Simplified Pathways for the Diagnosis and Management of Obstructive Sleep Apnea in Primary Care

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

Obstructive sleep apnea (OSA) is highly prevalent in the Australian community and throughout the world. With growing evidence linking OSA to adverse health consequences and development of effective therapies such as continuous positive airway pressure (CPAP), there has been a steady rise in the demand for laboratory-based sleep testing and specialist consultation. Alternative, cost-effective models of care for OSA are needed to increase patient access to sleep services. Primary care would be an ideal setting for development of a simplified strategy for OSA diagnosis and management.

In the first study (Chapter 2), we developed and validated a two-step diagnostic model for moderate-to-severe OSA consisting of a screening questionnaire and overnight home oximetry. Patients aged 25 to 70 years who were seeing their general practitioner (GP) for any reason at one of 6 primary care clinics completed an Epworth Sleepiness Scale (ESS) and Berlin Questionnaire. They underwent simultaneous recording with a two-channel ApneaLink monitor and full polysomnography (PSG) to identify variables predictive of OSA and to validate the portable monitoring device. Snoring, waist circumference, apneas and age were most predictive of OSA and incorporated into a screening questionnaire (receiver operating characteristic area under curve (ROC AUC) = 0.84 [95%CI: 0.75-0.94], $p<0.001$). ApneaLink oximetry with a ≥3% dip rate was highly predictive of OSA (ROC AUC=0.96 [0.91-1.0], $p<0.001$). The two-stage diagnostic model had a sensitivity of 0.97 [0.81-1.00] and specificity of 0.87 [0.74-0.95] in the development group, and sensitivity of 0.88 [0.60-0.98] and specificity of 0.82

[0.70-0.90] in the validation group. Thus, the two-step model was shown to be accurate in identifying patients with OSA in primary care.

The development and evaluation of a six-hour education program for GPs which was accredited by the Royal Australasian College of General Practitioners is described in Chapter 3. GPs completed an attitudes and knowledge questionnaire before and 2 weeks after attendance at the program, and then again after 17 to 30 months. Two weeks post-education, there were significant improvements in the level of confidence in managing OSA and CPA therapy, and an improvement in knowledge test scores. Improvements in attitudes and knowledge from baseline were sustained on long term testing.

Chapter 4 details the results of a prospective, randomised controlled study conducted to evaluate the clinical efficacy and cost-effectiveness of a simplified model of care for OSA in general practice. Patients with OSA were identified by GPs using the simple two-step diagnostic strategy described in Chapter 2, and were randomised to receive either primary care management led by their GP and a community-based nurse, or usual laboratory-based care in a specialist sleep centre. For the primary outcome, mean change in ESS at 6 months, primary care management was not inferior to specialist management (4.6 vs 5.1, adjusted difference -0.6 [lower bound 95% confidence interval: -1.8], p=0.37). There were no differences in secondary outcomes, including quality of life, OSA symptoms, treatment compliance and overall patient satisfaction. Within-study costs were lower in the primary care

arm, with savings of AUD$2157 (95%CI: $1293 to $3114) per patient.

A simplified model of care for the diagnosis and management of OSA based in the primary care setting is efficacious and cost-effective, and has the potential to reduce the burden of untreated OSA in the community.

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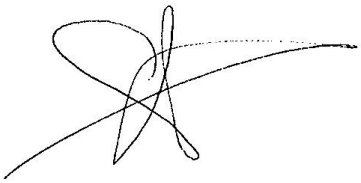
DECLARATION

I certify that this thesis does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.



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GLOSSARY

AASM	American Academy of Sleep Medicine
AHI	apnea-hypopnea index
ANCOVA	analysis of covariance
APAP	automatically-adjusting continuous positive airway pressure
AUC	area under curve
BMI	body mass index
BTS	British Thoracic Society
CAD	coronary artery disease
CHAID	Chi-square automatic interaction detection
CPAP	continuous positive airway pressure
CT90	cumulative time spent under SaO_2 of 90%
CVD	cardiovascular disease
ECG	electrocardiogram
EEG	electroencephalogram
EMG	electromyogram
EOG	electrooculogram
ESS	Epworth Sleepiness Scale
FOSQ	Functional Outcomes of Sleep Questionnaire
GP	general practitioner
ICER	incremental cost-effectiveness ratio
MAP index	Multivariable Apnea Risk index
MAS	mandibular advancement splint
MCQ	multiple-choice question

MSAC	Medical Services Advisory Committee
MVA	motor vehicle accident
NICE	National Institute for Health and Clinical Excellence
MBS	Medicare Benefits Scheme
NPV	negative predictive value
ODI	oxygen desaturation index
OSA	obstructive sleep apnea
PPV	positive predictive value
PSG	polysomnography
QA&CPD	Quality Assurance and Continuing Professional Development
QALY	quality adjusted life year
QOL	quality of life
RACGP	Royal Australasian College of General Practitioners
RDI	respiratory disturbance index
ROC	receiver operating characteristic
SACS	Sleep Apnea Clinical Score
SaO_2	arterial oxygen saturation
SAQLI	Sleep Apnea Quality of Life Index
SASQ	Sleep Apnea Symptoms Questionnaire
SF-36	Short-Form 36 Health Survey
SHHS	Sleep Heart Health Study
TBT	tennis ball technique
VSQ-9	Visit-Specific Satisfaction Questionnaire

CHAPTER 1: INTRODUCTION

1.1 INTRODUCTION

1.1.1 Prevalence of Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is a condition characterised by repetitive upper airway obstruction during sleep, resulting in oxygen desaturations, frequent arousals, sleep fragmentation and excessive daytime sleepiness. The severity of OSA is measured by the frequency of partial and complete breathing pauses (i.e. “hypopneas” and “apneas”) per hour of sleep, known as the apnea-hypopnea index (AHI). Important risk factors for OSA include male gender, obesity, increasing age, and alcohol consumption. OSA is common in the Australian community, as demonstrated by Bearpark et al who studied a population of middle-aged men from Busselton, Western Australia, and found a prevalence of symptomatic OSA (defined as an AHI ≥ 5 plus subjective daytime sleepiness) of 3%[1]. Another community-based study of men and women aged 35 to 69 years from Newcastle, New South Wales, reported a prevalence of OSA (defined as an AHI ≥ 15) of at least 3.6% (5.7% in men and 1.2% in women)[2]. These figures are in keeping with prevalence data from the US Wisconsin Sleep Cohort Study of 1993 which estimated that 4% of middle-aged men & 2% of middle-aged women suffer from symptomatic OSA[3]. These prevalence estimates derived from the early-to-mid 1990s are, however, likely to be an underestimate of the present rates of OSA given the dramatic rise in obesity rates since this time.

The causal association between body weight and sleep disordered breathing was demonstrated in a longitudinal study by Peppard et al[4] which showed that a 10% weight gain was predictive of a 32% increase in AHI and a 6-fold increase in the odds of developing moderate-to-severe OSA. The dramatic increase in the rates of obesity in the Australian population over recent decades has been demonstrated in a number of prevalence surveys. The AusDiab study, which recorded data using the measured heights and weights of over 11,000 Australians aged over 25 years during 1999-2000, revealed the prevalence of overweight and obesity in both men and women to be almost 60%[5]. A significant rise in obesity over time was also evident, with the proportion of obese men increasing from 9.4% to 16.9% between 1980 and 1999-2000, and from 7.8% to 19.8% for women during the same time period[6]. Thus, with the rapid increase in the rates of overweight and obesity in Australia, a parallel rise in the prevalence of OSA is also likely.

A recently published epidemiological study conducted in Sao Paulo, Brazil has found a higher prevalence of OSA compared to the epidemiological studies conducted in the early 1990s[7]. In a study sample representative of the Sao Paulo population, 32.8% of subjects were found to have obstructive sleep apnea syndrome (i.e. AHI 5 to 14.9/hr plus snoring, sleepiness, fatigue or breathing interruptions in sleep, or AHI≥15/hr regardless of symptoms), with 16.9% of the study sample having evidence of moderate-to-severe OSA (i.e. AHI≥15/hr) on polysomnography (PSG). The proportion of individuals with a body mass index (BMI) ≥25kg/m^2 was higher than that seen in previous epidemiological studies, and perhaps a more accurate reflection of

the prevalence of overweight and obesity in present times. 59.9% of subjects were overweight or obese, which is similar to the current proportion of overweight and obese adults in the Australian population. Other reasons suggested for the higher prevalence were inclusion of older groups, use of nasal pressure for detection of airflow, use of more recent American Academy of Sleep Medicine (AASM) hypopnea scoring criteria[8] and the different sampling and recruitment process.

Socioeconomic status has been shown to be associated with the prevalence of OSA. In a study by Ramsey et al[9], low socioeconomic status was found to be associated with greater severity of OSA with a higher AHI and more time spent with oxygen saturations <90%, as well as higher health care costs. Using data from the South Australian Health Omnibus Survey, Adams et al[10] assessed the prevalence of patients at high risk of OSA as determined using the STOP-BANG questionnaire. On multiple logistic regression analysis, a high risk for OSA was found to be associated with lower levels of education, lower household income and residence in regional areas compared to metropolitan Adelaide[11].

1.1.2 Health Consequences of OSA & Benefits of Continuous Positive Airway Pressure Therapy

Untreated, moderate-to-severe OSA has been linked to a number of adverse health consequences, including excessive daytime sleepiness, neurocognitive impairment, and an increased risk of motor vehicle accidents and cardiovascular disease. The primary form of therapy for moderate-to-severe OSA is with nasal continuous positive airway pressure (CPAP), which

acts as a pneumatic splint to prevent upper airways collapse during sleep. CPAP therapy has been shown in a number of studies to be effective in improving or preventing the health-related consequences of OSA[12].

An association between OSA and systemic hypertension has previously been documented, however, results from longitudinal studies are conflicting. A prospective, population-based study using the Wisconsin Sleep Cohort found evidence of a dose-response relationship between baseline severity of sleep disordered breathing and the presence of hypertension after 4 years of follow-up[13]. For patients with a baseline AHI≥15 events/hour, the odds of developing hypertension within 4 years was 2.89 times higher than those with an AHI of 0 events/hour, after controlling for known confounders. Furthermore, a number of randomised studies have shown small, but statistically significant, falls in blood pressure following treatment of severe, symptomatic OSA with nasal CPAP therapy[14-16]. A meta-analysis of 12 randomised controlled trials on the impact of CPAP therapy on blood pressure which included data from 572 patients with OSA revealed a net reduction of 1.69mmHg (95%CI: -2.69 to -0.69) in 24-hour mean arterial blood pressure with use of CPAP[17], thought to be sufficient to produce clinically significant reductions in cardiovascular risk in the population.

Interestingly, a prospective cohort study (i.e. Sleep Heart Health Study [SHHS]) involving middle-aged to older adults did not find an independent association between increasing baseline AHI and the incidence of hypertension after 5 years of follow-up, after adjusting for BMI[18]. A recently

published, longitudinal study of the Vitoria Sleep Cohort in Spain who were followed for a mean of 7.5 years also found no association between OSA and the incidence of hypertension, after adjustment for important confounders.

There is mounting evidence to support an independent association between OSA and other cardiovascular disorders such as coronary artery disease (CAD), cerebrovascular disease, heart failure and cardiac arrhythmias. A cross-sectional analysis of the Sleep Heart Health Study showed that the relative odds of cardiovascular disease (CVD) (including CAD, stroke and heart failure) was significantly greater at 1.42 (95%CI: 1.13-1.78) for the highest quartile of OSA severity (AHI≥11.0/hour) compared to the lowest quartile (AHI 0.0-1.3/hour), with a stronger association evident for heart failure and stroke than CAD[19]. A prospective, observational study of the incidence of CAD in patients with and without OSA who were free of cardiovascular disease at baseline, revealed an increased relative risk of 4.6 (95%CI: 1.8-11.6) for the development of CAD in patients with OSA after 7 years of follow-up, and effective treatment of OSA appeared to reduce the excess risk[20]. A study of long term cardiovascular outcomes in men with OSA by Marin et al showed that patients with untreated severe disease had a higher incidence of fatal and nonfatal cardiovascular events than patients treated with CPAP, those with untreated mild-moderate OSA, and simple snorers without OSA[21]. Another prospective, observational study conducted to investigate cardiovascular outcomes in treated versus non-treated patients with OSA revealed similar findings, with higher rates of fatal and nonfatal cardiovascular events (i.e. myocardial infarction, stroke, or need for

revascularisation procedure) for patients who did not use CPAP therapy compared to those who received treatment (28.3% versus 14.3%, p=0.009), and even those with only mild-moderate OSA (25.3% in untreated group vs 14.4% in treated group, p=0.024)[22]. Whilst these epidemiological studies strongly support a causal association between OSA and cardiovascular disease, their interpretation is limited due to potential confounders. For example, patients who declined CPAP treatment may also have been less compliant with treatment of potential cardiovascular risk factors and may have received less health care. Several large-scale, multi-centre, randomised controlled trials aimed at establishing a definitive link between OSA and CVD and the effects of CPAP therapy on CVD risk are currently underway.

OSA can result in excessive daytime sleepiness, as well as impaired alertness and concentration - important factors which are believed to contribute to an increased risk of motor vehicle accidents (MVAs). The association between OSA and MVAs was demonstrated in a case-control study by Teran-Santos et al which revealed that patients with an AHI ≥10/hour had an odds ratio for having a traffic accident of 7.2 (95%CI: 2.4-21.8) compared to controls after adjustment for potential confounders[23]. A more recent study by Mulgrew at al showed that not only did patients with OSA have increased rates of MVAs in general, but also that they were at higher risk of having MVAs associated with personal injury (i.e. more severe MVAs), compared to age- and sex-matched controls[24]. Studies have revealed reduced MVA rates in OSA patients following treatment with nasal CPAP. Findley et al showed that patients with OSA who were treated with

nasal CPAP had a lower crash rate in the 2 years after successfully commencing therapy compared to the 2 years prior to diagnosis and treatment (0 crashes versus 0.7 crashes per year, $p<0.03$), and that untreated patients with OSA continued to have a high crash rate (0.7 crashes per year before and after diagnosis)[25]. Similarly, in a study by George et al[26], rates of MVAs were shown to be significantly higher in patients with OSA in the three years prior to diagnosis and treatment at 0.18 accidents/driver/year compared to 0.06 accidents/driver/year for matched controls. The rate of MVAs was reduced to the same rate as control subjects (0.06 accidents/driver/year) in the three years following the initiation of CPAP therapy.

1.1.3 Alternative Treatment Options for Obstructive Sleep Apnea

Although CPAP can effectively minimise the health-related consequences of disease and is considered the treatment of choice for OSA, it is not always accepted by patients or well tolerated and alternative treatment options are often sought. A review by Weaver and Grunstein revealed that long term compliance with CPAP, as defined by an average of ≥4 hours usage per night can range anywhere from between 29 to 83%[27]. Long term compliance appears to be influenced by multiple factors, including baseline severity of OSA, degree of subjective sleepiness, nasal resistance and initial acceptance of CPAP therapy. Alternative therapeutic options for OSA include behavioural modifications (e.g. weight loss, attention to sleep posture), oral appliance therapy, and upper airway surgery.

For patients who are unable to tolerate or decline CPAP therapy, or for those with only mild to moderate OSA, treatment with a specialised dental appliance, known as a mandibular advancement splint (MAS) is often used. A MAS acts by producing forward protrusion of the mandible which is thought to improve upper airway patency by increasing the size of the oropharynx and by improving upper airway muscle tone. A number of randomised, controlled studies have demonstrated that oral appliance therapy can produce statistically significant reductions in AHI and improvements in symptoms, including sleepiness and snoring, in patients with OSA[28-30]. A previous review of the literature[31] showed that success of MAS therapy in reducing AHI is influenced by the severity of OSA, with higher success rates demonstrated in those with mild to moderate OSA (57-81%) compared to those with severe OSA (14-61%) (NB the criteria for "success" varied between studies, and ranged from a reduction in AHI to <5/hour [most stringent], to a 50% reduction in AHI [least stringent]). Use of a MAS has also been shown to be associated with a significant reduction in mean 24-hour diastolic blood pressure following 4 weeks of treatment compared to a control oral appliance in patients with OSA[32]. The updated AASM practice parameters for the treatment of snoring and OSA with oral appliances recommended in 2005 that: "Although not as efficacious as CPAP, oral appliances are indicated for use in patients with mild to moderate OSA who prefer oral appliances to CPAP, or who do not respond to CPAP, are not appropriate candidates for CPAP, or who fail treatment attempts with CPAP or treatment with behavioural measures such as weight loss or sleep position change"[33].

Surgical modification of the upper airway, has also been used to treat patients with OSA, and include procedures such as uvulopalatopharyngoplasty (UPPP), maxillo-mandibular advancement, (MMA), laser-assisted uvulopalatoplasty (LAUP), radiofrequency ablation (RFA) or a combination of surgical approaches, known as multilevel (or step-wise) surgery. A recent systematic review and meta-analysis of the evidence for upper airway surgery in the treatment of OSA revealed a paucity of high-level, randomised, controlled trial data, with most of the published literature consisting of small case series[34]. In addition, there was a lot of variability in preoperative assessment strategies, surgical techniques and in postoperative follow-up. Surgical therapy of OSA, is therefore, generally recommended only for patients who decline or are intolerant of CPAP or in whom oral appliance therapy is ineffective or undesirable[35].

In some patients with OSA, particularly those with less severe disease or those who have a strong positional component, lifestyle and behavioural modifications may be sufficient to effectively control disease and improve symptoms of OSA. Such measures include weight loss, sleep posture modification (to minimise supine sleep) and avoidance of alcohol and other agents (e.g. benzodiazepines) which can affect upper airway patency. A previous study which was conducted to evaluate the longitudinal association between weight change and severity of sleep disordered breathing revealed that a 10% loss of weight was associated with a 26% (95%CI: 18-34%) reduction in AHI from baseline[4]. Tuomilehto et al compared the effects of an

intensive lifestyle intervention for 1 year consisting of a very low calorie diet and regular nutritionist visits versus a single counselling session with general dietary and exercise advice as first-line treatment for patients with mild OSA[36]. The study showed significantly greater weight loss in the intervention arm (mean change in weight of -10.7kg [10.6% of initial weight], versus -2.4kg [2.6% of initial weight] in the control group, $p<0.001$) after 1 year of follow-up, and an improvement in AHI in the intervention arm with mean change of -4.0 events/hr which differed from controls whose mean change in AHI was +0.3 events/hr ($p=0.017$). OSA was considered objectively cured (i.e. AHI <5/hr) in 63% of the intervention group, versus only 35% of the control group ($p=0.033$).

Sleep posture modification can be an effective form of treatment for patients with positional OSA (i.e. OSA which is worse during supine, compared to lateral, sleep). A study assessing the effects of the “tennis ball technique” (TBT, i.e. wearing a tennis ball strapped to the back during sleep) showed that patients who reported good compliance with TBT had reductions in their supine sleep time and AHI, as well as subjective improvements in sleep quality, daytime alertness and snoring loudness compared to patients who had stopped using TBT and had not learnt to sleep in a lateral position[37]. Another study which used a prospective, randomised, crossover design to compare the effects of positional therapy versus CPAP also showed a reduction in the total amount of supine sleep and in AHI with use of a ball strapped to the back, and found improvements in daytime sleepiness (as measured by the Epworth Sleepiness Scale [ESS]), cognitive performance,

mood scores and quality of life measures which were comparable to CPAP[38]. However, long term compliance with TBT has been shown to be problematic[39], which may limit its effectiveness as a therapeutic option for OSA.

1.1.4 Economic Cost of OSA and Cost-Effectiveness of Treatment

In 2010, the total cost of sleep disorders in Australia was estimated to be AUD$36.4 billion, with OSA being the most common disorder[40]. The health costs directly related to sleep disorders, including inpatient hospital costs, medical practitioner encounters, pharmaceuticals, pathology, diagnostic imaging, aged care and research was estimated at AUD$818 million, of which OSA accounted for 79%. Direct health costs related to conditions attributed to sleep disorders, such as work-related injuries, MVAs, depression and anxiety, and cardiovascular disease, totalled AUD$544.1 million. Indirect financial costs for work-related injuries, MVAs and other productivity losses as a result of sleep disorders were enormous at AUD$4.3 billion.

Studies which have examined health care costs for patients with undiagnosed OSA have demonstrated that costs are significantly greater for patients in the years preceding diagnosis compared to controls, and excess costs appear to be related to disease severity at the time of diagnosis[41,42]. A retrospective cohort study comparing healthcare utilisation before and after the diagnosis and treatment of OSA with CPAP has shown that the number of physician visits and total physician fees were significantly higher in the

year before diagnosis compared to the fifth year before diagnosis, and then decreased in the five years after commencement on CPAP therapy[43].

The cost-effectiveness of CPAP therapy in the management of moderate-to-severe OSA has been consistently demonstrated in a number of studies. Most of these studies have investigated the cost-effectiveness of CPAP therapy expressed in the form of quality adjusted life years (QALYs). A QALY is a year of life adjusted for its quality or value, and is a currency used to assess the benefits gained from an intervention in terms of the health-related quality of life and survival. A year in perfect health is considered equivalent to 1 QALY, death equivalent to 0 QALYs and a year of less than perfect health being worth less than 1 QALY. Tousignant et al evaluated the QALYs added by treatment of OSA in 19 patients with moderate-to-severe OSA and found that an average of 5.4 QALYs was added by CPAP therapy[44]. When related to the cost of treatment, the cost-utility ratio was determined to be CAD$3,397 to $9,792 (AUD$3,620 to $10,440) per QALY, which is within the limits considered to be cost-effective when compared to other commonly used clinical interventions. Mar et al evaluated the cost-effectiveness of nasal CPAP in reducing MVAs, CVD and quality of life (QOL) in patients with moderate-to-severe OSA and found the incremental cost-effectiveness ratio (ICER) to be €4,938 (AUD$7,080) per QALY for the lifespan of the patient, or €7,861 (AUD$11,270) per QALY for a 5 year time horizon[45].

A study of the cost-effectiveness of CPAP therapy for moderate-to-severe OSA in reducing MVAs and improving QOL was conducted by Ayas et al, and showed that the ICER for CPAP was US$3,354 (AUD$3,780) per QALY from the third party payer perspective, and US$314 (AUD$350) per QALY from the societal perspective[46]. The same group have recently published results for a similar study of cost-effectiveness in British Columbia, finding an ICER of CAD$3,626 (AUD$3,870) per QALY gained from the third party payer perspective, and CAD$2,979 (AUD$3,180) per QALY gained[47].

In the United Kingdom, Guest et al undertook a study of the cost-effectiveness of CPAP in reducing cardiovascular events and MVAs in severe OSA, and found healthcare costs to the National Health Service to be higher over 14 years for untreated patients (£10,645 [AUD$18,660] per patient) compared to CPAP-treated patients (£9,672 [AUD$16,960] per patient)[48]. Treatment with CPAP for 1 year only was not cost-effective, with the estimated cost per QALY being >£20,000, but after 2 years, it is a cost-effective strategy, with cost per QALY <£10,000. After 13 years, CPAP becomes a dominant treatment (i.e. more effective and less costly than no treatment).

More recently, the National Institute for Health and Clinical Excellence (NICE) in the UK have undertaken an appraisal of CPAP, evaluating the effectiveness and cost-effectiveness of therapy. In the economic analysis commissioned by the National Health Service Health Technology Assessment (NHS HTA) Programme, the cost-effectiveness of CPAP was

compared with dental devices and lifestyle advice and evaluated health outcomes which included the impact of treatment on daytime sleepiness, blood pressure, and health-related quality of life (HRQoL)[47]. For the base-case analysis, the ICER for CPAP compared to dental devices was found to be £3,899 per QALY for men and £4,335 per QALY for women. Based on NICE's declared cost-effectiveness threshold value of £20,000 per QALY, the probability of CPAP being more cost-effective than dental devices or lifestyle advice was 0.78 for men and 0.80 for women. On subgroup analyses, the ICER for CPAP remained below £20,000 per QALY for severe and moderate OSA, but slightly exceeded the threshold in the mild severity subgroup (£20,585).

CPAP therapy for OSA can be viewed as a highly cost-effective strategy when considering the cost per QALY for other commonly used medical interventions. For example, the ICER for statin therapy when used in the primary prevention of coronary heart disease as per the Adult Treatment Panel III (ATP-III) guidelines has been estimated at US$42,000 per QALY[49]. The ICER of combined inhaled corticosteroids with long acting beta-agonists in the management of COPD was found to be similar, at a cost of US$43,600 (95%CI: $21,400-123,500) per QALY[50].

