Imperial College London

The diagnosis and treatment of sleep disordered breathing in patients with cardiovascular disease in England: current pathways and barriers to optimal care

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Statement of originality

I hereby declare that the research presented in this thesis is original and of my own. Information obtained and presented from other sources are is referenced accordingly and these are listed in the appropriate section.

Copyright Declaration

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Publications and presentations related to this thesis

- ASN **Malaweera**, JP. Riley, AK. Simonds, MC. Cowie. A qualitative study of the perceptions and experiences of healthcare professionals in identifying patents with cardiovascular disease and co-existing sleep disordered breathing. *4th Cardiosleep International Congress*, Paris, France (April 2015)

- **ASN Malaweera**, JP. Riley, AK. Simonds, MC. Cowie. Barriers to diagnosis and treatment of sleep disordered breathing in patients with heart failure: perceptions and experiences of healthcare professionals. *Heart Failure/2nd World Congress on Acute Heart Failure*, Seville, Spain (May 2015)

- **Anura SN Malaweera**, Jillian P Riley, Anita K Simonds, Martin R Cowie. Barriers to diagnosis and treatment of sleep disordered breathing and cardiovascular disease; a qualitative study (*manuscript in progress*)

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Abbreviations

ACS	acute coronary syndrome
AHI	apnoea hypopnoea index
ASV	Adaptive Servo Ventilation
BLF	British Lung Foundation
CCT	cluster randomised control trial
CI	confidence intervals
CPAP	continuous positive airway pressure
CPG	clinical practice guidelines
CRT	cardiac resynchronisation therapy
CSA	central sleep apnoea
CSR	Cheyne-Stokes Respiration
CVD	cardiovascular disease
ECG	electrocardiogram
EEG	electroencephalography
EF	ejection fraction
EMG	electromyography
EOG	electrooculography
ESS	Epworth Sleepiness Scale
GPs	General Practioners
HES	Hospital Episode Statistics
HSE	Health Survey for England
NICE	National Institute for Health and Clinical Excellence
NHS	National Health Service
NS	non significant
ODI	oxygen desaturation index
OR	odds ratio
OSA	obstructive sleep apnoea
$PaCO_2$	arterial blood carbon dioxide concentration
PAP	positive airway pressure
PCT	Primary Care Trust
PG	polygraphy
PSG	polysomnography
QI	quality improvement
RCT	randomised control trial
REM	rapid eye movement
RR	relative risk
SHHS	Sleep Heart Health Study
SpO_2	oxygen saturation

Chapter 1: Introduction

Cardiovascular disease (CVD) is a major health burden accounting for more than 30% of deaths worldwide,[1] but there have been significant advances in its management in recent years. Large clinical trials in heart failure treatment,[2,3] cardiac resynchronisation therapy,[4] percutaneous coronary intervention in acute myocardial infarction[5] and modifying risk factors such as blood pressure[6] and cholesterol,[7] have been shown to substantially reduce mortality. These findings have been adopted into clinical practice guidelines and standardised care pathways.[8] However, there is a mismatch between the widely perceived 'best practice' and how patients are actually managed in clinical practice.[9] Although some variation in care is acceptable, in most healthcare systems, the delivery of care is not standardised.

Sleep disordered breathing (SDB) has been traditionally considered as a discipline in respiratory medicine but its burden in CVD is beginning to be recognised. It is highly prevalent in patients with CVD and can further potentiate their cardiovascular risk and lead to adverse cardiovascular mortality.[10,11] Although, in principle, management of SDB has a clear patient pathway consisting of screening, diagnosis and treatment,[12] there are diagnostic challenges. Recent reports suggest that most patients with SDB are likely to be undiagnosed and untreated.[13] Patients with both CVD and SDB are likely to have multiple comorbidities requiring complex management strategies and input from several specialties, potentially leading to difficulties in coordinating care. Thus, the main aim of this thesis is to identify these practice barriers to diagnosis

and treatment in patients with SDB and CVD, using both quantitative and qualitative methodology. Identifying these barriers could potentially improve service delivery and patient care.

In the past two decades there has been a strong emphasis on improving the quality of patient care in the National Health Service (NHS).[14] Various quality improvement (QI) tools have been described in the literature,[15] which may help to overcome these barriers in healthcare. Although a large number of QI tools have been used widely in the management of cardiovascular disease, we do not know whether they change cardiovascular outcome. Identifying the most effective QI tools is important as the NHS faces new challenges with resource and service constraints. Thus, the secondary aim of this thesis is to identify effective QI methodology and utilise them to improve and redesign local practice, using SDB in patients with CVD as a template.

