academy of Sleep Medicine 1999].

Step III: Symptomatic patients with AHI of >5 and < 15 hour^{-1} were classified as mild SAHS.

Step IV: Patients without symptoms of SAHS and AHI <5 hour^{-1} were classified as normal controls for this study.

3.3.1.2 RCT

Patients with symptoms of SAHS (snoring & EDS) and evidence of nocturnal apnoeas or hypopnoeas with an apnoea hypopnoea index (AHI) of ≥ 15 hour^{-1} on their full inpatient polysomnography were diagnosed as SAHS for the purpose of this study [American Academy of Sleep Medicine 1999]. In epidemiological studies an AHI >5/hour is traditionally considered to be significant in the presence of symptoms [Young 1993] however the benefit of treating patients with mild SAHS (AHI >5 and <15/hour) is variable and often compliance with treatment is reported to be less than 50% [Engleman

1997a]. Hence the conventional threshold (AHI ≥15/hour) in widespread use in clinical practice was used in this trial, as the target patient group would then be representative of the patients attending secondary care sleep clinics in the UK.

3.3.2 Health status interview (baseline)

The baseline health status interview (HSI) interview was held in an office in the Department of Respiratory Physiology with a single interviewer (IC) and the patient accompanied by a partner. A written explanation of the signs and symptoms SAHS had been provided to the patient while obtaining consent for the trial a few days prior to the interview. Patients were requested to read this information in the presence of the interviewer and an opportunity was provided at the outset for any questions.

Explanation of the treatment available for SAHS was given in generic terms avoiding any clear prediction of the 'gold standard or best practice option'. It was explained that the only way to determine who would benefit from which specific treatment strategy depended on assessment of therapeutic trial data and on patient preference. Although surgical options may be relevant in particular cases this would only be decided after a trial of one of the 2 alternative conservative measures, namely lifestyle intervention and CPAP therapy. This interview was held prior to randomisation and hence there was no indication of patient's future treatment group available to both the interviewer and the patient. There was no indication given at any stage in the trial that a cross-over of treatment groups would be available and if patients were not satisfied with the trial treatment option them would be withdrawn from the trial and returned to the Sleep disorders clinic for further assessment and treatment.

The interview comprised of an explanation of the concept of utility/ valuation of health and the utility assessment method detailed;

- **Step 1:** Utilities were first obtained using the SG method utilising a colour coded probability pie chart

- **Step 2:** Subject was then given time to complete the battery of questionnaires un-supervised (SF36, EuroQol 5D, GHQ 28, HADS) & Trail-making test A &B.
- **Step 3:** completing the interview with the utility derived by the TTO approach using a graph
- **Step 4:** This was followed by random allocation of treatment groups based on a random number chart where even numbers were allotted to Group I = CPAP therapy and odd numbers were allocated to Group II - lifestyle intervention arm.

3.3.3 Group I: CPAP therapy

Patients who were randomized to receive CPAP therapy underwent a home-based CPAP titration study using the Autoset II CPAP system (*ResMed Plc, Abingdon, Oxford, UK*). This system used a validated algorithm based on the flattening of the inspiratory flow curve to detect obstructive apnoea and hypopnoea and auto-titrated the pressure to eradicate these events [Teschler *et al.* 1996] [Littner *et al.* 2002]. A 95% percentile pressure predicted by the overnight auto-titrating CPAP study was used to provide fixed CPAP machines (Sullivan V elite, ResMed Inc, USA) during the trial. Standard Mirage nasal masks were used according to best fit after a trial in the laboratory.

3.3.4 Group 2: Lifestyle intervention

Each patient (along with their partners or next-of-kin) received a standard verbal guidance and explanation on our intention to measure the effect of a conservative strategy on snoring, daytime symptoms and nocturnal sleep disruption.

A written leaflet listing the strategies for the following were provided (please see appendix);

1. Sleep hygiene
2. Quitting smoking
3. Reducing alcohol consumption and

4. Controlling stress was provided and discussed.

Patients were then weighed, neck measurements taken and given guidance by a dietician. Verbal and written advice was provided on ideal body weight, calorie-controlled weight reducing diet and the benefits of regular exercise.

Sleep Diary

Patients were asked to maintain a Sleep diary which was a log book recording the following;

- total number of hours slept,
- period of sleep including duration and timing of naps if any
- daytime alertness score (Visual analogue scale (VAS) from alert = 0 to extremely drowsy = 10)
- quality of sleep (VAS score from 0 = poor/ unrefreshed sleep to fully refreshed = 10)

. Follow-up appointments were arranged at 4 and 8 weeks for reinforcement of the lifestyle intervention strategy but no measurements were obtained.

3.3.5 Conclusion of trial

The duration of the trial was 3 months and concluded with an overnight polysomnography (this was conducted using the CPAP equipment in Group 1 patients). The morning after the PSG, patients completed the same battery of health related quality of life questionnaires, Trail making test and the concluding health status interview using the same format as the baseline.

Patients were weighed and neck measurements taken.

All patients in Group 2 were then offered a home CPAP therapeutic trial and Group 1 patients were given the option to continue with their CPAP therapy long term combined with lifestyle intervention strategies.

3.3.6 Outcome measures

Primary

- Cost per QALY gained
- Change in health utility *(U_{sg} measured by the SG method, U_{tto} measured by the TTO method and U_{eq} as derived from the EuroQol)* with intervention.
- Change in HRQL scores

Secondary

- Change in ESS scores.
- Change in body weight and sleep diary parameters (Sleep quality & Sleep period)
- Change in neuro-cognitive function (Trail Making test)
- Correlations between respiratory or sleep parameters and health status.

3.3.7 Health related quality of life measurement

3.3.7.1 Short form 36 (SF36)

3.3.7.1.1 Background

The SF36 questionnaire was developed by the Rand Corporation in the USA from an inventory of 149 items used in their batteries designed to assess general health in the Health Insurance Study/ Medical Outcomes study. The SF36 started life as a 20 item questionnaire including 17 original items and then was expanded into its current form [Ware *et al.* 1993]. The 35 items in the questionnaire are incorporated into 8 subscales indicative of the different dimensions of health related quality of life and are then further summated into 2 summary scales:- Physical & Mental component summary scale (PCS/ MCS). There is a single item which is not incorporated in the summary scales asking respondents for their perceptions of health change in the past 12 months.

Figure 3.1: Summary scales and their derivation for the SF36

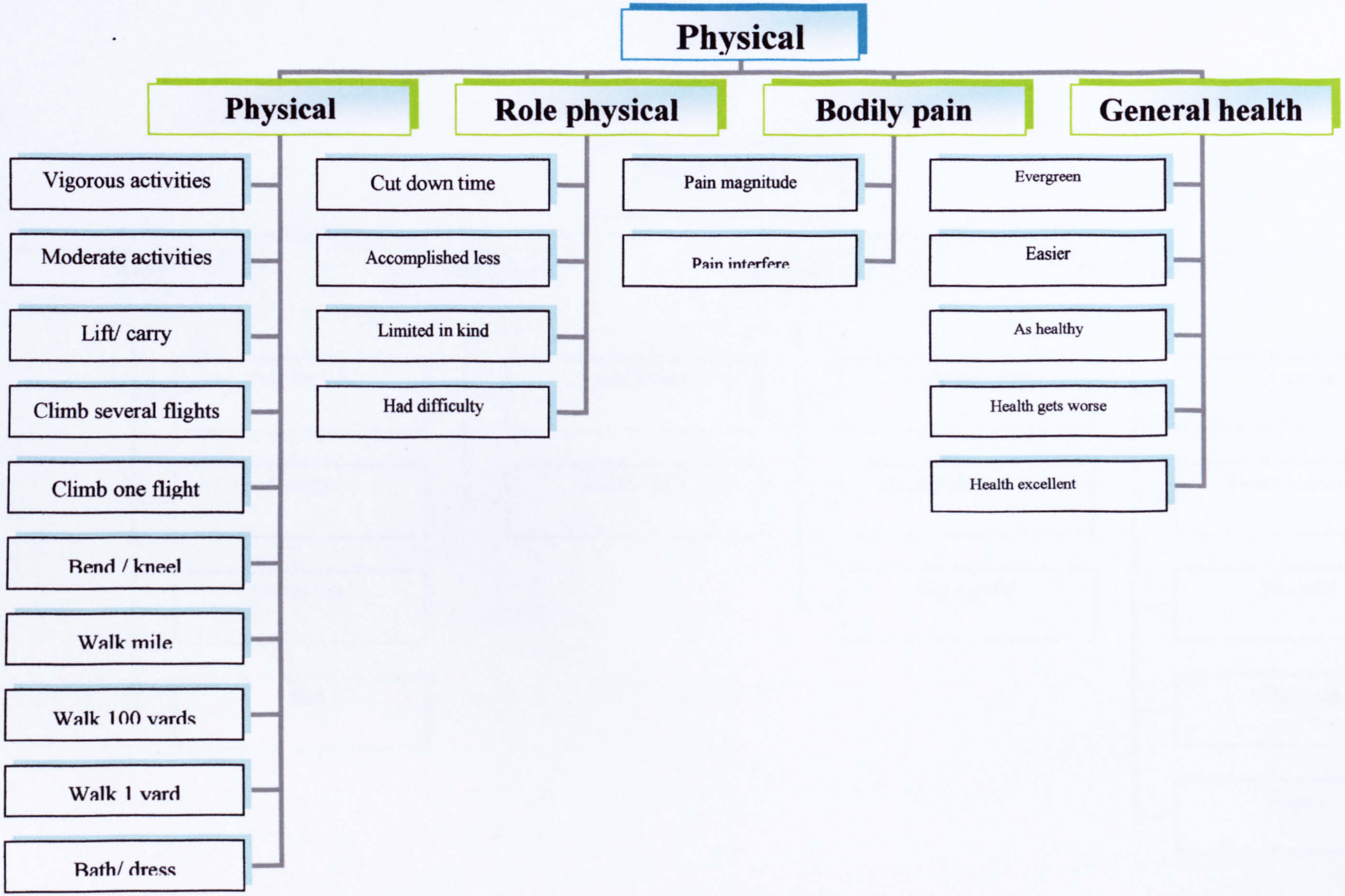
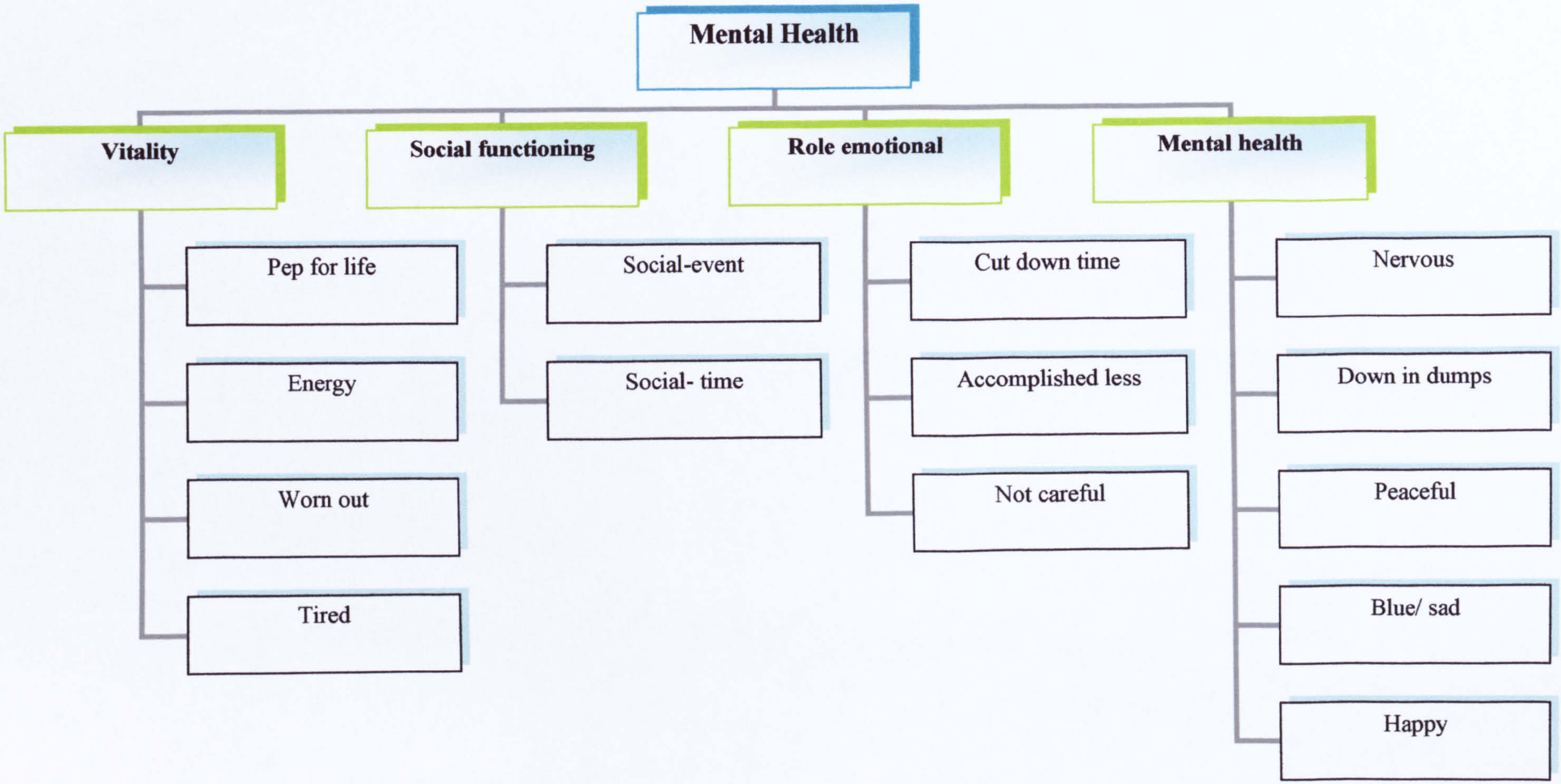


Figure 3.2: Summary scales and their derivation for the SF36



3.3.7.1.2 Scoring

Each subscale has its own response format from dichotomous yes/ no to the six-point scale of 'none to 'very severe'. Although different formats are not known to influence the outcome varying response styles have the potential of being visually confusing to respondents. The scoring algorithms are designed to increase the scales ability to compare results across different studies. Item scores for each of the 8 dimensions are summed and transformed into a scale from 0 = poor health to 100 = good health The scores are traditionally reported as mean scores and compared using parametric statistical methods without their frequency distribution, even though mean scores tend to be influenced by extreme outliers [Julious *et al.* 1995]. Factor analyses of correlations among the 8 SF36 subscales has consistently identified 2 factors accounting for over 80% of the reliable variance in different populations. These were the physical and mental components with 3 scales; 'physical functioning', 'role physical' and 'bodily pain' correlating highly with the physical component and 'mental health', 'social functioning' and 'role emotional' with the mental component. Using the psychometric techniques of principal factor analyses using rotated components the 2 summary scales were constructed and shown to be reliable in 23 different population groups tested. A by-product of this factor analyses led to identification of 10 items which contributed 90% of the variance in the 2 summary scores and hence the much shorter (SF12) survey questionnaire was launched. The subscales are not summed together to produce an overall score but transformed using United States normative population data to yield a score of 50 with SD of 10.

3.3.7.1.3 Steps in scoring the summary scales

- z-score transformation using means and standard deviations of SF36 scale scores from the general US population
- aggregation of scale scores using physical and mental score coefficients from the general US population
- transformation of summary scores to the norm based scoring (50, 10)

3.3.7.2 European quality of life questionnaire (EuroQol)

3.3.7.2.1 Background

EuroQol is a generic health related quality of life questionnaire which was developed by the EuroQol group formed in 1987[Brazier *et al.* 1993a]. One of the key aims of the group was to develop an instrument which would facilitate comparisons across nations and to generate a cardinal index of health with a potential for use in healthcare evaluation. The original 6 dimensional format was tested in Finland, The Netherlands, Norway, Sweden and the UK and this resulted in a standard 5 dimensional format, launched in 1991. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as population health surveys. EuroQol has been specially designed to complement other quality of life measures such as the SF-36, NHP, SIP or disease-specific measures. The current 3-level, 5-dimensional format of the EuroQol will remain unchanged for the immediate future.

EuroQol is designed for self-completion by respondents and is ideally suited for use in postal surveys, in clinics and face to face interviews. It is cognitively simple, taking only a few minutes to complete. Instructions to respondents are included in the questionnaire. There are 4 components in the questionnaire:

- Description of the respondent's own health by the EuroQol classification
- Rating of own health by means of the EuroQol thermometer
- Valuation of a standard set of health states defined by the EuroQol classification, and
- Background information about the respondent

3.3.7.2.2 HRQL component

Respondents describe their own health state in 5 dimensions; mobility, self-care, usual activities, pain/ discomfort and anxiety/ depression. Each dimension is described in 3 levels represented by numbers; no problem=1, some problem=2 and severe problem/ unable to perform = 3. Thus each state is described by a 5 digit number, table 3.1;

Table 3.1: EuroQol 5D choices illustrating a resultant health state = 11223

Dimension	***Level chosen***	**code**
Mobility	*No problems in walking about*	1
Self-care	*No problems in washing & dressing*	1
Usual activities	*Some problems*	2
Pain/ discomfort	*Moderate pain*	2
Anxiety/ depression	Extremely anxious/ depressed	3

The EuroQol health state thermometer is a visual analogue scale where respondents are asked to mark off their current health state between 0=*worse imaginable health* and 100= *best imaginable health* state. The final page of the questionnaire gathers demographic data on age, occupation/ activity, sex, education, smoking history, professional qualifications and postcode for geographical location. Thus the main uses of the EuroQol instrument as recommended by the EuroQol group are;

- Comparing respondents health state with general population and/ reference groups
- Valuation of classified health states using preferences elicited by a general population survey in 1993[Brooks 1996]
- Descriptive health state or valuations can be compared with the background variables i.e. age, sex, education etc.

3.3.7.3 General Health Questionnaire 28 (GHQ28)

3.3.7.3.1 Introduction

The GHQ 28 was designed to be a self-administered screening test aimed at detecting psychiatric disorders among respondents in community settings and non-psychiatric settings such as the general medical outpatients and primary care. The concept of psychiatric disorders emanates from the WHO's 'clinical descriptions and diagnostic guidelines of mental, behavioural and developmental disorders in the 10th revision of the International classification of diseases (ICD). The GHQ28 [Goldberg and Williams 1988] is designed with a view to identifying patients at a greater risk of developing a psychiatric

disorder. The threshold score is the premise that on independent and expert psychiatric assessment the probability that an individual identified by the GHQ28 will be positively diagnosed as having a psychiatric ailment, is >0.5. The GHQ28 was initially designed for identifying psychiatric disorders among Londoners but has since been translated and validated in 38 languages with similar validity. The questionnaire identifies a breakdown or deviation from normal functioning rather than lifelong traits, namely;

- inability to continue to carry out one's normal healthy functions, and
- appearance of new phenomena of a distressing nature

3.3.7.3.2 GHQ scoring

GHQ has a 4 point response scale as shown in table and utilises either a bimodal response for screening or a 4 stage Likert scale for profiling. The Likert scale was chosen in order to give a more detailed profiling of the 4 dimensions. The threshold for scoring cases was based on 16 studies where the modal value was 4/5 for each subscale. When comparing 2 samples for prevalence of psychiatric illness using GHQ scores the authors recommended statistics of dispersion (Mean & standard deviation) or proportion of high scorers in each sample.

Table 3.2: GHQ28 scoring systems

Question	*Less than usual*	*No more than usual*	*Rather more than usual*	*Much more than usual*
Likert score	*0*	*1*	*2*	*3*
GHQ- bimodal	*0*	*0*	*1*	*1*

In this study with SAHS patients the GHQ28 was used to assess the prevalence of psychiatric illness at baseline in each group comparing the scores and proportion of high scorers and then to assess the change in scores and proportions after 3 months of intervention. Secondly the GHQ28 scores have been compared with the main polysomnographic and demographic variables using a multiple regression analysis to determine the contribution to high scores [Singh *et al.* 1987]. Thirdly I have compared

the correlation of the scores obtained by the mental health dimensions from the SF36 and HADS scores with those obtained by the GHQ28, to assess their reliability.

3.3.7.4 Hospital Anxiety & Depression Scale (HADS) [Zigmond *et al.* 1983]

3.3.7.4.1 Introduction

The HADS instrument was developed in 1983 as a brief assessment of anxiety and depression using 14 items divided into 2 sub-scales. In order to correct for the common problems of physical illnesses influencing mood states the design of this tool excludes all items relating to both emotional and physical disorders. The design also attempted to distinguish between anxiety and depression by basing on the an-hedonic state as this responds best to anti-depressant drug therapy. While the anxiety subscale items are based on the psychic manifestation of anxiety neurosis from the present state examination.

3.3.7.4.2 Scoring

HADS is derived from clinical experience and not by factor analysis. Dependant on direction of the wording of each item they are scored from 0-3 or 3-0, representing the degree of distress; none = 0, a little = 1, a lot = 2 and unbearably = 3. On summation of individual scores and compared with clinical psychiatric diagnoses , a HADS depression ratings of less than 7 are considered to be non-cases, 8-10 as doubtful and >11 as definite cases [Carroll *et al.* 1993].

3.3.8 Economic evaluation

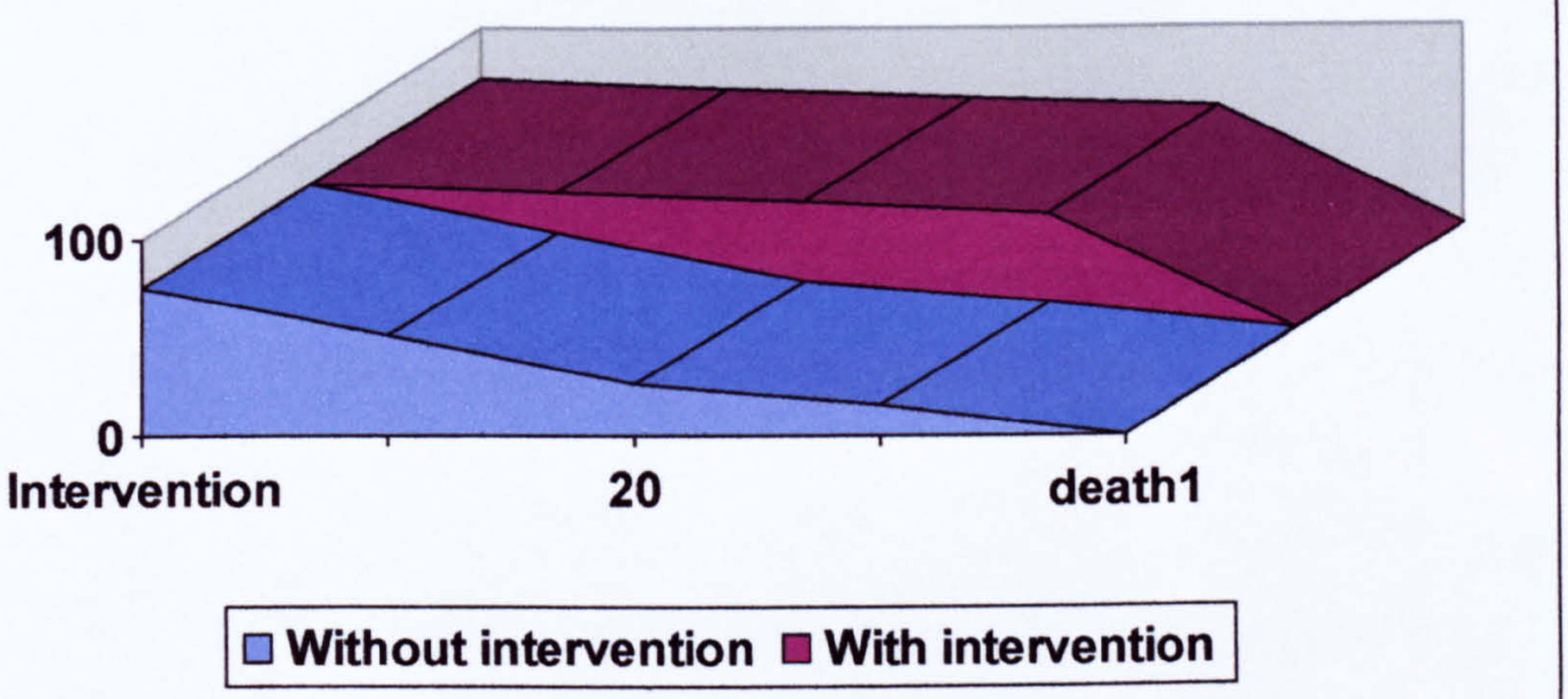
3.3.8.1 Tools for utility assessment

3.3.8.1.1 Quality adjusted life year (QALY)

The potentially insoluble economic problem of infinite health needs competing for finite health care resources has led to a variety of utility approaches to measure the value of health, sometimes incorporating HRQL with economic analyses to provide a fairer means of distributing health care funds [Fallowfield 1990]. The QALY was developed to combine

quantitative data such as increased survival and qualitative data concerning disability and distress with basic economic data like the cost of surgery or pharmacological therapy to provide a theoretical cost-per QALY gained [Weinstein *et al.* 1977].

Figure 3.3: Quality gained by an intervention



Thus the basic approach to calculating the QALY is by health status indices which are essentially weighting schemes. To satisfy the QALY concept the quality weights must be a) based on preferences, b) anchored on perfect health and death and c) measured on an interval scale [Drummond *et al.* 1997]. Each definable health status from death or coma to varying degrees of disability or disease to full health, accounting for age differences, is assigned a weight from 0 to 1. While zero is the only practical number that can be conceptually associated with death, the concept of full health being = 1 allows measurement in fractional terms (e.g. 0.5 years in full health = 0.5 QALY = 1 year in health state valued at 0.5) and thus allows compatibility with years of healthy life. When the number of years an individual expects to spend in current health state is multiplied by the weight allotted to that health state then the QALY is derived as a theoretical

equivalent of number of years in full health [Weinstein and Stason 1977]. The underlying rationale being that individual or communities are the best judge of their own welfare and likely to assign higher weights for more preferred health outcomes [Drummond, *et al.* 1993].

Calculating QALYs is based on the difference between the areas under the two curves illustrated in figure 3.1 but this is designated the QALY gained without discounting. As individuals tend to value immediate gains more than gain on a future date, QALYs are discounted to account for this time preference. The UK Department of Health recommends discounting at 6% for both costs and gains and the US Treasury recommends a more rigorous discounting at 4, 7 and 10% which is the system used in this study as this allows better comparability and sensitivity analysis. The method of discounting uses the concept of taking the gain for a year in the future and moving it back year by year to the present reducing the amount each year by r% of the remaining amount, where r = the annual discount rate [Drummond *et al.* 1997].

The most commonly used methods for eliciting individual preferences and thus assigning quality adjusted weights for health outcomes are; the rating scale, SG and TTO methods. While both the rating scale and TTO derive their weights under conditions of certainty are called 'values' the SG is based on uncertainty and hence caused 'utilities'.

Table 3.3: Methods for measuring preferences

Response method	Certainty (values)	Uncertainty (utilities)
Scaling	Rating scale Category scaling Visual analogue scale Ratio scale	
Choice	Time-trade off Paired comparison Equivalence Person trade off	Standard gamble

3.3.8.1.2 The Rating scale method

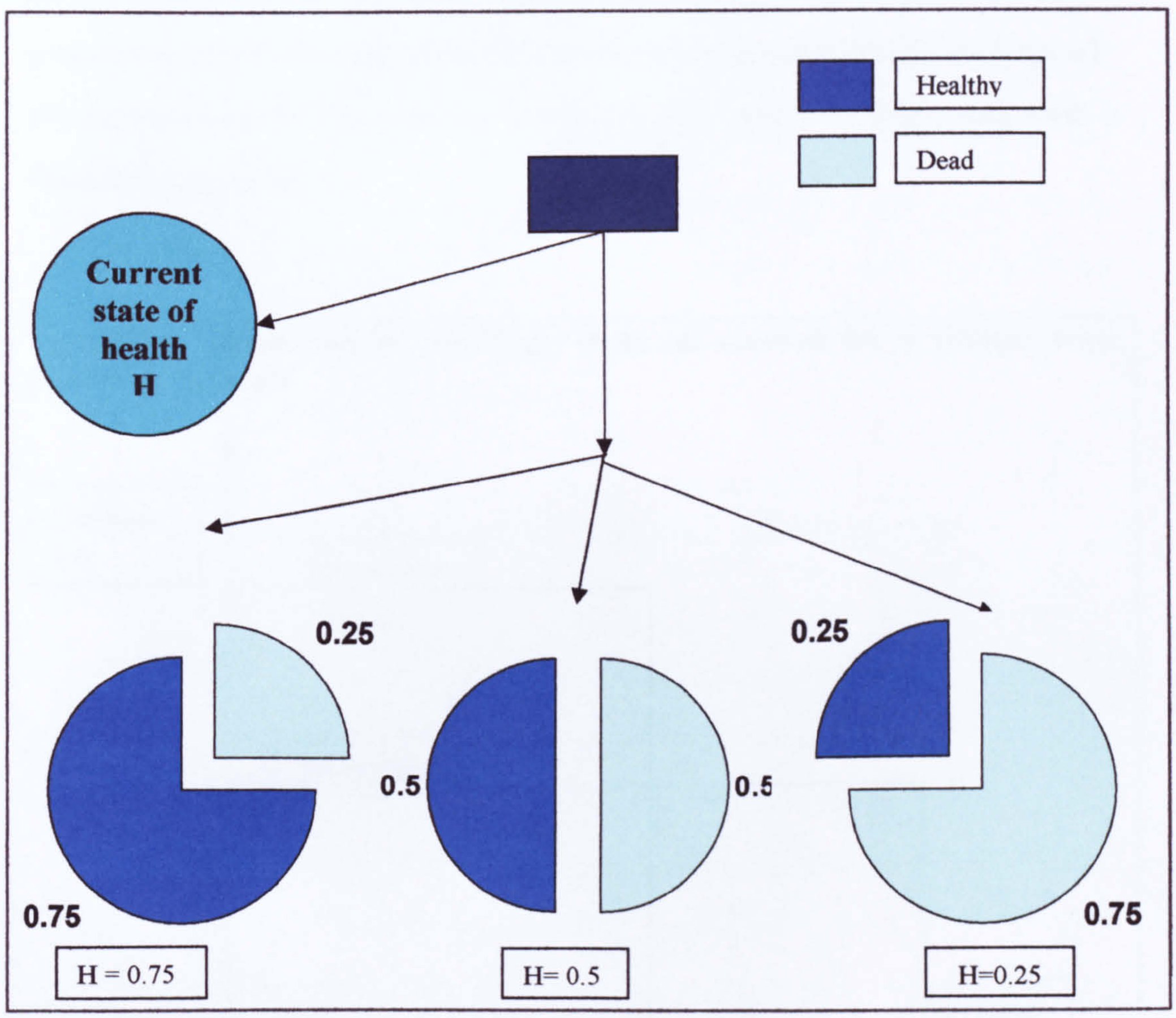
3.3.8.1.2.1 Standard Gamble method (SG)

Utility weights derived by the Utility theory of von Neumann and Morgenstern are based on individual decision making under conditions of uncertainty [von Neumann and Morgenstern 1944]. Utility is a preference that an individual will have on considering the consequences of different courses of action. The SG method captures the individual's attitude to risk and thus is influenced by whether an individual is risk-averse, risk indifferent or risk seeking. Although it is shown that individuals are risk averse for large gains, risk seeking for small gains or losses, a consistent risk attitude is modelled and assumed for practical convenience. Unlike scaling methods of eliciting a response by introspection as in HRQL methods on a numerical scale, utility/ value measurement is based on making a choice. Since future health or an individuals' response to a health care intervention is uncertain the preferred method for measuring preferences is with utilities [Mehrez and Gafni 1991]. The only caveat being that when utilities are aggregated in a sample to represent societal/ community preferences the utility theory no longer applies, unless it is assumed that 'society' is a single entity with utilities equal to mean utilities of the community.

The core of SG method is a paired comparison in which the respondent chooses between two alternatives with two possible outcomes: a good outcome with the probability p and a bad outcome with the probability of 1-p. The probability of outcomes is varied until the respondent is indifferent about the two alternatives. The SG begins with presenting a written description of the health state (a scenario) under evaluation. After reading the scenario, the respondent is asked to imagine a hypothetical situation in which he or she is confronted with a choice. The options available are to continue living in the state of health described in the scenario, or to take a gamble with two possible outcomes, e.g. perfect health and death. The probabilities in the gamble are systematically altered until the respondent cannot choose between the certainty of continued life in the described health state and the gamble. The utility for the evaluated health state = (probability of outcome A)* (utility of outcome A) + (probability of outcome B)* (utility of outcome B). As most subjects find it hard to relate to probabilities, the SG is supplemented by visual aids like a

probability wheel (an adjustable disk with 2 colour coded sectors which are changed as each option is presented to the subject, representing the probabilities of health or death as in figure). Where a temporary health state is being assessed which is worse than the current state but not death, this can be set = 0 and the same formula used. However if it is desirable to relate this worse temporary state to death on the 0-1 scale, a repeat SG approach is required [Drummond *et al.* 1997].

Figure 3.4: Illustration of the standard gamble method of eliciting a utility for a chronic health state preferred to death.



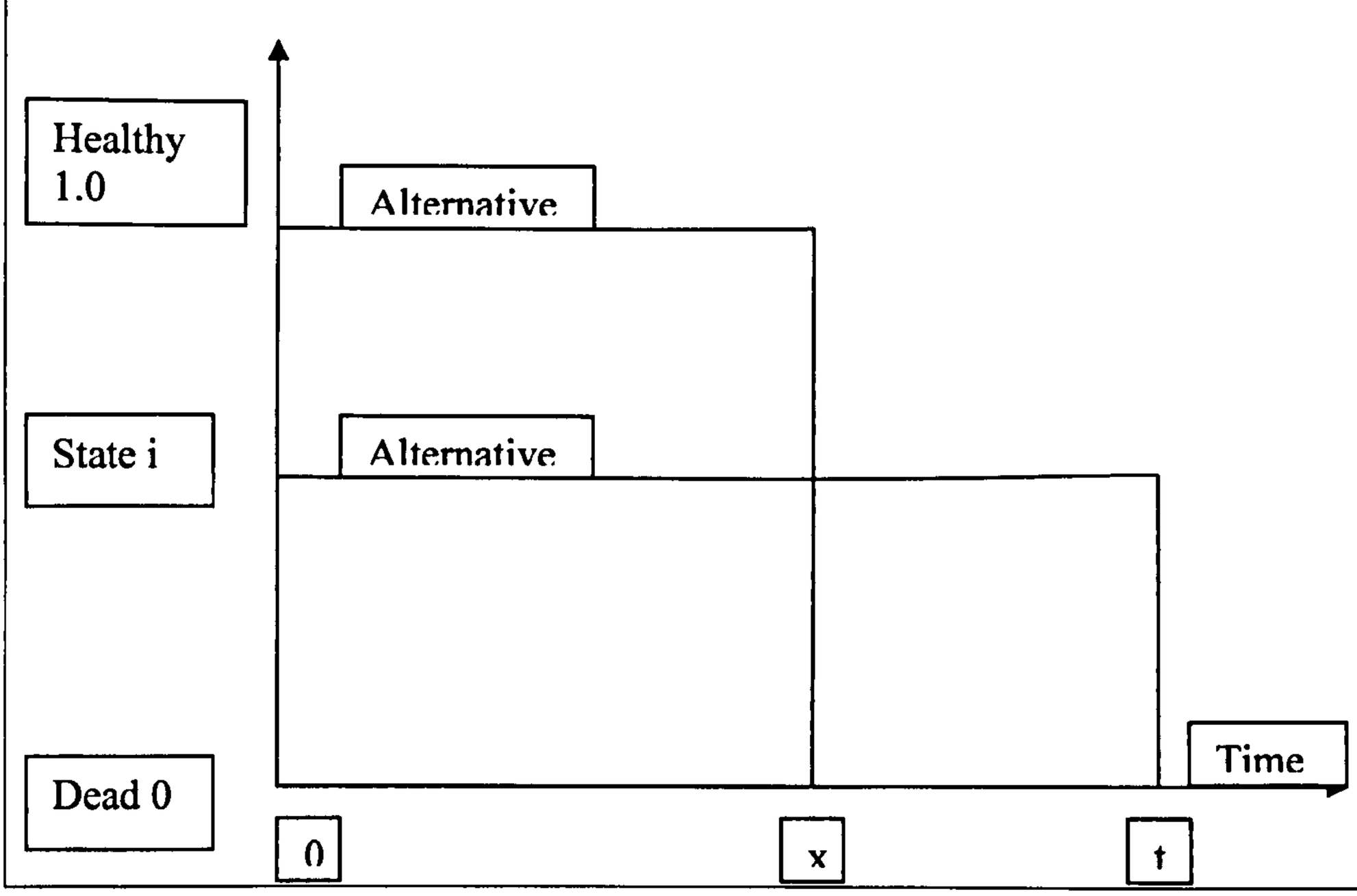
Since utility of death = 0 and for healthy state = 1; Utility for health state H = probability p for full health. In this illustration H = 0.75, 0.5 & 0.25 with the 3 probabilities presented.

When these utilities are multiplied by life-expectancy to calculate QALYs, it is assumed that utlities are independent, that the trade off is constant at the extremes of the health states and responders are risk neutral.

3.3.8.1.2.2 Time-trade off method (TTO)

The TTO method was developed for use in health care assessment as an easy to administer instrument, yet giving comparable scores to the often intuitively challenging Standard gamble method [Torrance, *et al.*1972b]. It is not related to any existing behavioural theory, but to a 'value function'. It enables the identification of different points on an individual's indifference curve in his evaluation space [Mehrez *et al.* 1990a]. The application of the TTO technique to a chronic state considered better than death is illustrated in figure 3.5.

Figure 3.5: Illustration of the Time trade off method for a chronic state preferable to death



The subject is offered 2 alternatives; 1) state i for time t (= life expectancy for the individual followed by death) in the current health state/ chronic condition or 2) healthy

for time x<t followed by death. The concept is a trade off of the quantity of life in the current less desirable state for less number of years in a state of best imaginable health. This time x is varied till the subject is indifferent between the 2 alternatives, at which point the value of state i;

$$h_i = x/t$$

There have been alternative suggestions to measuring in the dead to healthy scale by other researchers who have used 'daily TTOs' with a trade against unwanted sleep or annual TTOs where the trade off is against unwanted convalescence [Buckingham 1993]. As the purpose of the TTO weighting in this study is to derive QALYs we have chosen to the dead to healthy model. In the event of assessing the value of temporary states, TTO is derived in a 2 stage method with the temporary state being redefined as of a short duration followed by death due to a concern that imminent death would tend to distort the results [Cook *et al.*]. However there was no demonstrable difference when the individuals in this study were faced with outcome in 12 weeks or 12 years suggesting that the TTO was applicable to different time frames.

3.3.8.1.2.3 Reliability & validity issues for weighting methods

One of the main concerns raised against both of these weighting measures is the dependence on the assumption that chronic health states are constant, that death is the worst possible outcome and the lack of specific input of psychosocial parameters. It is assumed that individuals are prepared to sacrifice a constant proportion of their life span in order to achieve a given improvement in their present health state, which is irrespective of the absolute amount of remaining years [Loomes and McKenzie 1989]. It is argued that a younger individual faced with the prospect of 20 years in a state of ill health may be willing to trade off 10 years for improved health, while the same may not be true for an older individual faced with < 5 years of life expectancy [McNeil *et al.* 1981]. This would tend to overestimate the value of present health of an older individual compared to a younger individual.

On the other hand, there is evidence to show that both individuals and society tend to value utility obtained at a younger age greater than the same achieved at an advanced age. This is against the basic assumption that the preference of an individual will be towards maximizing his utility and is independent of age. In a study to test this hypothesis, individuals asked to rate the value of life, regardless of their age valued a life of a 30 year old as equivalent to 11 sixty-year olds. On average, people were willing to sacrifice 35 older adults (70-year-olds) to save one 30-year-old. It was also shown that a measure which increased life-expectancy by 1 year, conditional on having survived until the age of 75 years, is given a low weighting [Johannesson *et al.* 1996a].

Unlike classical psychometric approach, where each instrument has to undergo rigorous testing in different settings, economic analysis instruments are based on an underlying utility theory and its assumptions. Even when human behaviour deviates from that predicted by normative theory, it is suggested that we would prefer to achieve that which is better and more rational rather than unaided judgement for a complex and important decision [Howard 1988].

Others have reported that preference scores for a severe pain health state were not independent of time, hence not satisfying the assumptions of the utility theory [Bala *et al.* 1999]. When patients' raw TTO scores were adjusted using information on their utility functions for survival time, to derive a measure of health state utility equivalent to the SG in a sample of 199 cardiovascular patients; the raw TTO scores were significantly higher than SG scores, while the adjusted TTO scores were shown to be equivalent [Martin *et al.* 2000].

Conversely, in a sample of 30 disease-free testicular cancer patients, SG scores were significantly higher than unadjusted TTO scores for all profiles. As the majority of patients (85%) were risk-averse, certainty equivalent adjusted TTO scores were higher than unadjusted scores, and were not significantly different from those obtained from the SG for three of the four profiles [Stiggelbout *et al.* 1994].

Threats to validity include construct under-representation and construct-irrelevant variance. Construct under-representation occurs when a stimulus presented to a judge fails to fully represent the depth and complexity of information required in actual judgments. Construct-irrelevant variation occurs when factors irrelevant to preferences

influence measurements of utilities. Among several factors that cause construct-irrelevant variation are cognitive abilities, numeracy skills, emotions and prejudices, and the elicitation procedure. The validity of an elicitation protocol depends (1) on the degree to which its scaling method captures the relevant facets of utility and (2) on the degree to which measurements are influenced by construct-irrelevant variation.

Discrete-state health index models provide an alternative to direct elicitation of utilities and work by attaching fixed preference weights to observable health states. The creation of discrete-state models with current technologies requires the adoption of strong assumptions about the scaling properties of utilities. Because of the impact of variation in techniques on measurements, the combination of utilities elicited with different protocols is not recommended in cost-utility analysis in a league table [Lenert *et al.* 2000].

There is also evidence that suggests that various health status measures are at best only moderately correlated with SG and TTO utilities. Results from regression analysis, predicting SG or TTO utilities from combinations of health status scales, typically have an R^2 of 0.18 to 0.43. Preferences determined by rating scale methods are more strongly related to health status scores, but correlations are variable ranging from 0.17 to 0.46 and only about 27% to 34% of variance can be explained in regression models. The Quality of Well-Being Scale and other multi-attribute preference measures have low to moderate correlations with health status measures (r = 0.03 to 0.71). Health utility and psychometric health status scales may measure different attributes of health and are not interchangeable indicators of HRQL [Revicki *et al.* 1993].

3.3.8.1.3 EuroQol health index

The multi-attribute theory is an extension of the traditional utility theory by including an additional axiom of utility independence, which has three levels of assumptions. (i) First order utility independence assumes that there is no interaction between the preferences for one attribute and the fixed levels of other attributes and that the relative scaling within each sub-scale/ attribute remains constant. (ii) Mutual utility independence assumes that there is no interaction between the preferences for some attributes with fixed levels of

other attributes. (iii) The third assumption being the additive utility independence which states that there is no interaction for preferences among attributes at all.

The third method of deriving weights for QALYs is based on utilising the pre-existent multi-attribute scales such as the EuroQol, Quality of well being scale (QWB) and the Health utilities index (HUI). For the purpose of this study I chose the EuroQol as explained in section above.

EuroQol scores were calculated by comparing health states based on the 5 dimensions and 3 level design of the questionnaire with TTO scores for 243 potential health states obtained by a population study [Dolan *et al.* 1995]. The problem was that it was virtually impossible to generate direct valuations for all of these states, and thus it was necessary to find a procedure that allowed the valuations of all EuroQol states to be interpolated from direct valuations on a subset of these (42 health states were chosen for valuation) using a "tariff" of EuroQol values. Thus this model appeared to predict the values of the states for which there were direct observations and, thus, authors justified their use to interpolate values for the states for which no direct observations existed as shown in table 3.4.

Table 3.4: Coefficients for TTO tariffs used in EuroQol health states.[Dolan 1997]

Dimension	Coefficient
Constant	0.081
Mobility- level 2	0.069
Mobility – level 3	0.314
Self-care – level 2	0.104
Self care – level 3	0.214
Usual activity – level 2	0.036
Usual activity – level 3	0.386
Anxiety/ depression – level 2	0.071
Anxiety/ depression – level 3	0.236
N3	0.269

N3 signifies any attribute which receives a level 3 response

Table 3.5: Algorithm for calculating EuroQol health state values (example state 11223)

Full health	**1.000**
Constant term (for any dysfunctional state)	-0.081
Mobility (level 1)	-0
Self care (level 1)	-0
Usual activities (level 2)	-0.036
Pain and discomfort (level 2)	-0.0123
Anxiety and depression (level 3)	-0.0236
N3 (level 3 occurs in any 1 dimension)	-0.269
Therefore the estimated value of health state 11223	0.255

3.3.8.2 Measures of economic evaluation

3.3.8.2.1 Background

The role of economic evaluation in HTA includes a range of techniques that can be used to investigate the cost and consequences of different procedures or programs. There are various methods of analysis; cost of illness study, cost-minimisation study, cost effectiveness analysis, cost utility analysis and cost benefit analysis. Economic evaluation in the public sector was initially based on the cost-benefit analysis (CBA), which is an application of the theory of resource allocation at the core of welfare economics. Application of CBA was used in the public sector investment planning and environmental protection. It measures both the cost and benefits in monetary terms. The costs of a programme are measured in opportunity costs defined as the benefits of the best alternative programme. Benefits are defined as the best willingness-to-pay for the project. Using this method of analysis comparison is possible within and beyond the technologies/ programmes in the health care sector. Thus it is a method of establishing allocative efficiency of resources, provided all costs involved are known. However the economic evaluation in health care started off with cost of illness (COI) studies. Benefits were calculated as reduced treatment costs and reduced loss of production by a method known as the human capital approach. However it proved difficult in the health care setting to assess all the benefits in monetary costs. Hence this led to the development of the Cost

effectiveness analysis (CEA). In this system the costs are monetary but the benefits are measured in physical units and are studied with a societal perspective considering consequences not only within the health sector but beyond as well. Hence they are intuitively best designed to study the comparative benefits of a new technology compared with an alternative with homogenous outcomes. In the event of different outcome parameters CEA is not beneficial in allowing a rational comparison between 'unlike' benefits and is inconsistent with the welfare economic theory.

The cost utility analysis (CUA) was designed to overcome the restrictions of the CEA method with the utility based measure of outcome. Utilities measure individual preferences and hence intuitively assess the satisfaction derived by people with healthcare services. One of the primary goals of CUA was to allow comparison of different technologies in various different health care sectors with heterogeneous outcomes. Combining a utility with life expectancy in the QALY, a cost/QALY can be estimated and compared between different interventions in league tables, as long as the same method of assessment was used to derive the utility.

3.3.8.2.2 Costs

3.3.8.2.2.1 Introduction

Cost is the product of 2 elements; the quantity of resources used and the unit cost of the resources. Cost generating events (like hospital stay) can be usually measured in patient specific (stochastic) or non-patient specific (deterministic) ways. Costs may be unit cost for individual events or average costs (total cost/total number of patients or events) and marginal costs are calculated for individual extra events. While opportunity cost is the theoretical benefit that would have been derived with the 'next best' use of the same resources. Although costing can be in various ways as described in the table 7.6, the approach used here is partially stochastic where the average costs for the same cost-generating events are taken with patient specific effectiveness data available from the present RCT. Unlike the patient specific data which varies with individual patients in a trial and is collected for each patient's cost generating events; this method uses average

costs which an ideal patient would encounter when going through a standard diagnostic and treatment pathway in a typical DGH. This has been done to ensure that the cost data is more generisable and hence more useful in the context of HTA.

Table 3.6: Approaches to costing [Drummond *et al.* 1997]

Costing approach	Measurement of resource use and effectiveness data
Deterministic	Non-patient specific resource use /patient specific effectiveness data
Partially-stochastic	Non-patient specific resource/ patient specific effectiveness
Wholly stochastic	Patient specific resource use/ patient specific effectiveness data

3.3.8.2.2.2 Perspective

Costs are dependant on the viewpoint of any analysis (example the NHS as a provider, paying individual or an insurance agency covering a new technology provision) and certain overhead costs which may be common for both the technologies concerned need to be included in the analysis. Cost data is either collected on an individual case basis or on a general resource basis from hospital/ institutional records. Although the theoretical cost of any item is the opportunity cost (i.e. the value of foregone benefits because the resource is not available for its best alternative use) the pragmatic approach to costing is to take its existing market price or in the case of the NHS the subsidised price available due to a bulk purchasing agreement.

3.3.8.2.2.3 Types of costs

Traditionally the types of costs for potential inclusion in economic analysis are usually classified into 5 main groups [Drummond 1987];

- direct health care costs (cost of intervention, cost of treatment, future health service costs, trial costs)
- direct non-health care costs (other public sector costs, patient travel costs, patient's opportunity costs)
- indirect health care costs (cost of morbidity and mortality)

- indirect non-health care costs (productivity costs, future non-health service costs)
- intangible costs

The costs of various investigations in this study were taken from the departmental cost break-down (average costs-not patient specific) and included discounted bulk purchase prices available within the NHS. There were no clear cut price lists available for similar services within the private sector/ open market hence these could not be considered. However costs published from other UK institutions have been included in the analysis to allow comparison of cost/QALY values.

Valuation of non-market items such as leisure time is based on the price an employer would have to pay (i.e. overtime rates) to buy some of the worker's leisure time, similarly volunteer time is also calculated on minimum unskilled wages to average earnings depending on the situation. In this study, the patients were recruited during their routine visit to the hospital and underwent almost exactly the number of investigations as they would for a normal clinical diagnostic study. The extra 2 hours spent with interviews were the same for both groups of patients hence were excluded from the analysis.

Although most cost analysis studies report real costs, adjustment of costs are sometimes favoured when unadjusted prices would introduce substantial bias into a study and there is clear and objective way of making the adjustments [Drummond *et al.* 1997]. There is an argument for including costs incurred in future years as a result of keeping people alive as an indirect effect of a healthcare intervention. However there remains a lack of consensus in this matter and economists believe that an estimation of the average annual per capita cost may need to be added, either in primary or sensitivity analysis. Omission of such future costs may bias cost-effectiveness estimates against interventions which prolong life in favour of those which improve HRQL, especially in the elderly.

The impact of including these future costs on the cost- effectiveness of the treatment of hypertension was studied in Sweden. The cost/QALY gained was found to change little among young men and women due to the addition of future costs, but increased by about $14,000 for middle-aged men and women and about $27,000 for older men and women. When future costs were not included, the cost / QALY gained are generally lowest among older men and women, but when future costs are included, the cost per QALY gained is

generally lowest among middle-aged men and women. The authors concluded that the total resource consequences of changes in mortality should be routinely considered in cost- effectiveness analyses [Johannesson *et al.* 1997].On the other hand it has also been shown that adding such a cost makes little difference to the cost/life year gained and such unrelated healthcare costs are ignored without biasing the results significantly. In the case of SAHS, treatment with CPAP has been shown to improve HRQL and daytime functioning. It is also shown to reduce hypertension but there is as yet no clear epidemiological data showing a prolongation of life or reduction in mortality [Veale, *et al.* 2000] [Wright *et al.*1997a] hence unrelated health care costs in the future were considered not relevant to this study.

In the matter of dealing with overhead costs incurred within hospitals there is a simple formula proposed by Drummond;

1) Directly attributable costs for the programme implementation
2) Deduct from total hospital operating expenditure, the directly allocated costs and departmental costs not known to be involved with this program
3) Allocate remainder of hospital operating expenses on the basis of number of patient days
4) Undertake a sensitivity analysis

For the purpose of this study, the costs for each investigation, clinic visit, consultation with dietary services and inpatient tests were calculated inclusive of the hospital overhead/ operating cost attributable to the particular service within the prices provided by the Finance department of the Hospital. Hence a separate costing exercise has not been undertaken.

In this trial, the costs involved in the lifestyle arm are quantitatively less than the cost of CPAP therapy and inclusion of PSG costs may bias against the cost/QALY ratios obtained in the lifestyle arm. It may be argued that as PSG is not a standard test available in most DGHs it may be removed from the final cost/QALY analysis. However within the sensitivity analysis the impact of non-PSG (cheaper) tests may also be calculated to make the cost/QALY ratios more generisable.

3.3.8.2.2.4 Time horizon

The time horizon is the period of time for which costs and effects are measured. The time horizon is determined partly by the duration of the trial, by the perspective of the intervention under study and the duration that the policy maker is interested in which may be longer than the period under study [Davidoff *et al.* 1996]. Although the analysis can be performed for a variable periods of time, a long duration is usually recommended in order to incorporate the effect of changes in both costs and resources. Limiting the costs of analysis to a fixed period after the intervention may introduce bias into a cost comparison, especially at the beginning or end of treatment phase or life [Briggs *et al.* 1994]. In this case CPAP is known to affect a measurable benefit within days of institution of therapy and studies have shown the benefits obtained in the first 4-6 weeks to be maintained in the long term. As this is also a life-long treatment the conceptually appropriate measure was a product of the effect on utility with life-expectancy. However further analysis included a 5 year treatment perspective as well as future developments may significantly alter the treatment options and it may not be appropriate to consider CPAP usage in decade terms. The cost measurement year is 1999.

3.3.8.2.2.5 Economic welfare theory

Economic welfare theory concept underlines all the economic evaluation exercises and hence it is usually argued that opportunity and marginal costs should be included and should dictate how they are measured and valued. Based on this concept, the benefits of therapy for SAHS patients have a much wider societal aspect in reduction of RTAs, work related accidents, better productivity and reduction of psychological distress. Measuring this is beyond the scope of this study as only short term gain in health status is used, hence to use opportunity costs in economic analysis of SAHS patients i.e. 'time given up from work to undergo treatment' would be inappropriate and introduce a bias against the treatment. While in the case of CPAP therapy, cost/QALY may be over-estimated by ignoring societal benefits, in lifestyle intervention a 3 month trial duration may be a disadvantage as lifestyle changes are expected to take much longer to achieve (over

estimating cost/QALY). However it was decided that the current waiting list for SAHS patients in the UK varied between 3-9 months and it would not be un-ethical to conduct a 3 month trial denying the patients randomised to lifestyle intervention 'a physician led decision' on treatment. It was felt un-justified to increase the waiting period for a CPAP therapeutic trial (the current 'gold-standard') beyond this time horizon.

3.3.8.2.2.6 Discounting of costs

Discounting is based on the concept that any goods or benefits are more desirable at the present than in the future and this principle is called 'positive time preference' and intuitively exists even in the absence of interest rate structures. This is calculated by the formula [Drummond, *et al.*1997];

$$P = \Sigma^{3}_{N=1} F_n (1+r)^{-n}$$

Where P = present value, F_n = future cost at year n and r = annual interest / discount rate; $(1+r)^{-n}$ is the discount factor and can be calculated from tables/ formula.

However in the case of this study, there is an initial capital cost of equipment like the CPAP machine, masks which then need to be calculated based on an annual equivalent cost for the life of the equipment. In this case if the capital outlay is K, and the annual sum E which over n years at an interest rate of r will be equivalent to K is calculated by;[Drummond *et al.* 1997]

$$K = E\left[\frac{1+(1+r)^{-n}]}{r}\right.$$

The choice of the discount rate has been traditionally taken as 5% in the last 3 decades in most economic evaluation analyses as this was assumed to be the social rate of time preference (i.e. the measure of society's willingness to forego consumption today in order to have a greater consumption in the future). This has loosely been based on risk free investment like Treasury bonds and their prevailing rates. In the UK the public sector discount rate announced by the UK Treasury is used and this is currently 6% [Anon.1997b]. This is based on a social opportunity cost approach and is a general statement on social time preference.

In the USA the recommended approach is the shadow-price-of-capital approach (i.e. opportunity cost of a public programme is measured/ transformed in terms of the foregone private activities that would have to be given up). Some UK analysts recommend using 0%, 3% (representing real risk less discount rate) and 5% (as most studies in the last 3 decades have adopted this figure) but many cost-benefit analysis of public spending use 10% in their calculations and recommendations. The Panel for Cost effectiveness in Health Medicine in their consensus statement argue that a convention is required for a real discount rate (inflation adjusted) reflecting the societal time preference and direct evidence suggests a rate of 3% and conducting sensitivity analysis with rates of 0%, 5% and 7% [Siegel *et al.* 1996]. As this remains a matter of debate in various countries, I have adopted the widest possible discounting rates to allow a wider generalisability of the results. Hence, I have evaluated costs and benefits discounted at the US Treasury recommended rate of 0%, 4%, 7% and 10%, which gives the widest possible variation in the present climate. All costs are adjusted for the effect of inflation at 3%.

3.3.8.2.3 Sensitivity analysis for costs & benefits

Sensitivity analysis for cost/ QALY ratios is demonstrated by calculating the ratios at the 95% confidence intervals for the mean values of costs or benefits. The 95% confidence intervals are thus calculated using Mean value +/- standard error of mean (SEM) x factor (derived from the f distribution tables based on the number of freedom for the variable or n-1).

Comparison has been made with costs derived from a similar NHS based study [Chilcott.J *et al.* 2000] involving two different types of diagnosis and assessment procedures for SAHS patients as is currently used in non-specialist hospitals in the Midlands, UK dealing with such patients to give an idea of the cost/ QALY rations in other real life scenarios.

There are 3 steps in sensitivity analysis;

- identifying uncertain parameters
- specifying the range of variation by expert opinion, literature review and specified confidence intervals

- calculating study results based on best guesses, most and the least conservative estimates

3.3.8.2.4 Cost Utility analysis

Whereas the health effect of a healthcare intervention is expressed and can be measured in effect terms in CEA, although the current Panel on CEA recommendations propose the QALY, in a CUA the denominator is always measured in cost/QALY or Healthy year equivalent (HYE) terms. The denominator in CUA is generic and includes a valuation of health status or utility in its design and excludes intermediate data like improvement in morbidity or physical parameters. The second advantage of the CUA measure is the common outcome denominator of cost/QALY allows comparison between effects of different healthcare intervention programs. CUA is the preferred method used when HRQL is the main outcome measure as in the case of SAHS [Wright and Dye 1995] [D'Ambrosio *et al.* 1996].

CUA is not recommended when only intermediate data can be obtained, when alternative therapies are equally effective, when the intervention is shown to be unequivocally dominant both in clinical and cost effectiveness terms and when the extra cost of obtaining utility values is considered not to be cost effective. In the case of SAHS, there is a raging controversy in the literature and the public domain regarding effectiveness of CPAP therapy, the role of lifestyle changes and there is a dearth of clear Level I or II evidence on clinical effectiveness except in neuro-cognitive function, daytime sleepiness and energy/ vitality dimensions of HRQL [Engleman *et al.* 1997c;Stradling and Davies 1997;Wright *et al.* 1997b]. There are no economic evaluation data of Level I or II standard in SAHS till date in the body of literature, [Wright and White 2000] thus the CUA method was chosen for this study and different methods of obtaining the weighting for QALYs were compared. The methods for weighting QALYs and estimating costs have been discussed in section above.

3.4 Statistical Analysis

Data is expressed as mean and standard deviation (SD). A student's t test was used at baseline between Group 1 and Group 2. The non-parametric tests (Wilcoxon Rank Sum) test for paired samples was used to measure the change achieved in outcome parameters.

The individual relationships between health status and disease markers were measured using Spearman's rho. Missing values were replaced by baseline values with the intention to treat hypothesis and used in analysis. This was then multiplied by the life expectancy of each patient based on the United Kingdom 1996 population census to generate the QALYs gained by intervention, in each treatment group. All statistical analysis was done using SPSS v11.0 for Windows *(SPSS Inc, Chicago, IL, USA)*.

Sample size estimation was based on results obtained from the literature in change to SF36 sub-dimensions with CPAP treatment with a 95% confidence interval. The required number of patients was 72, but this was likely to be under-powered to detect changes in lifestyle intervention arm as the changes were expected to be modest.

Sample size = [change in variable/2 x SD] 100

3.5 Non- completions

In the CPAP group 8% of subjects failed to tolerate the treatment, a number comparing favourably with such 'failed therapeutic trials' reported in the literature (10-38%) [Monasterio, *et al.* 2001a]. The number of patients dropping out in the lifestyle intervention arm was 18%. Two patients chose alternative treatment options in the private sector and 4 did not return to complete the trial. Difficulty in maintaining subject motivation in trials involving lifestyle modification strategies is well-recognized [Sampol *et al.* 1998]. During the design phase of this study this potential for disenchantment amongst patients given lifestyle strategies was expected, and thus it was our deliberate intention not to offer alternate cross-over to the CPAP arm (to avoid positive CPAP bias) during the conduct of the trial. As an alternative study design a 'cross-over' design was discussed but it was felt that the patients on therapeutic CPAP may be expected to notice a symptomatic benefit with minimum effort, hence when crossed over to lifestyle strategy may create a negative bias against lifestyle modification.

For the purpose of the analysis all patients have been included (*intention to treat*) [Altman 1991], as this is the preferred statistical method to handle lost data, preserving the original randomisation and prevents the introduction of bias; this may undermine the benefit of lifestyle intervention by treating 'lost to follow up' patients as treatment failures.

CHAPTER IV

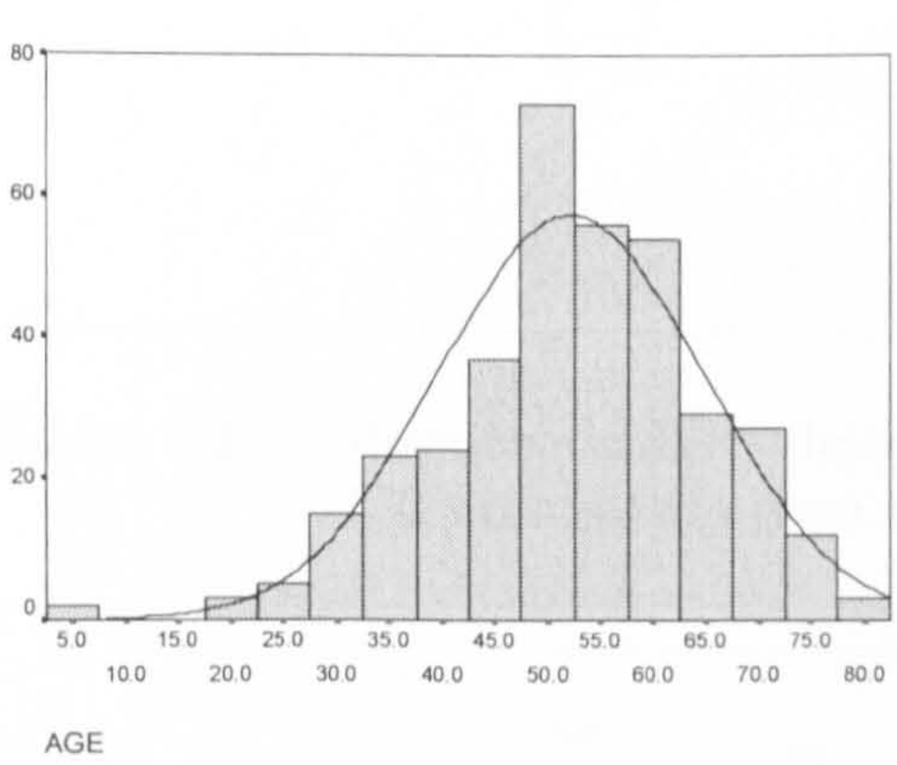
CLINICAL REVIEW

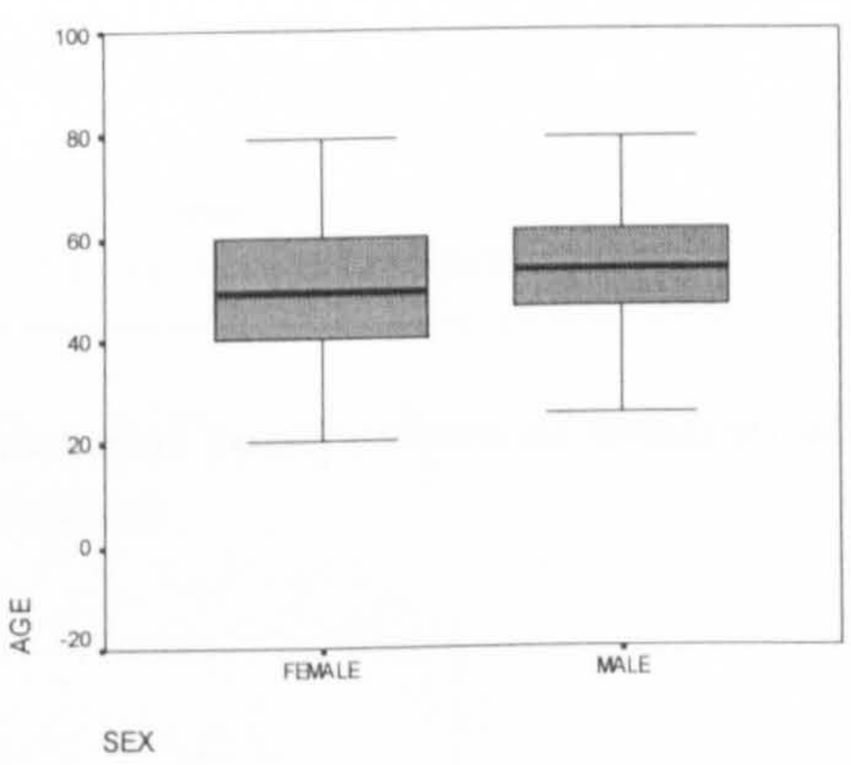
4.1 Results

4.1.1 Demographics

Of the 678 patients referred to the Birmingham Heartlands Hospital Sleep Disorders Clinic, 618 case notes were traced. Sixty records (42 males) were unavailable for analysis as they had been microfilmed and stored in an offsite storage facility, as was routine policy in the Trust for patients not under active treatment or follow up over 5 years. Fifteen patients with neuromuscular diseases and significant respiratory diseases were excluded from the analysis. The remaining 603 patients reviewed included 488 males (aged 53 ± 12 years) and 115 females (aged 51 ± 13 years), with a male: female ratio of 4:1.

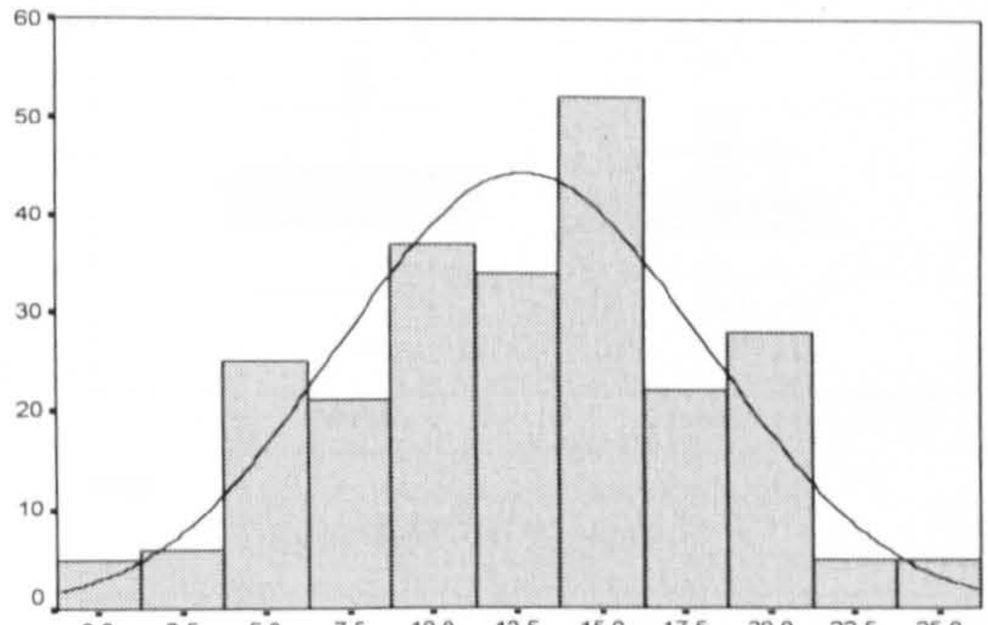
Figure 4.1: Histogram illustrating the age distribution in the referral population and box plot showing the median and inter-quartile ranges for age between males/ females.