1.1.5 Demand for Sleep Services in Australia and Worldwide

With growing awareness of the health consequences of OSA and availability of effective therapies, such as CPAP, there has been a progressive rise in the demand for sleep services in Australia and throughout the world, which,

combined with the paucity of qualified sleep specialists, has led to growing waiting lists for sleep physician appointments and laboratory-based PSGs. A report published in 2004 revealed that the average waiting time for initial sleep specialist consultation in Australia was 9 (range 1-32) weeks, with an additional 21 (4-68) weeks before diagnostic PSG in the public sector[51]. Waiting times for diagnosis and eventual treatment with CPAP were variable, ranging anywhere from 3 up to 16 months in some centres.

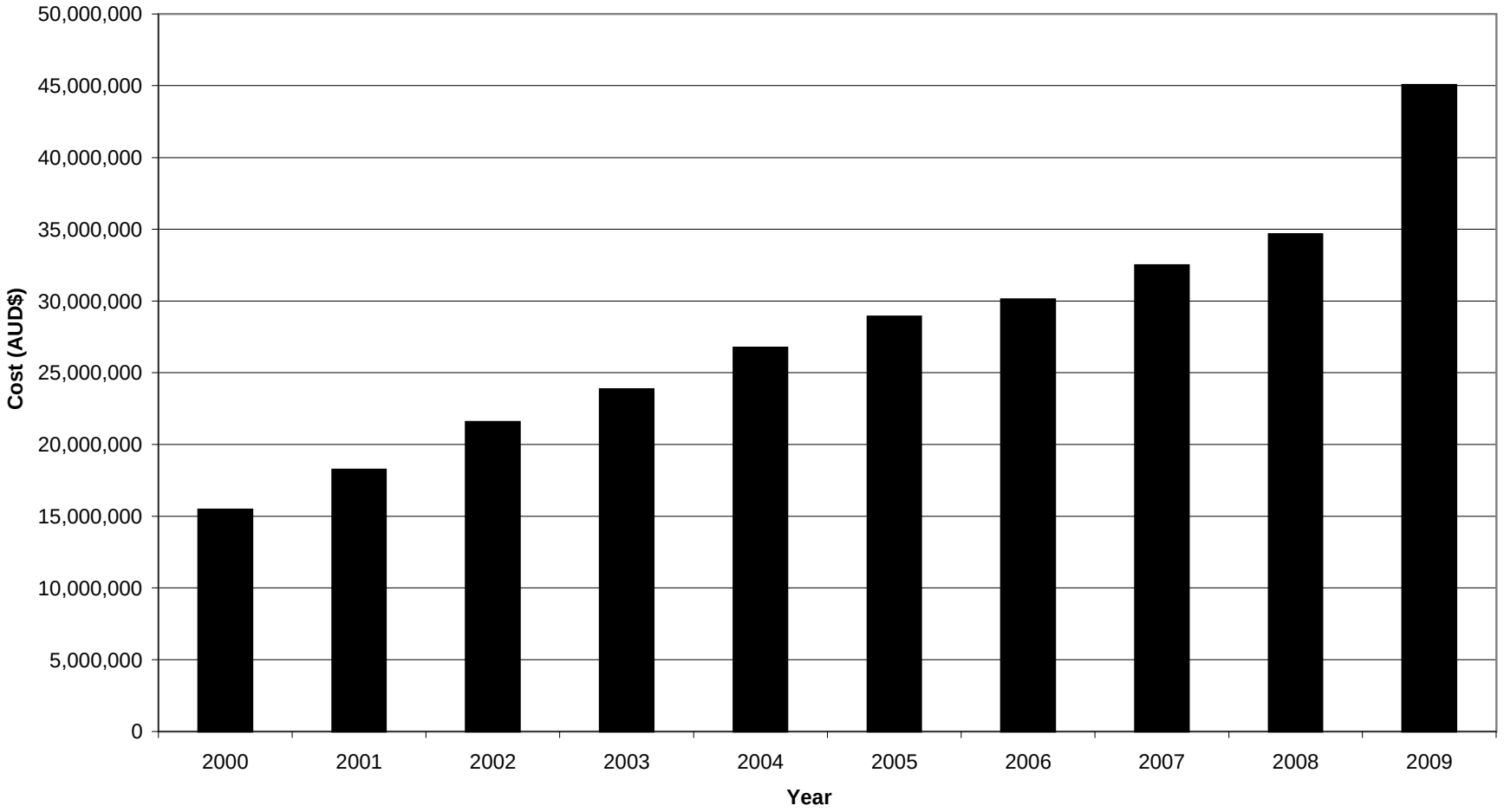
Since the introduction of publicly-funded reimbursement for PSG by Medicare in December 1989, there has been a steady rise in diagnostic sleep service provision across Australia. Between 2000-2009, the number of PSGs performed rose by an average of 6864 procedures per year, with the cost to the Medicare Benefits Scheme (MBS) over the ten year period totalling AUD$277.2 million for 674,849 PSGs (MBS item numbers 12203, 12207, 12210, 12213, 12215, 12217, 12250)[48]. The annual cost to the scheme has increased three-fold from AUD $15.5 million in 2000 to AUD $45.1 million in 2009 (see Figure 1.1). In 2004, per capita provision of PSGs in Australia was 308 procedures per 100,000 population, which was lower than that in the US and Canada, who performed 427 and 370 PSGs per 100,000 population in the same year, respectively[51]. In 2010, the per capita provision of PSGs in Australia reached 547 procedures per 100,000 population[48]. In their report, Flemons et al estimated that 2310 PSGs per 100,000 population per year would be needed to meet the demand for diagnosis and management of unrecognised moderate-to-severe OSA[51]. Thus, although sleep service provision in Australia has risen significantly in recent years, it may still be

insufficient to address the existing burden of disease in the community, and it is likely that a growth in PSG provision will continue to be seen over the coming years.

It was estimated in 1997 that 93% of women and 82% of men with moderate-to-severe OSA in the US general adult population had not been diagnosed[52]. Whilst corresponding figures for the present day are unknown, there is likely to have been some reduction in the proportion of undiagnosed patients with increased awareness of OSA amongst primary care providers and the general community, growth in the numbers of sleep service providers and increasing availability and use of unattended home sleep monitoring and auto-titrating CPAP devices. In more recent years, there has been growing interest in OSA screening and service provision from health care providers outside of sleep specialist centres, including pharmacists[53] and dentists[54], and utilisation of ambulatory diagnostic approaches incorporating clinical prediction questionnaires and portable home monitoring. Although these strategies may be seen to be addressing the need for increased sleep service access in the community, the evidence to support these ambulatory models is currently lacking. There are concerns about the potential for over-diagnosis, inadequate clinical input, and limited data on the accuracy and cost-effectiveness of such strategies. It also remains unclear as to whether outcomes for patients managed using a simplified approach outside of the sleep clinic setting are comparable to the usual standard of care. Higher diagnostic throughput without a parallel increase in the numbers of clinicians trained in the management of OSA can promote a unifocal and overly

simplistic approach to treatment, with excessive concentration on CPAP therapy. Many patients, particularly those with mild disease, may be more appropriately treated with other therapies such as weight loss, mandibular advancement splints, or sleep posture modification. Further research to clarify the role of home monitoring devices and community-based models of care for OSA is needed before widespread use can be recommended.

Figure 1.1. Cost of PSG to the Medicare Benefits Scheme 2000-2009



1.1.6 Screening Questionnaires and Clinical Prediction Models

Various screening tools and clinical prediction rules have been developed to help identify patients at high risk for OSA who may benefit from more urgent evaluation and treatment. Most of these have been developed from sleep clinic populations. Flemons et al found after conducting a survey in patients referred to a sleep disorders clinic that the variables most predictive of OSA (AHI≥10/hour) were neck circumference, hypertension, habitual snoring and partner reports of nocturnal choking or gasping and incorporated the four factors into a Sleep Apnea Clinical Score (SACS)[55]. They showed that the positive likelihood ratio for a diagnosis of OSA with a SACS >15 points was 5.17. The Multivariable Apnea Risk (MAP) Index was developed by Maislin et al, and consisted of the following factors which were found in a sleep clinic population to be predictive of OSA: snorting and gasping, loud snoring, breathing cessation, BMI, age and sex[56]. The MAP index was shown to have a receiver operating characteristic (ROC) area under the curve (AUC) value of 0.786 (SE 0.023, $p<0.0001$) for detecting a respiratory disturbance index (RDI) ≥10/hour. However, the MAP index, which was estimated using logistic regression modelling, consists of a complex mathematical formula which cannot be computed without access to a calculator, thus is unlikely to be used by physicians in a clinical setting. Rowley et al[57] prospectively evaluated the utility of 4 previously published clinical prediction models[55,56,58,59], including the SACS and MAP index, for detecting OSA (AHI ≥10/hour) and for prioritising patients for a split sleep study (AHI ≥20/hour) in 370 patients referred to a sleep disorders clinic. For an AHI ≥10/hour, the four models had generally high sensitivities of between 76-96% but low

specificity values of between 13-54%. All four models performed better in males (ROC AUC: 0.707-0.801) compared to females (ROC AUC: 0.611-0.648). For a higher AHI cut-off of ≥20/hour, the questionnaires had high specificity (87-93%) but sensitivity values decreased (33-39%).

Several authors have also evaluated the role of anatomical measures of the upper airway and craniofacial structures in the prediction of OSA risk. Kushida et al developed a predictive morphometric model for OSA syndrome (defined by an ESS ≥10 and PSG AHI ≥5/hour) which consisted of mandibular size, palatal height, BMI and neck circumference, reporting a sensitivity of 97.6% and specificity of 100%[60]. Tsai et al found that the presence of 3 anatomical variables - a cricomental space ≤1.5cm, pharyngeal grade >II and presence of overbite - had a specificity of 96% and positive predictive value (PPV) of 95% for an AHI ≥10/hour[61]. The sensitivity and negative predictive value (NPV) were low, however, at 40% and 49% respectively. The presence of a cricomental space > 1.5cm alone gave a NPV of 100% in both development and validation samples, thus effectively ruling out a diagnosis of OSA. Craniofacial phenotyping using a quantitative photographic analysis technique has recently been shown to have potential use in identifying patients with OSA. A study by Lee et al which compared a number of craniofacial morphological measurements in patients using photogrammetry demonstrated several phenotypic differences between subjects with and without OSA (AHI ≥10/hr), which were independent of obesity[62].

OSA screening tools have also been designed for use outside of the sleep clinic setting. The STOP questionnaire was recently developed by Chung et al from patients attending surgical pre-operative assessment clinics, consisting of 4 yes/no questions about **s**noring, **t**iredness, **o**bserved apneas and hypertension (blood **p**ressure)[11]. For severe OSA (AHI ≥30/hour), the STOP questionnaire was found to have a sensitivity of 79.5% and specificity of 48.6%. The addition of four additional factors (**B**MI, **a**ge, **n**eck circumference and **g**ender) to create the STOP-BANG questionnaire led to improvement in sensitivity to 100% at the expense of specificity which decreased to 37%.

The Berlin Questionnaire was developed in 1996 for use in primary care by US and German pulmonary and primary care physicians, and includes 11 items related to snoring, witnessed apneas, daytime sleepiness and self-reported obesity and hypertension. The individual items were selected by consensus, without formal assessment of their discriminatory value. The questionnaire was designed to categorise patients into either a high or low risk for OSA. A validation study was conducted by Netzer et al using 100 primary care patients who completed the Berlin Questionnaire and underwent portable sleep monitoring[61]. They found that the questionnaire could detect an RDI>5/hour with a sensitivity of 86%, specificity of 77%, PPV of 89% and likelihood ratio of 3.79. For moderate-to-severe OSA (i.e. RDI>15/hour), the questionnaire had a higher specificity of 97% and likelihood ratio of 16.62, but sensitivity was lower at 54%. Although published more than a decade ago, the Berlin Questionnaire has not been widely used by primary care

physicians, possibly due to the time required for patients to complete it and because of its cumbersome scoring system. The ideal screening tool for a busy primary care setting would consist of no more than five, easy-to-recall items and a simple scoring algorithm.

1.1.7 In-laboratory versus Home Sleep Monitoring

The current standard for the diagnosis of OSA is with attended, laboratory polysomnography (PSG). PSG is relatively costly, labour-intensive and time-consuming, requiring overnight attendance and monitoring by technical staff. This is further compounded by the limited number of trained sleep specialists, resulting in limited access to sleep services and prolonged waiting times before established diagnosis and treatment. To address these issues, a growing number of portable sleep study devices have been manufactured which can be conducted in the patients' own home environment. The different types of sleep study devices are classified according to the level of information recorded:

Type 1: Standard polysomnography, performed in a sleep laboratory with an attending sleep technician, with a minimum of 7 recording channels (electroencephalogram [EEG], electrooculogram [EOG], chin electromyogram [EMG], electrocardiogram [ECG], airflow, respiratory effort and oxygen saturation)

Type 2: Comprehensive portable polysomnography, unattended, with a minimum of 7 recording channels (as per type 1)

Type 3: Modified portable sleep apnea testing, with a minimum of 4 recording channels (ECG or heart rate, oxygen saturation, and at least 2

channels of respiratory movement or respiratory movement and airflow)

Type 4: Continuous recording using 1 to 3 recording channels (usually includes pulse oximetry)

Although considered the "gold standard" for sleep monitoring and diagnosis, Type 1 laboratory-based PSG is not without its limitations. Although the AHI derived from a PSG is commonly used by health professionals to define the presence and severity of OSA, there is currently no single, agreed-upon AHI cut-point to distinguish whether or not a person has OSA. There is also no clear consensus on what AHI cut-point defines the presence of clinically significant disease, with studies showing a poor correlation between objectively measured AHI and the severity of patient symptoms such as excessive daytime sleepiness[63]. An individual's AHI may vary from night-to-night[64], depending on factors such as bodily position during sleep, sleep quality and prior consumption of alcohol and other drugs. In addition, there may be considerable inter- and intra-scorer variability in AHI, and scoring rules for respiratory events can vary between sleep laboratories[65]. It has been clearly demonstrated that use of different hypopnea scoring criteria (i.e. 1999 AASM "Chicago criteria" versus 2007 AASM "recommended" or "alternative" criteria) can lead to substantial differences in the reported AHI[66].

Portable devices offer the benefit of being able to be conducted in the patients' own home environment without the need for continuous monitoring by a trained technician. Automated scoring of respiratory events using specialised computer software is also possible with some portable monitoring

devices. Thus, their use could result in potential cost-savings and enable increased patient access to diagnostic services, particularly for patients in rural and remote regions, as well as developing countries where health care resources are limited. Several limitations of portable sleep studies need to be considered however. One concern is the potential for signal loss when conducted in an unsupervised setting resulting in increased study failures. Type 3 and 4 portable monitoring devices have fewer recording channels than standard PSG and exclude the electrophysiological signals which record sleep (e.g. EEG, EOG, and EMG). As a result, it is possible that diagnoses such as nocturnal epilepsy or periodic limb movements could be missed when undertaking a limited sleep recording. However, appropriate clinical evaluation including a comprehensive sleep history will help to exclude conditions other than a sleep-related breathing disorder and in establishing a patient's suitability for a limited sleep study. Because the number of respiratory events are scored per hour of recording (i.e. "respiratory disturbance index" [RDI]) rather than per hour of sleep, the severity of OSA could potentially be underestimated if prolonged periods of wakefulness are present throughout the night. Also, the absence of EEG signals limits the ability to score hypopneas associated with arousals when using type 3 devices which could also result in underestimation of sleep disordered breathing.

A recent health economic analysis was conducted by Pietzsch et al using a Markov model to evaluate the cost-effectiveness of three diagnostic strategies for OSA (i.e. full-night PSG, split-night PSG and unattended

portable home monitoring) over a 10 year interval and the expected lifetime of a patient[67]. Interestingly, they found full-night PSG in conjunction with CPAP therapy to be the most cost-effective and preferred strategy when compared to both split-night PSG and unattended home monitoring, with an ICER of US$17,131 per QALY gained. Although up-front costs for full-night PSG are higher, the strategy was cheaper over the long term due to its superior diagnostic accuracy and significantly fewer false-negative and false-positive results compared with split-night PSG or unattended home monitoring. However, as pointed out in an accompanying commentary by Ayas et al, the model used to conduct the cost effectiveness analysis assumed that there would be dramatic reductions in cardiovascular events with CPAP use, which have not yet been substantiated by randomised controlled trial evidence and may have magnified the impact of false-negative and false-positive results[68]. The model also assumed that patients who had a false-positive home sleep study would have the same long term compliance with CPAP as those correctly diagnosed with OSA. This would seem unlikely and may also have inflated the costs associated with false-positive results. The study by Pietzsch et al did conclude, however, that in situations where full PSG is unavailable or waiting lists for laboratory-based studies are long, that portable home monitoring in populations with a high pre-test probability is a cost-effective strategy when compared to no diagnosis, at an ICER of US$19,707 per QALY gained.

In 2007, the Portable Monitoring Task Force of the AASM published clinical guidelines for the use of unattended portable monitors in the diagnosis of

OSA based on a review of the literature[69]. The paper served as an update to the review and practice parameter written earlier by the AASM, American College of Chest Physicians and American Thoracic Society in 2003 which did not support general use of portable monitoring over laboratory PSG due to a lack of sufficient evidence[70,71]. Following re-evaluation of the evidence for portable testing, the 2007 AASM Task Force recommended that unattended, portable monitoring (recording a minimum of airflow, respiratory effort and oximetry) may be used as an alternative to PSG for the diagnosis of OSA in patients with high pre-test probability of moderate-to-severe OSA without significant medical co-morbidities, in conjunction with comprehensive evaluation by a board certified sleep specialist. It stated that portable monitoring devices must allow display of raw data for manual scoring or editing prior to automated analysis, and should be reviewed by a board certified sleep specialist during interpretation and reporting. The guidelines also provided recommendations regarding the acquisition, analysis and interpretation of data and need for appropriate policies and procedures including a quality improvement program to assure reliability and validity of testing. Based on the recommendations of the 2007 AASM Task Force, the Centers for Medicare and Medicaid Services in the United States (US) approved the use of a limited home sleep recording device with at least 3 channels to diagnose OSA for the purposes of reimbursement for CPAP treatment.

More recently in Australia, an evaluation of the role of unattended sleep studies for the diagnosis and reassessment of OSA was conducted by the

Medical Services Advisory Committee (MSAC) to determine whether government reimbursement for testing be provided under the Medicare Benefits Scheme[72]. Following an assessment of the current evidence on the safety, effectiveness and cost-effectiveness of portable monitoring for OSA, the MSAC advised that public funding for unattended studies be confined to full PSG monitoring only (i.e. Level 2), and not for Level 3 or 4 studies. Although potential cost savings associated with the use of limited sleep studies were acknowledged, one of their main concerns was that cost savings would be cancelled if a high proportion of patients undergoing portable monitoring were to proceed to level 1 PSG prior to commencement of therapy.

1.1.8 Home Oximetry for Diagnosis of OSA

Home oximetry is an attractive option for the diagnosis of OSA, because of its simplicity and ability to provide important information about a patient's respiratory status during sleep at relatively low cost. In addition, oximetry is widely available, can be conducted in the patient's own home and data can be subject to automated analysis for prompt interpretation. The role of overnight oximetry in the diagnosis of OSA has been evaluated in a number of studies, however there appears to be large variability in results of diagnostic accuracy with sensitivities of 31-98% and specificities of 39-100% reported.

Most studies have evaluated an oxygen desaturation index (ODI) using a ≥4% cut-off (i.e. 4%ODI) with variable results (see Table 1.1). Early studies

have tended to report high specificity and relatively low sensitivity for detection of OSA. Gyulay et al reported a sensitivity of 40% and specificity of 98% when using a 4%ODI ≥15/hr for identifying an AHI ≥15/hr[73]. Similarly, in a retrospective comparison of home oximetry and laboratory PSG, a 4%ODI ≥31.4/hr diagnosed OSA (PSG AHI≥10/hr) with 97% specificity but only 32% sensitivity, however, in this study, there were wide time gaps between testing procedures (mean interval 12.8 month ± SD 10.1)[74]. Ryan et al conducted a study to validate the British Thoracic Society (BTS) guidelines issued in 1990 for the use of pulse oximetry in the diagnosis of OSA whose criteria specified that a diagnosis of OSA could be made with a 4%ODI ≥15 per hour in bed in the presence of an awake oxygen saturation above 90%[75]. They showed that, compared to full laboratory PSG, the BTS criteria for overnight home oximetry was highly specific (100%) for OSA, therefore a positive result could eliminate the need for full PSG. However, pulse oximetry had the potential to miss patients with disease (sensitivity 31%), which was thought to be due to the presence of hypopneas causing arousals in the absence of significant oxygen desaturation, and thus patients with a negative result and symptoms suggestive of OSA would still require further investigation. A study by Vasquez et al comparing laboratory PSG and the oximeter signal digitally recorded off-line for automated analysis showed that a 4%ODI ≥15 per hour of probe-on time had reasonably high sensitivity and specificity of 98% and 88% for detection of OSA (PSG AHI ≥15 per hour of sleep), which was not altered by inclusion of arousals in the definition of hypopneas when scoring PSGs[76]. Chiner et al also found that a 4%ODI ≥5 per hour of time in bed could diagnose OSA with reasonably high sensitivity of 80% and specificity of

89%[77]. However, in both of these studies, oximetry was conducted in the sleep laboratory setting on the same night as full PSG, and not in the unattended, home environment.

There are several reasons for the variability in results which have made direct comparisons between studies and meta-analyses difficult: (1) Different oximeter devices have been tested, with varying sampling rates; (2) Studies have evaluated different oximeter indices (e.g. oxygen destauration index [ODI], cumulative time spent under SaO_2 of 90% [CT90], oximetry variability [Δ index], or qualitative measures of oxygen desaturation) and varying cut-off values have been used; (3) different AHI cut-off values have been used to define clinically significant OSA for the reference standard (i.e. PSG); (4) different study populations have been tested; (5) studies conducted in laboratory versus unattended home setting; and (6) use of manual versus automated scoring of oximetry results. A study comparing the reliability of different oxyhaemoglobin indices showed that the ODI had a higher correlation with PSG-derived AHI and higher diagnostic sensitivity and specificity than time-domain (e.g. CT90) and frequency-domain (e.g. Δ index) indices at different levels of OSA severity (i.e. AHI>15/hr and >30/hr)[78]. Sampling rates have also been shown to significantly impact on the diagnostic accuracy of home oximeter recorders. One study compared home oximetry using a device with an 8-hour memory storage capacity which stores data points every 12 seconds to on-line oximetry recording during full laboratory PSG which collects data points every 2 seconds[79]. Home oximetry significantly underestimated the number of oxygen desaturation events,

which was thought to be due to the low sampling rate of the portable monitor. Using a cut-point of 10/hour for a 4%ODI, home oximetry studies had a specificity of 100% but sensitivity was only 41%. Thus, adequate sampling rates are an important consideration when using home oximetry for the diagnosis of OSA. A study comparing five different pulse oximeters showed that there were differences in response times between devices, underestimation of oxygen desaturation by all devices when compared to a simulator device, and marked variability in the level of desaturations recorded when the five oximeters were simultaneously tested in test subjects and patients, which was thought to be due to differences in the internal signal processing of the devices[80]. An understanding of the technical specifications (e.g. sampling rates, averaging times, etc) of the pulse oximeter used and determination of device-specific ODI thresholds for diagnosing OSA are crucial for meaningful interpretation of results.