In subsequent chapters of this MD thesis, the following objectives will be addressed. Firstly in chapter 2, the association between cardiovascular disease and SDB will be evaluated in relation to pathophysiology, screening, diagnosis and treatment. The current evidence for the management of SDB in CVD will also be reviewed in this chapter. In chapter 3, sleep services in the United Kingdom (UK) will be explored using both publicly available data sources related to SDB (such as Hospital Episode Statistics [HES data] and NHS RightCare), to help understand the variation in service provision and diagnostic rates. Chapter 4 will explore the potential underdiagnosis of SDB in UK primary care.

Chapters 5 and 6, will identify the barriers to diagnosis and treatment of patients with SDB and CVD in primary care (using a previously conducted GP and patient surveys) and in secondary and tertiary care (using semi-structured interview of healthcare professionals). These two chapters will use qualitative methodology. A separate methodology chapter is not included in this thesis. This is because, to explore the research questions, mixed-methods were used (i.e. both quantitative and qualitative methodology), and therefore, I considered it was appropriate to discuss the methods related to each chapter separately.

The seventh chapter will present a systematic review (of randomised/cluster controlled trials) exploring the impact of QI methodology on CVD outcome.

In the final chapter, using the QI tools that were shown to be most effective in improving cardiovascular outcome and mapping the current patient pathways, a novel pathway and aspects of service re-design to optimise the management of SDB in CVD will be proposed. Further, clinical implications of the findings and future directions for research will be discussed in this final chapter.

Chapter 2: Sleep disordered breathing and association with cardiovascular disease

2.1 Aims

The aim of this chapter is to review the pathophysiology, screening, diagnosis, and treatment of SDB. Further, the current evidence relating to the association between SDB and CVD will also be explored.

2.2 Background

SDB or "sleep apnoea" includes a spectrum of sleep conditions, but mainly obstructive (OSA) and central sleep apnoea (CSA). Both have the common feature of cessation or reduction in breathing during sleep that leads to a reduction in airflow.[16] As a result, a cascade of events are initiated such as poor oxygenation, repetitive cycles of autonomic nervous system activation and surges in blood pressure.[17] These effects can be directly detrimental to the cardiovascular system. SDB is common in patients with CVD and there is considerable overlap with other cardiovascular risk factors.[18] A number of studies have shown that SDB may lead to adverse patient outcome in patients with CVD.[19] Therefore understanding its pathophysiology, diagnostic and treatment options are important when managing these patients.

2.2.1 History of sleep disordered breathing

The first anecdotal case of SDB was likely written by Charles Dickens in 1800s.[20] In his novel, "The Pickwick Papers", he describes an obese servant-boy named "Joe" who is reported to be "*always asleep*" and "snores as he waits at the table". This was perceived as "odd" and "a natural curiosity" by the author, although this

was likely to be a depiction of a rare case of childhood OSA. Since then, the term "Pickwickian Syndrome" has been used to describe obesity-hypoventilation. However, the first clinical case report of OSA[21] was described by Burwell and colleagues at the Brigham General Hospital. They presented a case of a 51-year-old business executive who weighed ~120kg and complained of fatigue and excessive daytime somnolence. For example, he failed to take advantage of a "*full house*" while playing poker because he "*dropped off to sleep*". They described eight clinical features of this syndrome: obesity, somnolence, twitching, cyanosis, periodic respiration, secondary polycythaemia, right ventricular hypertrophy and right ventricular failure. Enforced weight reduction with an 800-calorie diet, resulted in the loss of 17.8 kg leading to improvements in alveolar ventilation, arterial oxygen saturation and resolution of his symptoms.

Periodic breathing in heart failure was first described in the 1800s by John Cheyne.[22] He presented a 60-year-old male who experienced ankle swelling, palpitation and pulmonary congestion. Cheyne described his breathing pattern as, "*for several days his breathing was irregular, it would entirely cease for a quarter of a minute, then it would become perceptible, though very low, then by degrees it became heaving and quick and then it would gradually cease again*". This waxing and waning breathing pattern was also described by William Stokes in his book "The diseases of the heart and aorta" in 1854.[23] This characteristic crescendo-decrescendo pattern, which is typically seen in heart failure and CSA, was ultimately named after these two physicians as "Cheyne-Stokes respiration".