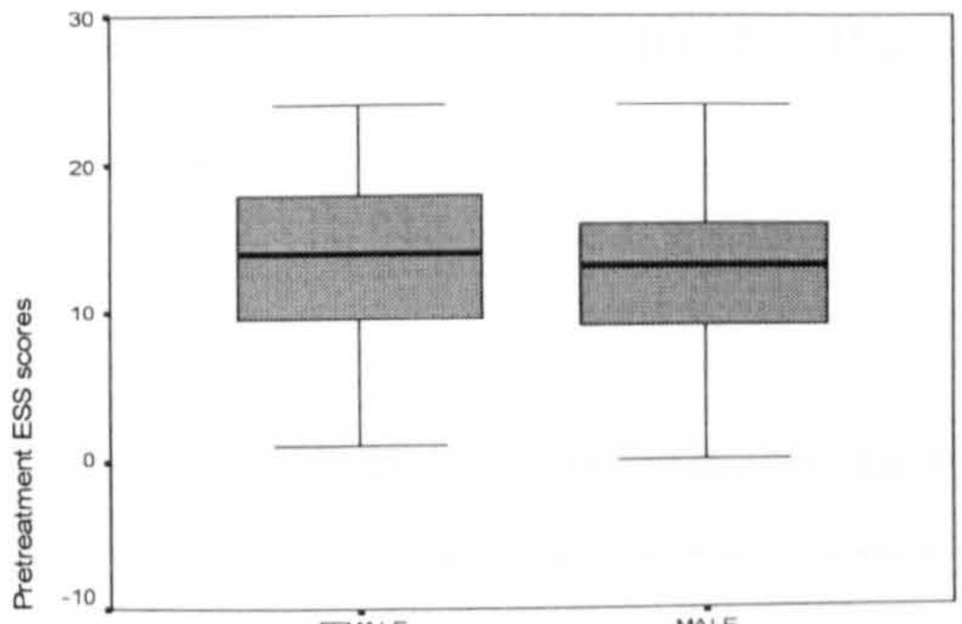


The mean BMI among female patients was greater than the male patients (33 ±9 vs. 31 ±6.6 kgm^{-2} for men, p= 0.003). However female patients had a lower ODI; [11.8 (Range 0-60) hour^{-1} vs. men 18 (Range 0-111), p=0.01] and AHI [14 (Range 1-76) hour^{-1} vs. men 21.2 (Range 0-111), p=0.02], but reported a similar degree of EDS measured by the ESS scores (12 ±6 vs. men = 12 ±5).

Figure 4.2: Epworth Sleepiness scale scores for the population and comparison of scores between men and women

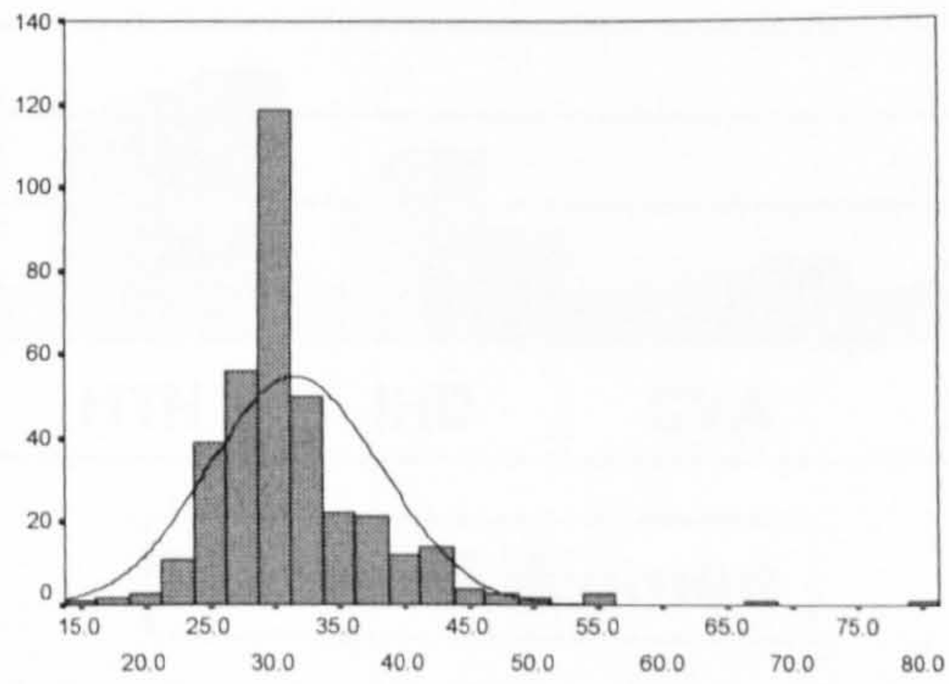


Y axis = number of cases; X axis = frequency of baseline ESS scores

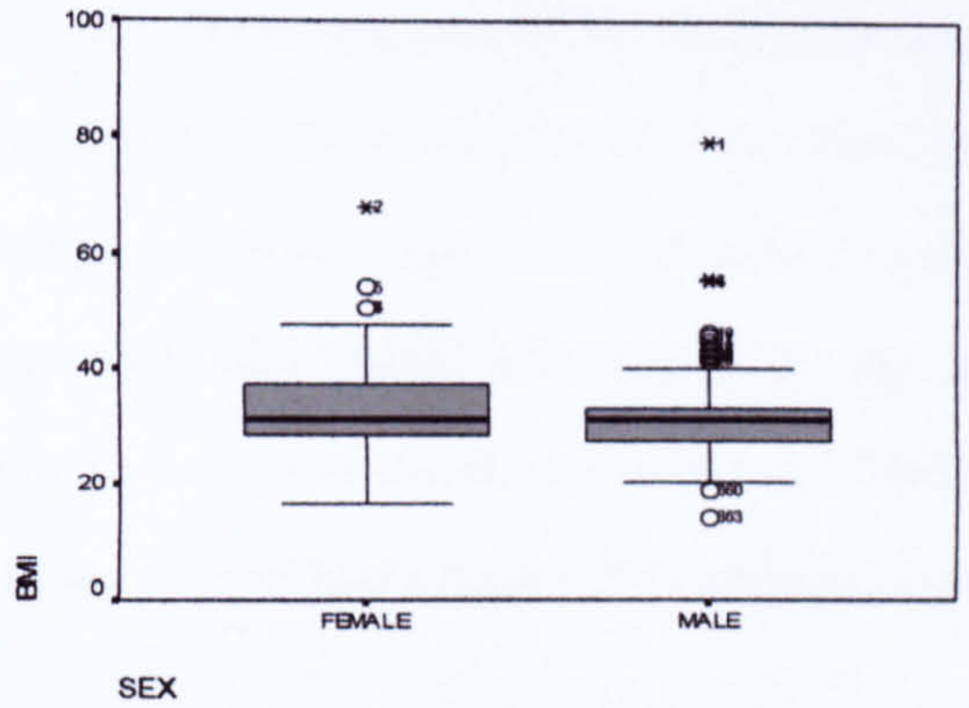


Y axis: Baseline ESS scores
X axis: Female or male (sex distribution)

Figure 4.3: Population BMI distribution and comparison of median and IRQ ranges for men and women



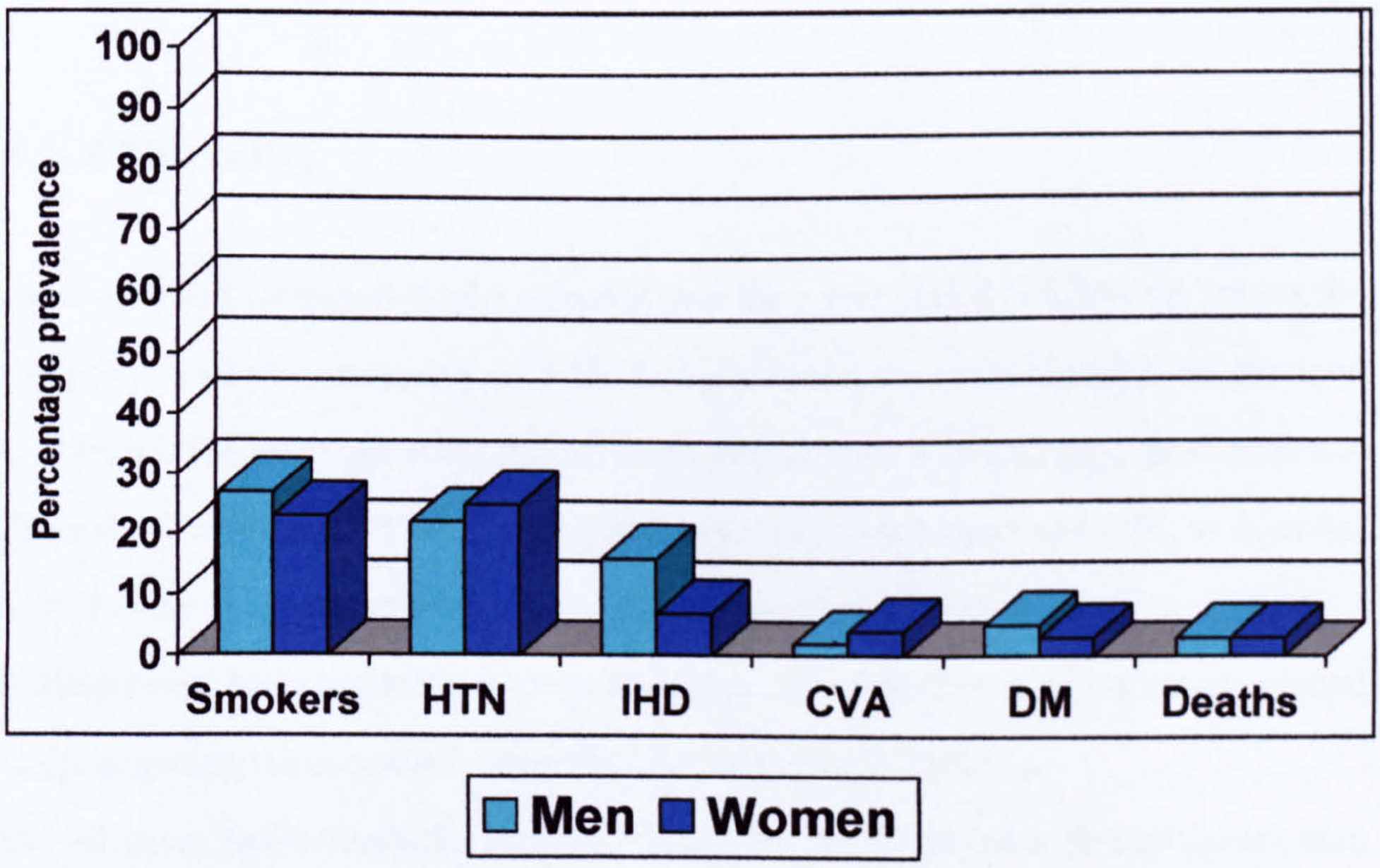
Y axis = frequency of BMI
X axis = BMI in kg/m2



Y axis: BMI in Kg/m2
X axis: Sex distribution female: male

Figure 4.4 shows a similar prevalence of smoking, hypertension, cerebrovascular disease, diabetes between men and women, except for ischaemic heart disease which was significantly higher among men (p=0.02).

Figure 4.4: Prevalence of mortality and co morbidity in the study population



HHTN hypertension, IHD Ischaemic heart disease, CVA cerebrovascular accident, DM diabetes mellitus

SAHS was diagnosed in 361 (62%) patients of the 603 patients reviewed, with a male predominance (male: female 7:1). There were 251 (30 females) patients with moderate-severe SAHS (Mean ODI 30 ±22 $hour^{-1}$, age 54±12 years, ESS 13±6, BMI 33±8 kgm^{-2}) and 110 (21 females) patients with mild SAHS (AHI 8±3 $hour^{-1}$, age 53±13 years, BMI 30±7 kgm^{-2}, ESS 13±5). Table 4.1 compares the characteristics of SAHS and controls showing that patients with SAHS were older, had a higher BMI and sleepier than controls.

Table 4.1: Characteristics of SAHS and non-SAHS patients; mean (SD)

	SAHS	Controls	p
n	361	242	
Age (years)	53 (12)	50 (12)	0.001
BMI kgm^{-2}	32 (8)	29 (5)	<0.001
ESS (0-24)	13 (5)	11 (5)	<0.001
AHI $hour^{-1}$	25 (21)	3 (2)	<0.001
ODI $hour^{-1}$	24 (21)	3 (3)	<0.001

4.1.2 Mortality

There were 22 (4 females) deaths recorded over the 7 year period of follow up, among the 603 patients whose notes were available for review, and the cause of death was obtained in 17 (77%). The mean age at the time of death was 62 years with a range of 39 to 70 years. There were no differences between the BMI [29.8 (23 to 50) kgm^{-2} and ODI; 31 (5 to 85) $hour^{-1}$] of the deceased patients compared to the population mean.

SAHS patients had a mortality of 4% and a higher risk of death; OR 5 (confidence interval 1.1-32.4, p=0.03) than controls (mortality 1%), as shown in Table 4.2.

The all cause crude mortality rate was higher for SAHS patients (6/1000/year) than controls (1.2/1000/year), p=0.03. The recorded cause of death was cardiac in 9 (53%) patients, respiratory in 7 (41%) and cerebrovascular/ stroke in one (6%), as detailed in Table 4.3

Table 4.2: Comparison of morbidity & mortality between SAHS and controls

	Controls Number (%)	SAHS Number (%)	p
n	242	361	
Deaths	2 (0.1)	15 (4)	0.03*
Hypertension	39 (17)	97 (27)	0.004*
Ischaemic heart disease	32 (14)	52 (15)	Ns
Diabetes	8 (3)	22 (6)	Ns
Cerebrovascular disease	5 (2)	10 (3)	Ns
Current smokers	52 (22)	104 (29)	Ns

Ns not significant, *significant at 95% level using $\chi 2$ test

Table 4.3: Available data on 17 of the 22 recorded deaths

Patients	Age	BMI	Sex	ODI	CPAP	Co-morbid	Cause of death
1	39	30.5	F	19	CPAP	COPD	Resp
2	39	31.3	M	35	RTND		Resp
3	44	25.5	M	15	RTND		Resp
4	52	50.4	M	25	CPAP	CABG, IHD	CVA
5	53	25.7	M	21	-	COPD	Resp
6	53	29.3	M	6	CPAP	HTN, IHD	Cardiac
7	57	40.1	M	25	CPAP	NIDDM, HTN	Cardiac
8	67	29.5	M	70	CPAP	HTN	Cardiac
9	68	32.6	M	10	CPAP	COPD, IHD	Cardiac
10	70	31.8	M	85	CPAP	COPD	Resp
11	70	26.3	F	5	-	COPD	Resp
12	71	33.1	M	60	CPAP	HTN	Cardiac
13	71	26.3	M	25	-	-	Cardiac
14	73	23.3	F	45	RTND	CCF, HTN	Cardiac
15	76	23.5	F	17	RTND		Resp
16	77	18.4	M	44	CPAP	CCF, COPD	Cardiac
17	82	29.9	M	15	CPAP	CCF, HTN	Cardiac
Mean	62	29.8		30.7			

HTN= hypertension, COPD= chronic obstructive pulmonary disease, RTND= returned CPAP machines, IHD= ischaemic heart disease, NIDDM= Non insulin dependant diabetes, CVA= cerebrovascular accident

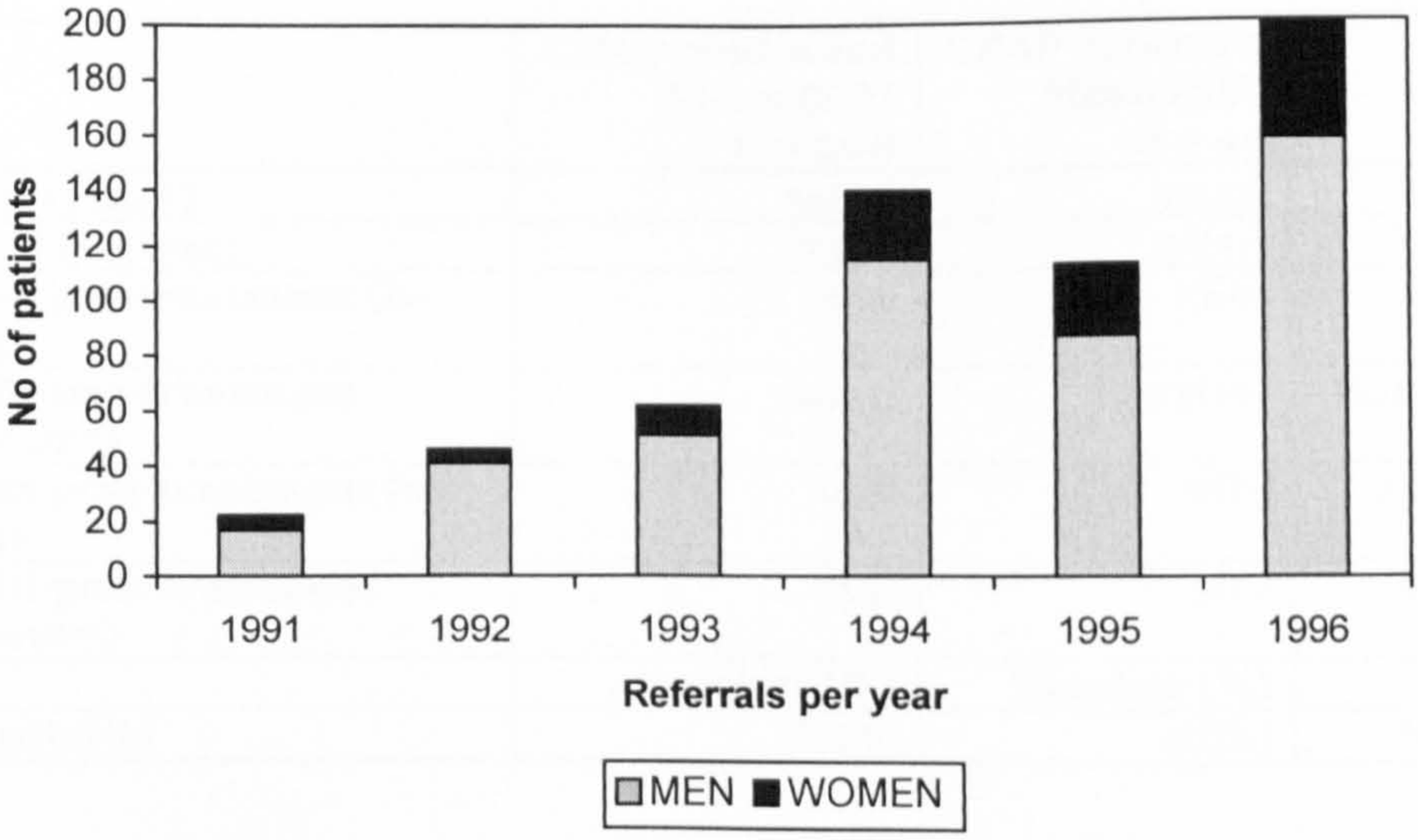
4.1.3 Co morbidity

Hypertension was significantly more prevalent in SAHS patients; the risk of being hypertensive at presentation being twice as high, (OR 2, CI 1.2-2.9, p=0.004). Though greater numbers of SAHS patients had documented ischaemic heart disease and cerebrovascular disease, these did not reach statistical significance.

4.1.4 Referral patterns

Annual referral rates increased 10 fold from 20 patients in 1990 to 200 in 1996 with an increasing proportion being women, figure 4.5. During this period, there was a similar increase in annual CPAP prescription rates from 5 in 1990 to 100 in 1996. GPs referred 263 (44%) patients to the Sleep clinic, while 173 (29%) patients were tertiary referrals from Otolaryngologists (ENT). Hospital physicians referred 167 (28%) patients. Diagnostic rates for SAHS were similar in all sub-groups of referrals regardless of source of referral (with 37% of ENT, 46% of GP and 47% of hospital physician referrals being subsequently diagnosed to be suffering from SAHS).

Figure 4.5 Annual referral rates for men and women



4.1.5 Role of arterial pulse oximetry

Fifty seven percent of patients (n=205) were diagnosed based on criteria including appropriate symptoms and a baseline ODI ≥15 hour^{-1}. The addition of PSG facilitated diagnosis in another 43% of patients (n=156).

4.1.6 CPAP usage

Therapeutic trials with CPAP were prescribed to 257 (72%) patients of whom 208 (81%) continued with treatment for a mean follow up of 3 ± 1.6 years. Annual follow up showed a reduction in ODI from 34 to 3 hour^{-1} and ESS scores reduced from 14 to 9 on treatment as shown in Table 4.4. Patients' mean self-reported compliance with CPAP was 5 ± 2.2 hours.night^{-1}. Patients who returned their machines having failed to benefit from a therapeutic trial had significantly lower ODI at baseline.

Of the 22 patients with SAHS who died during follow up, 8 had returned their CPAP machines failing to tolerate the treatment.

Table 4.4: **Comparing characteristics between SAHS patients continuing with CPAP therapy and those failing to tolerate CPAP**

	CPAP continued Mean (SD) n = 208	**CPAP returned Mean (SD) n = 49**	***p***
Age (years)	54(11)	52(13)	NS
BMI (Kg/m2)	33(7)	33(11)	NS
ESS pre-treatment (0-24)	14(5)	13(6)	NS
ODI pre-treatment (hour^{-1})	34(21)	23(18)	0.004
ESS post-treatment (0-24)	9(5)	12(6)	0.05
ODI post-treatment (hour^{-1})	3(5)	5(8)	NS
	Number (%)	**Number (%)**	
Mortality	8(4%)	4(8%)	NS

4.2 Discussion

4.2.1 Mismatch in service provision

This clinical review showed the first phase in the lifecycle of an innovation as it was introduced for use in a typical UK DGH setting. Although initially reported as an innovation in 1981 [Sullivan *et al.* 1981], CPAP as a commercial product only became available in 1990, when the first patients were referred to a newly established Sleep disorders clinic. The rising number of referrals from 1990 to 1997 shows the increasing awareness among both primary and secondary care physicians of this condition and reflects increasing public awareness. The RCPUK working party reported at the same time the increasing demand for sleep diagnostic and treatment services and identified the need for such provision across the country [Semple and Gibson 1993].

However population screening surveys in the USA at the same time, suggested prevalence for SAHS to be between 2-4% of middle aged adults [Young *et al.* 1993], the majority of whom were unlikely to be aware of their condition and unlikely to seek a referral and hence were likely to go untreated [Young *et al.* 1997a]. As almost half of all patients referred to the Sleep service were subsequently diagnosed to have clinically significant SAHS, suggesting that there were a number of people in the community with SAHS who were either unaware of their diagnosis or were inadvertently screened out by the referral process. The mismatch between demand and availability of sleep diagnostic services in the UK has been reported by the RCPUK working party again in 1998 [Gibson *et al.*1998] and by the multi-disciplinary expert group called the 'Sleep Alliance' in 2004 [Sleep Alliance. 2004]. Thus the present research into the diffusion and adoption of CPAP in the NHS would have to examine the factors leading to this apparent mismatch.

4.2.2 Morbidity & Mortality

The case-control study of SAHS patients compared to controls (with snoring without SAHS) highlighted the increased risk of hypertension and mortality in the SAHS group. Snoring has been reported as an independent risk factor for vascular complications such as hypertension [Lindberg *et al.* 1998] but may merely be a marker of underlying SAHS [Stradling and Crosby 1990;Stradling 1995b;Waller *et al.* 1989]. As the odds ratios

identified in this analysis are in comparison to patients with snoring, it is likely that the risks to SAHS patients are under-estimated in this analysis.

In this study, SAHS patients had a 5 times higher risk of dying compared to controls, with a significantly higher crude mortality rate (6/1000/year). This rate was greater even when compared to the mortality risk for ischaemic heart disease, certain cancers and respiratory diseases (3.2, 2.6, 2/1000/year respectively) estimated in England & Wales in 1998 [Office for National Statistics 1999]. The predominant cause of death among this group of SAHS patients was cardio-pulmonary as has been reported previously by other epidemiological studies on SAHS patients, which have also identified higher mortality rates [Mooe *et al.* 2001] [Veale, *et al.*2000]. An analysis involving 57 deaths from 1,620 SAHS patients followed up over 12 years, in Israel in 1995 identified cardiopulmonary causes for deaths in 53% [Lavie *et al.* 1995].

Obesity among SAHS patients can independently contribute to the increased mortality seen, however the mean BMI in this group was only marginally higher than the controls. A trend which is reflected in population characteristics in UK showing a majority of adults examined by the 1996 Health survey for England, reported that 62% of adult men and 53% of the adult women were overweight or borderline obese (BMI>25 Kgm^{-2}) [Joint Health Surveys Unit *et al.* 1997]. The influence of obesity was thus probably only marginal in contributing to the excess mortality seen in this analysis.

Daytime systemic hypertension is strongly associated with SAHS and an independent risk factor for increased vascular mortality and morbidity [Hla *et al.* 1994] [Young *et al.* 1997d]. In this study there was a higher prevalence of daytime systemic hypertension (27%) compared to controls (17%), the risk being twice. Pendlebury et al in 1997, reported a 46% prevalence of systemic hypertension among their clinic SAHS patients,[Pendlebury *et al.* 1997] while in 1990 Partinen and Guilleminault had reported a prevalence of 57% from a 7 year follow up study of SAHS, conducted at the Stanford Sleep Clinic [Partinen *et al.* 1990]. Both these studies were conducted in the tertiary care setting with a more selective process of referrals and hence perhaps accounting for the higher prevalence of co morbidity, compared to our patients who were principally referred by GPs or ENT surgeons.

The same unselected referral pattern for this study population probably accounted for no significant differences between the prevalence of ischaemic heart disease (15%), cerebrovascular disease (2-3%) and diabetes (5-7%), while significant associations have been reported in the studies from specialised clinics in both France and USA [Partinen & Guilleminault 1990] [Pendlebury *et al.* 1997].

Smoking as a contributing factor towards mortality risk was virtually excluded from this analysis, as we found the prevalence of smokers amongst our SAHS patients to be similar to the national prevalence [Joint Health Surveys Unit and Dept of Epidemiology & Public Health 1997]. Thus even among unselected secondary care SAHS patients we found strong evidence for the existence of a significantly higher risk of hypertension and mortality, though probably of multi-factorial origin.

4.2.3 Role of pulse oximetry in a diagnostic algorithm

This study demonstrated the clinical value of combining symptoms compatible with the SAHS [Whyte *et al.* 1989] with an ODI ≥ 15 hour^{-1} from domiciliary overnight arterial pulse oximetry; a diagnostic tool with a 99% specificity for identifying SAHS, albeit with only a 32% sensitivity [Gurubhagavatula *et al.* 2001;Ryan *et al.* 1995a;Wiltshire *et al.* 2001]. This strategy has enabled a definite diagnosis of SAHS in over half of referred patients without the need for expensive PSG studies [Epstein *et al.* 1998]. However it is recognised that absence of the characteristic episodic desaturation pattern in a 'normal' oximetry does not exclude SAHS[Pepin *et al.* 1991] [Svanborg *et al.* 1990] and hence all patients with relevant symptoms and a 'non-diagnostic' oximetry underwent multi-channel polysomnographic evaluation allowing diagnosis in a further 44% patients.

4.2.4 CPAP trials & compliance

CPAP treatment was successfully established in 82% of the patients with SAHS after undergoing therapeutic trials, who reportedly used their machines for a mean 5.5 hours every night. Though CPAP may be perceived initially as an intrusive form of treatment by a proportion of patients and reportedly associated with considerably variable usage, the compliance results compared favourably with figures of 4-5 hours per night, as reported from other centres [Meslier *et al.*1998;Zozula *et al.* 2001a] with objective usage monitors [Engleman *et al.* 1994c;Kaplan *et al.* 1994;McNicholas 1997]. Compared to usage reported

of prescribed treatment options in other chronic conditions such as asthma, hypertension and diabetes, the high proportion of patients using CPAP over a medium-long term period suggested its positive innovation characteristics such as patient acceptability, which will be further assessed during the third phase of this research project.

4.3 Conclusion

Data from this retrospective clinical review and case-control study demonstrated that since its commercial availability there has been a rise in the referral rates in a typical DGH Sleep clinic however the numbers are still likely to leave a large burden of unrecognised and untreated disease in the community.

SAHS patients are twice as likely to present with systemic hypertension and have a 5 times higher risk of mortality, which is multi-factorial in origin in comparison to controls with snoring.

Domiciliary overnight pulse arterial oximetry as an integral part of an SAHS diagnostic algorithm is likely to diagnose over 50% of patients and contribute to the economic efficiency of such units. However due to a low sensitivity and the likelihood of missing patients with UAR, such diagnostic algorithms should include a full PSG for negatives.

CPAP treatment as an innovation has been shown to have a high acceptance among SAHS patients and compliance achieved is comparable with many other chronic diseases. Hence this clinical review set the scene for the design of a prospective RCT into the efficacy and effectiveness of CPAP and examining characteristics of CPAP diffusion in the NHS.

CHAPTER V

CLINICAL EFFECTIVENESS

5.1 INTRODUCTION

One of the early assessments undertaken in the appraisal of a new technology involves the measurement of its safety and clinical efficacy. This chapter presents the data on the clinical efficacy and effectiveness of CPAP compared to lifestyle intervention in a prospective, randomised study.

5.2 RESULTS

5.2.1 Population

There were 141 new patients referred by their GPs with snoring and history suggestive of SAHS, to the Sleep disorders clinic at the Birmingham Heartlands Hospital (BHH) between June 1998 and October 1999. All patients were sent an information pack prior to their clinic appointments. This consisted of a Sleep apnoea leaflet and consent form including a brief outline of the proposed trial (appendix). Subjects were asked to communicate their decision during their clinic visit. One hundred and thirty two patients expressed a positive interest in the trial, while the remaining 11 patients declined to participate in the trial and were seen within the established clinical pathway of the clinic. Of the 132 patients who expressed an interest in the trial and underwent full, overnight, inpatient PSG, 82 (58%) were diagnosed to have moderate to severe SAHS (AHI≥15hour^{-1}) and were approached for written consent to participate in the trial. Seventy one patients gave written consent and were then randomised. The 11 patients with SAHS who declined participation in the trial were returned to the Sleep Clinic for appropriate management according to current clinical protocol. The numbers in each phase from referral to recruitment and randomisation are presented in table 5.1, while the demographics of above mentioned groups are presented in table 5.2.

Thirty-seven patients were randomised to Group I (CPAP therapy), 3 failed to tolerate CPAP, 1 subject preferred to proceed to a surgical option and another patient subsequently underwent surgery for a growth hormone secreting pituitary tumour.

There were 34 patients randomised to Group II (Lifestyle). Five patients were subsequently excluded due to health reasons (acute abdomen = 1, chest infection = 1,

initiating anti-convulsant therapy for newly diagnosed epilepsy = 1 and visual impairment = 2), 2 patients preferred to go for alternative therapies privately (CPAP & surgery) and 4 patients dropped out without communicating any reasons and did not take up written invitation to return to the Sleep clinic for further assessment and treatment. One patient found the travel from 20 miles distance for multiple visits to the hospital logistically and economically challenging and another patient had to be excluded due to poor comprehension of the health status valuation techniques and poor command of the language. Twenty one completed the study in the lifestyle intervention group. The demographics of the patients either excluded after recruitment or failing to complete the study are presented in table 5.1.

Table 5.1: Study population and randomisation into groups

	Numbers	**%**
New patients in clinic between 1/6/98 and 31/10/99	141	100
Patients undergoing polysomnography	132	94
Patients with SAHS (AHI ≥ 15 hour^{-1})	82	58
Recruited and randomised	71	50
CPAP group	37	100
CPAP - Completed	32	87
CPAP – exclusions total	5	
Lifestyle group	34	100
Lifestyle completed	21	62
Lifestyle exclusions total	13	
Total completed	53	75

Table 5.2: Demographics of the referral population undergoing polysomnography n=132, Mean (SD)

	Patients interested n=132	Patients with SAHS n=82	Patients recruited in the trial n=71	Patients failing to complete n=18
Age years	50 (13.6)	50 (9.9)	48 (12)	45 (16.5)
% male	77	75	79	72
AHI /hour	32 (21.5)	45 (28.3)	46 (26)	33 (23)
BMI kgm^{-2}	29 (4)	36 (10.7)	35 (10)	29 (6)

Table 5.3: Showing patients either excluded or not completing the study with their characteristics

Serial No	Sex	Age	BMI	AHI	Reason	Lifestyle/ CPAP
29	M	72	32	46	Excluded due to health	Lifestyle
90	M	43	31	34	Dropped out	Lifestyle
123	M	56	29	42	Logistical problem due to distance from hospital	Lifestyle
48	M	35	29	16	Opted for surgery	Lifestyle
74	M	55	29	77	Excluded due to failure to comprehend utility/ value methods & language	Lifestyle
78	F	67	38	74	Excluded due to poor vision	Lifestyle
15	M	70	35	29	Excluded due to health (chest infection)	Lifestyle
59	F	32	33	30	Opted out for CPAP	Lifestyle
91	F	33	24	18	Excluded due to starting anti-convulsants for epilepsy	Lifestyle
124	M	28	32	22	Excluded due to health (acute abdomen)	Lifestyle
2	F	32	31	17	Dropped out	Lifestyle
138	M	52	36	42	Dropped out	Lifestyle
102	M	26	33	22	Dropped out	Lifestyle
11	M	32	28	27	Opted out for surgery	CPAP
25	M	66	26	32	Failed	CPAP
108	M	52	36	78	Failed	CPAP
101	F	32	37	25	Failed	CPAP
99	M	66	30	43	Failed	CPAP
110	F	62	28	67	GSH tumour	CPAP

5.2.2 Study population characteristics (n=71)

The population (n=71) was predominantly male and middle-aged with a normal distribution *(figure 5.1 & 5.2)* with a mean (SD) 48 (12) years.

Figure 5.1: Sex (%) distribution in the study population

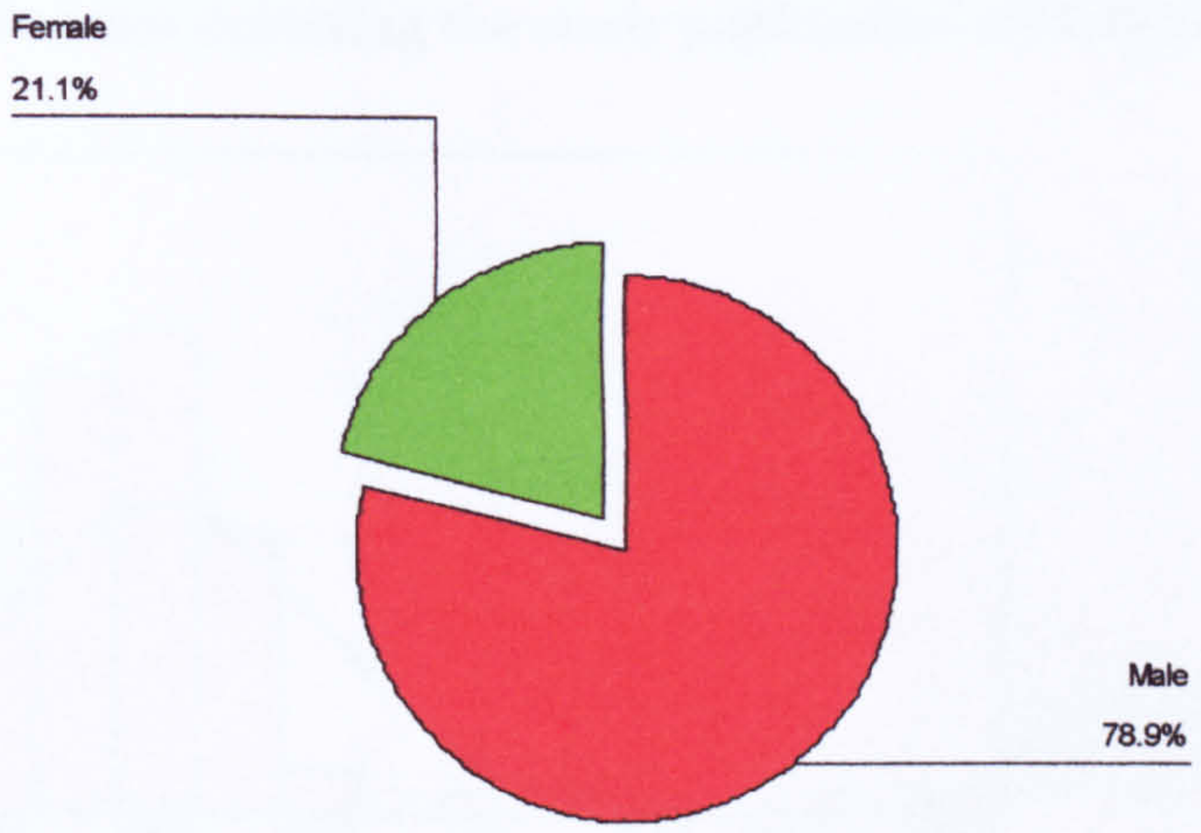
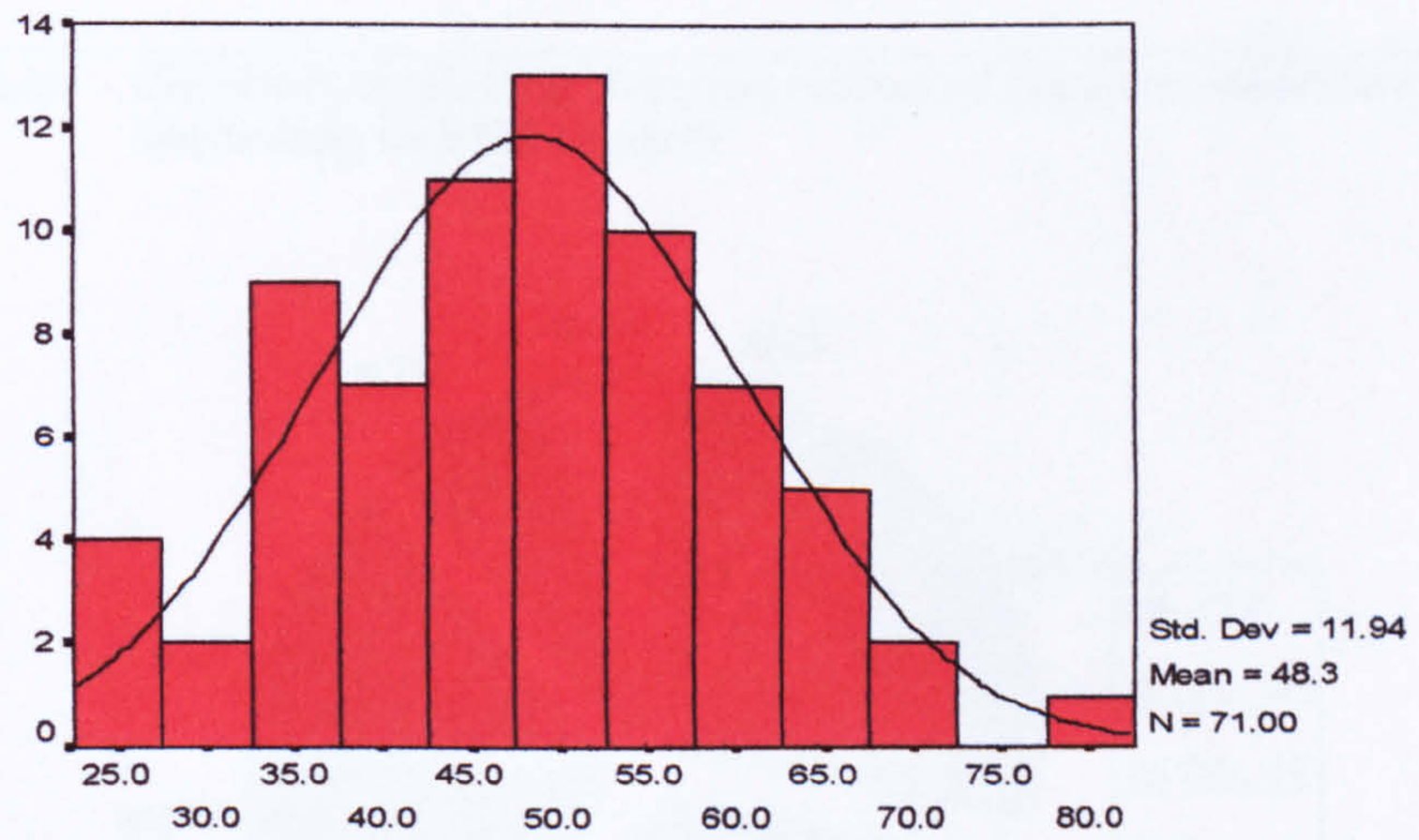


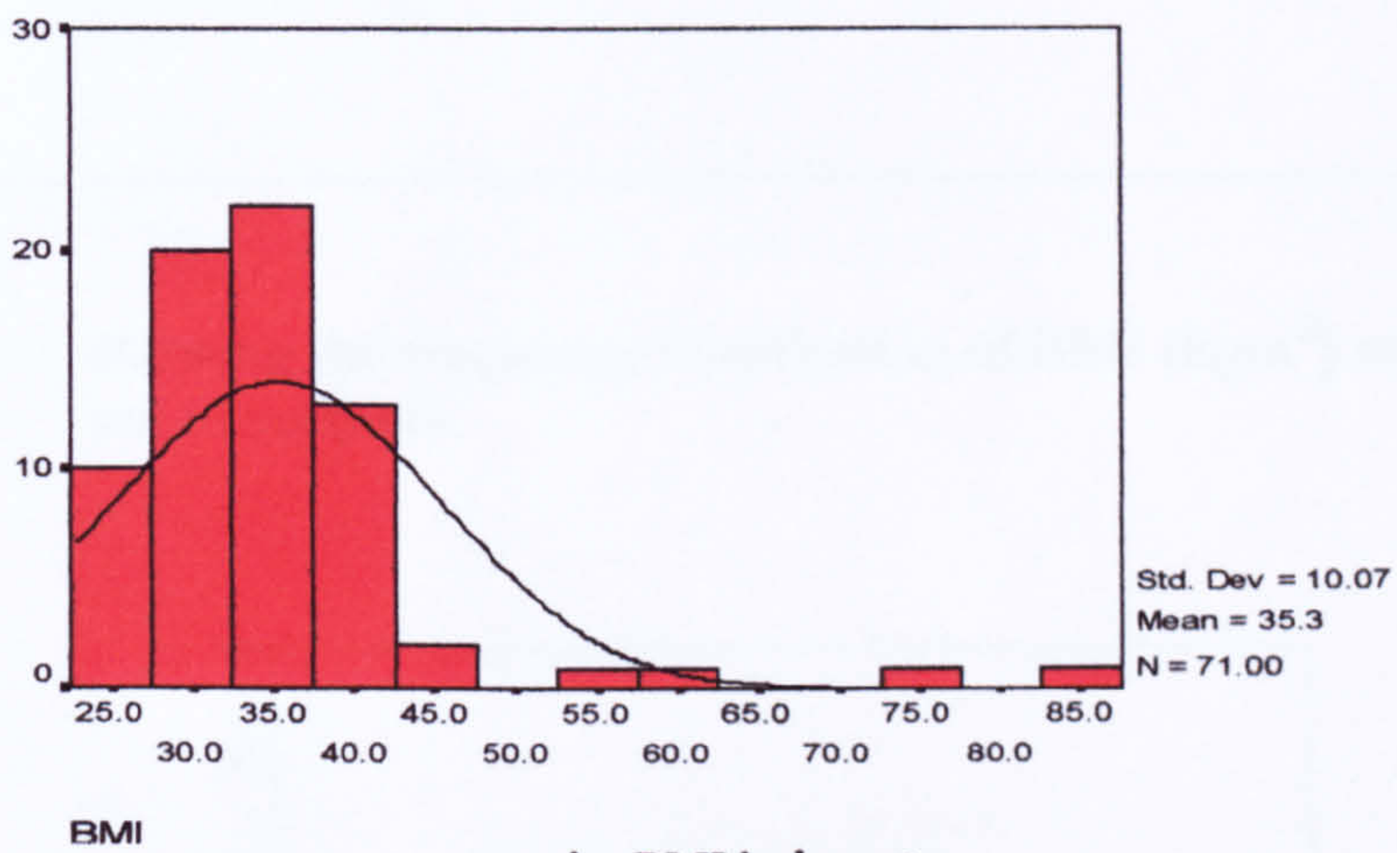
Figure 5.2: Histogram depicting the age distribution for the study population



Y axis: number of cases
X axis: Age in years

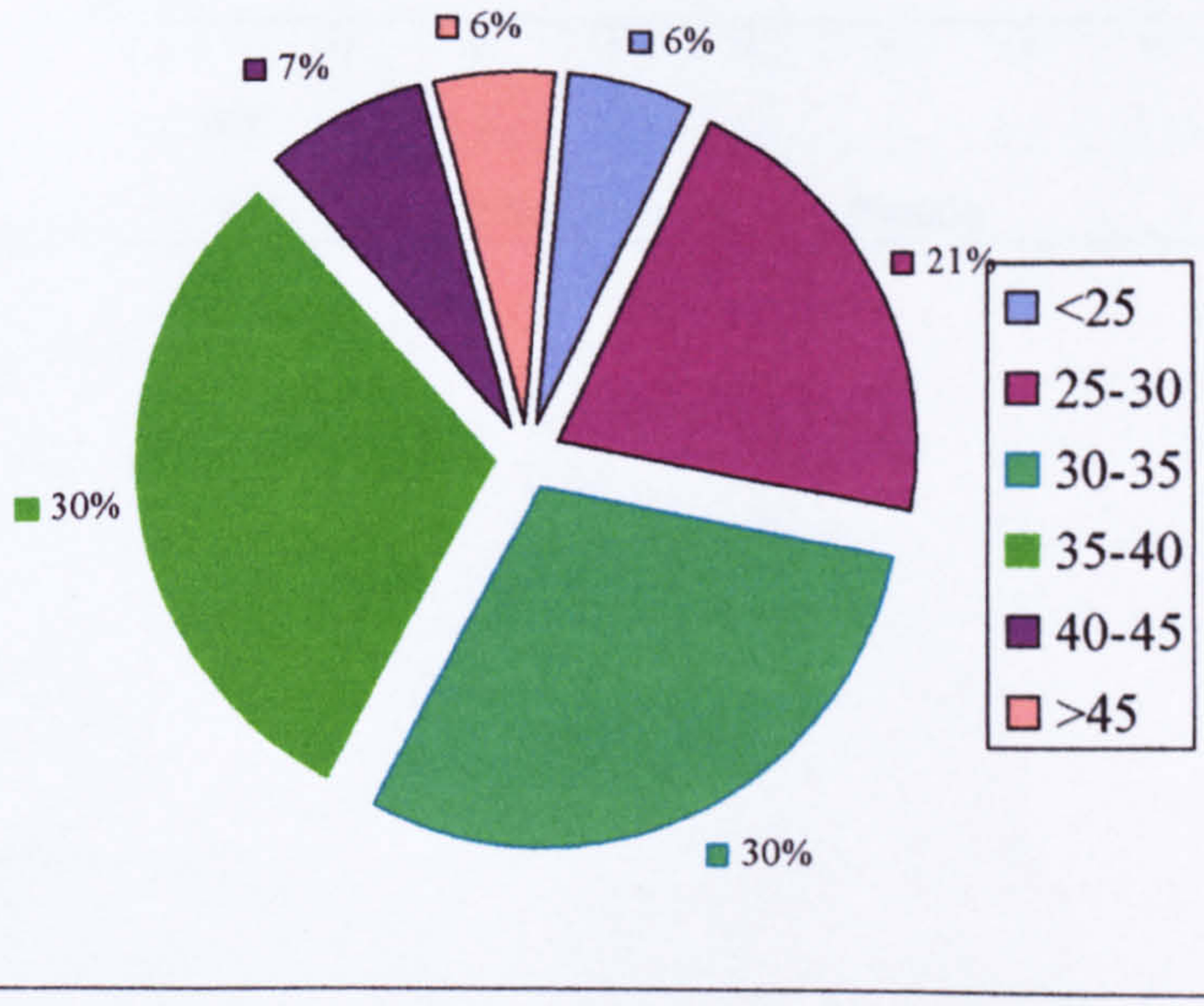
The BMI distribution was skewed due to 4 extremely obese subjects with BMI>45 kgm^{-2}, however the mean BMI was 35 (10) kgm^{-2}, *figure 5.3*. Six percent of subjects were in the conventionally accepted normal range (>20 and <25 kgm^{-2}) and 13% were extremely obese (>40 kgm^{-2}). Majority of subjects were either overweight (25-30 kgm^{-2} = 21%) or obese (mild-30-35 kgm^{-2} = 30%, moderate obesity 35-40 kgm^{-2} = 30%), *figure 5.4*..

Figure 5.3: Histogram depicting the study population BMI distribution



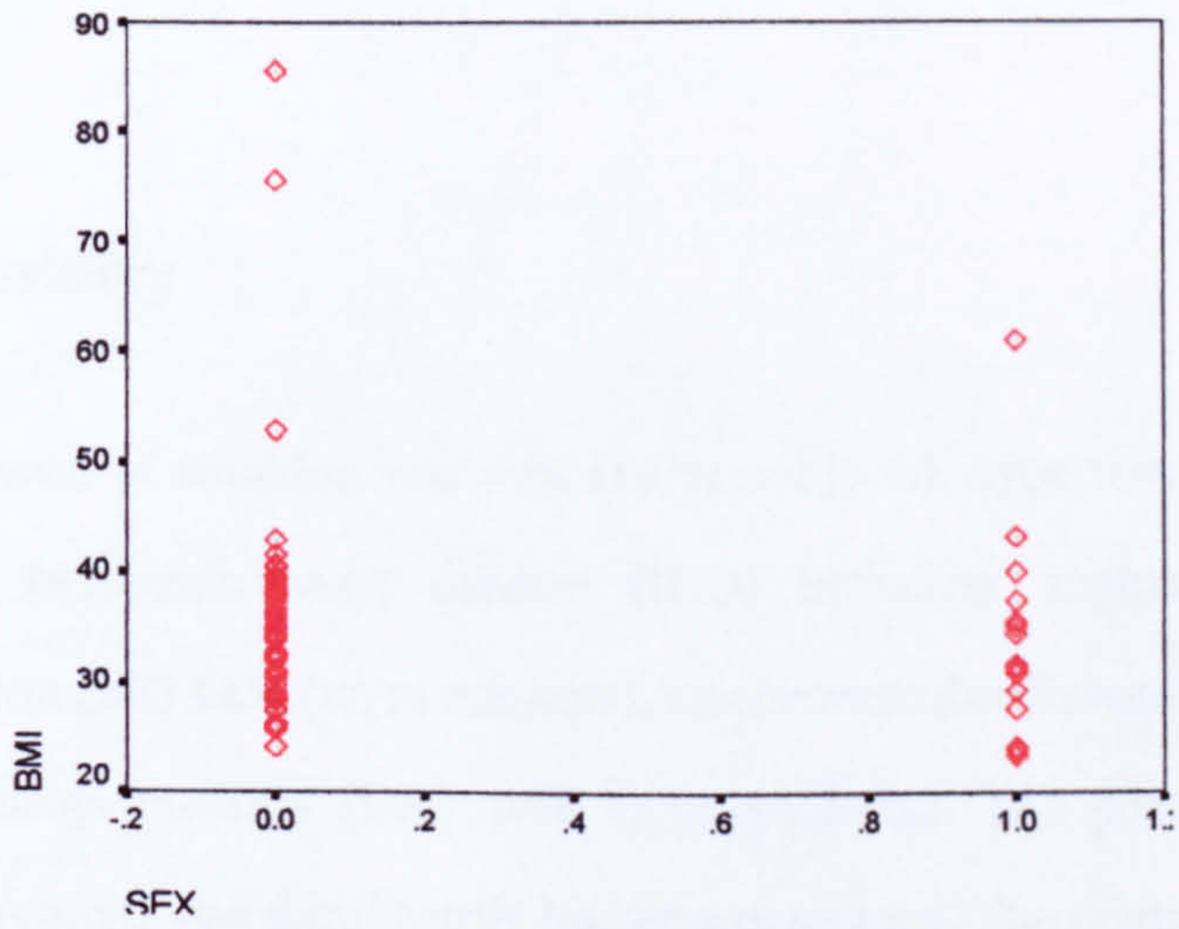
x axis: BMI in kgm^{-2}
y axis: number of cases

Figure 5.4: Pie chart depicting the proportion of subjects classified according to BMI (kgm^{-2}).



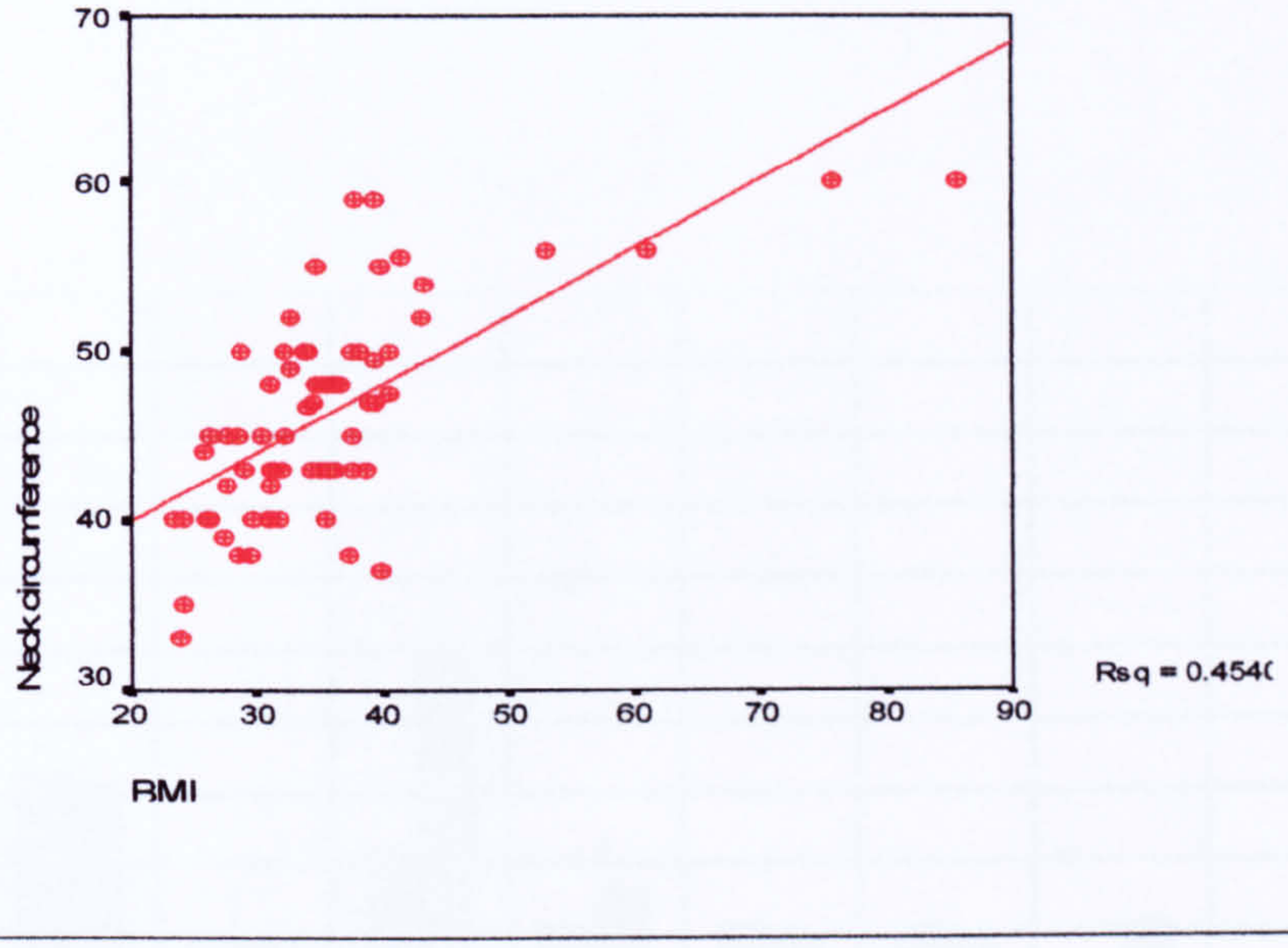
The BMI distribution was representative between men and women in the study population (excluding the extremely obese male subjects) as shown in *figure 5.5*, the mean BMI in men was 35.7 (10) and in women 34 (10) and the differences did not achieve statistical significance (p= 0.536). The neck circumference mean 46.2 (6.1) cm were closely related to the BMI, linear regression coefficient r^2=0.454, p<0.001 *(figure 5.6)*.

Figure 5.5 **showing the frequency distribution of BMI (kgm^{-2}) according to sex of subjects**



BMI in kgm^{-2}; Sex 0=male & 1= female

Figure 5.6: plots the relationship between BMI (kgm^{-2}) and neck circumference (cm)

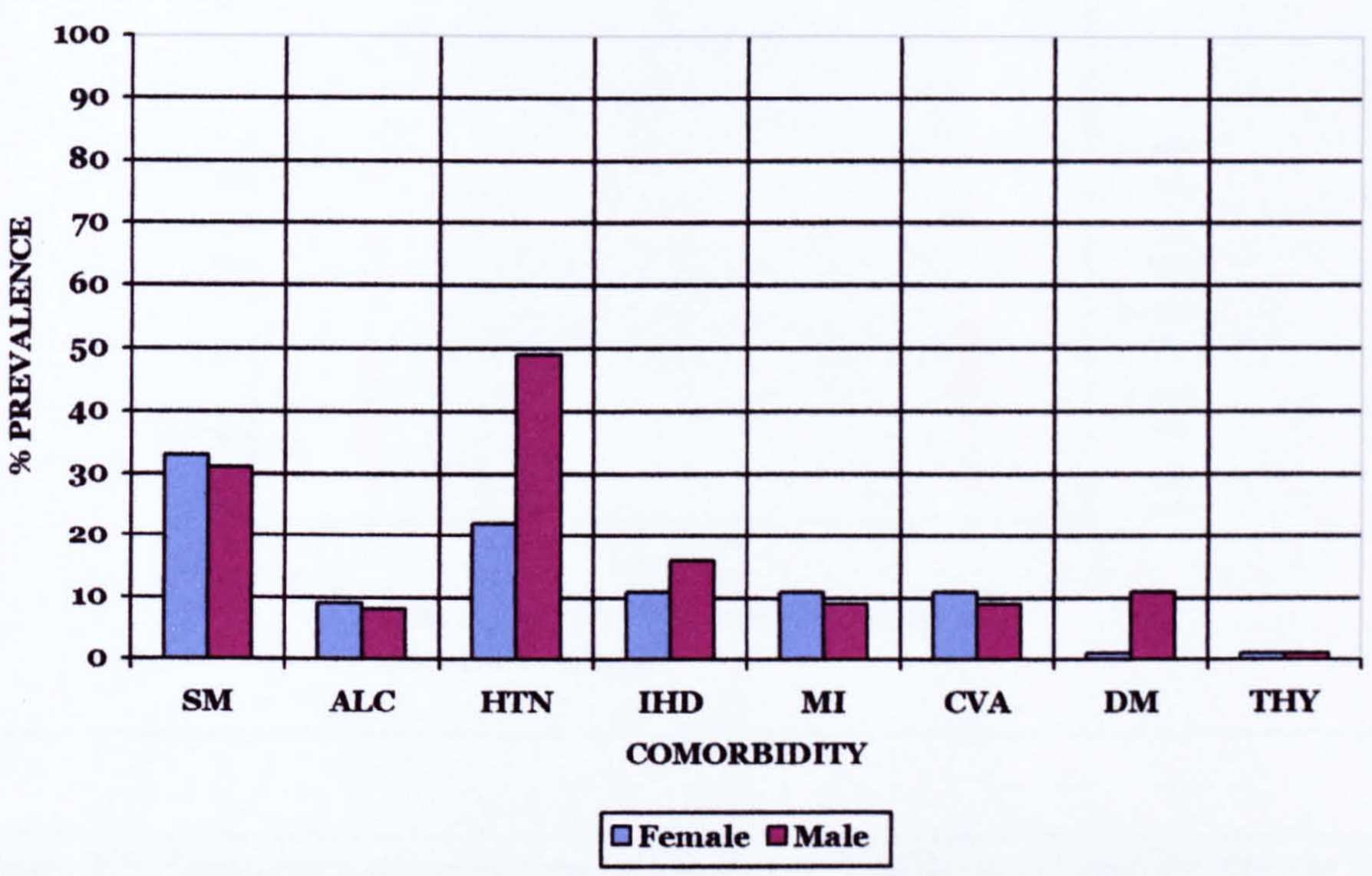


5.2.3 Co morbidity

The overall prevalence of smoking was 27% (19/71 subjects), hypertension (HTN) 39% (28/71 subjects), Ischaemic heart disease (IHD) including angina and previous myocardial infarction (MI) 24% (17/71 subjects), cerebrovascular disease (CVA) 6% (4/71 subjects) and diabetes mellitus (DM) 10% (7/71 subjects). The prevalence of HTN (relative risk 2.4, $p<0.05$) was significantly higher among men. The relative prevalence of smoking, IHD, CVA disease and diabetes and average weekly alcohol (ALC) consumption is shown in *figure 5.7*.

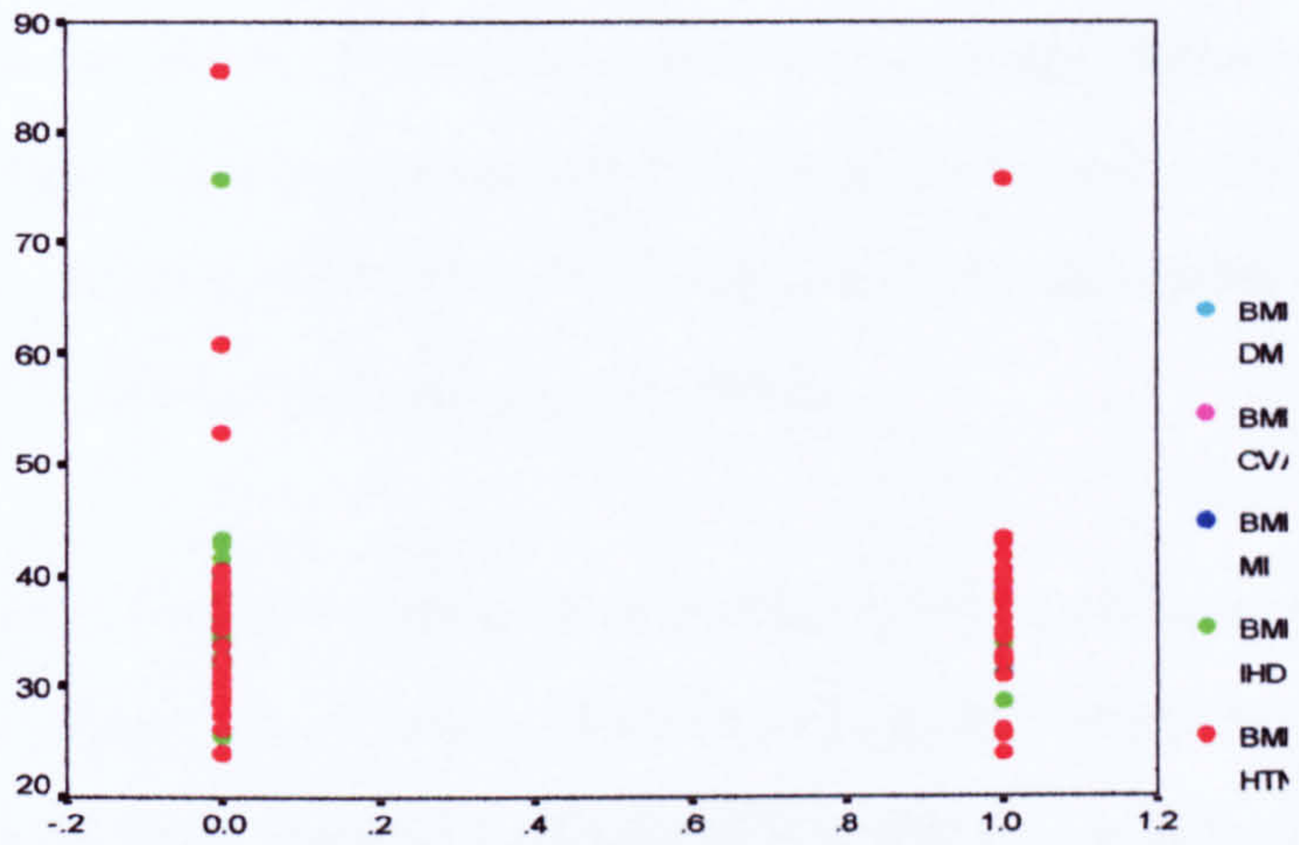
Co morbidity was unrelated to BMI and age in the population as shown in the frequency distributions in *figure 5.8 & 5.9*.

Figure 5.7 showing the % prevalence of co morbidity among male and female patients



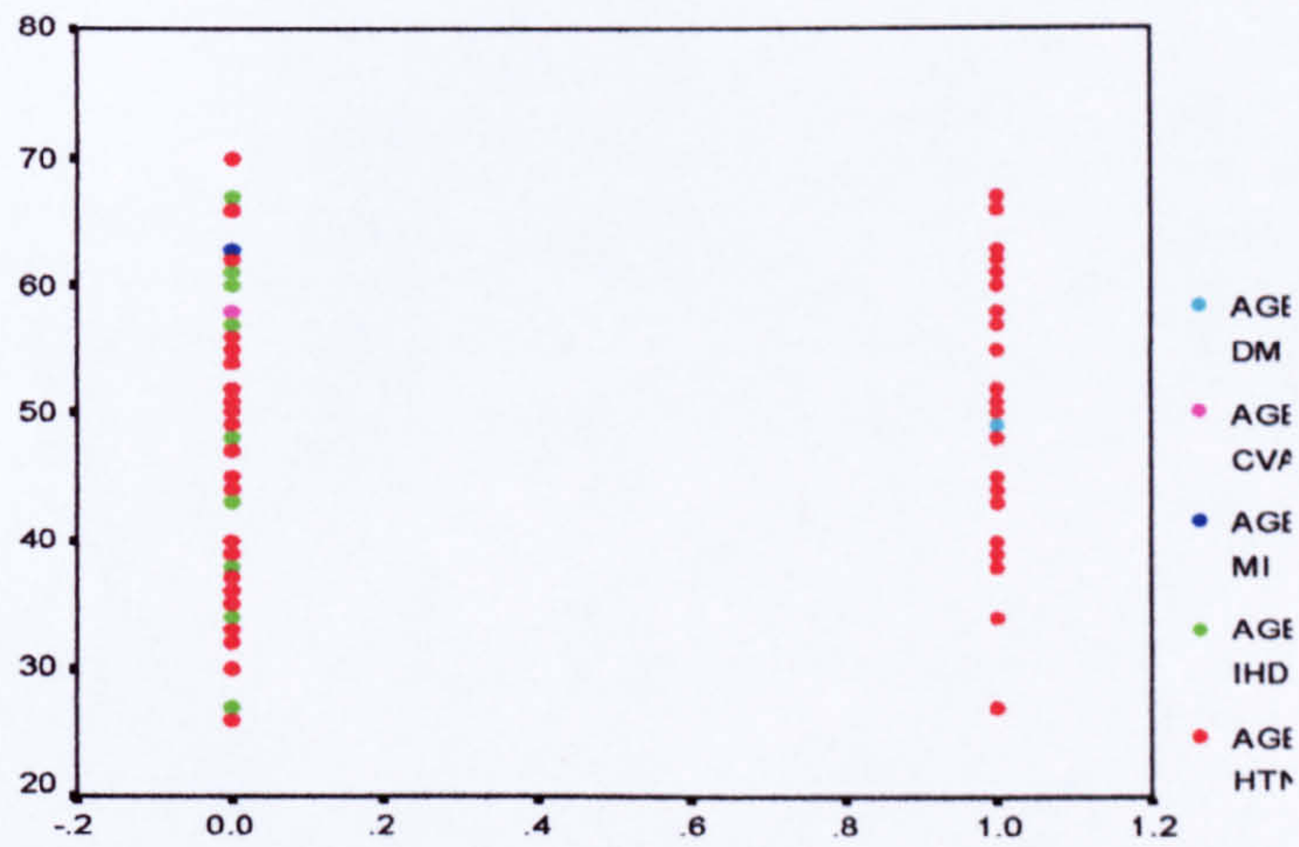
SM= smoking, Alc= units of alcohol consumed/ week, HTN= systemic hypertension, IHD= ischaemic heart disease, MI= Myocardial infarction, CVA= cerebrovascular attack, DM= diabetes mellitus and THY= thyroid disease.

Figure 5.8 Frequency distribution of BMI (kgm^{-2}) with co morbidity *(along x axis; 0=absence or 1=presence of co morbidity)*



x axis: co morbidity present=1, absent =0
y axis: BMI in kgm^{-2}

Figure 5.9 Frequency distribution of age (years) with co morbidity *(along x axis; 0=absence or 1=presence of co morbidity)*



x axis: presence (=1) or absence (=0) of co morbidity
y axis: age in years

5.2.4 Polysomnographic characteristics

Table 5.4 shows the baseline home (Minolta Pulsox-7) overnight oximetry and inpatient PSG characteristics of the population. The ODI was lower than the number of 6 beats/ min pulse rate variation (PRV) recorded during the home monitoring (both however being within the range for moderate to severe SAHS).