Table 1.1 Comparison of the diagnostic accuracy of oximetry for the diagnosis of OSA

Author (Year)	Study population, n	Oximeter	Sampling rate	Pulse oximetry criteria for OSA	Polysomnography criteria for OSA	PSG hypopnea scoring criteria	Sensitivity, %	Specificity, %
Jobin (2007)[81]	94	Remmers Sleep Recorder	1 Hz	4%ODI ≥5/hr	AHI ≥5/hr	Reduction in respiratory movement >50% of baseline, or <50% when associated with ≥4% O_2 desaturation	75.3	81
Wiltshire (2001)[79]	84	Biox 3740, Ohmeda	every 12s	4%ODI ≥10/hr	4%ODI ≥10/hr	N/A	41	100
Vazquez (2000)[76]	246	Healthdyne 202-11 oximeter	1 Hz	4%ODI ≥15/hr	AHI ≥15/hr	Reduction in respiratory movement >10s associated with ≥4% O_2 desaturation	88	95
Chiner (1999)[77]	275	N-200, Nellcor Inc	every 6s	4%ODI ≥5/hr	AHI ≥15/hr	50% reduction in flow or respiratory movement >10s associated with ≥4% O_2 desaturation or microarousal	82	76
Golpe (1999)[74]	116	AVL-Minolta Pulsox 7	every 5s	4%ODI ≥31.4/hr	AHI ≥10hr	Discernable reduction in airflow ≥10s with ≥4% O_2 desaturation &/or an arousal	32	97
Yamashiro (1995)[82]	269	Biox 3740	2 Hz	3%ODI >5/hr	AHI ≥5/hr	N/A	94.2	73.5
Ryan (1995)[75]	69	Minolta Pulsox-7	1 Hz	4%ODI ≥15/hr	AHI ≥15/hr	Reduction in chest wall movement >25%, abdominal wall movement >15% and paradoxical movement with airflow reduction >25%	31	100
Gyulay (1993)[73]	98	Biox 3700, Ohmeda	every 12s	4%ODI ≥15/hr	AHI ≥15/hr	Reduction in oronasal airflow to 50% or less than normal breathing for >10s	40	98

PSG = polysomnography; AHI = apnea-hypopnea index; N/A = not available

1.1.9 Auto-titrating Continuous Positive Airway Pressure

The current standard of care for determination of effective CPAP pressure is with manual titration conducted during an attended, laboratory-based PSG, which is labour intensive, relatively costly and time-consuming. Automatically-titrating CPAP (APAP) can detect sleep disordered breathing events by continually monitoring respiratory parameters (e.g. snoring, flow, impedence, etc) during use and adapts CPAP pressure to ensure optimal control of OSA. They have been proposed as an alternative means for titrating CPAP pressure and can be conducted in the home environment without the need for technical staff. In 2007, the American Academy of Sleep Medicine (AASM) updated their 2002 practice parameter report for the use of autotitrating CPAP following a review of the literature to include the following recommendation: “certain APAP devices may be used in an unattended way to determine a fixed CPAP treatment pressure for patients with moderate to severe OSA without significant comorbidities (CHF, COPD, central sleep apnea syndromes or hypoventilation syndromes)[83].

The largest randomised, controlled trial to evaluate patient outcomes following APAP titration was published by Masa et al[84] in 2004 and involved a total of 360 patients with severe OSA (i.e. AHI≥30/hr and ESS≥12) who were randomly assigned to one of three groups: (1) standard laboratory-based manual CPAP titration; (2) home APAP titration; and (3) titration using a prediction formula. In the APAP group, the fixed CPAP pressure was determined by visual inspection of raw data and use of the 90th percentile pressure when at an acceptable level of leak (<0.4L/sec). The study found

that after 12 weeks of follow-up, improvements in subjective sleepiness (i.e. change in ESS score) and AHI were similar in all 3 groups, with no significant differences in objective CPAP compliance. However, the degree of improvement in some quality of life measures (i.e. SF36 physical and EuroQol) was lower in the APAP group than the standard titration group.

A more recent randomised, controlled trial was conducted in Australia by McArdle et al who evaluated the clinical outcomes and costs of APAP titration with standard manual titration[85]. Their study involved 249 patients with moderate-to-severe OSA (i.e. AHI≥15/hr and ESS≥8) who were randomised to either manual titration, laboratory APAP or home APAP titration to determine a fixed CPAP pressure. In the APAP group, the fixed treatment pressure was frequently determined on the basis of the 95th percentile pressure. Following 4 weeks of treatment, they found no significant differences in average nightly CPAP use, polysomnographic outcomes, subjective sleepiness (ESS), quality of life (SF-36), or cognitive function in the per-protocol groups. Furthermore, the total direct costs for home APAP titration (AUD$132.09) were much lower than the costs for laboratory APAP (AUD$647.56) and manual titration (AUD$817.84).

1.1.10 Simplified, Ambulatory Models of Care for OSA

To address the problem of long waiting lists and rising costs of laboratory-based sleep services, several studies have recently evaluated the outcomes of alternative, simplified models of care for OSA utilising portable sleep monitoring devices combined with auto-titrating CPAP. Ambulatory

management of OSA has the potential to improve patient access to diagnostic sleep services and expedite treatment for patients at high risk of disease. This would be of particular benefit for patients in rural and remote areas, who may travel extensive distances for review and testing at a tertiary sleep centre. A model of care involving simplified home monitoring and auto-titrating CPAP could also be of potential interest to developing nations, such as China and India, which have large populations but only limited health care resources. For example, in India, with increasing urbanisation and adoption of Western diets and sedentary lifestyles, obesity rates have been climbing with a likely parallel rise in OSA prevalence. In 2006, Sharma et al estimated from a community-based study in a semi-urban population in Delhi, India, that the prevalence of OSA (i.e. AHI>5/hr) was 13.74% and for OSA syndrome (i.e. AHI>5/hr and ESS>10) was 3.57%, similar to previous estimates for OSA in Western countries[86].

The first randomised, controlled trial assessing an ambulatory model of care for OSA was conducted by Mulgrew et al, whose simplified strategy consisted of a diagnostic algorithm (i.e. Epworth sleepiness scale [ESS] score ≥10, Sleep Apnea Clinical Score ≥15 and RDI ≥15/hour on overnight home oximetry [i.e. type 4 device]), followed by auto-CPAP titration to determine a fixed treatment pressure in those confirmed to have moderate-to-severe OSA[87]. After 3 months of treatment, no statistically significant differences were observed between patients randomised to the ambulatory model versus those who received the usual standard of care involving laboratory PSG in terms of the residual AHI on CPAP, nor in the change in

ESS or Sleep Apnea Quality of Life Index (SAQLI) scores from baseline. However, CPAP adherence was higher in the ambulatory care arm (median 6.0 versus 5.4 hours/night, p=0.021).

A similar study was conducted by Berry et al amongst US veteran patients who had been referred to a sleep centre for investigation of suspected OSA[88]. 106 patients were randomised to either portable sleep monitoring with a 4-channel device (Watch PAT100) followed by auto-titrating CPAP for pressure determination, or to laboratory-based full or split-night diagnostic PSG and CPAP titration. At 6 weeks after commencing therapy, no significant differences were observed in CPAP compliance (ambulatory arm: mean ± SEM 5.2 ± 0.28 versus PSG arm: 5.25 ± 0.38, $p>0.05$), change in ESS (-6.50 ± 0.71 versus -6.97 ± 0.73, $p>0.05$), change in Functional Outcomes of Sleep Questionnaire (FOSQ) (3.10 ± 0.05 versus 3.31 ± 0.52, $p>0.05$), patient satisfaction with CPAP or mean residual AHI on CPAP between the two groups.

Kuna et al compared an ambulatory model of care for OSA versus laboratory-based testing, with evaluation of functional outcome and treatment adherence after 3 months of follow-up[89]. In their study, 296 patients consecutively referred to two Veteran Affairs medical centres in Pennsylvania, USA, were randomised into either a home testing pathway utilising a type 3 monitoring device and auto-titrating CPAP, or an in-laboratory testing pathway. Their final analysis included only those patients confirmed to have OSA and who were commenced on CPAP therapy. They

found that functional outcome, as measured by the FOSQ, for patients in the home testing group was not clinically inferior to usual laboratory-based testing when using an *a priori* noninferiority margin of -1.0 for the difference in mean change in FOSQ score at 3 months (home mean change of 1.74 versus laboratory mean change of 1.85, adjusted difference 0.0, lower bound of one-sided 95%CI: -0.54). They found that CPAP adherence in the home testing group was also not inferior to the laboratory-based testing group, with mean ± SD daily use of 3.5 ± 2.5 hours versus 2.9 ± 2.3 hours, respectively, using an a priori noninferiority margin of -0.75 hours (adjusted difference 0.55, lower bound of one-sided 95%CI: 0.03). Furthermore, there were no statistically significant differences in the change in ESS score, psychomotor vigilance, health outcomes as measured by the Short Form 12 Health Survey (SF-12) or depression scale scores between the two groups.

Researchers have also examined the potential role for alternative health care providers, other than sleep physicians, in the ambulatory management of OSA. Antic et al evaluated a simplified model of care for OSA in which management was led by a specialist nurse rather than a sleep physician[90]. In this Australian, multi-centre study, diagnosis was established using overnight home oximetry and 195 patients found to have moderate-to-severe OSA (i.e. >2% oxygen desaturation index >27/hour, ESS ≥8 and history of snoring) were randomised into either a simplified, nurse-led model of care consisting of home APAP to determine a fixed CPAP pressure, or to traditional, physician-led management including laboratory-based PSG and manual CPAP titration. After 3 months of follow-up, simplified nurse-led

management was found not to be inferior to physician-led care in terms of the primary outcome, the mean change in ESS score after CPAP therapy (4.02 vs 4.15, difference -0.13, 95%CI: -1.52 to 1.25) using an *a priori* noninferiority margin of -2.0. The study also showed no significant differences in objective sleepiness by Maintenance of Wakefulness Test, quality of life measures (i.e. total FOSQ and SF-36 scores), executive neurocognitive function or CPAP adherence at 3 months. Whilst overall patient satisfaction was no different between the two arms of care, results for 4 out of 9 items within the Visit-specific Satisfaction Questionnaire (VSQ-9) questionnaire (relating to time waited, explanation, information provided and time spent with health care professional) were in favour of the nurse-led model. Thus, this study showed that management of selected patients referred with a suspicion of OSA could be undertaken by appropriately-trained specialist nurses without compromising patient outcomes.

Another trial by Andreu et al[91]has evaluated the role of nurses in home follow-up of patients diagnosed with OSA using an ambulatory diagnostic approach. This study involved 66 patients (22 per treatment arm) referred to a specialist sleep centre with a high clinical suspicion for OSA (i.e. ESS ≥12 and SACS ≥15) who were randomised into one of three management groups: (1) home sleep monitoring and home follow-up by a hospital-based nurse; (2) hospital PSG and hospital follow-up; and (3) home sleep monitoring and hospital follow-up. The CPAP treatment pressure for all patients was determined using a prediction equation based on body mass index, neck circumference and AHI. After 6 months of follow-up, they found no

differences between study groups in CPAP compliance, ESS, FOSQ or symptom scores. However, this small study was likely to have been underpowered to show clinically meaningful differences in some of these important patient outcomes, and to exclude inferiority.

These studies enrolled patients referred to specialist sleep centres but tended to have restrictive entry criteria. With the exception of the study by Kuna et al[89] which was reported to have had less restrictive entry criteria, patients with conditions such as major psychiatric disorders, neuromuscular disease, severe chronic obstructive airways disease, ischemic heart disease and cardiac failure were specifically excluded from participation[87,88,90,91]. Patients had been referred to specialist centres from primary care providers with suspected OSA, and inclusion criteria included symptoms such as chronic snoring, witnessed apneas and daytime sleepiness based on ESS score thresholds. Thus, study participants had a high pre-test probability of OSA. Furthermore, these studies targeted moderate-to-severe disease. It is, therefore, difficult to generalise the findings of these studies to those with only mild OSA, patients with significant respiratory, cardiac or psychiatric disease, or to broader populations within the community (e.g. primary care setting) where pre-test probability of disease might be lower.

1.1.11 A Role for General Practitioners in the Diagnosis and Management of Obstructive Sleep Apnea

General practitioners (GPs), who are often the first point of care for patients with a sleep-related health complaint, are ideally situated to take on greater responsibility for the diagnosis and treatment of OSA. Over the past decade,

there have been a growing number of funding incentives introduced by the Australian Government to promote integrated health care for patients with chronic disease, including the Enhanced Primary Care (EPC) package which incorporate GP management plans (GPMP) and team care arrangements (TCA) for patients requiring multidisciplinary care, Practice Incentives Payments (PIP), Service Incentive Payments (SIP) for conditions such as asthma and diabetes, and specific Medicare item numbers for practice nurses. The majority of general practice consultations relate to the management of chronic diseases, including diabetes, obesity, cardiovascular disease, and hypertension – conditions which are known to be associated with OSA. GPs offer continuity of care which is important for ensuring optimal compliance with recommended therapies and also for identification, management and prevention of potential medical co-morbidities. With long waiting times for patients with suspected OSA to access specialist care, there has been an increasing trend for GPs to refer patients to sleep services offering unattended, portable monitoring with only limited sleep physician input. As a result, many GPs are taking on primary responsibility for the management of OSA and other sleep disorders when they may lack the necessary skills and confidence to do so.

1.1.12 Prevalence of OSA in General Practice

The prevalence of OSA is likely to be higher in primary care compared to the general population, in view of the large numbers of patients seen by GPs who suffer from conditions such as obesity and hypertension, which are known risk factors for OSA. Studies have shown that a significant proportion

of patients attending primary care clinics will have symptoms suggestive of OSA and other common sleep disorders, such as insomnia and periodic limb movement disorder, when asked about their sleep health. A large survey involving 3,915 consecutive patients from 40 primary care centres in the US and Europe who were visiting their physician for any reason revealed that 32.3% had symptoms which were indicative of a high risk for OSA based on responses to the Berlin Questionnaire (i.e. snoring, witnessed apneas, sleepiness, and self-reported hypertension and obesity)[92]. In another survey of 1934 primary care patients from 5 family practice offices in North Carolina, US, 1070 (55.4%) patients complained of excessive sleepiness at least once a week, 638 (33%) reported snoring and 262 (13.6%) reported stopping breathing or gasping for breath during sleep[93]. Similarly, in a study of 1254 patients attending a rurally-based primary care clinic in Idaho, US, 66.2% complained of “excessive sleepiness, tiredness or fatigue” and 23.6% (32.3% of men and 16.3% of women) had symptoms suggestive of obstructive sleep apnea syndrome (i.e. loud snoring and/or witnessed apneas plus excessive daytime sleepiness)[94].

Stoohs et al conducted a survey of 852 primary care patients from northern California, US, using a 21-item questionnaire, including the Epworth Sleepiness Scale (ESS) to detect signs and symptoms of sleep disordered breathing, periodic limb movement disorder and insomnia[95]. They found that approximately one-half (49.9%) of patients were snorers and 12% (18.2% of men and 7.2% of women) reported partner-witnessed apneas during sleep. Using a previously validated diagnostic algorithm for OSA, they estimated

that 20% of patients were at high risk of OSA. A more recent South Australian Health Omnibus Survey, which included a representative sample of the adult South Australian population and used the STOP-BANG questionnaire to evaluate prevalence of symptoms and risk for sleep disordered breathing, found that more than half of males (57.1%) and 19.3% of females surveyed could be classified as being at high risk for OSA[10]. Although these studies examined symptomatic prevalence rather than true diagnosed cases of OSA, they do indicate that there are a substantial number of patients in primary care and the community who are at risk for OSA and would benefit from further diagnostic evaluation.

1.1.13 Under-Recognition of OSA in Primary Care

Although symptoms of OSA are common in the primary care population, a substantial number of people in the community remain undiagnosed and untreated. This is believed to be the result of under-reporting of symptoms by patients themselves, who tend to underestimate the importance of sleep complaints, and also because of failure by general practitioners to ask patients about sleep-related problems. Despite a growing recognition that untreated OSA poses a significant health problem, the level of awareness and knowledge amongst GPs about this important sleep disorder is generally low. A prospective study to assess the awareness level of OSA in primary care physicians using a standardised patient approach[96] showed that during an unstructured interview, only 10% of physicians asked sufficient questions relevant to sleep apnea syndrome. Only 1 doctor asked specifically about fall-asleep episodes during routine tasks or driving. In addition, once

informed of the diagnosis of OSA, education of the patient about complications related to the disorder was poor. Most (84%) did not discuss the problem of an increased risk of motor vehicle or work accidents, and only one half informed the patient about possible cardiovascular problems associated with untreated OSA.

Studies have also shown significant delays between time of onset of OSA symptoms and diagnosis. A study involving chart reviews and interviews with 97 patients diagnosed with OSA at a sleep centre in Chicago, US, revealed that the average time between first recognition by the patient of OSA symptoms and referral to a sleep centre was 87.5 (± SD 93.1) months[97]. In 94% of cases, the referral resulted from the patient presenting to their primary care provider with an OSA-related complaint, with only 4% of cases being physician-initiated as a result of the physician recognising important features of OSA. Furthermore, 21% of patients were not immediately referred for further investigation after a major feature of OSA was known to be present by their primary care physician, and waited an average of 37.5 months for sleep centre referral.

In a recent study of 395 patients who were approached whilst waiting to see their primary care physician, 187 (47%) were found to be at high risk of OSA based on their responses to the Berlin Questionnaire[98]. The Berlin Questionnaire is a previously designed and validated screening tool for primary care and stratifies patients into either a high or low risk category for OSA based on questions about snoring, witnessed apneas, daytime

sleepiness and self-reported hypertension and obesity[99]. When the medical records of the patients were reviewed, it was found that only 19% of patients considered at high risk of having OSA had ever been referred for PSG testing or had an existing diagnosis of OSA. Interestingly, two years after completion of the study, 86% of patients who were at high risk who had not had a previous PSG or review by a sleep specialist had still not been referred for further evaluation, even though primary care physicians had been notified by study authors of their patients' Berlin Questionnaire risk status. Potential reasons for the failure to refer patients for specialist consultation include the barriers to accessing sleep services, a lack of awareness by primary care physicians about the importance of diagnosing OSA in high risk patients and risk for potential health consequences of untreated disease, and/or a lack of confidence about the management of OSA.

1.1.14 Education on Obstructive Sleep Apnea

One of the major reasons for the under-recognition of OSA in general practice is the lack of education on sleep disorders at both undergraduate and postgraduate levels, relative to the rapid growth in research and clinical practice of sleep medicine in recent decades. A substantial proportion of GPs have received little or no formal education in the basic physiology of sleep or clinical management of sleep disorders during their undergraduate medical training. A national survey of 126 accredited US medical schools conducted by the National Commission on Sleep Disorders Research in 1990/91 revealed that a mean of only 1.16 (± 0.58 SEM) hours was devoted to teaching about sleep and sleep disorders during the preclinical years and

less than 1 hour (0.9 ± 0.46 hours) during the clinical years[100]. 37 out of the 126 schools reported no formal teaching in sleep at all, and only 4 medical schools offered clinical electives in sleep medicine for fourth year medical students. Major obstacles identified included a lack of time permitted in the curriculum, absence of qualified instructors and clinical supervisors, lack of clinical facilities, lack of interest and training among clerkship directors, and failure of medical school administration to support sleep medicine teaching.

When a second national survey was repeated a decade later, there had been little change in time dedicated to sleep medicine training, with a mean teaching time of only 2.11 hours (SD = 1.98; range 0.75 to 10.0 hours) reported, which was occurring mainly in the second year of medical school and predominantly in lecture format[101]. Again, the major barriers reported were a lack of time, absence of resources and a need for more clinical materials. Whilst research evaluating sleep medicine education in Australia has not been previously reported, it is likely to be comparable to that in the US.

The lack of education on OSA provided at undergraduate and postgraduate levels has been reflected in several knowledge surveys of medical students and primary care physicians. A study of the attitudes and knowledge of sleep medicine in 46 second year medical students, 26 physician-postgraduates and 40 specialists showed that overall knowledge of sleep medicine was poor in all three groups[102]. Significantly higher knowledge scores were seen in the postgraduate physicians compared to medical students (proportion of

correct scores 0.50 versus 0.41, p=0.05), but no difference was evident between students and specialists or between postgraduates and specialists. In a survey of the attitudes and knowledge of 105 primary care practitioners, the majority agreed or strongly agreed that OSA is potentially life-threatening and a common problem[103]. However, when asked to rate their knowledge of sleep disorders, 90% of physicians responded with “fair” or “poor”, which was reflected by scores on the multiple choice questionnaire in which physicians averaged only 34% correct responses (range: 3% to 94%).

1.1.15 Impact of Sleep Medicine Education

Education in sleep medicine is effective in improving knowledge and influencing the behaviour of physicians. Haponik et al compared the frequency of sleep history-taking of simulated patients in 20 experienced primary care physicians, 23 uninstructed medical interns and 22 interns who had received prior education about sleep disorders[104]. None of the primary care physicians and only 13% of uninstructed medical interns asked their patients questions relating to sleep. In contrast, 82% of interns who had received previous training in sleep health took a sleep history from their patients. Another, non-randomised, study of third year medical students compared 130 students based at a clerkship site with exposure to a 1-hour lecture and case-based discussions on OSA versus 129 students at clerkship sites without formal sleep medicine education[105]. The authors found that students who received formal teaching on OSA had higher scores for an OSA station at an end-of-term Objective Structured Clinical Examination with a mean score (SE) of 51.9% (1.4%) compared to 44.4% (1.0%) ($p<0.016$) for

those who did not receive teaching on OSA, whilst scores for stations on history-taking, physical examination and overall scores remained similar between groups.

An educational intervention in the US city of Walla Walla in Washington proved successful in improving the diagnosis and management of OSA in an entire rural community[106]. The aims of the Walla Walla Project were to educate primary care physicians and the local community, provide equipment and technical expertise for the diagnosis and management of sleep disorders, and to evaluate the outcome of these interventions. The intervention involved a weekend course for primary care physicians on sleep disorders presented by 2 sleep specialists, a lecture for the general public, provision of sleep laboratory equipment and training for a local sleep technologist, and weekly teleconferences to discuss sleep study results and case management. As a result, 2 of the primary care physicians developed a specialised interest in sleep disorders, and acted as local "supervising physicians". Prior to the project, in only 6 out of 752 patient charts which were randomly reviewed from the Walla Walla Clinic was there a sleep disorder suspected, with only 2 (0.27%) referred for polysomnography (PSG). After the first 2 years of the project, referrals for PSG at the clinic increased by approximately 8-fold to 2.1% (294 of 14330 reviewed cases), of which 122 (34%) were seen by the supervising community physicians. 96 (26%) of patients with sleep disorders were managed solely by their own primary care physician, without the need for formal consultation from the supervising physicians or a sleep specialist.

1.1.16 A Role for Practice Nurses in the Management of Obstructive Sleep Apnea

With a range of incentives introduced by the Australian Government over the past decade, there has been an expansion of practice nurse roles in primary care focussed predominantly on the prevention and management of chronic disease. Significant government funding has been provided since 2001, mainly through the Practice Incentives Program (Practice Nurse Incentive), to increase the numbers of practice nurses employed in rural and remote regions, which has since expanded to include urban areas of workforce shortage. The aims of the Australian Government's Nursing in General Practice Training and Support Initiative announced in the 2005-06 Federal Budget were to: (1) relieve workforce pressure in general practice; (2) improve the prevention and management of chronic disease; and (3) improve access to, and the quality and integration of, patient care, through the effective employment of practice nurses[107]. According to the National Practice Nurse Workforce Survey Report 2007, the estimated number of practice nurses in Australia was 7,824 which represented a 59% increase over 2 years, with approximately 58% of general practice clinics employing at least one practice nurse. Medicare Benefits Schedule (MBS) item numbers are now available for practice nurses to conduct a number of services on behalf of a general practitioner, including immunisation, wound care, cervical smear screening and to provide monitoring and support for patients with chronic illness as part of the Enhanced Primary Care program.

The study by Antic et al showed that patient outcomes following a simplified, nurse-led, ambulatory model of care for OSA in a tertiary care setting was not inferior to usual management by a sleep specialist, with significant savings in health care costs[90]. The nurses involved this study were experienced in sleep disorders management and use of CPAP, and had previously worked an average of 8.3 years in the field of sleep medicine. With provision of adequate training and supervision, and implementation of a formal credentialing process, there would be significant potential for practice nurse involvement alongside GPs in the care of patients with OSA and other common sleep disorders in the primary care setting. Potential roles for practice nurses in the management of OSA include the organisation of portable home sleep studies, OSA screening, patient education, and establishment and follow-up of patients on CPAP or alternative OSA therapies.

A model of care for OSA based in primary care which is closely linked to a tertiary sleep centre consisting of a simplified diagnostic and management approach involving GPs and their practice nurses, coupled with an education program to up-skill GPs on sleep disorders medicine could potentially fill the void in knowledge whilst addressing the growing need for sleep apnea services in the community.