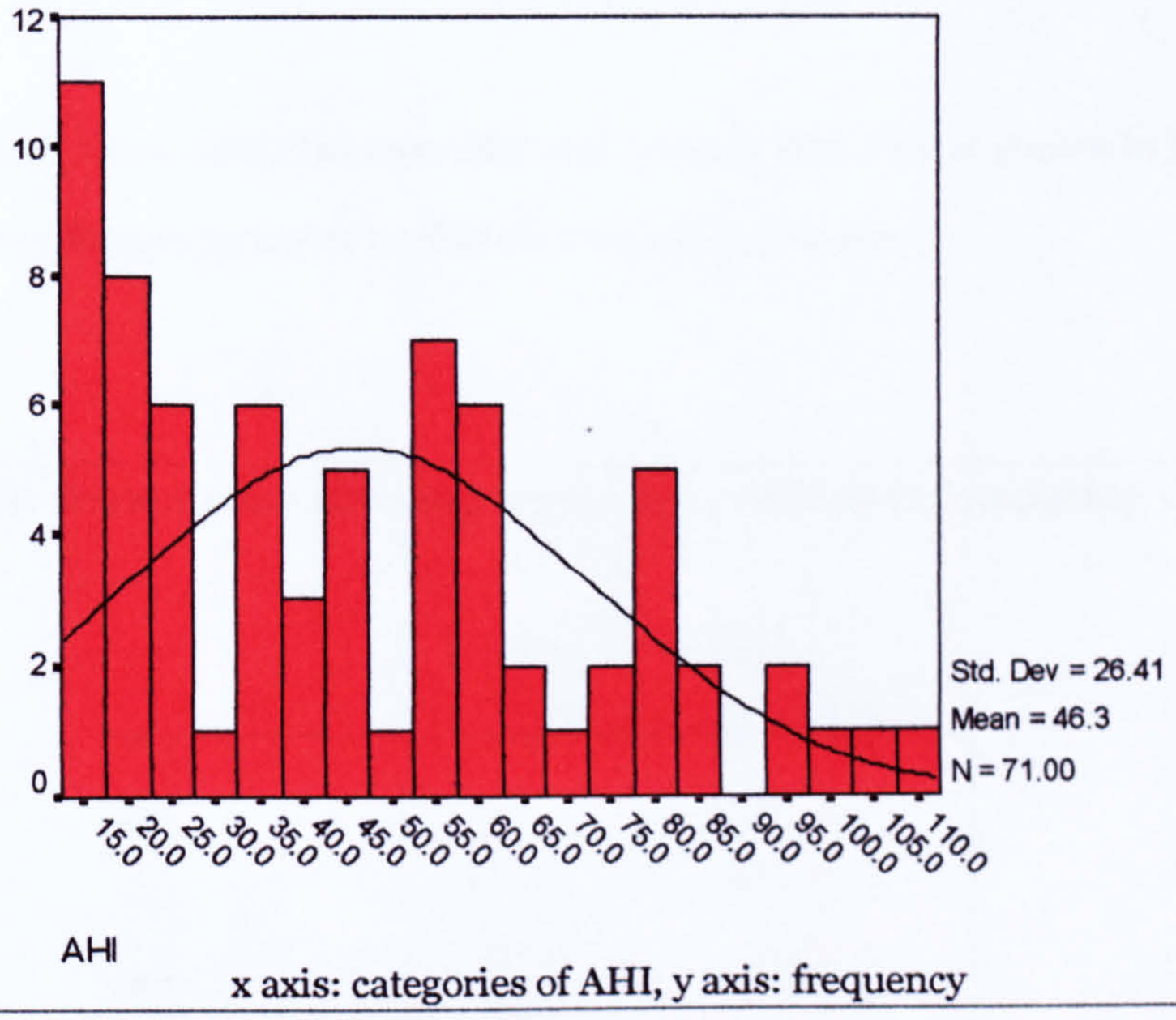
The sleep variables suggest a mean total sleep time of less than 6 hours with variability. The mean sleep latency was 28 minutes, REM latency was 2 hours and the sleep efficiency was reduced in the whole population. The majority of time was spent by subjects in Stage II sleep (almost 3 hours) and the least amount of time (i.e. > 1 hour) was spent in slow wave sleep (comprising of Stage III and Stage IV sleep).

The AHI had a skewed distribution as shown by *figure 5.9* showing a tri-modal spread with peaks at 15-20 $hour^{-1}$, 50-55 $hour^{-1}$ and 70-75 $hour^{-1}$ and the AI showed a normal spread with a peak at 55-60 $hour^{-1}$, *figure 5.10*.

Table 5.4: Home oximetry and PSG variables at baseline

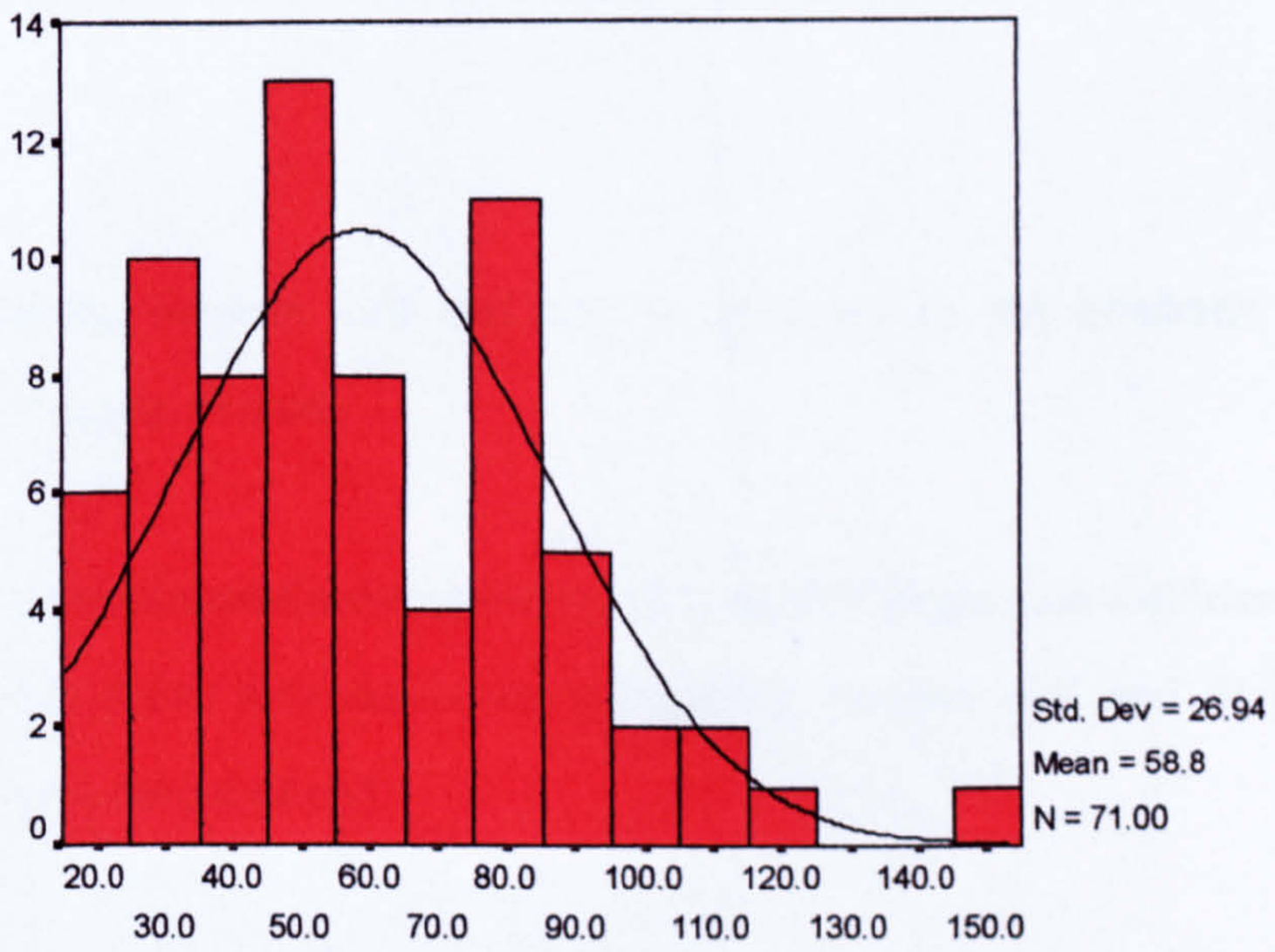
Home pulse oximetry variables	Mean	SD	SEM
4% ODI	25.2	28.8	3.9
Mean SaO2 (Pulsox)	93.1	2.9	0.4
HRV (6bpm)	47.1	25.1	3.3
Mean HR	67.0	8.8	1.1
Polysomnographic variables			
NREM obstructive apnoea index	18.4	21.5	2.8
NREM hypopnoeas index	24.3	19.1	2.5
NREM central apnoea index	0.4	1.1	0.2
NREM AHI	43.6	32.0	4.2
REM obstructive apnoea index	16.9	20.2	2.8
REM hypopnoeas index	29.6	17.0	2.3
REM central apnoea index	1.1	3.0	0.4
REM AHI	48.4	25.5	3.5
Mean AHI	46.3	26.4	3.1
Longest apnoea (seconds)	46.5	25.7	3.4
Longest hypopnoea (s)	58.4	31.0	4.1
Mean apnoea/ hypopnoeas duration (s)	21.5	4.7	0.6
Mean SaO2 (%)	91.4	4.3	0.6
MinSaO2 (%)	74.9	16.1	2.1
Mean SaO2 desaturation (%)	6.6	7.6	1.0
Sleep latency (min)	27.9	30.9	4.0
REM latency (min)	129.0	80.4	10.5
Total sleep time (min)	412.2	111.4	14.5
STAGE1 (min)	10.2	8.7	1.1
STAGE2 (min)	185.7	69.7	9.2
STAGE3 (min)	52.9	28.3	3.7
STAGE4 (min)	16.8	22.0	2.9
REM time (min)	86.4	41.7	5.6
AI	58.8	26.9	3.2
Sleep efficiency (%)	68.5	16.7	2.2

Figure 5.10 Histogram depicting the frequency distribution of AHI (hour^{-1})



x axis: categories of AHI, y axis: frequency

Figure 5.11: Histogram depicting the AI distribution

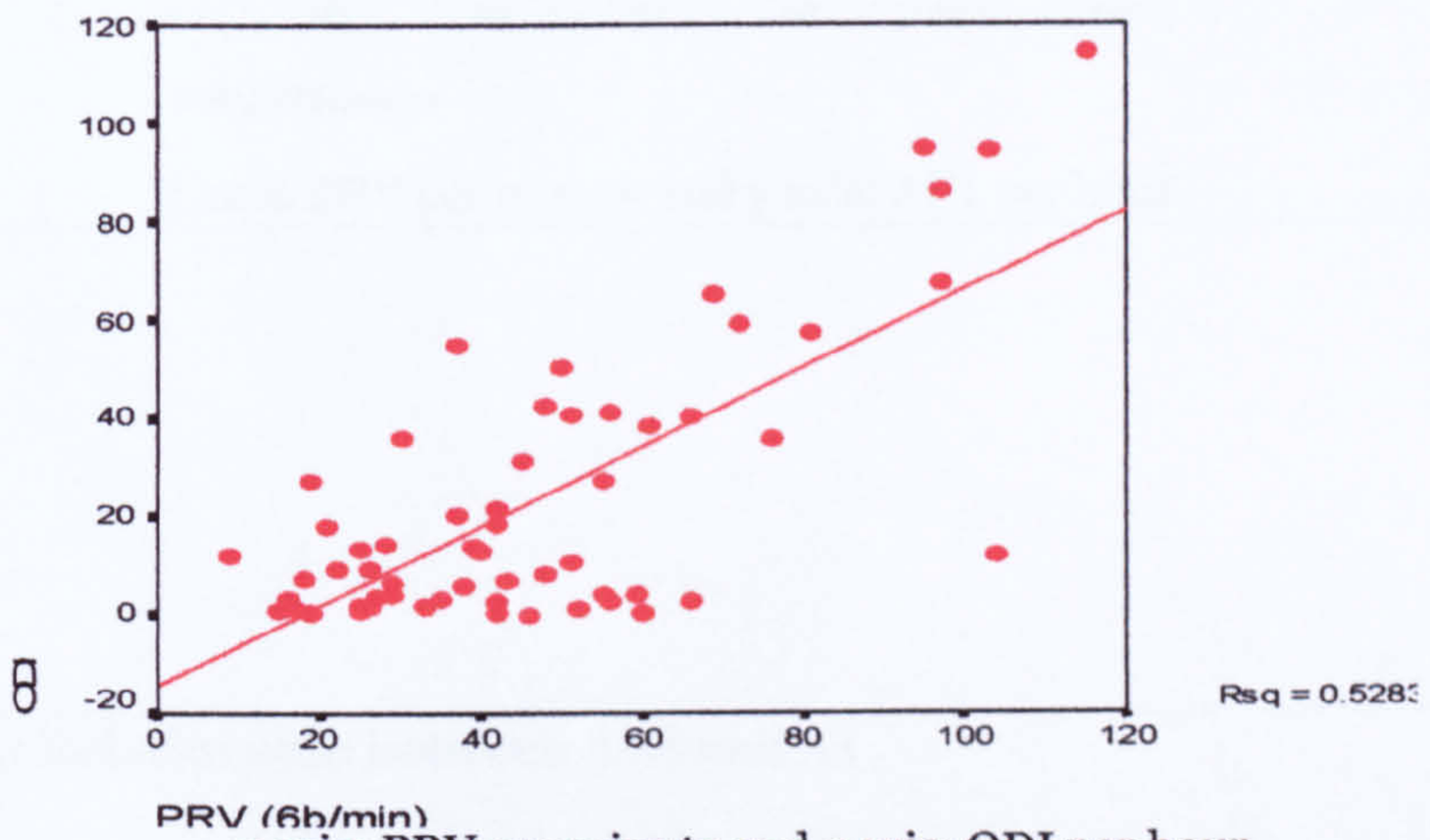


x axis: categories of arousal index AI, y axis: frequency

5.2.5 Interactions between home oximetry and inpatient PSG

The predictive relationship between ODI and 6 beats/ min PRV is shown in *figure 5.10*, which shows a linear regression coefficient r^2=0.5283, p<0.001.

Figure 5.12: Scatter plots showing regression coefficient comparing ODI vs. PRV

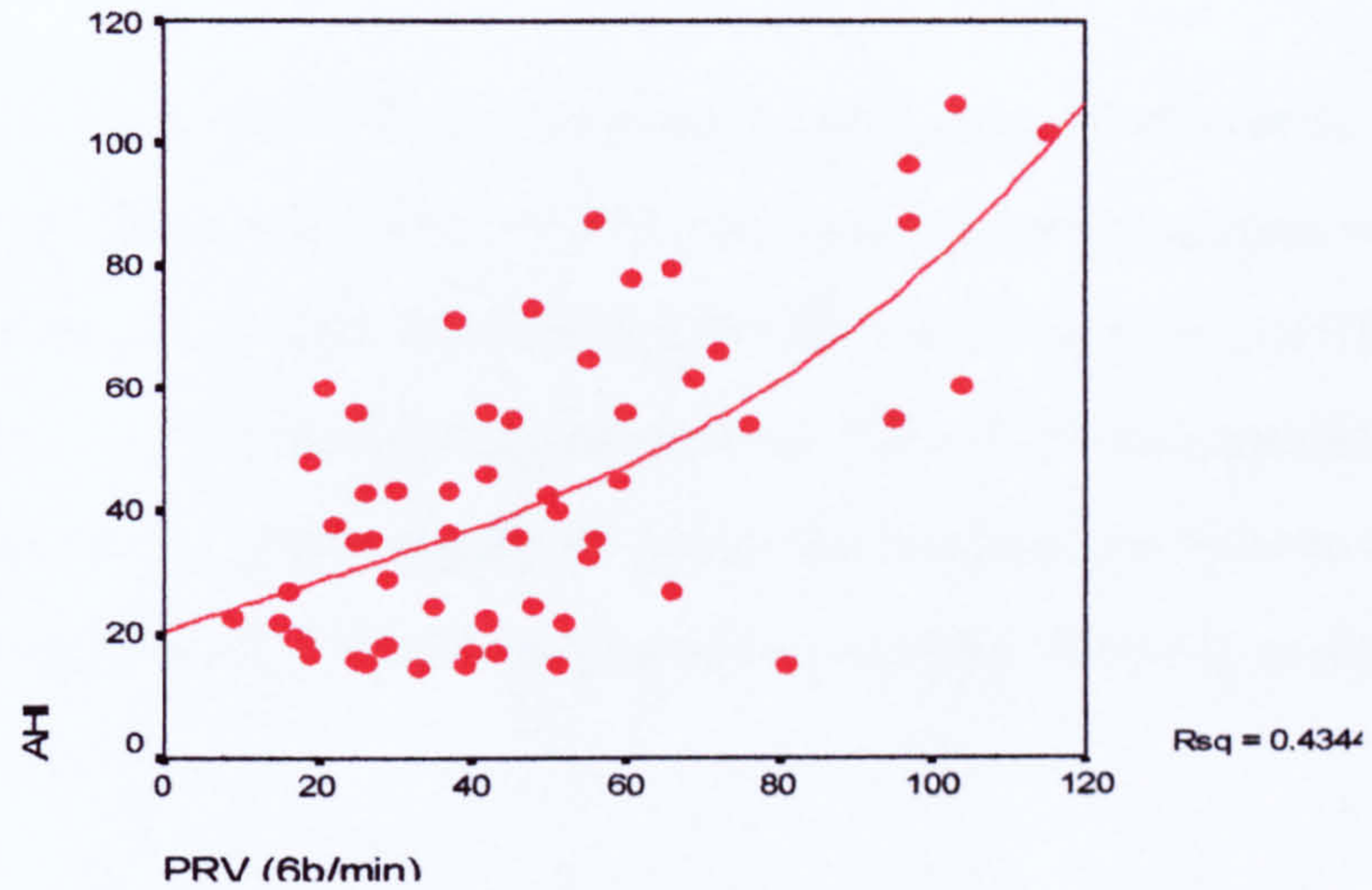


x axis: PRV per minute and y axis: ODI per hour

The relationship between ODI and AHI is predicted by the quadratic regression coefficient r^2=0.543, p<0.001.

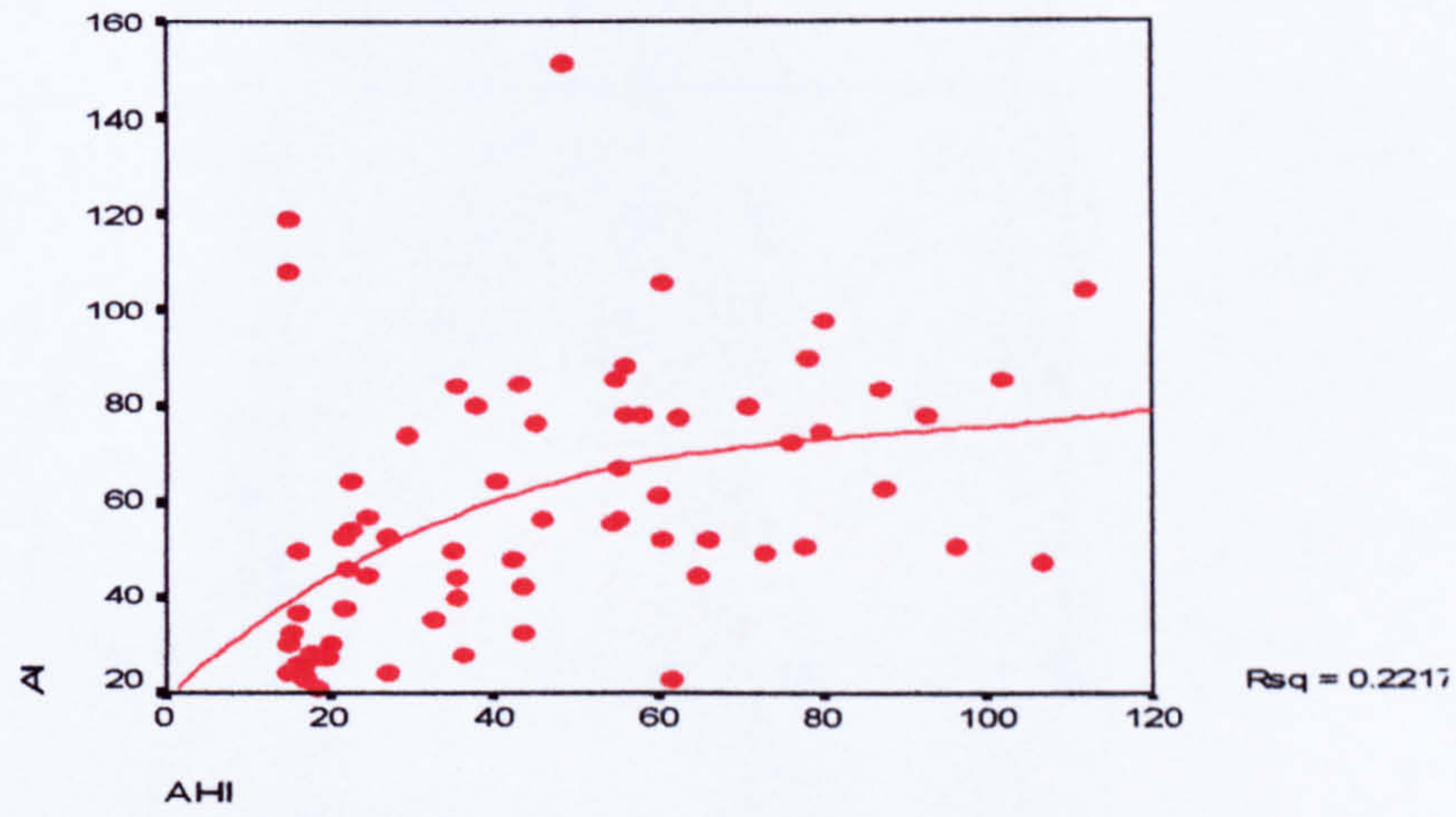
Figure 5.11 shows the relationship between AHI and PRV (regression coefficient r2=0.434, p<0.05) while *figure 5.12* shows the relationship between AHI and AI (regression coefficient r2=0.2217, p<0.05).

Figure 5.13 Scatter plot depicting the relationship between AHI & PRV



x axis: PRV per minute and y axis: AHI per hour

Figure 5.14: Relationship between AHI and AI

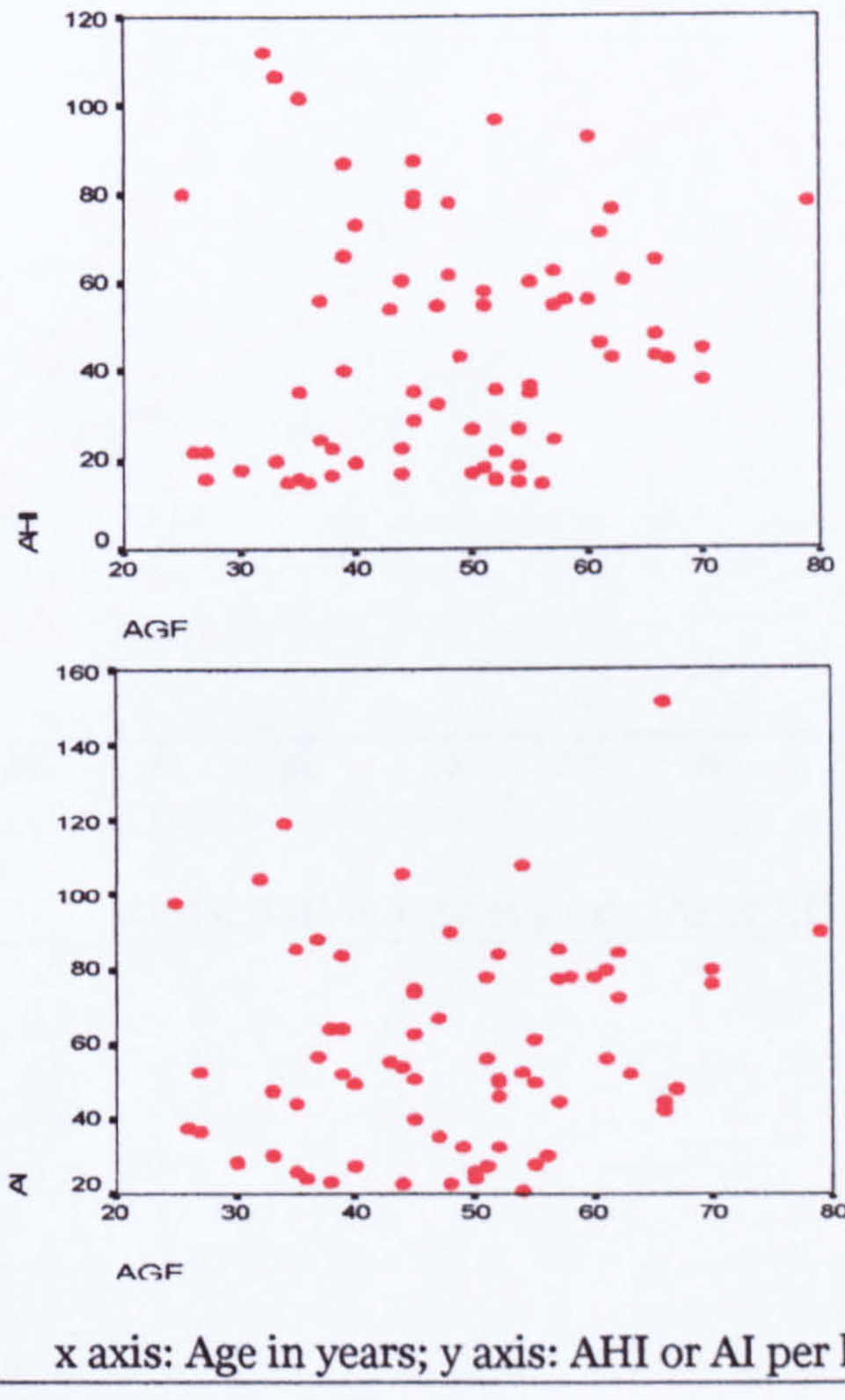


x axis: AHI per hour and y axis: AI per hour

5.2.6 Relationship between PSG & anthropometric variables

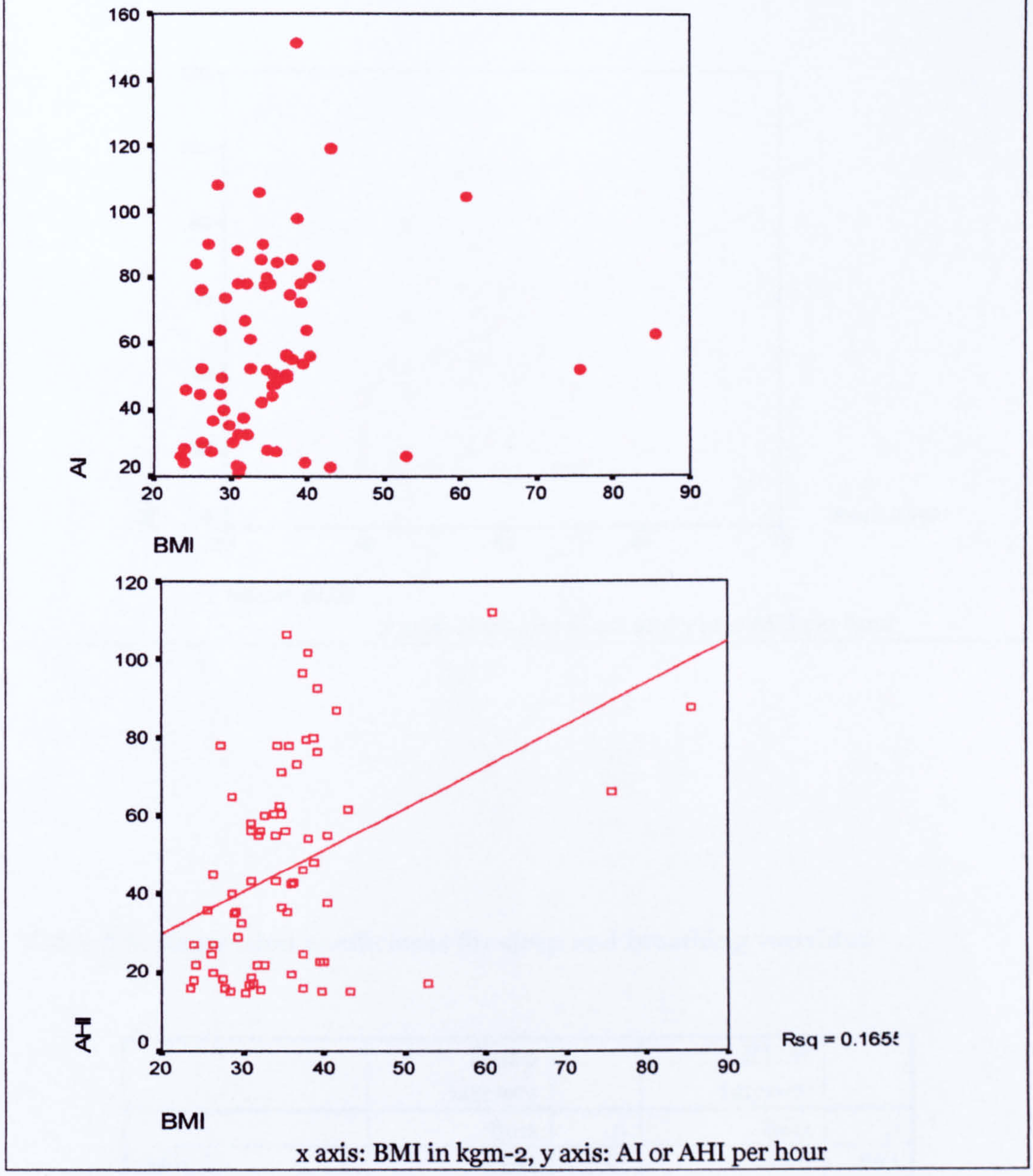
Exploration of the data interactions using scatter plots (*figure 5.13*) shows that the age of subjects was not significantly related to AHI or AI. Among polysomnographic variables, BMI showed a significant linear relationship only with AHI (r^2=0.15, p<0.001) but not with AI, *figure 5.14*. Neck size showed a relationship with AHI (r^2=0.14, p=0.001, *figure 5.15*) but none of the polysomnographic sleep variables (sleep latency, REM latency, time in SWS) were significantly related to sleep-breathing variables (AHI/ AI), as shown in *Table 5.6*.

Figure 5.15: Relationships between age & AHI or AI



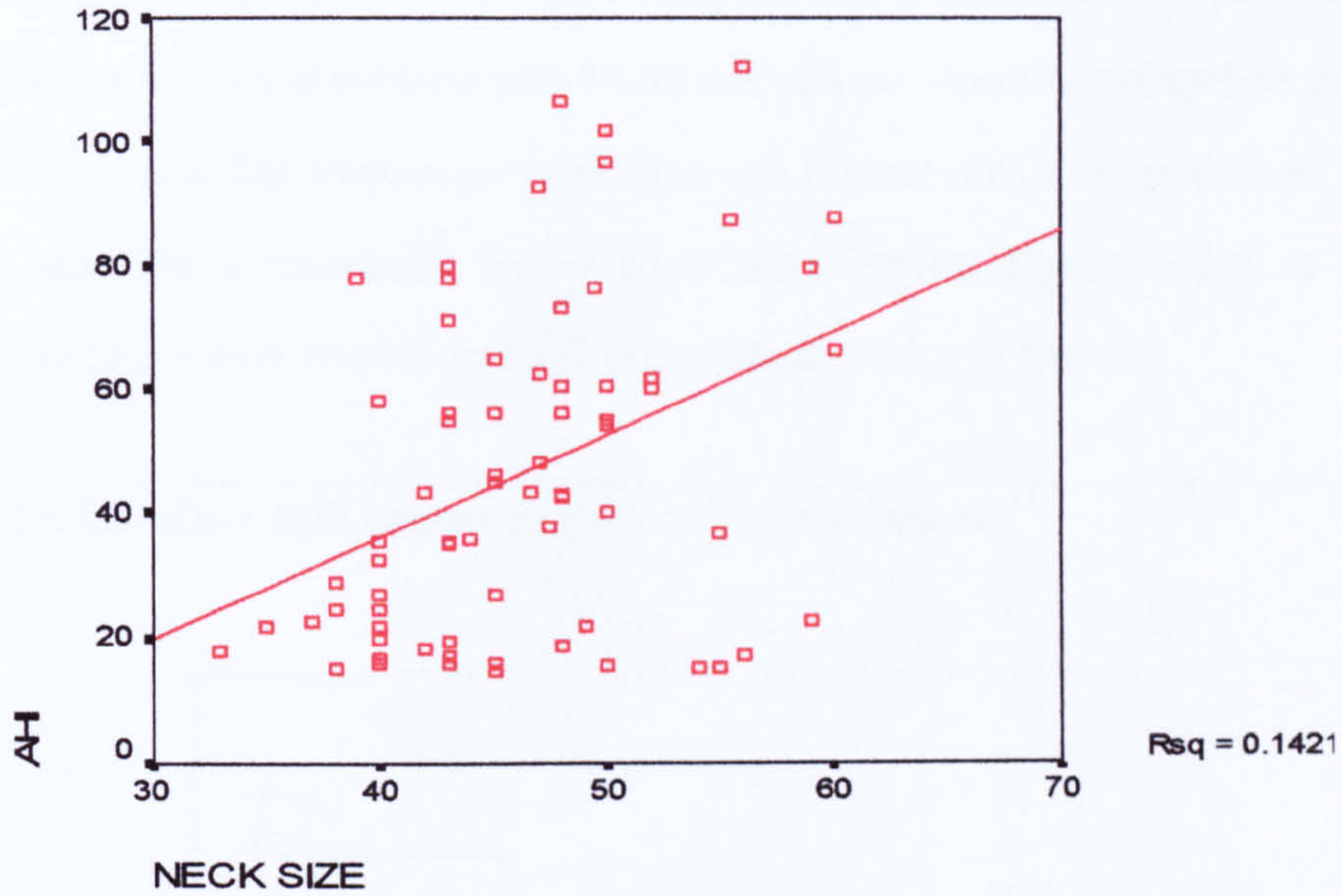
x axis: Age in years; y axis: AHI or AI per hour

Figure 5.16: Relationship between BMI and AHI or AI



x axis: BMI in kgm-2, y axis: AI or AHI per hour

Figure 5.17: Relationship between AHI and neck size



x axis: Neck size in cm and y axis AHI per hour

Table 5.5: Regression coefficients for sleep and breathing variables

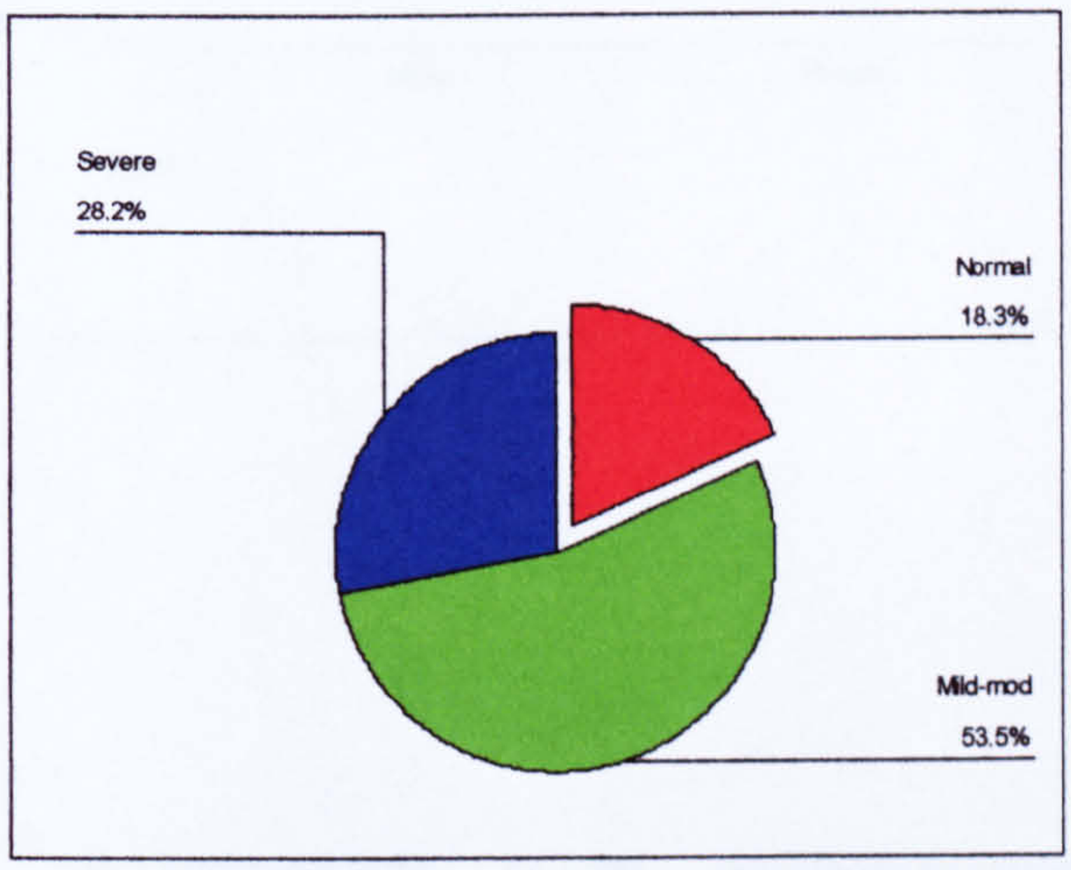
	Sleep latency		REM latency	
	Beta	p	Beta	p
AHI	-.151	.357	-.026	.883
AI	.310	.058	.055	.754
Min SaO2	.216	.162	.169	.312
Total sleep time	-.102	.509	-.086	.601
Time in stage III	-.051	.768	-.223	.226
Time in stage IV	.161	.294	.079	.628
Sleep latency			.008	.958

Using multiple linear regression models with sleep latency and REM latency as dependant variables

5.2.7 Excessive daytime sleepiness (EDS)

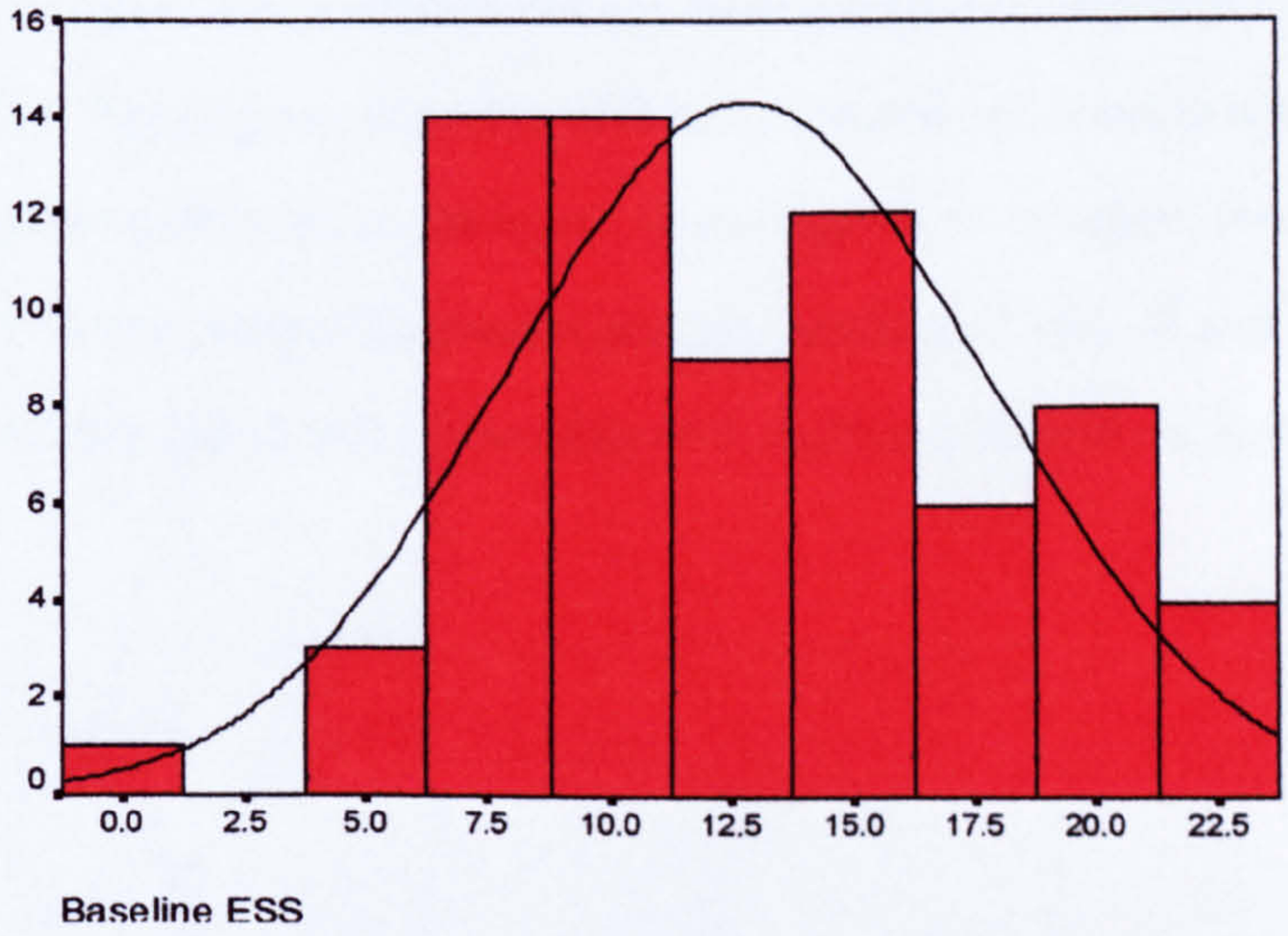
Excessive daytime sleepiness was measured using the ESS questionnaire at baseline in all patients. There were 18% of subjects with SAHS who did not report EDS based on the ESS questionnaire results. The frequency distribution was normal with a mean score of 13 (5), with men reporting a marginally higher score than women, Men: median 12 (Inter quartile range IRQ = 6) & Women 10 (IRQ 11), as shown in *figure 5.16-18.*

Figure 5.18: Baseline ESS scores in the study population



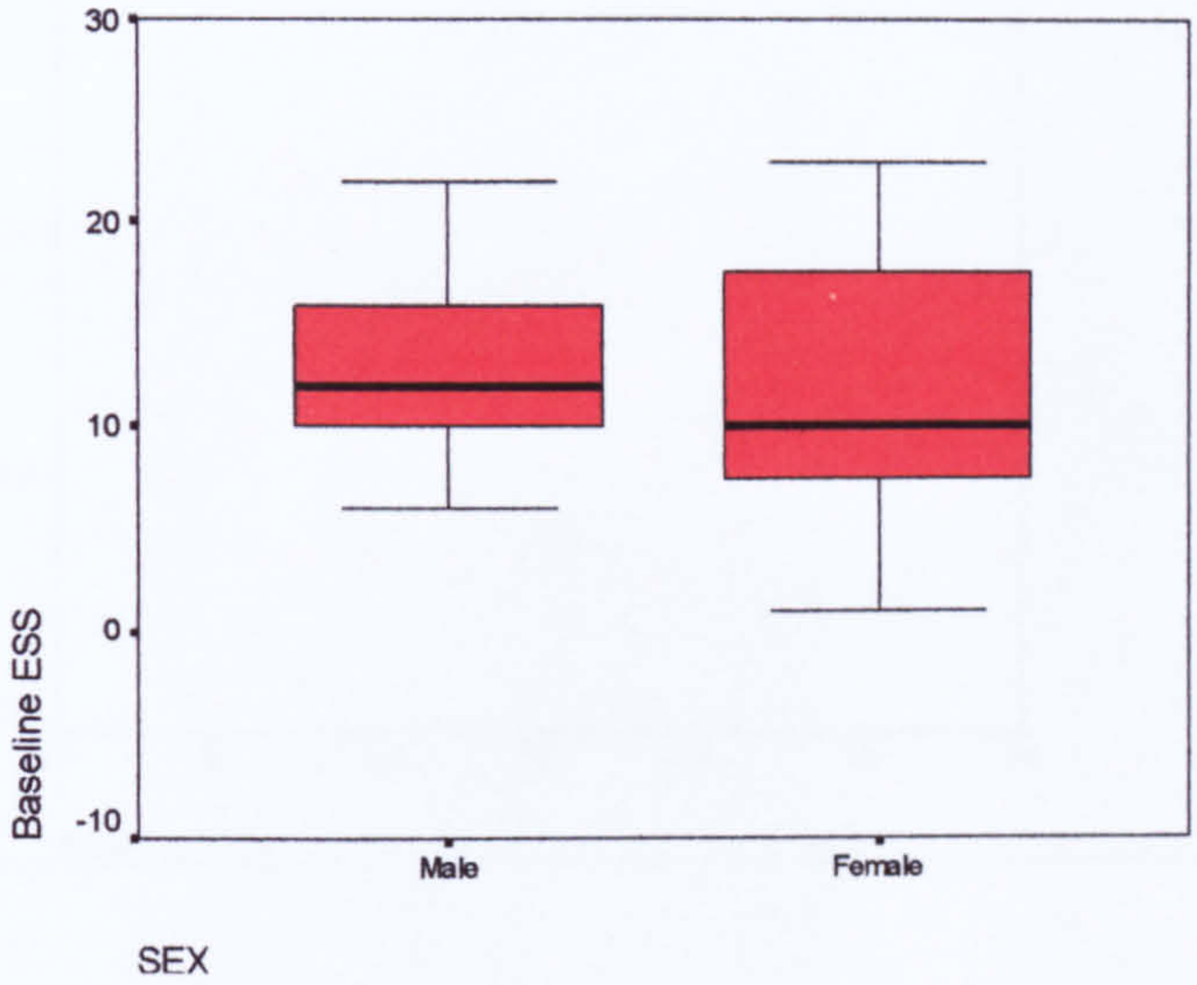
(Proportions in order of severity; normal<8, mild-moderate 8-15 and severe 16-24)

Figure 5.19: Histogram depicting the ESS scores at baseline



x axis: frequency & y axis: ESS scores

Figure 5.20: Distribution of ESS scores between male and female patients at baseline



5.2.8 ESS - relationship with anthropometric & PSG variables

The chronological age of study subjects did not show any relationship with their predicted self-reported EDS (*figure 5.19*). However BMI had a positive relationship with ESS in this dataset with a plateau between 30-40 kgm^{-2}, (cubic regression equation, $r^2=0.2$, $p=0.04$), *figure 5.20*. The three primary polysomnographic variables of AHI, AI and sleep latency did not demonstrate a significant relationship with daytime somnolence, *figure 5.21*.

Figure 5.21: Relationship between baseline ESS scores and age

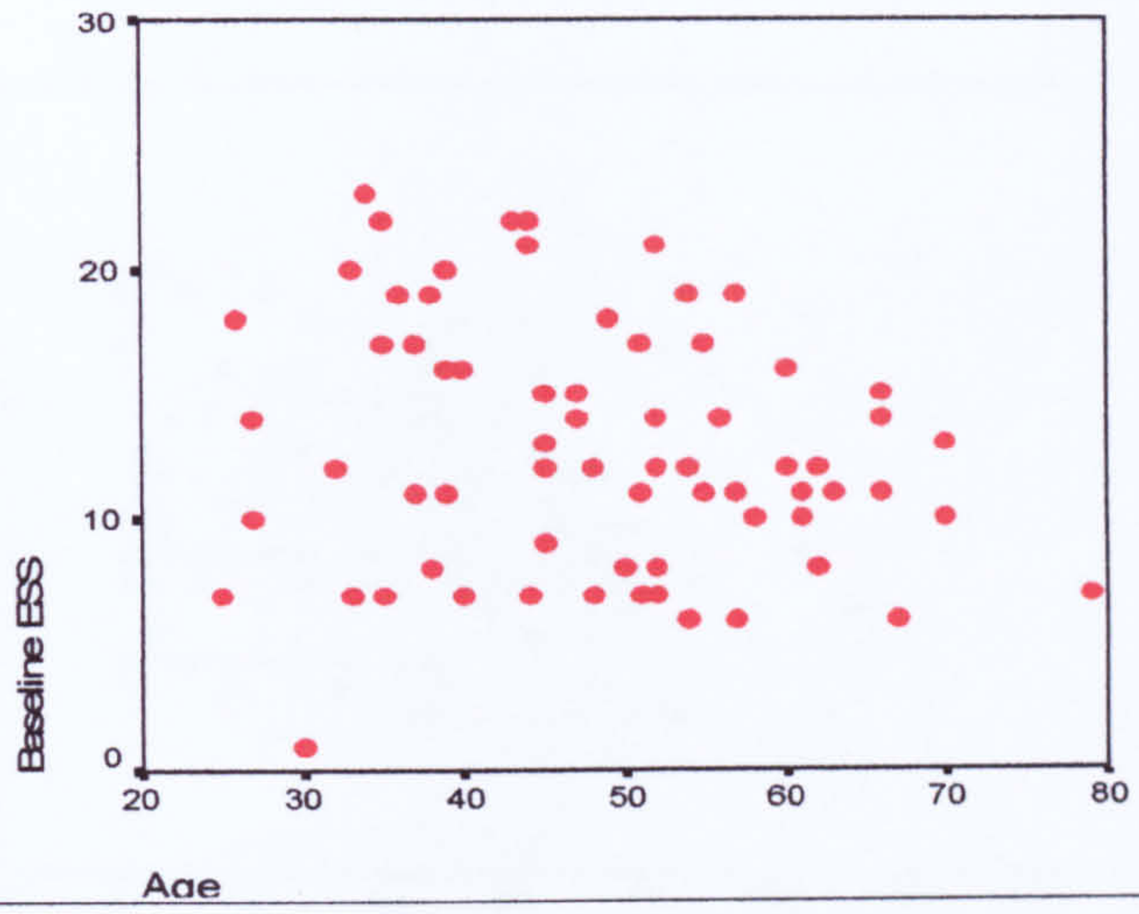


Figure 5.22: Relationship between BMI and ESS at baseline

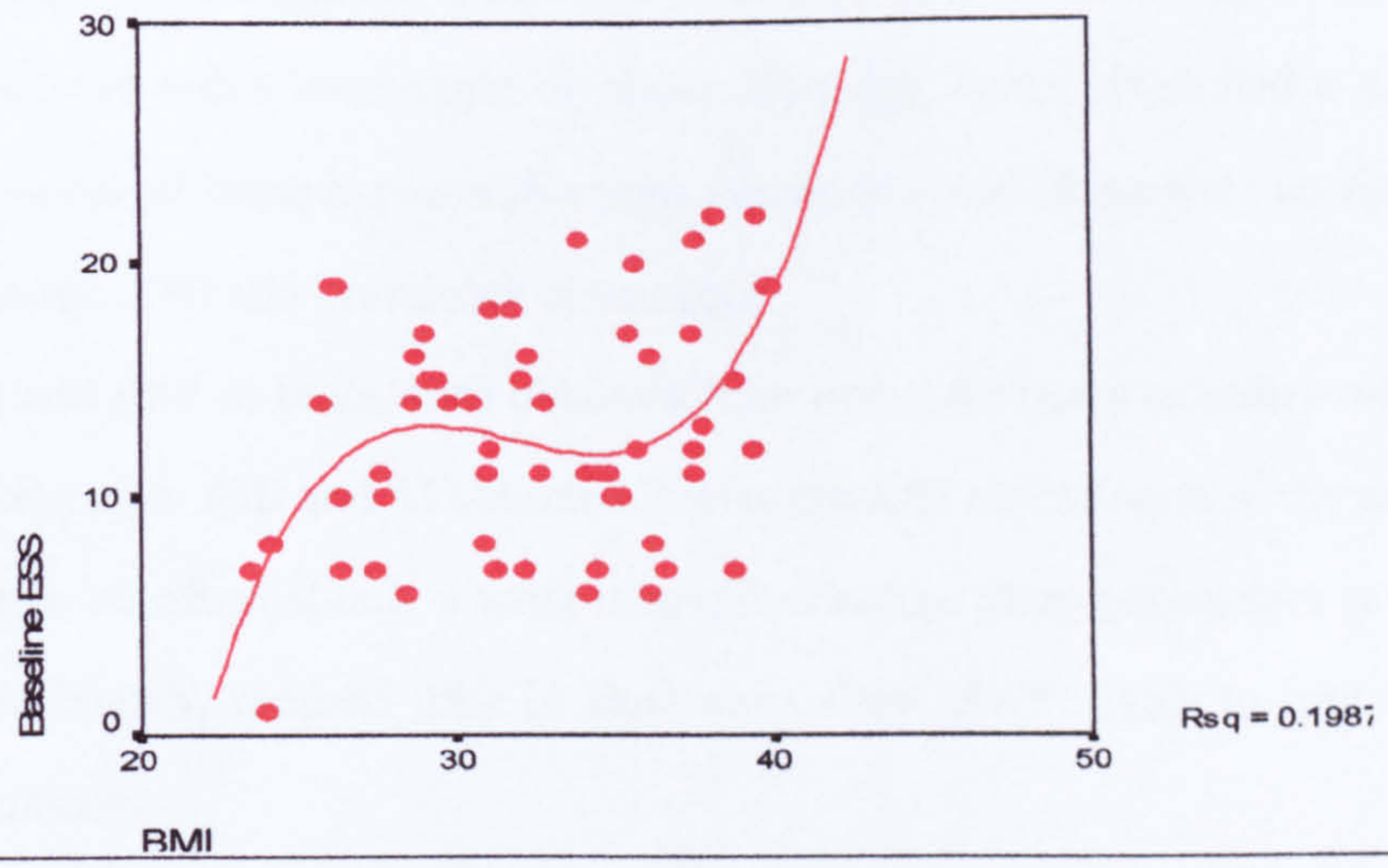
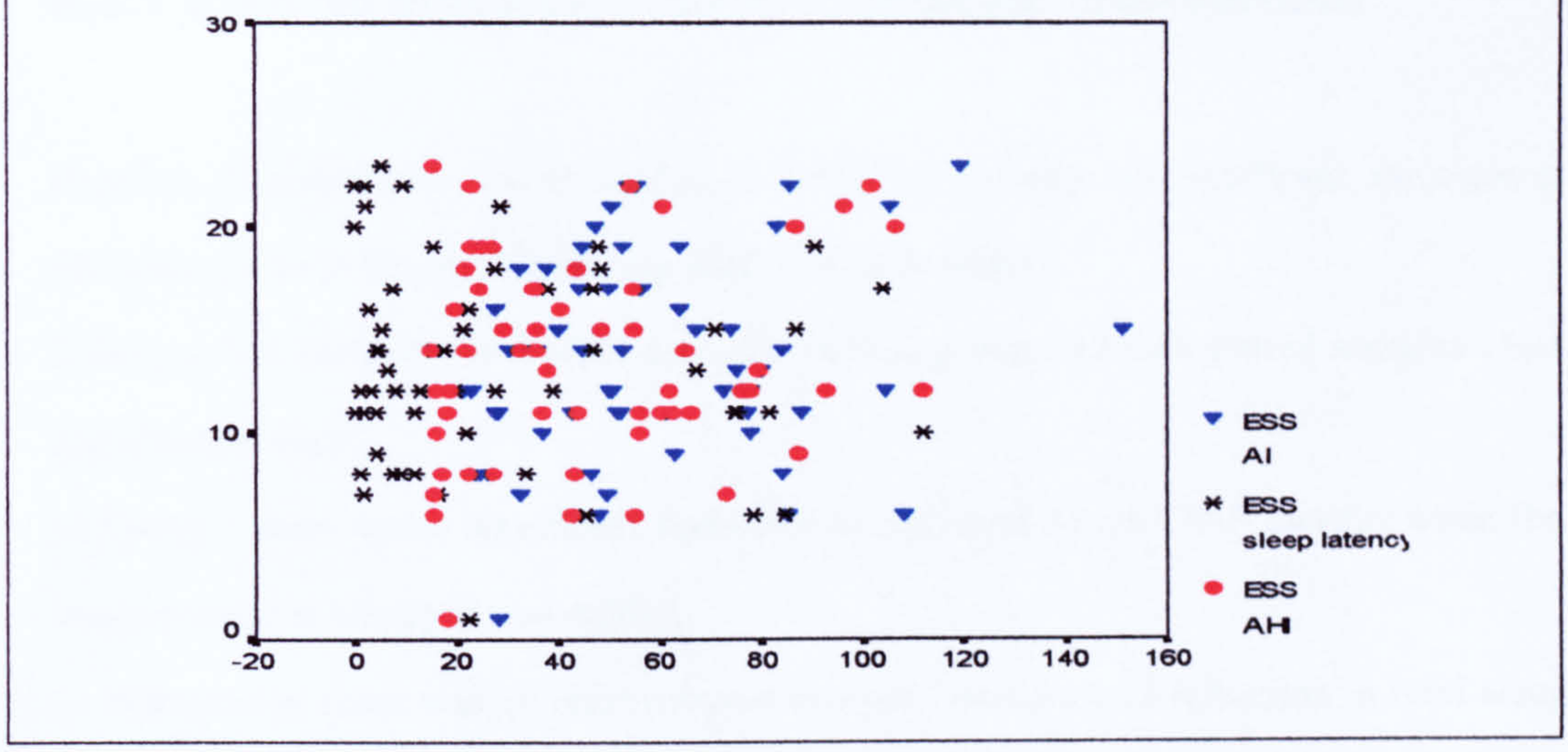


Figure 5.23: Relationship of ESS scores with PSG variables



5.2.9 Summary of baseline population data

Unlike a population survey, study subjects were recruited from patients referred from primary care with history suggestive of SAHS hence due to a positive selection bias, the proportion of subjects diagnosed SAHS and percentage of males were higher (78%) and 80% subjects were either overweight or obese (BMI >25 kgm^{-2}). Men had a 2.4 times higher relative risk of being hypertensive than women although there were no significant differences in age, BMI and prevalence of smokers.

The 4% ODI and PRV (6 beats/min) obtained from overnight home oximetry recordings was closely related to AHI and AI obtained. The mean AHI and AI were in the moderate to severe range but showed only a weak inter-relationship. Sleep parameters revealed a delayed REM latency, reduced time in slow wave sleep (SWS) likely to contribute to daytime sleepiness.

The BMI increments were weakly predictive of higher AHI and ESS scores but did not show a similar relationship with any of the other sleep variables.

5.3 CLINICAL EFFECTIVENESS

5.3.1 Clinical efficacy of CPAP/ Lifestyle intervention

Baseline characteristics are presented in *table 5.6* showing no significant inter-group differences except Group II spending shorter time in Stage I.

Table 5.7 lists the post- intervention results in each group and their paired samples t test significance values.

In Group I there was a significant reduction in AHI and AI on CPAP therapy while the improvement in Group II was milder.

In both groups there was an improvement in sleep latency and a reduction in total sleep time.

Group I patients report marked improvement in daytime somnolence with ESS scores reduced from 13.7 (5.6) to 7.1 (4.6), $p<0.001$ but patients in group II did not report a significant improvement; ESS scores 13 (3.7) to 11.6 (4.7), $p=0.164$ as shown in *figure 5.22.*

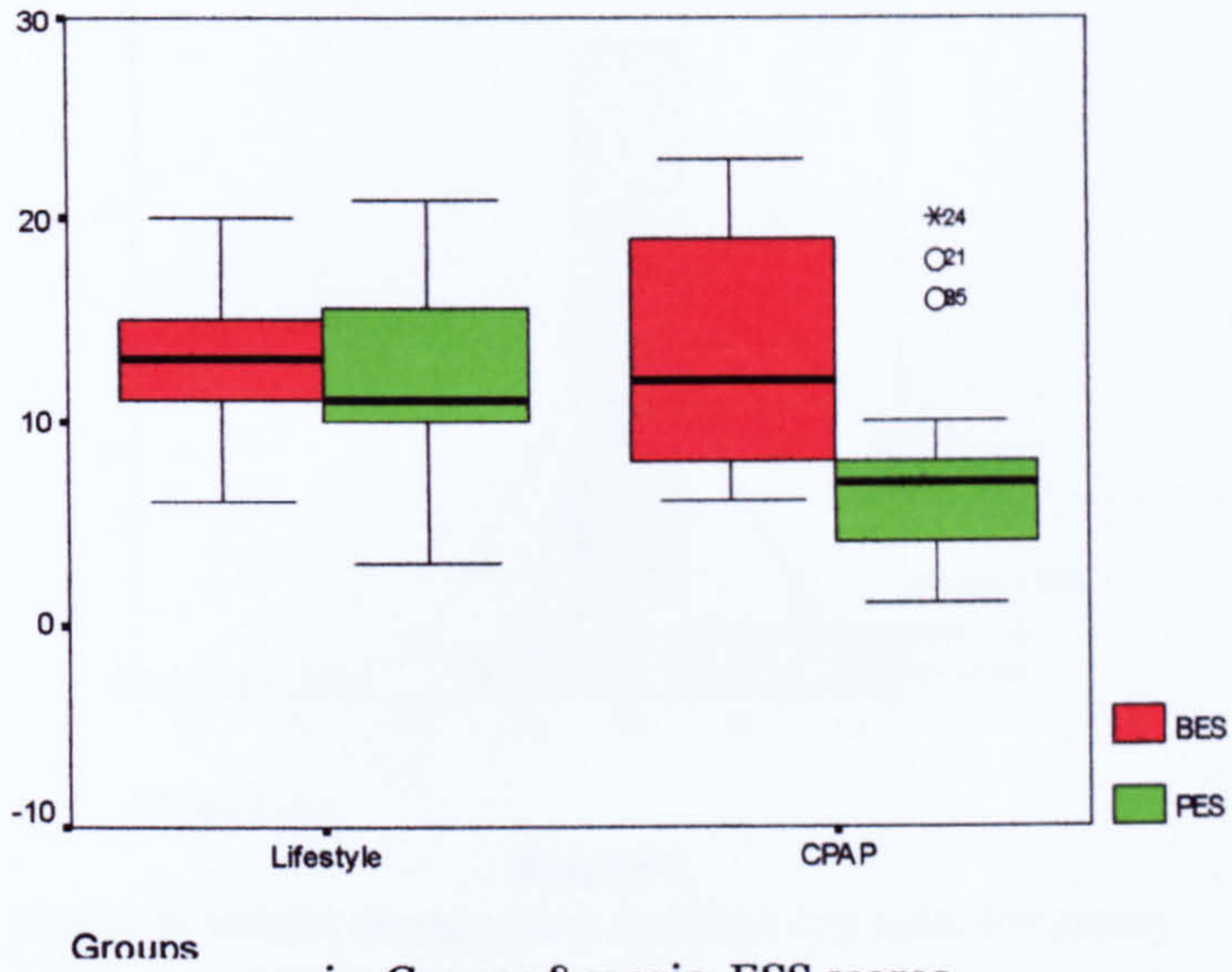
Table 5.6: Baseline Group Statistics

	Groups	**Mean**	**SD**	p
Age (years)	Lifestyle	51.3	12.2	
	CPAP	46.3	11.3	**0.082**
BMI (kgm-2)	Lifestyle	34.0	5.5	
	CPAP	34.3	9.2	**0.897**
Neck size (cm)	Lifestyle	44.9	4.8	
	CPAP	46.5	6.5	**0.249**
ODI (hour-1)	Lifestyle	19.2	25.9	
	CPAP	31.2	27.3	**0.066**
PRV (hour-1)	Lifestyle	42.1	18.3	
	CPAP	51.7	26.5	**0.087**
AHI (hour-1)	Lifestyle	36.3	24.4	
	CPAP	46.6	27.2	**0.066**
Sleep latency (min)	Lifestyle	36.5	35.2	
	CPAP	22.4	25.9	**0.088**
REM latency (min)	Lifestyle	140.1	79.8	
	CPAP	118.1	83.2	**0.314**
Total sleep time (min)	Lifestyle	422.5	118.2	
	CPAP	402.5	113.0	**0.274**
STAGE I time (min)	Lifestyle	7.1	7.2	
	CPAP	12.7	9.6	**0.026***
STAGE II time (min)	Lifestyle	195.4	76.3	
	CPAP	175.4	53.4	**0.190**
STAGE III time (min)	Lifestyle	53.4	25.8	
	CPAP	54.5	31.0	**0.702**
STAGE IV time (min)	Lifestyle	22.6	30.8	
	CPAP	16.1	19.9	**0.695**
REM period (min)	Lifestyle	81.2	42.9	
	CPAP	86.3	40.4	**0.776**
AI (hour-1)	Lifestyle	59.1	35.6	
	CPAP	53.4	22.7	**0.113**
Sleep efficiency (%)	Lifestyle	66.5	17.6	
	CPAP	70.0	16.5	**0.447**
Mean SaO2 (%)	Lifestyle	91.5	5.0	
	CPAP	91.7	3.5	**0.849**
Min SaO2 (%)	Lifestyle	77.7	11.0	
	CPAP	74.4	17.6	**0.427**
Baseline ESS	Lifestyle	13.0	3.7	
	CPAP	13.7	5.6	**0.183**

TABLE 5.7 Paired samples of patients completing the study at baseline and post-intervention

	CPAP n=37			Lifestyle n=34		
	Mean	SD	P	Mean	SD	p
Base BMI (kgm-2)	34.3	9.2		34.0	6.0	0.03
Post BMI	34.1	9.2	Ns	33.3	5.5	
Base neck size (cm)	46.5	6.5		44.9	4.8	
Post neck size	47.5	4.3	Ns	45.4	3.8	Ns
Base AHI (hour-1)	46.6	27.2		36.3	24.4	
Post AHI	7.7	4.3	<0.001	28.6	22.9	0.02
Base AI (hour-1)	53.4	22.7		59.1	35.6	
Post AI	18.9	6.9	<0.001	40.6	23.3	0.01
Base sleep latency (min)	22.4	25.9		36.5	35.2	
Post sleep latency	31.2	29.4	0.04	48.1	44.4	<0.05
Base REM latency (min)	118.1	83.2		140.1	79.8	
Post REM latency	111.0	70.5	Ns	113.7	62.3	Ns
Base stage I time (min)	12.7	9.6		7.1	7.2	
Post stage I time	18.2	18.3	Ns	14.8	26.0	Ns
Base stage II time (min)	175.4	53.4		195.4	76.3	
Post stage II time	153.6	44.1	Ns	176.9	69.1	Ns
Base stage III time (min)	54.5	31.0		53.4	25.8	
Post stage III time	54.3	30.0	Ns	66.1	35.8	Ns
Base stage IV time (min)	16.1	19.9		22.6	30.8	
Post stage IV time	15.1	10.4	Ns	17.4	19.2	Ns
Base REM period (min)	86.3	40.4		81.2	42.9	
Post REM period	82.8	30.0	Ns	84.5	49.5	Ns
Base total sleep time (min)	402.5	113.0		422.5	118.2	
Post total sleep time	338.3	65.3	0.004	357.6	113.9	0.02
Base sleep efficiency (%)	70.0	16.5		66.5	17.6	
Post sleep efficiency	70.0	14.6	Ns	68.2	16.8	Ns

Figure 5.24: showing the baseline median ESS scores and inter-quartile ranges before (BESS) and after (PESS) treatment.



x axis: Groups & y axis: ESS scores

5.3.2 Change in lifestyle parameters

5.3.2.1 Weight

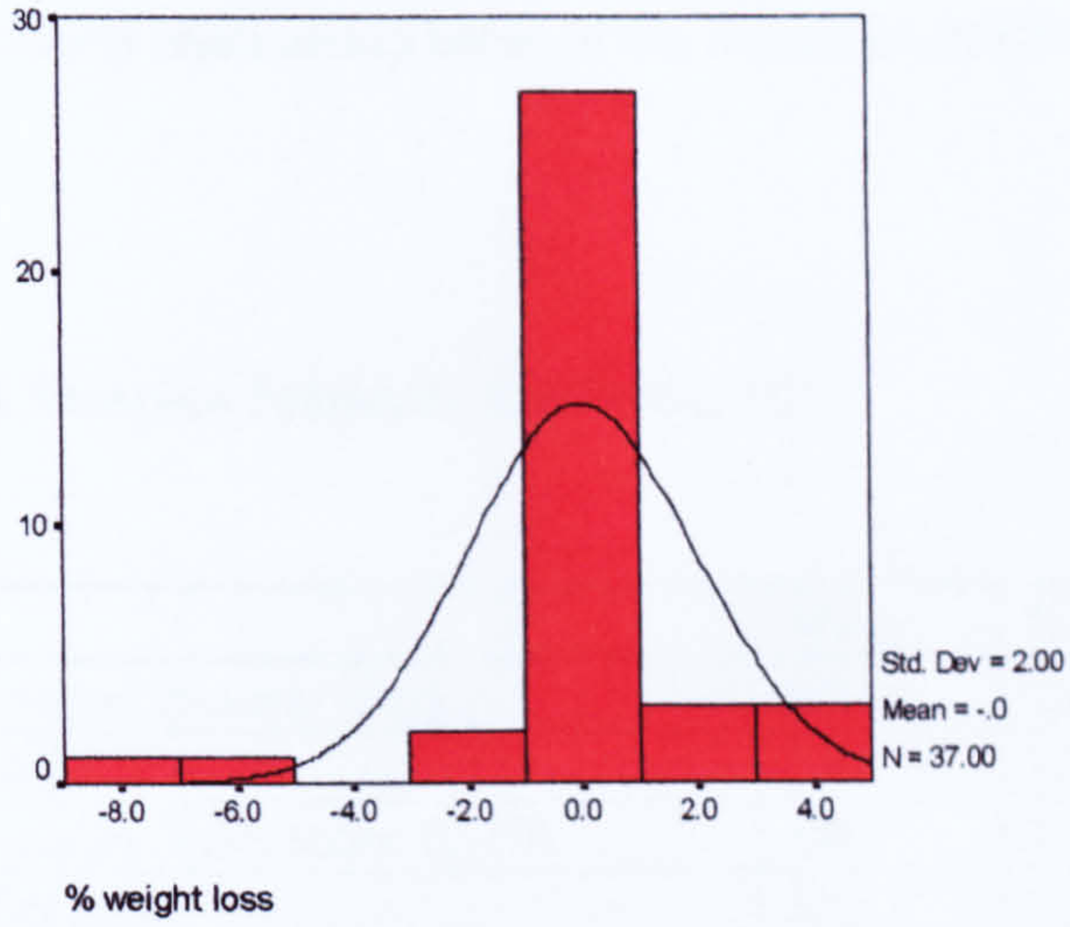
Group I patients had no overall change in body weight during the trial period; Median 0 (ranging from gaining 3.3 kg to losing 7.4 kg of their own accord.

However in group II, the median weight loss achieved was 3.2 kg with a range from 4.1 kg gain to 13.4 kg loss.

The histograms in *figure 5.23* illustrate the distribution of the percentage change in weight from baseline achieved. The change in BMI in group II was 0.7 kgm-2, (p=0.03).

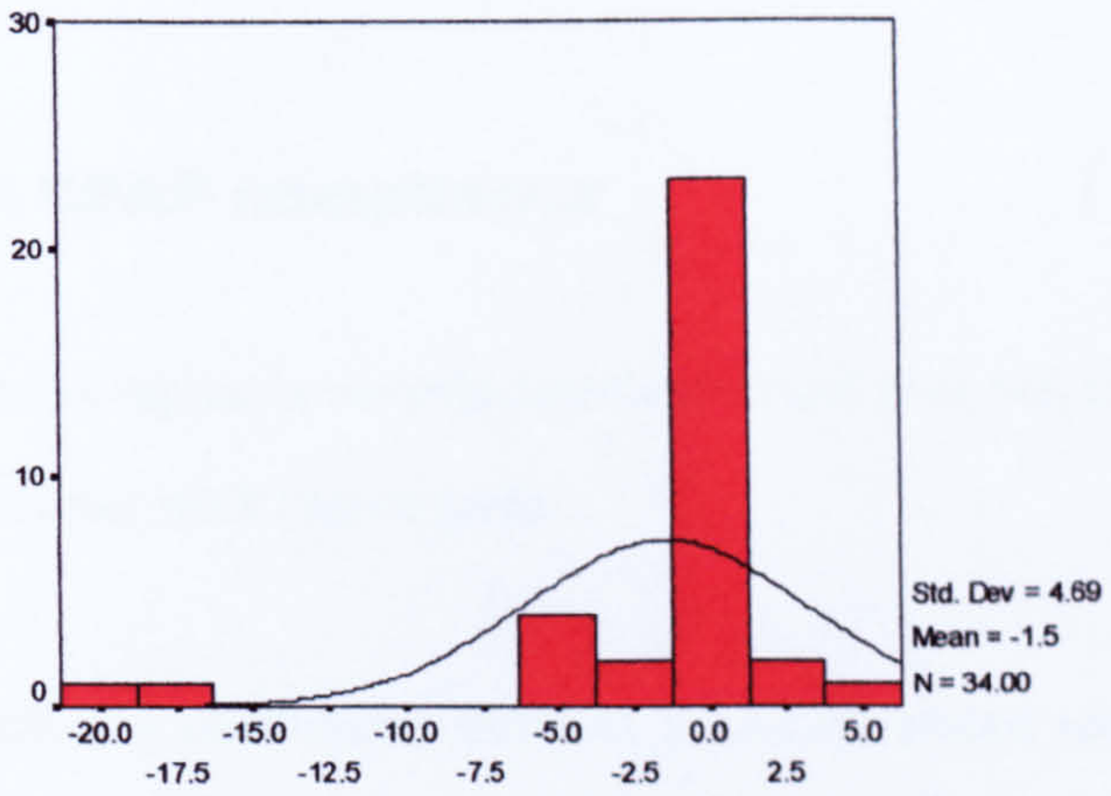
The change in weight and BMI showed no significant relationship with alteration in AHI or AI in Group II patients.

Figure 5.25: Histograms of weight change post trial (% of baseline weight in kg)



Group I

x axis: % weight change from baseline & y axis: frequency



Group II

x axis: % weight change from baseline & y axis: frequency

5.3.2.2 Sleep diary

Group II patients did not demonstrate a change in the sleep period based on their diary records, between the first fortnight and the last fortnight of the 3 month trial period, the average sleep period was 7 hours/ night.

There were significant improvements recorded in the VAS scores for the quality of nocturnal sleep (p=0.001) and in reduction of the feeling of sleepiness on waking (p=0.002) after lifestyle intervention, as shown in table 5.8.

There were no significant relationship between the difference in ESS scores and the sleep diary variables.

Table 5.8: Paired Samples Statistics for Group II

	Mean	SD	P
Baseline sleep period (hours/ day)	6.9	1.2	
Post sleep period	7.0	1.0	**0.401**
Baseline sleep quality VAS score (0-10)	4.9	1.3	
Post sleep quality score	5.4	1.5	**0.001**
Baseline daytime sleepiness VAS score (0-10)	5.5	1.2	
Post daytime sleepiness VAS score	3.7	1.2	0.002

5.3.3 Group I CPAP compliance

Computerised CPAP compliance records downloaded and analysed showed an average of 33.5 (14.3) hours use per week (figure 5.26).

There was no significant relationship between the CPAP usages with reduction in AHI (figure 5.27) seen after the treatment phase or (Spearman rho = 0.339, p=0.07) when compliance data was plotted against change in EDS (measured by ESS scores), figure 5.28 not reaching statistical significance.

The regression equation did not predict a change in ESS scores with mean hours of CPAP usage as an independant variable. However when baseline AHI was added as an independent variable, the model adjusted R^2 = 0.238 (p=0.022) and coefficient β= 0.492, p=0.014 for baseline AHI. With the addition of baseline ESS scores to the above model, the adjusted R^2 improves to 0.589, p<0.001 and the coefficient β for baseline ESS = 0.563, P=0.001. There was no change with the addition of baseline BMI to the regression model.

The above results demonstrate that baseline AHI and ESS scores are the most strong predictors of improvement in daytime hypersomnolence, whereas mean hours of CPAP usage is suggestive but does not reach statistical significance to be a predictor of treatment success.

Figure 5.26: CPAP usage

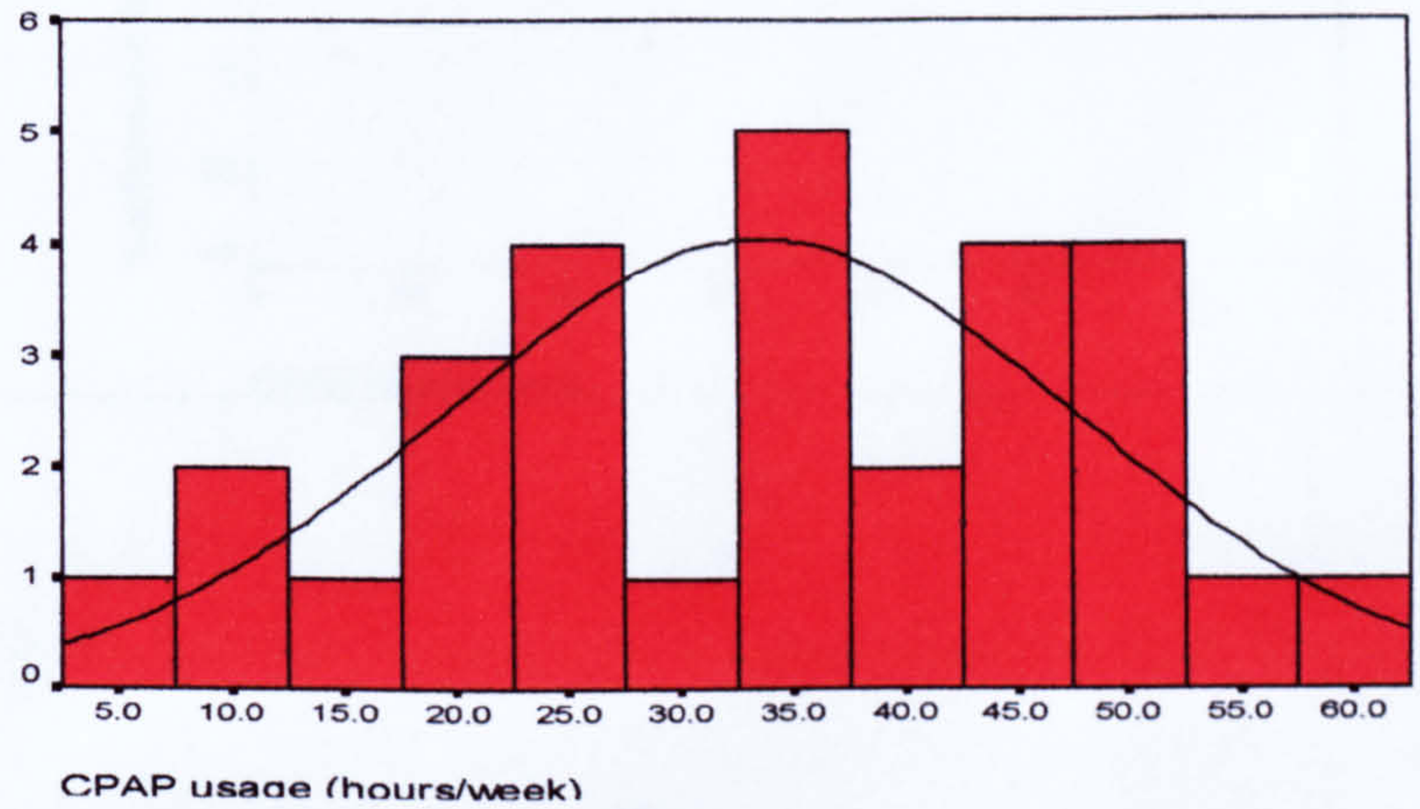


Figure 5.27: Compliance in CPAP patients and relationship with δ AHI

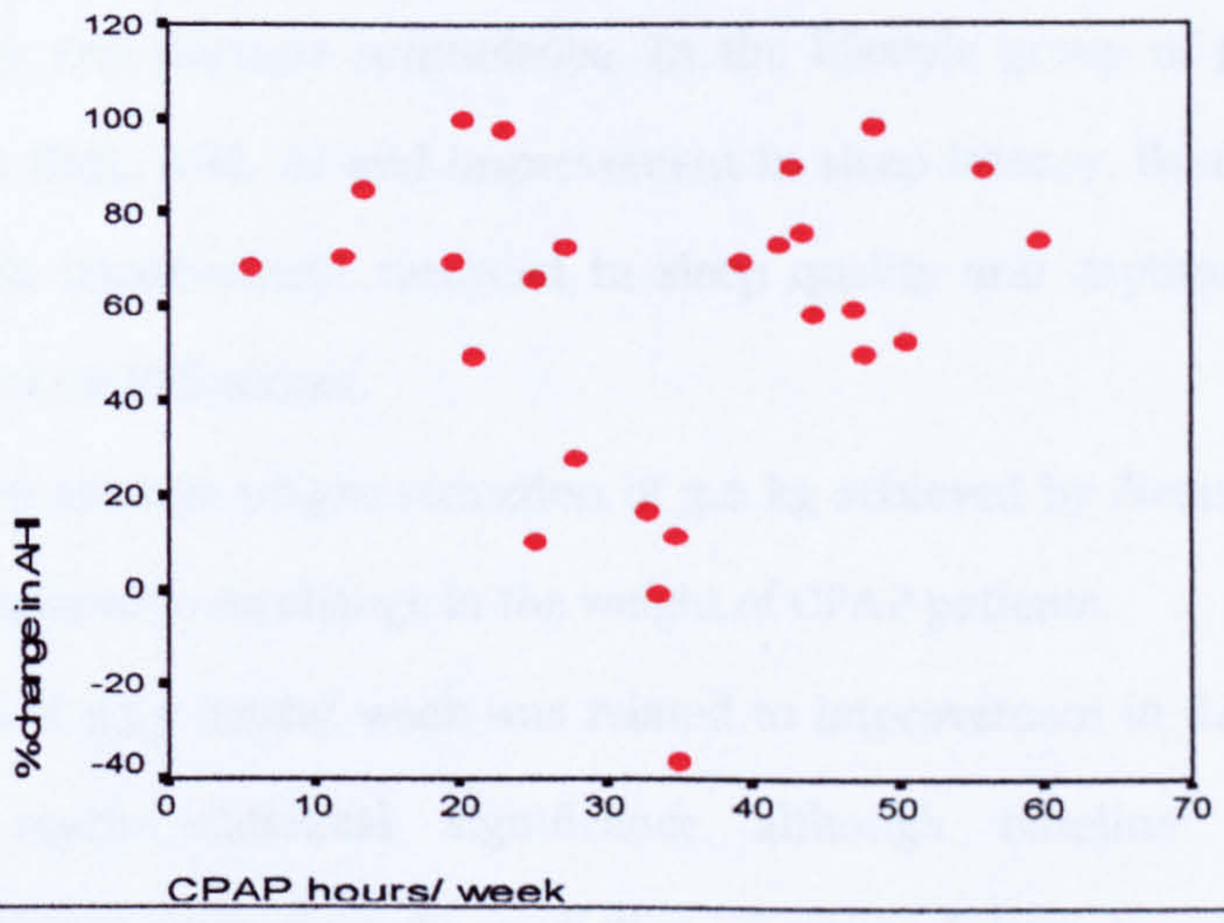
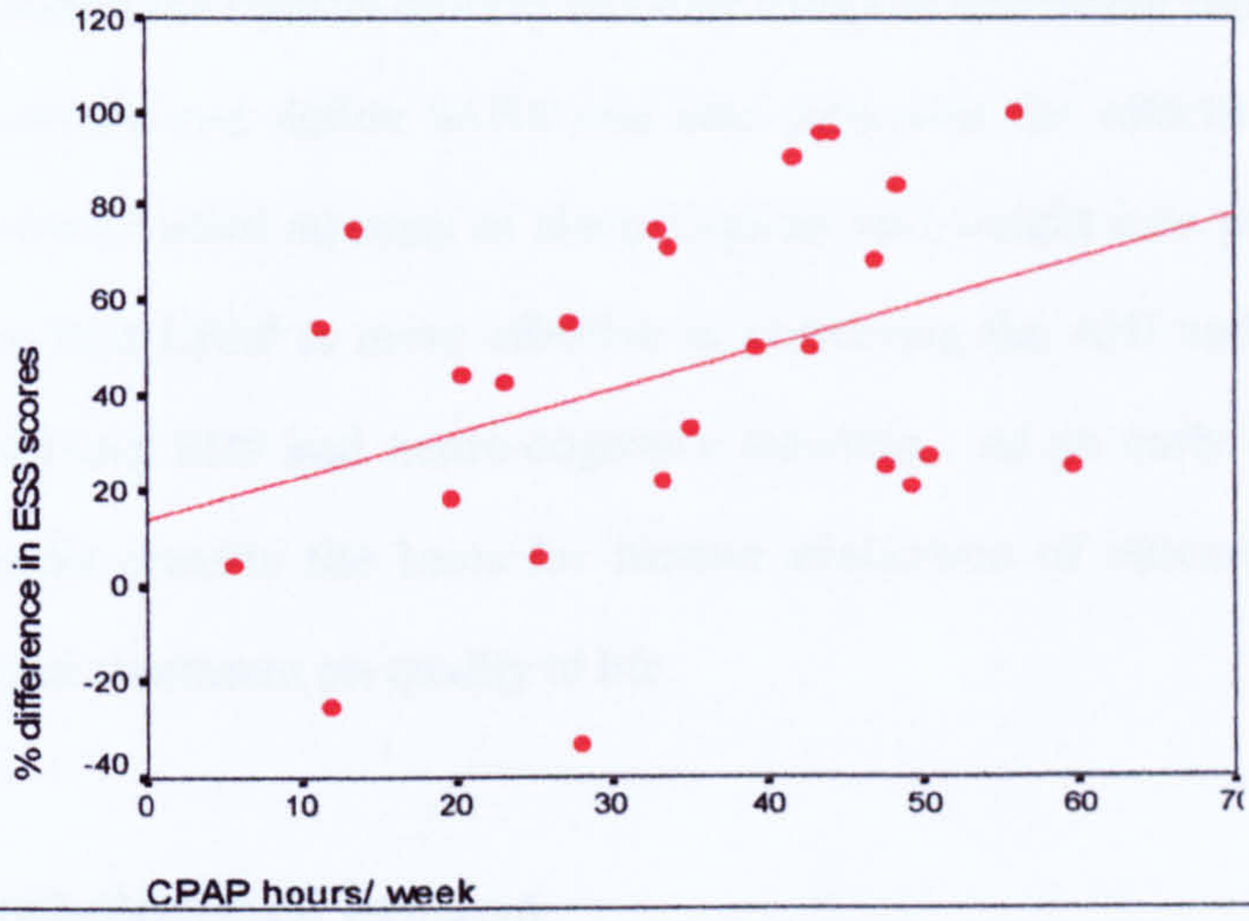


Figure 5.28: Compliance with CPAP related to δ ESS scores



5.3.4 Summary of clinical efficacy

There was a significant improvement in nocturnal parameters of breathing disturbance and sleep fragmentation in patients on CPAP therapy reflected by an improvement in sleep latency and daytime somnolence. In the lifestyle group of patients there was a reduction in BMI, AHI, AI and improvement in sleep latency. Based on the sleep diary there was an improvement recorded in sleep quality and daytime sleepiness on VAS scores but not on ESS scores.

There was an average weight reduction of 3.2 kg achieved by dietary advice in Group II patients compared to no change in the weight of CPAP patients.

CPAP usage of 33.5 hours/ week was related to improvement in daytime sleepiness but failed to reach statistical significance although baseline AHI and daytime hypersomnolence were strongly predictive of successful treatment. None of the sleep variables were significantly related to improvement in EDS in both groups of patients.

5.4 DISCUSSION

This chapter examines the clinical efficacy of CPAP usage in correcting the nocturnal PSG variables that quantify and define SAHS and also compares the effectiveness of CPAP against a more conservative strategy of sleep hygiene and weight loss programme. The data demonstrate that CPAP is more effective in correcting the AHI and AI of patients with SAHS, improving EDS and neuro-cognitive function. As an early step in HTA of CPAP, these results provide the basis for further evaluation of outcome measures to assess the impact of treatment on quality of life.

5.4.1 Methodological issues

The current definition of SAHS includes the clinical scenario of snoring and EDS combined with physiological evidence of sleep fragmentation due to apnoeas, hypopnoeas or UARS [American Academy of Sleep Medicine 1999]. In epidemiological surveys, the usual threshold value of AHI used in syndrome definition is 5 hour^{-1}. However evidence from clinical studies and from the treatment of patients with mild SAHS (AHI 5 to <15 hour^{-1}) suggest that almost 50% are either asymptomatic, intolerant of CPAP or may not report an improvement in symptoms after treatment with CPAP [Engleman *et al.* 1997b;Monasterio *et al.*2001a]. Even patients with AHI>30 hour^{-1} but in the absence of self reported EDS, fail to show a positive response to CPAP treatment [Barbe *et al.* 2001]. Unlike this poor uptake amongst mild SAHS patients, there is good evidence from studies suggesting that in symptomatic (ESS score >8-10/24) moderate to severe SAHS patients (AHI >15-30 hour-1) the uptake of CPAP may be as high as 81% in the first 3 months and up to 68% in 5 years [McArdle et al 1999]. This was compatible with the data from the retrospective clinical review reported in chapter IV of the long term follow up patients with SAHS, where a similar proportion (81%) of patients offered therapeutic trials, continued to use the treatment for a mean follow up of 3±2 years. Hence the decision to recruit patients to this study based on ESS>8/24 and AHI≥15 hour^{-1}.

As the perspective of this research was to determine the evidence of effectiveness among patients seen within typical clinical settings, the recruitment of patients was not based on

epidemiological methods of random selection from populations but based on the primary care physician referrals to the sleep clinic. In order to avoid selection bias, patients were sent invitations with their appointment letters to the sleep clinic before they were seen in the clinic and diagnosis discussed. They were randomised into each treatment phase only after their diagnostic PSG. In order to avoid a potential pro-CPAP / machine bias among the participants the predicted success with each treatment strategy was deliberately not discussed with participants and there was no indication given of any crossover to the alternative therapeutic option at the end of the trial.

5.4.2 Population

SAHS is a disease prevalent in all age groups but the maximum impact of the resultant disability is reported by patients in the middle-aged group on work performance and family. This study had a recruitment age range of 16-80 years with a mean age 48 years which was representative of similar populations. The Sleep Health Heart Study which recruited over 6000 patients older than 40 years reported a mean 63 years [Baldwin *et al.* 2001] and the Wisconsin Sleep Cohort have looked at the working age group of patients (30-60 years) [Hla *et al.*1994]. Similar age range has been reported by most other surveys on patients.

There was an expected male predominance (4:1) seen in this population compatible with the gender ratios reported in other sleep clinic populations. Whereas epidemiological surveys have reported a 2: 1 male predominance, clinic based populations have been typically 4 to 8:1. [Redline *et al.* 1994]. Women in this study were on average 10 years younger then the men (mean age for men 50 years and women 40 years). In population studies women with SAHS tend to be older then men but have similar BMI, while in clinic populations women tend to be younger and more obese. Postmenopausal women (without hormone replacement therapy) often have a prevalence of SAHS that is 4-5 times higher than premenopausal women and almost similar to that of men [Bixler *et al.* 2001]. There is evidence that women tend to have the same degree of symptoms as men with SAHS [Ferini-Strambi *et al.* 1999;Young *et al.* 1998], yet tend to have a greater degree of under-reporting and under-diagnosis. It has also been argued that this apparent

reluctance of women to report their symptoms and seek medical attention may account for a delayed diagnosis and an increased mortality similar to post-menopausal women with ischaemic heart disease [Wilhoit *et al.* 1987].

5.4.3 Obesity & weight loss

At baseline BMI was significantly related to AHI (p=0.001), a finding in support of the hypothesis suggesting that obesity contributes to the severity of SAHS[Kopelman *et al.* 1986;Young *et al.* 2002b]. It is also known that obesity can be independently related to EDS even in the absence of SAHS [Resta *et al.* 2001]. ESS scores (representing the most commonly reported symptom of SAHS) were demonstrated to be independently related to BMI (p=0.04), this in turn adds to the confounding potential for obesity in assessing the severity of SAHS due to the overlap of the daytime symptom complex [Grunstein and Wilcox 1994]. On the other hand ESS scores were not found to be significantly related to AHI or AI. This highlights the absence of a simple linear relationship between the physiological markers of nocturnal breathing disorder with daytime symptoms. Thus a simple correction of nocturnal apnoeas may not be the best predictor of the effectiveness of therapy in these patients.

The effect of weight loss is seen in the lifestyle group patients where there is a subjective improvement in sleep quality and a reduction in VAS scores for daytime sleepiness, although the reduction in ESS score does not reach statistical significance. There is also evidence of improvement in AHI, AI and sleep latency which is compatible with the symptomatic improvement but without evidence of a predictable relationship with the degree of weight loss. Hence although there is evidence of improvement in symptoms and AHI/ AI with lifestyle strategies, the causal hypothesis linking BMI, AHI/ AI and EDS remains to be established. A cephalometric study among Japanese SAHS patients found that in obese patients, upper airway soft tissue enlargement may play a more important role, whereas in non-obese patients, bony structure discrepancies may be the dominant contributing factors [Sakakibara *et al.*1999] [Watanabe *et al.* 2002]. The problem may also lie in the way that obesity is measured as suggested in a study finding a more consistent relationship between waist circumference with AHI then was seen with more traditional measures i.e. BMI/ neck circumference [Grunstein *et al.* 1993].

Thus, for the purpose of assessing the clinical effectiveness of therapy in SAHS, the physiological measures are unlikely to be related to, or predict the net outcome in patients and thus are unsuitable for use in appraisal of health technology.

However, obesity increases the risk of morbidity and mortality several fold in patients, irrespective of the presence or absence of SAHS [Anon.2000]. When present in SAHS patients, it further worsens the general health status and may synergistically multiply the overall risk of these patients. There are reports of a faster rate of desaturation in obese patients with SAHS compared to non-obese patients with the same duration of apnoeas. This suggests that abdominal obesity in SAHS patients may therefore aggravate the risk of cardiovascular disease. This study was not designed to investigate the effect of obesity on pathophysiology and long term health outcomes in obese patients with SAHS. However the evidence that simple conservative lifestyle advice combined with weight loss strategies improves AHI, AI, quality of sleep and daytime somnolence within 3 months suggests that this form of lifestyle modification strategy is certainly an adjunct to the holistic treatment of these patients and may improve outcome even more in the long term [Young *et al.* 2002a] [Barvaux *et al.* 2000].

The mean weight loss achieved in this group given conservative written advice was modest (1.5%), ranging from a loss of 20% to a gain of 5% of baseline body weight. Within this 3 month period the majority of patients showed no change in weight. Other researchers have reported similarly modest weight change on conservative approaches [Ballester *et al.*1999]. Prior to the introduction of newer pharmacological agents as an adjunct to exercise and diet programs for weight loss, the only success has been reported from surgical measures, i.e. gastric banding / bypass [Rajala *et al.* 1991]. Although surgical measures with their inherent mortality and morbidity cannot be recommended except in rare cases [Lee *et al.* 1997], there is perhaps a potential in using either Orlistat [Ballinger 2000;Foxcroft and Milne 2000] or Sibutramine[Bray *et al.* 1996] as an adjunct to low calorie diet in the treatment of obese SAHS patients.

5.4.4 Co morbidity

The prevalence of systemic hypertension in the study subjects was almost twice as high (49%) for men compared to UK population surveys. The prevalence in women however

was half that of the men and similar to UK adult women (22%) [Joint Health Surveys Unit and Dept of Epidemiology & Public Health 1997]. SAHS has been associated with, and considered in the aetiology of, systemic hypertension [Alchanatis *et al.* 2000] [Davies *et al.* 2000a] [Lavie *et al.* 2000], drug resistant hypertension [Logan *et al.* 2001], ischaemic heart disease [Fletcher 1996b], cardiac arrhythmia [Peker *et al.* 1999], pulmonary hypertension [Marrone *et al.* 1997], cerebrovascular disease [Mohsenin 2001] and diabetes mellitus [Elmasry *et al.* 2001]. There is now data from a prospective cohort study [Peppard *et al.*2000] of the new development of hypertension among SAHS patients under follow up.

The causal hypothesis linking SAHS with increased incidence of vascular diseases involves elevated sympathomimetic activity [Elmasry *et al.* 2002], increased occurrence of atherosclerosis [Friedlander *et al.* 1999;Saarelainen *et al.* 1999] and reduced daytime efferent vagal tone [Hilton *et al.* 2001]. Lifestyle factors such as smoking, increased alcohol consumption, sedentary lifestyle and obesity [Diaz, 2002] have also been implicated independently in increased cardiovascular morbidity hence tend to confound the interpretation of the link with SAHS [Stradling and Crosby 1990].

For men in this study population the prevalence of documented IHD was 25%, for DM was 11% and for cerebrovascular disease was 9%. As the mean age for men was 50 years, the prevalence of IHD may be definitely significant in reducing the overall life expectancy in this population. In the case of women who were almost 10 years younger then the men in this study population, a prevalence of documented IHD of 22% was much higher then would be expected from general population surveys. It has been hypothesised that patients (especially men) with SAHS who also have other independent risk factors for hypertension, increased cardiovascular morbidity and mortality are likely to be at a significantly greater risk [Wilcox *et al.* 1998]. Hence a focus on lifestyle alteration and tackling obesity is considered to be a logical approach to improve the health and prevent morbidity and mortality in such patients.

5.4.5 Polysomnography & Pulse oximetry

The results from the clinical review of SAHS patients showed almost two thirds of symptomatic patients could be diagnosed on the basis of their domiciliary, overnight

pulse oximetry. However as this method of screening tends to rely on the presence of 3-4% desaturations for diagnosis, many patients with predominant hypopnoeas and UARS are likely to be missed, thus reducing the sensitivity of this technique. When 4% ODI and PRV (obtained from pulse oximetry) in the prospective study patients, were plotted against AHI and AI they demonstrated strong correlations. The PRV (6 beats/ min) showed a stronger relationship with AHI and AI than ODI, suggesting that change in heart rate may be an autonomic marker of arousals [Stradling *et al.* 2000] and hence a stronger predictor of sleep breathing disorder, especially in patients without desaturations. Other researchers have shown the potential for ODI for diagnosis of SAHS [Choi *et al.* 2000] and the enhanced sensitivity when combined with PRV in symptomatic patients [Gurubhagavatula *et al.*2001;Ryan *et al.*1995b] Although definition of SAHS involves the demonstration of nocturnal sleep disorder, PSG variables have traditionally shown little relationship with daytime symptoms, except perhaps AHI and AI. Most patients with significant SAHS generally report a sleep latency of <10 minutes although this is more likely to be the case in Narcolepsy patients. PSG variables at baseline suggested sleep deprivation which then improved by almost 40% with treatment with CPAP and by 32% in lifestyle patients.

Although one study has reported an increase in the mean SWS after CPAP treatment in the first and second sleep cycles the significance of this change remains uncertain [Heinzer *et al.*2001]. In this study, there was no significant increase in mean total SWS after treatment with CPAP but the duration of stage II sleep and total sleep period were reduced. As these patients also had significantly reduced daytime somnolence, this may indeed be a reflection of reduced sleep deprivation and a restoration of the balance between Stage II and SWS.

5.4.6 Sleep hygiene

Patients in the lifestyle group given written advice on sleep improvement measures reported a significant improvement in sleep quality (VAS score) and daytime sleepiness (VAS score). Whether the demonstrated improvement is as a result of sleep hygiene and weight reduction strategy or merely a placebo effect is uncertain, and a question that the

design of this study is unable to establish with certainty. When this subjective improvement is compared to PSG variables there is a definite change in sleep latency, combined with a reduction in AHI, which is compatible with objective improvement in sleep quality. There were trends towards improvement in SWS and REM sleep but these did not reach statistical significance. Other researchers have reported evidence of sleep quality being affected by diurnal work pattern and nocturnal distractions such as television and smoking habits [Wetter *et al.* 1994] [Wetter *et al.* 1995]. Although there is not much research evidence of the effectiveness of sleep hygiene strategies in SAHS patients, other studies investigating the effect of sleep hygiene measures on sleep quality have reported benefit from behavioural strategies in patients with depression and insomnia which may be sustained in long term follow up [Hauri 1997]. Among SAHS patients there was little prior evidence of improvement with sleep hygiene measures [Monasterio *et al.* 2001b]. In the only other similar study, the authors reportedly recruited an average of 65 -77 mild SAHS patients who were given either CPAP or a sleep hygiene and/ weight loss program. Although the patients on weight loss and sleep hygiene noticed an improvement in clinical symptoms, the change in ESS scores and HRQL scores did not reach clinical significance. Similarly in the present study the reduction in total ESS scores did not reach significance during the trial phase in patients on lifestyle intervention program.

5.4.7 CPAP group

Patients given CPAP therapy demonstrated improvement in self-reported daytime symptoms (ESS scores, $p>0.001$) and in objective PSG variables. Sleep latency improved by 40%, AHI returned to normal range ($p<0.001$) and AI improved to normal ($p<0.001$). Thus there was clear evidence of the correction of both the nocturnal sleep breathing disorder and daytime somnolence after treatment. Patients who spent more time using their CPAP reported a greater change in the ESS scores, suggesting that duration of CPAP use may reflect in better tolerance and greater benefit in symptom control. There is an accumulating body of data that CPAP treatment not only corrects AHI but also improves

EDS compared to placebo and oral devices [Wright and White 2000] in symptomatic patients. Unlike earlier uncontrolled trials this data has been gathered using either oral placebo or sub-therapeutic-CPAP [Montserrat *et al.* 2001] in a RCT design and in one trial compared to conservative lifestyle advice [Ballester *et al.*1999]. One hundred and five consecutive predominantly male patients of a similar age group (53 ±10 years, BMI = 32 ±6 kgm-2) with moderate to severe SAHS (AHI 56 ±20 hour-1, ESS 12 ± 5) where 37 patients were randomly allocated to conservative program of sleep hygiene and weight loss (Group 1) and Group 2 (n = 68) received, in addition, treatment with CPAP. The odds of experiencing a treatment response with CPAP + conservative strategy compared with conservative strategy alone were 6.5.

In a further study with 111 subjects (48% females) with mild SAHS (AHI 5-30 hour-1), given CPAP treatment or conservative weight reduction advice and/or nasal dilators / nasal corticosteroid sprays. At the end of the trial period, there was no change in MSLT results in both the groups although the patients on CPAP reduced their ESS scores by 2/24 and there was a significant reduction in RDI in both the groups but greater in the CPAP group. Almost half of the patients on CPAP reported improvement in HRQL compared to 25% on conservative therapy. Analysis of patients based on treatment response identified a group with AHI>15 hour-1 and MSLT <8 min who also had underlying co morbidity who responded well to CPAP therapy [Redline *et al.* 1998].

These two studies although initially designed to investigate two different levels of SAHS severity concluded that patients with significant symptoms (EDS) and AHI>15 hour-1 were most likely to respond to treatment with a reduction in AHI, improvement in daytime symptoms. Both studies found little correlation between the AHI and daytime symptoms and polysomnographic variables remained poor predictors of treatment response.

5.4.8 CPAP compliance

The number of hours of CPAP usage may reflect on the degree of benefit obtained from this treatment. The average CPAP usage per week recorded in this population given the standard direct contact with experienced technicians, (which was the normal practice in

this institution) was similar to that reported by most other researchers. My analysis showed a significant relationship between 'duration of CPAP use' and 'reduction in ESS scores'. There is some evidence that patients who self-refer themselves as well as those given intensive follow up and encouragement tend to use their CPAP machines for longer durations and hence experience a greater improvement in symptom control and daytime function [Hoy *et al.* 1999]. Even with intensive support the mean duration reported in the above study was 5.4 hours versus 3.9 hours on normal follow up. As the need for sleep has a wide variability between individuals, the optimum period for sleep in humans is difficult to quantify and hence the optimum duration of CPAP use is also variable [McNicholas 1997]. Most studies and clinic patients usually report usage between 3-6 hours. Patients with less severe SAHS are more likely to discontinue CPAP treatment. The risk of experiencing nasal and pharyngeal side-effects of such severity that the patient stops using CPAP increases with age and patients who have undergone UPPP [Janson *et al.* 2000]. However 36/39 patients on CPAP therapy preferred to continue with their treatment compared to 13/46 given conservative therapy in an American study [Redline *et al.*1998]and similar results have been reported by Monasterio et al with 62% accepting treatment with CPAP in patients with an AHI of 10-30 $hour^{-1}$ [Monasterio *et al.* 2001a].

As an innovation, CPAP shows characteristics of widespread potential user group, good user acceptance and tolerance with minor side-effects including discomfort from the mask, dryness of mouth and difficulty adapting to positive pressure [Massie *et al.* 1999], which even in long term follow up does not reduce the compliance or the perceived benefit [Zozula and Rosen 2001a].

5.5 CONCLUSIONS

As a first step in the HTA of CPAP the data from this research confirms that it is indeed effective in reducing or correcting nocturnal sleep breathing disorder which is reflected in an improvement in daytime symptoms of EDS. As an innovation, CPAP demonstrates good tolerability and acceptance with mild side-effects both in the short term as shown in this study and also in the long term based on reports from other studies. The duration of CPAP use also relates to greater improvement in control of EDS.

It is shown that obesity is an independent factor contributing to both EDS and AHI. Conservative lifestyle modification and weight loss strategy achieved only a modest weight loss in 3 months, but demonstrated an improvement in nocturnal sleep quality, daytime sleepiness along and PSG variables (sleep latency, AHI and AI).

As this population of SAHS patients (similar to other groups) has a high prevalence of obesity, systemic hypertension and IHD, a holistic strategy involving lifestyle measures is likely to be more successful in reducing morbidity and mortality, although the current study was not designed to investigate the effect on long term health.

The polysomnographic variables (AHI and AI) of sleep breathing disorder show little predictability for daytime symptoms and hence are unlikely to be suitable for use as generic outcome measures for measuring the benefit from therapy.

CHAPTER VI

HEALTH RELATED QUALITY OF LIFE

6.1 INTRODUCTION

With the improved control of diseases due to advanced technological innovations and health care provision in the developed countries, the traditional measures of mortality and survival became insensitive to further improvement in the health of populations. As explained previously this led to a change in the focus of health care provision from negative (eradication of disease and prevention of death) to positive health including well-being, mental and spiritual health and the fulfilment of life. This transformation of the focus of health measurement to 'quality' terms happened in the last two decades. Surveys have shown a substantial rise in the scientific literature measuring or mentioning quality of life changes in the last three decades [Muldoon *et al.* 1998].

6.2 METHODOLOGY

6.2.1 Generic HRQL tools

The initial controversy regarding the perspective of HRQL measurement (whether professional or patient's own) was decided by a spate of studies which showed wide discrepancies between professional or patient's own approach to their HRQL [Slevin *et al.* 1988] . As it became established that patient's own self-esteem, individual preference and subjective measures of benefit were by far more relevant in promoting good health, there were further issues in establishing validity and reliability of these HRQL measures. Most HRQL measures available have been developed by professionals including items which were weighted 'professionally' then assessed among subjects in trials; an aspect which some purists believe interferes with the basic patient orientated HRQL concept [Kelly *et al.* 2001] [Bowling 1992].

However there are some measures which are specifically designed to accurately measure the different aspects of HRQL that tend to be affected by specific disease states. Hence these disease-specific measures demonstrate a greater sensitivity in these population groups, whereas other measures which incorporate the more widespread aspects of health and HRQL tend to allow widespread use among different populations and different

disease states. From a health technology appraisal perspective, the 'generic' HRQL measures hold promise in measuring the impact of a specific intervention and still having the ability of comparison with competing technologies.

Generic measures have been broadly divided into those which measure objective functional status and others measuring subjective well-being [Muldoon *et al.*1998]. The effects of health on HRQL have been further characterised in terms of physical and mental domains. The physical HRQL domain includes an individual patient's perception of the way their physical symptoms or disability impact on the various aspects of their lives. The mental domain focuses on the anxiety or mood states and includes emotional support and relationships.

There are various questions of validity of the HRQL measures used in medical research. Primarily this involves establishment of the fact that a questionnaire measuring physical well-being should reflect accurately objectively measured changes in the physical state/ symptoms of the patient (*criterion validity*). Most HRQL instrument also have to demonstrate construct validity by showing that they are not only reflecting the changes seen with other disease related measures but also that they are not related to anthropological measures such as height, weight, age and sex but to other measures of the particular disease state under study (*convergent-discriminant validity*) [Bowling 1992]. It is also known that extraneous factors such as marital status, employment, geographical clusters and social acceptability may influence responses to these HRQL measures, which tend to make interpretation complex.

For SAHS patients the impact of their disease on their physical and mental state can be profound. The chronic fatigue and daytime sleepiness can adversely impact on physical functioning, driving performance, work, relationships, social embarrassment, change of personality and even depression [Flemons and Tsai 1997a]. Disease specific measures such as Stanford Sleep Scale [MacLean *et al.* 1990] and Sleep Apnoea Quality of Life Index (SAQLI) [Flemons 2000] tend to be sensitive to the specific HRQL deterioration in these patients. But generic measures have also been shown to be effective in measuring the impact of disease and treatment in some studies [Jenkinson *et al.* 1998] [Finn *et al.* 1998b] [Montserrat *et al.* 2001] [Engleman *et al.* 1999].

There were two problems using HRQL measures in SAHS patients. Firstly there was little correlation reported between physiological measures of disease severity and HRQL measures and secondly variable effect sizes [Finn *et al.* 1998b] [Yang *et al.* 2000] were reported by different researchers [Montserrat *et al.*2001] within individual sub-scales of instruments and between different instruments [Jenkinson *et al.* 1998]. Therefore for the purposes of this study, in order to measure the outcome of CPAP versus lifestyle intervention, four questionnaires were used and are discussed in Chapter III.

1. **Short form 36 item general health questionnaire (SF36)** was chosen because it had widespread use both in the USA and UK, with normative data existent in both populations which would allow for comparisons. It had also been shown to be sensitive to change in certain dimensions in SAHS patients.
2. **European quality of life questionnaire (EuroQol):** This was specifically designed for use in the UK and Europe and has been used extensively in health status assessment for use in economic evaluation.
3. **General Health questionnaire (GHQ28)**: for assessment of psychiatric disability in these patients
4. **Hospital anxiety and depression scale (HADS)**: psychiatric assessment

After the diagnosis of SAHS was discussed with patients and their partners and both verbal and written information (Appendix ii) on clinical and management options provided, they were then asked to complete the following health related quality of life questionnaires unsupervised both before and after the trial period.

6.2.2 Mental health assessment tools

Sleep disorders have been strongly associated with psychiatric illness in meta-analyses of epidemiological surveys in chronic disease. The involvement of SAHS with psychiatric illness goes beyond un-refreshing and unfulfilled sleep to anxiety and clinical depression [Klonoff *et al.* 1987] [Millman *et al.* 1989]. There is a considerable overlap in the symptomatology associated with depressive illness and SAHS. Evidence suggests that both SAHS and depressive illnesses have both far reaching social and physical

consequences including an increased independent risk of coronary artery disease [Wells *et al.* 1998] [Pratt *et al.* 1996]. Hence it is was considered important to screen patients presenting with SAHS for psychiatric illnesses and to measure the effect of treatment using standard screening tools like the General Health Questionnaire and the Hospital Anxiety and Depression Scale.

The HADS and GHQ28 have been shown to be reliable instruments for case distinction and screening in general population, clinic and psychiatric populations with strong internal consistency and convergent validity with other comprehensive and gold standard measures, hence they are used in this study to assess the prevalence of anxiety and depression. They are also used to assess the difference in scores after intervention and compared with the mental health dimensions of the SF36.

6.2.3 Neuro-cognitive test (Trail making Test A & B)

The trail making tests are part of a standard battery of neuro-cognitive function testing which measures both mental dexterity and hand-eye-coordination. This involves Test-A which is a series of numbers on a sheet in disorderly fashion which needs to be joined in order and the time to complete the test is measured. Test-B involves alternate letters and numbers which then have to be joined in order alternately (number alternating with letter) with a measurement of time taken to complete.

All such neuro-cognitive battery tests have been shown to improve in repeated testing due to a process of learning, however in this study they were used only on 2 occasions, 3 months apart minimising the 'learning effect'.

In SAHS patients Trail making tests along with other neuro-cognitive battery tests have been shown to be abnormal at baseline [Redline *et al.* 1997] and sensitive to the effect of treatment with CPAP even in short-term studies [Borak *et al.*1996] [Henke, Grady, and Kuna 2001] [Engleman *et al.*1994b]. In common with other neuro-cognitive tests there is seldom a strong association with disease parameters except in patients with dementia [Kingshott *et al.* 1998].

6.3 RESULTS

6.3.1 Short form 36 questionnaire survey

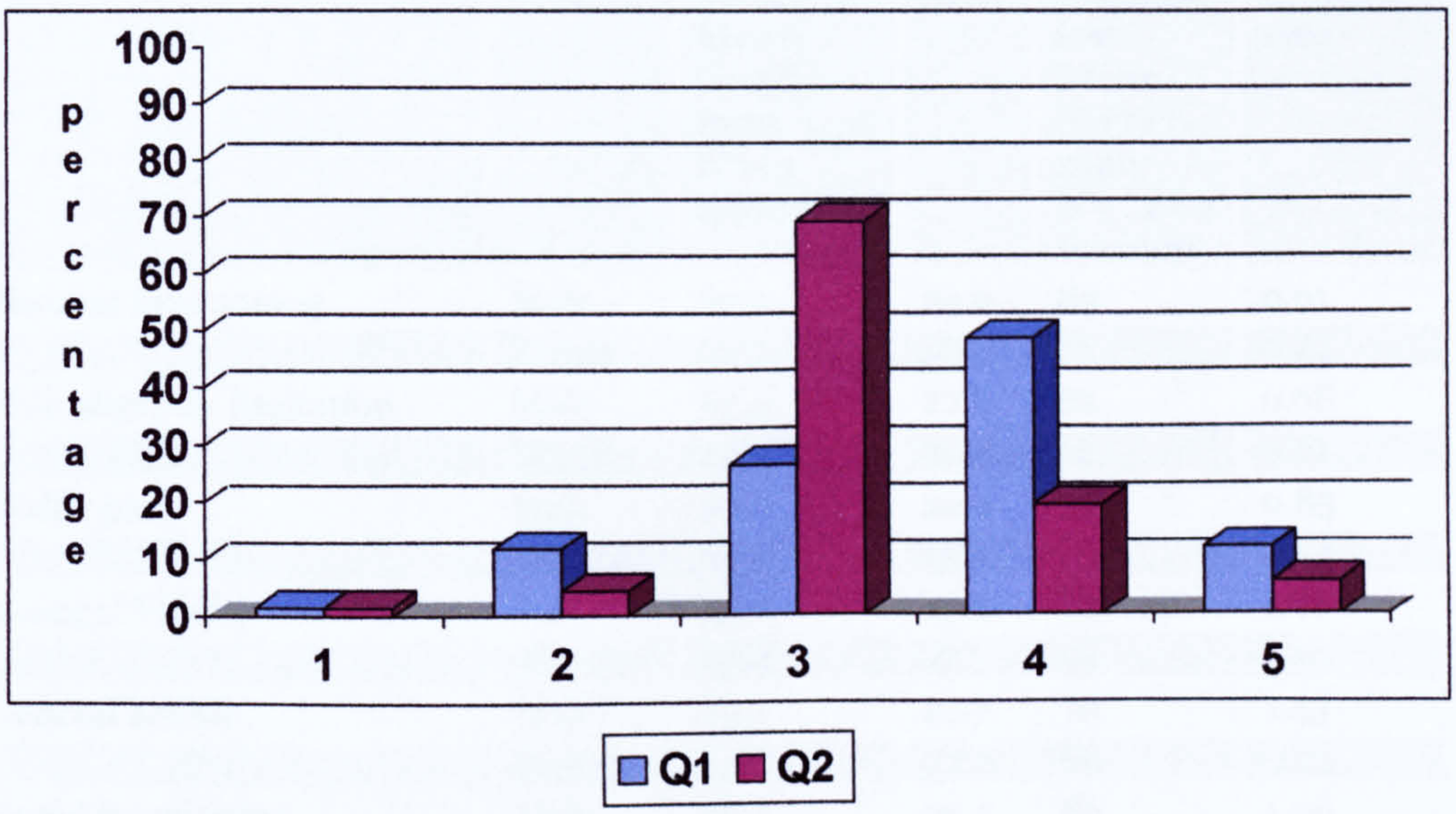
6.3.1.1 Baseline results for study population

The baseline scores in the 8 dimensions of HRQL computed from the SF36 questionnaire are presented in table 6.1 with the summary scores in physical and mental summary scales. Figure 6.1 illustrates the distribution of the responses to questions 1 & 2 referring to HRQL status in the last 12 months and the expectation for the future. Nearly 60% of the population of SAHS patients rated their health status in the last 12 months to be fair to poor. In response to Q2 70% expected their health status to remain the same in the near future and 25% expected their HRQL to deteriorate.

Table 6.1: Baseline population mean (SD) for SF36 survey results

Dimensions	Mean	SD
Physical functioning (PF)	62.4	23.6
Role Physical (RP)	63.3	26.1
Bodily pain (BP)	60.8	21.6
Energy/ Vitality (VT)	38.1	17.9
General Health (GH)	49.8	21.8
Social functioning (SF)	58.7	23.7
Mental health (MH)	65.0	18.4
Role emotional (RE)	77.9	20.9
Physical component summary (PCS)	39.6	9.8
Mental component summary (MCS)	46.1	9.3

Figure 6.1: SF36 question 1 & 2 - proportional results for study population



Q1: 1=excellent health, 2= very good health, 3= good health, 4= fair health, 5= poor health
Q2: 1= much better than 1 year ago, 2= somewhat better, 3= about the same, 4=somewhat worse, 5= much worse.

When the scores were compared to UK population norms there were significant lower scores seen in all the HRQL dimensions except in emotional role limitation as shown in table 6.10.

The most deterioration was seen in energy/ vitality and social functioning dimensions. Women scored their HRQL lower than men in mental health, social functioning and energy vitality while men scored lower in physical dimensions.

Table 6.2: SF 36 survey results according to sex compared with UK population results*

	SEX	Study Mean N=58 men N=13 women	SD	Population Mean N=787 men N= 884 women	Effect size
Physical functioning	Male	60.7	24.6	83	0.91
	Female	69.1	18.1	77	0.44
Role physical- limitation	Male	63.3	27.5	82	0.68
	Female	63.4	20.8	76	0.61
Bodily pain	Male	60.0	22.4	79	0.85
	Female	63.8	18.9	74	0.54
Energy/ Vitality	Male	39.6	17.8	66	1.48
	Female	32.4	17.7	59	1.50
General health	Male	49.1	21.7	70	1.43
	Female	52.8	22.8	69	0.71
Social functioning	Male	59.3	25.3	86	1.06
	Female	56.5	16.3	82	1.56
Mental health	Male	65.5	19.4	78	0.64
	Female	63.2	14.8	73	0.66
Role emotional - limitation	Male	79.0	20.8	85	0.29
	Female	73.8	21.8	81	0.33
Physical component summary	Male	39.3	10.5		
	Female	40.5	6.4		
Mental component summary	Male	46.4	10.1		
	Female	44.9	5.6		

* Health survey for England 1996, West Midlands age standardized population results
Effect size- difference in means/ SD

6.3.1.2 Relationships between sleep, anthropometric and SF36 baseline values

The demographic variables (age & BMI) and polysomnographic variables (AHI & AI) were not related to any of the SF36 subscales except for sleep latency which demonstrated a significant negative correlation with physical role limitation (Pearson's correlation coefficient -0.341, p=0.009) and social functioning (Pearson's correlation coefficient -0.297, p=0.025).

The inter-class correlations for the physical (PF, RP, BP & GH) and mental dimension subscales (VT, SF, MH & RE) with an average of 0.46, are demonstrated in table 6.3 a&b also with coefficients for the component summary scales. The energy/ vitality and general

health dimensions show considerable overlap between the mental and physical dimensions.

The Cronbach's α coefficient for intra class reliability assessment was 0.87 at baseline and 0.91 after intervention.

Table 6.3a: Inter-scale correlations between sub-scales for SF36 at baseline

	PF	RP	BP	VT	GH	SF	MH	RE
PF	1							
RP	0.62	1						
BP	0.59	0.50	1					
VT	0.30	0.44	0.41	1				
GH	0.62	0.68	0.58	0.50	1			
SF	0.33	0.36	0.50	0.68	0.42	1		
MH	0.14	0.15	0.28	0.69	0.34	0.75	1	
RE	0.21	0.39	0.25	0.51	0.36	0.52	0.70	1
PCS	0.75	0.67	0.64	0.27	0.77	0.38	0.10	0.17
MCS	0.01	0.08	0.14	0.71	0.19	0.66	0.89	0.74

Average correlation 0.46 (ranging from 0.14 to 0.75)
PF-physical functioning, RP-Role limitation physical, BP-Bodily pain, VT-Energy/ vitality, GH-General health, SF-Social functioning, MH-Mental health, RE-Role limitation emotional, PCS-Physical component summary, MCS-Mental component summary

Table 6.3b: Inter-class correlation for subscales of SF36 post intervention

	PF	RP	BP	VT	GH	SF	MH	RE
PF	1							
RP	0.73	1						
BP	0.55	0.58	1					
VT	0.54	0.54	0.48	1				
GH	0.60	0.66	0.45	0.64	1			
SF	0.49	0.57	0.40	0.69	0.58	1		
MH	0.27	0.38	0.23	0.58	0.41	0.67	1	
RE	0.45	0.63	0.47	0.61	0.46	0.70	0.75	1
PCS	0.89	0.83	0.71	0.54	0.74	0.45	0.11	0.37
MCS	0.12	0.24	0.23	0.62	0.40	0.74	0.87	0.75

Average correlation was 0.53 (range from 0.02 to 0.89)
PF-physical functioning, RP-Role limitation physical, BP-Bodily pain, VT-Energy/ vitality, GH-General health, SF-Social functioning, MH-Mental health, RE-Role limitation emotional, PCS-Physical component summary, MCS-Mental component summary

Patients in Group I on CPAP therapy demonstrated a significant improvement in social functioning (21%, effect size 0.8, p=0.001), energy/ vitality (16%, effect size 0.7, p 0.001), mental health (10%, effect size 0.5, p=0.003) and physical role limitation (8%, effect size 0.3, p=0.04) in the SF36 questionnaire after treatment.

The change in ESS scores correlated with general health (Spearman's correlation coefficient 0.61, p=0.001) and mental health dimensions (coefficient 0.4, p<0.05). Using a linear regression model, 40% (adjusted r^2=0.4) of the variation in mental health scores after treatment could be attributable to ODI, sleep latency and REM latency (r^2= 0.6, p=0.015).

The patients in Group II on lifestyle intervention did not show any significant improvement at the end of the trial period, as shown in table 6.4.

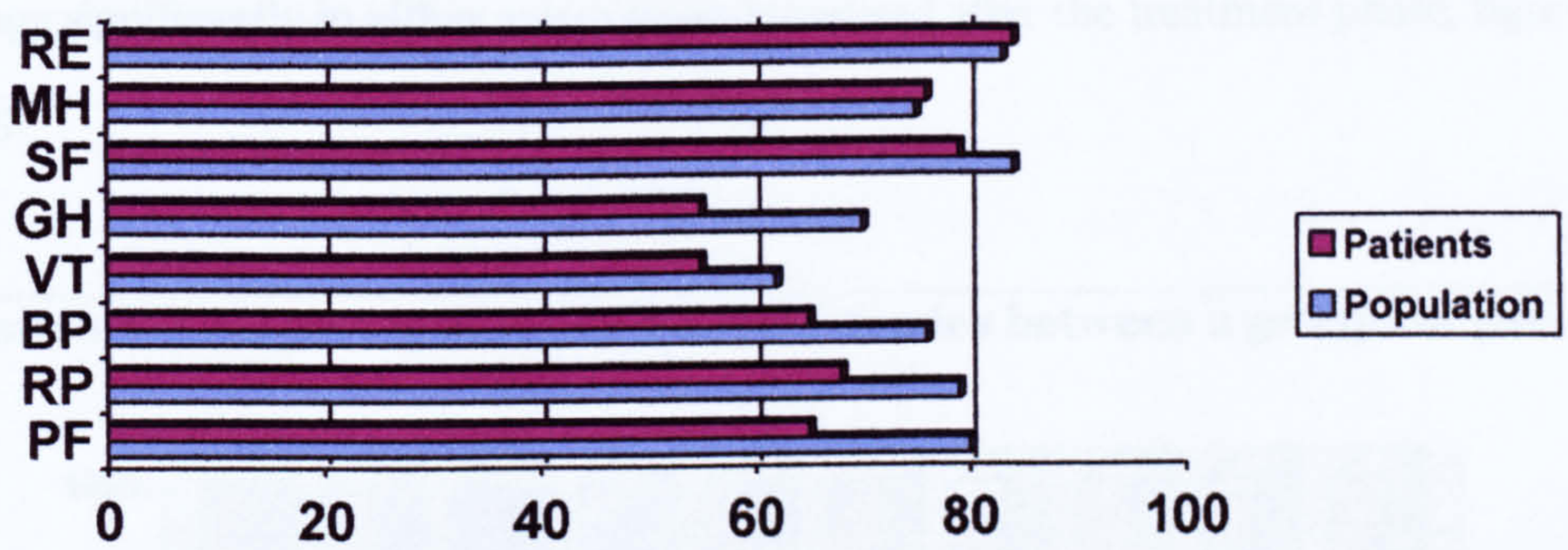
Table 6.4: Paired samples statistics for SF36 variables before and after intervention

	CPAP				Lifestyle		
	Mean	**SD**	**P**		**Mean**	**SD**	**P**
Base PF	63.9	28.1			61.4	25.5	
Post PF	65.3	26.5	0.658		63.9	26.7	0.756
Base RP	59.8	31.1			66.6	25.5	
Post RP	68.2	28.1	0.037*		71.9	21.5	0.349
Base BP	61.5	25.4			62.0	24.7	
Post BP	64.7	21.7	0.308		62.0	21.9	0.998
Base VT	38.9	22.0			36.6	19.0	
Post VT	55.2	19.3	<0.001*		39.1	18.9	0.623
Base GH	48.6	23.2			49.7	27.3	
Post GH	55.4	23.5	0.058		47.3	21.5	0.726
Base SF	57.7	26.7			60.1	26.3	
Post SF	78.7	22.3	0.001*		66.5	20.6	0.392
Base MH	66.0	21.5			62.0	20.4	
Post MH	76.2	20.2	0.003*		65.9	17.5	0.514
Base RE	79.1	23.7			75.6	24.3	
Post RE	84.3	20.8	0.072		76.9	19.3	0.828
Base PCS	39.4	12.2			40.4	9.3	
Post PCS	40.9	10.5	0.281		41.5	9.7	0.634
Base MCS	46.5	10.2			44.1	11.3	
Post MCS	53.2	9.2	<0.001*		46.4	7.6	0.436

PF-physical functioning, RP-Role limitation physical, BP-Bodily pain, VT-Energy/ vitality, GH-General health, SF-Social functioning, MH-Mental health, RE-Role limitation emotional, PCS-Physical component summary, MCS-Mental component summary

Figure 6.2 shows that for CPAP patients mean SF36 scores return to population normal figures in the mental health dimensions but the physical dimensions remain below normal even after 3 months of therapy including the general health dimension, which is derived predominantly from questions related to the physical aspects of HRQL.

Figure 6.2: Post CPAP SF36 scores compared to UK population mean scores



PF= physical functioning, RP= role limitation physical, BP= bodily pain, VT= energy & vitality, GH= general health, SF= social functioning, MH= mental health, RE= role limitation emotional.

6.3.1.3 Summary of SF36 data

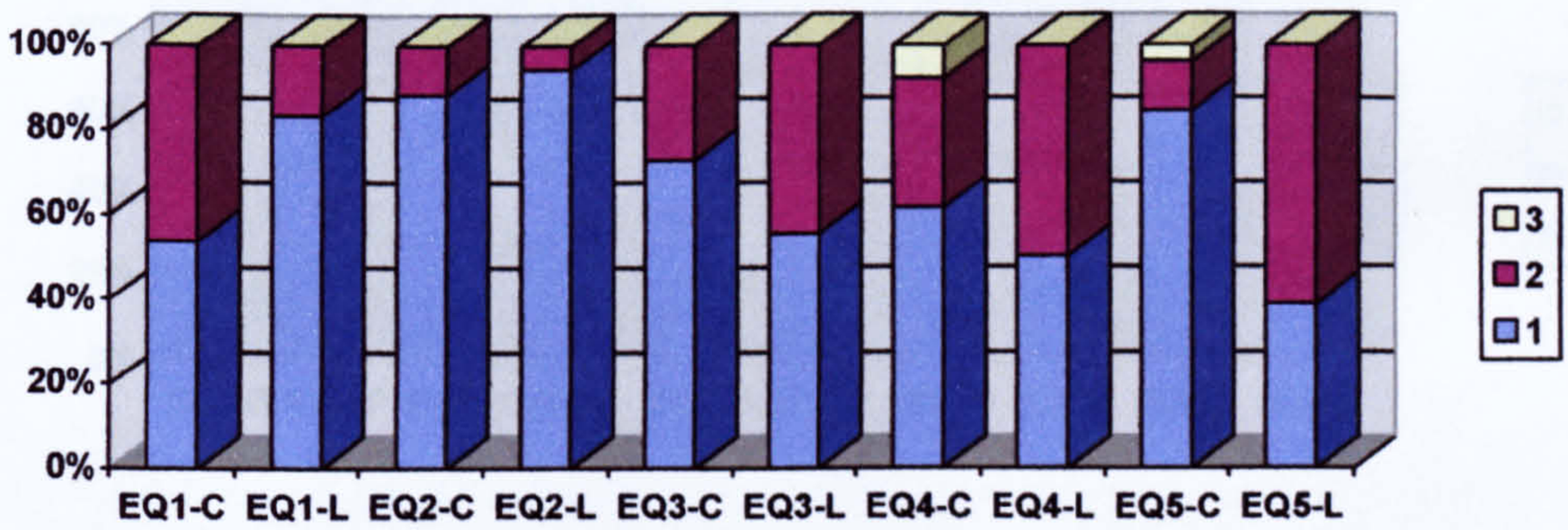
The SF36 questionnaire demonstrated excellent intra-class and inter-class reliability with Cronbach's alpha = 0.8-0.9 among sleep apnoea patients. All SAHS patients demonstrated the poorest HRQL scores in Social Functioning and Energy/ Vitality dimensions and subsequently in patients on CPAP the greatest improvement was seen in mental health dimensions (SF & VT). Men had poor scores in General Health, Physical Functioning and Bodily Pain dimensions. Women reported their worst HRQL score in the Social Functioning dimension. SAHS patients on lifestyle arm did not show any significant improvements while in the CPAP arm, post treatment SF36 scores were improved but did not reach population normative values in the physical dimensions. Sleep latency was negatively correlated to physical role limitation.

6.3.2 European Quality of Life Questionnaire (EuroQol)

6.3.2.1 EuroQol 5 dimension

Patients reported moderate problems in mobility, usual activities, pain and anxiety/ depression. There were no significant intra-group differences in the distribution of grades of severity reported by patients, except in anxiety/ depression as shown in figure 6.3 (Chi sq test, p=0.002). In both the groups there were moderate problems reported in usual activities, pain and anxiety/ depression dimensions at baseline which does not change significantly in either group when measured after the treatment phase, figure 6.4 & 6.5.

Figure 6.3: Comparing baseline EuroQol grades between 2 groups of patients



The 5 dimensions of the EuroQol questionnaire (1=mobility, 2=self-care, 3=usual activities, 4=pain/ discomfort and 5=anxiety/ depression) classify the quality of life in 3 levels (1=no problems, 2= some problems and 3= severe problem/ unable to perform. C=CPAP & L=Lifestyle

The 5 dimensions of the EuroQol questionnaire (1=mobility, 2=self-care, 3=usual activities, 4=pain/ discomfort and 5=anxiety/ depression) classify the quality of life in 3 levels (1=no problems, 2= some problems and 3= severe problem/ unable to perform. B=Baseline & P=Post-treatment

Figure 6.4: Proportion of Lifestyle group patients scoring 1-3 in the EuroQol and the effect of therapy

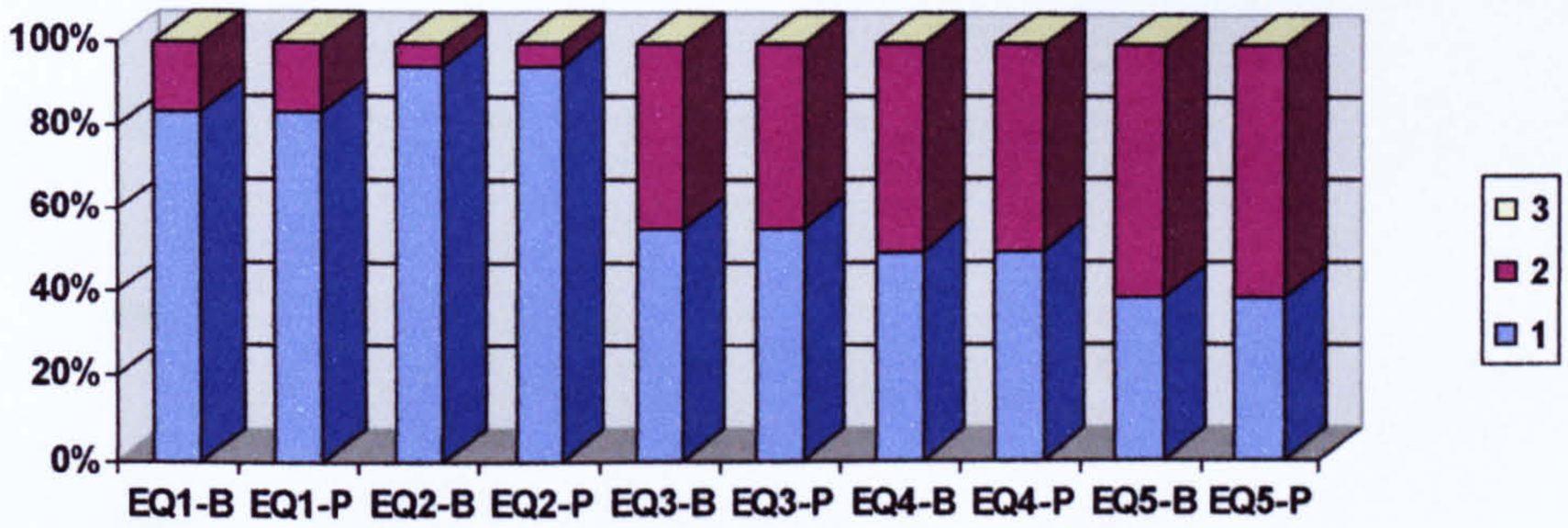
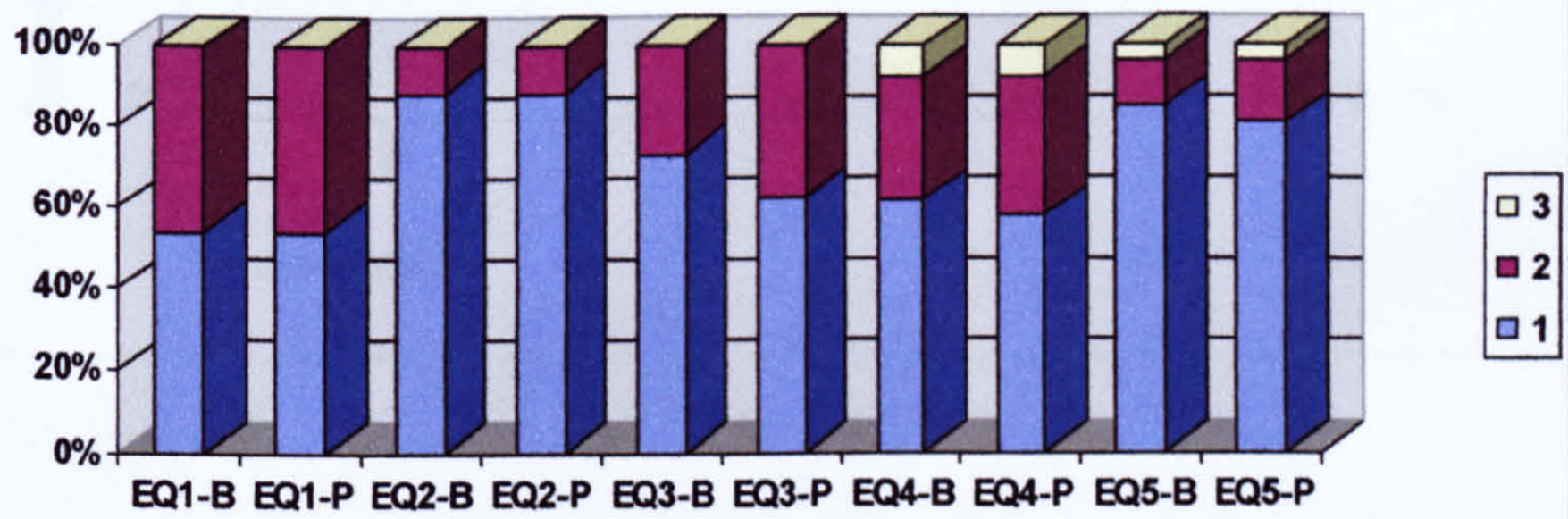


Figure 6.5: Proportion of CPAP group patients scoring 1-3 in the EuroQol and the effect of therapy



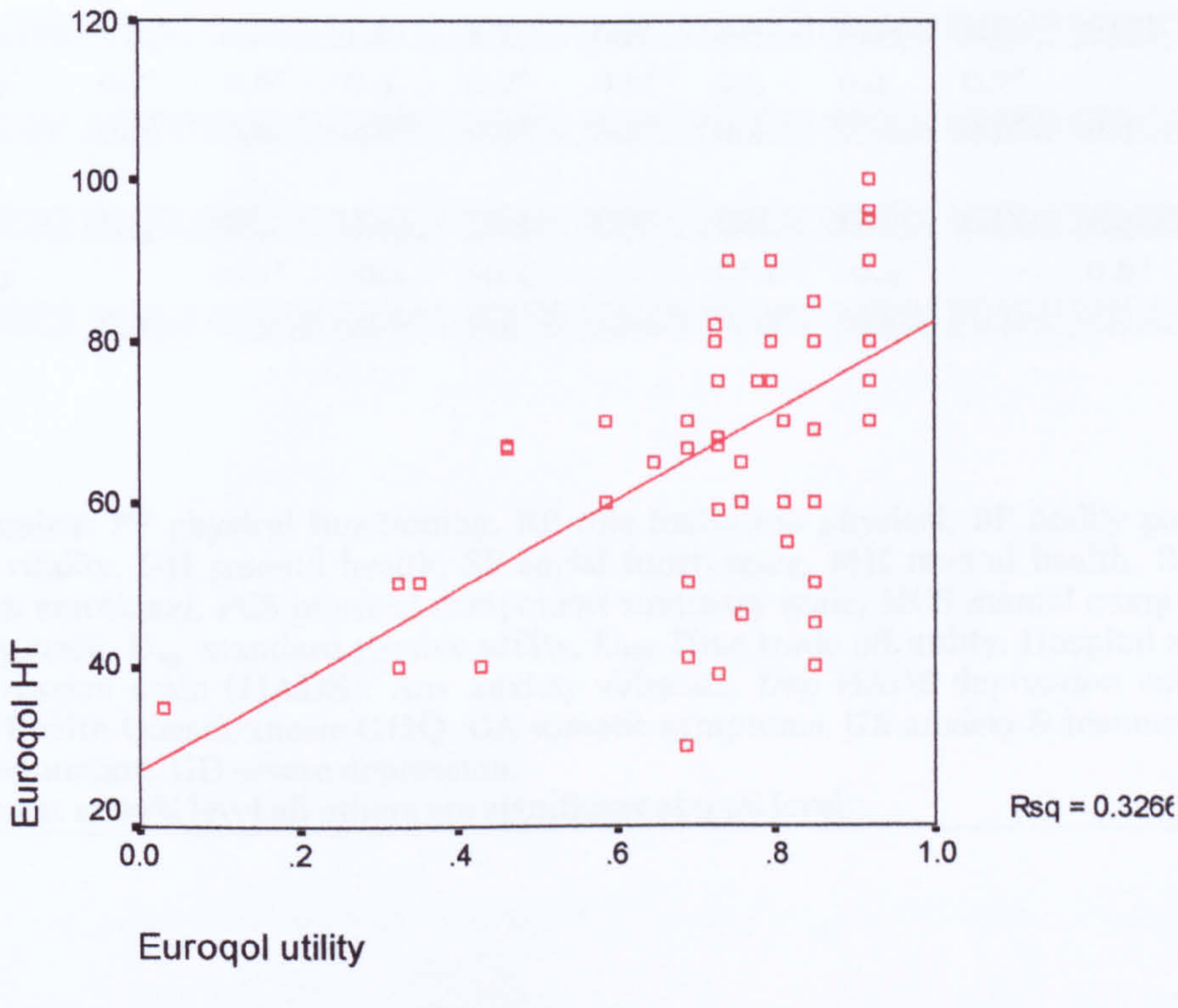
The 5 dimensions of the EuroQol questionnaire (1=mobility, 2=self-care, 3=usual activities, 4=pain/ discomfort and 5=anxiety/ depression) classify the quality of life in 3 levels (1=no problems, 2= some problems and 3= severe problem/ unable to perform. B=Baseline & P=Post-treatment

6.3.2.2 EuroQol health thermometer

The population mean score on the visual analogue scale (EuroQol-HT) depicting current health status on a scale from 0 to 100 incorporated in the EuroQol was 66.8 (16) compared to the UK population mean of 83.