1.2 AIMS OF THE THESIS

With increasing awareness about OSA and its health consequences by health care professionals and the general community, there has been a steady growth in diagnostic sleep service provision in Australia and throughout the world. The current system of sleep specialist review and laboratory-based sleep study testing for diagnosis and management of OSA is becoming increasingly overwhelmed, resulting in long waiting times between suspected diagnosis and eventual treatment for many patients. Alternative, simplified models of care for OSA which are more readily accessible and cost-effective are needed to address the growing burden of disease in the community. Primary care, which is often the first point of contact for patients with a sleep disorder, is an ideal location for development of a simplified diagnostic and management strategy for OSA.

The first study (Chapter 2) was conducted to develop and validate a simplified diagnostic model for identifying patients with moderate to severe OSA in primary care. The diagnostic model consists of two stages – (1) an initial screening questionnaire designed to increase the pre-test probability of OSA, followed by (2) overnight home testing with a portable, level 4 sleep monitoring device. The only OSA questionnaire previously designed for use in the primary care setting has been the Berlin Questionnaire. However, it has not proven to be an ideal screening tool for primary care as it has an excessive number of items as well as a relatively complex scoring system. One of the objectives of this study, therefore, was to develop a brief screening questionnaire consisting of only 4 or 5 items identified as being

highly predictive for moderate-to-severe OSA, and to devise a scoring system requiring only a simple mental computation without reference to specialised tables or a calculator.

The level 4 sleep monitor evaluated was the ApneaLink device (ResMed), a two-channel, portable system capable of recording oxygen saturation and nasal pressure. Data stored on the device can be subject to automated analysis using specialised ApneaLink software to obtain an oxygen desaturation index (ODI) and a nasal pressure-derived apnea-hypopnea index (AHI), enabling prompt interpretation of results. In this study, the ApneaLink-derived ODI and AHI were compared to the reference standard, i.e. full PSG, to determine which was the most accurate and reliable parameter, and also to establish an appropriate cut-point for identification of moderate-to-severe OSA (i.e. AHI ≥30/hr). The diagnostic accuracy of the simplified two-stage model of screening questionnaire and portable sleep monitoring was then prospectively evaluated.

The impact of an education program about OSA and common sleep disorders on the attitudes and knowledge of general practitioners is discussed in Chapter 3 of the thesis. Knowledge about OSA and its management amongst general practitioners has generally been poor and education on sleep disorders medicine at both undergraduate and postgraduate levels is currently scarce. GPs involved in the study undertook a six-hour education program on OSA, CPAP therapy and common disorders causing excessive daytime sleepiness. The OSA education program was

developed specifically for GPs participating in the study, and was accredited by the Royal Australasian College of General Practitioners (RACGP) as part of their Quality Assurance and Continuing Professional Development (QA&CPD) Program. The immediate and long term change in attitudes and knowledge of GPs about OSA and common sleep disorders following participation in the education program was examined in this prospective, before-and-after intervention study.

Chapter 4 reports on the results of a randomised, controlled trial of primary care-based management of OSA versus the usual standard of care involving sleep specialist consultation and laboratory-based sleep testing. Whilst previous studies have evaluated ambulatory models of care for OSA utilising portable sleep monitoring and auto-titrating CPAP operating out of sleep specialist centres, this is the first to report on a simplified management strategy based specifically in the primary care setting involving GPs and community-based, sleep-trained nurses. Participating GPs recruited patients into the study using the simplified diagnostic model of screening questionnaire and home oximetry described in Chapter 2 to identify patients with moderate to severe OSA. In the primary care arm, patients with OSA were managed by their GP who was assisted by a community-based nurse, with CPAP pressure determination achieved using home auto-titrating CPAP. Patient outcomes, including sleep apnea symptoms, quality of life, patient satisfaction, CPAP compliance and health care costs were evaluated after a period of 6 months of follow-up, with the primary outcome measure being the mean change in the level of daytime sleepiness as measured by the ESS.

The main objectives of this study were to: (1) establish whether outcomes for patients managed using an ambulatory model of care in the general practice setting are comparable to usual care in a specialist sleep centre and (2) determine the cost-effectiveness of a primary care-based, simplified management strategy for OSA.

CHAPTER 2: DEVELOPMENT AND VALIDATION OF A SIMPLIFIED DIAGNOSTIC MODEL FOR IDENTIFYING OSA IN PRIMARY CARE

2.1 INTRODUCTION

Obstructive sleep apnea (OSA) is a common clinical disorder affecting 9-24% of middle aged adults, with symptomatic disease including daytime sleepiness affecting at least 4% of men and 2% of women.[3] These figures, however, likely underestimate the current prevalence of OSA given more recent population trends in obesity[4,108]. OSA is associated with an increased risk of hypertension, motor vehicle accidents, neurocognitive impairment, reduced quality of life and cardiovascular disease[13,21,23,109]. Treatment of OSA with nasal continuous positive airway pressure (CPAP) can reduce the health-related consequences of disease[21,26] and is highly cost-effective[45]. Despite increasing awareness of its adverse health consequences in many Western countries, community surveys suggest that OSA remains significantly underdiagnosed[52,110]. In the developing world there remains widespread under-recognition and under-treatment of OSA.

One major impediment to OSA service access is the reliance on laboratory-based polysomnography (PSG) for diagnosis, which is labour intensive, relatively costly and has limited availability[51]. Another impediment to patient access to care is the relative dearth of qualified specialist sleep physicians. A

number of simplified strategies have been proposed to address these issues, including clinical prediction models for OSA[55,56,61,111,112] and home-based strategies incorporating portable sleep monitoring and auto-titrating CPAP[87]. A recent study showed that primary responsibility for the care OSA can be assumed by sleep-trained nurses, and therefore potentially other health professionals, without compromising patient outcomes[90].

Significant potential exists to broaden the scope of OSA diagnosis and management within the primary care setting. Almost one third of primary care patients surveyed in the United States and Europe have a high likelihood of OSA[92] yet primary care physicians often fail to ask their patients about features of OSA, and patients frequently fail to report sleep-related symptoms[97]. A possible barrier to the identification of OSA is the absence of a simple, validated screening tool suitable for use in a busy primary care environment. The ideal diagnostic screen would contain no more than five items and be quick to administer and interpret without the need for specialised equipment or examination techniques.

The Berlin Questionnaire is the only OSA questionnaire developed for and validated in primary care[99]. It categorises patients as either high or low risk for OSA based on self-reports of snoring, daytime sleepiness, hypertension and obesity. The eleven questions were chosen by a panel of sleep physicians without prior evaluation as to their respective discriminatory values. Although published a decade ago, the Berlin Questionnaire has not been widely used by primary care providers, possibly because of the time

required to administer it and because of its relatively cumbersome scoring system. Other diagnostic screening tools have been developed but have only been tested in specialist sleep centres on selected populations[55,56,61,111]. Like the Berlin Questionnaire they also have complex scoring systems[55,56,111] and/or require specialised measurements of facial or oropharyngeal anatomy[61]. Nevertheless, questionnaires alone may not provide a sufficient basis for diagnostic and treatment decisions in OSA. Consequently, suitably simple, accurate and validated strategies capturing both symptomatology and objective signs of overnight breathing disturbances are needed to support the diagnosis of OSA.

2.2 METHODS

The study protocol was approved by institutional research ethics committees at the Repatriation General Hospital and Flinders Medical Centre, South Australia, and participants provided written informed consent. The study was designed to meet the STARD guidelines for reports of diagnostic accuracy[113]. The two-stage diagnostic model was developed and then prospectively validated in separate patient samples.

2.2.1 Survey Distribution and Patient Selection

Patients aged between 25 to 70 years attending six primary care clinics for any reason between June 2007 and April 2008 were asked to complete a general health questionnaire, Epworth Sleepiness Scale (ESS) and Berlin Questionnaire. The ESS provides a subjective measure of daytime sleepiness by asking patients to rate their chance of falling asleep in eight commonly encountered scenarios[114]. Surveys were offered to patients by reception staff on arrival at the clinic or by research staff in the waiting room. Pregnant women and patients with significant cognitive impairment, a poorly-controlled psychiatric disorder, or who had previously received treatment for OSA were excluded.

Reasoning that the true prevalence of moderate-to-severe OSA in our study population would be relatively low and to minimise the confidence intervals around the point estimates for sensitivity and specificity of our diagnostic model, we chose an “OSA-enriched” patient sample for home sleep studies.

Based on a previous report of the diagnostic utility of the Berlin Questionnaire in the primary care setting[112], we selected approximately 4 “high risk” patients to every 1 “low risk” patient for simultaneous home PSG (Somte, Compumedics, Melbourne, Australia) and monitoring with a two-channel portable device (ApneaLink, ResMed, Sydney, Australia) which records oxygen saturation and an airflow-based apnea-hypopnea index (AHI). Home sleep studies were offered to all high risk participants, and patients at low risk were randomly sampled to achieve the desired 4 to 1 (high risk to low risk) ratio for a target of 150 patients. The first and second half of patients recruited formed development and validation groups respectively.

2.2.2 Home Sleep Studies

Patients were visited in their homes by a trained sleep nurse who measured subjects’ neck, hip and waist circumference, height and weight, and attached the sleep recording devices. Patients were asked to complete a sleep diary including estimation of sleep onset and wake times. Sleep monitoring equipment was returned to the sleep nurse the following morning for download and analysis.

Full PSG was conducted as the reference standard using a Somte multi-channel recorder which consists of an EEG, EOG, chin EMG, respiratory bands, ECG, finger oximeter probe, limb movement sensors, position sensor and nasal cannulae to measure airflow, pressure and snoring. Whilst unattended home PSG is not considered the true gold standard for the diagnosis of sleep disordered breathing, the portable Somte device used in

our study has been previously validated against a full PSG system in a laboratory setting, showing good agreement in AHI, with a mean difference of -0.5 events/hour (95%CI: -4.4 to 5.4, p=0.83)[115]. Also, a study of patients in the Sleep Heart Health Study cohort comparing unattended PSG recordings conducted in the home versus a supervised laboratory setting showed no significant difference in the median respiratory disturbance index (RDI), and only minor differences in some sleep parameters[116]. It could also be argued that sleep studies conducted in the patients' own home environment may reflect a more accurate measure of their usual physiological state during sleep compared to when conducted in an unfamiliar, laboratory setting.

A single, experienced sleep technician, who was blinded to the results of the questionnaire data, performed manual scoring of all home PSGs according to internationally agreed criteria for clinical research studies (American Academy of Sleep Medicine [AASM] 1999, "Chicago Criteria")[117]. An apnea was defined as a cessation of nasal flow lasting ten seconds or longer. An hypopnea was defined as a 50% decrease in nasal flow (or in both of the thoracic and abdominal excursions) lasting a minimum of 10 seconds, or a discernable decrease leading to a ≥3% oxygen desaturation or an EEG arousal. A study was considered satisfactory if there was at least 6 hours of technically adequate data (i.e. concurrent EEG and either nasal flow and/or thoracic and abdominal excursion signals) and 3 hours of sleep.

We defined moderate-to-severe OSA as an AHI≥30/hr. In our study, PSGs were scored using AASM 1999 "Chicago criteria"[117] which is highly sensitive

for detecting respiratory events and tends to result in relatively high AHI values. A recent study by Ruehland et al[66] has shown that an AHI value of 30/hr obtained using AASM 1999 “Chicago criteria” is equivalent to an AHI cut-point of 10.8/hr by current “recommended” AASM 2007 clinical sleep study scoring criteria in which hypopneas are defined by the presence of ≥30% airflow reduction and ≥4% desaturation[118]. Thus, we chose an AHI of 30/hour to define the cut-point between mild and moderate OSA.

The ApneaLink device is a portable, battery-powered, two-channel monitor which records oxygen saturation and nasal flow with sampling rates of 1Hz and 100Hz, respectively. The device consists of a pulse oximeter and nasal cannulae which are worn by the patient and plugged into a small case attached to an elasticised band which is strapped around the patient’s chest. Patients were instructed to switch the device on prior to bedtime and to turn it off on awakening. Data from the device were automatically analysed using ApneaLink software version 6.00 to derive an AHI from the airflow signal and an oxygen desaturation index (ODI) using the following parameters: (1) $AHI_{20,50}$, with apnea defined as a reduction in airflow to less than 20% of baseline and hypopnea as a reduction in airflow to 20% to 50% of baseline, for more than 10 seconds, and (2) ODI with ≥3% oxygen desaturations (3%ODI). A study was considered acceptable if nasal flow and oxygen saturation evaluation periods on the ApneaLink exceeded 4 hours and a sleep duration of at least 3 hours was reported on sleep diaries. Patients who failed either the PSG or ApneaLink study were asked to repeat simultaneous home monitoring.

2.2.3 Data Analysis and Statistics

Data for the baseline characteristics of patients in the development and validation groups are presented as mean ± SD for Normally distributed data, median [interquartile range (IQR)] for non-Normally distributed data, and n (%) for categorical data. Statistical comparisons for differences in baseline characteristics between development and validation groups were conducted using an independent samples Student's t test for Normally-distributed continuous data, a Wilcoxon rank-sum test for non-Normally-distributed continuous data, and a chi-square test for categorical data (STATA 11.0, Statacorp LP, USA).

Data from the development group were used to design the screening questionnaire and to assess the accuracy of the ApneaLink device against PSG in identifying cases of moderate-to-severe OSA. Chi-square automatic interaction detection (CHAID)[119] was used to identify variables predictive of an AHI≥30/hr and thus of potential use in the screening questionnaire. CHAID is an exploratory statistical technique which was first described in 1980 and developed to study relationships between a dependent variable (in our case, moderate-to-severe OSA) and potential predictor variables, using a series of chi-square analyses to form a classification tree, with progressive "splits" in the tree based on the variables which can best predict the dependent variable. CHAID analysis has been used previously in other fields of medicine, for example, to identify clinically important predictors of patient outcomes following surgery or trauma[120-122]. The statistical package CHAID

for Windows version 6 (Statistical Innovations Inc., 1993) was used for the analysis. Potential predictor variables used included gender, age group (<50 years and ≥50 years), individual ESS and Berlin Questionnaire items, total ESS score, BMI, and obesity classified by waist circumference (cut-off of >102cm for males and >88cm for females) and neck circumference (cut-off of ≥39.5cm for males, and ≥36.5cm for females). The age group cut-off of < or ≥50 years was selected based on the mean age of patients in the development group, which was rounded to the nearest 10 years, to provide a number which was simple for GPs to remember and which people could easily relate to. Variables most predictive of moderate-to-severe OSA on CHAID analysis were dichotomised and entered into a logistic regression analysis, and a simple scoring algorithm derived using the regression coefficients to determine the weighting for each item. Regression coefficients were rounded up to the nearest whole number to provide an individual score, and when added together, enabled a maximum total score of 10 points to be calculated for the questionnaire. Receiver operating characteristic (ROC) curve analysis was performed to assess the accuracy of the screening questionnaire for identifying moderate-to-severe OSA (Custom macros developed in Microsoft® Office Excel 2003, Microsoft Corporation).

We aimed for a sample size of approximately 75 patients in both the development and validation groups. Draper and Smith[123] have previously recommended a minimum sample size of 10 patients per predictor when conducting regression analysis. Assuming a final model with approximately 4-5 predictors, it was thought that a sample size of at least 75 patients per

group would be more than adequate to meet this criterion. This sample size provides more than 80% power to detect an overall R^2 value of 0.5, using a criterion for the F-statistic of the regression model (F0.05, k, n-k-1) and the formula that relates F to R^2 i.e. R^2=kF/(n-k-1+kF), where n is the sample size and k the number of parameters in the model.

To evaluate the predictive ability of the ApneaLink device in detecting OSA, ROC curve analyses were performed for the $AHI_{20,50}$ and 3%ODI against a PSG AHI≥30/hr. Based on the ROC area under curve (AUC), the superior ApneaLink parameter was selected for inclusion in the second step of the diagnostic model. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive and negative likelihood ratios and overall test accuracy were calculated for both the questionnaire and ApneaLink monitor to determine optimal cut-off values to maximise diagnostic efficiency. The accuracy of the final two-stage model for moderate-to-severe OSA was then evaluated in the validation group.

2.3 RESULTS

The patient recruitment pathway is outlined in Figure 2.1. Of the 1,251 questionnaire packs returned from the primary care clinics, 461 patients (188 at high risk and 273 at low risk for OSA on Berlin questionnaire) were eligible for selection for home sleep studies. 176 patients underwent home monitoring, with 157 performed successfully (123 patients at high risk and 34 at low risk for OSA). 19 patients were excluded due to failed sleep studies, mainly from inadequate recording times or equipment failure, and either failed their second attempt or declined a repeat study. The development group consisted of the first 79 patients, whilst the remaining 78 patients made up the validation group.

Patient characteristics for the development and validation groups are shown in Table 2.1. While both groups comprised of predominantly middle-aged and overweight to obese individuals with approximately equal numbers of males and females, the development group was slightly older and had higher BMI, neck, waist and hip circumference measurements. The proportion of patients with moderate-to-severe OSA was higher in the development group. There was no difference in Berlin questionnaire risk rating or ESS score.

Figure 2.1. Patient recruitment pathway

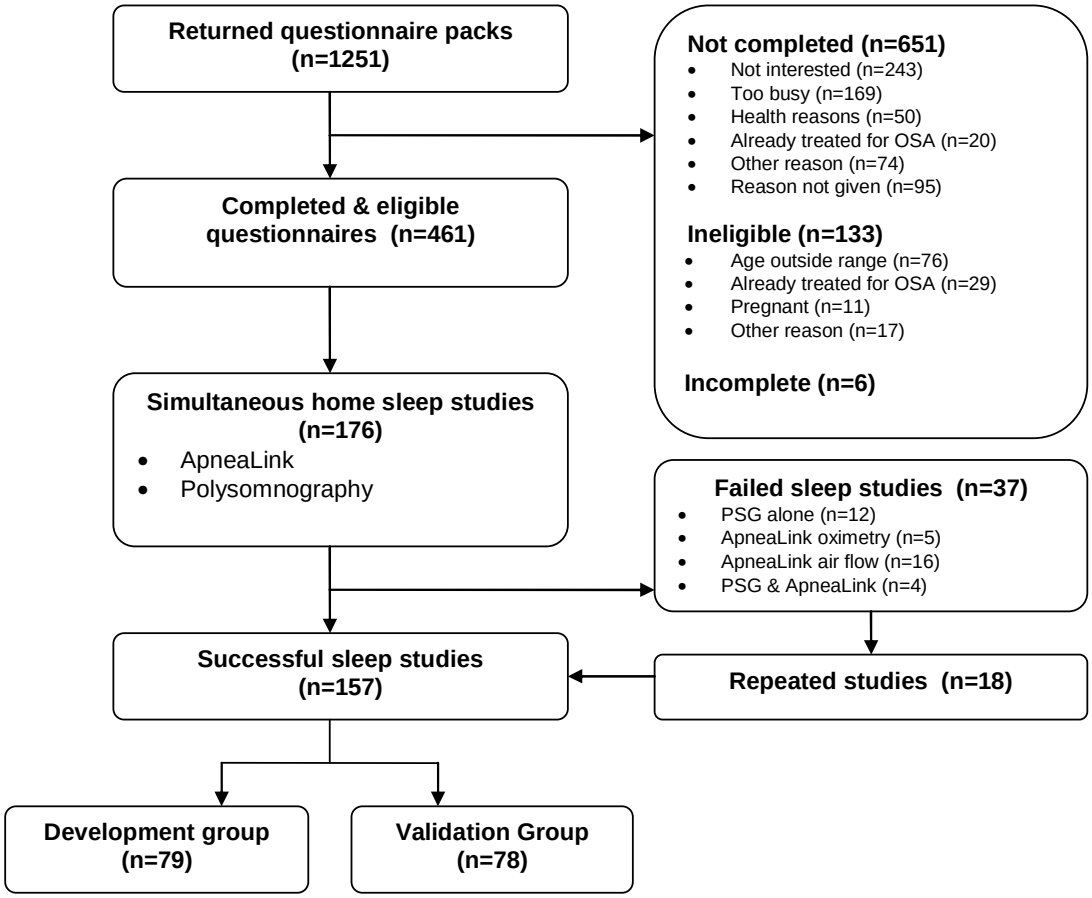


Table 2.1. Characteristics of patients in development and validation groups.

	Development Group (n=79)	Validation Group (n=78)	p value
Age, yr	55 [45-62]	50 [40-58]	0.015
Males, n (%)	42 (53%)	34 (44%)	0.230
BMI, kg/m^2	31.7 [28.8-36.1]	29.3 [25.5-33.8]	0.014
Neck circumference, cm	40.3 ± 4.2	38.6 ± 4.1	0.011
Waist circumference, cm	106.7 ± 13.9	101.3 ± 15.8	0.024
Hip circumference, cm	113 [105.5-121]	106.5 [100-117]	0.004
ESS	8.0 [4-10]	7 [5-10]	0.997
High risk, n (%)	65 (82%)	61 (78%)	0.521
Total AHI, /hr	20.9 [13.1-41.3]	16.5 [9.6-28.2]	0.018
AHI≥30/hr, n (%)	31 (39%)	16 (21%)	0.010

Data are presented as mean ± SD, median [IQR] or n (%).
BMI = body mass index; ESS = Epworth sleepiness scale; AHI = apnea-hypopnea index.

2.3.1 Development Data Set

2.3.1.1 Screening Questionnaire Development

Four variables were significantly predictive of moderate-to-severe OSA: (1) Berlin questionnaire item 4, “Has your snoring ever bothered other people?”; (2) Waist circumference, males >102cm, females >88cm; (3) Age ≥50years; (4) Berlin questionnaire item 5, “Has anyone noticed that you stop breathing during your sleep?”. The results of the logistic regression analysis are shown in Table 2.2. A four-item screening tool was created and named the “OSA50” questionnaire (Figure 2.2). Points are allocated to each question, with snoring and waist circumference having the highest score of 3 points each, and age and witnessed apneas gaining 2 points each, to give a maximum total score of 10 points. On ROC curve analysis, the OSA50 questionnaire was significantly predictive of moderate-to-severe OSA, with an AUC of 0.84 (95% CI: 0.75–0.94, $p<0.001$) (Figure 2.3). Using a cut-off score ≥5/10, the screening questionnaire had a sensitivity of 100% (95%CI: 86-100%), NPV of 100% (73-100%), specificity of 29% (17-44%) and PPV of 48% (35-63%).

2.3.1.2 Validation of ApneaLink Monitor

Two patients with successful home PSGs included in the questionnaire development had failed ApneaLink studies and were excluded from further analysis, leaving 77 patients for validation of the ApneaLink monitor and analysis of the overall two-stage diagnostic model. ROC curves for the ApneaLink 3%ODI and $AHI_{20,50}$ against PSG in the development group are shown in Figure 2.4. Both the 3%ODI and $AHI_{20,50}$ were highly predictive of moderate-to-severe OSA, with ROC AUC values of 0.96 (95%CI:0.91-1.00,

Table 2.2. Logistic regression analysis – factors associated with an AHI≥30, as determined by CHAID analysis

Factors	Regression coefficient	Standard error	p value	Odds ratio
Snoring	2.51	1.11	0.02	12.3
Waist circumference	2.22	0.92	0.02	9.2
Apneas	1.84	0.72	0.01	6.3
Age 50+	1.49	0.66	0.02	4.4

Figure 2.2. OSA50 screening questionnaire

		If yes, SCORE
Obesity:	Waist circumference* - Males >102cm or Females >88cm	3
Snoring:	Has your snoring ever bothered other people?	3
Apneas:	Has anyone noticed that you stop breathing during your sleep?	2
50:	Are you aged 50 years or over?	2
	TOTAL SCORE:	…….. / 10 points

* Waist circumference to be measured at the level of the umbilicus.