Figure 6.6 shows the linear relationship between the EuroQol HT and the EuroQol indirectly derived utility.

Figure 6.6: Scatter plot showing the linear regression between EuroQol HT and EuroQol utility.



The baseline EuroQol HT scores were not related to any of the baseline parameters (age, BMI, neck size, AHI, AI, sleep latency, REM latency). At baseline EuroQol-HT correlated strongly with SF36 subscales, utility values from standard gamble and time-trade off methods, as shown in table 6.5.

The negative correlation with scores from the HADS anxiety and depression subscales is due to the higher scores indicating worse mental health state unlike the higher score representing a better health state perception in the EuroQol-HT.

Table 6.5: Spearman correlation coefficients for relationship between EuroQol HT and other HRQL measures

	PF	RP	BP	VT	GH	SF	MH	RE	PCS	MCS
Eq utility	0.7*	0.6*	0.4	0.7*	0.6*	0.3	0.4	0.7*		
Eq -HT	0.6*	0.5	0.6*	0.7*	0.5*	0.4		0.6*	0.4	-0.4
	U_{sg}	**U_{tto}**	**Anx**	**Dep**	**GA**	**GB**	**GC**	**GD**	**EqHT**	
Eq-utility		0.7*	-0.4	-0.4		-0.4	-0.4		0.6*	
Eq-HT	0.3	0.5	-0.6*	0.6*	-0.4	-0.6*	-0.5			

SF36 scales: PF physical functioning, RP role limitation physical, BP bodily pain, VT energy/ vitality, GH general health, SF social functioning, MH mental health, RE role limitation emotional, PCS physical component summary scale, MCS mental components summary scale. **U_{sg}** standard gamble utility, **U_{tto}** Time trade off utility. Hospital anxiety and depression scale (**HADS**): Anx anxiety subscale, Dep HADS depression subscale. General Health Questionnaire **GHQ**: GA somatic symptoms, GB anxiety & insomnia, GC social dysfunction, GD severe depression.
* Significant at 99% level all others are significant at 95% level.

The pre-treatment mean score for Group I (CPAP) was 66(16.6) improving to 73(13.2), p=0.009. In Group II (Lifestyle) the mean baseline score of 67.7(15.6) does not change significantly after treatment 67.4(13.7).

6.3.3 General Health Questionnaire (28-item)

6.3.3.1 Proportion of cases vs. non-cases

Using a threshold value for the GHQ28 total score of 11/12 for identifying significant psychological distress/ disease in the study population, there were an overall 64/71 patients affected. After treatment with CPAP there was a 43% reduction in proportions of patients with significant psychiatric distress/ disease ($\chi 2 = 8.29$, p=0.004; Odds ratio 6.3, 95%CI = 1.7 to 28.7). In Group II, there were 32 patients with psychiatric distress at the end of the trial compared to 31 at baseline.

6.3.3.2 Reliability

The inter-item correlations for the 4 sub-scales are given in table 6.6 the average being 0.58 and the coefficient of reliability Cronbach's α was 0.84.

Table 6.6: showing the inter-class correlation for GHQ subscales

	GHQ-A	GHQ-B	GHQ-C	GHQ-D
GHQ-A	1			
GHQ-B	0.60	1		
GHQ-C	0.56	0.57	1	
GHQ-D	0.53	0.61	0.60	1

GHQ-A=Somatic symptoms, GHQ-B=anxiety & insomnia, GHQ-C=Social dysfunction, GHQ-D=severe depression

Figure 6.7: Frequency distribution of baseline scores for GHQ28 total score & subscales

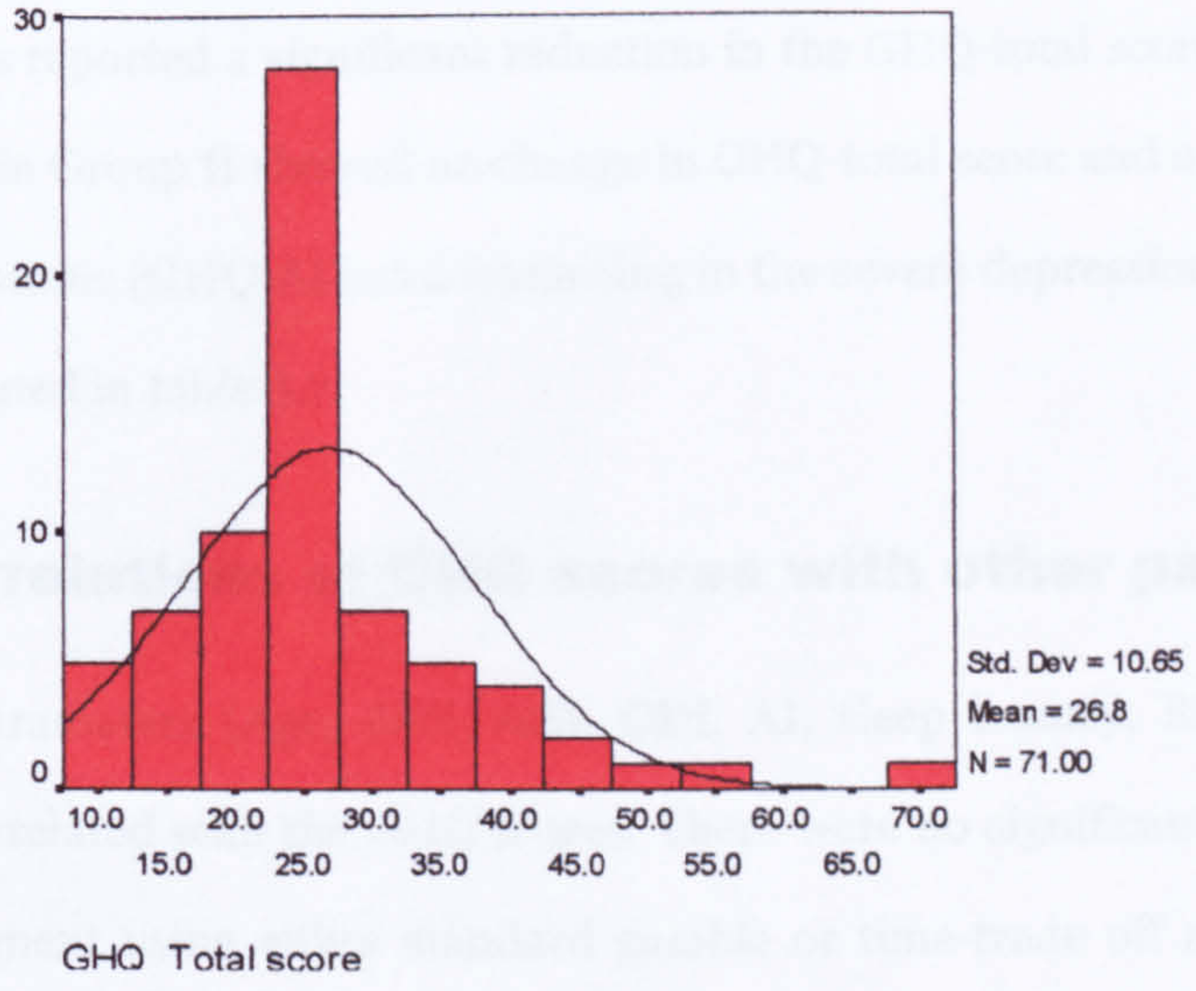


Table 6.7: Paired samples statistics for GHQ scores before and after the trial

		Lifestyle Mean	p	CPAP Mean	p
GHQ-A Somatic symptoms	Base	7.7 (3.4)		8.3 (3.8)	
	Post	6.8 (2.4)	0.049*	3.9 (2.5)	<0.001*
GHQ-B Anxiety & insomnia	Base	6.6 (2.6)		6.9 (4.5)	
	Post	5.9 (2.0)	0.072	2.9 (2.6)	<0.001*
GHQ-C Social dysfunction	Base	9.4 (2.5)		9.7 (2.8)	
	Post	8.9 (2.2)	0.296	5.8 (2.2)	<0.001*
GHQ-D Severe depression	Base	2.3 (2.4)		3.0 (3.8)	
	Post	2.9 (2.9)	0.031*	1.2 (2.1)	0.002*
GHQ-TOTAL	**Base**	**25.9 (9.1)**		**27.8 (12.5)**	
	Post	**24.4 (7.1)**	**0.249**	**13.9 (7.3)**	**<0.001***

6.3.3.3 Effect of treatment on GHQ scores

Group I patients reported a significant reduction in the GHQ-total score and in all 4 sub-scales. Patients in Group II showed no change in GHQ-total score and a modest reduction in somatic symptoms (GHQ-A) but a worsening in the severe depression sub-scale (GHQ-D) as demonstrated in table 6.7.

6.3.3.4 Correlations of GHQ scores with other parameters

None of the parameters (Age, BMI, AHI, ODI, AI, sleep latency, REM latency) were significantly correlated with the GHQ scores. There were no significant correlations with utility measurement using either standard gamble or time-trade off methods, and only weak relationship with the indirectly derived EuroQol utility index. There were significant relationships between the GHQ subscales and the SF36 and HADS questionnaire, as shown in table 6.8.

Table 6.8: Spearman's correlation coefficients of GHQ subscales with other HRQL measures

	PF	RP	BP	VT	GH	SF	MH	RE	PCS	MCS
GHQ A	-0.4	-0.5*	-0.7*	-0.6	-0.5*	-0.6*	-0.6*	-0.6*		-0.7*
GHQ B			-0.5	-0.4	-0.5	-0.8*	-0.8*	-0.7*		-0.8*
GHQ C	-0.4		-0.7*	-0.4	-0.5	-0.6	-0.6*	-0.6*		-0.6*
GHQ D		-0.4		-0.4	-0.5	-0.6*	-0.7*	-0.7*		-0.6*

	U_{sg}	U_{tto}	Anx	Dep	Eq HT	Eq Utility
GHQ A			0.6*	0.6*	-0.6*	-0.4
GHQ B			0.7*	0.7*	-0.4	
GHQ C			0.5*	0.7*	-0.6*	-0.4
GHQ D			0.7*	0.7*	-0.5	-0.4

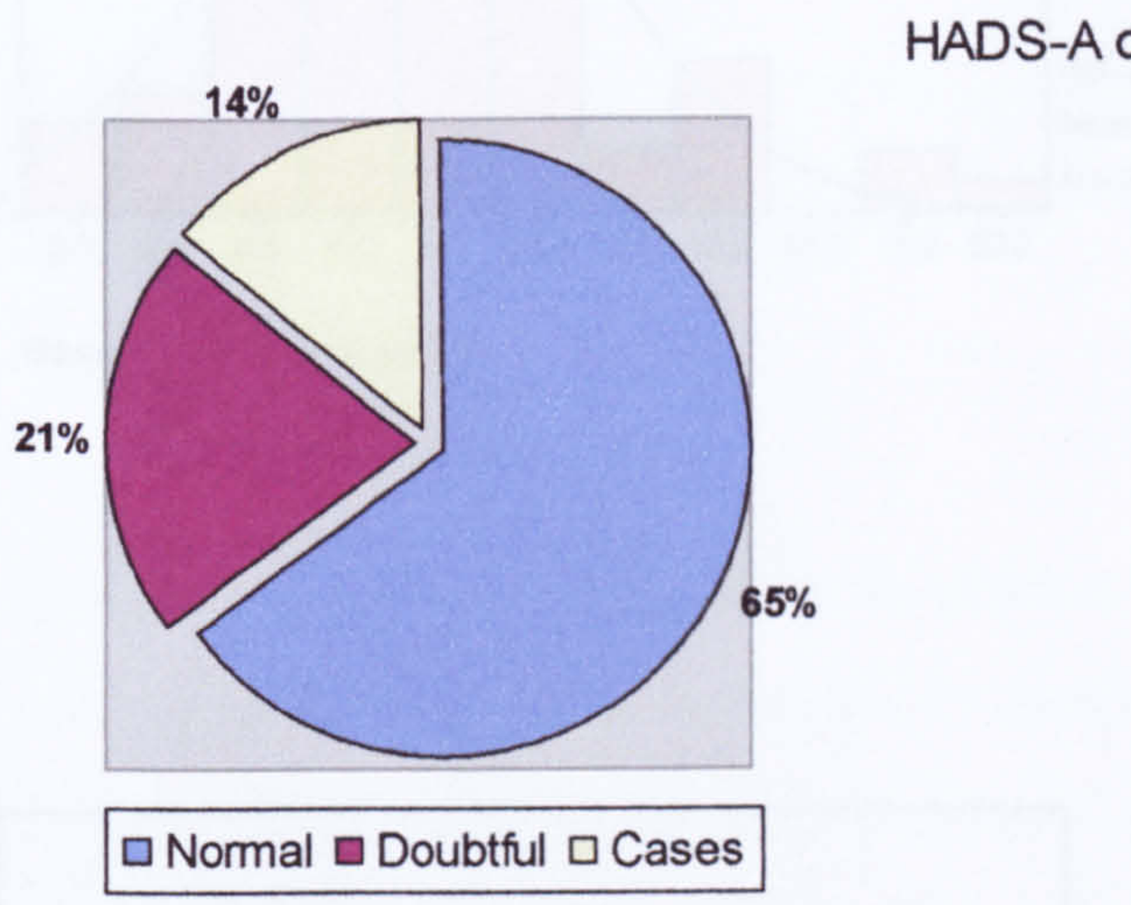
F36 scales: PF physical functioning, RP role limitation physical, BP bodily pain, VT energy/ vitality, GH general health, SF social functioning, MH mental health, RE role limitation emotional, PCS physical component summary scale, MCS mental components summary scale.
U_{sg} standard gamble utility, **U_{tto}** Time trade off utility.
Hospital anxiety and depression scale (**HADS**): Anx anxiety subscale, Dep HADS depression subscale. General Health Questionnaire
GHQ: GHQ-A somatic symptoms, GHQ-B anxiety & insomnia, GHQ-C social dysfunction, GHQ-D severe depression. Only significant correlation values have been shown; * significant at 99% level others at 95% level

6.3.4 HOSPITAL ANXIETY & DEPRESSION SCALE

6.3.4.1 Cases

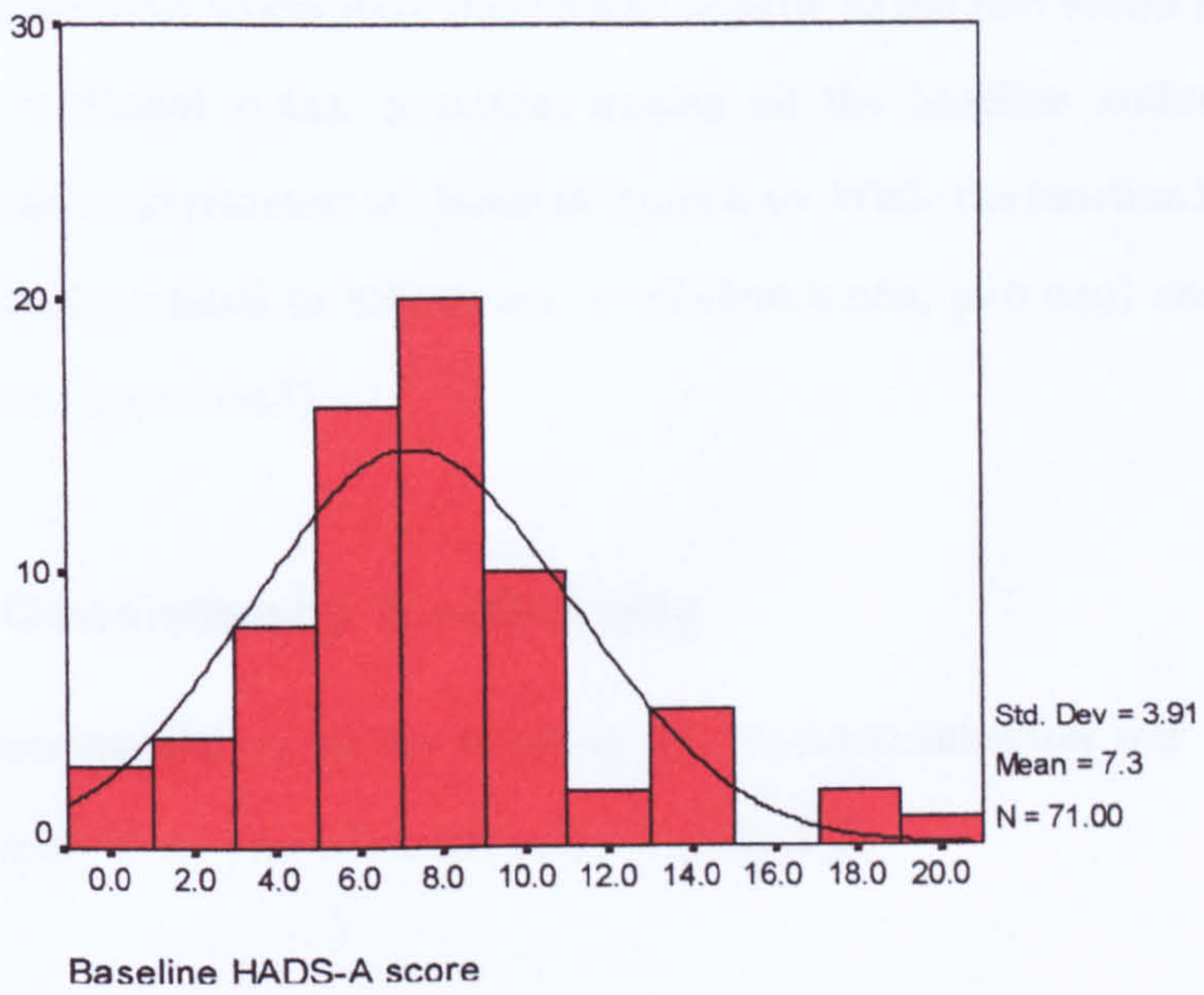
There were 14% cases with anxiety disorder and 8% with significant depression in the study population, as shown in figure 6.10. The figure 6.8 shows the frequency distribution of the HADS subscale scores.

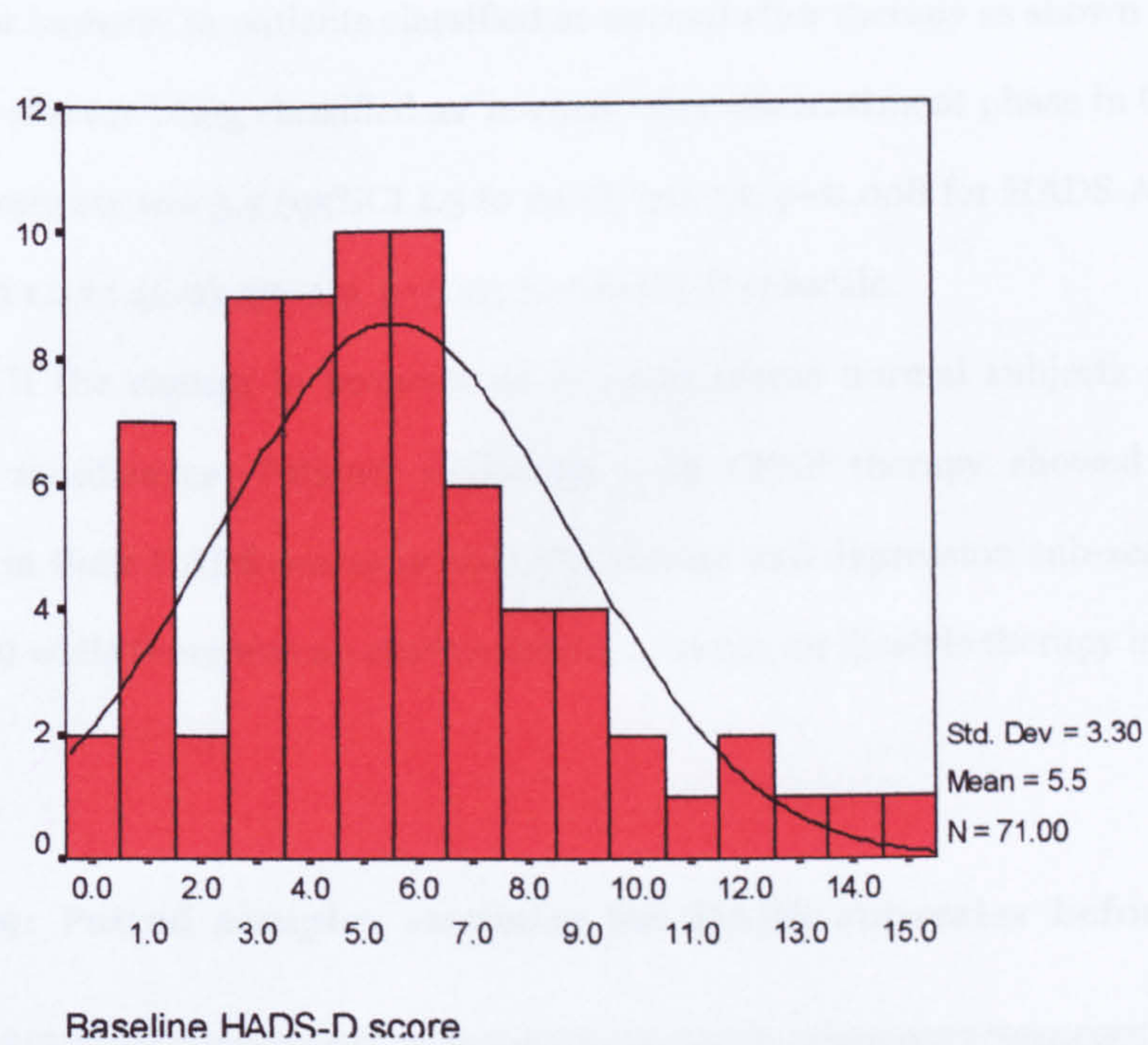
Figure 6.8: Proportions of cases, doubtful and normal patients classified according to HADS scores



The established criteria for diagnosis of cases based on the HADS scores for each subscale (HADS-A anxiety & HADS-D depression) a score ≤ 7 is normal, 8-10 is considered to be doubtful and ≥ 11 is considered to be a case with significant psychiatric disorder.

Figure 6.9: Distribution of baseline HADS subscale scores for study population





6.3.4.2 Correlations

The baseline HADS-A scores were related significantly to the ESS scores measuring EDS (regression coefficient 0.343, p=0.004) among all the baseline anthropometric and polysomnographic parameters as shown in figure 6.10. While the baseline HADS-D scores were significantly related to ESS scores (coefficient 0.262, p=0.049) and sleep latency (coefficient 0.319, p=0.008).

6.3.4.3. Consistency & reliability

The inter-item correlation for the HADS-A and HADS-D subscales was 0.7534 and the Cronbach's α coefficient for reliability analysis was 0.8594.

6.3.4.4 Effect of treatment

There was a reduction in the proportion of patients classified as cases in Group I and a consequent increase in patients classified as normal after therapy as shown in figure 6.11. The odds ratio for being classified as 'normal' after the treatment phase in Group I based on HADS criteria was 5.5 (95%CI 1.5 to 23.9); $\chi 2=7.1$, p=0.008 for HADS-A subscale and 6.7 (95%CI 1.2 to 46.9); $\chi^2=4.9$, p=0.03 for HADS-D subscale.

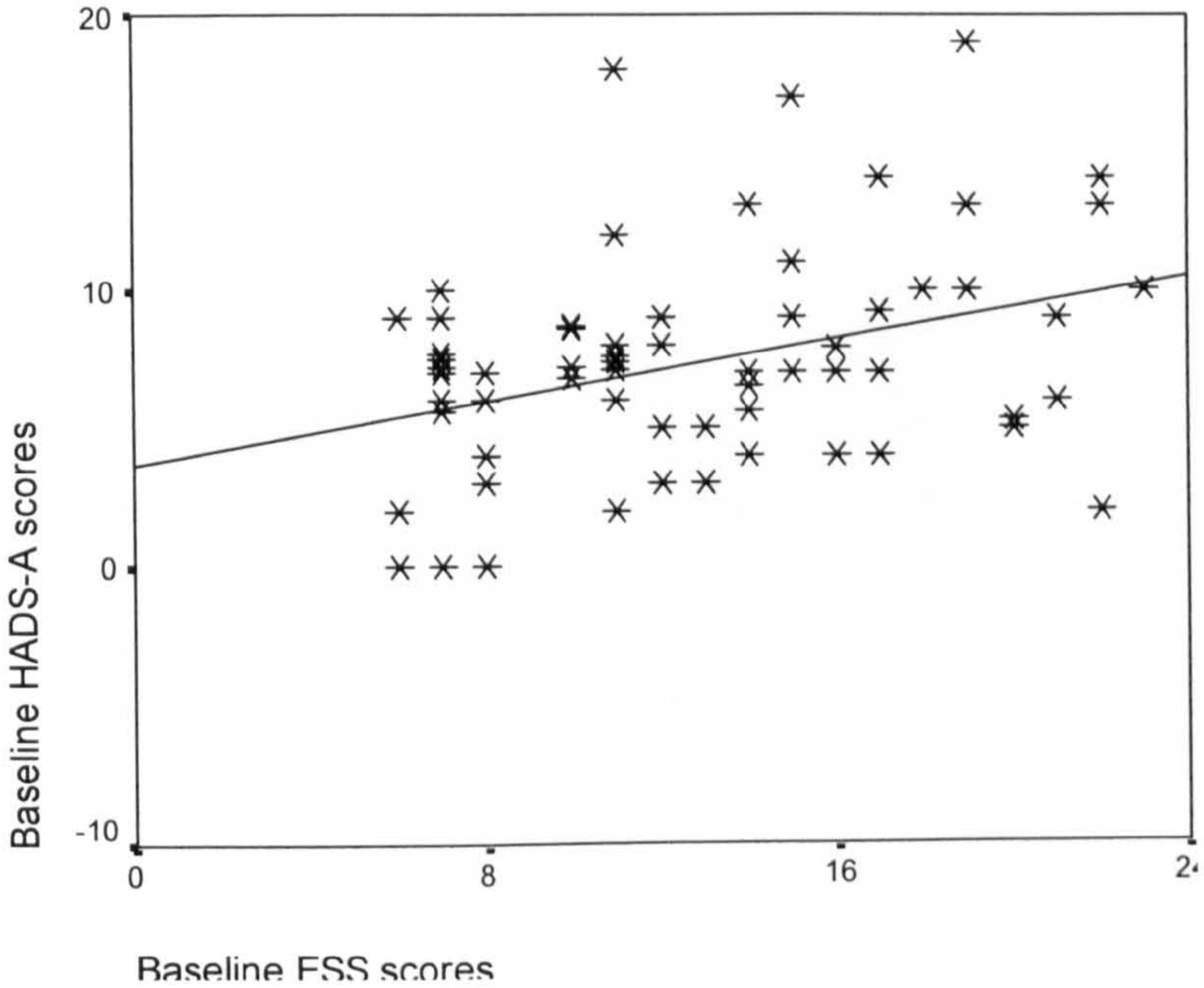
In Group II the change in proportions of cases versus normal subjects did not reach statistical significance. Patients in Group I on CPAP therapy showed a significant reduction in their HADS scores in both the anxiety and depression sub-scales, as shown in table 6.9 while there was no change seen in patients on lifestyle therapy in Group II.

Table 6.9: Paired samples statistics for HADS subscales before and after therapy

		Lifestyle Mean	Lifestyle SD	p	CPAP Mean	CPAP SD	p
HADS-A	Base	7.8	3.4		7.2	4.5	
	Post	7.3	2.8	Ns	4.4	3.6	<0.001*
HADS-D	Base	5.3	3.0		6.1	3.7	
	Post	5.4	2.5	Ns	2.6	2.5	<0.001*

Ns=not statistically significant

Figure 6.10: Scatter plots showing linear relationship of HADS scores with baseline ESS scores



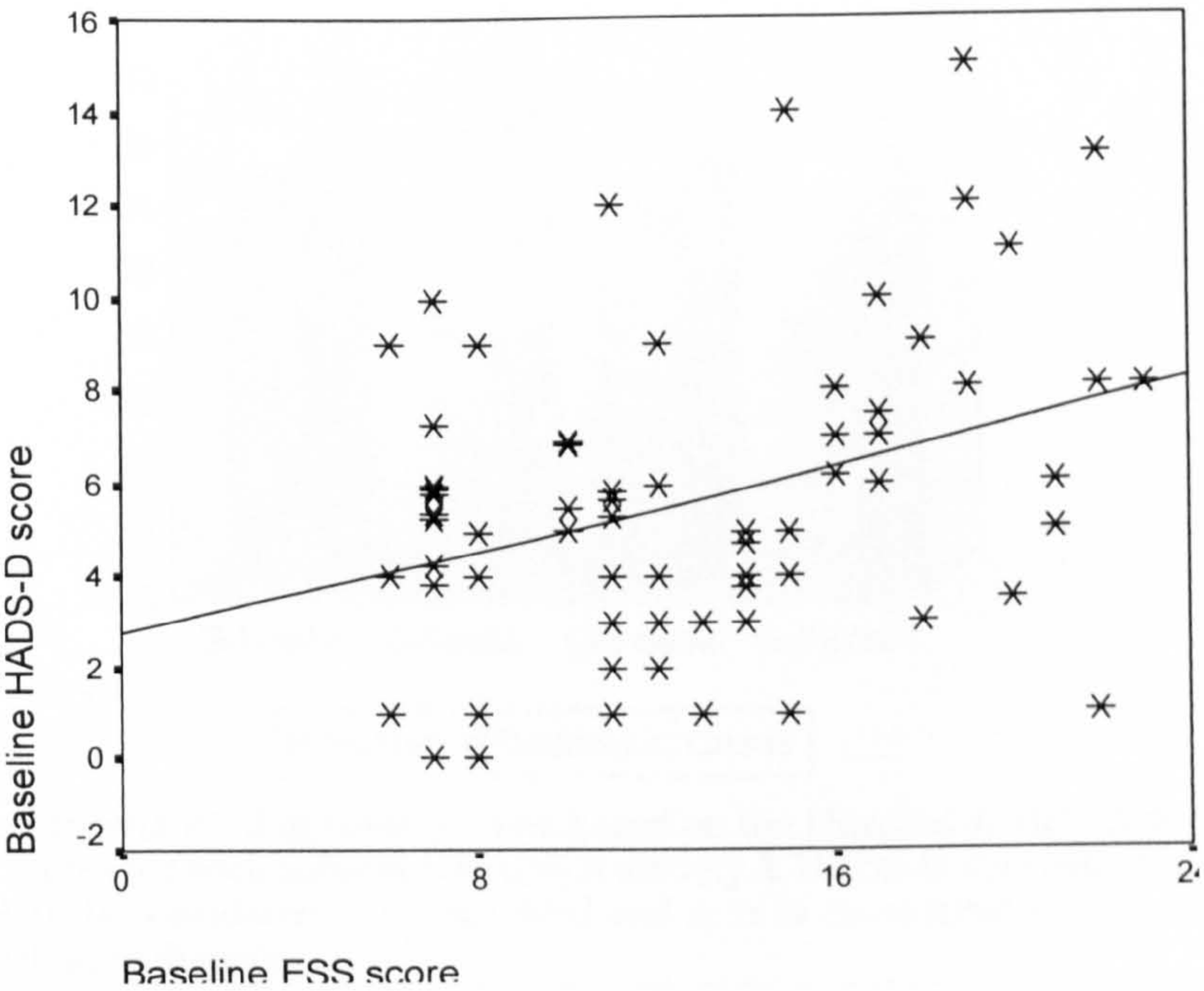
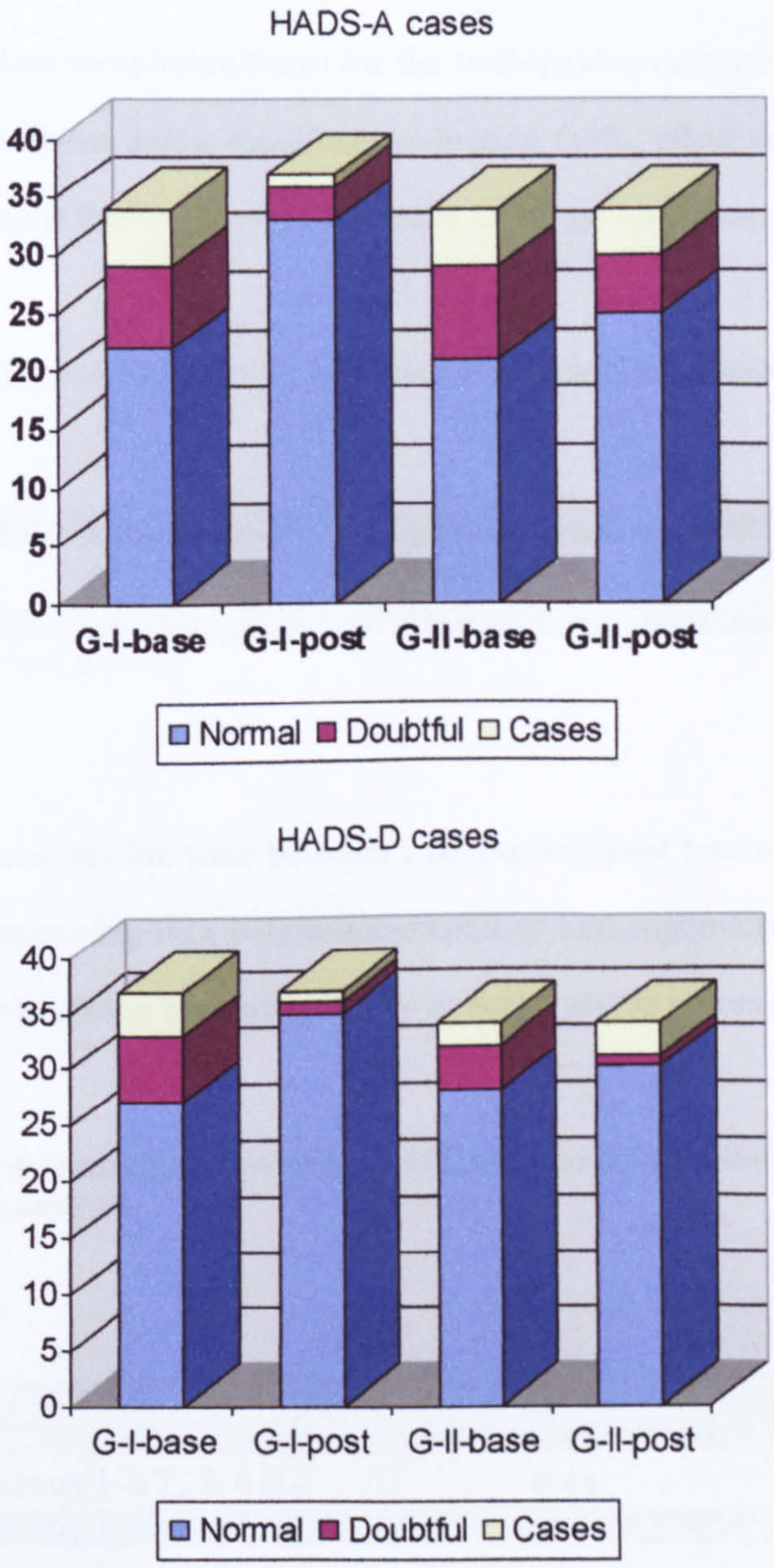


Figure 6.11: showing the alteration in proportion of cases and normal subjects based on HADS classification before (base) and after therapy (post) (Group I=GI & Group II-GII)



The established criteria for diagnosis of cases based on the Hospital anxiety & depression scale (HADS) scores for each subscale (HADS-A anxiety & HADS-D depression) a score ≤ 7 is normal, 8-10 is considered to be doubtful and ≥ 11 is considered to be a case with significant psychiatric disorder.

6.3.5 Neuro-cognitive function (Trail-making test A & B)

Although the baseline completion times for the trail-making exercise was similar in both groups of patients, there was a significant reduction (18%, effect size 0.53, $p<0.05$) in time taken to complete the Trail-making B test in CPAP group I compared to group II.

Table 6.10: Trail-making test A & B completion time (seconds) before and after treatment

	CPAP pre	CPAP post	Lifestyle pre	Lifestyle post
A	38 (13.6)	34 (11.2)	36.6 (20.2)	33.4 (11.9)
B	90.9 (31.4)	74.4 (30.5)*	94.8 (56.7)	86.9 (40.7)

* paired samples t test $p<0.05$

The difference in completion time between baseline and post treatment test (δT_a and δT_b) showed no relationship with polysomnographic or anthropometric parameters. There was a significant correlation seen with change in health status scores as follows;

Table 6.11: Non-parametric correlations between health status and difference in Trail-making scores

	Spearman's coefficient	p
Group I: δT_a & δU_{sg}	0.44	0.02
Group I: δT_b & δU_{tto}	-0.4	0.04
Group II: δT_a & δT_b	0.8	<0.001
Group II: δT_b & δU_{tto}	-0.6	0.01
Group II: δT_a & δU_{tto}	-0.4	0.06

6.3.6 Summary of HRQL findings

Sixty percent of patients rate their health to be fair to poor at baseline (SF36) while 25% expected their health to deteriorate in the next 12 months (SF36). Compared to normal UK population, women with SAHS reported HRQL deterioration in Social Functioning, Energy/Vitality and General Health with effect sizes >0.7 (moderate to severe). Among men with SAHS, the maximum HRQL decrements were in the Energy/Vitality, General Health, Social Functioning, Physical Functioning and Bodily Pain (effect sizes >0.7).

The SF36 scale properties showed concurrent validity (physical role limitation and social functioning related to sleep latency), intra-class reliability (Cronbach's α = 0.87), and good inter-class reliability (coefficient >0.6).

PSG measures of AHI and AI were not significantly related to any of the sub-scales of SF36. Patients on CPAP showed improvement in Social Functioning, Energy/ Vitality, Mental Health and Physical Role Limitation (SF36).

After successful treatment with CPAP, mental dimension scores return to normal values (GH, RE and MH) but physical dimension scores remain lower than population values. No significant change was observed in the patients on lifestyle modification (SF36).

Baseline EuroQol scores indicate moderate problems in usual activities, pain and anxiety/ depression dimensions. There was no significant improvement in EuroQol scores after treatment in both groups. EuroQol scores and health thermometer scores (VAS) were correlated with SF 36 subscales (PF, RP, VT, GH and RE) but not with SF dimension of SF36 (which showed the greatest change with CPAP treatment). EuroQol health thermometer scores improved after CPAP treatment but not with lifestyle intervention.

GHQ28 identified 64/71 (90%) patients as potentially having significant psychiatric morbidity. After treatment with CPAP, there was a 43% reduction in 'cases', but no significant change in the number of patients classified as cases in the lifestyle modification arm. After CPAP, there were improved scores in all 4 dimensions of GHQ28 but only somatic symptoms (GHQ-A) subscale showed a modest

improvement in the lifestyle arm. Scores for severe depression (GHQ-D) sub-scale of the GHQ28 showed significant worsening in the lifestyle arm.

HADS classified 8% patients with severe depression and 14% with significant anxiety at baseline. HADS scores showed a significant relation to sleep latency and daytime hyper somnolence (ESS scores). Odds ratio for improvement in HADS scores to normality was 5.5-6.7 for patients in the CPAP arm but no change was seen in the lifestyle arm.

CPAP patients improve timing on Trail making test B (effect size 0.5)

6.4 DISCUSSION

6.4.1 Overview

Health care provision in the last 2 decades has not only focussed on control of diseases and reduction in mortality but in the promotion of positive health and a sense of mental and physical well-being. Hence appraisal of new innovations has to take into account patients' self reported health related quality of life along with physiological measurements. While the debate continues on the most suitable HRQL tool which will not only demonstrate a high degree of reliability and validity but also sensitivity to the needs of individual patients and disease groups, across the world various different tools are being used in clinical trials.

In SAHS patients the disease severity measured using nocturnal PSG variables have been shown to be poor predictors of daytime dysfunction [Kingshott *et al.*1998]. On the one hand even patients with no evidence of apnoeas/ hypopnoeas (i.e. UARS) [Guilleminault *et al.* 2001] are shown to suffer a similar level of disability, while patients with clear apnoeas/ hypopnoeas at night may not suffer any daytime disability and hence do not respond to treatment [Barbe, *et al.*2001]. This complex relationship between disease processes as it is understood, with patients' reported disability levels creates problems for assessing outcome of intervention in this sector.

Studies using HRQL measures have demonstrated a reduced self-reported quality of life among these patients, which tends to respond to treatment. In this study, two widely used multi-dimensional HRQL tools were studied head –to- head along with 2 specific measures of psychiatric morbidity. The results show firstly that the majority of SAHS patients report not only poor HRQL in almost all dimensions but also report symptoms suggestive of psychiatric morbidity. Treatment with CPAP does produce a significant change in Mental Health, Social Functioning and Energy/ Vitality dimensions of SF36. Interestingly there is only a small change in the EuroQol Health thermometer scores with CPAP treatment. Lifestyle modification strategy does not reflect in any change in HRQL measures, except an increase in severe depression scores of the GHQ28 instrument. None of these HRQL measures demonstrate any relationship with physiological markers.

Thus the suitability of these HRQL measures in assessing the overall impact of a healthcare intervention remains uncertain, especially as variable results in different population groups may lead to unfair prioritisation in health policy decision-making.

6.4.2 Methodological issues

The purpose of this part of the research was not to assess the validity and reliability of the 4 HRQL measures chosen, as all of them had been validated and extensively tested in large population studies in several countries. It was however the intention of this HTA appraisal to assess their suitability for measuring HRQL deterioration among SAHS patients and to assess their sensitivity in measuring the impact of treatment. However, in the population studied the psychometric properties of these measures were compatible with previously reported results and all four demonstrated good inter and intra-class reliability. When the scores in mental dimensions were compared between those generated by SF36, GHQ28 and HADS, they showed moderate correlations supporting their convergent validity. Similarly there was compatibility between the EuroQol physical disability scores and the physical components of the SF36.

However, the EuroQol scores for anxiety/ depression showed almost 20% patients reporting moderate to severe problems, similar to 14% with depression and 8% with anxiety on the HADS but in contrast to 90% being classified as having significant psychiatric morbidity by the GHQ28.

None of these questionnaires showed any relationship with age, sex, BMI or any other variable unrelated to the patient's condition, suggesting a good discriminant capability. These questionnaires were perhaps focussing on the mental and social aspects of HRQL affected by SAHS. This is likely a manifestation of the principal reported problems of chronic fatigue and daytime somnolence which interferes with work and sometimes embarrassingly with social life in SAHS patients [Flemons *et al.* 1997b] [Veale *et al.*2002]. While reports that SAHS patients, suffer breakdown of relationships and an increased tendency to seek comfort in alcohol and depression [Veale *et al.* 2002], are reflected by the high prevalence of psychiatric morbidity reported by the GHQ28 and HADS. Thus these questionnaires demonstrate construct validity, and would appear to measure what they set out to measure, among SAHS patients in the present study.

Although it can be established that these HRQL tools do appear to measure relevant disabilities among SAHS patients, where there remains uncertainty is in their criterion validity. In other words, are the disabilities measured related to the underlying disease process being assessed? For example when the traditional measures of disease severity were compared to the scores measured by these instruments, none was found to show any significant relationship excepta negative correlation between physical role limitation and sleep latency.

A lower score on physical role limitation translates to a poorer function and is correlated with a higher sleep latency. Physical role limitation is less important in SAHS patients and shows only a modest change with treatment. However, physical role limitation is more likely to be a result of concurrent comorbidity such as osteoarthritis (which is more prevalent in obese individuals) and thus interfere with getting to sleep (hence, increasing sleep latency).

Hence it is uncertain whether the HRQL deterioration measured by these instruments are a direct consequence of SAHS disease process as measured by PSG parameters (i.e. absence of criterion validity). This deficiency of generic measures may conceptually be addressed by disease specific tools, but with a likely decline in sensitivity and the inherent difficulties in comparisons across the disease spectrum (a vital ingredient for any health technology appraisal system). In other research, when a disease specific assessment tool was compared to a generic tool such as the SF36 among patients attending a rheumatology clinic, the disease specific measure detected more problems in patients with osteoarthritis [Brazier *et al.* 1999]. However, Brazier et al found that SF36 demonstrated a greater insight in to the patient's general health and was more sensitive to the change with treatment in a more diverse population of rheumatological diseases [Brazier *et al.* 1999]. Thus, in conditions such as Diabetes Mellitus, COPD, rheumatoid arthritis and SAHS where the disease process tends to have a multi-faceted impact on general health, generic tools may show a greater sensitivity to change.

Although, a disease specific measure such as the SAQLI [Flemons and Reimer 2002] has been designed specially to identify the HRQL consequences of sleep deprivation/ fragmentation, SF36 has been shown to be sensitive to quality of sleep in subjects with

SAHS [Smith *et al.* 1995]. Even the disease specific SAQLI showed little or no correlation with markers of nocturnal sleep disturbance, which are considered the hall-mark of SAHS pathophysiology [Lacasse *et al.* 2002b]. Perhaps the only evidence for criterion validity for the SF36 comes from large population studies suggesting that patients with severe SAHS (higher AHI levels) tend to report lower HRQL scores in multiple dimensions compared to patients with milder disease [Finn, *et al.*1998b], but only in the case of the Energy/ Vitality dimension of SF36 is there a demonstrable relationship [Baldwin *et al.*2001].

There have been differences in reporting of results of SF36 questionnaire scores between researchers. While the predominant way has been to measure the score (0-100) and run parametric tests of significance, more recently there has been a trend to report effect sizes (difference in scores/standard deviation).

6.4.3 SF36 & EuroQol

Compared to normative population data (age and sex matched) baseline SF36 scores in the study population showed significant HRQL deterioration in almost all HRQL sub-scales. The lowest scores were recorded in Social Functioning, Energy/ Vitality and General Health in both men & women. Men also reported lower scores in Bodily Pain and Physical Functioning. SAHS patients are known to suffer the consequence of daytime fatigue and somnolence on their work and personal life, hence they are likely to report lower scores in the mental health dimensions including Energy/ Vitality and General Health dimensions of SF36 [Finn *et al.* 1998a] and when using the mental health instruments (GHQ28 & HADS).

In the Sleep Health Heart Study surveying nearly 6000 subjects, HRQL was assessed using the SF36. Baldwin et al found that in moderate SAHS lower scores were reported predominantly in the energy/vitality dimensions while more severe SAHS patients reported a more multi-dimensional decline, although no clear relationship with nocturnal PSG parameters were identified [Baldwin *et al.* 2001]. Surveys have also shown that SAHS patients tend to perceive almost equivalent HRQL decline as do patients with other chronic diseases [Baldwin *et al.*2001]. Smith et al reported lower scores in almost all dimensions of SF36 in SAHS patients, although mainly in Energy/Vitality and Social

Functioning compared to a normal population. SF36 has also demonstrated sensitivity to the correction of nocturnal sleep apnoea by CPAP after 6 months with Energy/Vitality scores returning to expected normal values but not Social Functioning [Smith and Shneerson 1995]. In an uncontrolled trial with 29 SAHS patients given 8 weeks of CPAP therapy D'Ambrosio et al reported improvement in energy/vitality, social functioning and mental health dimensions of SF36 and similar to my findings also reported no relationship between SF36 parameters with physiological markers of SAHS disease severity [D'Ambrosio *et al.*1999].

In a similar RCT, Ballester et al randomised SAHS patients to conservative therapy (weight loss and sleep hygiene) or conservative therapy + CPAP. They measured HRQL using the SF36 and found the maximum decline in Energy/ Vitality and Social Functioning which improved among CPAP patients after 3 months of treatment. The likelihood of experiencing a treatment response was reported to be 6 times that in the patients given conservative treatment (range for odds ratios 2.5 to 17.5) [Ballester *et al.* 1999].

The proportion of SAHS patients at baseline reporting moderate problems in usual activities, pain discomfort and anxiety/ depression dimensions of the EuroQol questionnaire remained unchanged at the end of the trial phase. The EuroQol-HT similarly showed a lower mean score than UK population norms (66.8 vs. 83). This demonstrated a moderate improvement in patients treated with CPAP at the end of the trial (effect size = 0.4, p=0.009), although still not reaching population normal values. Compared to the SF36 questionnaire this demonstrates a lack of sensitivity to change in the EuroQol questionnaire, especially in the SAHS patient group. This may be due to the inherent properties of the EuroQol which is designed as a simpler HRQL assessment tool with an emphasis on physical functioning [Jenkinson *et al.* 1997c]. However, both these questionnaires have demonstrated evidence of HRQL deterioration even in chronic conditions such as irritable bowel syndrome [Akehurst *et al.* 2002], osteoarthritis of the knee [Brazier *et al.* 1999], stroke [Dorman *et al.* 1998] and inflammatory bowel disease [Konig *et al.* 2002].

However in patients with chronic fatigue syndrome, both the SF36 and EuroQol are reported to being over sensitive to the impact of the disease on mobility and physical functioning [Myers *et al.* 1999]. In head –to-head comparisons between the EuroQol and SF36, studies have suggested that although it has a better response rate compared to SF36, the EuroQol showed a lower sensitivity for transitional health states and a floor effect in measurement of lower health states compared to the SF36 [Brazier *et al.* 1993b]. In SAHS patients the EuroQol has been found to be insensitive to the HRQL decline suffered both at baseline and after treatment when compared to SF36 and the Functional Limitation Profile [Jenkinson *et al.* 1998]. Similar insensitivity has also been reported in patients with multiple sclerosis [Nicholl *et al.* 2001]. It is not unusual for different HRQL tools to show discrepancy in measuring the condition–specific deterioration in general HRQL similar to that seen in this case [Crockett *et al.* 1996]. In a review of HRQL tools, the authors concluded that there were perhaps no uniformly 'worst' or 'best' performing instruments. The decision to use one over another, to use a combination of 2 or more, to use a profile and/or a preference-based measure or to use a generic measure along with a targeted measure should be driven by the purpose of the measurement. In addition, the choice may depend on a variety of factors including the characteristics of the population (e.g. age, health status, language/culture) and the environment in which the measurement is undertaken (e.g. clinical trial, routine physician visit) [Coons *et al.* 2000]. In the case of SAHS patients EuroQol showed a lack of sensitivity and discriminant properties hence is likely to be unsuitable for use as an outcome measure in health technology appraisal.

While the SF36 dimensions of Energy/Vitality and Social Functioning showed both sensitivity and discriminated between the groups on the basis of treatment response. The SF36 may still demonstrate uncertainty in measuring the impact of competing technologies in different patient groups, due to the variable amplitude of the responses seen in different sub-dimensions. The physical sub-dimension scores of the SF36 failed to return to population norms after CPAP treatment suggesting that the deterioration seen at baseline were either unrelated to SAHS and / or CPAP treatment did not impact on these dimensions.

6.4.4 Mental Health

6.4.4.1 Cases versus non-cases

Both the GHQ28 and HADS identified proportions of cases with significant psychological morbidity in the study population but with a discrepancy between them. The majority of SAHS patients were classified as 'cases' based on the GHQ28 while only a quarter were classified as having 'anxiety/ depression' by the HADS instrument. The prevalence of anxiety (19%) and depression (21%) was similar to those seen in patients with acute coronary related chest pain in a survey using HADS [Goodacre, et al 2001]. In addition to anxiety and depression, the GHQ28 also measures psychiatric co-morbidity due to somatic symptoms and social dysfunction, which may account for the higher prevalence for psychiatric co morbidity. Patients on chronic haemodialysis report a high prevalence of psychological co-morbidity using the GHQ28 [Petrie 1989] (far less than SAHS patients), although the GHQ has been reported to be less sensitive than other screening tools like the mental health inventory and somatic symptom scale in primary care [Weinstein *et al.* 1989].

The only GHQ28 sub-scale which showed a significant relationship with both HADS subscales was GHQ-D (severe depression). GHQ28 is perhaps more comprehensive in its assessment of psychiatric morbidity secondary to a physical illness then the more specific HADS system. In a similar study examining psychiatric disability secondary to physical illness there was no significant difference between the screening properties of HADS and GHQ28, however GHQ was considered more specific for the diagnosis of depression [Clarke *et al.* 1993].

Compared with the mental health sub-scales of the SF36 (VT, MH, SF, RE and GH) there were significant correlations seen with GHQ28 and HADS scores, as has been reported by other researchers [Failde I. *et al.* 2000].

Patients with significant depression or psychological co morbidity have a lower utility of health, physical and social functioning and a worse outcome [Wells *et al.* 1999]. Hence one of the benefits of using screening tools in non-psychiatric practice [Wilkinson *et al.* 1988] is that they tend to increase the sensitivity of identifying the prevalence of psychological distress and hence offer an opportunity for appropriate therapy. This was

demonstrated in a primary care survey where the diagnosis of depression and psychiatric morbidity was doubled when GHQ was used in screening 1600 patients and compared to physician led diagnosis [Smith 1998a].

In common with the generic tools, both the HADS and GHQ28 did not show any predictable relationship with PSG parameters of SAHS disease severity except for HADS-D (depression) scale and sleep latency. Although, sleep onset insomnia is a recognized feature of depressive illness, in patients with sleep fragmentation and sleep debt due to apnoeas/ hypopnoeas the inherent short sleep latency may even be reversed by the effect of co-existent depression.

At the conclusion of the trial phase there was a significant decline in all the 4 GHQ28 and 2 HADS sub-scale scores for patients given CPAP therapy. The number of patients on CPAP reporting psychiatric co-morbidity was reduced significantly. Both these instruments with a high specificity for psychiatric co morbidity demonstrated a significant improvement not only in mental health status but also a decline in psychiatric co morbidity in the absence of behavioural / formal psychiatric therapy. This is perhaps strong evidence in favour of sleep abnormality (both insomnia & sleep fragmentation-hypersomnia) being an aetiological factor for depression [Breslau *et al.* 1995] and psychiatric illness. Even a reversal of the sleep fragmentation for a short 3 month period is enough to reverse severe depression symptoms in these patients [Millman *et al.* 1989] and the effect may be preserved for 24 months.

Unlike the CPAP group there was a distinct worsening of GHQ-D (severe depression) scores seen in lifestyle patients, which may be a manifestation of the disappointment developing from a failure to improve symptoms in these patients. There is however a mixed picture with some patients on lifestyle strategy reporting improvement in somatic symptoms, which may be a placebo effect or due to sleep hygiene/ weight changes.

6.5 CONCLUSIONS

Patient preferences, which should ideally drive treatment decisions, are related to mental and social health nearly as much as they are to physical health. The contribution of mental health to preferences is known to be stronger in patients with chronic conditions. Thus, medical practice should strive to balance concerns for all three health domains in making treatment decisions, and health care resources should target medical treatments that improve mental and social health outcomes [Sherbourne *et al.* 1999] as well as physical health. Thus patients with SAHS not only suffer the physiological consequences of sleep fragmentation and consequent EDS but also demonstrate lower HRQL scores in a multi-dimensional fashion. The adverse HRQL impact is mostly visible in mental health dimensions of SF36 (energy/ vitality, social functioning, mental health and general health), EuroQol (anxiety/ depression, usual activities, pain and discomfort), GHQ28 and HADS instruments. These HRQL effects show a significant improvement with CPAP treatment but remain unrelated to PSG variables of SAHS severity, suggesting a complex interaction.

EuroQol shows a lack of sensitivity to the transition after CPAP treatment and in discriminant properties between the treatment groups, perhaps due to the focus on physical functioning, except in EuroQol-HT scores.

The amplitude of mental health HRQL improvement after CPAP tends to vary depending on the tool used and population studied; hence this may not be very suitable for use as an outcome measure in health technology appraisal where comparisons with competing technologies are likely to be needed.

CHAPTER VII

ECONOMIC EVALUATION

7.1 BACKGROUND

Health care providers and those responsible for health policy and purchasing are increasingly expected to make their decisions on allocation of resources based on evidence of cost-effectiveness [Kopp 2000]. Similarly, when an innovation is undergoing a health technology appraisal an evaluation of its economic impact (both costs and benefit) becomes imperative for health care decision making, in the face of increasing costs and limited resources. Compared to the early years (pre-1990) when very few cost-effectiveness studies were reported in clinical trials, more recently an increasing proportion of trials tend to include an economic evaluation exercise as part of the study design. Although there are many controversies regarding the methodology for collection and reporting of such 'economic' data this information is considered essential in current policymaking. Along with the uncertainties in collection of cost data there are uncertainties in the suitability of 'benefit' data used to measure the impact of treatment.

There are inherent problems in making health policy decisions based on the measured impact on HRQL, as there is considerable variation in the magnitude of such impact in different HRQL dimensions and in different disease/ patient groups. Thus the problems of comparing competing technologies remain in health policy prioritisation. Some authors have recommended a combination of disease specific measures (which are expected to be more sensitive to change) with generic measures (comparable between diseases) to produce outcome variables [Ballester, *et al.*1999]. This approach tends to detract from the measurement properties of each instrument and may undermine their construct validity and reliability.

An alternative approach to using traditional life expectancy/ survival/ physiological data for example survival in patients given cholesterol lowering agents [Thorne 2000] or improved blood pressure control in type II diabetic patients [Anonymous 1998b]) is to use patient-based-preference measures to assess the impact of outcome in clinical trials and in HTA [Nathan 2002]. In combination with the current 'gold standard' RCTs,

patient based preference measures (i.e. health status) have been increasingly used in many disease scenarios as a primary measure of treatment outcome for example the use of recombinant insulin-like growth factor in amyotrophic lateral sclerosis using SG approach [Ackerman *et al.* 1999]; transmyocardial laser revascularisation for the treatment of refractory angina compared to conventional revascularisation [Campbell *et al.* 2001].

Thus when information is needed about the overall value of a health care intervention, in a way that permits comparison with other interventions, then utilities tend to provide unified outcomes mostly in the form of QALYs [Torrance 1986b].

Theoretically it can be proven that an optimal allocation of resources within a constrained budget can be reached by considering cost-effectiveness ratios (CERs). While priority setting in the context of compatible alternatives may refer to the selection of more than one, possibly all, alternatives, a situation frequently seen in health care is of a set of incompatible alternatives where only one alternative can be selected.

The arbitrary value that society attaches to a unit of effectiveness (e.g. a QALY) has an important impact on the priority ranking of medical interventions [Ament *et al.* 1997]. Because the cost-effectiveness ratio (cost/QALY) is sensitive to the method chosen to calculate QALYs, results need to specify the appropriate method for calculating outcomes in order to produce comparable results [Gafni and Birch 1993a].This part of the research presents the findings of individual patient preference methods to generate utility using the SG, TTO and the derived preference measures obtained from the EuroQol instrument in a cost-utility analysis of CPAP versus lifestyle intervention in SAHS patients.

7.2 RESULTS

7.2.1 Health status measurement

7.2.1.1 Baseline population health-status

The baseline mean utility score was lower as obtained by the SG method; Mean U_{sg} 0.35(0.18), compared to the TTO utility scores; Mean U_{tto} 0.59 (0.17) and EuroQol derived utility; Mean U_{eq} 0.73 (0.16), the frequency distributions are shown in figures 7.1 & 7.2.

The mean U_{tto} and U_{sg} were significantly related (Spearman's correlation coefficient of 0.32, p=0.02), the best relationship was obtained using a cubic model (Usg = constant + $Utto^3$; r^2=0.293, p=0.001).

There were no significant correlations with the U_{eq}. The baseline U_{sg} and U_{eq} did not show any significant relationship with ESS scores, age, BMI, AHI, AI, sleep latency, REM latency and the lowest SaO_2 recorded during sleep.

The U_{tto} however was negatively related to AHI (linear regression coefficient -0.42, p=0.005), sleep latency (linear regression coefficient -0.29, p=0.04) and positively to age (linear regression coefficient 0.42, p=0.004).

The individual relationships between U_{tto} and age and AHI are shown in figure 7.3.

Figure 7.1: Frequency distribution of mean baseline utility scores

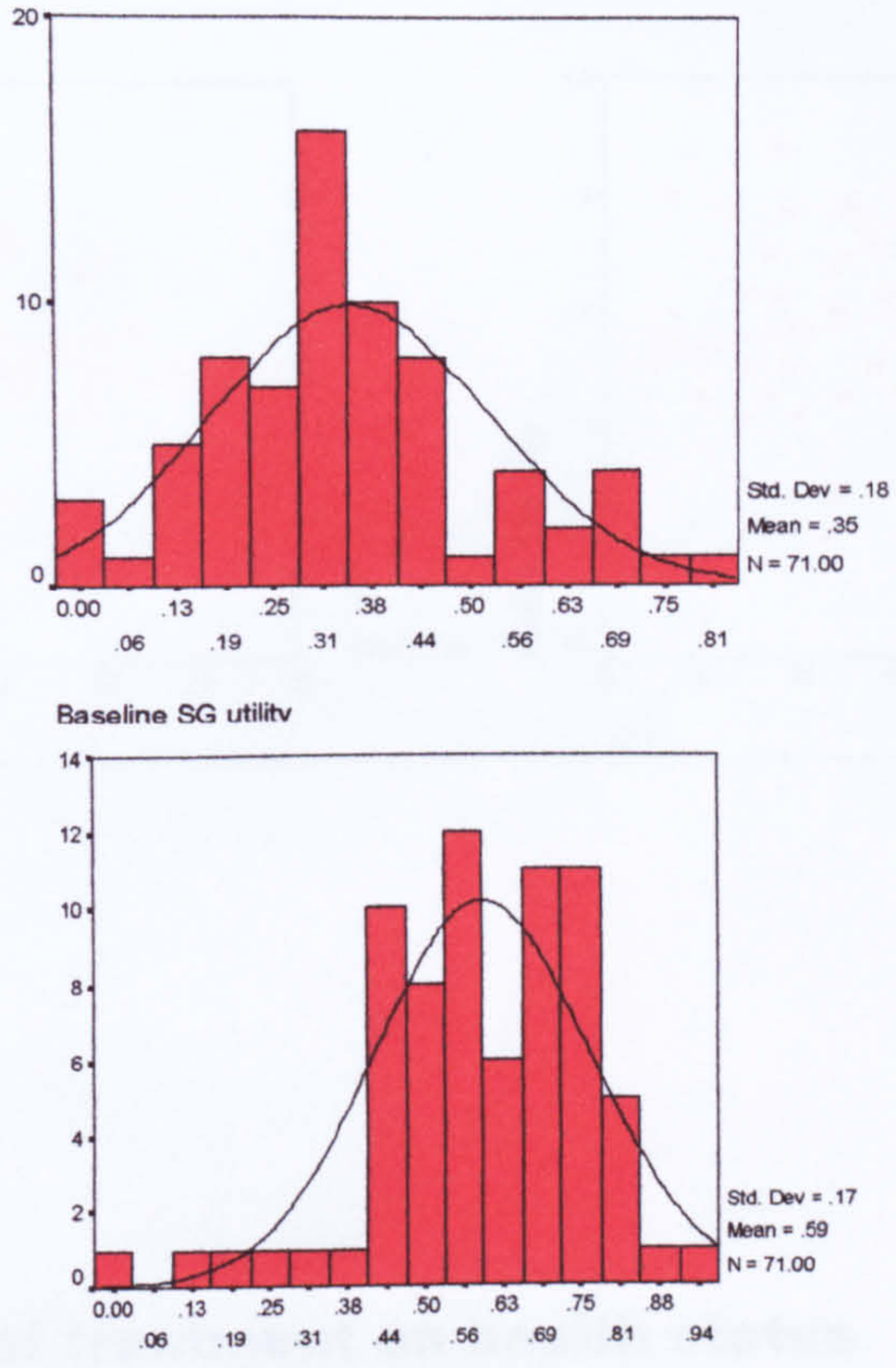


Figure 7.2: Frequency distribution of the EuroQol utility scores.

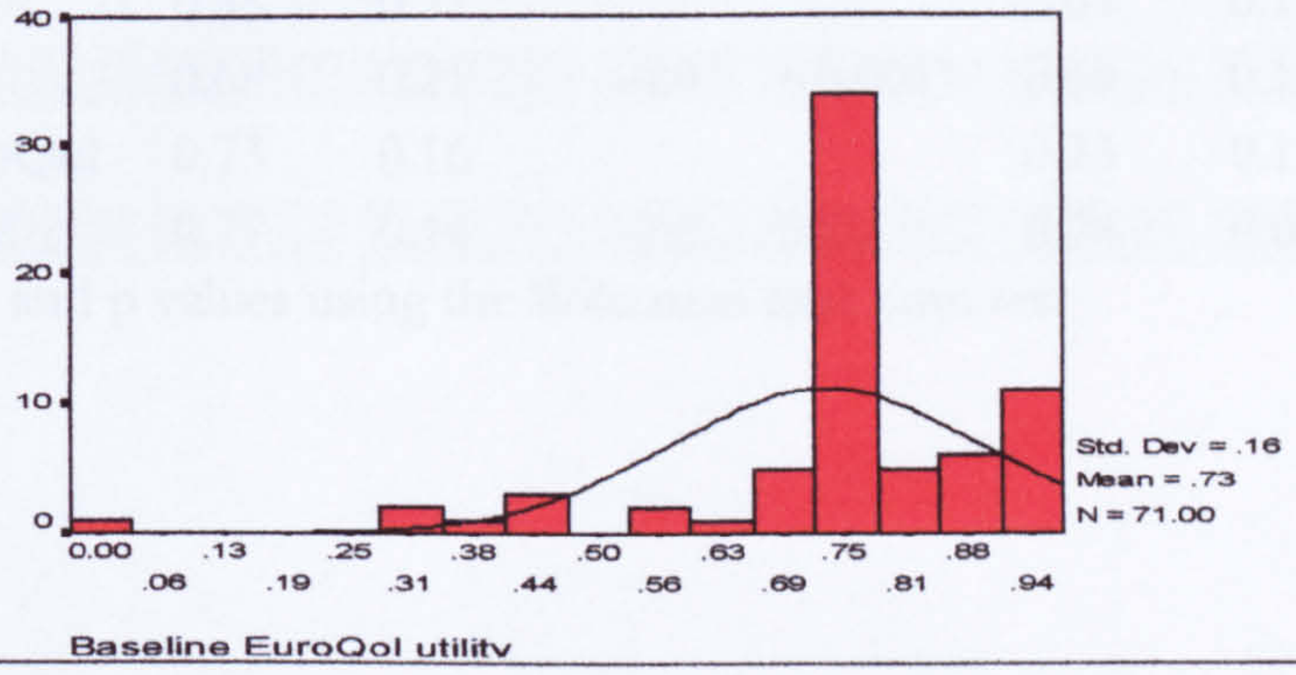
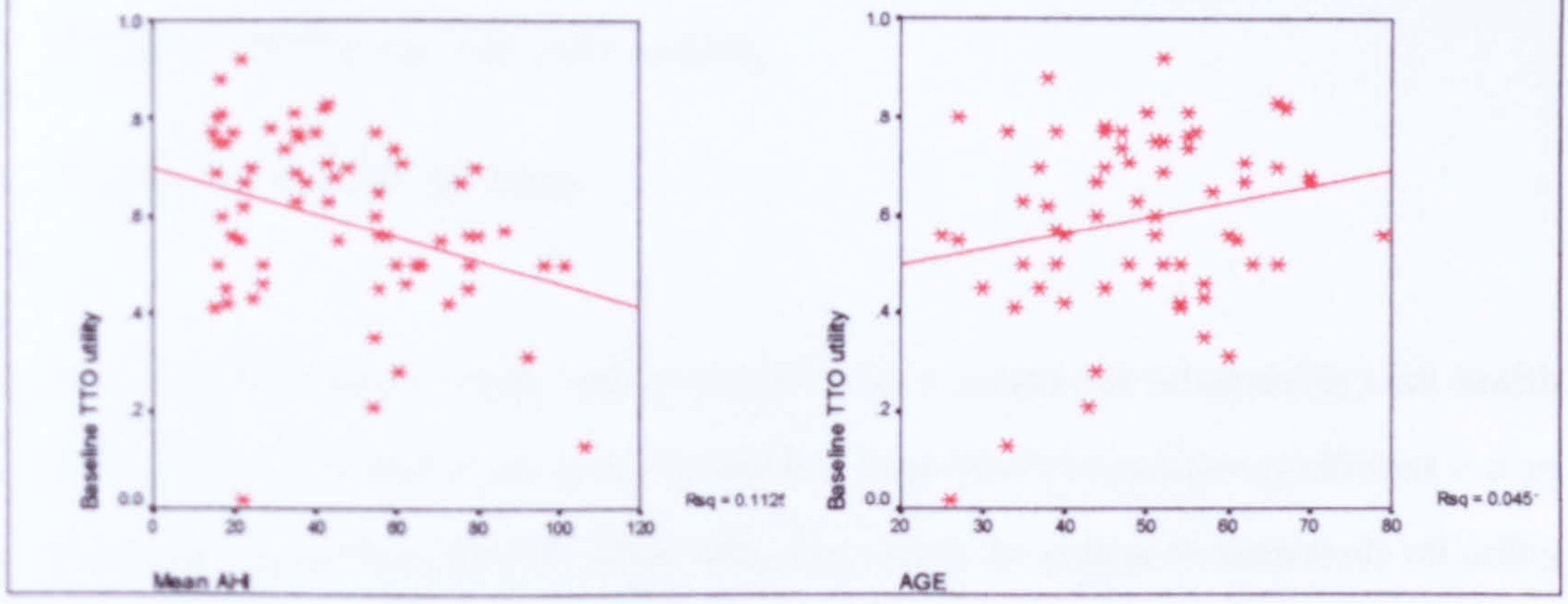


Figure 7.3: Scatter plots demonstrating the relationship between TTO utility and age/AHI



7.2.1.2 Effect of treatment on health status

Table 7.1: Effect of treatment on utility scores

Utility methods	CPAP Mean (sd)	CPAP SD	Z	p	Life-style Mean (sd)	Life-style SD	Z	P
Baseline SG	0.31	0.19			0.38	0.17		
Post SG	0.49	0.27	-3.5	<0.001*	0.43	0.17	-2.2	0.03*
Baseline TTO	0.55	0.21			0.64	0.13		
Post TTO	0.68	0.21	-4.0	<0.001*	0.69	0.14	-2.9	0.04*
Baseline EuroQol	0.73	0.16			0.73	0.17		
Post EuroQol	0.77	0.14	-2.0	0.05	0.78	0.08	-1.8	0.07

Z = Z scores and p values using the Wilcoxon rank sum test

7.2.2 Correlations with HRQL measures

7.2.2.1 SF36 vs. health utility

7.2.2.1.1 CPAP group:

The only dimension of SF36 which demonstrates a significant relationship with health utility scores is change in physical functioning; Spearman's correlation coefficient = 0.39 for change in standard gamble utility ΔU_{sg} (p=0.017), for change in time-trade off utility ΔU_{tto} = 0.382 (p=0.034) and change in EuroQol utility ΔU_{eq} = 0.479 (p=0.015).

7.2.2.1.2 Lifestyle group

Change in physical functioning score correlated with change in standard gamble utility; Spearman's correlation coefficient = 0.342, p=0.048. The change in weight (**Δ weight**) correlated with change in the following dimensions;

Δ BP	= 0.51	p=0.002
Δ SF	= 0.64	p<0.001
Δ RE	= 0.43	p=0.012
Δ MCS	= 0.44	p=0.01

7.2.2.2 Utility correlations

7.2.2.2.1 CPAP group

7.2.2.2.1.1 Standard gamble utility

In the CPAP group, the change in Usg (Δ sg) with treatment was closely related to change in Utto (coefficient = 0.76, p<0.001) and the following demographic and sleep variables at baseline;

Δ sg with BMI	= 0.48, p=0.003
Δ sg with neck size	= 0.56, p<0.001
Δ sg with ODI	= 0.53, p=0.002
Δ sg with AHI	= 0.41, p=0.01
Δ sg with sleep latency	= -0.48, p=0.01
Δ sg with lowest SaO2 in sleep	= -0.5, p=0.003
Δ sg with Δ SF 36-PF	= 0.39, p=0.017
Δ sg with Δ ESS scores	= 0.44, p=0.02

7.2.2.2.1.2 Time trade off utility

Δ tto with Δ weight	= -0.38, p=0.04
Δ tto with BMI	= 0.42, p=0.02
Δ tto with neck size	= 0.36, p=0.049
Δ tto with sleep latency	= -0.37, p=0.047
Δ tto with lowest SaO2 in sleep	= -0.47, p=0.008
Δ tto with Δ SF36-PF	= 0.38, p=0.03
Δ tto with Δ ESS	= 0.55, p=0.004

7.2.2.2.2.1.3 EuroQol utility

Δ eq with neck size = 0.44, p=0.028

Δ eq with SF36-RE = -0.44, P=0.04

Δ eq with SF36-MCS = -0.49, p=0.04

Δ eq with Ueq at baseline = -0.47, p=0.019

Δ eq with Δ SF36-PF = 0.48, p=0.015

Δ eq with Δ SF36-PCS = 0.51, p=0.009

Using the above variables in a linear regression model the adjusted r^2 for Δ sg = 0.46, p=0.03 and for Δ tto the adjusted r^2=0.62, p=0.003. Thus 46% and 62% of the change in the Δ sg and Δ tto respectively can be predicted by the change in the above variables.

7.2.2.2.2 Lifestyle group

In the lifestyle group patients there were significant correlations seen between the changes in U_{sg} with change in U_{tto}. There were significant relationship between the change in U_{tto} and U_{sg} with GHQ A (somatic symptoms) and HADS Anxiety subscales. The GHQ subscale B (self-care) and SF36 emotional role limitation (RE) subscale were related with the Δ tto as shown below;

Δ sg with Δ tto = 0.66, p=0.001

Δ sg with GHQ-A = -0.55, p=0.01

Δ sg with HADS –A = -0.48, p=0.004

Δ sg with Δ SF36 PF = 0.34, p=0.048

Δ tto with GHQ-B = -0.47, p=0.04

Δ tto with GHQ-A = -0.76, p<0.001

Δ tto with HADS-A = -0.54, p=0.01

Δ tto with SF36-RE = 0.51, p=0.04

Δ tto with SF36 Δ MH= -0.43, p=0.046

7.2.2.3 Measuring the agreement between SG and TTO methods

The traditional method of examining the agreement between two measurement techniques has been to plot their values on a scatter diagram and assess their correlation and regression relationships.

Figure 7.4 illustrates the cubic and linear regression between the SG and TTO utility values at baseline. However another recommended method [Bland & Altman 1986] to assess the agreement between two measurement techniques is by plotting their difference against the combined mean as illustrated in figure 7.5.

Thus at baseline there is a weak correlation between the U_{sg} and U_{tto} (Spearman's coefficient 0.32, p=0.008) and this is shown in the scatter plot of their difference with combined mean, figure 7.7 suggesting poor agreement between the methods (mean difference is 0.24 with SEM 0.03).

In the CPAP group, when the change in SG and TTO values are plotted there is a stronger correlation (Spearman's coefficient 0.66, p=0.001), the cubic regression coefficient r^2=0.262, p=0.017, and the plot of the differences Δsg and Δtto against their combined means shows that that there is considerable agreement between the methods (adjusted r^2=0.223, p=0.004) as seen in figure 7.6.

The mean of the difference between Δsg and Δtto was 0.07, SEM 0.03. No such agreement is seen in the lifestyle treatment group results.

Figure 7.4: Plot demonstrating the regression curves between baseline SG and TTO utilities

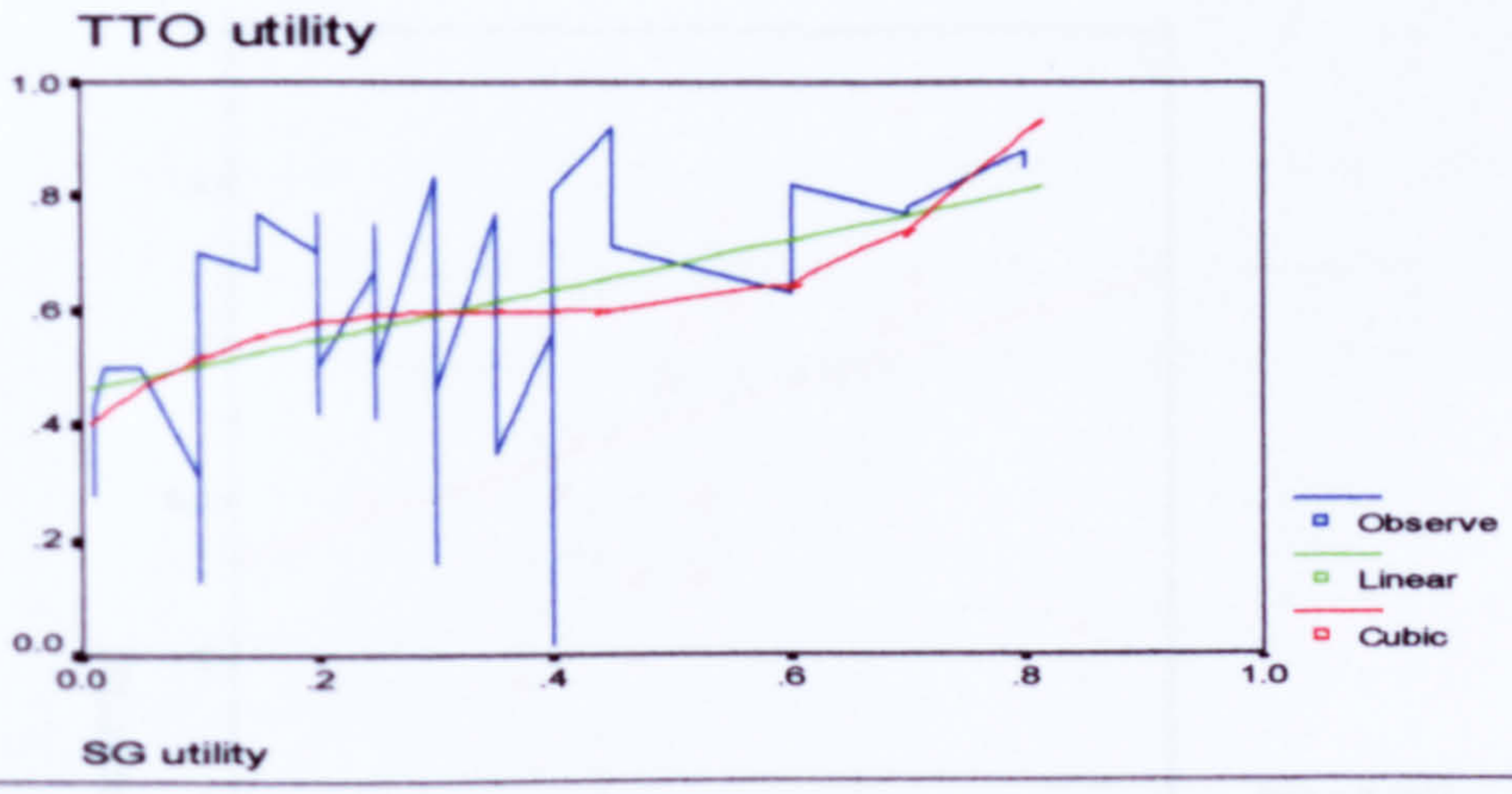


Figure 7.5: showing the relationship between the difference between SG and TTO scores at baseline (sgttodf) against their combined mean (sgttomn).

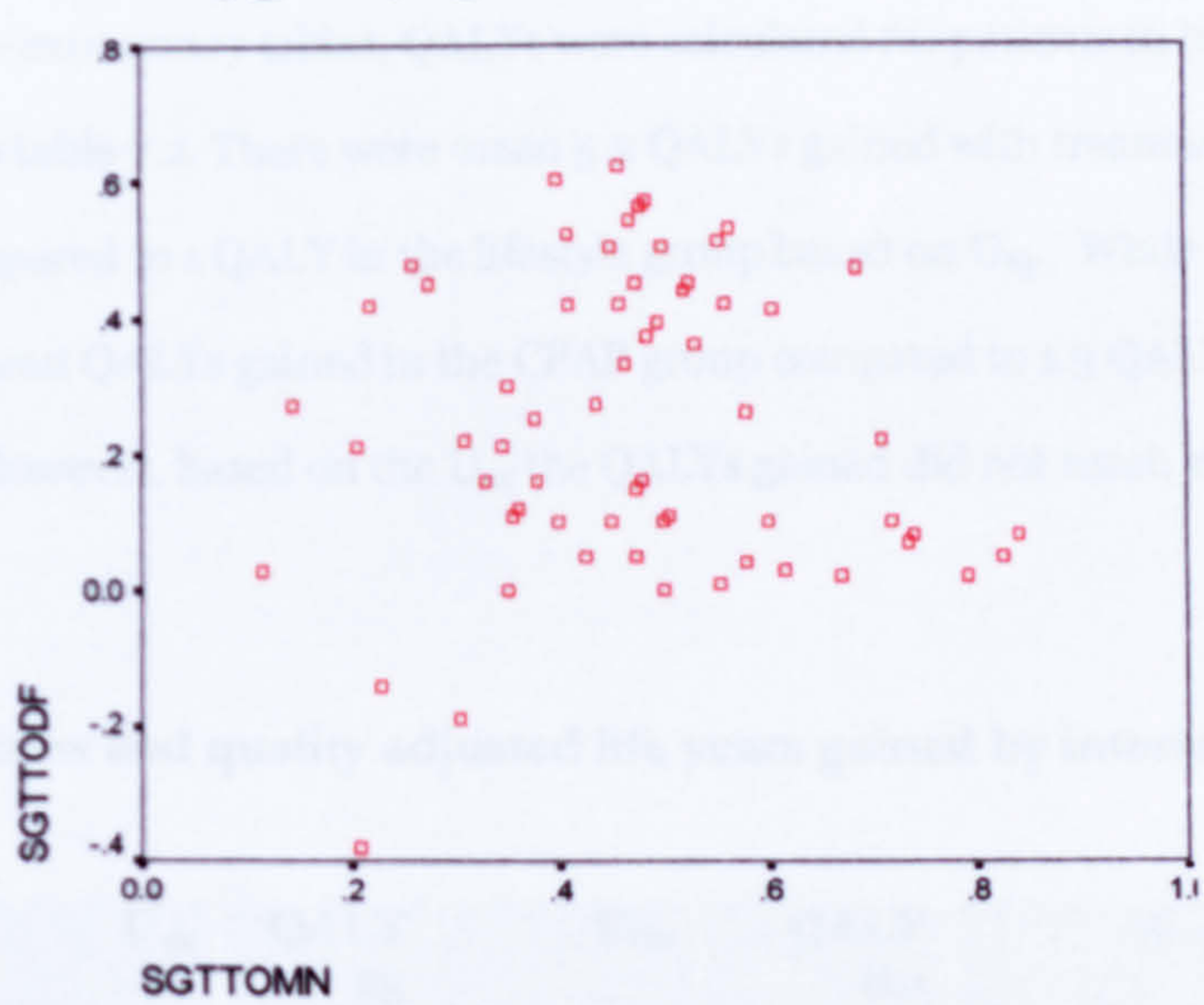
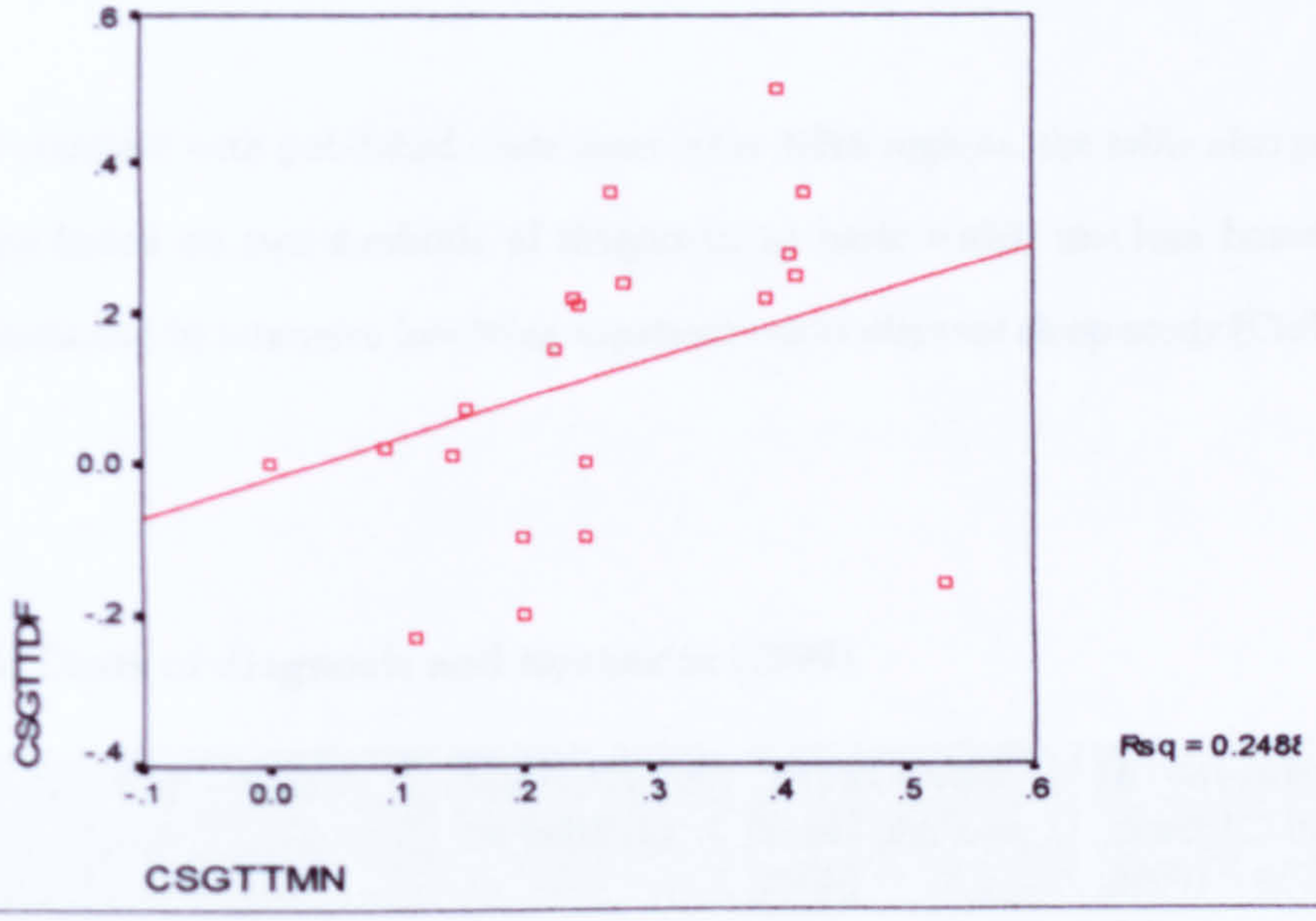


Figure 7.6: illustrating the relationship of the difference between ΔSG and ΔTTO (csgttdf) with CPAP treatment with their combined mean (csgttmn).



7.2.3 COST UTILITY ANALYSIS

Using the UK life-expectancy tables, QALYs were calculated for patients in both groups and are shown in table 7.2. There were mean 5.2 QALYs gained with treatment in the CPAP group compared to 1 QALY in the lifestyle group based on U_{sg}. While based on U_{tto} there were 4.4 mean QALYs gained in the CPAP group compared to 1.3 QALYs in the lifestyle group. However, based on the U_{eq} the QALYs gained did not reach statistical significance.

Table 7.2: Utilities and quality adjusted life years gained by intervention

	U_{sg}	QALY sg	U_{tto}	QALY tto	U_{eq}	QALY eq
CPAP pre	0.31 (0.2)		0.55 (0.2)		0.70 (0.3)	
CPAP post	0.49 (0.3)**	5.2 (7)	0.64 (0.1)**	4.4 (5)	0.76 (0.3)	1.9 (5)
Lifestyle pre	0.38 (0.2)		0.68 (0.2)		0.72 (0.3)	
Lifestyle post	0.43 (0.2)*	1 (3.1)	0.69 (0.1)*	1.3 (2.6)	0.78 (0.1)	1 (4)

* P<0.05, ** P<0.001

The mean costs used for the cost-utility analysis are presented in table 7.3 and include typical costs in the present study population based on Birmingham Heartlands Hospital finance department figures.

In order to compare with published costs from other NHS regions, the table also presents typical costs based on two methods of diagnosis; a) basic which involves home based screening tests and b) intensive involving inpatient multi-channel sleep study [Chilcott, et. al 2000].

Table 7.3: Costs of diagnosis and treatment (1999)

Diagnosis & set up costs	**BHH Costs in GBP(£)**	**Trent basic costs** [Chilcott, 2000]	**Trent intensive costs** [Chilcott, 2000]
Consultation	75	120	120
Baseline lung function studies	125	60	60
Blood tests	90		
Sleep studies*	1000	190	490
CPAP	350	250	250
Mask + tubing	50		
Total	**1690**	**620**	**1000**
Annual costs			
CPAP peripherals + service	150	160	160
Follow up consultation	75	90	90
Total	**225**	**250**	**250**

Trent basic based on oximetry + ESS questionnaire + home CPAP trial + clinic follow up & Trent Intensive includes a limited sleep study + a wakefulness test.

The diagnostic cost for SAHS is the same in each group- £1290. The treatment cost for Group I patient is (CPAP) - £400 and annual maintenance cost of £150+75=£225. For a Group II patient the set-up cost was £75+33x3 = £174.

Assuming Group II patients remained in the lifestyle intervention program, the maintenance cost is estimated to be £75+33 per annum, table 7.3.

Hence the mean(SD) total cost of treating the Group I patients on CPAP for the rest of their lives would be equal to £8920 (435) assuming that the CPAP machine will last a lifetime compared to Group II patients £4243 (228).

7.2.4 Effects of uncertainty

The effect of uncertainty on cost/QALY ratios at 95% confidence intervals for mean values is shown in table 7.4 and 7.5. The results indicate that even at extreme mean values the cost/QALY remains significantly better in CPAP treated patients (as measured using the SG and TTO methods).

In Group II, ratios remain robust using the TTO method only although cost/ QALY is greater than £10000 at the lower 95% level for mean benefit. The utility index measured using the EuroQol does not show sensitivity and reliability at extreme values for mean in either group.

Table 7.4: Sensitivity analysis of benefits & calculated costs per QALY

	Group I QALYs gained	Cost/QALY	Group II QALYs gained	Cost/QALY
U_{tto}				
Lower 95%	2.7	3304	0.4	10608
Mean	4.4	2027	1.3	3264
Upper 95%	6	1487	2.2	1929
U_{sg}				
Lower 95%	2.9	3076	-0.05	
Mean	5.2	1716	1	4243
Upper 95%	7.5	1189	2.1	2021
U_{eq}				
Lower 95%	-0.2		-1.2	
Mean	1.9	4695	1	4243
Upper 95%	3.9	2287	3.1	1369

Using 95% confidence intervals of mean QALY values

Table 7.5: 95% confidence intervals for mean costs and calculated cost/QALY

	Group I Costs	Cost/QALY	Group II Costs	Cost/QALY
U_{tto}				
Lower 95%	8038	1839	3779	2952
Mean	8920	2041	4243	3315
Upper 95%	9803	2243	4707	3677
U_{sg}				
Lower 95%	8038	1550	3779	3678
Mean	8920	1720	4243	4129
Upper 95%	9803	1891	4707	4581
U_{eq}				
Lower 95%	8038	4322	3779	3978
Mean	8920	4796	4243	4466
Upper 95%	9803	5270	4707	4955

7.2.5 Discounting

The effect of variation on cost/QALY is presented in table 7.6 (based on 4, 7 and 10% rates for future benefits and costs). The cost/ QALY ratios remain significant and viable for Group I patients when measured using SG and TTO methods.

The discounted mean costs in group I was: at 0% 8920(435), at 4% 5550(133), at 7% 4415(63) and at 10% 3756(33). While in group II they were: at 0% 4243(228), at 4% 3062(96), at 7% 2628 (62) and at 10% 2364(46).

The effect of discounting on cost/QALY ratios for group II patients were much wider and did not achieve statistical significance.

Table 7.6: Discounted benefits and cost/QALY ratios at 4, 7 & 10% rates

Discount rate	QALYs in Group 1	Cost/QALY in Group 1	QALYs in Group 2	Cost/QALY in Group 2
U_{tto}				
0%	4.4 (1.0)	2027*	1.3 (0.7)	3264
4%	2.5 (0.5)	2313*	0.44 (0.5)	7291
7%	1.8 (0.3)	2597*	0.33 (0.4)	8760
10%	1.4 (0.3)	2889*	0.26 (0.3)	10278
U_{sg}				
0%	5.2(1.2)	1716*	1(0.5)	4243
4%	3.1(0.7)	1790*	0.7(0.3)	6062
7%	2.2(0.5)	2007*	0.6(0.3)	7072
10%	1.7(0.4)	2209*	0.5(0.2)	8487
U_{eq}				
0%	1.86	4796	0.95	4467
4%	0.95	5842	0.6	5103
7%	0.67	6590	0.48	5475
10%	0.51	7365	0.39	6062

The independent samples Student's t test * $p<0.05$ Group I significantly different to Group II.

Assuming that CPAP machines will need replacing due to usage related deterioration or need replacement due to advancing technology in 5, 10 or 15 years and the cost of CPAP rising along with inflation, further calculations are presented in table 7.7 showing the increasing cost of CPAP replacement on cost/QALY ratios.

As shown in table 7.7, the cost/QALY ratios remain viable and well below the UK NICE recommended threshold of 20,000 GBP/QALY [NICE 2004].

Table 7.7: Effect of incremental cost of replacing CPAP equipment at 5y, 5+10y and 5+10+15y on cost/QALY

Discount rate	Present value for 5y replacement		Present value for 5+ 10 y replacement		Present value for 5+10+15y replacement	
U_{tto}		Cost/QALY		Cost/QALY		Cost/QALY
4%	381	2471	745	2623	1091	2767
7%	331	2792	604	2952	830	3085
10%	288	2889	496	3037	703	3185
U_{sg}						
4%	381	1945	745	2064	1091	2177
7%	331	2138	604	2261	830	2363
10%	288	2338	496	2458	703	2578

Cost of machine present £400, at 5 years £464, at 10 years £538 and at 15 years £623 incremental values of machines based on an inflation rate of 3%

Table 7.8: Comparing cost per QALY among different treatment scenarios

	Cost per QALY (1990)
General practitioner advice to stop smoking	220
Antihypertensive therapy to prevent stroke (45-65 years)	940
Pacemaker implantation	1100
Hip replacement	1180
Cholesterol testing and treatment	1480
CPAP therapy for SAHS	**1716-2027**
CABG (L main disease + severe angina)	2090
Lifestyle intervention for SAHS	**3264-4243**
Kidney transplantation	4710
Breast cancer screening	5780
Heart transplantation	7840
CABG (One vessel + moderate angina	18830
Continuous ambulatory peritoneal dialysis	19870
Hospital haemodialysis	21970

Adapted from Maynard [Hill *et al.* 1996]

7.3 DISCUSSION

7.3.1 Overview

To make the best use of scarce health care resources the diffusion and adoption of new technologies should be linked to the evidence of their clinical and cost-effectiveness [O'Callaghan] [Harrison *et al.* 1997]. Hence health technology appraisal involves an economic evaluation exercise. Although sleep related disorders are known to cause adverse effects to the individual their impact then extends to the society in general. However, the contribution from individual disease processes, i.e. the effect of SAHS on RTAs is difficult to measure in an RCT. Thus when the impact of treatment on SAHS patients is measured in clinical or HRQL terms, such an analysis tends to underestimate the benefits on society.

However in terms of health care provision (involving resources for providing adequate diagnostic and treatment facilities) the benefits need to be measured on individual terms. With the assumptions that firstly, any patient specific tools are likely to underestimate the societal effects of the SAHS; and secondly, that any health benefits provided for by CPAP or lifestyle intervention that is measured using patient specific tools is going to underestimate the societal benefits; the cost/ QALY analysis provided through this study would be over-estimating the costs and hence may show the health care intervention in less than favourable light.

The second issue in HTA of SAHS involves the choice of an outcome measure for economic evaluation. This should not only show sensitivity to the health status effects of the disease process and reliability but also be generisable to other diseases and/ or patient groups. This comparability would allow use in health policy and resource allocation among competing technologies. The results presented and discussed in previous chapters (chapters V & VI) demonstrate the difficulty in using either physiological markers or HRQL measures for such outcome analysis.

It is possible to use an alternative patient preference approach to measure the impact of health care intervention on health status. The data presented in this chapter compares the two most commonly used tools with an indirect measure (EuroQol). Both the standard gamble (which incorporates the concept of risk) and time-trade off methods demonstrate

sensitivity to change and reliability in SAHS patients, unlike the EuroQol health index. Thus QALYs generated by these methods were used to provide the 'effectiveness' / benefit side of the cost/QALY ratio.

Even with a potential negative bias because of the study design not incorporating the impact of societal benefit of intervention, the data from the RCT demonstrates a cost/ QALY ratio for CPAP treatment of SAHS patients which is well within the accepted norms for an economically acceptable ratio below 20,000 GBP [Birch and Gafni 2002].

7.3.2 Methodological issues

The main methodological issue with an HTA involves the perspective chosen for the economic evaluation. Sleep disorders cost the US economy almost 40 billion USD in 1988 for RTAs, 720 billion USD for public transportation accidents and 15 billion USD due to work-related accidents [Leger 1994]. Hence the economic benefit to society of treating patients with sleep related disorders is also potentially very large. On the other hand, it is estimated that diagnosis and treatment of sleep disorders in the USA cost an estimated 270 billion USD in 1990. Although, these figures incorporate the impact of all sleep related disorders, with a prevalence of SAHS second only to that of insomnia, it can be presumed that SAHS contributes a major portion to the above costs. No such economic data is currently available for the UK.

Compared to the potentially large benefit to society, that may be produced by allocating health resources to the diagnosis and treatment of SAHS patients, the restriction of the cost-effectiveness appraisal to the health service costs only, may produce a negative bias against the intervention.

However, SAHS patients seek medical advice for the relief of individual symptoms of EDS and clinicians provide treatment, mainly for symptom relief. Thus in health care provision terms, the control of a patient's individual symptoms/ HRQL/ health status assumes prime importance and thus may be chosen as an outcome measure for HTA.

The main factors driving the diffusion and adoption of this new technology is likely to be based on individual patient and clinician decisions for the relief of symptoms. Thus

ignoring the societal perspective for both costs and benefits of treatment of SAHS, may be appropriate in conducting an HTA for use in health service policy making.

7.3.3 Utility measurement

In SAHS patient group outcome measures such as survival, mortality, change in physiological measure of disease severity show uncertainty in measuring the impact of treatment. HRQL measures also demonstrate a wide variation in sub-dimensions between tools and magnitude of responses, thus posing inherent difficulties in comparison with competing technologies. While utility measurement, shows the distinct advantage of capturing the net impact of health care intervention in terms of the patient preferences.

Both the traditional measurement of utility (based on the von Neumann & Morgenstern utility theory) [von Neumann and Morgenstern 1944] and the time-trade off method show significantly lower health status at baseline in the study patients. The U_{sg} which involves an element of risk with a prospect of the respondent's health state worsening or even death occurring if a gamble fails produces lower results compared to TTO. This may be a reflection of either the severe degree of health status deterioration in these patients or the greater promise of a return to normality which leads to risk-taking behaviour.

Firstly, in this RCT, SAHS patients were asked to consider failure of treatment to equate to a health state equivalent to death. Under risk-neutrality (which is a requirement of the utility theory) the utility of a gamble is equivalent to its expected value and the marginal utility of living in a given unit of time is the same regardless of when it occurs. As most patients are either risk-seeking or risk-averse this influences trade-offs between short term gains and long term survival and their interpretation. Thus the proportional time-trade off will under or over estimate the disutility of an inferior health state, depending on whether patients are either risk-seeking or risk-averse [Cher *et al.* 1997]. Lower U_{sg} results compared to U_{tto} would indicate that U_{tto} tends to under-estimate the disutility of health state demonstrating a net risk-seeking behaviour in this group of patients.

Secondly, it is possible that this risk-seeking behaviour in the study patients with SAHS may be due to their prior knowledge that treatment failure may not lead to death/ equivalent state, hence creating a bias towards a risk-seeking behaviour more acceptable.

Others have reported higher scores for U_{sg} compared to U_{tto} in patients with risk- adverse behaviour [Stiggelbout, *et al.* 1994].

7.3.4 Validity

Similar to ESS and HRQL scores presented in chapter VI, the U_{sg} does not show any relationship with any of the physiological parameters at baseline and is seen to be independent of anthropometric variables. Unlike the U_{tto} which demonstrates a significant relationship both to AHI and sleep latency. This suggests criterion validity for the TTO method of assessing health status.

Reassuringly, the outcome measures are not influenced by potentially confounding anthropometric variables except U_{tto} (which shows a relationship with age, demonstrating a disproportionately higher value with increasing age). Older patients when considering a diminished life expectancy as a trade off for health state improvement; tend to be biased towards preservation of the quantity of life, thus yielding inappropriately higher values for the health state. This discrepancy between the U_{sg} and U_{tto} is shown to be best related by a cubic regression model in this study and explained by a power relationship. Other researchers have used different survival functions to adjust the TTO values towards SG values [Martin *et al.*2000].

Given that none of the symptoms, HRQL effects and health state values for SAHS can be sufficiently explained by the physiological PSG parameters, it may be argued that there are yet unknown complex relationship between the disease process and its health effects.

7.3.5 Impact of treatment

However both these utility measures show discriminant validity after the treatment phase in measuring the impact of change. The change in U_{sg} and U_{tto} are shown to be significantly related to the baseline anthropometric, PSG, ESS and baseline HRQL scores. Thus the greater the severity of SAHS (PSG variables) and BMI the greater is the change seen with treatment.

With CPAP treatment, both U_{tto} and U_{sg} show a significant improvement in health state. In terms of effect sizes the change is larger in U_{sg} (U_{sg} effect size = 0.95, $p<0.001$ vs. U_{tto} effect size= 0.62, $p<0.001$). This would again be compatible with the risk-seeking

behaviour seen in this group of patients. The change in U_{tto} and U_{sg} were also shown to be closely related in CPAP patients suggesting that both were measuring the same change in health state with treatment.

On the contrary, among patients on lifestyle strategy there was a modest change seen after completion of the trial. This could be a result of weight change and sleep hygiene modification strategies which were seen in the patient self-reported VAS scores for sleep quality and daytime sleepiness. Interestingly the change in U_{tto} and Usg scores in this group is shown to be related negatively to the psychiatric morbidity (higher scores on GHQ28, HADS and MH scales of SF36). This in turn suggests a lack of motivation and resistance to lifestyle changes in these patients with greater psychiatric morbidity, making it more likely that such strategies will fail.

7.3.6 EuroQol utility

The U_{eq} is derived indirectly from a rating scale and hence has its roots in the basic five dimensions of mobility, self-care, usual activities, pain and anxiety/ depression. If SAHS does not significantly impact on these particular dimensions as has been seen in chapter VI with EuroQol scores, then it is unlikely that the derived utility will have discriminant properties. The results show a much higher baseline U_{eq} score compared to the U_{tto} and U_{sg}, which then changes minimally (not reaching statistical significance) in both the groups. Thus the EuroQol utility does not discriminate between the treatment effects seen with almost all other instruments in this RCT.

The change seen in EuroQol index scores in liver transplant patients at 3 months were statistically insignificant when patients who died were removed from the analysis, suggesting a reduced sensitivity compared with most dimensions of the SF36 [Ratcliffe *et al.* 2002]. The EuroQol index also reportedly failed to discriminate between the treatment effects in patients with benign hypertrophy of the prostate undergoing trans-urethral resection compared to SF36 which demonstrated greater sensitivity [Jenkinson *et al.* 1997a]. The magnitude of change measured by the EuroQol is also reported to be

small, suggesting that larger sample sizes may be necessary to demonstrate significant responses [Roset *et al.* 1999].

In other patient groups, where physical functioning (mobility/ self-care or pain) is reported to be important, the EuroQol index has been shown to be both sensitive to HRQL decline and discriminatory to change on appropriate intervention; for example for patients on a waiting list for lung transplantation (baseline U_{eq} of 0.31 in waiting list patients compared to 0.61 for single lung, 0.82 for double lung and 0.87 for heart-lung transplantation recipients) [Anyanwu *et al.* 2001], in patients with intermittent claudication [Bosch *et al.* 1999], inflammatory bowel disease [Konig *et al.*2002], fracture neck of femur [Tidermark *et al.* 2002], advanced treatment for breast cancer [Conner-Spady *et al.* 2001] and rheumatic diseases [Hurst *et al.* 1997] also showing good test-retest reliability [van Agt *et al.* 1994].

Valuation studies for the EuroQol have demonstrated that ability to perform usual activities (especially leisure activities) has a large contribution to the valuation in societal preferences [Taylor *et al.* 2001]. Hence patients with chronic fatigue syndrome [Myers and Wilks 1999] and fibromyalgia may be over-estimating their health disutility, while the index is less discriminant to patients with moderate osteoarthritis [Fransen *et al.* 1999].

As in patients with stroke, where there was little correlation between the anxiety/ depression rating of EuroQol compared to SF36 [Dorman *et al.* 1999] [Dorman *et al.*1998], the predominant effect of SAHS is seen in the mental health related quality of life; hence among SAHS patients EuroQol may be less sensitive to change. It is also possible that the relatively small study size in this RCT may be a reason for not observing significant change even in the CPAP treated patients. As other studies have shown that patients tend to derive higher scores for their health state valuations directly using the EuroQol then when derived via societal preferences [Polsky *et al.* 2001] [Selai *et al.* 1995].

7.3.7 Costs

The costs used in this analysis were based on the 'typical cost' of each investigation or intervention as calculated by the finance department of the hospital, and not a summation of the actual cost involved in treating each individual participant. The advantage of such

typical costs are the inclusion of a proportion of the overheads (building, maintenance, labour, intellectual costs) which are then standardised for cost generating activity per patient episode. For the size of the hospital and the level of care provided such costs are most likely to be similar in other hospitals within the NHS structure and hence are portable and comparable across NHS trusts [Chilcott.J *et al.*2000]. As all participants in the trial underwent PSG a practice which is not usually followed for standard clinical practice the cost generated per patient was much higher than would be the case in real life situations both at BHH sleep clinic and in other similar hospitals. Hence cost data published in the report from three NHS trusts involving two different levels of investigation [Chilcott.J *et al.*2000] (BHH £1690; Trent basic £620; Trent intensive £1000) were incorporated in the cost/ utility analysis. The additional cost of replacement CPAP machines at 5, 10 and 15 years was incorporated within the cost/utility analysis. In normal practice the CPAP machines are designed to last at least 10-15 years with minimum maintenance, hence such additional capital cost for equipment is likely to increase the cost/ QALY ratio.

However, even after including the above additional potential costs, the cost/QALY ratio for CPAP treatment in patients with moderate to severe SAHS remains well within the acceptable norm of 20000 GBP/QALY in the UK [NICE 2004]. The cost/QALY ratios also remain viable and robust after testing for uncertainty and after discounting of both benefits and costs.

Both the SG and TTO methods produced results which were comparable unlike the cost/QALY generated by the EuroQol method. QALYs generated by lifestyle intervention in Group II were very small and although the costs were still within recommended thresholds [Birch and Gafni 2002].

Treatment of obesity has been rarely shown to have lasting benefits on morbidity and mortality or to improve the SAHS symptoms [Shneerson and Wright 2001] [Sampol *et al.*1998] in the absence of CPAP [Barvaux *et al.*2000], although there is a reduction in the prevalence of hypertension [Kansanen *et al.* 1998], autonomic dysfunction and better control of diabetes [Anon.1998]. Weight loss on its own has been shown to improve health state by 0.017/one unit change in BMI [Hakim *et al.* 2002]. The addition of weight reducing agents with a low calorie diet may have a better probability of success but when

three large multi-centre trials were reviewed, the cost-utility ratio for weight loss even with the help of pharmacological agents (i.e. Orlistat) was found to range between 14,000 to 132,000 GBP/QALY [Foxcroft and Milne 2000] and hence remains largely economically unviable.

7.4 CONCLUSIONS

The results from the cost-utility analysis show that treatment of SAHS patients (moderate to severe) with CPAP even for a short period of time is economically viable and that its impact may be reliably measured using the QALY approach generated by the traditional methods of SG and TTO. The indirect derivation by EuroQol questionnaire has not been shown to be sensitive to the changes seen in SAHS patients and hence cannot be reliably used for measuring benefit or in economic evaluation. When QALYs are used in comparison of competing technologies one has to take into account the method of QALY generation and whether this method demonstrates validity, sensitivity and reliability as in the case of SG and TTO in this study.

Although obesity remains a major influence on the disability suffered by SAHS patients, current conservative strategies remain largely unsuccessful in achieving a sufficiently significant weight reduction to impact on the SAHS severity or HRQL disability. Where weight loss has been achieved, the net benefit in health status terms remains minimal. Although the costs involved in providing lifestyle intervention are well within the NICE recommended thresholds, larger studies are needed with longer term follow and with the addition of weight reducing pharmacological adjuncts. The addition of pharmacological agents to aid weight reduction are likely to increase the cost/QALY ratios further and make the option even less attractive to health planners [Foxcroft and Milne 2000]. Thus CPAP on its own remains a largely cost effective option for the treatment of these patients.

CHAPTER VIII

DIFFUSION OF INNOVATION

8.1 DIFFUSION OF CPAP- AN OVERVIEW

CPAP therapy was first introduced as an innovation in early 1980s in Australia [Sullivan *et al.*1981]. It was an innovation created by an academic team led by Professor Colin Sullivan, mainly to satisfy a need for a new modality of treatment, for an increasingly recognised condition, which was less invasive, caused less morbidity, was reversible and would in turn hold the potential for wide applicability.

Compared to the surgical approaches of laser UVPPP or facio-mandibular mobilisation CPAP provided many distinct advantages; namely a simple underlying principle of stenting the airway with positive airway pressure, a simple construction with available motors/ air compressors, tubing and moulded plastic masks, trial ability without any irreversible adverse effects and freedom from pain, bleeding and the many complications of surgery/ anaesthesia.

As it was born within an academic hospital, with direct trials on patients providing the initial evidence of its efficacy, it found easy acceptance within the user/ adopter community in Australia without the need for extensive marketing. In 1986, Professor Colin Sullivan and the Baxter Centre for Medical Research started work on commercial production of the CPAP device which was launched in 1988. A year later the management headed by Peter Farrell bought out CPAP from the parent company and formed the ResMed Inc aided by Australian government grants of 200,000 (Australian Dollar= AUSD).

The potential for the commercial utilisation was so great in the target population which included 2-4% or more of the adult population that it created the impetus for the birth of a new industry arm and *ResMed Inc* grew to have 74 branches worldwide with a net revenue of 50 million USD in 1997/98 recording a 10 year annualised growth rate of 25% [ResMed Inc, 2003]. Although a global company, ResMed Inc has 83% of its business in 3 countries (50% in USA, 22% in Germany & 11% in France). It has been listed as the Fortune Magazine's top 100 hot growth companies from 1999-2001 [irasia.com 2002].

At the same time as CPAP machines became commercially available outside the tertiary academic institutes; by 1990 sleep centres in the UK had grown in number and saw a rise in the referrals from primary care physicians for the treatment of SAHS. There was an enhanced interest in the treatment of patients with SAHS, as the CPAP treatment modality allowed professionals, other than surgeons, like Respiratory Physicians the ability to treat this condition, previously beyond their reach. The Royal College of Physicians estimated that there was a large deficit in the availability of diagnostic and treatment centres in the UK [Stradling 1993].

There have been considerable improvements (re-invention) in technology in the last decade with the CPAP machines becoming smaller, lighter and quieter. The masks which were initially moulded to individual patients were then manufactured in standard sizes and facial shapes. As the seal of the mask to the face was a serious factor for both patient comfort and efficient delivery of the positive pressure, the traditional mask, went through rapid cycles of change. They gradually became lighter, more comfortable and versatile leading to improvement in the quality of sleep on CPAP machines. The addition of heated humidification has also improved patient acceptance and comfort [Neill *et al.* 2003].

In the last five years there have been very few changes in the CPAP machine technology except for the introduction of bi-level machines and automatic titrating devices for general use. There exists a physiological variability in the upper airway resistance within the same night and over a period of time in patients depending on stage of sleep, external factors such as alcohol consumption or exhaustion or internal variation in body weight / collar size.

Automatic titrating devices were conceptually attractive but have yet to demonstrate sufficient improvement in patient comfort or compliance [Teschler *et al.* 2000] to warrant the extra expenditure over and above the fixed pressure type CPAP machines in widespread use [Boudewyns *et al.* 1999]. These auto-CPAP machines have failed the request for classification as a separate device priced between CPAP and the more expensive Bi-level ventilators in the Medicare reimbursement classification [Sullivan 2004]. This may be a factor in slowing down of the adoption of this variation of CPAP in the USA which remains the largest market for these devices.

Interestingly there are significant differences in the annual growth of CPAP market in the different countries; 26% in the USA, 15% in Germany-France, 9% in Spain and <5% in the UK and this position has remained unchanged since 1995/96 [Newby 2002].

It has been reported that the facilities for the investigation and treatment of patients with SAHS in the UK are subject to severe financial constraints and the availability of CPAP treatment lags markedly behind that in other countries [Gibson *et al.* 1998]. In 1995/96 an estimated 2310 CPAP units were provided for the treatment of SAHS patients and 7071 CPAP machines were in use out of an estimated 180,000 needing CPAP therapy [Gibson *et al.*1998]. A recent yet unpublished survey suggested that 101 sleep centres in the UK were prescribing an average 6000 CPAP machines with a total of 37000 patients established on CPAP machines. The comparative figures for year 2001 were 30,000 units for Germany, 15000 units for France and 8000 units for Spain [Newby 2002].

This variation in CPAP provision among countries in Western Europe and USA is considered to be due to a variety of vital differences between the health care structures and funding. Although there is no published evidence on the diffusion of CPAP, empirical data would suggest that are a variety of potential influences.

In the USA there are active public awareness programs such as the National Sleep Awareness Week [Anon.2004a] & Sleep in America Polls. These are initiated by both government agencies (National Sleep Disorders Centre) and non-governmental bodies (National Sleep Foundation) [Anon.2004b]. There appears to be a comparative lack of awareness among the general public in the UK, on the symptoms of sleep deprivation due to SAHS. This is usually manifest by the average time between a patient becoming aware of his daytime hyper somnolence or being told by a partner about breathing pauses during sleep to reporting to his/ her primary physician for help being 2 to 10 years.

Public awareness is dependant on media interest which has been variable and usually linked to sleep related accidents like after the events leading to the loss of life associated

with the Selby train crash in 2001 [Anon.2001]. There has been some increase in the level of local public awareness and knowledge with the activities of the patient self-help groups, usually inspired or supported by larger sleep disorder centres (e.g. Sleep Apnoea Trust) [Anon.1994].

Since the popularity and availability of the internet among the general population there has been an increase in public awareness from medical/ health orientated websites [Bernhardt *et al.* 2004;Siow *et al.* 2003]. However there are a few professionally supported and run web sources of information on health among many more either commercially orientated or not run by professionals [Childs 2004]. However, this new technology also hides several shortcomings, such as: (i) uneven quality of medical information available on the internet; (ii) difficulties in finding, understanding and using this information; (iii) lack of access for the unconnected population; and (iv) the potential for harm and risks of over-consumption [Benigeri *et al.* 2003].

When a patient becomes aware of sleep related breathing disorder or seeks help for daytime somnolence his / her contact is with his primary care physician. In the UK, there is a variable degree of knowledge among primary care physicians in sleep disorders and hence many patients are known to have waited for over two years before being referred onto Sleep Disorder centres. Again there is a geographical variability among primary care physicians depending on public awareness and the proximity to sleep diagnostic centres. There are an estimated 25000 patients referred to 112 sleep centres in the UK annually with 73% being referred with snoring and / SAHS [Gibson *et al.* 1998].

In secondary care, there is wide variation in the level of personal interest among Respiratory Physicians and Otolaryngologists who have traditionally been referred patients with snoring and sleep disordered breathing. Hence the facilities for diagnosis and treatment for sleep related breathing disorders have varied across the country dependant on local champions, expertise and funding mechanisms and priorities. The absence of a UK national framework is perhaps further compounded by a lack of formal appraisals from bodies such as NICE and may have contributed to heterogeneity in availability of facilities for diagnosis and treatment.

Although, there had been many studies showing that CPAP was efficient in neutralising the nocturnal observed apnoeas and hypopnoeas, there were few well designed RCTs aiming to tease out the influence of confounding co-morbidities and obesity. In 1997 a review into the health effects of sleep related breathing disorders and the effectiveness of treatment undertaken by the Nuffield Institute in Leeds in association with the University of York reported that there was little evidence to support the prescription of CPAP except in the case of improving neuro-cognitive function and EDS. This perhaps led to a change in the funding situation for CPAP machines in various parts of the UK leading to longer waiting times and fewer patients receiving treatment for SAHS [Wright *et al.* 1997a] [Stradling 1997].

In a Royal College of Physicians survey in 1998, 34 out of 43 respondents from Sleep diagnostic and treatment units in the UK reported serious financial hurdles in funding the service, with 6 physicians reporting complete rejection. Another 14/43 physicians reported imposition of limits on CPAP provision, which were below expected numbers [Gibson *et al.*1998].

Only an estimated 10% of the diagnostic tests for SAHS are paid for privately by individuals in the UK, with costs ranging from £600 to £1000. The NHS reference cost for elective overnight studies ranges from £204 to £2818 with a mean of £532 [Anon.2002a]. Unlike in the UK, in North America, funding of investigation and treatment of SAHS is predominantly reimbursed by health insurance contributions.
Industry estimation of the worldwide non-surgical SAHS treatment market in 2000 was 315 million USD (210 million GBP) with Respironics holding 54%, ResMed 22%, Nellcor Puritan Bennett 16%, and others 8% market share. This was projected to rise to 560 million USD (373 million GBP) by end of 2001 [Mack 1999].

The probable causes of the relative lagging behind of the UK market compared to France, Germany and the US markets in CPAP use other than the public and professional awareness gap described above are:

1. Lack of standardised facilities and national guidelines/ practice framework for the diagnosis of SAHS in the secondary care level [Gibson *et al.* 1998] [Gibson *et al.* 1997].
2. Patients being variably referred to Otolaryngologists, Respiratory physicians, Neurologists or Metabolic physicians from primary care, possibly leading to delay in diagnosis and treatment. Even in conditions where national and international guidelines have been widely disseminated as in the case of Asthma, the management of patients has been shown to vary widely [Wright *et al.* 2003].
3. Restrictive governmental funding perhaps as SAHS is not perceived to be a life-threatening or debilitating condition like heart disease, diabetes mellitus, breast and lung cancer [Gibson *et al.* 1998].
4. Relative absence of consensus guidelines (till the recent publication of the SIGN document [Scottish Intercollegiate Guidelines Network 2003]), in the diagnosis and management of SAHS.
5. Absence of accredited courses for training of technicians in Sleep investigation and reporting in the UK hence restricting capacity even of tertiary sleep centres to cope with patient/ referral numbers [Gibson *et al.*1998].
6. Lack of concerted lobbying capability among medical professionals, scientific organizations and patient self-help groups unlike other chronic diseases such as heart disease (British Heart Foundation)[Shillingford 1984] and asthma (Australian National Asthma Campaign) [Comino *et al.* 1997].
7. Lack of popular and powerful national patient self-help groups unlike the National Sleep Foundation [Anon.2004b] in the USA.
8. Classifying CPAP as equipment for loan to patients, thereby restricting the budget within restrictive business plans unlike drugs or masks which are considered 'disposable' although relative costs are comparable (£250-300 for a CPAP

machine with a life of 10-15 years compared to £85 x 2 per annum for disposable masks).

The principles of the diffusion of innovation theory provide a framework for an investigation of the process of diffusion of CPAP within the highly regulated and managed NHS health care sector. The Respiratory Physicians in DGHs who are likely to be providers of sleep diagnostic and treatment facilities and considered to be disseminators of specialist knowledge about this treatment modality are likely to be early adopters or early majority (in their adoption behaviour) They may provide insights into the early diffusion stages, innovativeness, innovation –decision formation, innovation period. Some of them are likely to act as change agents catalysing diffusion/ adoption behaviour through their links with academicians, social networks both with innovators and early majority and leading by example.

While the primary care physicians, who are likely to be in the late majority, are dependant on diffusion reaching critical mass, dependant on local availability of specialist knowledge and facilities, inter-personal networks for the diffusion of information to assist them in their adoption decision for appropriate referral.

Therefore the aim of the diffusion of CPAP research was to investigate the influences among the whole spectrum of early adopters to late majority i.e. secondary care specialist centres to the general practitioner who remain at the patient-health care interface. This would help understand the positive and negative influences and the rate of diffusion of innovation within the NHS health care sector.

8.2 PRIMARY CARE SURVEY

8.2.1 Aim

This survey was designed to collect and assess data on the following;

1. Demographics of GPs and their practices.
2. To assess the Primary care physicians direct experience of dealing with SAHS patients.
3. To assess their opinion on the relative (clinical) effectiveness of three principal therapies available for the treatment of SAHS.
4. To assess the characteristics of CPAP as a healthcare innovation.
5. To identify the knowledge of primary care physicians on the existent pathways for knowledge diffusion on CPAP or a similar innovation in the NHS infrastructure.
6. To assess the primary care physician's opinion on the future of therapy for SAHS patients.

8.2.2 Survey design & protocol

8.2.3 Pilot study

A questionnaire was designed with 4 items on demographics & practice parameters (Q1 age group of respondents, Q2 sex, Q3 type of practice- single/ multiple, teaching/ non-teaching & urban/ rural). Question 5 & 6 established whether the respondents had patients with SAHS in their practice and for how long they had referred patients with suspected SAHS, in order to establish respondents' experience with SAHS patients.

Questions 7-11 were designed to determine respondent's opinions regarding the effectiveness of the therapy options for SAHS patients (Q7), acceptability to the patient (Q8), ease of use of CPAP (Q10) and characteristics of CPAP as an innovation (Q9 & 11).

Question 12 was designed to establish the pathways of knowledge diffusion bearing the most influence on the respondent's opinion regarding treatment of patients with SAHS and the final question 13 asked the respondent's view on the likely future of treatments for SAHS.

The pilot questionnaire survey was conducted among 100 randomly selected primary care practices in London and Hertfordshire. There was a standard covering letter explaining

the purpose of the survey and reply paid envelopes were provided for returning the questionnaires. Respondents were asked to comment on the questionnaire and any other free text comments they wished to offer on the subject. No incentives were offered for completing the survey and no follow up questionnaires were sent to non-responders, as there was no way of identifying non-responders. There was a 35% response from this pilot survey and the final questionnaire was edited in the light of the respondent comments.

A major change occurring at this time in UK primary care was the introduction of Primary care Trusts (PCTs) with centralisation of the purchase decisions on innovations and the pooling of individual specialist interests/ skills into a unitary authority. Hence the individual respondents' demographic characteristics, experience with SAHS and practice parameters were becoming less relevant within the larger decision-making processes introduced within each PCT.

8.2.4 Primary care survey

The re-designed questionnaire version II was targeted to the PCTs and had the following structure;

Q1&2: asked whether there were SAHS patients in the practice and how long patients were being referred with suspected SAHS to specialist centres, to establish the depth or duration of experience

Q3-6: investigated the respondent's opinion on the primary indication for offering treatment to patients with SAHS, the clinical effectiveness of CPAP in the context of the available treatment options and characteristics of CPAP as an innovation.

Q7-9: determined current pathways of knowledge diffusion, self-assessment of innovativeness and views on existing technology diffusion process.

Q10: asked the respondent their opinion regarding the factors influencing the diffusion and adoption of CPAP

The number of items was reduced from 13 in the pilot questionnaire to 10 in order to fit within the 2 A4 page model and improve response rate. The basic framed design with the same colour coding was kept as the pilot questionnaire.

The questions regarding the demographics of the respondent and the practice parameters were removed as the target for this survey was the newly formed PCT. The questionnaire had the name of the PCT integrated in the heading hence identification of responders/ non-responders was ensured, although the individual respondent on behalf of the PCT would remain anonymous to the investigator, thus ensuring confidentiality.

The questionnaires were mailed to 300 PCTs, addressed to the Chief Executive, with a personal covering letter requesting a response from physicians with special interest in SAHS or with responsibility for purchasing services for new innovations. No incentives were offered and the reply paid (stamped) envelopes was addressed to the investigator (IC) at the University of Warwick. A second mailing was undertaken 6 weeks later to non-responders with a covering letter.

8.2.5 Data analysis

Data from completed questionnaires was entered into a spreadsheet (SPSS) which allowed grouping and calculation of frequencies and proportions.

8.3 SECONDARY / TERTIARY CARE SURVEY

8.3.1 Introduction

A questionnaire survey was conducted among 261 Respiratory Consultants in the UK based on the Directory of Respiratory Services published in 2001. Each secondary/ tertiary care hospital received one questionnaire addressed to the physician with special interest in Sleep/ ventilation services. In secondary care centres where special interest in Sleep services was not listed in the directory, the questionnaire was addressed to the physician listed first, with a covering letter requesting that they forwarded the questionnaire to colleagues who may have a special interest.

No incentives were offered and reply paid envelopes were provided for returning the questionnaire to investigator (IC) at University of Warwick. A follow up questionnaire was sent after 6 weeks to non-responders.

8.3.2 Questionnaire aims

1. To assess the respondent's personal experience with SAHS patient management and the hospital's availability of facilities for the diagnosis & treatment of SAHS patients.
2. To assess the respondent's opinion on the comparative 'clinical' effectiveness of the four therapeutic options available for SAHS patients.
3. To assess the respondent's opinion on the characteristics of CPAP as a healthcare innovation.
4. To assess the respondent's experience with the pathways of knowledge diffusion, innovativeness and social networks within the NHS infrastructure.
5. To assess the respondent's opinion on the factors influencing the diffusion and adoption of CPAP in their own hospitals and healthcare regions.

8.3.3 Questionnaire content & design

The questionnaire was designed in monochrome with frames and boxes for ticking responses with 16 questions. The questions were in 3 groups;

1. About the hospital/ firm section contained 7 questions on type of hospital, facilities for diagnosis and treatment of sleep breathing disorders, SAHS treatment facilities available, patient load and CPAP provision and estimated expansion in service / patient numbers.

2. The next section comprising Q8-11, explored the respondents opinion on SAHS treatment, efficacy & clinical effectiveness and characteristics of CPAP as an innovation.

3. The final section comprising Q12-15, explored the knowledge diffusion pathways, innovativeness, existence of social networks and the current state of play with adoption of CPAP within their institutions. The final question (Q16) asked the respondent on their view about the future of CPAP in the treatment of SAHS patients.

8.3.4 Data analysis

Completed and returned questionnaire data was entered into an SPSS datasheet and frequencies calculated along with qualitative assessment of the implication of responses.

8.4 Industry and patient self-help group surveys

Attempts to contact the representatives of the CPAP industry and patient self-help group met with little success both by letter and telephonic contact. The only response was from the General Manager of one of the CPAP manufacturing companies who granted a comprehensive interview on the industry perceptions and priorities in this sector relevant to the UK.

8.4 RESULTS

8.4.1 Primary care trust survey

8.4.1.1 Characteristics of the Respondents

There were 136 responses (45%) received from mailings to 300 Chief Executives of PCTs in England & Wales. Table 8.1 shows the age-group distribution of the respondents. Majority of respondents were male with a 2.7:1 male to female ratio.

Table 8.1: Age group of respondents

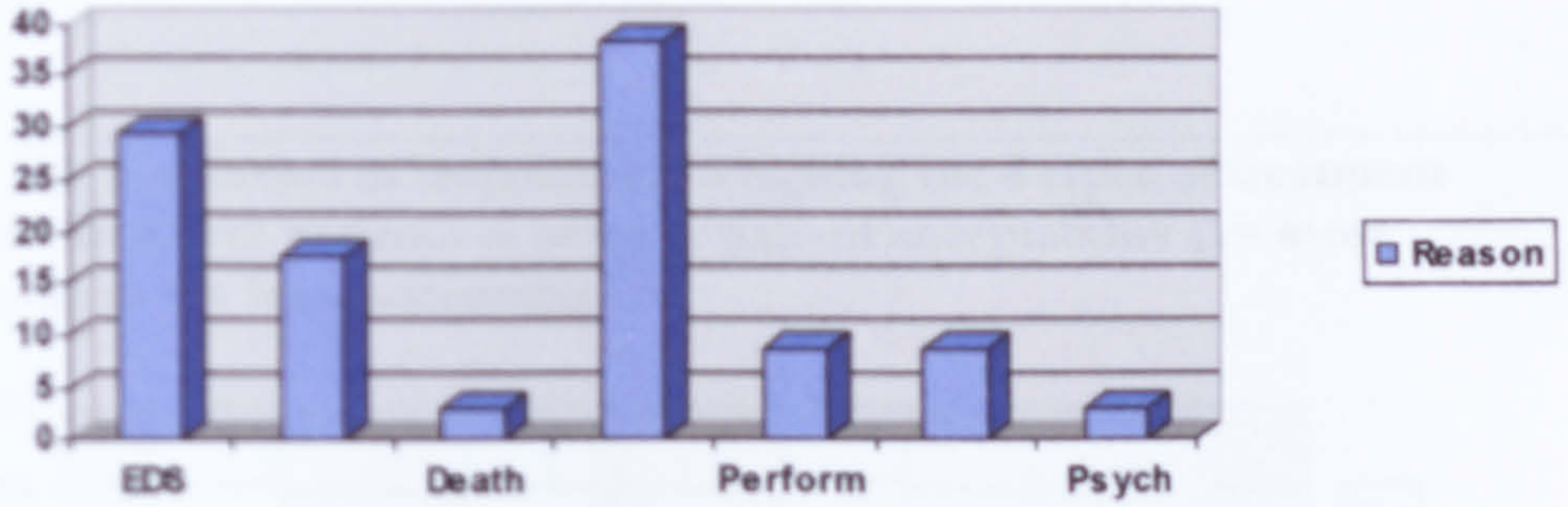
Group	Frequency	%
<30 years	0	0
30-39 years	20	15
40-49 years	63	46
50-59 years	49	36
>60 years	4	3

All but 3% of respondents were in a practice with multiple partners, 58% were in practices classified as 'teaching practices', 85% were urban with 78% having specialist services (Specialist nurses, Dieticians or Specialist clinics).
There were 94% of respondents who had SAHS patients within their practice with 28% having referred patients with suspected SAHS for less than 5 years, 60% for 5-10 years, 11% for 10-20 years and 1% for more than 20 years.

8.4.1.2 Indication for treatment

In the primary care physicians' opinion, the principal reason for treatment of patients with suspected SAHS was predominantly improvement in HRQL and EDS. Reduction in cardiovascular sequelae, reduction of risk from sleepiness while driving and improvement in daytime performance at work were the other reasons cited with frequencies of these responses shown in figure 8.1.

Figure 8.1: Frequency of primary reason to offer treatment to patients with SAHS

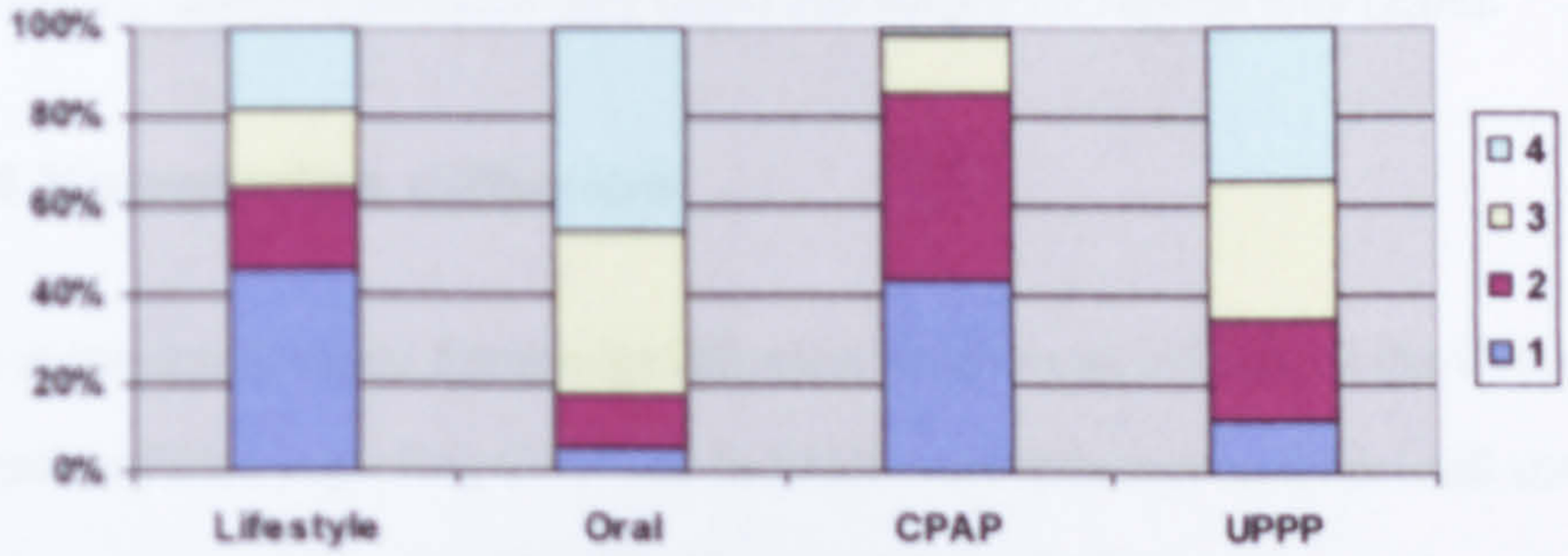


EDS= excessive daytime sleepiness, CVS= cardiovascular sequelae, Death= risk of death during sleep, HRQL= health related quality of life, Perform= daytime work performance, Driving= reduction of risk from driving while sleepy and Psych= improvement in the psychological consequences of SAHS

8.4.1.3 Characteristics of CPAP

When asked to rate the 4 major forms of treatment available for patients with SAHS, on the basis of clinical effectiveness, majority of respondents considered both lifestyle intervention and CPAP to be the most effective. The relative proportions of responses graded 1= most effective to 4= least effective are shown in figure 8.2.