Figure 2.3. Receiver operating characteristic curve showing the performance of the OSA50 screening questionnaire in discriminating patients with moderate-to-severe OSA (AHI≥30/hr) in the development group (n=79)

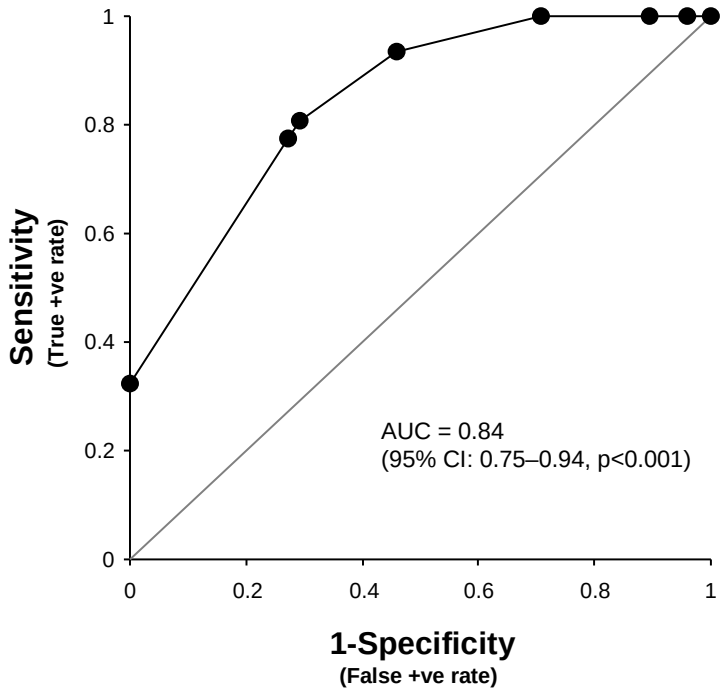
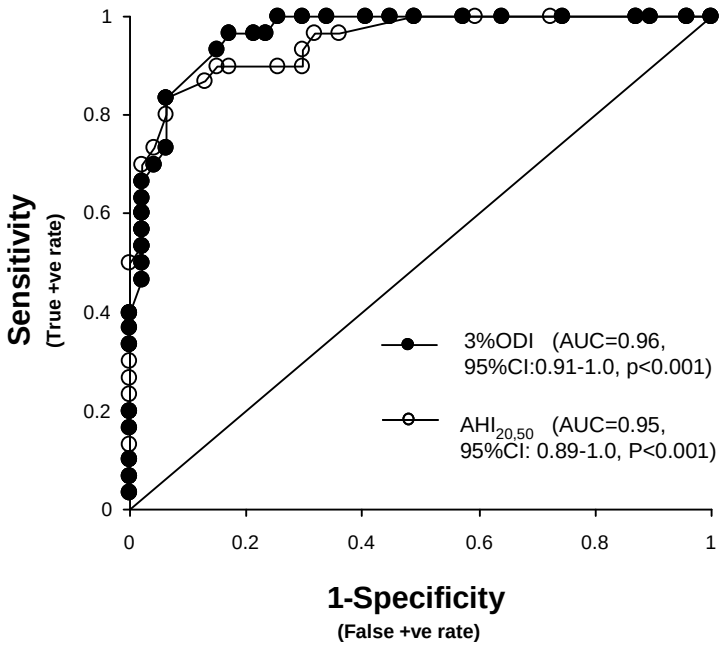


Figure 2.4. Receiver operating characteristic curves showing the performance of the ApneaLink 3%ODI, and $AHI_{20,50}$ in diagnosing moderate-to-severe OSA (AHI≥30/hr) in the development group



p<0.001) and 0.95 (0.89-1.0, P<0.001), respectively. The 3%ODI was selected for use in the two-stage model because oximetry was technically more reliable than nasal airflow measurements. 16 (9%) of the 176 initial home sleep studies failed due to an inadequate airflow signal, compared to only 5 (3%) with failed oximetry.

2.3.1.3 Two-Stage Diagnostic Model

The diagnostic characteristics of the two-stage model are shown in Tables 2.3A and 2.4. 30 patients in the development group had an AHI≥30/hr. Using cut-off values of ≥5/10 for the OSA50 questionnaire and ≥16/hr for the 3%ODI, the two-stage model was capable of identifying moderate-to-severe OSA with a high sensitivity and specificity, and had an overall diagnostic accuracy (sum of the true positive and true negative rate) of 91%.

2.3.2 Validation Data Set

The two-stage model was prospectively applied to the validation sample (Tables 2.3B and 2.4). 16 (21%) patients in the validation group were confirmed to have moderate-to-severe OSA. The performance of the OSA50 questionnaire in the validation group was similar to that in the development group, with a ROC AUC of 0.75 (0.59-0.90, p<0.001). 20 out of the 78 (26%) patients in the validation sample would have been excluded from further testing on the basis of a negative OSA50 questionnaire, only 1 of whom was positive for moderate-to-severe OSA on PSG. The two-stage model correctly identified moderate-to-severe OSA with sensitivity and specificity over 80%, a

very high NPV and overall diagnostic accuracy of 83%.

Table 2.3. Contingency tables for development and validation groups

A. Development Group (n=77)

		Moderate-to-severe OSA (AHI≥30/hr)	
		+ve	-ve
OSA50 & 3%ODI	+ve	29	6
	-ve	1	41

B. Validation Group (n=78)

		Moderate-to-severe OSA (AHI≥30/hr)	
		+ve	-ve
OSA50 & 3%ODI	+ve	14	11
	-ve	2	51

Table 2.4. Accuracy of two-stage diagnostic model (OSA50 score ≥5 & ApneaLink 3%ODI ≥ 16/hour) for identifying moderate-to-severe OSA.

	Moderate-to-severe OSA (AHI≥30)	
	Development Group	**Validation Group**
Sensitivity	0.97 (0.81-1.00)	0.88 (0.60-0.98)
Specificity	0.87 (0.74-0.95)	0.82 (0.70-0.90)
PPV	0.83 (0.66-0.93)	0.56 (0.35-0.75)
NPV	0.98 (0.86-1.00)	0.96 (0.86-0.99)
LR+	7.57 (3.58-16.03)	4.93 (2.80-8.70)
LR-	0.04 (0.01-0.26)	0.15 (0.04-0.56)

Data are presented as estimate (95% confidence intervals).
PPV = positive predictive value; NPV = negative predictive value; LR = likelihood ratio.

2.4 DISCUSSION

Our results demonstrate that a simplified diagnostic model consisting of a screening questionnaire followed by home oximetry can identify patients in primary care with moderate-to-severe OSA with an overall accuracy exceeding 80%. We targeted moderate-to-severe OSA, as more severely affected patients have the highest morbidity, and also adhere and respond to therapy better than those with mild disease[124]. Compared to the standard pathway of care involving specialist review and laboratory-based testing, our diagnostic model has the potential to offer a low cost and easily accessible strategy which can be initiated in primary care.

Our clinical prediction questionnaire is only the second such questionnaire to be developed specifically for primary care and is a significant advance on the Berlin questionnaire[112] because of its brevity and simple 10-point score. Previously published questionnaires have been derived from sleep clinic populations[55,56,61,111], and require complex calculations or reference to specialised tables for interpretation. We created the OSA50 questionnaire with the hope that primary care providers would find it ideal for routine clinical use.

The four factors most predictive of OSA were the waist circumference, snoring, witnessed apneas, and age, with similar variables identified in other studies. Two previously published screening tools include the multivariable apnea risk (MAP) index[56] and the sleep apnea clinical score (SACS)[55], both derived from sleep clinic cohorts. The MAP index is calculated using self-

reports of snoring, gasping, witnessed apneas, BMI, age and gender[56]. The ROC AUC for an AHI≥10/hr was 0.79, with a sensitivity and specificity of 88% and 55%, respectively. Flemons et al[55] found the strongest clinical predictors to be neck circumference, hypertension, snoring and partner reports of gasping or choking. For a SACS >15, the authors report a positive likelihood ratio of 5.2 and post-test probability of 81% for an AHI>10/hr. Other studies have incorporated craniofacial and oropharyngeal measurements into their prediction models[61], however, it is unlikely that primary care providers would adopt a screening tool which required unfamiliar anatomical measurements not routinely used in clinical practice.

Although previously found to be an independent predictor of OSA[125], hypertension was not predictive of OSA in our study. Neck circumference has also been identified as a predictor of OSA[125]. Interestingly, we found waist circumference to be a stronger predictor of OSA than other markers of obesity, with at least two other studies reporting similar findings[111,126]. This is in keeping with the tracheal traction hypothesis for OSA, in which central obesity is believed to cause a reduction in lung volume during sleep leading to a loss of caudal traction on the upper airway thereby promoting pharyngeal collapse[127]. As a questionnaire item, waist circumference is a simpler measure than BMI, and is likely to be more familiar to patients compared with neck circumference. Patients should be aware of their pants size, of which a US men's size of "40 inches" and women's "size 16" are equivalent to the questionnaire cut-off values of >102cm and >88cm, respectively. Also, the National Cholesterol Education Program – Adult Treatment Panel (NCEP-

ATP III) guidelines have included waist circumference in the diagnostic criteria for the metabolic syndrome using the same cut-off values[128]. Primary care physicians are advised to promote intensive lifestyle modifications for patients with metabolic syndrome[129], which is associated with OSA and an independent risk factor for cardiovascular disease.

The diagnostic ability of four clinical prediction formulas, including the MAP index and SACS, was previously evaluated[57]. The prediction models had high sensitivities of between 76-96%, with relatively low specificities of 13-54% and ROC AUC values of 0.67-0.74, similar to the results achieved by our OSA50 questionnaire. Whilst the OSA50 questionnaire alone is not sufficiently accurate to discriminate between those with and without OSA, it is of value in confidently ruling out OSA and directing patients at high risk of disease for further diagnostic evaluation. To improve the accuracy of our diagnostic strategy, we have combined the OSA50 questionnaire with a second simple step of home sleep monitoring. We selected oximetry over nasal pressure for our two-stage model because the failure rate for the oximetry signal (3%) was less than one-third that of the nasal pressure signal (9%). We also felt that primary care physicians would be more familiar with the concept of oximetry measurement and have greater confidence in their ability to interpret study results. In contrast to laboratory-based PSG, overnight oximetry is less costly and can be self-administered in the patient's home without the need for technical staff. In 2007, the cost to Medicare (Australia's national health insurance system) for PSG was AUD$485.65 per patient, compared to AUD$106.45 for overnight oximetry. In our validation

Table 2.5. Baseline characteristics of the 11 false positive patients in the validation group

	Age (yrs)	Gender	BMI (kg/m^2)	Berlin Questionnaire Risk	PSG AHI (events/hr)	ESS	OSA50 Questionnaire Score	3%ODI (events/hr)
1	46	F	51.15	HR	25.8	20	6	28
2	55	F	37.79	HR	19.2	13	8	18
3	40	F	36.57	HR	18.9	5	6	18
4	49	F	30.27	HR	28	17	6	18
5	63	M	31.01	HR	20.4	7	10	19
6	60	F	31.29	HR	21.6	2	10	17
7	61	M	38.5	HR	29.7	6	10	18
8	69	M	31	HR	26.5	12	5	16
9	57	F	24.2	HR	22.1	2	7	46
10	70	M	23.8	LR	20.7	4	5	20
11	38	M	26.4	HR	29.2	12	5	16

BMI = body mass index; PSG = polysomnography; AHI = apnea-hypopnea index; 3%ODI = 3% oxygen saturation index; F = female; M = male; HR = high risk; LR = low risk

sample, the two-stage diagnostic model accurately identified patients with moderate-to-severe OSA with sensitivity and specificity >80%, with a negative result confidently ruling out disease (NPV 96%). Whilst the PPV appeared lower than ideal at 56%, review of the 11 patients classified as "false positives" showed that all had evidence of at least mild OSA (minimum PSG AHI of 18.9/hr) and half reported excessive daytime sleepiness with ESS scores ≥12 (see Table 2.5), and, therefore, would likely obtain benefit from a trial of therapy.

Of note, neither the total ESS score nor individual items related to excessive sleepiness were predictive of OSA, similar to previous reports[55,111]. Thus, whilst a common complaint, daytime sleepiness *per se* is not predictive of disordered breathing during sleep. Hypersomnolence, however, is an important determinant of whether CPAP should be recommended. Patients complaining of excessive sleepiness are most likely to respond to treatment and be compliant with CPAP compared to those with few symptoms[130,131]. Our diagnostic model could be further refined by addition of a minimum ESS score cut-off, thereby specifically targeting hypersomnolent patients who would more likely benefit from urgent therapy.

A two-stage method for OSA using the MAP index and nocturnal oximetry was previously evaluated[132], and for an AHI≥30/hr, had a sensitivity of 85%, specificity of 97%, PPV of 94% and NPV of 92%. Mulgrew et al used a simplified diagnostic algorithm as part of an ambulatory management strategy for moderate-to-severe OSA which incorporated an ESS, SACS, and

home oximetry[87]. Of the 36 patients who scored positively on the diagnostic algorithm, 94% (95%CI: 81-99%) were correctly identified as having an AHI>15/hr on subsequent PSG. These models, however, were evaluated in sleep disorders clinic populations that have a high pre-test probability of disease. To our knowledge, our study is the first to evaluate a primary care population, where a significant disease burden remains under-recognised.

We attempted to optimise the precision around our estimates by enriching samples with a higher proportion of “high risk” patients by Berlin Questionnaire, which may raise concerns regarding whether our results can be generalised to a “non-enriched” population. Theoretically, changes in disease prevalence do not affect the sensitivity or specificity of a test, but importantly influence predictive values of positive and negative test results. However, by enriching the study population with the Berlin Questionnaire it is possible that high risk OSA patients were more likely to score positive responses to selected items on the Berlin Questionnaire compared to an unselected OSA patient sample. This could have influenced final OSA50 screening questionnaire content and the sensitivity and specificity of the overall diagnostic process. A further effect of enriching a population with cases of moderate-severe OSA may be to falsely elevate the positive predictive value of the 2-stage diagnostic screen. As it turned out, however, in our study the employment of the “enrichment” strategy had quite different effects in the development and validation samples. It markedly increased the prevalence of moderate-severe OSA in the development group, but had little impact on prevalence of moderate-to-severe OSA in the validation group

since in the validation group “high” and “low” risk patients had similar rates of disease (21% and 18%, respectively). The reasons for this difference are not clear but may relate to the lower age and obesity rate in the validation group compared with development group. We estimate, using back-extrapolation, that 20% of our original, non-enriched primary care population would have had moderate-to-severe OSA, which is consistent with recent prevalence estimates from the general population[7]. The estimated prevalence of moderate-to-severe OSA in the “enriched” validation group was 21%, which is virtually identical. Thus we believe estimates of diagnostic accuracy from the validation sample are likely to be similar to that in a non-enriched primary care population. Furthermore, given similar overall rates of moderate to severe OSA in both the high and low risk groups in the validation sample, and face validity of the final questionnaire items, the impact of the potential bias from using an enriched population would appear to be limited.

When applying sensitivity and specificity values obtained from our development and validation groups to a primary care population with a disease prevalence of 20%, the PPV is in the range 55-65% and NPV in the range 97-99%. Therefore, the two-stage model has its greatest value in ruling out disease. Patients considered “false positive” are likely to have evidence of at least mild OSA (see above), and if treatment decisions are based around symptoms, such as sleepiness, then a trial of CPAP therapy is likely to be worthwhile with minimal risk of harm.

In summary, a two-stage diagnostic model consisting of a screening

questionnaire followed by home oximetry can identify patients with clinically significant OSA in a primary care population with a high degree of accuracy. The model could potentially offer a cost-effective solution to the problem of currently overwhelmed laboratory-based sleep services and would be of particular benefit for rural and remote regions, as well as developing countries, where access to sleep services is limited. This simplified strategy, in conjunction with education of primary care physicians and provision of primary care-based management regimens, has the potential to significantly improve patient access to care and expedite treatment for this common sleep disorder.

CHAPTER 3: AN EDUCATION PROGRAM FOR GENERAL PRACTITIONERS TO IMPROVE THEIR AWARENESS AND KNOWLEDGE OF OBSTRUCTIVE SLEEP APNEA

3.1 INTRODUCTION

Obstructive sleep apnea (OSA) is a condition characterised by repetitive upper airway obstruction during sleep, resulting in recurrent oxygen desaturations, frequent arousals, and complaints of excessive daytime sleepiness. Untreated, moderate-to-severe OSA has significant health consequences and is associated with an increased risk of hypertension, cardiovascular disease, motor vehicle accidents (MVAs) and neurocognitive impairment[13,21,23,109]. The mainstay of treatment for OSA is with continuous positive airway pressure (CPAP) therapy, which is effective in minimising the health-related consequences of disease[21,26]. OSA was estimated in 1995 to affect at least 3% of middle-aged Australian adults[1]. This figure is likely to have subsequently increased substantially due to the rising prevalence of obesity in the Australian community[6] and the known causal relationship between excessive weight and OSA[4]. Despite a substantial increase in the recognition of the potential importance of OSA in the general population and amongst health care providers over the last decade, which has been mirrored by a large increase in diagnostic testing for the condition (see below), OSA remains frequently under-recognised in primary care. There is also a dearth of knowledge at the primary care level regarding management strategies and

specific treatment options.

Patients attending general practice clinics will often have clinical features suggestive of OSA if questioned about their sleep health, which is not surprising given the high rates of obesity and hypertension in the primary care population. Almost one-third (32%) of patients surveyed in primary care clinics in the United States (US) and Europe had symptoms consistent with a high likelihood of OSA[92]. In another study of adult primary care patients, 23.6% of patients reported symptoms of loud snoring and/or witnessed apneas plus excessive daytime sleepiness[94]. From our own survey conducted at six Australian primary care practices, we estimated that 20% of adults who were seeing their GP for any reason had evidence of moderate-to-severe OSA on polysomnography. Despite the high prevalence of OSA in primary care, the level of awareness and knowledge amongst GPs about this sleep disorder is generally low. During an unstructured interview of a standardised patient, only 10% of GPs asked sufficient questions relevant to obstructive sleep apnea syndrome[96]. Furthermore, education of the patient about complications related to OSA was poor, with 84% of GPs failing to discuss an increased risk of MVAs and only half informing the patient about potential cardiovascular complications. In a study of GP knowledge and attitudes about sleep disorders, most GPs rated their own knowledge as either “fair” or “poor”, and achieved a mean score of only 34% correct answers to a multiple choice questionnaire[103].

One of the major reasons for the under-recognition of OSA in general

practice is the lack of education on sleep disorders at both undergraduate and postgraduate levels, relative to the rapid growth in research and clinical practice of sleep medicine in recent decades. A substantial proportion of GPs have received little or no formal education in the basic physiology of sleep or clinical management of sleep disorders during their undergraduate medical training. A survey of US medical schools in 1990 revealed that an average of only 2.1 hours was dedicated to teaching in sleep and sleep disorders for undergraduates[100], with no substantial increase in teaching time evident when the survey was repeated a decade later[101]. Research evaluating sleep medicine education in Australia has not been previously reported, but is likely to be comparable to that in the US.

Despite a lower than ideal appreciation of the importance of OSA and sleep history in general practice, there has nevertheless been a steady rise in the provision of diagnostic sleep services across Australia. According to data from the Medicare Benefits Scheme, in the ten year period between 1995-2004, the supply of polysomnography in Australia has risen by an average of 4541 studies per year[133]. The annual cost to the scheme has increased four-fold from AUD $9.2 million in 1995 to AUD $38.8million in 2009. There has also been a surge in the number of diagnostic sleep service providers conducting home-based, portable sleep monitoring, which are frequently utilised by patients referred from general practice, and often with minimal clinical input from sleep specialists. The rapid growth in service provision has not been mirrored by an increase in undergraduate or postgraduate sleep medicine education for primary care providers. Thus, GPs who are frequently

required to be the principal provider of advice to patients with OSA may lack the necessary skills and confidence in managing this common sleep disorder.

As part of a research study examining a simplified model of care for OSA in primary care, we set out to develop and evaluate an education program for GPs on OSA and common sleep disorders causing excessive daytime sleepiness.

3.2 METHODS

3.2.1 Development of the Education Program

In consultation with GPs involved in the research project, the medical education department of General Practice Network South and the Discipline of General Practice at Flinders University in South Australia, we developed a six-hour education program designed to fulfil the criteria for an Active Learning Module under the Quality Assurance and Continuing Professional Development (QA&CPD) Program of the Royal Australasian College of General Practitioners (RACGP). The aim of the education program was to provide GPs with a greater understanding of the pathophysiology, health consequences, diagnosis and management of OSA as well as the differential diagnosis of excessive sleepiness using a variety of delivery modes (e.g. case discussion, presentations, patient interviews, demonstration and practical sessions) to maximise opportunities for GP interaction and feedback. The education program and key learning objectives for the education program are outlined in Figure 3.1. Each participant was given a folder containing presentation notes, case studies and answers, relevant journal articles, and quick-reference guides on OSA and CPAP management. This work was approved by institutional research ethics committees at the Repatriation General Hospital and Flinders Medical Centre, South Australia, and participating GPs provided written informed consent.

3.2.2 Program Delivery

GPs participated in the education program prior to their involvement in a randomised controlled study evaluating a simplified ambulatory model of care

for OSA based in the primary care setting versus usual specialist sleep centre management. The 6-hour education program was delivered as two 3-hour sessions, held on consecutive evenings or one week apart, and was conducted at four locations within metropolitan and rural regions of South Australia where the GPs and their practices were located (i.e. Adelaide, Victor Harbor, Riverland and Barossa Valley). Educational programs were held between June 2008 and July 2009. An attitudes and knowledge questionnaire was completed by GPs before and 2 weeks after the education sessions. The questionnaire was then repeated a third time at the conclusion of the randomised controlled study, which occurred between 17 to 30 months after their participation in the education program. The attitudes component was derived from a previously validated questionnaire[134], and asked GPs to rate their agreement to five statements about the importance of OSA and level of confidence in their ability to diagnose and manage OSA using a 5-point Likert scale. The knowledge component of our questionnaire consisted of ten multiple-choice questions (MCQs) which were designed to test GPs' knowledge of issues related to OSA and conditions associated with excessive daytime sleepiness. A program evaluation form was also given to GPs at the conclusion of the education sessions. Using a 5-point Likert scale, GPs were asked to evaluate the quality and relevance of the course, whether information was presented at an appropriate level, if learning needs were addressed and how well each learning objective was met by the program.

Figure 3.1. Education Program – OSA Diagnosis and Management in General Practice

Session 1 (3 hours)

1) Introduction: OSA Management in General Practice (15 min)
2) Presentation: Epidemiology and Clinical Features of OSA (30 min)
3) Case Study: Part 1 (30 min)
4) Sleep History Taking & Examination: Real-Life Patients with OSA (30 min)
5) Presentation: Daytime Sleepiness and Sleep Laboratory Investigations (30 min)
6) Demonstration: Home versus Laboratory Sleep Studies and Interpretation (45 minutes)

Session 2 (3 hours)

1) Presentation: Treatment of OSA and Implications for Driving (30 min)
2) Practical Session: How to Manage Patients on CPAP Therapy (90 min)
3) Case Study: Part 2 (30 min)
4) Question and Answer Time (15 min)
5) Research Study: Simplified Management of OSA in Primary Care (15 min)

Learning Objectives:

1) To increase knowledge about the diagnosis of OSA
2) To increase knowledge about the treatments for OSA
3) To increase knowledge about the causes of daytime sleepiness
4) To increase knowledge about the use of CPAP therapy for OSA
5) To understand how to apply a 4-item screening questionnaire and home sleep study to identify patients in general practice with moderate-to-severe OSA

3.2.3 Data Analysis

Differences in attitudes and knowledge questionnaire scores before and after the education program were compared for GPs who completed the entire 6-hour course, and also for GPs who attended only one of the two 3-hour sessions. Paired data (i.e. pre-education versus 2 weeks post-education; pre-education versus long term; and 2 weeks post-education versus long term) were analysed using a Wilcoxon signed-rank test for non-parametric data (STATA 11.0, Statacorp LP, USA) with adjustment for multiple comparisons using Dunn-Sidak correction. Results are presented as median score (interquartile range [IQR]) for each component of the attitudes questionnaire, the total attitudes score and the total knowledge score. The percentage of GP responses were calculated for each component of the program evaluation form.

3.3 RESULTS

A total of 41 GPs presented to at least one of the two 3-hour sessions, with 33 GPs attending the entire 6-hour course. 8 GPs were unable to attend one of the two sessions because its timing clashed with their work or personal schedules. 31 out of the 33 GPs who completed the entire education program returned both pre- and 2 weeks post-event questionnaires, and were included in the analysis. 21 GPs completed the questionnaire at the third testing occasion and were included in the analysis of long term data. The results of the attitudes and knowledge questionnaire are presented in Table 3.1 and Figures 3.2 and 3.3.