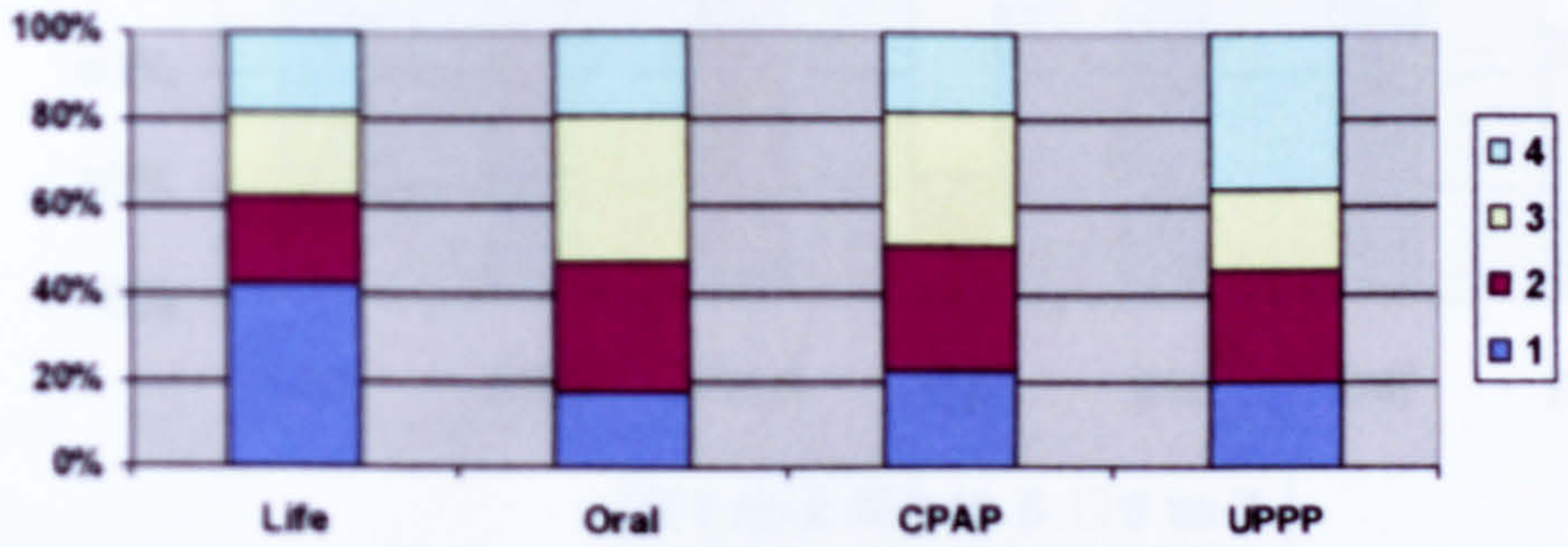
Figure 8.2: Proportion of respondents weighing the 4 types of treatment available for SAHS patients in order of clinical effectiveness (1= most effective & 4 = least effective)



Lifestyle = lifestyle intervention, Oral= Oral appliances, CPAP & UPPP = surgical Uvulopalatopharyngoplasty

When asked to rate the 4 available therapeutic options according to acceptability to patients, primary care respondents rated lifestyle intervention as the most acceptable and UPPP as the least, results shown in figure 8.3.

Figure 8.3: Proportion of respondents weighing the 4 types of treatment available for SAHS patients in order of patient acceptability (1= most acceptable to 4 = least acceptable)



Lifestyle = lifestyle intervention, Oral= Oral appliances, CPAP & UPPP = surgical Uvulopalatopharyngoplasty

Assessing CPAP as a healthcare innovation, 73% of respondents felt it offered distinct advantages over the other alternative therapies, 55% felt that CPAP was compatible with normal sleep. When asked about the complexity of CPAP use, 58% felt it was moderately complex for the average patient, 25% felt it was easy to use and 17% felt it was too complex.

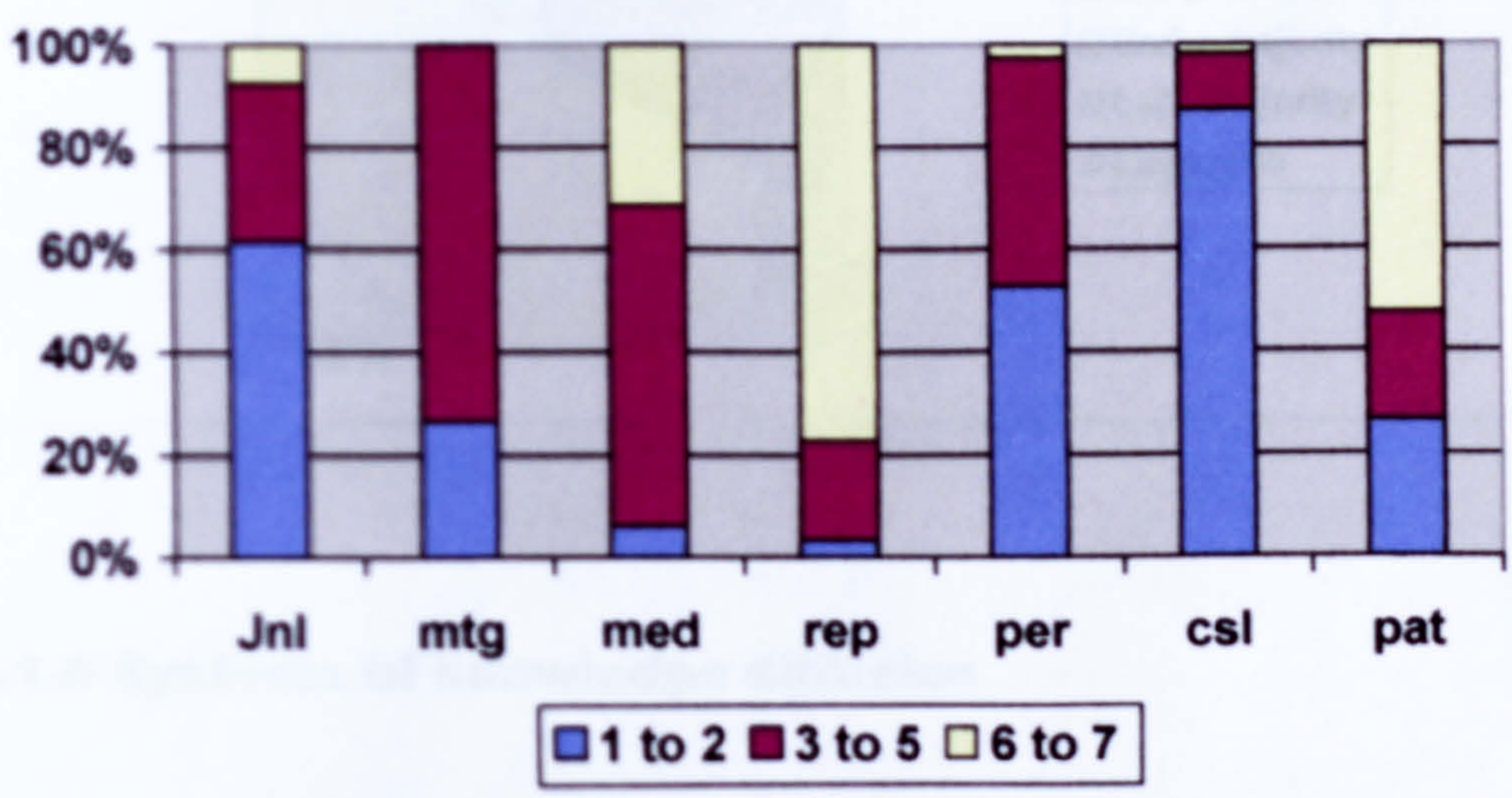
Assessing the benefit of CPAP therapy was possible by both objective and subjective methods (62%), objective methods only (15%) and subjective reports only (23%).

8.4.1.4 Knowledge diffusion

Methods of communication/ knowledge diffusion which most influenced the GPs clinical and scientific opinion regarding CPAP use in SAHS were information from local specialist Consultants, peer contacts and scientific journals. While the least effect on the opinion of primary care physicians were from representatives of industry, the media and patient

groups. The relative proportions of respondents grading the different methods of knowledge diffusion are shown in figure 8.4.

Figure 8.4: Relative proportions of modes of knowledge diffusion reported as influencing the opinion of respondents

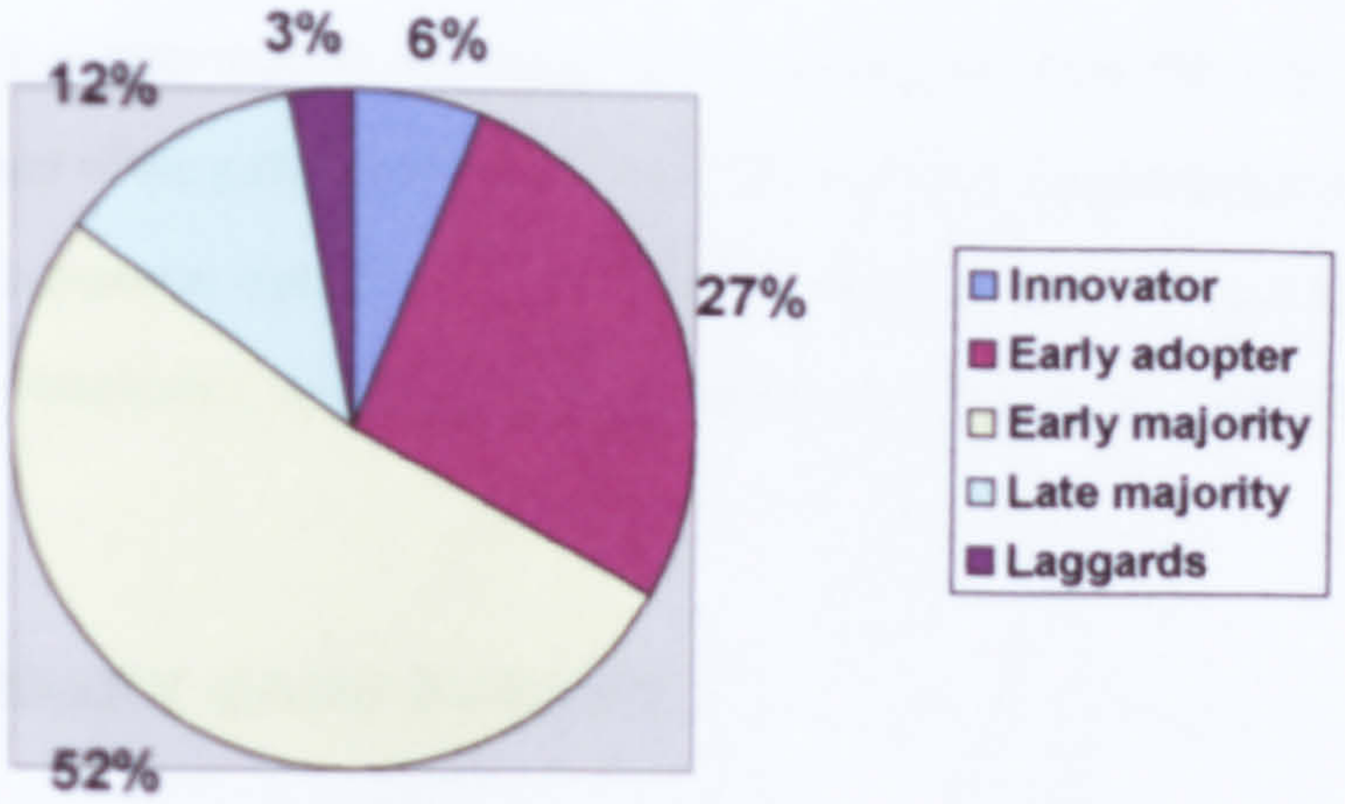


Jnl = scientific Js, **mtg** = Scientific meetings/ seminars, **med** = Media reporting, **rep** = Industry representatives, **per** = peer contacts/ networks, **csl** = Hospital consultants through lectures, **pat** = pressure of lobbying from patient groups/ individual patients.

8.4.1.5 Adopter categories

Based on the adopter categories, almost a third of respondents considered themselves as either innovators or early adopters, 67% of respondents were in the early and late majority groups with a very few in the resistance to change group/ laggards, as shown in figure 8.6.

Figure 8.5: Adopter categories for primary care respondents



8.4.1.6 Systems of knowledge diffusion

Fifteen percent of primary care respondents felt there was an effective and appropriate local system for the transfer of technological/ innovation knowledge from experts to the primary care physician within the NHS infra-structure, 55% said there was no existing system available and 30% felt peer-peer contact was the only way existing for knowledge diffusion.

None of the respondents mentioned the recent introduction of a system/ infrastructure for knowledge diffusion.

8.4.1.7 Hindrances to receiving appropriate therapy for SAHS patients

Eighty five percent of respondents felt that their patients with suspected SAHS were not receiving their diagnosis and treatment without any major hurdles. The major hindrance cited was lack of resources/ restricted resources (64%), lack of specialists or inordinately long waiting times (42%), lack of adequate diagnostic and treatment facilities (40%) and poor patient awareness (40%) leading to patients not receiving their treatment appropriately.

8.4.1.8 The future of CPAP treatment for SAHS

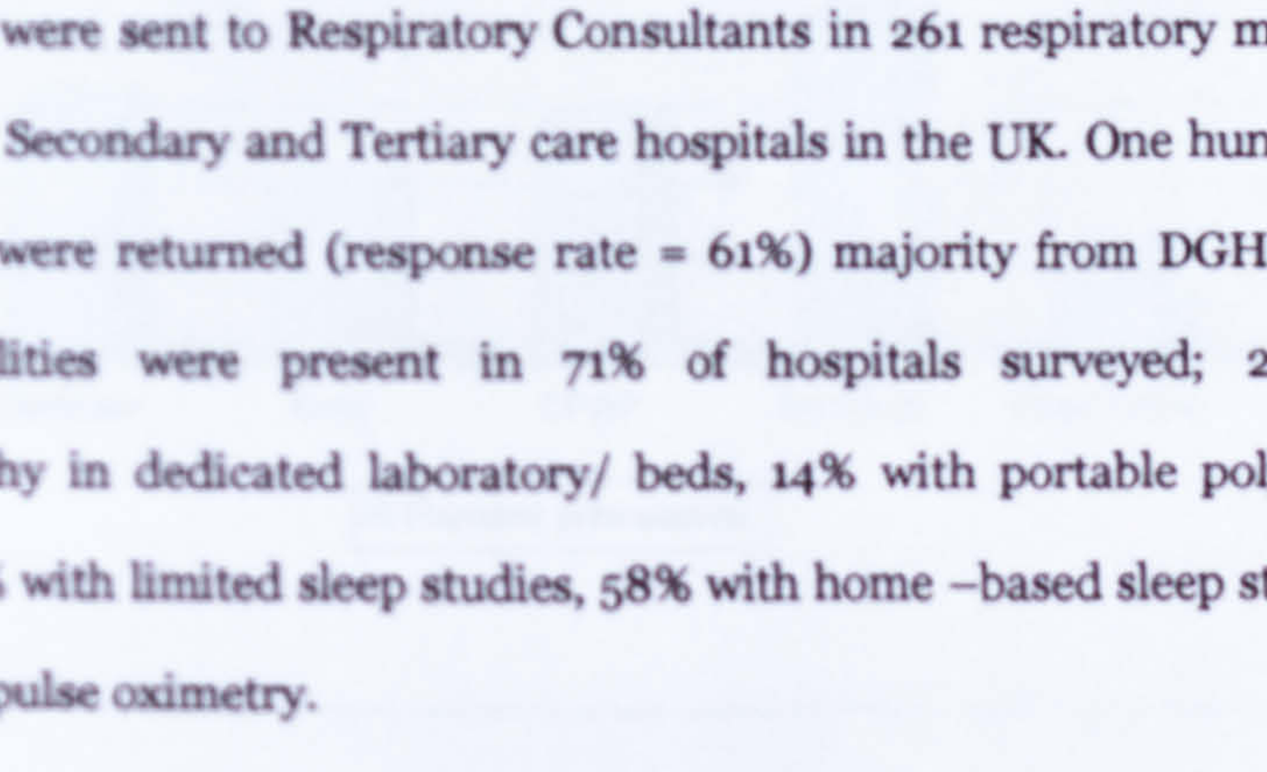
Only thirty percent of respondents felt that CPAP is likely to remain the most effective therapy in the future while 52% felt that CPAP will be replaced / superseded by a more patient friendly therapeutic option and 13% felt it is likely to be replaced by a more clinically effective treatment option (4% respondents did not agree with the above options)

8.4.2 SECONDARY CARE SURVEY

8.4.2.1 Respondents

Questionnaires were sent to Respiratory Consultants in 261 respiratory medicine firms/ departments in Secondary and Tertiary care hospitals in the UK. One hundred and sixty questionnaires were returned (response rate = 61%) majority from DGHs (72%). Sleep diagnostic facilities were present in 71% of hospitals surveyed; 20% with full polysomnography in dedicated laboratory/ beds, 14% with portable polysomnography equipment, 41% with limited sleep studies, 58% with home –based sleep studies and 72% with overnight pulse oximetry.

Figure 8.6 Prevalence of sleep diagnostic facilities

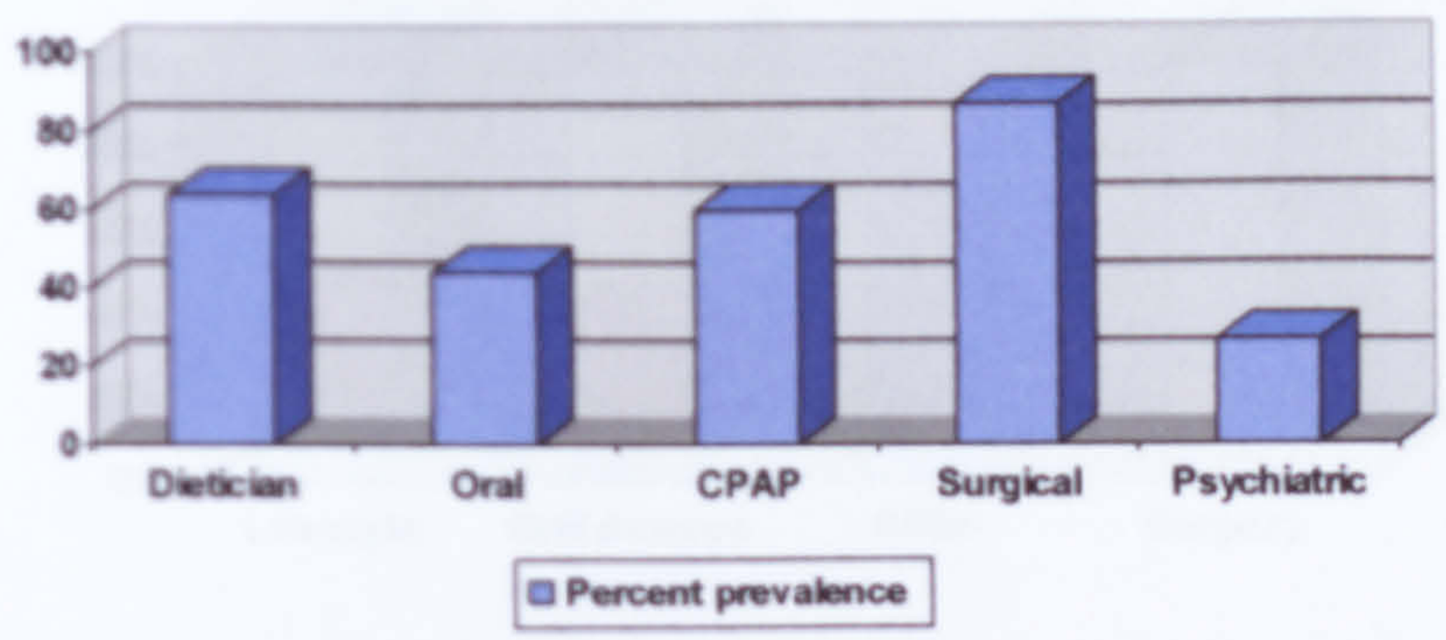


Poly= polysomnography, Port=portable polysomnography, Lim=limited sleep studies, Home=home sleep studies, Pulsox= overnight oximetry

8.4.2.2 Treatment facilities

The survey results showed a far greater availability of surgical options for the treatment of SAHS compared to the availability of CPAP and oral devices. Specialist dietary services were available in just over half (60%), while psychiatric assessment and support in only a quarter of the hospitals surveyed.

Figure 8.7: Percentage prevalence of treatment facilities among the surveyed hospitals



8.4.2.3 Patient activity

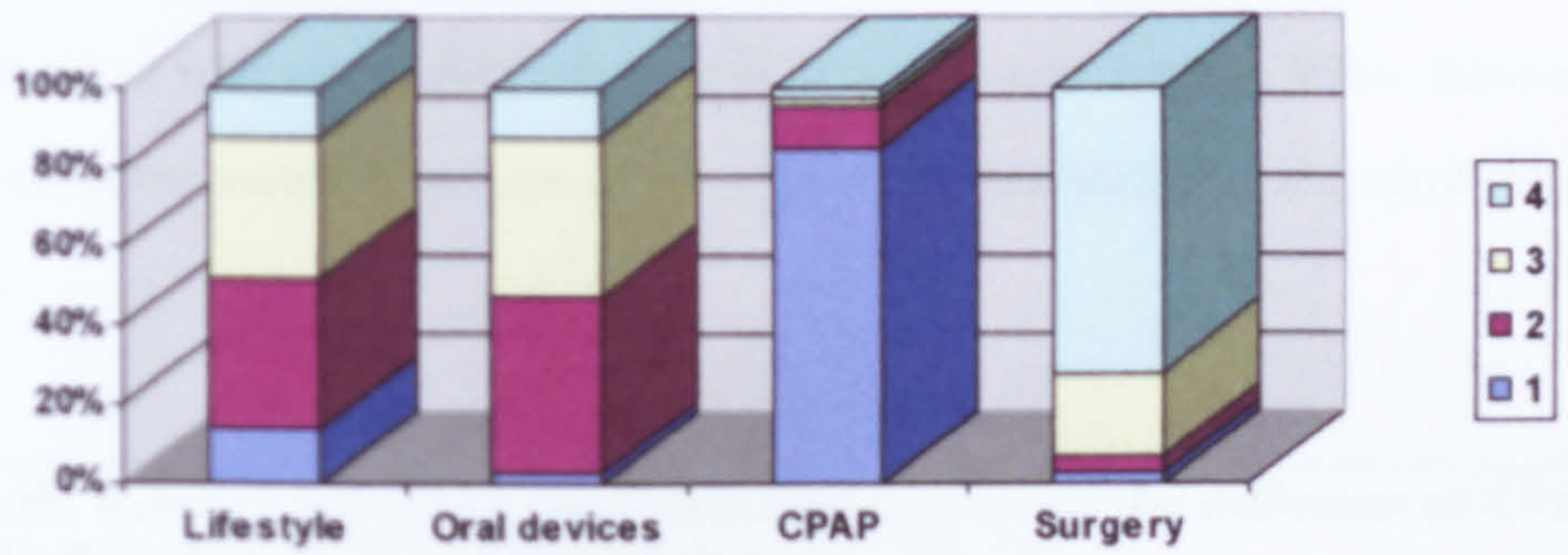
Annual referral patterns suggested that 35% of the hospitals surveyed had <50 patients referred, 21% had between 51-100 patients, 15% had between 101-150 patients and 29% had >150 patients. There were an estimated total of <100 current SAHS patients in over half of the surveyed firms (61%), while 22% had between 101-500 patients and 17% had >500 patients under follow up.

There were either none or less than 50 patients on CPAP in 69% of the surveyed hospitals, 25% had between 51-200 patients and 6% with over 200 patients on CPAP. The rate of annual expansion in patients numbers based on referrals were estimated to be; <5% in 27/160 hospitals, 5-10% in 42/160, 11-15% in 25/160 and >15% in 57/160 hospitals.

8.4.2.4 Disease and treatment characteristics

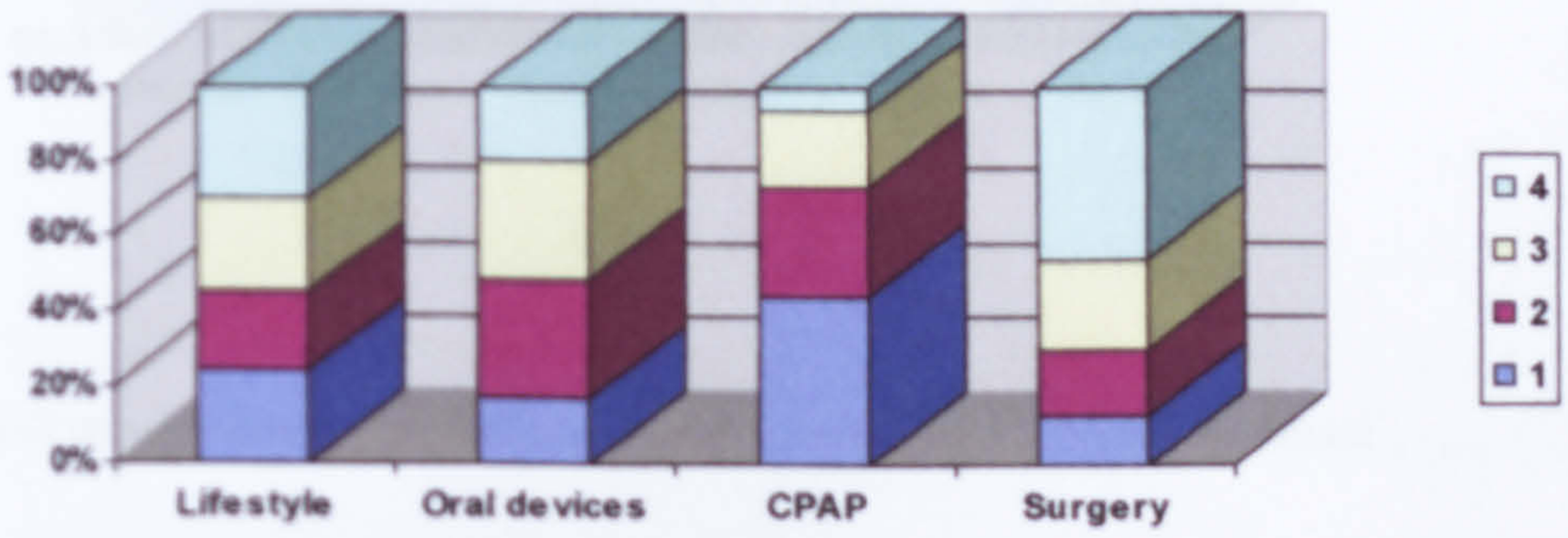
The majority of consultants surveyed identified improvement in daytime somnolence (61%) as the most common indication for treating SAHS, followed by improvement in HRQL (30%). The other indications such as reducing road traffic accidents, preventing cardiovascular sequelae, improving performance at work only accounted for <10%.

Figure 8.8: Effectiveness of treatment options in SAHS based on survey of Respiratory consultants



1= most effective to 4= least effective

Figure 8.9: Acceptability of the different treatment options in SAHS based on survey of Respiratory consultants



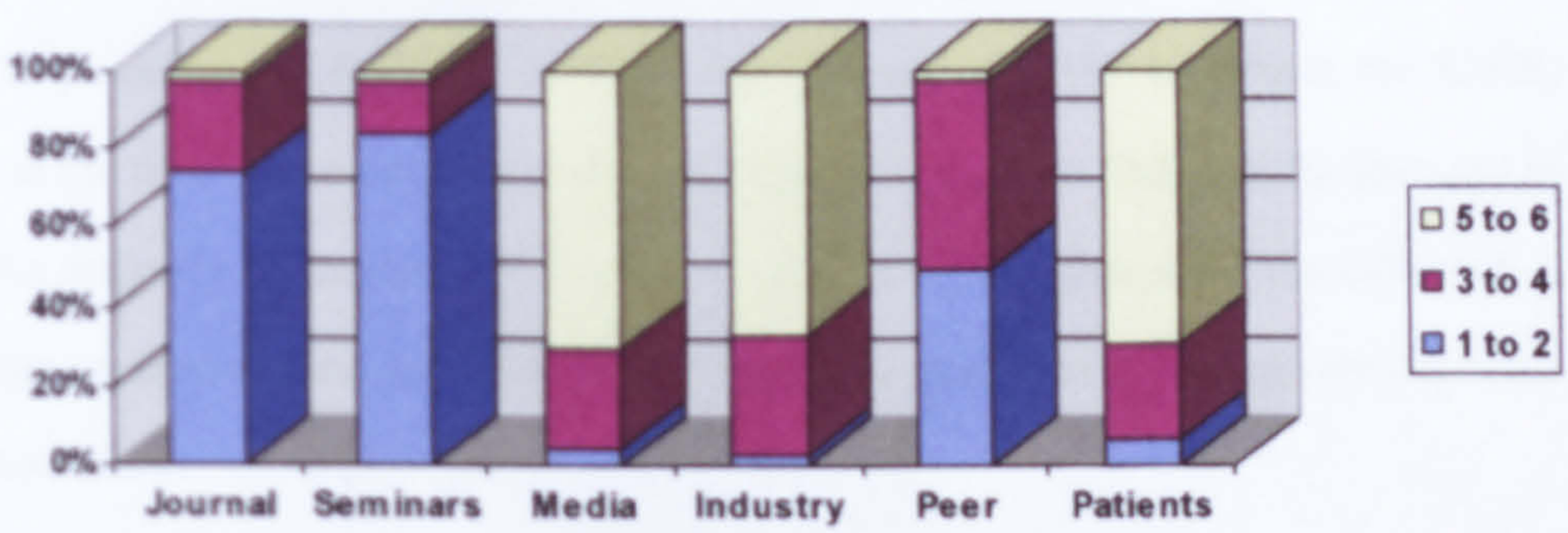
1=most effective to 4=least effective

Ninety six percent of respondents felt that CPAP offered an advantage over concurrently available treatment for SAHS, 88% felt that CPAP use was compatible and was unlikely to adversely impact on the lifestyle of users, 88% felt that CPAP was not too complex for the majority of their patients to understand and operate effectively, 97% felt that therapeutic trials could be provided without permanent or irreversible adverse effects and 95% felt that the benefits of CPAP could be assessed objectively in individual patients.

8.4.2.5 Diffusion

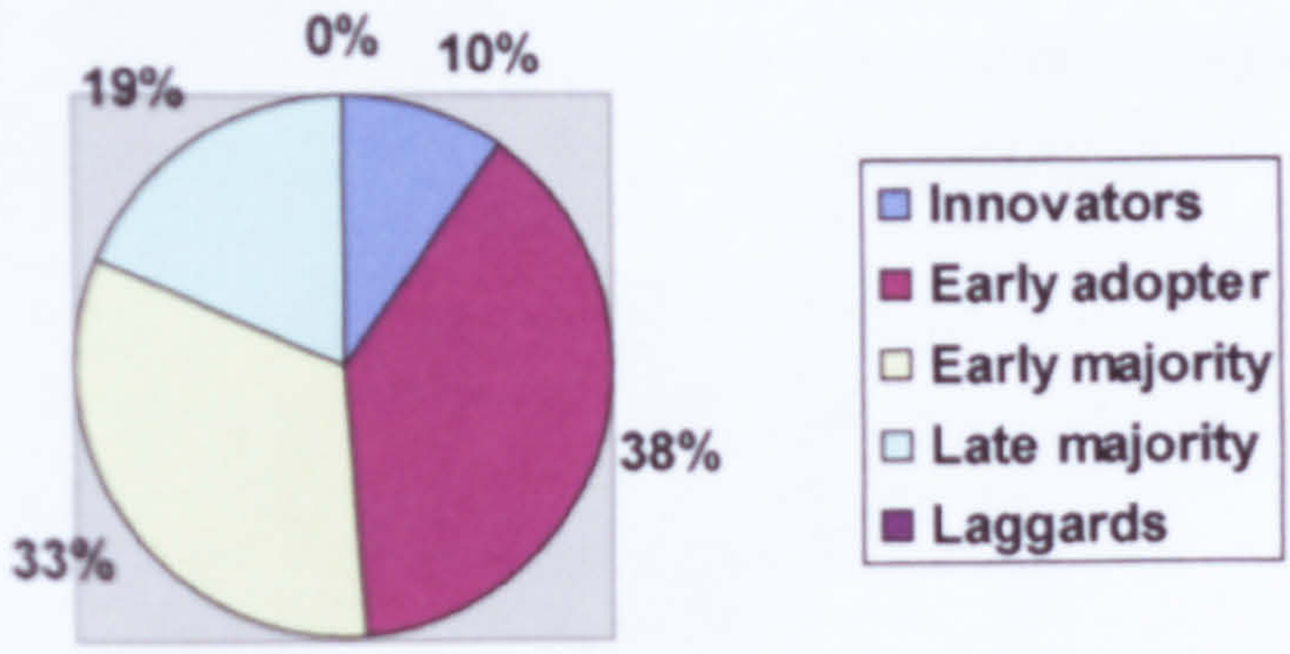
The survey results showed that Scientific meetings/ seminars followed by scientific journals contributed mostly to the diffusion of knowledge regarding the treatment of SAHS with CPAP with a moderate influence from peer-to-peer contact. While there was very little apparent contribution from media, industry representatives and patient groups in the UK.

Figure 8.10: Relative contribution of different factors on the diffusion of CPAP in the UK; Based on survey of Respiratory consultants



1-2 most influence, 3-4 moderate influence and 5-6=least influence

Figure 8.11: Classification of respiratory consultants on the basis of their adoption behaviour



Within the NHS infra-structure there were only 17% respondents who felt there was a system in place for the diffusion of knowledge (regarding CPAP treatment for SAHS) existent at the time of the survey and 4% indicated that a system had recently been put in place. The majority of respondents (35%) had no access to a system for the diffusion of knowledge on innovations and insteadd depended on scientific meetings/ seminars for acquisition of such knowledge (48%).

Almost 50% of the respondents reported a low level of adoption of CPAP treatment for SAHS within their hospitals. The main reasons cited by the respondents for the lack of treatment provision (CPAP) were; lack of adequate facilities (50%), lack of adequate resources (69%), lack of awareness of patients (38%) and lack of adequate specialists or inordinate delays from referral (43%).

On qualitative analysis, almost 10% of respondents identified a restriction by local funding authorities on CPAP provision, except by referral to specialist centres, even in the

presence of increasing numbers of referrals and apparent delays to secure diagnosis and treatment in these centres.

8.4.2.6 Future

A majority of respondents agreed with the statement that CPAP is likely to remain the most effective treatment for SAHS in the future (78%) and is unlikely to be replaced by a more effective treatment (78%) or a more patient friendly option (70%).

8.5 Discussion

Within the managed care setting in the UK, the primary care physicians occupy the first point of contact between the health care system and the community. Thus the first phase of the diffusion survey was designed to examine the knowledge base and perceptions among primary care physicians about the treatment of SAHS patients. While the secondary care physicians are responsible for the diagnosis and treatment of diseases in the hospital setting. Any innovation or healthcare intervention is thus unlikely to be successful unless the knowledge of its benefits reaches the frontline of the health care delivery system.

The results indicate a close agreement between the primary and secondary care physicians in the principal indication for the provision of treatment of patients with SAHS (i.e. reduction in EDS and improvement in HRQL). Recent RCTs and the Cochrane review of the effectiveness of CPAP therapy in SAHS [Wright and White 2000] have consistently indicated clear benefit in these two parameters [Ballester *et al.*1999]. While there is academic interest among sleep apnoea researchers in the link between SAHS and cardiovascular diseases (IHD, Hypertension and strokes) the evidence of causation is still lacking and hence alleviation of this risk is still not a primary indication for the provision of this treatment in the UK.

Characteristics of an innovation often determine the rate of its diffusion and adoption within a target user community. In the case of CPAP the survey results indicate a consensus among all respondents on the specific characteristics of CPAP which may have been responsible for its speedy diffusion since its inception. CPAP offered a safe and potentially reversible therapeutic option which could be offered to a much larger group of patients with SAHS than hitherto available surgical options; thus had a distinct advantage. It also offered the ease of instituting safe and reversible therapeutic trials to assess individual responses, offered the opportunity to objectively assess benefit and appeared acceptable and was relatively easy to use.

Whereas the majority of secondary care physicians agreed that CPAP would remain the most effective therapy in the near future and was unlikely to be replaced by a more effective and acceptable option for patients, primary care physicians felt otherwise. Most clinical trial data on compliance report a CPAP acceptance rate of between 50-80% (similar to the results presented in chapter IV) suggesting that it was probably both an effective and a popular therapeutic option, and likely to remain so in the future. However when CPAP is prescribed to patients at the milder end of the spectrum (AHI 5-15 hour^{-1}), the acceptance rate is seen to fall to 50% [Engleman *et al.* 1999].

However, it is reported that even in patients with evidence of physiological disease (AHI>30 hour-1), the absence of daytime symptoms is likely to make treatment ineffective [Barbe, *et al.* 2001] and hence adversely affect adoption. Thus the absence of a clear relationship between symptoms and nocturnal sleep disturbance may allow for scepticism about the future of CPAP among physicians.

Patients have reported dryness of the oro-pharynx, fitting of the mask and associated leaks, excessive air pressure, machine noise and cumbersome apparatus as common reasons to discontinue treatment in the absence of a significant symptom benefit. Primary care physicians closer to patients may reflect this reservation of patients regarding long term usage of CPAP, and hence may be looking for an alternative which would be more acceptable to majority of patients. This probably accounts for the divergence seen in the responses for the future of SAHS therapy, between primary and secondary care respondents.

When an innovation is introduced in the health care system, one of the determinants of the rate and extent of its adoption is the communication pathways and networks existent within the system. The diffusion survey indicates a definite lack of a systematic pathway for knowledge diffusion from innovators to secondary care and from secondary care to primary care physicians. The survey results indicate a dependence on personal initiative and personal peer-to-peer networks along with meetings chaired by hospital consultants for the diffusion of expert knowledge in primary care. The traditional format of scientific

meetings and journal articles were cited as the most important determinants by hospital consultants. Interestingly there is hardly any role of patient self-help/ lobby groups, media and industry representation in influencing the diffusion of knowledge or the adoption of CPAP.

In the USA, the presence of a national body (American Academy of Sleep Medicine) and the mixed professional-patient led National Sleep Foundation has been shown to play a major role not only in public awareness campaigns but also in securing government funding, lobbying for legislation and setting up a national framework within the National Heart, Lung and Blood Institute. Attempts to initiate contact with the registered patient's self-help bodies in the UK did not meet with much success suggesting their relative dormancy and there was only 1/5 responses from the industry representatives. The British Sleep Society (a group of professionals) and the British Thoracic Society have yet to demonstrate a role in either lobbying the government (Department of Health) or in setting up a national framework to allow a homogenous approach to resource allocation for SAHS sufferers in the UK. While in other chronic diseases such as asthma, diabetes and ischaemic heart disease there is a major role played by bodies such as the National Asthma Campaign [Comino *et al.*1997] and British Heart Foundation [Shillingford 1984] in raising awareness among the public, lobbying the government for resources, raising funds for research and supporting physicians and researchers in their efforts. Similar efforts by the National Sleep Foundation [Anon.2004b] in conjunction with the professional bodies have raised the profile of sleep disorders in the USA. This strategy has been successful in establishing an professional academy for sleep medicine accreditation and establishing a national priority with sleep awareness campaigns [National Sleep Foundation 1999] and national level plans for sleep research [Phillips *et al.* 1996].

To date there have been two reports published by a specialist committee of the Royal College of Physicians and more recently a practice guidelines published by the Scottish National Sleep Group [Scottish Intercollegiate Guidelines Network 2003]. It is likely that the current disparity in funding identified by the present survey among the majority of hospitals/ health authorities in the UK (identified by survey respondents as the major

cause of lack of the availability of appropriate treatment in SAHS) is a result of a variety of factors such as; a lack of a national consensus both among professionals, competing interests from diseases with higher public and political profile like cancer [Clive *et al.* 1995], multiple sclerosis [Nicholl *et al.* 2001] and heart disease, lack of patrons or champions both professional [Lau *et al.*1998] and public and confounding with obesity and lifestyle prototypes in the public and professional mind [Wright, *et al.*1997a]. In the case of hepatitis B such champions have often arisen outside of the public health establishments that are mandated to play that role. In New Zealand it was left up to one unusual and determined man to not only discover the seriousness of the hepatitis B epidemic but to practically single-handedly force a reluctant government to acknowledge the threat and act to contain it. He accomplished this by combining high quality scientific research with unrelenting political pressure generated by appeals to the public by means of the mass media [Muraskin 1995].

The mere production and distribution of guidelines is unlikely to make a significant impact on the adoption of innovative therapies in general use [Grimshaw & Russell 1993]. Specifically relevant are the instances of poor adoption of asthma guidelines [Cowie *et al.* 2001] and those for use of statins in heart disease [Goff, Jr. *et al.* 2002] [Shea *et al.* 1990]. If guidelines are issued as a national service framework by regulatory bodies or by government departments, and may be considered mandatory for service provision across the whole country then adoption will be influenced [Halpin, 2004].

The present survey also found that over 50% of hospitals reported an annual expansion in patient referrals in excess of 10%. This rapid expansion in demand combined with the majority who are likely to still remain undiagnosed in the community [Phillips 1996b;Silverberg *et al.* 1997], is likely to present the health planners with a widening chasm between existing facilities, funding allocation and spiralling demand [Gibson 1998] [Phillipson 1993;Wright *et al.* 1998a].

8.6 Conclusions

The survey results demonstrate that there is a consensus between the primary and secondary care adopters in the UK NHS regarding the characteristics of CPAP which would provide it with an advantage over and above co-existent therapeutic options like oral devices, lifestyle intervention and surgical options.

The three major determinants which are shown to be absent from the factors influencing the UK diffusion of CPAP compared to the USA are; (i) lack of a national consensus opinion and a champion body (whether professional, public or mixed) for raising public and professional awareness and hence commanding a political imperative; (ii) restrictions and disparities in the funding of diagnostic/ treatment facilities within the UK health regions; and (iii) lack of structured pathways for the dissemination of expert knowledge from innovators/ early adopters to the majority.

Interestingly the lack of correlation between physiological parameters of severity and daytime dysfunction did not seem to impact on diffusion of CPAP; the effect of untreated SAHS on cardiovascular disease and mortality did not feature in the indication for treatment in the UK, in contrast to the USA where this is a prime driver for more funding and resource allocation.

Survey respondents remained divided on the future of CPAP, with primary care physicians predicting a change from CPAP, and secondary care physicians thinking this unlikely in the near future.

CHAPTER IX

DISCUSSION & CONCLUSION

9.1 OVERVIEW

Health technology appraisal and diffusion of innovations in chronic diseases: CPAP in SAHS

Since the discovery of vaccination by Edward Jenner in 1798 [Jenner 1801] the progress of science and technological innovation in many industrialised countries of the world, has reached a point where recent innovations are concerned not with the traditional reduction in mortality; but with improvement in quality of life of sufferers with chronic conditions [Berwick 1989]. The technological imperative in health care, which has driven progress, is the beneficial impact of innovations, but there is also the added responsibility for the recognition and avoidance of adverse effects [Annas and Elias 1999]. Technology appraisal was born initially to ensure the safety and efficacy of any new technology before being put to common use [Banta *et al.* 1980]. Whereas regulatory authorities are entrusted with the responsibility of preventing harm to people and society, health purchasers are concerned with the effectiveness of innovations [Banta 1994] and comparison of competing technologies in order to ensure the best use of limited resources for the greater good [Maynard and Bloor 1995] [Rutten and Drummond 1994].

However, even within the structured environment of the NHS in the UK, the pathway from innovation to adoption of new health technologies has a widespread variability and liable to be influenced by a variety of factors [Rosen and Mays 1998]. Newell et al discovered that the process of knowledge generation about best practice and its transfer within the NHS does not follow a regulated and hierarchical pathway [Newell *et al.* 2003]. The way an organisation (*like the NHS*) deals with technology adoption is likely to be either slowed down by an institutional inertia or be reactive based on short-term organisational goals, rather than being proactive and driven by concrete evidence [Miller *et al.* 2001]. One may argue that an early regulatory structure and appraisal of new innovations in their infancy (*before they have had a chance to diffuse within early adopters and be enriched by the process of feedback and re-invention*) may identify non-starters and save vital resources being spent in unnecessary adoption. This 'early' regulation is feared on the other hand, to create insurmountable hurdles to

innovativeness and potentially slow down technological progress, perhaps compromising patient care in the long run. The effect of regulation may be seen in a slowing down of the rate of introduction of innovations when compared to the rate of expansion of scientific knowledge [Williams 2004]. The ideal pathway from innovation to adoption is uncertain and various models and hypothesis currently exist [Rogers 1995].

SAHS provided the ideal case study where the advent of a new modality of treatment (CPAP) demonstrated a potential for alleviating the adverse effects of a chronic syndrome on sufferers. The characteristics of CPAP made it possible to widen the applicability of this treatment compared to previously available surgical options [Sullivan *et.al.*1981]. However, since this device became commercially available in 1990, there has been a variable adoption in the USA and Western Europe, judging by industry estimates [Newby 2002] [Mack 1999].

In 1997, a systematic review of the evidence base for usage of CPAP in SAHS patients in the UK identified deficiencies in the evidence of clinical effectiveness and the interference of confounders [Wright *et. al.*1997b]. This led to a decline in resources available for the provision of these devices for the treatment of patients, also leading to widespread regional variability [Gibson and Prowse 1997]. Three years later in 2000, a further systematic review identified six RCTs with evidence that CPAP improves HRQL among sufferers, when compared to mandibular advancement splints and laser palatoplasty. But mandibular devices were preferred by patients due to ease of use and less interference with sleep [Wright and White 2000].

Till now the situation identified by the RCP expert report in 1993 [Stradling *et al.* 1993] and 1998 [Gibson *et al.*1998] of under-diagnosis and under-treatment of SAHS patients remains valid in the UK. Under-diagnosis has also been reported from population surveys in the USA [Phillips 1996a]. Patients in most centres are currently subject to 9-12 month waiting list for diagnosis and treatment. Due to a lack of a consensus national strategy for the treatment of sleep disorders and availability of evidence of cost –effectiveness,

individual clinicians have had to negotiate local funding. This has led to a further widening of the regional disparity in service provision.

During the same period in the USA, the American Sleep Disorders Association has been upgraded to form the American Academy of Sleep Medicine (AASM) with formal responsibility of accreditation of professionals and laboratories and to achieve consensus via research and monitoring of services [American Academy of Sleep Medicine 1999]. The US national imperative is further demonstrated in the form of government led research initiatives through the National Heart, Lung and Blood Institute funding and public health programmes [Anon.2004a]. There is also a major public initiative in education, research and policy in the form of an active National Sleep Foundation (NSF) [Anon.2004b].

The situation in the UK has lagged behind with a lack of consensus regional or national strategy leaving individual clinicians to negotiate funding of services locally. The first UK national guidelines for Sleep related disorders were produced in 2003 in Scotland [Scottish Intercollegiate Guidelines Network 2003]. Sleep is still not an independent speciality discipline in the UK and management of patients is shared by professionals in different specialities, thus creating hurdles to a concerted approach. There is little sleep-related education featuring in the UK medical curricula [Stores and Crawford 1998] and sleep disorders do not yet feature in the government's *'health for all'* strategy [Childs 2004]. There is also little demonstrable influence of patient groups, on sleep related health policy or public awareness campaigns [Sleep Alliance. 2004].

Thus CPAP use in SAHS patients thus presented an ideal context for the study of technology appraisal and factors affecting its diffusion and adoption.

9.2 Mortality

The retrospective case-control study presented in chapter IV, demonstrated an increased relative risk for mortality and for being hypertensive in SAHS patients compared to the

control group. Some of this increased mortality could be contributed by the excess of obesity seen in this group which is known as an independent risk factor. The increased prevalence of hypertension is also known as an independent contributor to increased cardiovascular and cerebrovascular mortality [Anon, 1996a; Fletcher, 1996; Lavie, 1995]. Cardiovascular causes dominate in the 'all cause mortality' seen in SAHS patient groups [Mooe, 2001; Shepard, 1992]. The AHI has been linked to the increased mortality in studies at a level of >20/hour [He 1988]. In large scale follow up studies, patients below the age of 50 years are known to have an increased risk of cardiovascular mortality in the presence of untreated SAHS [Veale, 2000]. The mortality rate is the same as non-SAHS patients in older individuals. It is also argued that the combination of obesity, hypertension, diabetes and SAHS may further multiply the mortality risk in patients and hence need to be addressed holistically.

9.3 Mismatch in diagnostic and treatment facilities

Data from 1990 to 1997 collected from the clinical review (*chapter IV*) demonstrated a gradually increasing referral number with a 10 fold increase over 7 years. This was probably a reflection of the increasing awareness of this condition among patients and primary care physicians. Similar annual growth figures were reported from a majority of the secondary care physicians surveyed in chapter VIII. However the total number of patients diagnosed and treated annually were only a small fraction of the estimated number based on population studies (For 250000 adult population covered by Birmingham Heartlands Hospital, there are an estimated 5000 men and 2500 women with SAHS who would qualify for diagnosis and treatment) [Young *et al.* 1993]. A population based study undertaken in the USA has estimated that a large proportion of subjects with nocturnal apnoeas/ hypopnoeas and daytime symptoms usually remain under-diagnosed and treated (almost 93% of women and 82% of men) [Young *et. al.*1997a].

Thus data from chapters IV and VIII demonstrate the increase in public awareness of SAHS and improved knowledge diffusion in sleep related disorders amongst primary care physicians (estimated from increased referrals). But diagnostic and treatment facilities

have not expanded to match the increasing demands. Diagnostic facilities in the UK were considered severely inadequate by the Royal College of Physicians Working party survey in 1993 and 1998 [Semple and Gibson 1993] [Gibson *et al.* 1998]. Data from the secondary care survey presented in chapter VIII, also demonstrated the lack of diagnostic facilities and resources and these are reported as significant factors in the slow adoption of CPAP in the UK.

One of the potential ways to increase diagnostic capability without impacting adversely on limited resources would be to use less expensive and home based methods thus reducing the waiting list for more expensive hospital based in-patient polysomnograms. As demonstrated by the data presented in chapter IV, almost two thirds of the patients eventually diagnosed and treated in the Sleep clinic could have been diagnosed using a combination of symptoms and overnight oximetry criteria (4% ODI>15 $hour^{-1}$) [Ryan *et al.* 1995b]. Similar research has shown that various limited sleep studies using overnight oximetry and symptoms/ questionnaires [Netzer *et al.* 2001] [Boehlecke 2001] are useful in reducing the number of patients requiring full polysomnography. Using an ODI>15 $hour^{-1}$ can increase the specificity of moderate to severe SAHS diagnosis to 98-100% although the sensitivity is in the order of 30-40% [Wiltshire, *et al.*2001]. Others have used automated and spectral analysis of the pulse oximetry data to improve the specificity to 67%-88% [Zamarron *et al.* 1999] [Vazquez *et al.* 2000]. This reduces the pressure on limited availability of diagnostic facilities, speeds up the treatment of patients [West, et al 2001] and may reduce the economic impact of such labour and equipment intensive diagnostic tests [Chervin *et al.* 1999;Epstein and Dorlac 1998] [Kristo *et al.* 2001].

Although an oximetry based approach tends to hold great potential benefit for centres where waiting lists are large, there are concerns regarding the limitation of this approach in picking up non-apnoeic disorders, i.e. UARS, Narcolepsy, Restless leg syndrome and Periodic limb movement disorders. In the USA, the trend has been to continue full PSG but with a telemedicine approach in transferring sleep studies online to a central laboratory, thus achieving a 44% cost reduction [Kristo *et al.* 2001] [Pelletier-Fleury *et al.*1999].

Similar to the guidelines on practice parameters established in the USA, there have been specific guidelines published in Scotland in 2003 [Scottish Intercollegiate Guidelines Network 2003]. Theoretically these national guidelines produced by consensus of expert committees may provide a framework for estimating the need for facilities in the UK and for recommending appropriate resource allocation. However sleep disorders still lack a place in the government agenda for health improvement and do not yet have a place in established national service frameworks [Childs 2004].

9.4 EFFICACY & EFFECTIVENESS

9.3.1 New evidence of effectiveness

Appraisal of a new technology first involves assessment of its safety and clinical effectiveness. There were two systematic reviews examining the evidence base in SAHS published in 1997-1998 which had come to divergent conclusions. Wright et al [Wright *et al.*1997a] concluded that a significant proportion of the normal population report symptoms of snoring and daytime hypersomnolence and hence there was insufficient data to justify treatment purely on the basis of improvement in daytime symptoms. They identified an absence of well-designed RCTs which controlled for confounding influence of obesity, sleep deprivation and a lack of placebo-controlled trials. There was insufficient trial data to justify treatment on the basis of reductions in mortality and cardiovascular morbidity. The authors recommended firstly that randomised, placebo-controlled trials were needed to examine the effectiveness of treatment options, secondly that the contribution of lifestyle factors (obesity, sleep hygiene, smoking & alcohol) also needed to be examined, and that more research was needed to evaluate the link between cardiovascular morbidity and mortality with SAHS [Wright *et al.* 1997a].

This led health authorities in the UK to place a low priority on commissioning sleep related facilities and treatment. In Bristol, restrictions were placed on clinical treatment of patients only with jobs dependant on safe driving [A Kendrick, 1998].

In contrast, a subsequent review of a set of small number of RCTs using either an oral placebo or sub-therapeutic CPAP, demonstrated that CPAP improved daytime somnolence, neuro-cognitive function and HRQL in SAHS patients [Douglas 1998].

The technology appraisal of CPAP presented in this thesis was initiated during this period and an RCT was designed to address the weaknesses identified in the scientific debate as illustrated here, and to compare the impact of CPAP against a control group given standardised lifestyle intervention. The data presented in chapter V demonstrates that CPAP is effective in reduction of nocturnal disease parameters of AHI, AI, and subjective daytime sleepiness compared to lifestyle intervention. Anthropometric variables (i.e. age, sex, BMI) did not have any demonstrable relationship with markers of nocturnal sleep apnoea/ hypopnoea (AHI & AI).

Although traditionally SAHS has been defined on the basis of nocturnal sleep fragmentation combined with daytime symptoms (of sleepiness), research evidence has shown only weak correlation between AHI and AI with symptoms [McArdle *et al.* 2001a] [Heinzer *et al.*2001]. There is also evidence to suggest that even in patients with (moderate to severe; AHI>30 $hour^{-1}$) SAHS (and sleep fragmentation), the absence of symptoms predicts an absence of response to CPAP treatment [Barbe *et al.* 2001]. Thus there appears to be a disengaged relationship between the symptoms / disability suffered by patients with SAHS and their nocturnal disease severity.

This can create uncertainty in planning health service resource allocation on the basis of population estimates (based on severity markers) which may not be of relevance in real life treatment of patients. The assessment of response of interventions based on physiological parameters may be less relevant in SAHS than in conditions such as diabetes (glucose monitoring [Wright *et al.*2003]) and hypertension (blood pressure monitoring [Benigeri and Pluye 2003]) where they are directly related to outcomes. Thus the complex interaction of various factors which give rise to a patient's perception of disability suffered due to a disease process needs to be better understood. But it is often suggested that that patient generated measures should be given prominence in assessing

the impact of intervention and health policy decision-making in chronic management [Sherbourne *et. al.*1999].

9.5 HEALTH RELATED QUALITY OF LIFE

9.4.1 Generic vs. disease specific

Patients with untreated SAHS report HRQL scores which are lower in almost all dimensions measured by different tools when compared with normal population values [Flemons and Tsai 1997b]. HRQL data from the RCT presented in chapter VI, shows that SAHS patients report lower pre-treatment scores in all dimensions of SF36 with the maximum deterioration seen in mental health dimensions (energy/vitality, social functioning, general health for both men & women) and also in EuroQol thermometer scores.

When HRQL is measured after treatment with CPAP, the SF36 dimensions of energy/vitality, social functioning and mental health showed the maximum improvement, while patients with lifestyle intervention reported no improvement.

The lower scores recorded in the physical health dimensions showed no change in either of the treatment arms in the study but remained consistently below the population norms. These results suggest firstly, that the disability associated with SAHS is perhaps predominantly linked to mental health and social functioning; and that the con-comitant lower scores seen in physical health domains are either un-related to SAHS or untreated by CPAP therapy. Interestingly the scores recorded using the EuroQol health thermometer only demonstrated a small change with treatment.

As different disease processes produce their adverse effects within different organ systems of the body, there is some value in measuring disease specific variables to accurately estimate the impact of health care interventions. Thus in SAHS patients the change in daytime somnolence and daytime neuro-cognitive function would be a sensitive measure to use when comparing different health care interventions i.e. laser UPPP or

Oral devices against CPAP. However to the health policy decision-maker, where competing interventions are being assessed for impact on the health of the population, disease specific measures provide results which are not comparable.

Thus generic measures tend to be preferred which then can provide a more comparable currency for such competing interventions. With this purpose in mind, researchers have used a variety of HRQL tools in SAHS patients which have demonstrated changes in various domains as listed in table 9.1. As illustrated, there are a variety of tools which have been used to measure any deterioration from normal of HRQL dimensions in SAHS patients and the change with various treatment options. HRQL measures which have different measurement properties and sensitivities may produce varied amplitude of results in the same population group. When comparing the impact of competing technologies in different disease-patient groups, any lack of uniformity in responses would make resource allocation difficult. Thus one cannot effectively compare the change in physical limitation scores in osteoarthritis in a specific population given total knee replacement, with mental health improvement seen after control of pain in patients with cancer, using a single HRQL tool.

There is also the evidence that patients with psychosocial disability as a result of disease tend to report HRQL assessments which may be more severely depressed than predicted by their disease severity [Allsup *et al.* 2002].

The EuroQol and SF36 or SF12 are currently being used widely with population norms being developed from various countries. This study demonstrates by the differences in this SAHS population group, that they may need further refinement before they can be recommended for use in health policy and planning [Jenkinson *et al.* 1998]. Table 9.1 illustrates the variety of sub-domain responses, effect sizes reported from different trials measuring the impact on HRQL in SAHS.

Table 9.1: HRQL domains showing change in SAHS patients

Study	no of patients	HRQL tools used	Domains involved	Conclusion
Wisconsin Sleep Cohort Study [Finn, *et al.* 1998b]	737	SF36	All except bodily pain & role emotional limitation	Social functioning & general health worst affected in AHI>15 hour^{-1}
Sleep Heart Health Study [Baldwin, *et al.* 2001]	5816	SF36	Vitality related to sleep disordered breathing	Severe SAHS showed lower scores in all dimensions
Jenkinson et al [Jenkinson *et al.*1997c]	90 (5 weeks on CPAP)	SF36, Functional limitation profile, EuroQol	Energy/ vitality, mental & physical component summary	FLP similar improvement; EuroQol no change
Ballester et al [Ballester, *et al.* 1999]	105 CPAP vs. CPAP+ conservative therapy	SF36	Energy/ vitality, mental health	6.5 Odds ratio for improvement
Yang et al [Yang, *et al.* 2000]	46 (AHI<5) 16 (AHI 5-15) 21 (AHI>15)	SF36	Mild-moderate = low physical functioning & role limitation physical	Severe = vitality, current health perception, positive affect
Meslier et al [Meslier, *et al.*1998]	3225 on CPAP (9 months)	Nottingham Health Profile	75% good scores in all dimensions	Scores linked to compliance (self-reported)
Sanner et al [Sanner, *et al.* 2000]	39 treated for 9 months (CPAP)	NHP, Complaint list, Verbal analogue scale	NHP=emotional & energy improvement	No difference in pain, social isolation, mobility, sleep & verbal analogue scale
Bolitschek et al [Bolitschek, *et al.*1998]	67 (CPAP) 21 (SAHS) 113 (Controls)	Munich Life Quality Dimension List	Physical condition, psyche, social life, everyday life deterioration	Treated same as controls
Lacasse et al [Lacasse, 2002a]	82 males	186 item questionnaire	Daytime symptoms, nocturnal symptoms, limitation of activities, emotions, inter-personal relationships	
Reda et al [Reda *et al.* 2000]	191 snorers 57 SAHS 105 12 months post UPPP	NHP	All 6 dimensions deterioration	Energy, emotional reaction improved
Walker-Engstrom et al [Wilhelmsson, *et al.* 1999]	37 oral appliance 43 UPPP	Minor symptom evaluation profile	Vitality, contentment & sleep	All dimensions improved, UPPP more contented

9.4.2 Mental health measures

Patients with SAHS in the RCT (*chapter VI*) reported a high prevalence of psychological co-morbidity with the GHQ28 and of anxiety/ depression based on the HADS questionnaire. A similar prevalence of psychological comorbidity is reported in patients presenting to casualty with chest pain and suspected coronary artery disease [Goodacre *et al.* 2001] and in surveys assessing the need for mental health services in primary care populations [Shapiro *et al.* 1985]. Both these measures were developed to identify psychological morbidity in patients with chronic diseases which may otherwise be missed and in order to focus specialised psychiatric care. By the nature of the disability suffered by SAHS patients in functioning at work, with family and friends and their chronic fatigue state, this condition lends itself to generate psychological debility, as reported by Veale et al from their qualitative study of the concerns expressed by SAHS patients [Veale *et al.*2002].

Thus there are 3 questions posed by this high prevalence;

(i) Is SAHS an independent cause of psychological disability among sufferers?

(ii) Is the disability suffered by patients due to SAHS, liable to be over-represented in HRQL and health status measurements due to their psychological co-morbidity?

(iii) Could the apparent lack of correlation between SAHS markers and HRQL decline be due to the influence of psychological co-morbidity?

The answer to the first question is available from the results of the RCT (*chapter VI*) which shows both a reduction in the prevalence of 'cases' of psychological morbidity and the scores on anxiety and depression in patients treated with CPAP. Compared to the improvement with CPAP use, patients in the lifestyle group tended to have a worse score on depression sub-scales. Similar improvement in mental health parameters is reported in the early literature [Millman *et al.*1989] although studies over 3 months, 12 months and 24 months have reported variable results. In an uncontrolled study 26/41 patients reported symptoms compatible with depression at baseline, 12 months after treatment

with CPAP only 50% reported improvement in mood [Yamamoto *et. al.*2000]. A case-controlled study with 60 patients and 80 controls, found no change in anxiety/ depression after 12 months of otherwise successful treatment with CPAP [Munoz *et. al.*2000].

The answer to the second question is less clear as evidence suggests that anxiety or major depression may result in a misappraisal of benign body symptoms in normal subjects [Spinhoven *et al.* 1997], and may also worsen the perceived health state in patients with physical illnesses [Sherbourne *et al.* 1999] [Wells and Sherbourne 1999]. Even fit and healthy individuals (aged 55-74 years) who reported increased anxiety/ depression scores on HADS were found to report lower health status after flu-vaccination compared to those without anxiety/ depression [Allsup and Gosney 2002].

Does psychological morbidity confound the relationship between nocturnal sleep variables and health status? There were no relationships seen between PSG variables and mental health scores in the study patients. The improved scores were related to baseline mental health scores but not to PSG variables. In another study, anxiety and mental stress was found to be related to AHI [Borak *et al.*1996] but the contribution of depression to symptoms of chronic daytime fatigue was found to be ten times that of nocturnal sleep disordered breathing in SAHS patients [Bardwell *et al.* 2003].

The overlap between the symptom complex associated with psychological co-morbidity (predominantly depression) and SAHS may contribute to the HRQL scores reported by patients at baseline, hence the benefits of technological innovation may not be accurately estimated if such HRQL tools are used in their appraisal. Thus resource allocation based on such measurements may be liable to a positive bias. While the first type of patient may not respond to treatment of SAHS and may require specialised psychiatric input, those with SAHS-related psychological co-morbidity may benefit from SAHS treatment.

The HRQL debility suffered by SAHS patients is predominantly related to mental health dimensions and related social functioning. Thus the SF36 (mental health dimensions)

and the mental health tools (GHQ28 & HADS) which both measure psychological co-morbidity possibly associated with or resulting from SAHS related disability and are closely related, suggesting a convergent validity. Thus while they may be used to measure the impact of disease and benefit of treatment options in SAHS patients, they would not be suitable for comparing the impact of treatment of other diseases or patient groups which may not have a similar mental health related component.

9.6 Lifestyle factors

Obesity and sleep hygiene factors may contribute individually to the disability suffered by SAHS patients and thus play an important role in planning health promotion strategies in this group. The initial concern expressed by Wright et al [Wright *et al.*1997a] of the confounding potential of obesity in assessing the impact of intervention in this group has been addressed by RCT design (*chapter V*) and controlling for obesity in statistical analysis.

The two remaining issues are, what is the contribution of obesity in the excess cardiovascular morbidity and mortality attributed to SAHS in population studies and secondly whether reduction of BMI contributes to improvement in health status for these patients. The design of the prospective RCT presented in chapter V does not help answer the first of these questions and there is scant (if any) evidence available from research in this field [Shneerson and Wright 2001]. Evidence for the reduction in mortality associated with intentional weight loss remains uncertain. Most large epidemiological cohort studies have failed to show a clear benefit in mortality with intentional weight loss, and have often suggested an increase in non-cardiovascular mortality [Dyer *et al.* 2000;Williamson *et al.* 1999] [Klein 2001].

Does reduction in BMI improve nocturnal sleep fragmentation parameters?

The data presented in chapter V suggests that there is a modest reduction in AHI and AI in these patients and a rise in sleep latency after intentional weight loss. Whether the improvements seen in (VAS scores) nocturnal sleep quality and reduction in daytime

sleepiness are a result of weight loss, sleep hygiene measures or merely a placebo effect remains uncertain. The change in ESS scores, do not reach statistical significance. There is some evidence that nocturnal apnoea frequency may be reduced after weight loss in SAHS patients but this is usually transient and only effective in severely obese patients after surgical weight loss strategies from uncontrolled trial data [Jones *et al.* 2004;Scheuller *et al.* 2001].

Thus there is insufficient evidence from well-designed trial data to support a major imperative into tackling obesity in non-diabetic, obese SAHS patients using non-conventional strategies. Use of conservative dietary and exercise strategies may be beneficial in improving sleep quality and daytime symptoms and reduction of cardiovascular risk factors in these patients. The contribution of newly licensed pharmaceutical agents such as Sibutramine [Bray *et al.*1996] and orlistat [Ballinger 2000] to weight reduction strategies remains to be assessed in this population group.

9.7 ECONOMIC EVALUATION

9.7.1 Health status measurement

Unlike the HRQL measurement techniques which are basically rating scales in each dimension, an alternative approach to health status measurement is patient preference assessment using utilities. Health status was measured using an interview based approach using the classical vonNeuman-Morgenstern theory [von Neumann and Morgenstern 1944] based standard gamble incorporating risk and the time-trade off method [Churchill *et al.* 1987] devised specifically for health status measurement. The third measurement method was based on the rating scale derivative indirectly from population values (EuroQol utility). In the absence of a 'gold standard' with total acceptability [Giesler *et al.* 1999] most researchers have used a combination of these methods in trials and compared their properties in individual disease scenarios.

Interestingly the SAHS patients in the study reported poor health status at baseline using both SG and TTO methods. Both these scores showed close relationship with each other and with the HRQL measures suggesting a convergent validity. The health status measures showed independence from confounding anthropometric variables except for TTO which had a positive relationship with increasing age. The TTO utility was the only outcome variable with a significant relationship seen with the primary SAHS disease marker (AHI) suggesting criterion validity.

Table 9.2 illustrates typical utility values obtained from different patient-disease combinations showing that SAHS patients rate their health status worse than many severe chronic debilitating illnesses.

Patients with psychiatric morbidity demonstrate health state preferences which are much lower than most physical conditions and in line with severe physical restriction e.g. major stroke risk < severe depression < untreated $SAHS^{sg}$ < cancer with a two-year survival and severe emesis < advanced Amyotrophic lateral sclerosis < untreated $SAHS^{tto}$. Patients with concurrent depression have been shown to be willing to accept a greater risk of death than those with no psychiatric disability [Schaffer et al 2002]. This has been a cause of debate and concern among researchers as there is a theoretical likelihood that health policy decision-making which is dependant on such assessments, might over-value the health impact of mental health interventions [Lenert *et al.* 1999] over others targeted at physical disability.

The utilities generated by this study have a very important difference when compared to SG/TTO based health status reported from many other studies. The SG utilities are lower than those obtained by the TTO method, although both show equivalent properties of reliability, sensitivity and discriminant validity. Most of the comparisons in the literature have found SG values to be higher than TTO values in the same disease-population scenario [Lundberg *et al.* 1999] [Morimoto *et al.* 2002]. This has been attributed to the inherent nature of patients (posed with the uncertainty of the preferences and the possibility of death in the event of a failure) to adopt a risk-averse attitude; which may

lead to higher values [Woodward *et al.* 1998]. Conversely SG obtained under certainty or linked (chained) [Jansen *et al.* 1998] to intermediate health states may produce values which are more in line with those obtained by TTO utilities.

The differences between SG and TTO utilities is probably attributed to differences in probability weighting, loss aversion and scale incompatibility which usually leads to higher values in SG and may increase/ decrease the TTO values [Bleichrodt 2002]. Table 9.2 illustrates the range of utilities obtained in different diseases using common methods.

On the contrary, in this RCT, SAHS patients with significant psychological co-morbidity (based on GHQ28, HADS & SF36) showed a risk-affinity and were less concerned with the possibility of death (in the event of failure) and may thus have produced lower preferences for their health states (compared to TTO utilities).

Similar to HRQL scores which tend to be lower in patients with significant psychological co-morbidity, this study demonstrates that the probable influence of psychological disability suffered by SAHS patients may lead to worse health state preferences.

Table 9.2: Utilities obtained from different disease-patient combinations

Study	Clinical scenario	Utility method	Values
Laupacis et al [Laupacis *et al.* 1996]	ESRD-Renal transplantation	SG	0.57-0.70
Revicki et al [Revicki 1992]	Depression	SG	Severe=0.3, Moderate= 0.55 -0.63, mild=0.64-0.73, on medic=0.72-0.83
Stavem [Stavem 1998]	Epilepsy	SG/TTO	SG=0.99, TTO=0.98
Tsevat et al [Tsevat *et al.* 2000]	Bipolar disorder-cure	SG/TTO	SG=0.70-0.77 TTO=0.61-0.71
Lundberg et al [Lundberg, *et al.* 1999]	Psoriasis Atopic eczema	RS/SG/TTO	RS=0.69, TTO=0.88, SG=0.97 RS=0.73, TTO=0.93, SG=0.98
Brown et al [Brown *et al.* 1999]	Diabetic retinopathy	SG/TTO	SG=0.88, TTO=0.77
Smith et al [Smith *et al.* 2002b]	Radical prostatectomy	SG	Baseline=0.9, sexual dysfunction=0.87-0.89, sexual urinary dysfunction=0.77-0.82, no complications=0.92-0.96
Kiebert et al [Kiebert *et al.* 2001]	Amyotrophic lateral sclerosis	SG	Stage I=0.74, Stage 4=0.45
Post et al [Post *et al.* 2001]	Stroke (meta-analysis)	SG/TTO	At risk=major 0.26-minor 0.55, recovered=0.4 major-0.72 minor, not recovered= 0.32 major-0.71 minor
Kok et al [Kok *et al.* 2002]	Benign Prostatic hypertrophy	TTO (public)	Worst =0.87
Coffey et al [Coffey *et al.* 2002]	Diabetes mellitus	SG	Type II Uncomplicated=0.69-0.65, Type I uncomplicated= 0.67-0.64
Grunberg et al [Grunberg *et al.* 2002]	Emesis/survival in cancer patients	SG (healthy volunteers)	6y/no emesis=0.89, 2y/emesis=0.46, survival 2-6y=0.67-0.78, emesis- no emesis=0.57-0.88
Tengs et al [Tengs *et al.* 2002]	Acquired Immuno Deficiency Syndrome	TTO	AIDS=0.7, Symptomatic HIV=0.82, Asymptomatic HIV=0.94
Siderowf et al [Siderowf *et al.* 2002]	Parkinson's disease	EuroQol/HUI mk II	0.58

9.7.2 EuroQol utilities

Health state preferences derived from the EuroQol questionnaire (*chapter VII*) showed higher baseline values when compared to those derived by SG/ TTO methods; and the change with treatment was also substantially smaller. This apparent discordance with the impact of treatment measured by the other methods in the same population has been reported similarly in the literature in SAHS patients [Jenkinson *et al.*1998]. Measures such as the EuroQol are now widely used in assessing the impact of healthcare interventions in various countries especially in Western Europe and incorporated in economic evaluations.

The discordance with values obtained by other methods raises two main issues; (i) Is the indirect assessment tool sufficiently sensitive to measure the impact of treatment in different patient-disease combinations? (ii) And should societal norms be given precedence over patient's own assessment in matters of resource allocation? Unlike the directly obtained utility values (as in SG/ TTO methods) the EuroQol derives its utility values indirectly based on population norms. Thus the potential of administering a simple questionnaire to assess both HRQL and health status in one sitting offers logistical advantages in large scale assessments. However such disparity of results obtained in certain patient populations may undermine the validity of the health policy decisions made on their basis.

It has been suggested that the EuroQol is 'less sensitive' to the impact of the disability suffered by SAHS patients [Jenkinson *et al.*1998], while it has a variable confidence in the results obtained in rheumatologic [Hurst *et al.* 1994] where it shows moderate to high correlations with measures of impairment and disability; or neoplastic diseases [Conner-Spady, *et al.* 2001]. Many patients with low EuroQol scores (including some with health states that were 'worse than death') had high health thermometer scores. In addition, the 'severe' value is so extremely abnormal that few patients endorse it especially in physical functioning dimensions. Penalty scores are applied to those with at least one maximally

abnormal score hence the scoring properties and distributional aspects of the EuroQol may indicate a lack of homogeneity in the lower end of the scale [Wolfe *et al.* 1997].

SAHS patients (*chapter VII*) with severely reduced utility values obtained by SG methods had higher values from EuroQol reflecting an opposite phenomenon (compared to stroke [Dorman *et al.* 1997] or rheumatologic diseases [Hurst *et al.*1994]) where patients are reluctant to report severe disability in physical dimensions. Thus due to the variable weighting of the physical and anxiety/ depression questions the results obtained in different diseases may be substantially different. There is also evidence of EuroQol being less sensitive at the ceiling (i.e. low levels of perceived ill-health) and throughout the range of health states when compared to the SF36, while skewed values are obtained in the physical dimensions [Brazier *et al.* 1993a].

The weighting in EuroQol is derived from population studies where typical case scenarios are presented to normal responders and utilities obtained by TTO method. Thus compared to directly obtained values of utility from patients (patient's preferences) the EuroQol indirectly derives these from population perspective. While EuroQol may be valid in comparing the effect of different technologies in the similar patient groups, it may not be comparing 'like for like' in diseases causing predominantly physical versus mental health problems. Recently methods have been suggested to minimise this skew in favour of physical disability [Brazier *et al.*1993a], however one may argue that in matters of health policy it is the population's imperative to decide whether allocation of resources should be preferably given to patients with disability in physical functioning rather than mental/ social functioning.

9.7.3 QALY

The incremental individual health preferences (utility) when combined with their life-expectancy generates 'the QALY gained', which has been used extensively in health economics and to guide resource allocation when comparing the impact of competing health care interventions. Compared to the conservative lifestyle intervention group, CPAP patients gained between 0.9 to 4.2 QALYs. Conceptually, the QALYs gained by

different health care interventions can then be compared in a head-to-head fashion in assessing the cost-utility ratios in health care resource allocation. Because the QALY conceptually encapsulates either a patient's own preference for a health state or a community perspective (when subjects are asked to value different health state scenarios), resource allocation based on such preferences are considered ethically justified in a welfarist perspective *(maximisation of health benefits from given resources*). The community perspective in this study is derived from the study population by summing the individuals' values. It is usually argued that this method of QALY generation and obtaining community preferences by summation of individual values is only valid under the principle of uncertainty i.e. using the standard gamble approach [Torrance 1986a;Torrance *et al.* 1989; Torrance 1986b].

QALYs generated by the three different methods (SG, TTO or rating scale i.e. EuroQol) were found to produce different results in this study, hence potentially reducing the certainty of basing resource allocation on such variable results. Since the SG method is based on the traditional utility theory and encapsulates the individual's health state preference under risk (or uncertainty) it is regarded as the 'gold standard' method by purists. However the utility values obtained by the TTO method [Torrance *et al.* 1972a] under certainty and the EuroQol derived index have been considered unsuitable for summation to obtain community preferences in the same way by some authors [Gafni *et al.* 1995] [Gafni *et al.* 1993c]. Similar discrepancies in health state utilities have been reported when different methods have been used to generate them and attempts have been made in various ways to resolve these differences [Hornberger *et al.* 1992; Read et al 1984; Mehrez *et al.* 1990b].

The health economic theory of utility generation and cost-effectiveness maximisation as a predominant vector in resource allocation decision-making, is still a matter of debate and some authors have highlighted that QALYs do not indicate the need of patients for a treatment, something which is considered important in health care provision [Cohen 1996].

Thus although QALYs demonstrate the benefit obtained by treatment with CPAP in this study (*chapter VII*), the amplitude of such a benefit as obtained by SG method was larger than that obtained by TTO; that generated by the EuroQol method was not statistically significant. All three were closely correlated with each other and with HRQL measures suggesting their convergent validity.

There have only been two other studies examining the cost-effectiveness of treatment in SAHS patients. In a retrospective and uncontrolled study with 19 SAHS patients established on CPAP therapy for a mean period of 9 months, Tousignant et al [Tousignant *et al.* 1994] demonstrated 5.4 QALYs gained by treatment (using the SG approach). However, the lack of randomisation, absence of a control group and retrospective assessment of successfully treated patients cannot guard against a treatment bias in the results.

The QALYs obtained were based on individual health preferences and summed to generate the community perspective; an approach considered compatible with economic theory. Although these patients had much higher health state utilities at baseline than in the present research (maybe subject to a positive recall bias), the number of QALYs gained from CPAP treatment were similar [Tousignant *et al.* 1994]. Similar results obtained from the Canadian study (mean duration of 9 months) compared to those obtained from 3 months of CPAP would suggest a maintenance of the benefit obtained on long term therapy.

In the only other published study with 46 SAHS patients (AHI>30 $hour^{-1}$) in a Spanish Hospital Sleep clinic, utilities were derived using the EuroQol health index. The baseline utility of 0.74 was reported to have improved by a modest 0.073 after 3 months of CPAP therapy [Mar et. al. 2003]. The main problem in this study was once again a lack of randomisation and absence of a control group. The authors have justified the use of EuroQol (previously demonstrated to be insensitive to the HRQL change in SAHS patients [Jenkinson *et al.* 1998]) by suggesting that they were interested in generating preferences and not HRQL.

On the basis of QALYs gained by CPAP over those gained by the control group, there is a clearly demonstrable 'effectiveness' of this form of therapy. This is in conjunction to the benefits demonstrated by other measures of effectiveness i.e. HRQL tools, ESS scores etc. and thus can be assumed to reflect a real impact of the health technology.

The question which remains is whether the size of change obtained by the SG method (under uncertainty) and that obtained by TTO method (under certainty) can be considered equally robust in health economic assessments. For the data presented in this research from SAHS patients, both the SG and TTO utilities demonstrate significant relationships with PSG variables (sleep latency, oxygen desaturation and AHI), demonstrating their construct validity, unlike EuroQol utilities. However, the impact of change with treatment may be exaggerated due to the psychological distress suffered by these patients, leading to a risk-affinity; hence higher SG changes in utility.

Furthermore, the SG method incorporates the concept of death in the event of treatment failure, which to SAHS patients may not be a 'real' possibility (except in RTAs). Hence utilities obtained via the TTO method are possibly more representative in chronic conditions such as SAHS, where death is not a 'real' possibility and patients are willing to exchange 'years of life' for perfect health.

Until such time as a 'gold standard' is reached most health economic assessments may need to use a variety of methods to generate the utility weights for QALYs and comparisons should take into account the method used in order to avoid bias.

9.7.4 Cost-utility

While the denominator in the cost-utility ratio i.e. benefit / utility has been established with the results of the RCT (*chapter VII*), there are certain issues regarding the cost framework used. Primarily SAHS is a disease causing mental health and social dysfunction with effects on job performance [Ulfberg *et al.* 1996], neuro-cognitive

function [Engleman and Douglas 1993b], accidents [Teran-Santos *et al.* 1999] and consequent health care resource use [Rodenstein 2000] [Douglas and George 2002] [Pelletier-Fleury *et al.* 2004]. The cost perspective used in this study was deliberately kept to NHS direct treatment costs with data collected for the NHS cost of a patient going through the study protocol. This faithfully mirrored the 'real life' scenario in the Birmingham Heartlands Hospital sleep service.

The only caveat to the above 'real life pathway' was not using the screening advantage of overnight home oximetry in addition to symptoms of snoring and SAHS to 'fast-track' patients through to treatment; this relatively inexpensive procedure may have bypassed the labour (and cost) intensive full polysomnography in some patients. Within the sensitivity analysis, costs obtained from three other NHS regions have been incorporated and presented in table demonstrating the stability (& generalisability) of the inferences drawn from the results obtained in the study centre.

The cost analysis did not take into account the societal perspective (i.e. increased performance, reduced driving risk, cost of accidents [Teran-Santos *et al.*1999] [Sassani *et al.*2004] [Pack and Pien 2004], insurance claims, job losses [Ulfberg *et al.* 1996], reduced use of hospital resources [Pelletier-Fleury *et al.* 2004] [Pack *et al.* 1999] other than for sleep disorder diagnosis & treatment). Inclusion of these broader costs to society would be likely to improve the cost /benefit ratio in further favour of the intervention [Pack and Gurubhagavatula 1999] [Rodenstein 2000].

The final results obtained show that treatment of moderate to severe SAHS patients with CPAP over their lifespan would cost between £1189 to £3034 per QALY gained (SG and TTO approach after discounting both costs and benefits) which falls below the 20000 GBP/QALY range recommendation for highly cost-effective interventions proposed by NICE in the UK [Tamisier, *et al.*2004]. These somewhat arbitrary cost/QALY thresholds proposed for such decisions vary according to national socio-economic norms and expectations [Franco 2004]. Table 9.3 presents a range of cost/ QALY ratios from a

literature survey conducted recently showing that the SAHS cost/ QALY ratios are likely to be well placed in the top five categories for cost-effectiveness.

There is an emerging trend for generating cost-effectiveness ratios for most interventions (table 9.3) as a method of changing decision-making behaviour and improving the efficiency of healthcare resource allocation [Alban 1994].

In the UK, recommendations by NICE based on cost-effectiveness along with professional analysis is currently being recommended for commissioning health care intervention [Hutton *et al.* 2000]but purchasers remain sceptical about affordability of such recommendations by the health services [Davies and Littlejohns 2002].

Table 9.3: Cost/ QALY ratios for various healthcare interventions

Intervention	Cost/ QALY £(s)
Cataract surgery in the first instance [Busbee *et al.* 2002]	1263 (2020)
Total hip replacement for >85 year olds [Chang *et al.* 1996]	2875 (4600)
Low molecular weight heparin for thrombotic disease [Gould *et al.* 1999]	4888 (7820)
Smoking cessation program using nicotine patches[Cromwell *et al.* 1997] [Fiscella *et al.* 1996]	3097-6839 (4955-10943)
Docetaxel vs. Paclitaxel for treatment of Breast cancer [Brown *et al.* 1998]	5384 (8615)
Carotid endarterectomy in asymptomatic patients [Cronenwett *et al.* 1997]	5000 (8000)
Cardioversion + Amiodarone vs. Cardioversion + Warfarin [Catherwood *et al.* 1999]	5813-11813 (9300-18900)
Screening for hypothyroidism [Danese *et al.* 1996]	5764-14122 (9223w-22595m)
Cervical cancer screening for HIV patients [Goldie *et al.* 1999]	8000-17250 (12800-27600)
Cochlear implantation in Large vestibular duct syndrome [Bichey *et al.* 2002]	11145 (17832)
Intensive therapy for IDDM vs. NIDDM [Herman *et al.* 1997]	12500-10000 (20000-16000)
Percutaneous stent insertion for Iliac arterial obstruction [Bosch *et al.* 1998]	12500 (20000)
Mechanical ventilation for Chronic obstructive pulmonary disease [Anon *et al.* 1999]	16427-27877 (26283-44602)
Drivers airbag vs. passenger airbag use [Graham *et al.* 1997]	15000-38125 (24000-61000)
Screening for carotid atherosclerotic disease high vs. low prevalence [Derdeyn *et al.* 1996]	21956-32868 (35130-52588)
Screening > 25 year olds for Type II diabetes [Anonymous 1998b]	35406 (56649)
Insulin like growth factor in amyotrophic lateral sclerosis [Ackerman *et al.*1999]	42150 (67440)
Prostatic biopsy for PSA levels at 20 mg/ml to 0mg/ml> 50 year olds [Gottlieb *et al.* 1996]	42500-171875 (68000 to 275000)
Angiography, SPECT over Stress echocardiography, PET for Ischaemic heart disease [Garber *et al.* 1999]	58750,46875,400000 (94000,75000, 640000)
Erythropoeitin for Chemotherapy induced anaemia [Barosi *et al.* 1998]	118533 (189652)
Transmyocardial laser revascularisation for angina [Campbell *et al.*2001]	142500 (228000)
Interferon β in progressive Multiple sclerosis patients [Forbes *et al.* 1999]	1024667 (1639467)

9.8 DIFFUSION & ADOPTION

The pathway for an innovation from the bench to the end-user is conceptualized to pass through a staged process of diffusion, dissemination, and implementation/ adoption. Using a staged model of behaviour change, diffusion is seen as a precursor for dissemination activities, which in turn prepares physicians to consider change in their practices. In the case of CPAP use in SAHS patients, the rate of adoption has been variable in different parts of the world.

9.8.1 Innovation characteristics

Prior to the introduction of CPAP as a treatment option for SAHS in 1981 [Sullivan *et al.*1981], and its subsequent commercial availability in 1990 the treatment for this chronic condition involved surgery, which due to increased associated mortality and morbidity tended to be reserved for the more severe end of the disease spectrum. Compared to the alternative therapies (i.e. laser palatoplasty [Littner *et al.* 2001] and mandibular advancement devices [Marklund *et al.*2004]), CPAP had a number of advantages as an innovation. Unlike surgery, CPAP could be potentially used in almost all patients with SAHS regardless of severity, it was a reversible option, it was painless, it was not associated with any therapy related mortality risk and even morbidity associated with its use was less than with surgery [Meslier *et al.*1998]. Yet the benefits were apparent after the first nights' use by the patient [Karlawish *et al.* 2001].

CPAP also had a reported acceptability of 85% [Engleman *et al.* 1993c] [Engleman *et al.*1994c] [Meslier *et al.*1998] [Noseda *et al.* 2000] [Zozula and Rosen 2001a] among moderate to severe SAHS patients as demonstrated in [Popescu *et al.* 2001] [Meslier *et al.*1998]chapter IV. Some patients may report discomfort from the tight-fitting mask [Janson *et al.*2000] and dryness of the oral mucosa [Massie *et al.*1999]. These are usually solved by simple measures such as humidification [Massie *et al.* 1999] and do not appear to interfere with long term usage [Meslier, *et al.*1998] [Popescu *et al.*2001]. CPAP is known to be preferred over placebo [Montserrat *et al.* 2001] or surgery [Lojander *et al.* 1996] [Pepin *et al.* 1996] by a majority of patients, although oral devices were found to be

the most favourable [Wright *et al.* 1998b]. Compliance studies have found an average use of between 3-5 hours/ night for most patients on the CPAP, with almost equivalent clinical and symptomatic improvement [McNicholas 1997].

From the professional point of view, the questionnaire survey results in chapter VIII demonstrated that the majority of primary and secondary care physicians prefer CPAP over surgical UPPP and oral devices, believe that benefit can be measured both in subjective and objective terms, and that it is relatively easy to use and understand for most of their patients. The primary indication for CPAP prescription was to alleviate their patients' symptoms. The properties of an innovation to provide benefits at a reduced risk to the user and it's relative ease of use, when compared to established options, may have a significant favourable impact on diffusion [Batz *et al.* 1999].

CPAP as an innovation demonstrates characteristics which should have favoured its rapid diffusion and adoption among SAHS patients and their clinicians. However, the possibility of a permanent cure from surgical options may seem more attractive to some patients (more often younger and male) rather than merely achieving control offered by CPAP [Gregg *et al.* 2000].

The post-introduction technological development of an innovation may impact on its rate of adoption [Andolfatto *et al.* 1998]. However the developments in CPAP technology (i.e. reduction in size, operating noise) and the use of auto-titrating machines have not been shown to improve patient compliance significantly to justify the additional costs [Ayas *et al.* 2004]. Although some researchers argue that these auto-titrating machines may have a role in home-based titration thus reduce the operational cost of service provision [Lloberes *et al.* 1996] [Teschler *et al.* 1997] [Berry *et al.* 2002].

Unlike the first masks used which were moulded to take the shape of the individual patient [Sullivan *et al.*1981], recent commercially available masks have limitations in balancing the air-tight fit on widely variable cranio-facial architecture with a comfort level which is conducive to sleep [Janson *et al.* 2000]. Whether user-feedback from patients

would have helped to change the mask production systems and improve acceptability is not known and may be an issue which manufacturers may be persuaded to address in the future (personal communication from ResMed R&D chief in the USA). Innovations are often enhanced with end-user participation /feedback helping to shape and make the innovation more widely acceptable [Abed *et al.* 2000].

9.8.2 Innovativeness

Data from the questionnaire survey (*chapter VIII*) indicate that of the primary care physicians with an interest in sleep disorders, almost a third were early adopters/ innovators while half were in the early majority. Similar ratios of innovativeness were also found among secondary care respondents. This suggests a positive adoption bias for new technology among primary (and secondary) care respondents.

As the primary care questionnaire was sent to PCT Chief Executives with a covering letter requesting them to forward it to GPs who either had an interest in sleep related disorders or in new technology or responsible for healthcare commissioning, there may be a higher proportion of 'more innovative' individuals in the group surveyed. When the diffusion and adoption of coronary stents were compared with that of the magnetic resonance imaging (MRI) scanners or the introduction of cholesterol lowering agents in the West Midlands region, enthusiastic individuals (opinion leaders and early innovators) had a significant role in the rapid diffusion of stents [Booth-Clibborn *et al.* 2000].

Innovativeness also is known to depend on a clinician's position within a social network, where secondary care physicians are likely to be more innovative (as seen in the survey) than primary care physicians [Burt 1980]. Although physician conservatism is often identified as one of the primary causes of slow diffusion [Banta *et al.* 1993] the findings from this survey (*chapter VIII*) would make this unlikely as a cause for the slow adoption of CPAP in the UK.

9.8.3 Physician networks & geographical influence

In the case of diffusion of CPAP, physician networks (peer-to-peer) were reported to play a major role in the dissemination of information between secondary and primary care.

This may have influenced an increased professional awareness of SAHS among primary care physicians and resulted in the increased number of referrals received by secondary care physicians providing diagnostic and treatment facilities, as demonstrated in chapter IV and chapter VIII. The survey (*chapter VIII*) respondents also reported an absence of a defined structure for the distribution of such 'expert' information from secondary to primary care, with a view to increasing adoption and making such treatment more widely available in the NHS.

The survey of primary care physicians identified personal contact with local expert physicians (90%) as one of the primary ways of influencing referral behaviour for SAHS. This was followed by scientific journals (62%) and peer-to-peer (55%) informal contact. Media representation was the least likely factor to influence decision-making among the majority of primary and secondary care physicians in the questionnaire survey. While in diseases such as cancer, acquired immune deficiency syndrome or dissemination of family planning education, mass communication agencies have important roles [Alcalay 1983;Gupta 1996] [McAlister 1991] [Piotrow *et al.* 1991].

Diffusion is also dependant on the position of the prescriber in the social network structure, where 'local experts', consultants in DGHs with an interest in a technology may play an important role in the diffusion of knowledge on its diagnosis and treatment for their local primary care contacts [Burt 1980].

When asked about the existence of a proper structure of knowledge diffusion from secondary to primary care within the NHS majority of primary care physicians denied that such a system existed (85%). Even among the secondary to primary care, diffusion of knowledge the system seemed to be informal. Both lack of adequate information [Brown 1984] and spontaneous diffusion of knowledge [Buss *et al.* 1999] is known to be an important factor in the poor adoption of technology.

In the absence of a national framework or guidelines in the UK, local innovators/ early adopters are likely to have a significant role in regional differences in availability of

diagnostic facilities and adoption of CPAP innovation. Such examples of local initiative have been found to be significant in influencing diffusion compared to national strategies in quality improvement adopted in hospitals in Finland [Baptista 2000] [Brommels *et al.* 1997].

9.8.4 Patients

End user demand for an innovation is one of the factors influencing the rate of diffusion of technology [Byungryong *et al.* 1996]. Although there has been a steady increase in the number of patients approaching their GPs with symptoms of EDS suggestive of SAHS (*as seen in chapter IV and reported by respondents in chapter VIII*), there is hardly any visible influence of patient organisations in the diffusion of CPAP in the UK.

Unlike the USA, where organizations such as the National Sleep Foundation [Anon.2004b] wield a significant influence on policy making and patient self-education in this field, such activities have not yet made a significant contribution in the UK. The Sleep Apnoea Trust [Anon.2004c] (a patient led self-help organization), British Thoracic Society, British Sleep Society (an association of professionals with an interest in sleep disorders) have little demonstrable influence on the media, governmental agencies responsible for health policy and resources, or in mass education/ awareness programmes. In comparison, the National Asthma Campaign, British Lung Foundation, British Heart Foundation and the Cystic Fibrosis Trust have an important role in raising the profile of the disease to the public through mass education, dissemination of material to the media, raising funds for dedicated research, self-help and influencing policy.

9.8.5 Industry

Commercial production of CPAP was commenced by ResMed Inc in 1990 [irasia.com 2002;Mack 1999;ResMed Inc 2003] and since then the company has grown in size and capital at a rate of almost 20% per annum [Mack 1999].The survey results indicate however that industry has had little influence in the diffusion and adoption of this technology in the UK. Whereas in Australia and USA, CPAP manufacturers are acknowledged for their role in the support of research and development, maintaining close links with the medical fraternity and engaging in governmental dialogue, there is

little evidence of such an impact in the UK [irasia.com 2002]. Both primary and secondary care physicians placed influence from industry low in their profile of factors influencing decision-making in the UK survey (*chapter VIII*).

In the news letter the Sleep Apnoea Trust has commented on the lack of industry support for their educational activities [Anon.2004c]. Personal interviews with industry sources [Newby 2002] have identified that the slow diffusion and growth of the regulated UK market in CPAP devices acts as a deterrent for provision of resources for the support of patient awareness campaigns and research grants.

Another factor in the lack of industry engagement in the UK NHS sector is due to the NHS purchasers negotiating lower prices based on the power of buying machines in large numbers, hence reducing unit prices and profit margins. This phenomenon has not been balanced by sufficient growth in number of machines in order to justify the lower prices from the manufacturer's perspective. Such a strategy although artificially driving prices down to the benefit of the consumer, has had a negative impact on the growth of the CPAP industry. Thus price regulation without the benefit economics of scale in a managed care environment may have a negative influence on the diffusion and adoption of new technology [Banta *et al.* 1983].

Commercial promotion or marketing by manufacturers are important in expediting diffusion in the case of statins [Booth-Clibborn *et al.* 2000] but there is little evidence of large scale marketing of CPAP in the UK and hence little impact on its adoption.

The failure of further technological improvement in CPAP technology (i.e. the introduction of automatic CPAP titrating machines) to impact on the growth of the CPAP market in the UK has had a negative impact on the resources available from the industry for professional and public awareness campaigns. A study of innovation in cotton spinning machines demonstrated that expectations of continuing incremental change may have actually slowed diffusion, while potential for increased profitability from their adoption did not reinforce the rate of change resulting in a slow down in the industry [Antonelli 1989]. Hence the focus of the CPAP manufacturers has shifted towards finding

wider uses for the CPAP therapy in patients with heart failure, cerebrovascular disease, Alzheimer's disease- extending beyond the SAHS horizon [ResMed Inc 2003].

While emerging research evidence on extended roles of CPAP in such diseases in the USA [Yan *et al.* 2001] [Bradley *et al.* 2001] has a positive role in further improving adoption of such machines, there is little demonstrable transfer of this evidence in the UK medical community. Hence the disparity in the rates of diffusion of this technology between the USA/ Europe and UK is likely to continue at a potential disadvantage to the sufferer.

9.8.6 Organisational factors

Primary and secondary care physicians responded to the questionnaire highlighting financial restrictions as the most important factor responsible for their patients not receiving therapy for SAHS. The lack of adequate facilities for diagnosis [Semple and Gibson 1993], long waiting times, lack of patient education campaigns and lack of governmental imperative [Sleep Alliance. 2004] were also shown to be responsible for the slow adoption of CPAP within the NHS in the UK.

Financial regulation and the absence of incentives (in a managed care scenario) may have had a role in slowing down the adoption of innovations (as in the case of MRI scanners between 1980 and 1990), regardless of their clinical effectiveness [Baker 2001]. Similar budgetary constraints have been found to slow down the diffusion of minimally invasive therapy in Europe [Banta 1993].

Although professionals often are highly respectful of scientific endeavours, in reality, daily decision making is shaped more by power structures, ingrained routines, and established resource configuration than by current scientific findings. In most organizations, standard operating procedures and behavioural norms are the major influences on workplace practices; scientific evidence plays a minor role [Rosenheck 2001]. A logistical barrier in the application of the research in complex organisations such as the NHS may require the collaboration of multiple individuals and dynamic environments with an extensive turnover. This may result in constant personnel changes and diminished

commitments. Success may depend on the commitment of key people (opinion leaders) within the organization to see the activities through from planning to implementation to evaluation [Rosenheck 2001].

CONCLUSIONS

9.9.1 Contribution to new knowledge

The research undertaken and presented in this thesis was designed to appraise CPAP as a health technology and explore its diffusion, and has contributed significantly to new knowledge in this field. This includes one of the first prospective, randomised controlled trials to assess the clinical and cost effectiveness of CPAP against a standardised lifestyle intervention strategy; the second known study world-wide to apply and assess generic health related quality of life, mental health tools and health status measures in this patient group, and the first to do this prospectively; and the only study to date which has explored factors influencing diffusion and adoption of CPAP in the UK.

Thus firstly, this research has addressed the dearth of well-designed RCTs in assessing the impact of SAHS, and in particular the principal criticism of previously published studies regarding the influence of co-morbidities (i.e. hypertension, cardiovascular disease etc...) and lifestyle factors such as obesity and smoking. The RCT data (*chapter V*) showed that CPAP demonstrated a significant efficacy in reducing the baseline AHI, AI and EDS and improving neurocognitive function in these patients. The lifestyle intervention in the control arm of this RCT was designed to evaluate the impact of this strategy in a real life DGH scenario potentially applicable to all secondary care sleep clinics in the UK. The data demonstrated that lifestyle intervention was also modestly effective in reducing weight and improving sleep-related disease parameters.

Secondly, the research evaluated the reliability and validity of 2 widely used generic multi-dimensional HRQL tools (SF36 & EuroQol) in the assessment of the impact of CPAP in SAHS patients and compared them to the mental health assessment instruments (HADS & GHQ28), chapter VI. Patients on CPAP demonstrated significant improvement in social functioning, energy/vitality and mental health dimensions of SF36. The changes in the physical dimensions were significantly less and remained sub-normal compared to population values. The mental health assessment tools showed a reduction in anxiety and depression scores and the number of patients classified as 'cases' with significant

psychiatric morbidity versus 'normals'. The EuroQol thermometer visual analogue scores (VAS) showed an improvement and discriminated between the groups but the EuroQol scores were less sensitive. Patients in the lifestyle intervention arm demonstrated modest improvement in VAS but not in HRQL measures. There was even a trend to increased the numbers of 'cases' with psychiatric morbidity and depression scores in this group.

Thirdly, the research evaluated and compared 3 different methods of generating QALYs using the standard gamble (SG), time-trade off (TTO) and EuroQol utilities, chapter VII. Both the SG and TTO methods demonstrated construct and convergent validity and showed improvement in health status after intervention. The improvement recorded in the lifestyle intervention arm was modest compared to the CPAP arm. The EuroQol index did not demonstrate sensitivity to changes with intervention and failed to discriminate between the groups after treatment suggesting that it may not be an appropriate measure for use in this disease or patient group.

The direct QALYs generated in this prospective, randomised controlled trial were used to undertake a cost-utility analysis of CPAP in SAHS. This is the first and presently the only such economic evaluation study in SAHS. The cost/QALY ratios obtained were well below the £20,000 / QALY threshold recommended by NICE in the UK [NICE 2004]. The cost utility ratios remained robust when incorporating costs from other NHS regions a sensitivity analysis was undertaken [Chilcott.J, 2000]. Patients with SAHS demonstrated a risk-affinity resulting in utilities generated by SG method being lower than those generated by TTO method at baseline. Thus, the increment in utilities obtained by SG method was higher than TTO generated utilities with intervention. The TTO generated utilities demonstrated a relationship with age, where at extremes of age, respondents have been known to over-estimate or under-estimate their health status [Martin, 2000].

Fourthly, the research on factors influencing diffusion and adoption of CPAP presented in this thesis is the only study of its kind in the area of SAHS, chapter VIII. This research demonstrated that CPAP, although known to have characteristics which may favour its adoption by secondary and primary care prescribers as well as patients, had a slow and

variable adoption in the UK compared to Australia, USA and similar economies in Western Europe. As an innovation, CPAP demonstrated a high rate of acceptability and tolerability among patients included in therapeutic trials and followed up over the seven year retrospective study period (*chapter IV*). This was also demonstrated in the RCT presented in chapter V where 34/37 of trial subjects continued to use their CPAP for the trial period. In addition, the questionnaire survey respondents in chapter VIII also reported the tolerability and acceptability of CPAP to be strong predictors of its successful adoption by patients. The majority of respondents to the primary and secondary care survey demonstrated a clear understanding of the benefits of the CPAP therapy and the indications for treatment.

While the primary care respondents felt that CPAP may be replaced by a more effective and patient friendly option in the future, the secondary care respondents felt CPAP was likely to remain the most effective option in the near future.

Both primary and secondary care respondents considered themselves high in the innovativeness scale (innovators or early majority) and gained most of their knowledge from local experts, informal peer-to-peer social networks and scientific journals.
They reported absence of structured communication pathways for the education of fellow professionals, which may slow down the rate of knowledge diffusion and may be affected by geographical availability of local experts. The absence of a structured dissemination mechanism for expert knowledge on such systems within the NHS led to increased reliance on local champions and local experts and informal diffusion of knowledge, which may have had an adverse effect on adoption.

The respondents reported little influence of media or patient-support groups on the diffusion and adoption of CPAP in the UK. This may be why there is limited impact on the public and therefore influence health policy makers and resource allocation.
There was little or no reported influence from the CPAP manufacturing industry especially in the feedback-reinvention of CPAP loop in the UK and in increasing public and professional awareness.

One of the major hurdles in the diffusion and adoption of CPAP was reported to be budgetary restraints within the NHS and the inadequate availability of diagnostic and treatment facilities in the UK, leading to a time lag.

9.9.2 Recommendations

1. Improving the nationwide uniform availability of diagnostic and treatment facilities for SAHS in the UK would help to reduce the number of untreated patients, improve the rapid access to treatment and have a positive impact on individual HRQL and benefit to society.
2. The cost of untreated disease to society (manifest in losses through accidents, poor performance, etc.) and the potential benefit from treatment provision needs to be assessed in future studies and balanced against the cost of treatment provision, in SAHS. This would accurately reflect the cost-benefit ration for healthcare intervention in this sector.
3. The benefit of lifestyle intervention in SAHS would need to be assessed using larger trials, longer periods of follow up and by the incorporation of pharmacotherapy in the reduction of obesity.
4. Whereas variation in the impact of different therapeutic options in a particular patient/ disease group can be assessed using disease specific measures, the concurrent use of generic measures (especially patient preference variables) routinely in trials would help achieve universality and allow for their use in prioritisation and resource allocation decisions.
5. There is a need to investigate with population based prospective cohort studies whether patient with SAHS are at risk of increased mortality due to the condition itself and whether initiation of CPAP therapy modifies this risk. As the presence of obesity, hypertension and other co-morbidities may impact adversely on this perceived increased risk. Further studies are needed to categorise the contribution of SAHS to increased cardiovascular, cerebrovascular or diabetic risk controlling for the risk from obesity, smoking and hypertension
6. Fast-tracking of symptomatic patients by using overnight, arterial pulse oximetry/ limited sleep studies would reduce cost of investigation and potentially reduce waiting times.

7. Conducting larger scale RCTs in patients with different levels of SAHS severity in order to assess cost-effectiveness of healthcare intervention using patient preferences (utilities).

8. Health technology appraisal of established innovations needs to be conducted alongside RCTs, especially incorporating generic outcomes data and cost-effectiveness analysis.

9. There is a need for further research to identify 'gold standard' in measuring patient preferences which demonstrate good sensitivity, specificity and reliability in majority of chronic conditions to allow comparisons. Although HRQL measures are important in identifying the degree and type of disability suffered by patients it is not appropriate for use in resource allocation as patient preferences are not incorporated.

10. Encouragement of mutual cooperation and coordination of the activities of patient self-help groups and professional bodies to increase public awareness and improve provision of resources for treatment of SAHS patients.

11. Systematic dissemination of clinical and economic evaluation data to adopters of healthcare innovations at various levels within the NHS, purchasing authorities and health policy makers may help to set priorities at local and national level and help achieve uniformity in healthcare provision across the country.

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APPENDIX

APPENDIX I

BIRMINGHAM HEARTLANDS HOSPITAL RESEARCH AND ETHICS COMMITTEE
APPLICATION

Title of the project:
A Study of the Prevalence, Quality of Life and Health Economic Impact of Sleep Apnoea/ Hypopnoea Syndrome and the effectiveness of treatment with nasal Continuous Positive Airway Pressure in patients with and without cardiovascular co-morbidity.

2. **Background of the project**:

The Sleep Apnoea/ Hypopnoea Syndrome (SAHS) is the commonest of the sleep-wake disorders. Although, public and professional awareness has increased rapidly over the last two decades, research, diagnosis and treatment in the UK lags behind Australia, USA and other European countries. The SAHS is characterised by recurrent obstruction or narrowing of the upper airway during sleep, causing episodic asphyxia leading to recurrent arousals and disrupting sleep to the point of injurious daytime consequences.

Prevalence studies in the adult population [2] found that 2% of women and 4% of men had both significant daytime sleepiness and an apnoea/hypopnoea index (AHI) of >5/hr of sleep; thus assuming the dimensions of a major health hazard.

The manifold consequences[6] of untreated SAHS from published epidemiological studies with cohorts followed up for more than 7 years, include cardiovascular and cerebrovascular disease, (hypertension, heart attack, stroke)[4], neuro-physiological disorders, (depression, loss of memory, loss of concentration, deterioration in intellect, alteration in personality and impotence in men), and social consequences (adverse effects on capacity to work, marital harmony) and road traffic accidents. In patients with Congestive cardiac failure the prevalence of SAHS is estimated to be 40%-50% contributing significantly to mortality, deterioration of cardiac function and arrhythmia.

Nasal continuous positive airway pressure (CPAP), first described in 1981 [9], is a simple and effective treatment. Other treatment modalities include laser palatal surgery and mandibular advancement devices. Their efficacy is not proven.

Recently, a major re-appraisal of CPAP treatment has been triggered by the publication of a systematic review into the health effects of SAHS. 'Health effects of Obstructive sleep apnoea and the effect of treatment with nasal CPAP(Wright et.al) Investigation and treatment of the SAHS has been adversely affected by this document, although the authorship of this publication did not include a specialist physician working in the field of sleep disorders. Evaluated within the current concepts of evidence based medicine, much of the earlier published literature in sleep apnoea has been criticised for small sample sizes, poor design, lack of correction for confounding variables, few double blind trials and lack of stratification for severity of the disorder. Although there is evidence of the effectiveness of CPAP in improving daytime somnolence, there are few data on its effect on health and the quality of life. Also, there are no studies on the health economic impact of the disease and the cost-benefit analysis of its treatment with CPAP.

In the light of current financial constraints, within the Health service, there is an emergent need to assess the quality of life (QOL) and cost-benefit ratio of CPAP treatment of SAHS; in order to justify public funding and release further much needed resources, for the management of this common and disabling condition. Preliminary studies have shown a tremendous beneficial effect of treatment of

patient's with cardiovascular co-morbidity in reducing hospital admissions, transplant lists and improving survival. Data on quality of life and health economics is needed.

3. **Hypothesis:**

(a) The Obstructive Sleep Apnoea/ Hypopnoea syndrome (SAHS) adversely affects health and quality of life. It incurs a significant cost to the individual, health services and society.

(b) This can be effectively improved by treatment with nasal continuous positive airway pressure, (CPAP) resulting in a significant saving in Health care resources.

(c) To calculate the cost-benefit ratio of treating patients with varying severity of SAHS and CCF, based on physiological and symptomatic parameters and hence developing guidelines for selecting the at risk group, with a potential for most health, quality of life and economic benefit.

(d) To develop and validate a questionnaire for SAHS, which would be specific to the different dimensions of disruption of health (both mental and physical) and quality of life as well as being sensitive to identify change due to treatment.

4. **Design of the Trial:**

All patients aged (18-70 years) from the BHH clinic referral population, with snoring, daytime somnolence, and symptoms to suggest CCF, would, after informed consent, be recruited into a prospective study. After assessment of baseline general health, QOL and Epworth Sleepiness Score (ESS), patients would undergo screening oximetry and polysomnography (including EEG) to diagnose and quantify SAHS. Cardiac status would be assessed using New York Heart Association (NYHA) dyspnoea scale, Echocardiography and MUGA scanning. Patients would be grouped into isolated SAHS, SAHS with CCF and CCF without SAHS. Based on AHI, a measure of the number of episodes of obstructed breathing per hour of sleep, patients would be stratified into mild (AHI >5-10) and moderate to severe (AHI >10). This would follow prescription of formalised and written lifestyle advice, including dietetic support, and advice on stopping smoking and reducing alcohol consumption.

Patients with SAHS and SAHS+CCF would be randomised into a double-blinded, placebo-controlled trial of CPAP treatment. The treatment phase would consist of a therapeutic level of CPAP for 6/12months.

Health, QOL, ESS, physiological parameters and a cost-benefit analysis (utilising time-trade off principles) would be assessed at baseline, and after completion of the double-blinded treatment phase. During this stage monthly diaries will be collected, recording data on health, GP visits, hospital admissions, clinic visits, days off work, marital relations, mood scores and employment, to assess economic impact of the treatment.

Data Analysis:

Primary variable for comparison is the effect size in QOL scores before and after treatment with CPAP.

Secondary variable is the quality adjusted life years added by treatment with CPAP and cost-effectiveness analyses.

Tertiary variables include change in ESS, AHI, Oximetry, echocardiography, NYHA dyspnoea score, Health related activities, days off work, marital relations, mood score and employment.

All the variables would be compared within the group of patients with moderate to severe sleep apnoea, to evolve a statistically significant, selection criterion for prescription of CPAP to the patients with a definite demonstrable potential for benefit.

Data from the generic quality of life questionnaires and the cost-benefit analyses would be used to compare with other chronic, disabling disorders in the Quality Adjusted Life Years (QALY) league tables, to help rationalise distribution of resources in healthcare.

5. **Patient Selection Criteria and Population Size**

All willing adults aged 18-70 years referred to the Medical & Sleep Clinics in Birmingham Heartlands Hospital from the commencement of the study with; snoring and disabling daytime somnolence or ESS >12 or symptoms suggestive of SAHS and CCF. Oximetry dip index of >5/hr, AHI >5/hr of sleep during polysomnography.

Criteria for the treatment group; AHI >10/hr of sleep during polysomnography

Exclusions; (i) inability to comply with protocol
(ii) Inability to undergo polysomnography
(iii) Inability to have a trial of CPAP.

Number of patients; Based on very few published trials in the literature and effect size, our estimate is that 100 patients would be adequate for statistical analysis and to detect change in primary variable

6. **Measurements to be made & Assessment of risks**:

(i) General Health: clinical examination, blood pressure, urine biochemistry, blood biochemistry and thyroid function tests.
(ii)Physiological: Oximetry, Pulmonary function tests, Capillary blood gases, ESS, Sleep specific questionnaire, and Polysomnography (Compumedics sleep system with EEG, ECG, EOG, EMG, movement score, noise recording and infra-red video of sleep activity)
(iii) Cardiac investigations; echocardiography, MUGA scan, NYHA dyspnoea score
(iii)QOL: Short Form36 (SF36) and European Quality of Life (EUROQOL) generic quality of life questionnaires.
(iv)Health economics: Quality adjusted life years generated from time-trade off scores, with the help of scenarios and questionnaires.

All the above parameters are measured routinely in all patients referred to the clinics and involve no perceivable risks. The questionnaires are simple, straight- forward and designed to be done in less than thirty minutes.
The treatment with CPAP is an established safe treatment modality since 1983 and only very few reported side-effects are noise, nasal congestion and skin excoriation in areas of contact with ill-fitting masks.

7. **Names of Investigators**:

Dr. R M Cayton MD FRCP, Consultant Physician
Dr JM Beattie FRCP, Consultant Physician
Dr. I Chakravorty MRCP, Clinical Research Fellow
Mr. M Hilton BSc, Clinical Scientist
Ms. S Sapiano , Senior Technician

Ms. H K Ruprai, Sleep Technician
Heartlands Sleep Clinic, Department of Respiratory Physiology, BHH
Cardiology Clinic, BHH

8. **Duration of the Project**:
Recruitment of patients; Nov'97-Jun'98
Follow up and replacement of drop-outs; July'98-Jun'99
Data Analysis and writing up; Jul'99-Oct'99

9. **Venue:**
Depts of Respiratory Physiology, Cardiology and The Sleep Laboratory on Ward 10 in Heartlands Hospital.

10. **Nature of Consent**:
Written Informed Consent

11. **Remuneration of the subjects**:
None

12. **Financial Interest to Department/Investigator**:
None

13. **Involvement of other Depts**:
Clinical Pathology and Dietetic Departments in the Heartlands Hospital
(As part of routine assessment of patients)

14. **Approval of patient's General Practitioner**:
It is envisaged that formal approval would not be necessary but GP would be kept informed of details of patient's progress.

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Dated: 28th Aug'97

Dr. R M Cayton MD FRCP
Consultant Physician
Dept. of Respiratory Physiology
Birmingham Heartlands Hospital.

FORM I A

Projects involving Drugs or Appliances

1.**Name of Appliance**: CP 90, Device for delivering Continuous Positive Airway Pressure. Manufactured by Devillbiss, ResMed, etc.

2.**Pharmacology/Principle**: Generation of a continuous positive pressure with a facial mask delivery system for ramping open the collapsible upper airway during the low muscle tones associated with deep sleep.

3.**Side-effects**:
Noise, nasal congestion and skin excoriation in case of ill fitting masks. Used in the treatment of patients since 1983 with more than 2500 machines prescribed every year in 12 centres in UK.

4.**Project**:
Product licence
Clinical Trials Certificate
Clinical Trials Exemption
None of these.*

5.**Supported by an Industrial Company**:
Not yet.

6.**Clinical Trials Compensation Statement from Sponsoring Company**:
Na

7.**Radioisotopes used**:
Not used

PATIENT INFORMATION SHEET

A study of the clinical, quality of life and economic effectiveness of continuous positive airway pressure therapy for the Sleep Apnoea Hypopnoea Syndrome.
Heartlands Sleep Disorders Clinic
Department of Respiratory Physiology, Birmingham Heartlands Hospital

The combination of **snoring, excessive daytime sleepiness** and a lack of energy is due to a condition called the **sleep apnoea hypopnoea syndrome,** which may go largely unrecognised both by the sufferer and his doctors. This condition occurs due to the repeated partial or complete obstruction of breathing associated with the muscle relaxation during sleep, causing a lack of oxygen in the body. This in turn causes the sufferer to wake up many times during the night, leading to an un-refreshed sleep and serious daytime consequences.

Untreated sleep apnoea is associated with many adverse health effects including high blood pressure, irregularities of the heart, heart attacks, stroke, irritable personality, depression, impotence, loss of memory and poor intellectual capacity. It is being increasingly identified as a cause of serious lack of concentration and excessive sleepiness leading to accidents on the roads and at work.

A simple and relatively new treatment option is sleeping with a mask over the nose connected to a small machine (**CPAP**) which keeps blowing air at a higher pressure to keep the airways open. This prevents snoring and normalises breathing during sleep, hence improving sleep quality, daytime performance and reversing the serious health consequences of sleep apnoea hypopnoea syndrome.

We need your help in conducting a trial to find out more about the adverse health effects of sleep apnoea and to assess the effectiveness of this relatively new form of treatment. This trial may provide the essential scientific proof of the usefulness of this treatment and help provide for allocation of further resources to diagnose and treat more people affected by this condition.

If you decide to participate in this study, you will be having the investigations which Help to diagnose sleep apnoea, including routine blood tests, a recording of your heartbeat and an overnight sleep test in a special bedroom. The test involves sleeping with an elastic band around your chest and abdomen and a few leads stuck with tape, to record your heart rate, movements, breathing and stages of sleep. If you have sleep apnoea, you would then have an equal chance of receiving CPAP treatment immediately or after 3 months of measures to improve your sleep quality and general health. Except for slight nasal congestion in some people there are no un-wanted effects of this treatment.
During this study, we would request you to fill out simple questionnaires to help us identify what benefit you think the machine has on your health and quality of life. If found to be beneficial you would be offered treatment with this machine for life.

You are free to withdraw from the study, at any stage without having to give any reason. This would not affect your future medical care in the clinic. The Ethics Committee of the Birmingham Heartlands Hospital are satisfied that this is an ethical study and in the best interests of yourself and other patients. If you have any concerns on any aspect of this study please contact the *Secretary of the Ethics Committee* on **0121 7666611 ext: 4791.**
For any other queries regarding this trial, please contact *Dr I Chakravorty* on **0121 7666611 page 2513/ ext: 5796** or *Dr RM Cayton's* secretary on **0121 7666611 ext: 5192**

FORM OF CONSENT

PATIENT

I ,---------- of ----------
---------- have read the explanation overleaf of the proposed Study of the clinical, quality of life & economic effectiveness of CPAP therapy in the Sleep Apnoea Hypopnoea Syndrome, which forms part of this consent. The aims and purposes of the study have been explained to me by :----------
---

I agree to take part in this study and I understand that I am free to withdraw from the study at any time without having to give any reason.

Signature:----------

Date:----------

DOCTOR

I confirm that the above named patient has read the explanation overleaf and this consent and that I have explained the study to the patient and answered any questions arising from this.

Signature:----------

Date:----------

WITNESS

I confirm that I am satisfied that the patient has read and understood the explanation and consent.

Signature: ----------

Date:----------

APPENDIX II

INFORMATION

Obesity is an important risk factor for snoring and OSA. However, rather substantial amounts of weight loss are often required to produce a significant improvement in symptoms. Most studies looking at this factor show that the weight loss must be of the order of 20 - 30%. This can be very difficult to achieve. The success rate for sustained weight loss of 10 - 15% through diet and exercise is only about 5 - 10%.

Drugs such as Fenfluramine are now frequently prescribed for the treatment of obesity. A rare complication of prolonged use of this and similar drugs is a condition called Pulmonary Hypertension. This condition is usually fatal and there is no effective treatment apart from heart-lung transplantation. In cases of severe obesity, **surgery** to reduce the capacity of the stomach can result in more dramatic weight loss and significant improvement in OSA. However, these operations should only be performed at specialised centres. There are numerous medical complications as well.

Smoking is another important factor. However, smoking is now known to be a powerful addiction. There are a number of medical aids to quitting smoking such as nicotine replacement and drugs to decrease nicotine withdrawal symptoms. Unfortunately, success rates for quitting smoking are of the order of 10 - 15%, even with the best programs. It takes persistence and determination to quit.

Alcohol when consumed in excess can exacerbate snoring and OSA. Intervention is not usually required if a person drinks heavily on a few special occasions such as one's birthday. However, for alcoholics, the increase in apnoea due to muscle relaxation and sedation may be the cause of the "hangover". Again, treatment is more difficult in those who need it the most.

Sleep Habits are also important. A poor night's sleep can worsen snoring and OSA on the following night. This can create a vicious cycle that leads to rapid worsening of snoring and OSA.

GUIDE TO GOOD SLEEP HYGIENE

Good sleep hygiene consists of practices that reinforce the body's natural tendency to sleep at night.
Maintain a regular bedtime and awakening time. For most people, nightly time in bed should be no longer than 7 hours since excessive time in bed may fragment sleep. Get out of bed at the regular time even if sleep was poor, as "sleeping in" can disturb sleep the following night.

1. Do not nap during the day as these results in poorer sleep at night.
2. Do not drink alcoholic beverages in the evening as this disturbs sleep.
3. Avoid caffeinated beverages after noontime, as caffeine disturbs sleep. Limit total caffeine consumption to no more than two beverages per day.
4. Do not smoke just before bedtime or during the night as this disturbs sleep.
5. Exercise regularly during the day, but avoid exercise in the evening within 3 hours of bedtime.
6. Do not use the bed or bedroom for anything other than sleep and sexual activity. If the bedroom is used for non-sleep activities (such as watching TV), it may become a stimulus for alertness, rather than for sleep.
7. Establish a routine in preparation for sleep. Engaging in frustrating activities or excessive worry close to bedtime may result in arousal and prevent sleep.
8. Maintain a comfortable temperature in the bedroom.
9. Keep the bedroom dark and quiet. Try to screen out any disturbing noise or light. One of the most effective ways to relax at the end of a stressful day is to do some abdominal breathing. Put on some relaxing musing or nature sounds (the sound of rain or running water). Dim the lights or turn them off. Stretch out on the bed or sofa and roll your shoulders around a few times. Now you can focus on your breathing.

Take note of the following:
•Is your breathing rhythmic?
•Is your breathing relaxed?
•Is your chest moving up and down?
•Is your abdomen moving in and out?
When you are tense, breathing can be irregular and forced. Most people also use their chest to breath when they are upset. The most natural way to breath is to use the diaphragm which pushes down into the abdomen. Breathing should be relaxed and rhythmic.
Try the following exercises:
•Breath without using your chest at all. Support your head on a pillow in order to relax your neck muscles. •Take several deep breaths into the abdomen. Exaggerate this motion to give yourself a better sense of which muscles are involved. •Place a book on your chest and another on your
abdomen. The book sitting on the chest should remain still. The book on the abdomen should clearly move up and down in time with your breathing. Practice these exercises for a minimum of 30 minutes each day so that the abdominal breathing becomes a habit that you do without thinking.
Once you have formed this habit, you are ready to move on to the next phase. In this phase, you simply add a brief pause at the end of each breath. Therefore, the breathing cycle becomes: inhale, exhale, pause... inhale, exhale, pause...
If you find that the worries of the day are intruding on your breathing exercises, simply say to yourself: "Ah ha, my mind has wandered. Let's return to the breathing task."
If this is not successful in getting you refocused on the breathing, try repeating a simple two syllable expression to yourself. Some examples are "one-two", "deep down", and "in-out".
Remember, practice makes perfect.

SPECIMEN LETTER ACCOMPANYING PILOT PCT SURVEY

September 2001

«Title» «FirstName»«LastName»
«Address1»
«Address2»
«City»
«PostalCode»

Dear «Title»«LastName»□□□□,

Nasal continuous positive airway pressure in Sleep apnoea
General Practitioner survey

Although Sleep apnoea is now recognised as a common condition causing daytime dysfunction among a large number of patients and relatively effective therapeutic options are available within the NHS, there is a wide regional variation in the provision and utilisation of the diagnosis and treatment facilities in the UK.

The purpose of our study is to examine CPAP as a health technology innovation and evaluate the influences within the healthcare structure that determine its availability and take up. At this time of change for the future of the NHS, vital lessons can be learned about the utilisation of resources and provision of new health technology innovations.

As the general practice provides the primary pathway for patients to seek health care intervention, we are keen to seek your opinion on this subject. We would be extremely grateful for your assistance in this survey.

We would welcome any additional comments or observations that you wish to make from your experience.

Thank you for valuable time and comments.

With kind regards.

Indranil Chakravorty
SpR Thoracic Medicine
Harefield Hospital
i.chakravorty@rbh.nthames.nhs.uk

Ala Szczepura
Professor & Director
Centre for Health Services Studies
University of Warwick
a.szczepura@warwick.ac.uk

CPAP therapy for obstructive sleep apnoea
General Practice Survey

		Yes	No
1. Age group	**<30 years**	☐	
30-39 years		☐	
40-49 years		☐	
50-59 years		☐	
60-65 years		☐	
2. Sex			
Male		☐	
Female		☐	
3. Type of practice			
Single		☐	
Multiple partners		☐	
Teaching		☐	
Non-teaching		☐	
Urban		☐	
Rural		☐	
4. Does your practice have..			
Nurse practitioner/ specialist		☐	☐
Dietician		☐	☐
Specialist clinics/ services		☐	☐
5. Have you got any patients with Sleep apnoea in your practice?		☐	☐
6. How long have you been referring patients with Sleep apnoea			
< 5 years		☐	
5-10 years		☐	
10-14 years		☐	
15-19 years		☐	
> 20 years		☐	
Therapy for Sleep apnoea			
7. How would you rate the following options in order of clinical effectiveness? 1= most effective			
Lifestyle strategy (Weight reduction + sleep hygiene)		☐	
Oral devices/ mandibular splints		☐	
CPAP		☐	
Laser palatoplasty		☐	
8. How would you rate the following options in order of patient acceptability? 1= most acceptable			

Lifestyle strategy (Weight reduction + sleep hygiene)	☐	
Oral devices/ mandibular splints	☐	
CPAP	☐	
Laser palatoplasty	☐	
9. Characteristics of CPAP		
Does CPAP have any advantages over other options	☐	☐
Is CPAP compatible with normal sleep	☐	☐
10. Is CPAP therapy for your average patient		
Too complex	☐	☐
Easy to understand & operate	☐	☐
Moderately complex	☐	☐
11. Can the benefit of CPAP therapy		
Objectively evaluated	☐	☐
Subjective reporting only	☐	☐
Both	☐	☐
12. Which of the following had the most influence on your opinion about CPAP therapy		
Journal articles	☐	
Scientific meetings/ seminars	☐	
Media	☐	
Advertising by manufacturers/ reps	☐	
Information from peers	☐	
Information from Hospital Consultants	☐	
Patient pressure	☐	
13. The future of CPAP in Sleep apnoea		
CPAP is likely to remain the most effective therapy	☐	
CPAP will probably be replaced by more effective therapy	☐	
CPAP will be replaced by more patient friendly therapy	☐	
None of the above	☐	

PCT QUESTIONNAIRE SURVEY

Nasal continuous positive airway pressure therapy in Obstructive sleep apnoea Primary Care Survey- I

About you/ your PCT (**South East Sheffield PCT**)		
1. Are there any patients with snoring or sleep breathing disorders in your practice?	Yes ☐	No ☐
2. If yes, please indicate how long have you/ your practice been referring patients with snoring / suspected Sleep breathing disorders?		
< 5 years	☐	
5-10 years	☐	
10-20 years	☐	
>20 years	☐	
Continuous Positive Airway Pressure (CPAP) therapy for Sleep breathing disorders (Your opinion as a Primary care physician)		
3. What would you consider to be the primary reason for treatment in your patients with Sleep apnoea? *Please tick only one response.*		
Reducing excessive daytime sleepiness	☐	
Preventing cardiovascular sequelae	☐	
Reducing risk of death during sleep	☐	
Quality of life improvement	☐	
Better performance at work	☐	
Avoidance of sleep related driving risk	☐	
Psychological improvement	☐	
4. Please would you rate the following treatment options for sleep apnoea (in order of clinical effectiveness) in your opinion or your patient's experience? *1 = most effective & 4 = least effective*		
Lifestyle strategy (weight reduction + sleep hygiene)	☐	
Oral devices/ mandibular advancement splints	☐	
Continuous positive airway pressure device (CPAP)	☐	
Laser uvulopalatopharyngoplasty (UVPPP)	☐	
5. Please would you rate the following options in order of patient acceptability in your opinion? *1 = most acceptable & 4 = least acceptable*		
Lifestyle strategy (weight reduction + sleep hygiene)	☐	
Oral devices/ mandibular splints	☐	
CPAP	☐	

Laser UVPPP	☐
6. In your opinion is CPAP therapy for your average patient	
Too complex	☐
Easy to understand & operate	☐
Moderately complex	☐
7. Which of the following pathways of knowledge diffusion do you think had the most impact on shaping the opinion of primary care physicians on CPAP therapy for Sleep apnoea? *1 = most impact & 7 = least impact*	
Scientific/ professional journal articles	☐
Scientific meetings/ seminars	☐
Media reporting	☐
Advertising by manufacturers/ reps	☐
Direct information from peers	☐
Information from Hospital Consultants/ Specialists	☐
Patient/ patient group pressure	☐
8. Which of the following groups do you consider your viewpoint to a new innovation to be closest to ? *(Groups are described using standard diffusion literature terms)*	
Innovators	☐
Early adopter	☐
Early majority	☐
Late majority	☐
Resistant to change	☐
9. Do you feel that a clear pathway/ system exists for the diffusion of knowledge about new innovations from the experts to the primary care physicians (with reference to CPAP in Sleep breathing disorders)?	
Yes, there is an existing system of knowledge diffusion and adoption in my primary care experience	☐
A system has recently been put in place in my PCT	☐
There is no clear system but some sporadic lectures/ meetings etc..	☐
No system except personal initiative and peer contacts	☐
Any other	☐
10. The current state of play with CPAP in Sleep breathing disorders; Do you think majority of patients with sleep apnoea are easily receiving the treatment needed in your patient group?	Yes
If no; where do you think the hurdles lie?	
Lack of diagnostic facilities in your local DGH	☐
Lack of adequate resources	☐
Lack of patient awareness of their problems	☐
Lack of physician time/ initiative in the district	☐
Any other	☐

SPECIMEN LETTER ACCOMPANYING SECONDARY CARE SURVEY

«First_Name» «Last_Name»
Consultant Respiratory Physician
«Hospital»
«Address_Line_1»
«Address_Line_2»
«City»
«ZIP_Code»

November 2002

Dear Dr «Last_Name»,

Nasal continuous positive airway pressure in Sleep apnoea
Respiratory Specialist survey

Although Sleep apnoea is now recognised as a common condition causing daytime dysfunction among a large number of patients and relatively effective therapeutic options are available within the NHS, there is a wide regional variation in the provision and utilisation of the diagnosis and treatment facilities in the UK.

The purpose of our study is to examine CPAP as a health technology innovation and evaluate the influences within the healthcare structure that determine its availability and take up. At this time of change for the future of the NHS, vital lessons can be learned about the utilisation of resources and provision of new health technology innovations.

As a Respiratory Specialist in secondary or tertiary care your firm/ unit would be the first port of call for primary care physicians faced with a patient with a suspected sleep breathing disorder, hence we are keen to seek your opinion on this subject. We would be extremely grateful for your assistance in this survey. (Please feel free to forward this to a colleague who you feel may have a greater personal interest in this subject)

We would welcome any additional comments or observations that you wish to make from your experience.

Thank you for valuable time and comments.

With kind regards.

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Nasal continuous positive airway pressure therapy in Obstructive sleep apnoea: Respiratory Specialist Survey- I

ABOUT YOUR HOSPITAL/ FIRM («HOSPITAL»)		
1. Is your hospital		
DGH	☐	
Teaching Hospital with A/E	☐	
Tertiary Care without A/E	☐	
2. Does your hospital have facilities for the diagnosis of Sleep breathing disorders?	Yes ☐	No ☐
If yes; please tick the options applicable		
Dedicated sleep laboratory with full polysomnography	☐	
Portable polysomnography on the ward	☐	
Limited inpatient sleep studies (without EEG/ sleep staging)	☐	
Home based sleep studies	☐	
Overnight pulse oximetry	☐	
Any other	☐	
3. Are there facilities for the provision of the following in your hospital?		
Specialised dietary/ obesity services	☐	
Mandibular advancement devices	☐	
CPAP	☐	
ENT surgical option locally (Palatoplasty)	☐	
Mental health support	☐	
4. How many referrals does your hospital/ firm receive annually with suspected snoring / sleep breathing disorder?		
<50	☐	
51-100	☐	
101-150	☐	
>150	☐	
5. How many patients approximately do you have under your department's care with sleep disordered breathing?		
<100		
101-250		
251-500		
501-1000		
>1000		
6. How many CPAP machines does your department prescribe/ provide in a year?		
<50		
51-100		
101-200		
>200		

7. What is the estimated annual expansion in the number of patients prescribed CPAP machines in the last 10 years?		
<5%		
6-10%		
11-15%		
>15%		

8. What in your opinion is the primary indication for treating patients with sleep disordered breathing? Please tick only one		
Reducing excessive daytime sleepiness	☐	
Preventing cardiovascular sequelae	☐	
Reducing risk of death during sleep	☐	
Quality of life improvement	☐	
Better performance at work	☐	
Reduction of sleep related driving risk	☐	
Psychological improvement	☐	
9. Please would you rate the following treatment options for clinically significant sleep disordered breathing (in order of clinical effectiveness) in your opinion? *1= most effective & 4 = least effective*		
Lifestyle strategy (weight reduction + sleep hygiene)	☐	
Oral devices/ mandibular advancement splints	☐	
Continuous positive airway pressure device (CPAP)	☐	
Laser uvulopalatopharyngoplasty (UVPPP)	☐	
10. Please would you rate the following options in order of patient acceptability in your opinion? *1= most acceptable & 4 = least acceptable*		
Lifestyle strategy (weight reduction + sleep hygiene)	☐	
Oral devices/ mandibular splints	☐	
CPAP	☐	
Laser UVPPP	☐	
11. Do you agree with the following statements about CPAP therapy?	Agree	Disagree
Has a relative advantage to other forms of therapy?	☐	☐
Is compatible with patient's lifestyle, sleep and home environment	☐	☐
Is not too complex for an average middle-aged patient?	☐	☐
It is possible to provide a trial without permanent/ irreversible effects	☐	☐
The benefits can be objectively assessed	☐	☐
12. Which of the following pathways of communication/ knowledge diffusion do you think had the most impact on shaping the opinion of Respiratory physicians on CPAP therapy for Sleep disordered breathing? *1= most impact & 7 = least impact*		
Scientific/ professional journal articles	☐	
Scientific meetings/ seminars	☐	
Media	☐	
Advertising by manufacturers/ reps	☐	
peer-peer contact	☐	
Patient/ patient group lobbying	☐	

13. Which of the following groups do you consider your viewpoint towards a new innovation to be closest to? *(Groups are described using standard diffusion literature terms)*		
Innovators	☐	
Early adopter	☐	
Early majority	☐	
Late majority	☐	
Resistant/ reluctant to change easily	☐	
14. Do you feel that a clear pathway/ system is available for the diffusion of knowledge about new innovations from the experts to the primary care / secondary care physicians within the NHS (with reference to CPAP in Sleep breathing disorders)?		
Yes, there is an existing system of knowledge diffusion & adoption in my district	☐	
A system has recently been put in place	☐	
There is no clear system but some sporadic lectures/ meetings etc..	☐	
No system except personal initiative and peer contacts	☐	
Any other	☐	
15. The current state of play with CPAP in Sleep breathing disorders; Do you think majority of patients with sleep disordered breathing are easily receiving the treatment needed in your catchment area?	Yes ☐	No ☐
If no; where do you think the hurdles lie?		
Lack of diagnostic facilities in your hospital	☐	☐
Lack of appropriate resources	☐	☐
Lack of patient awareness of their problems	☐	☐
Lack of physician time/ initiative in general practice	☐	☐
Any other	☐	☐

16. YOUR OPINION FOR THE FUTURE OF CPAP IN SLEEP APNOEA	YES	NO
CPAP is likely to remain the most effective therapy	☐	☐
CPAP will probably be replaced by more effective therapy	☐	☐
CPAP will be replaced by more patient friendly therapy	☐	☐
None of the above	☐	☐

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