3.3.1 Attitudes & Knowledge at Baseline &Two Weeks Post-Education

Prior to their attendance at the OSA education session, most GPs felt that, as a clinical disorder, OSA was either very or extremely important, and gave a similar rating for the importance of identifying patients in general practice with OSA. Whilst GPs were confident at identifying patients at risk for OSA, they were less confident in their ability to manage patients with the condition, particularly those on CPAP therapy. Following the OSA education program, statistically significant improvements in GP ratings were seen for all five components of the attitude questions and for the attitudes score as a total which increased from a median score of 17 (IQR 12-23) to 21 (IQR 16-24) out of a possible 25 points (Table 3.1). There was also a significant improvement in knowledge test scores, with a median of 6.0 (IQR 5-8) out of 10 questions answered correctly prior to the program, which increased to a

median score of 9 (IQR 8-10) ($p<0.001$) 2 weeks after GPs attended the education sessions (Figure 3.2).

Questionnaire data collected pre-education and 2-weeks post-education were available for 7 out of the 8 GPs who only attended one three-hour session. For the attitudes components of the questionnaire, there appeared to be a trend towards an increase in mean total attitudes score from 17 (IQR 16-18) to 20 (IQR 20-20), however this did not reach statistical significance ($p=0.052$). There was also no statistically significant improvement in knowledge test scores at 2 weeks after the education program for GPs who attended only one of the two education sessions. The mean total knowledge score was 7 (IQR 5 to 7) prior to attendance at the education session and was 7 (IQR 5-10) post-education ($p=0.24$).

3.3.2 Program Evaluation

The program was rated very positively by participating GPs on post-activity program evaluation forms (Table 3.2). All GPs agreed or strongly agreed that the information was presented at an appropriate level and that their learning needs were met by the education program. 95% of GPs rated the overall quality of the educational components as either “good” or “excellent”, and 93% agreed or strongly agreed that the information was relevant to their practice. When asked to rate how well learning objectives were met by the program, participants gave a median score of 5 (IQR 4 to 5) out of a possible 5 points (from 1 = not met at all, to 5 = completely met) for the learning objectives related to increasing knowledge about the diagnosis of OSA,

treatment of OSA, and use of CPAP therapy. A median score of 4 out of 5 (IQR 3 to 5) was given for the learning objective related to increasing knowledge about the causes of daytime sleepiness.

3.3.3 Long Term Data

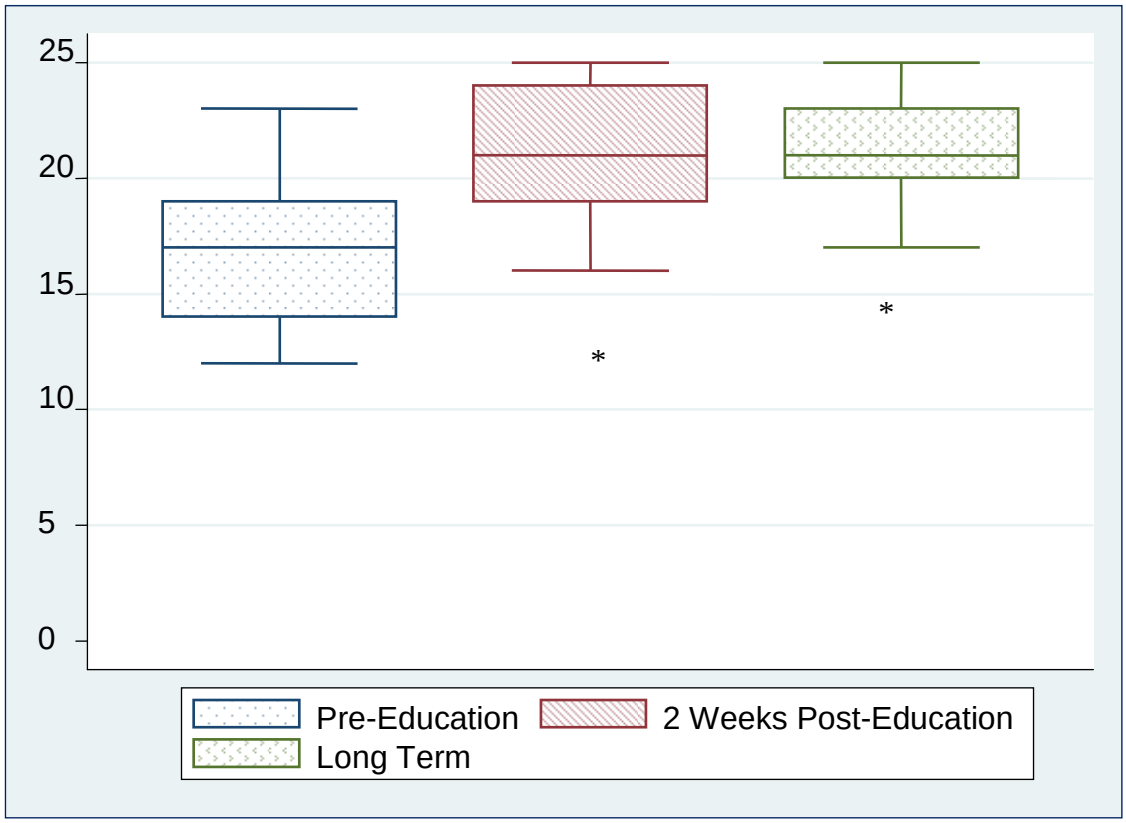
When GPs were tested again between 17 to 30 months after the education program, scores for all five attitudes components remained similar to that seen at 2 weeks post-participation, and continued to remain significantly higher than pre-education scores (Table 3.1). The median total attitudes score was 21 (IQR 20-23) which was similar to the score at 2 weeks post-education ($p=0.75$), and remained significantly higher than the baseline score ($p=0<0.001$) (Figure 3.2). The median total knowledge score fell slightly from that at 2 weeks post-education to 7 (IQR 7 to 9) on long term testing ($p=0.011$), but was still significantly higher than the median score at baseline ($p=0.036$) (Figure 3.3).

Table 3.1. Attitudes Questionnaire

Attitudes	Pre-Education Scores (n=31)	Two Weeks Post-Education Scores (n=31)	Long Term Scores (n=21)
1) As a clinical disorder, OSA is: 1 = not important, 2 = somewhat important, 3 = important, 4 = very important, 5 = extremely important	4 [4 to 4]	4 [4 to 5]*	4 [4 to 5]†
2) Identifying patients in general practice with possible OSA is: 1 = not important, 2 = somewhat important, 3 = important, 4 = very important, 5 = extremely important	4 [3 to 4]	4 [4 to 5]**	4 [4 to 5] †
3) I feel confident identifying patients at risk for OSA†	4 [3 to 4]	4 [4 to 5]**	4 [4 to 5] ‡
4) I am confident in my ability to manage patients with OSA†	3 [2 to 4]	4 [4 to 5]**	4 [4 to 5] ‡
5) I am confident in my ability to manage patients on CPAP therapy†	2 [2 to 3]	4 [4 to 4]**	4 [3 to 4] ‡
Total attitudes score	17 [12 to 23]	21 [16 to 25]**	21 [20 to 23] ‡

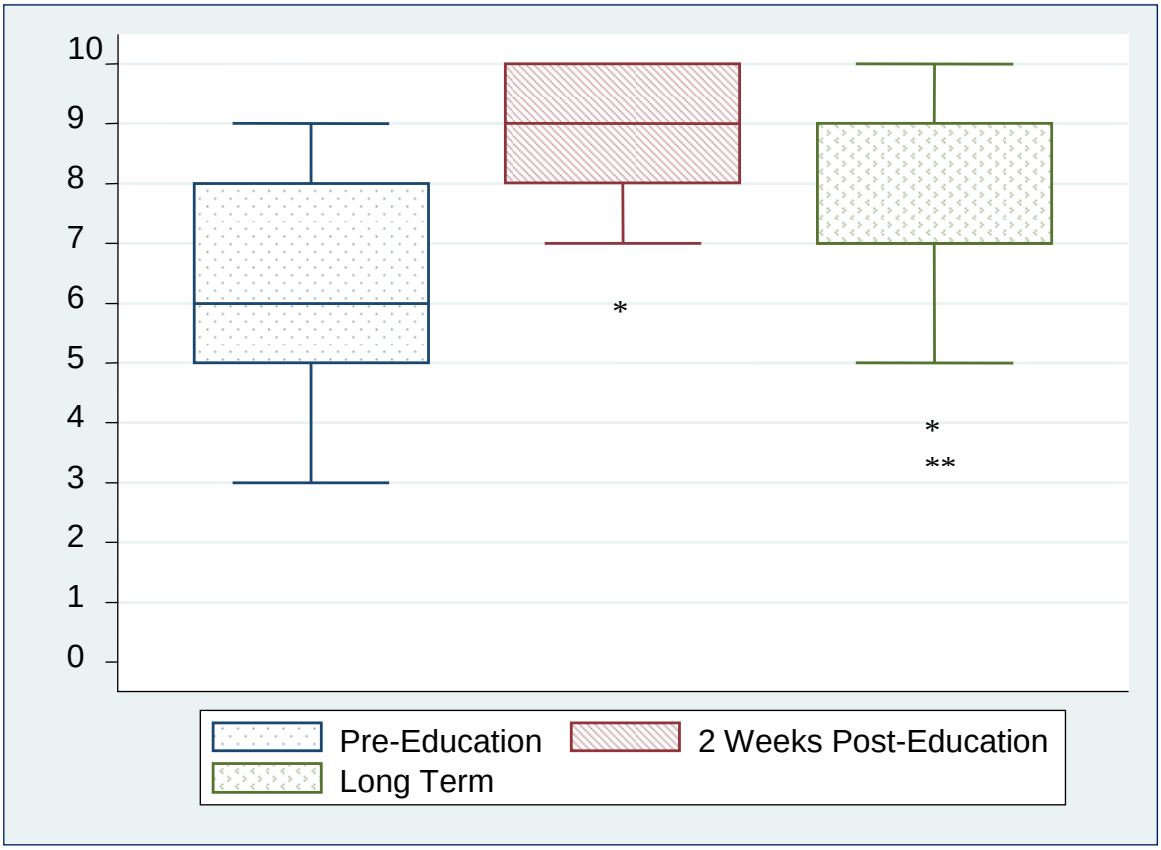
Results displayed as median [interquartile range]
† Likert scale: 1 = strongly disagree, 2 = disagree, 3 = neither agree nor disagree, 4 = agree, 5 = strongly agree
* $p<0.05$ for the difference in pre- and 2 weeks post-education scores
** $p<0.001$ for the difference in pre- and 2 weeks post-education scores
† $p<0.05$ for the difference in pre-education and long term scores
‡ $p<0.001$ for the difference in pre-education and long term scores
NB. p values have been adjusted for multiple comparisons using a Dunn-Sidak correction.

Figure 3.2. Total Attitudes Score



* p<0.05 compared to pre-education scores

Figure 3.3. Knowledge Test Scores



* p<0.05 compared to pre-education scores

** p<0.05 compared to 2 weeks post-education scores

Table 3.2. Program Evaluation

1) Please rate the overall quality of the educational components as a learning experience:

Poor	Below average	Average	Good	Excellent
0%	0%	5%	52%	43%

2) The information presented was relevant to my practice:

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
0%	0%	7%	34%	59%

3) The information was presented at an appropriate level:

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
0%	0%	0%	50%	50%

4) My learning needs were met by the education program:

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
0%	0%	0%	52%	48%

3.4 DISCUSSION

The 6-hour RACGP-accredited Active Learning Module on obstructive sleep apnea was rated highly by participants and appeared to be successful in increasing the confidence of GPs in their ability to manage patients with OSA and in the use of CPAP therapy, which was sustained on long term evaluation. An increase in GPs' knowledge of OSA and common sleep disorders was reflected by the improvement in MCQ test scores when assessed two weeks after the education program and when tested again at least seventeen months later. A program such as this, aimed at primary care physicians at the postgraduate level, while not a substitute for improved educational opportunities at the medical undergraduate level, can help fill the gaps in sleep medicine education and has the potential to improve diagnosis and management of OSA in the community. The education program could be adapted into a course suitable for web-based teaching, enabling broader access for GPs nationwide. This would be particularly important for primary care practitioners located in rural and remote areas, who have limited access to educational resources. Increasing the level of education on basic sleep science and sleep disorders management in undergraduate medical schools will also be vital in improving the knowledge and competence of future GPs. A study comparing the frequency of sleep history taking in a simulated patient revealed that 82% of interns who had received prior training in sleep medicine asked the patient about sleep problems, whilst none of the primary care practitioners and only 13% of interns who had no formal sleep training inquired about sleep[104].

The GPs who have participated in the education program have been involved in a randomised controlled trial which has required them to identify patients in their practice with OSA using a validated diagnostic strategy consisting of a screening questionnaire and home sleep monitoring[135]. The study will compare outcomes for patients managed in primary care by their GP and a community-based sleep nurse, versus usual care in a specialist sleep centre. Participation in the Active Learning Module has provided GPs with the knowledge base from which they will be able to competently manage patients with OSA in their practices. The results from this study will provide further information on the value of the OSA education program and will potentially establish a role for GPs in the diagnosis and management of this common sleep disorder.

3.4.1 Methodological Limitations

The major limitation of this study lies in its before-and-after trial design and lack of a matched control group. Because we did not evaluate the knowledge and attitudes of participants who had not attended the education program, this may limit our ability to definitively conclude that the improvements seen were due entirely to the education program itself, as GPs may have been influenced by factors outside of the intervention. However, due to the relatively short duration of time between completion of the first and second questionnaires (between 2 to 4 weeks for most GPs), it would seem unlikely that other factors would have significantly influenced the outcomes. Also, unlike GPs who completed the entire 6-hour program, for those who attended only one 3-hour session, we found no statistically significant improvement in

either the attitudes or knowledge components of the questionnaire at 2 weeks post-event, although there did appear to be a trend towards improved attitudes towards OSA diagnosis and management overall. Another possible limitation of this study is that GPs were given the same knowledge questionnaire on three testing occasions, thus there was potential for bias from a learning effect. The knowledge questionnaire was not formally validated prior to its use in the study, however, was created and reviewed by expert sleep physicians and the 10 items were thought to cover important aspects of OSA management and common sleep disorders. GP participants were a self-selected group, and may have had a higher degree of motivation and interest in OSA &/or research compared to the average GP. Thus, it is possible that these findings may not be generalisable to GPs as a whole. Also, GPs completed the 2 week post-education questionnaire as part of their Active Learning Module and responses were not anonymous, which may have influenced them to report greater benefits from the program than actually perceived. However, this was thought to be highly unlikely, as credits for completion of the Active Learning Module were granted irrespective of their responses to the questionnaires and program evaluation forms. 8 GPs who were involved in the study did not attend both education sessions and 2 GPs who completed the entire 6 hour education program did not return their 2 weeks post-event questionnaires. Furthermore, an additional 10 GPs who were included in the initial pre-education versus 2 weeks post-education analysis did not repeat the questionnaires at long term follow-up, which may have biased the results.

Ultimately, a randomised controlled study design would have been the best way to evaluate the effects of an education program on changes in knowledge & attitudes by minimising potential confounders. However, we conducted the study using a before-and-after trial design as we were limited by the resources which were available. Future studies evaluating GP education programs on OSA and common sleep disorders using a randomised controlled design involving larger numbers of GPs from multiple sites are needed.

3.4.2 Conclusions

With growing public awareness of the health consequences of disease and the rapid rise in diagnostic sleep service provision, there is an increasing expectation that GPs will take on greater responsibility for the identification and management of OSA. Provision of education on OSA and common sleep disorders for primary care physicians, which has so far been lacking at both undergraduate and postgraduate levels, is therefore paramount. A moderate-intensity active learning module such as this appears to successfully increase GPs' confidence and knowledge about OSA diagnosis and management, and should become more widely available for GPs across both metropolitan and rural regions.

CHAPTER 4: A RANDOMISED CONTROLLED TRIAL TO EVALUATE AN AMBULATORY MODEL OF CARE FOR OBSTRUCTIVE SLEEP APNEA IN GENERAL PRACTICE

4.1 INTRODUCTION

Obstructive sleep apnea (OSA) is a condition characterised by repetitive upper airway obstruction during sleep, loud snoring, oxygen desaturations, sleep fragmentation and complaints of excessive daytime sleepiness. Untreated OSA has been associated with a number of adverse health consequences, including an increased risk of hypertension[13], motor vehicle accidents[23], neurocognitive impairment[109] and cardiovascular disease[21]. Symptomatic OSA was estimated during the early 1990s to affect 3-4% of middle-aged males and 2% of middle-aged females[1,3], however, a significant increase in obesity rates have occurred since that time which is likely to have resulted in a parallel rise in the prevalence of OSA. In fact, a more recent population-based study in Sao Paulo, Brazil, revealed the prevalence of obstructive sleep apnea syndrome (i.e. apnea-hypopnea index [AHI] of 5-14.9/hr plus at least one of the following: snoring, daytime sleepiness, fatigue and apneas; and AHI ≥15/hr, regardless of symptoms) to be approximately 40% in men and 25% in women[7].

Current gold standard practice for management of patients with suspected OSA involves referral to a sleep specialist, overnight polysomnography (PSG) in a sleep laboratory, and, if confirmed to have significant disease

requiring treatment with continuous positive airway pressure (CPAP), a repeat overnight PSG for CPAP titration. With increasing awareness of the health consequences of OSA by health professionals and amongst the general public, the demand for sleep service provision in specialist centres has escalated dramatically in recent decades. This has led to growing waiting lists for sleep physician consultation and laboratory-based polysomnography[51]. To address the high demand for sleep service provision, there has been increasing interest in the development of alternative models of care for OSA, including use of clinical prediction models to identify patients who are at high risk for disease, portable, home sleep monitoring, auto-titrating CPAP devices, and provision of diagnostic and management services by health care professionals other than a sleep physician[87,88,90].

General practitioners (GPs) are often the initial point of contact for patients who have concerns about their sleep health. Sleep-related complaints are common in the primary care setting, with approximately one-third of patients reporting symptoms which are suggestive of OSA[92]. However, despite the high prevalence of OSA in primary care, the level of awareness and knowledge amongst GPs about this sleep disorder is generally low[96,103]. In an attempt to circumvent long waiting lists for laboratory-based PSG and specialist consultation, there has been an increasing trend for GPs to refer patients to diagnostic service providers which utilise home sleep monitoring devices. However, sleep physician input may be limited to only sleep study reporting with no formal review of patients, forcing GPs to become the principle provider of care and advice for patients with OSA when they may

lack the necessary skills and confidence to do so. With appropriate training, provision of simplified management tools as well as support from a specialist sleep centre, GPs and their practice nurses would be ideally positioned to take on a greater role in the diagnosis and management of OSA.

In Chapter 2, we validated a simplified, two-stage model for the diagnosis of moderate-to-severe OSA in primary care consisting of a 4-item screening tool (i.e. “OSA50” questionnaire) and home oximetry[135]. A number of randomised controlled studies have previously shown that ambulatory management strategies for OSA involving home sleep monitoring and auto-titrating CPAP are not clinically inferior, or produce similar patient outcomes, to laboratory-based testing and usual care in a specialist sleep centre[87,88,90,136]. However, none of these studies have been conducted in the primary care setting. Thus, the aim of this prospective, randomised controlled trial was to compare the efficacy and cost-effectiveness of OSA management in primary care by a GP and community-based nurse utilising an ambulatory model of screening questionnaire, home oximetry and auto-titrating CPAP versus currently recommended management in a specialist sleep centre. The study was designed to assess for non-inferiority of the primary care-based management arm versus specialist sleep centre care for the primary outcome measure, the change in Epworth Sleepiness Scale (ESS) score after 6 months of follow-up.

4.2 METHODS

A prospective, randomised, controlled, non-inferiority study was conducted to compare a simplified management strategy for OSA in primary care versus the usual standard of care in a specialist sleep centre. The research protocol was approved by institutional research ethics committees at the Repatriation General Hospital and Flinders Medical Centre, South Australia and the study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12608000514303). Patients and participating GPs provided written, informed consent.

4.2.1 Participants

Patients aged between 25 to 70 years who were attending a primary care consultation for any reason were screened by their GP for potential eligibility using a simplified two-step diagnostic strategy consisting of the OSA50 questionnaire and oximetry which has previously been validated for identification of moderate-to-severe OSA in primary care[135]. The OSA50 questionnaire consists of 4 items: (1) Waist circumference >102cm in males, or >88cm in females; (2) Has your snoring ever bothered other people?; (3) Has anyone noticed that you stop breathing during your sleep?; and (4) Age ≥50 years. A positive response to the items on waist circumference and snoring are given a score of 3 points each and, for witnessed apneas and age ≥50 years, a score of 2 points each, to provide a maximum total score of 10 points.

Thirty-four GPs from 6 Adelaide metropolitan clinics (9 GPs) and 10 country clinics (25 GPs) in three major rural regions of South Australia (i.e. South Coast, Barossa Valley and Riverland) agreed to participate and referred patients for the study. Inclusion criteria were: (1) moderate-to-severe OSA diagnosed using the previously validated simple two-step method[135], i.e. positive OSA50 questionnaire and overnight 3% oxygen desaturation index (3%ODI) ≥16/hr; and (2) at least mild daytime sleepiness (Epworth Sleepiness Scale (ESS) ≥8) or persistent hypertension despite use of two or more antihypertensive agents. Exclusion criteria were: (1) severe morbid obesity (BMI >50kg/m2); (2) neuromuscular disease; (3) unstable psychiatric disease or cognitive impairment considered likely to prevent the patient complying with instructions, completing the study and/or managing CPAP at home; (4) hospitalisation in the previous 3 months for myocardial infarction, unstable angina, cardiac failure or cerebrovascular accident, or New York Heart Association Class III or IV symptoms; or (5) lung disease with awake resting oxygen saturation <92%.

Patients who fulfilled the entry criteria were randomised into one of the following two groups for further management: (1) Primary care management; or (2) Specialist sleep centre management. Randomisation was conducted by a telephone call to a clinical trials pharmacist independent of the study, who determined group assignment according to the next allocation on a computer-generated random numbers list.

4.2.2 Models of Care

4.2.2.1 Primary care management

Patients were managed by their GP and a community-based nurse. Prior to patient recruitment, GPs and nurses participated in a six-hour education program, accredited by the Royal Australasian College of General Practitioners (RACGP) and the Australian College of Rural and Remote Medicine, on OSA and its management, as well as common sleep disorders causing excessive sleepiness. Patients were reviewed by one of four sleep-trained nurses who held clinics at five community locations. One nurse had 15 years of experience working in a tertiary care sleep medicine service. The other nurses were newly trained in OSA management, but had worked as rural-based practice nurses prior to their involvement. Their sleep training also involved 5 days of in-service training with specialist sleep nurses at the tertiary sleep centre. Home auto-titrating CPAP (REMstar Auto, Respironics or S8 AutoSet Spirit, ResMed) was used over 3 consecutive nights to determine a fixed treatment pressure based on the 90th (REMstar Auto) or 95th (S8 AutoSet Spirit) percentile pressure. CPAP devices were then converted to a fixed pressure mode for the duration of the study. Although CPAP was considered the primary treatment, GPs were educated about alternative therapies for OSA, including lifestyle measures, a mandibular advancement splint (MAS) or upper airway surgery, and advised that they could be recommended as deemed appropriate. GPs were provided with contact details of a dentist expert in the fashioning of mandibular advancement splints (SomnoDent MAS, SomnoMed Ltd, Crows Nest, New South Wales, Australia). CPAP and MAS were available free of charge to participants. GPs were advised that a sleep physician could be contacted for

advice or to request a formal consultation. Patients were followed up by their nurse with a telephone call within two weeks of commencing therapy, and then by direct consultation at 1, 3 and 6 months, and seen by their GP at 3 and 6 months.

4.2.2.2 Specialist sleep centre management

Patients were referred to one of 9 participating sleep specialists at the Adelaide Institute for Sleep Health, Repatriation General Hospital, South Australia for ongoing management. At the initial consultation, sleep specialists were provided with the patient's ApneaLink report (including the 3%ODI and printout of the overnight summary of the oximetry trace), and undertook a full history and physical examination. The decision to undertake further investigations to confirm the diagnosis of OSA or to exclude other sleep disorders (e.g. with full diagnostic or split laboratory PSG), and treatment recommendations for OSA and other sleep disorders or co-morbidities were left to the discretion of the treating physician. Laboratory-based sleep studies were scored by sleep technicians using American Academy of Sleep Medicine 1999 "Chicago criteria"[117], i.e. an apnea was defined as a cessation of nasal flow lasting ten seconds or longer and an hypopnea was defined as a 50% decrease in nasal flow (or in both of the thoracic and abdominal excursions) lasting a minimum of 10 seconds, or a discernable decrease leading to a ≥3% oxygen desaturation or an EEG arousal. CPAP titration, if recommended, was conducted manually during laboratory PSG or by home auto-CPAP titration. The same models of CPAP machines were used as in the primary care arm. CPAP nurses based at the specialist sleep centre provided support for CPAP set-up and education.

Follow-up occurred at the same time points as in the primary care arm.

4.2.3 Outcome Measures

The primary outcome measure was the change in ESS score from baseline to 6 months of follow-up. Secondary outcome measures were the Functional Outcomes of Sleep Questionnaire (FOSQ)[137], Sleep Apnea Symptoms Questionnaire (SASQ)[138], Short-Form 36 Health Survey (SF-36)[139], CPAP compliance, blood pressure and BMI which were measured at baseline and 6 months. A Visit-Specific Satisfaction Questionnaire (VSQ-9)[140] was completed by each patient at the conclusion of the study.

4.2.4 Sample Size

This study was powered to assess for non-inferiority of the primary care-based arm versus the specialist-led arm in terms of the mean change in ESS score after 6 months of follow-up. A sample size of 138 patients (69 patients in each arm) was required to demonstrate non-inferiority of primary care-based management with 90% power and an alpha of 0.05, assuming a non-inferiority margin of -2.0 and a standard deviation of 4.0 for the change in ESS score. A total of 155 patients were recruited to account for potential withdrawals and loss to follow-up.

4.2.5 Statistical Analysis

Statistical analyses were performed using STATA/IC 11.2 for Windows (StataCorp LP, College Station, Texas, USA). Baseline demographic and anthropometric data were summarised for each study group. Comparisons between groups for the mean change in ESS, FOSQ, SASQ, SF-36, BMI and

blood pressure after 6 months were conducted in an intention-to-treat manner using analysis of covariance (ANCOVA), with adjustment for baseline scores. Missing results at 6 months for the ESS, FOSQ, SASQ, and SF-36 were replaced with baseline data. A Student's t-test was used to evaluate for group differences in CPAP use and VSQ-9 scores. Statistical significance was determined using an alpha of 0.05. The difference in the mean change in ESS score and FOSQ score from baseline to 6 months were evaluated for non-inferiority of the primary care-based arm compared to the specialist-led arm using non-inferiority margins of -2.0 and -1.0, respectively. In other words, we wanted to show that management in the primary care arm would be no worse than the specialist arm by more than 2 points in the mean change in ESS or 1 point in the mean change in FOSQ score. The decision to use these non-inferiority margins were based on previously published literature[89,90], as well as prior professional consensus amongst sleep physicians at the Adelaide Institute for Sleep Health as to what constituted a minimum clinically relevant change in score. Non-inferiority can be demonstrated (i.e. the null hypothesis of inferiority of the primary care arm can be rejected) if the lower limit of the one-sided 95% confidence interval for the difference in mean change in score lies above the pre-specified non-inferiority margin.

4.2.6 Health Economic Analysis

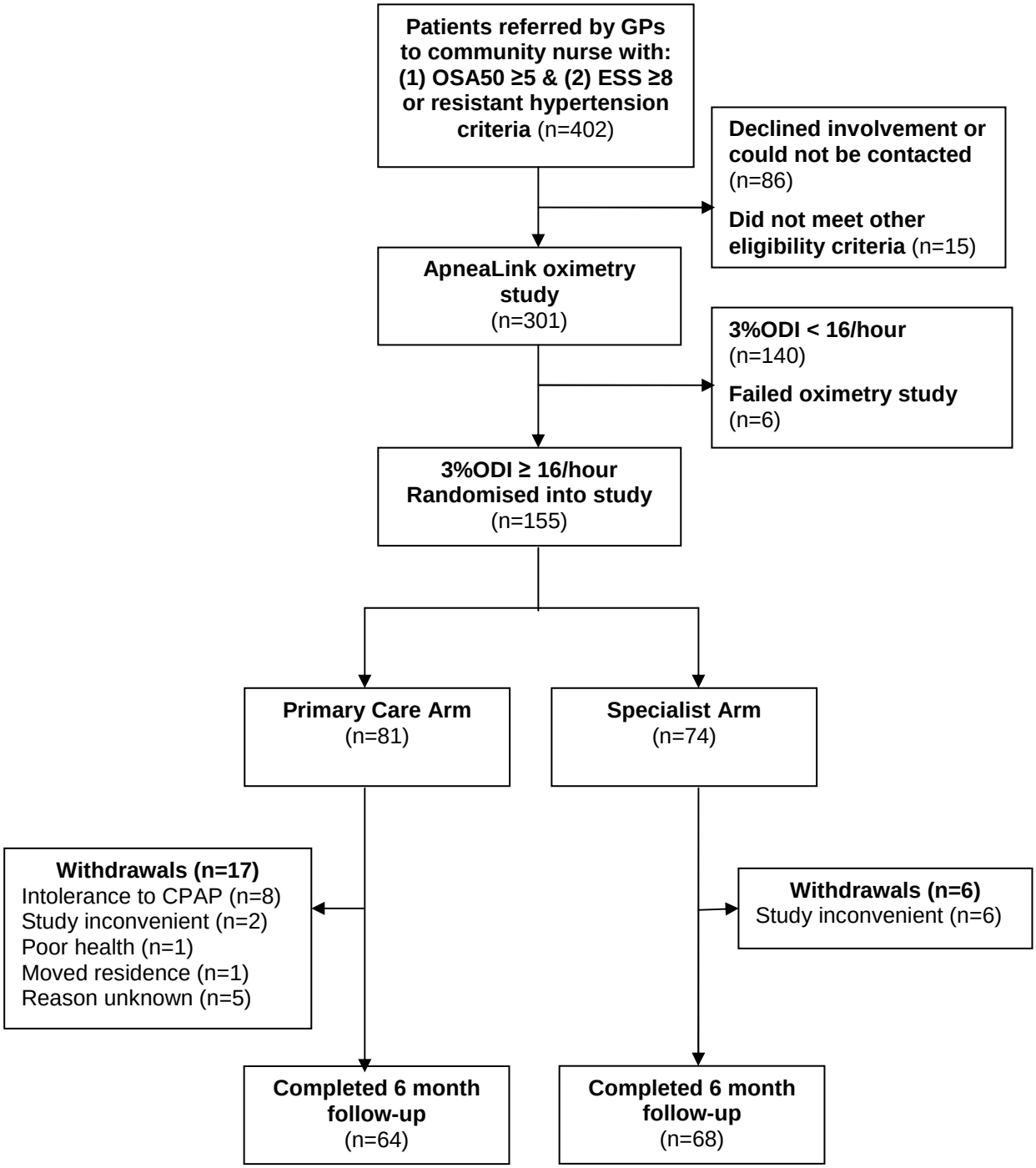
Within-study resource use and associated costs were collected during the 6 month follow-up period and included nursing time, travel costs, inpatient hospital admissions, and data from Medicare Australia (i.e. GP and/or

specialist visits, use of diagnostic services and medication costs). Re-sampling with replacement (bootstrapping) of patient data associated with their costs and outcomes enables robust assessment of within-study incremental cost effectiveness and non-inferiority of GP versus specialist care, allowing for covariance between cost and effects[141,142]. Although the cost of educating GPs and community-based nursing staff on OSA management within the trial is important to consider, we would expect that in reality, with increasing awareness of the importance of OSA and its management, these costs would eventually be subsumed within existing undergraduate and postgraduate training programs offered, for example, as part of University education, and through the RACGP and the Australian College of Nursing. Thus, these costs were not factored into our analysis.

4.3 RESULTS

A flow diagram outlining the recruitment and randomisation pathway for patients in the study is shown in Figure 4.1. 402 patients were referred by PCPs after initial screening to community-based nurses for review of eligibility criteria and oximetry monitoring. Of these, 86 patients declined further involvement in the trial and 15 patients were found to be ineligible for study participation following closer review the inclusion and exclusion criteria. Thus, a total of 301 patients underwent overnight oximetry monitoring using the ApneaLink monitor. 39 of the 301 (13%) patients had a failed ApneaLink study on the first testing occasion, 36 of whom agreed to undergo repeat monitoring. Nine of the 36 patients failed their repeat ApneaLink test, of whom 8 patients agreed to a second repeat study. 2 patients failed their second repeat test and were excluded from further participation. The majority of failed ApneaLink studies were due to inadequate oximetry recording times (<4 hours) and/or subjectively-recorded sleep duration (<3 hours). 155 patients who had successful ApneaLink studies were found to have a 3% oxygen desaturation index (3%ODI) of 16 or more events per hour and were randomised into either the primary care or specialist-led management arms. 140 patients had a 3%ODI<16/hour and 6 patients had failed ApneaLink recordings (despite a maximum of up to 3 attempts), and were excluded from further participation.

Figure 4.1. Flow diagram of participant recruitment and randomisation



GPs = general practitioners; 3%ODI = 3% oxygen desaturation index

4.3.1 Baseline Characteristics

Of the 155 patients included in the study, 81 were randomly allocated to the primary care arm, and 74 to the specialist group. The baseline characteristics of patients in the two arms are shown in Table 4.1. The two groups were comparable in terms of their gender distribution, age, BMI, and waist circumference. Severity of OSA was also similar between patients in primary care and specialist arms as determined by OSA50 questionnaire scores, ESS and ApneaLink oximetry. Study participants consisted of predominantly middle-aged, obese males from rural regions of South Australia with at least a mild degree of daytime sleepiness.

Table 4.1. Baseline characteristics of patients in primary care and specialist arms

	Primary Care Arm (n=81)	Specialist Arm (n=74)
Males, n (%)	69 (85%)	57 (77%)
Age, years	57.2 ± 10.9	54.5 ± 11.8
Region		
Metropolitan, n (%)	21 (33%)	18 (24%)
South Coast, n (%)	3 (4%)	1 (1%)
Riverland, n (%)	27 (33%)	29 (39%)
Barossa Valley, n (%)	24 (30%)	26 (35%)
BMI, kg/m^2	33.1 ± 5.5	33.7 ± 5.6
Waist circumference, cm	111.2 ± 13.6	113.1 ± 14.5
OSA50 questionnaire score	8.2 ± 1.5	8.1 ± 1.7
ESS total score	12.8 ± 3.9	12.5 ± 3.9
ApneaLink 3%ODI, events/hr	32.7 ± 18.2	35.7 ± 17.4

Data are presented as mean ± SD or n (%)
3%ODI = 3% oxygen desaturation index; ESS = Epworth Sleepiness Scale; BMI = body mass index

4.3.2 Treatment

The principal forms of treatment recommended at baseline and treatments used at 6 months are outlined in Table 4.2. At baseline, almost all patients (90%) in the primary care arm were commenced on CPAP therapy, 1 patient (1%) was referred for a mandibular advancement splint (MAS) and 2 patients (2%) were managed using conservative measures only (i.e. advice regarding good sleep hygiene, avoidance of a supine sleep posture, and/or weight loss and other lifestyle modifications). 5 patients in the primary care arm withdrew from the trial prior to commencing therapy.

In the specialist arm, 73 of 74 patients had a laboratory-based full (n=38) or split-night (n=35) diagnostic PSG. One patient in the specialist arm withdrew from the study prior to their initial appointment with the sleep physician and did not undergo sleep testing. 47 patients (64%) had an apnea-hypopnea index (AHI) ≥30/hr, 17 patients (23%) had an AHI 15-30/hr; and 9 patients (12%) had an AHI <15/hr. Compared to the primary care arm, fewer patients in the specialist arm were commenced on CPAP therapy (n=52 [70%]) and a higher proportion of patients were managed initially with conservative measures alone (n=18 [24%]).

Three patients randomised to the primary care arm were referred for sleep specialist input during the course of the study. One patient reported ongoing daytime sleepiness despite good CPAP compliance and was found to have severe periodic limb movements causing sleep fragmentation on a laboratory

PSG. The other two patients were referred because they had difficulty tolerating CPAP during their home auto-titration study, one of whom experienced retrograde movement of air through their nasolacrimal duct with CPAP use causing swelling and irritation around the left eye.

After 6 months follow-up, the proportion of patients being treated with CPAP were similar in the primary care and specialist arms (63% and 61%, respectively). By 6 months, more patients had withdrawn from the study in the primary care arm (n=17 [21%]) compared to the specialist group (n=6 [8%]). In the primary care arm, the reasons given by patients for withdrawal were intolerance to CPAP therapy (n=8), study inconvenient (n=2), poor health (n=1), moved residence (n=1) and reason unknown (n=5). In the specialist arm, all 6 patients who withdrew gave the reason “study inconvenient”. Baseline characteristics of patients who withdrew were similar to patients who completed the study protocol (see Table 4.3).

Table 4.2. Principle treatment recommended to patients at baseline and used at 6 months

Recommended at Baseline:

Principle treatment	Primary care (n=81)	Specialist sleep centre (n=74)
CPAP	73 (90%)	52 (70%)
Conservative measures only	2 (2%)	18 (24%)
MAS	1 (1%)	3 (4%)
Patient withdrew	5 (7%)	1 (1%)

Used at 6 months:

Principle treatment	Primary Care (n=81)	Specialist sleep centre (n=74)
CPAP	51 (63%)	45 (61%)
Conservative measures only	7 (9%)	12 (16%)
MAS	6 (7%)	11 (15%)
Patient withdrew	17 (21%)	6 (8%)

Data is presented as n (%)
CPAP = continuous positive airway pressure; MAS = mandibular advancement splint

Table 4.3. Baseline characteristics of patients who withdrew from the study compared to those who completed the study protocol to 6 months.

Baseline characteristics	Withdrew from study (n=23)	Completed study to 6 months (n=132)
Age, years	57.6 ± 13.1	55.6 ± 11.1
Males	19 (83%)	107 (81%)
Region		
Metropolitan	11 (48%)	34 (26%)
Rural	12 (52%)	12 (74%)
BMI, kg/m^2	33.7 ± 5.9	33.3 ± 5.5
Waist circumference	110.5 ± 14.1	112.5 ± 14.0
ESS	12.7 ± 3.8	12.6 ± 3.9
OSA50 score	7.3 ± 1.7	8.3 ± 1.6
ApneaLink 3%ODI, events/hr	29.4 ± 15.8	35.0 ± 11.1

Data are presented as mean ± SD or n (%)
BMI = body mass index; ESS = Epworth Sleepiness Scale; 3%ODI = 3% oxygen desaturation index

4.3.3 Outcomes

4.3.3.1 Daytime Sleepiness: Epworth Sleepiness Scale (ESS)

The mean ESS score improved significantly in both study arms after 6 months follow-up by 4.6 units in the primary care arm (95% confidence interval [95%CI]: 3.4 to 5.8, p<0.001) and 5.0 units in the specialist arm (95%CI: 3.9 to 6.2, p<0.001) (see Table 4.4). After controlling for baseline ESS score, the adjusted difference in mean change in ESS score was -0.6 (lower bound of one-sided 95%CI: -1.8, p=0.37). These results support non-inferiority of primary care management since the lower bound of the one-sided 95% confidence interval is greater than the a priori noninferiority margin of -2.0 (see Figure 4.2). Similar results were obtained when the analysis was restricted to those patients who completed the 6 month study protocol.

4.3.3.2 Functional Outcomes of Sleep Questionnaire (FOSQ)

The mean FOSQ total score improved significantly in both study arms at 6 months in the intention to treat analysis by 2.3 (95%CI: 1.6 to 3.0, p<0.001) points in the GP arm, and by 2.6 (95%CI: 2.0 to 3.2) points in the specialist arm. The adjusted change in mean FOSQ total score at 6 months, after controlling for baseline FOSQ total score, was -0.03 (lower bound of one-sided 95%CI: -0.64, p=0.94) (see Table 4.5). Since the lower bound of the one-sided 95% confidence interval is greater than the a priori non-inferiority margin of -1.0, these results support non-inferiority of primary care management (see Figure 4.3). Analysis of data when only those patients who completed the study to 6 months were included produced similar results.

Table 4.4. Change in Epworth Sleepiness Scale score at 6 months

	Primary Care Arm (n=81*)		Specialist Arm (n=74*)					
	Mean	**SD**	**Mean**	**SD**	**†Adjusted difference in mean change**	**SEM**	***p* value**	**Lower bound of one-sided 95% CI**
Baseline ESS	12.8	3.9	12.5	3.9				
6 month ESS	8.2	4.6	7.5	4.4				
Change in ESS	4.6	5.2	5.0	5.1	-0.63	0.71	0.37	-1.80

ESS = Epworth Sleepiness Scale; SD = standard deviation; SEM = standard error of the mean; MD = mean difference; CI = confidence interval
*Baseline observation carried forward for missing data
†Analysis of co-variance (ANCOVA), adjusted for baseline ESS score.

Figure 4.2. Graph demonstrating non-inferiority of the primary care arm for the change in Epworth Sleepiness Scale score at 6 months

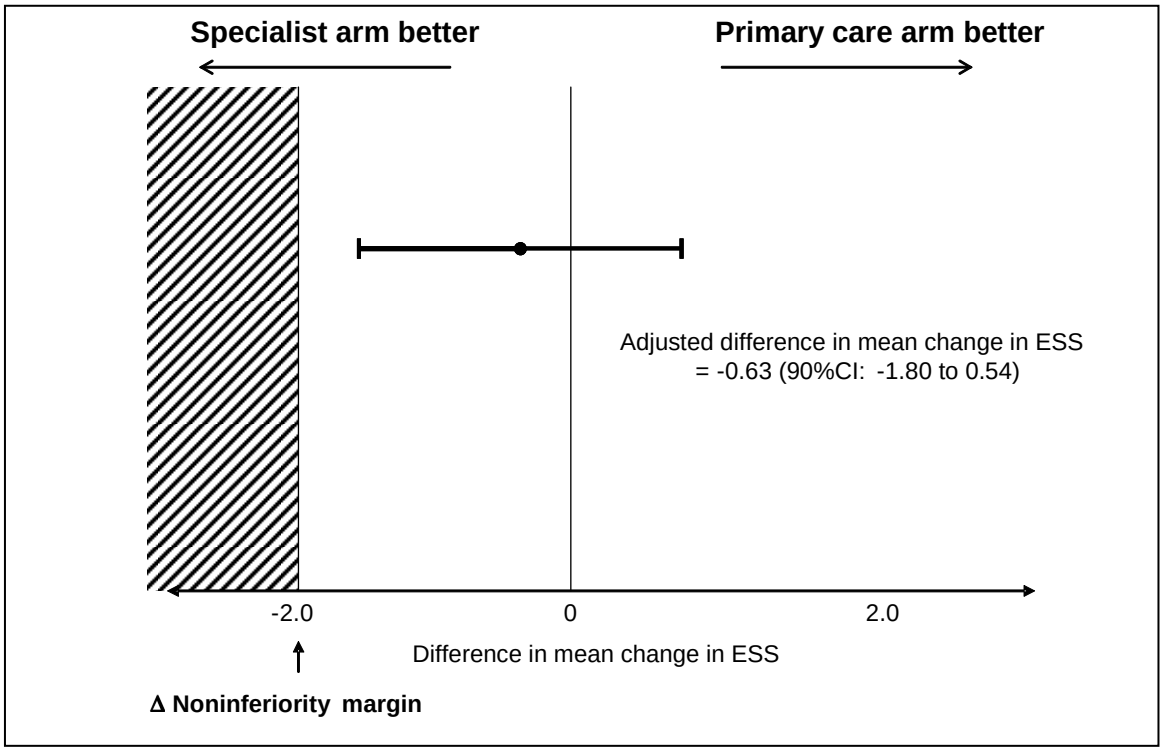
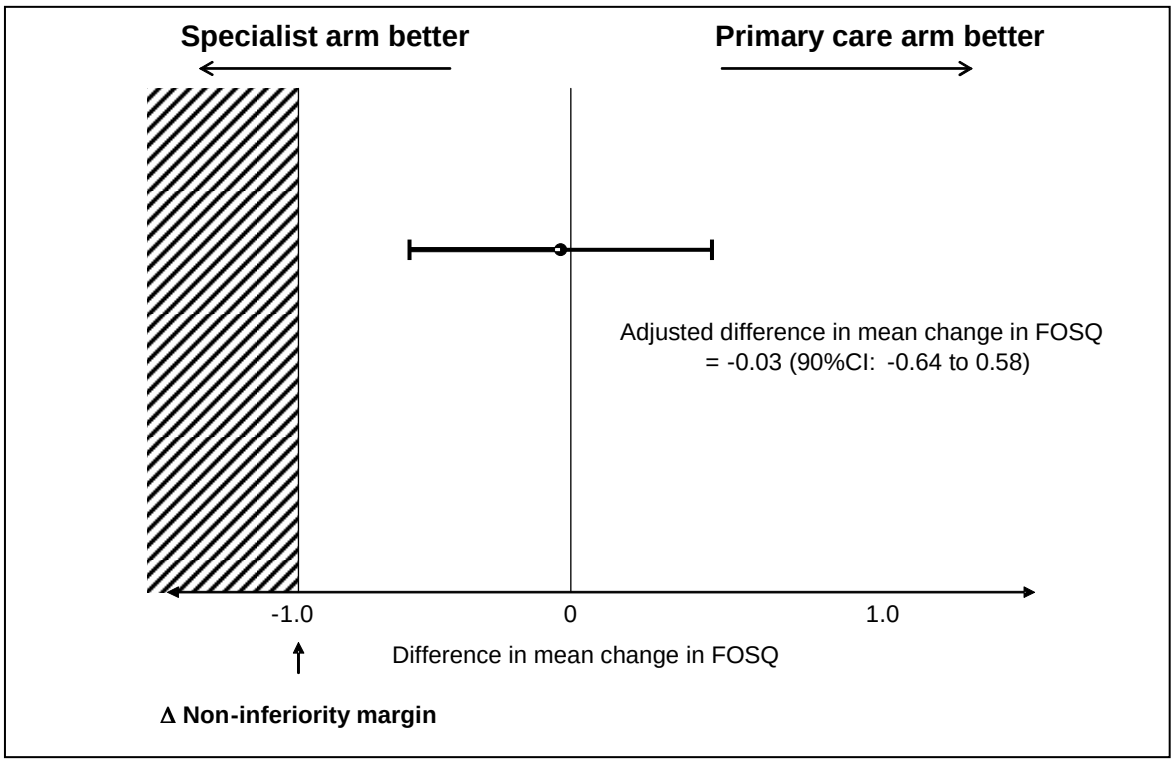


Table 4.5. Change in Functional Outcomes of Sleep Questionnaire at 6 months

	Primary Care Arm (n=81*)		Specialist Arm (n=74*)					
	Mean	SD	Mean	SD	†Adjusted difference in mean change	SEM	*p* value	Lower bound of one-sided 95% CI
Baseline FOSQ	14.7	3.1	14.2	2.9				
6 month FOSQ	17.0	2.5	16.8	2.8				
Change in FOSQ	2.3	3.0	2.6	2.5	-0.03	0.37	0.94	-0.64

FOSQ = Functional Outcomes of Sleep Questionnaire; SD = standard deviation; SEM = standard error of the mean; MD = mean difference; CI = confidence interval
*Baseline observation carried forward
†Analysis of co-variance (ANCOVA), adjusted for baseline ESS score.

Figure 4.3. Graph demonstrating non-inferiority of the primary care arm for the change in Functional Outcomes of Sleep Questionnaire at 6 months



4.3.3.3 Sleep Apnea Symptom Questionnaire (SASQ)

SASQ scores improved significantly in both primary care and specialist arms at 6 months. The mean SASQ decreased by 22.9 points (95%CI: 17.2 to 28.6, p<0.001) in the primary care arm, and by 28.6 points (95%CI: 21.5 to 35.7, p<0.001) in the specialist arm. There was no difference in the change in mean SASQ score at 6 months between the two groups, when adjusted for baseline SASQ score (see Table 4.6).

4.3.3.4 SF-36 Health Survey - Vitality & Mental Health

In previous studies, measures of Vitality and Mental Health are the components of the SF-36 Health Survey which have been most responsive to the effects of CPAP treatment in OSA[143,144], therefore, only changes in these two scores are reported here (Table 4.6). The SF-36 Vitality and Mental Health scores improved significantly after 6 months of treatment in both treatment groups, but there were no differences in the change in mean scores between primary care & specialist arms for either the Vitality or Mental Health components of the SF-36 Health Survey.

4.3.3.5 CPAP Compliance

CPAP compliance in patients using CPAP at 6 months was not different between the two groups, with mean usage of 4.8 ± 2.1 hours per night in the primary care arm and 5.4 ± 0.3 hours per night in the specialist arm (p=0.11). (Table 4.6).

4.3.3.6 Blood Pressure

No change in systolic or diastolic blood pressure was evident in either the primary care or specialist arms at 6 months, and there was no difference in the change in blood pressure at 6 months between groups (Table 4.6).

4.3.3.7 Body Mass Index

At baseline, mean BMI in the primary care and specialist arms were similar at 33.1 ± 5.5 and 33.7 ± 5.6 kg/m2, respectively. There was no change in BMI at 6 months in either of the two arms, and no difference between groups in the change in BMI after 6 months was evident (Table 4.6)

4.3.3.8 Visit-Specific Satisfaction Questionnaire-9 (VSQ-9)

There were small, but statistically significant, differences for 5 out of the 9 items in the VSQ-9 (i.e. $p<0.05$), all in favour of the primary care arm (Table 4.7). These were related to patient satisfaction with the time waited to see the health care professional at each appointment, personal manner of health care professionals, time spent with the health care professional at each visit, adequate explanation of treatment, and sufficient information provided by the health professional to make appropriate choices. However, there was no difference in overall satisfaction with treatment (Question 9) between primary care and specialist arms.

Table 4.6. Secondary outcome measures at 6 months

	Primary Care Arm		Specialist Arm				
	n	**Mean ± SD**	**n**	**Mean ± SD**	**Adjusted mean difference**	**SEM**	***p* value**
Change in FOSQ	81	2.3 ± 3.0	74	2.6 ± 2.5	-0.03	0.37	0.94
Change in SASQ	81	-22.9 ± 25.7	74	-28.6 ± 30.7	-5.1	4.0	0.20
Change in SF-36 vitality	81	13.0 ± 19.6	74	18.4 ± 22.6	-0.6	3.0	0.83
Change in SF-36 mental health	81	6.1 ± 13.1	74	7.5 ± 15.7	0.1	2.2	0.95
Change in systolic BP, mmHg	64	-2.2 ± 16.7	62	-4.8 ± 18.7	-2.2	2.8	0.44
Change in diastolic BP, mmHg	64	-2.0 ± 12.3	62	-0.4 ± 12.0	1.4	1.8	0.42
Change in BMI, kg/m^2	64	-0.2 ± 3.2	63	-0.4 ± 2.8	0.5	0.5	0.30
6 month CPAP use, hrs/night	51	4.8 ± 2.1	44	5.4 ± 1.8	-0.7	0.4	0.11

SD = standard deviation; SEM = standard error of the mean; FOSQ = Functional Outcomes of Sleep Questionnaire; SASQ = Sleep Apnea Symptoms Questionnaire; SF-36 = Short Form 36 Health Survey; BP = blood pressure; BMI = body mass index; CPAP = continuous positive airway pressure

Table 4.7 Visit-specific Satisfaction Questionnaire-9 (VSQ-9) responses at 6 months

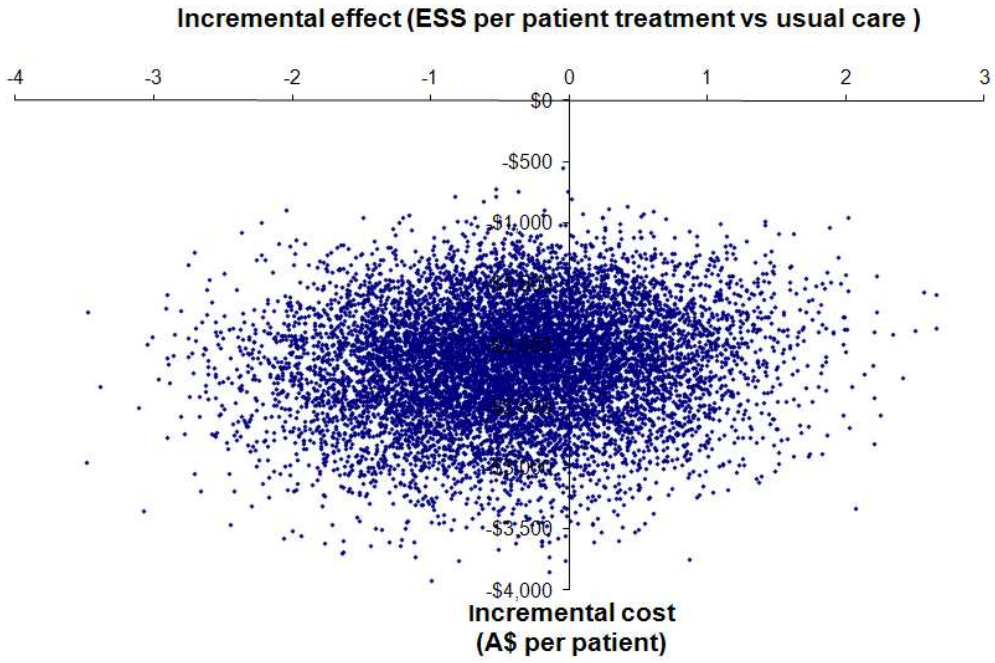
	Primary Care Arm n = 64		Specialist Arm n = 66		
	Mean	SEM	Mean	SEM	*p* value
1. Satisfaction with time waited from time of referral until first appointment	3.66	0.06	3.53	0.07	0.171
2. Impression of time waited to see health care professional at each appointment	3.73	0.06	3.56	0.06	0.039
3. Impression of personal manner of ancillary staff	3.74	0.06	3.65	0.06	0.297
4. Impression of personal manner of health care professionals	3.88	0.04	3.71	0.06	0.029
5. Impression of competence of health care professional	3.88	0.04	3.76	0.05	0.086
6. Satisfaction with time spent with health care professional at each visit	3.86	0.04	3.71	0.06	0.042
7. Adequate explanation at each step of treatment	3.83	0.05	3.67	0.06	0.035
8. Sufficient information given by health care professionals to make appropriate choices	3.80	0.05	3.62	0.07	0.047
9. Overall satisfaction with treatment	3.78	0.06	3.71	0.06	0.415

SEM = standard error of the mean
Higher scores for VSQ-9 items, which have a maximum score of 5 points, indicate increased levels of patient satisfaction

4.3.4 Health Economic Analysis

The average cost of primary care management was AUD$2610, compared to AUD$4767 in the specialist arm. There was a statistically significant cost saving of AUD$2157 (95%CI: $1293 to $3114) per patient in the primary care arm within study with 100% chance of cost saving, and a non-significant, minor reduction in the mean change in ESS score of 0.4 per patient (95%CI: -1.1 to 1.7) with 97.2% chance of treatment being non-inferior (i.e. equivalent or superior) at the pre-specified non-inferiority margin. The bootstrapped joint sample distribution of within-study incremental costs and effect is shown in Figure 4.5. All 10,000 bootstrapped replicates had a negative incremental cost (i.e. cost saving) while only 280 of 10,000 bootstrap replicates had a reduction in the change in ESS score of greater than 2 units. Thus, while both GP and specialist care were effective for treating moderate-severe OSA, the cost of primary care management was significantly lower.

Figure 4.4. Bootstrapped joint distribution of incremental costs (Australian dollars per patient) and effects (Epworth Sleepiness Scale [ESS] per patient) for treatment in the primary care arm versus the specialist arm.



4.3.4.1 Translation of trial results into practice

When implementing a diagnostic strategy for OSA in practice, rather than a trial setting, overnight home oximetry monitoring would be included in the primary care arm, but not necessarily in the specialist arm, whilst the OSA50 screening questionnaire would be expected to be undertaken prior to specialist referral or more expensive testing and therefore applied in both primary care and specialist pathways. Thus, the inclusion of oximetry monitoring in the diagnostic build up in the primary care arm only would result in an additional oximetry cost per diagnosed patient, dependent on the prevalence of moderate-to-severe OSA in the tested population. In this study, 301 patients underwent ApneaLink oximetry testing, of whom 155 were randomised into the study with moderate-to-severe OSA using a 3%ODI≥16/hr. On average, each patient underwent 1.13 ApneaLink studies which were performed at a cost of $169. Hence, an incremental oximety cost of $329 ($169 x 301/155) per patient diagnosed with moderate-to-severe OSA could arise in practice.

4.4 DISCUSSION

In this study, patients attending primary-care practices who were identified by a simple two-step screening process as having a high likelihood of moderate-severe OSA, and who were at least mildly sleepy, were randomised to either continue their care under the supervision of their GP and a community-based nurse, or to be evaluated and managed in a university hospital specialist sleep centre. Significant improvements in the primary outcome measure, daytime sleepiness, were observed following treatment in both settings and the outcomes for patients managed in primary care were not inferior to those experienced by patients in the specialist sleep centre. In addition, no differences could be found between treatment groups for secondary patient outcomes, including OSA symptoms, disease-specific and general quality of life, blood pressure, BMI, CPAP adherence and overall satisfaction with treatment.

These results extend the findings of previously published studies of ambulatory models of care for OSA deployed in specialist sleep centres. Mulgrew et al[87] utilised a simplified strategy of portable monitoring and auto-titrating CPAP and found no significant differences in major outcomes, including change in ESS and quality of life, compared to laboratory-based care. Furthermore, CPAP adherence was higher in the ambulatory care arm. Berry et al[88] conducted a similar study in a veteran population whereby patients with OSA were randomised to either portable monitoring and auto-titrating CPAP, or to laboratory PSG and CPAP titration. After 6 weeks follow-up, no differences were observed in CPAP compliance, change in ESS or

FOSQ scores, patient satisfaction with CPAP or residual AHI. More recently, Kuna et al found that functional outcomes and CPAP adherence were not inferior to usual laboratory-based care using an ambulatory management strategy for OSA[89]. None of these studies assessed the relative cost-effectiveness of the simplified management strategies.

Our group have previously conducted a randomised controlled trial to evaluate a simplified model of care for OSA led by sleep-trained nurses in a tertiary care setting[90]. The primary outcome, mean change in ESS at 3 months, for patients managed using an ambulatory, nurse-led approach was not clinically inferior to specialist-led management and nurse-led management was cheaper, with cost savings of AUD$1,111 per patient. These results led us to consider the potential role of primary care physicians and nurses in the diagnosis and management of OSA.

The present study which recruited patients from metropolitan and rural communities had a longer period of follow-up than previous studies (i.e. 6 months compared to 1-3 months). We believe that important elements in the success of the study were the training given to GPs and community nurses in OSA management and potential differential diagnoses, and that they were encouraged to seek advice from sleep physicians and/or experienced sleep nurses if they encountered any uncertainties in management. Thus, while GPs and community nurses were encouraged to take primary responsibility for patient management, this simplified strategy was designed as a “hub-and-spoke”-like model of care, with a central specialist sleep centre overseeing

and supporting a number of primary care-based OSA clinics. If this model were to be used in other communities by GPs, a similar model of intensive training and enhanced access to sleep specialists should be used. Of note though is that GPs cross-referred only 3 of 81 patients to sleep specialists for a second opinion. This could be because two-thirds of the study population were recruited in rural regions located 90 to 240km from the city-based specialist sleep service. However, only 1 out of 21 (5%) metropolitan-based patients enrolled in the primary care arm were cross-referred suggesting perhaps that, at least in the context of the research study, GPs and nurses were reasonably confident in their management decisions.

At baseline, CPAP was recommended more frequently in the primary care arm. However, by 6 months a considerable number of patients in the primary care arm had stopped using CPAP, and the proportion of patients on CPAP was similar to the specialist arm. Average daily CPAP use at 6 months was no different between arms. These observations may suggest that specialists, who are provided with additional information from a full or split-night laboratory PSG and are more experienced at OSA management, may be better at predicting which patients will adhere to CPAP in the long term. Alternatively, the effect of attending a specialist consultation and/or nurse review at a tertiary sleep centre may itself have had an influence on increasing patients' long term adherence. There also may be an effect of experience such that with time, the GPs may become more confident with managing sleep apnea and thus promote greater adherence. However, it is interesting to note that, in spite of the different approaches to management,

patient outcomes were ultimately similar in the two arms.

A particularly important finding of this study was the health economic analysis, which revealed a substantial within-study cost saving of AUD$2157 per patient in the primary care arm relative to the specialist arm. Recent debate has been sparked by a study by Pietzsch et al[67] which showed full-night PSG to be more cost-effective than unattended home monitoring in the management of OSA, due to its superior diagnostic accuracy. It was pointed out in an accompanying editorial[68], however, that several assumptions used in their modelling could have magnified the effects of false positive and negative results and elevated the costs of portable monitoring. Our study evaluated within-study costs only and did not assess the long term economic implications of an ambulatory strategy in primary care, thus further research in this area is needed.

The excessive prescription of CPAP by GPs at baseline, which was later discontinued by a significant proportion of patients during the six month follow-up period, may have impacted on the results of the health economic analysis by inflating the cost of primary care management. However, despite this, overall within-study costs remained cheaper in the primary care arm relative to specialist management, due predominantly to savings from the absence of laboratory-based sleep study testing and specialist consultations. One would anticipate that with increased education focusing on the indications for alternative treatment options for OSA as well as with greater experience over time, GPs and community-based nurses are likely to

develop increased confidence in recommending other therapies for OSA beyond CPAP, including conservative measures, when appropriate. Thus, this could potentially lead to further cost savings beyond what was seen in the study.

Several limitations of our study are acknowledged. We excluded patients with a BMI>50kg/m^2, neuromuscular disease, significant respiratory illness, a recent cardiovascular event or NYHA Class III or IV heart failure, psychiatric illness or serious cognitive impairment. Thus, the results of this study cannot be generalised to these populations. It is possible that patients with predominantly central sleep apnea, including Cheyne Stokes respiration, may have been misdiagnosed in the primary care arm, since only oximetry was used to identify patients with disease. However, we excluded patients with disorders prone to central sleep apnea (e.g. heart failure) and residual AHI was monitored on CPAP devices during follow-up appointments. At 6 months follow-up, only 1 patient in the primary care arm had a residual AHI on CPAP which exceeded 15/hr.

For reasons which are not entirely clear, more patients withdrew from the primary care arm. It is possible that patients were more inclined to remain in the study if they were receiving specialist consultations. Alternatively, participants may have had less faith in the advice of the primary care team. Although overall patient satisfaction was no different between groups, the opinions of patients who withdrew were not sampled. Interestingly, one-half of patients who withdrew from the primary care arm did so because of “CPAP

intolerance" whilst this was not cited as a reason for withdrawal in the specialist group. It is possible that the higher number of withdrawals in the primary care arm may have biased study results by excluding data from patients with worse outcomes. However, our analysis was conservative in that it carried forward baseline data for missing observations, thus assuming that patients who withdrew had no improvement in outcomes. This is likely to have biased outcomes towards the primary care arm having an inferior result compared to the specialist arm. Despite this, patient outcomes in the primary care arm remained clinically non-inferior.

In conclusion, this prospective, randomised controlled study has shown that a simplified management strategy for OSA based in primary care which utilises the skills of GPs and community-based nurses is not clinically inferior to standard laboratory-based care in a specialist sleep centre. Furthermore, primary care management of OSA is cost-effective with savings of over AUD$2000 per patient. Thus, with adequate training of GPs and their practice nurses and appropriate funding models to support an ambulatory strategy, primary care management of OSA has the potential to reduce the burden of disease in the community by improving patient access to sleep services. This would be particularly beneficial for rural and remote regions, as well as developing nations, where access to specialist services is limited. Further studies to evaluate the cost-effectiveness of ambulatory management strategies in primary care beyond the 6 month follow up in this study are likely to be valuable.

CHAPTER 5: CONCLUSION

OSA is highly prevalent in the Australian community and worldwide, with the rates of disease rising in parallel with the growing rates of obesity. There has been increasing demand for laboratory-based sleep testing and sleep physician consultation which has resulted in growing waiting lists and delays in patient diagnosis and treatment. Alternative, validated strategies for the diagnosis and management of OSA which are easily accessible to patients, simple to apply and cost-effective are urgently needed. The overall objectives of this thesis were, therefore, to develop and evaluate the effectiveness of a simplified model of diagnosis and care for OSA to be applied in the general practice setting, utilising the skills of GPs and their practice nurses.

In Chapter 2, we developed and validated a simple two-step diagnostic strategy for identifying patients with moderate-to-severe OSA in primary care, consisting of a screening questionnaire followed by the use of overnight home oximetry. Based on the analysis of demographic, anthropometric and sleep survey data from patients in primary care, we were able to identify four items which are most predictive for a diagnosis of moderate-to-severe OSA. These are (1) obesity by waist circumference; (2) snoring; (3) witnessed apneas; and (4) age over 50 years. These four items were used to create a screening questionnaire with a simple 10-point scoring algorithm titled the “OSA50” questionnaire, which is ideal for use in a busy primary care setting.

In this chapter, we also evaluated the accuracy and reliability of a level 4

home monitoring device called an ApneaLink, which records overnight oxygen saturations and nasal pressure, and can be downloaded and automatically scored using specialised software to give an oximetry dip rate and an apnea-hypopnea index. Our results demonstrated that, whilst both the oximetry dip rate and nasal airflow-derived AHI were highly accurate (i.e. ROC AUC values ≥0.95) in identifying patients with moderate-to-severe OSA, oximetry was the more reliable measure with fewer study failures compared to nasal pressure recordings.

Using cut-points of ≥5 out of 10 for the OSA50 questionnaire and a 3% oxygen desaturation index ≥16/hr, the combined two-step diagnostic model had a sensitivity of 88%, specificity of 82% and overall diagnostic accuracy of 83% for identifying OSA in our validation sample. Thus, we were able to demonstrate that use of a screening questionnaire followed by home oximetry could accurately identify patients with moderate-to-severe OSA in primary care.

Prior to involving GPs in a study of OSA management, it was important to ensure that they had an appropriate level of knowledge and confidence in their ability to diagnose and treat patients with OSA. Previous studies have demonstrated a paucity of education in OSA for GPs at both undergraduate and postgraduate levels, and, consequently, low rates of identification of OSA in primary care patients. In Chapter 3, the results of a before-and-after study are reported comparing the results of a knowledge and attitudes questionnaire completed by GPs prior to and following their participation in a

six-hour education program on OSA and common sleep disorders. The education program was accredited by the Royal Australasian College of General Practitioners, and designed to meet the requirements for an Active Learning Module as part of their Quality Assurance and Continuing Professional Development program.

Prior to receiving OSA education, GPs felt reasonably confident in diagnosing OSA, but were much less confident in their ability to manage OSA, especially patients on CPAP therapy. Two weeks after participation in the education program, GPs reported significant improvements in their levels of confidence in diagnosing and treating OSA and also had increased knowledge test scores. These improvements in attitudes and knowledge from baseline were sustained on long term follow-up when GPs were asked to repeat the questionnaires at least 17 months after attending the educational sessions. This study, however, was limited by the lack of a matched control group and incomplete responders on long term testing. The effectiveness of an education program on OSA and common sleep disorders in primary care would be best evaluated using a study with a randomised, controlled design involving larger numbers of GPs.

As reported in Chapter 4, a prospective, randomised, controlled, non-inferiority study was conducted to assess the clinical efficacy and cost-effectiveness of a simplified model of care in general practice compared to sleep specialist management. GPs were asked to use the simple 2-step diagnostic process of screening questionnaire and home oximetry to identify

patients with moderate-to-severe OSA from their practices. Patients with OSA and who reported at least mild daytime sleepiness or suffering from resistant hypertension were then randomised to either continue with an ambulatory management strategy under the care of their GP and a community-based nurse, or to standard laboratory-based care in a specialist sleep centre.

Following six months of treatment and follow-up, the primary outcome, change in subjectively-measured daytime sleepiness, was not inferior for patients managed in the primary care arm relative to the specialist arm. No differences were evident in any of the secondary outcome measures, including changes in sleep apnea symptoms, disease-specific and general quality of life, average nightly CPAP use, blood pressure or patient satisfaction with management. Furthermore, primary care management of OSA was associated with significant within-study cost savings of over $2000 per patient.

It is important to note that the results of this study do not support the role of untrained GPs, nor other community health professionals (e.g. pharmacists or CPAP providers), functioning independently in the diagnosis and/or management of OSA without support from a specialist sleep service. We believe that several key elements were crucial to the success of this project. Firstly, all GPs and community nurses in the study participated in an accredited training program on OSA, its management, and common sleep disorders. Patients were appropriately screened by GPs utilising a validated

diagnostic strategy and exclusion of patients with significant respiratory or cardiac disease who could potentially be misdiagnosed with the use of overnight oximetry. Although GPs and community nurses were encouraged to take primary responsibility for patient management, they were closely linked to and supported by a specialist sleep centre to whom they could refer to for advice or formal consultation.

It is possible that some sleep physicians may view a primary care-based model for the diagnosis and management of OSA as being somewhat competitive and a potential threat to their specialty. However, it is important to remember how the management of other prevalent chronic diseases, such as diabetes mellitus and asthma, have evolved over time. Historically, these conditions were once managed only by specialist physicians but are now commonly treated in general practice, with referral to specialists only in the case of more complex disease. Thus, an alternative view is that primary care management of OSA could be seen as being complementary to specialist sleep services by enabling greater access to diagnosis and treatment for patients with more severe disease which would open up a pathway to address the excess burden of disease which currently exists in the community. A survey to establish the attitudes of sleep physicians would therefore be important in determining whether they would welcome a role for GPs and their practice nurses in the diagnosis and management of OSA and to determine the barriers for the development of primary care-based models of care.

In this research study, we were able to demonstrate that a simplified, ambulatory model of care for OSA in general practice, utilising the skills of appropriately trained GPs and community-based nurses, is both efficacious and cost-effective. Following on from this work, the next step would be translation of these research findings into practice with a focus on conducting dissemination and implementation research. A needs analysis survey of primary care providers would be important to establish the needs and interest of GPs with regard to the diagnosis and management of sleep disorders in their local communities, as well as in determining the opportunities and barriers to effective integration of our research findings into clinical practice.

Before such a model could be implemented more widely, it would be important to establish appropriate funding models to support the use of ambulatory care models for OSA in general practice. However, in order to influence policymakers, further research to evaluate the long term financial implications of the use of ambulatory management strategies for OSA in primary care will also be important. This will need to take into account the accuracy of our simplified diagnostic strategy (i.e. false positive and false negative results), as well as the anticipated benefits of CPAP therapy on cardiovascular disease as emerging evidence from large randomised controlled trials come to light.

Strategies to increase opportunities for education and training on OSA and general sleep medicine for GPs and practice nurses to improve their overall awareness and knowledge will also be critical to the success of a primary

care model, and needs to be targeted at both undergraduate and postgraduate levels. Development of the RACGP-accredited education program on OSA and common sleep disorders into a web-based training package would enable broader access to GPs and other primary care providers both nationally and internationally, and is likely to be of particular benefit to health professionals located in rural and remote areas where educational opportunities are likely to be more limited. Further research using a randomised, controlled study design aimed at evaluating the effectiveness of the education program, including its impact on the attitudes and knowledge of primary care providers on the diagnosis and management of OSA and common sleep disorders will also be important.

In recent years, the Australian Government have committed a significant level of funding into the establishment of a network of GP Super Clinics. These extended general practice facilities house a number of professionals from various disciplines which support the delivery of multidisciplinary care and aim to facilitate the integration of primary care services, particularly for patients suffering from chronic illness. OSA is a chronic disease which is closely associated with other co-morbid conditions and modifiable lifestyle factors commonly encountered in primary care, including obesity, hypertension, cardiovascular disease, diabetes mellitus, alcoholism, smoking, depression and male impotence. Patients with OSA who are managed in general practice would therefore likely benefit from a comprehensive package of care that is tailored to the individuals needs of the patient and includes input not only from GPs and their practice nurses, but

also dieticians, exercise physiologists, psychologists and mental health services, drug and alcohol services, sexual health services, and podiatry, etc. A potential area for further research would be to evaluate the effectiveness of a comprehensive package of care utilising a multidisciplinary approach to the management of OSA and related co-morbidities in the primary care setting compared to the current standard of care involving referral to a specialist sleep centre.

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