Despite these early reports, the clear distinction between obstructive events and central events were not made until 1970s. Guilleminault and colleagues demonstrated this experimentally in non-obese patients.[24] In this study, central apnoea was classified as an absence of airflow during an overnight polysomnographic study (indicated by a flat tracing in both nasal and buccal thermistors) and accompanied by the absence of respiratory effort (indicated by flat tracings in the abdominal and thoracic strain gauges). In addition to these abdominal and thoracic strain gauges, they used an oesophageal pressure transducer to monitor respiratory effort more accurately. They studied a mixed population of 250 patients, which included patients with other sleep disorders such as insomnia, narcolepsy and hypersomnia, in addition to pure OSA or CSA. The distinction between an obstructive and a central event is illustrated in figure 2.1 from a 49-year-old patient.[24]

The relationship between sleep and Cheyne-Stokes respiration (CSR) in heart failure was systematically studied only in the 1980s. One such study was carried out by Hanly and colleagues,[25] and included 10 patients with stable congestive heart failure (NYHA class III-IV) with an ejection fraction of 22±5%. All patients had predominant CSA with CSR. This study demonstrated that severe hypoxia (defined as the proportion of total sleep time having an arterial SpO_2<90%) was closely related to the duration of CSR (correlation coefficient=0.66; $p<0.05$). Although, these patients were on 'maximal' therapy, which mainly consisted of diuretics and digoxin (in the 1980s), only one patient was on an ACE inhibitor and two on spironolactone. This study was conducted before any hard outcome

data related to beta-blockers[26], ACE inhibitors[27] and aldosterone receptor antagonists[28] were available.

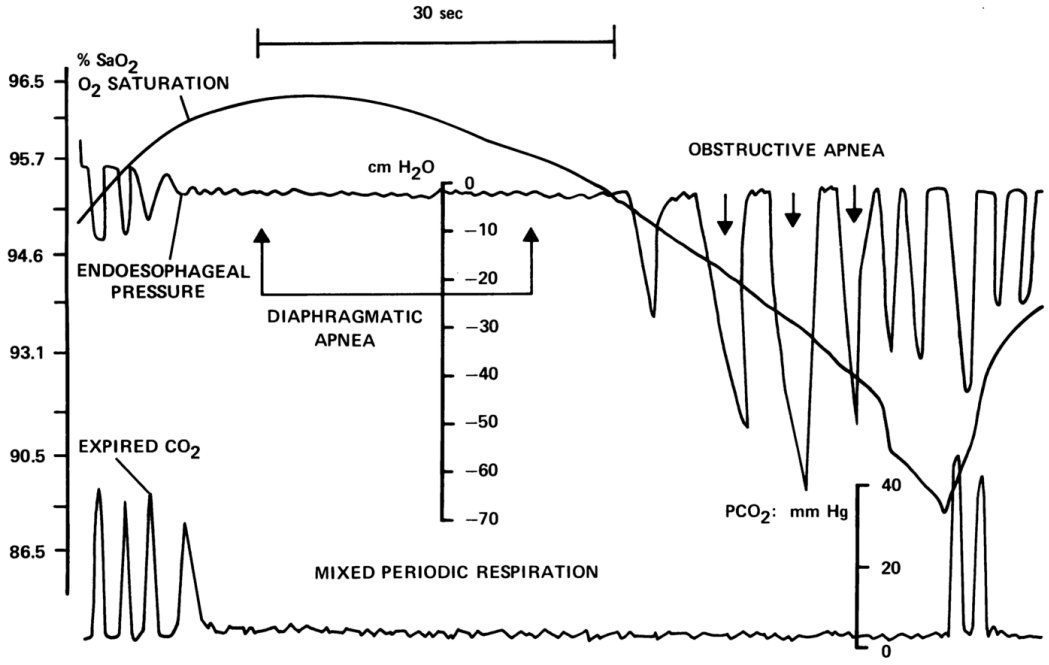


Figure 2.1 Illustration of a central and an obstructive event

The static oesophageal pressure trace in the early part (i.e. diaphragmatic apnoea with no thoracic effort) shows the central event and the large swings in oesophageal pressure (i.e. indicative of thoracic effort) in the latter part of the trace shows the obstructive event. Both events are characterised by static end-tidal CO_2 (i.e. no airflow)
(Adapted from Guilleminault et al.[24])

2.2.2 Screening and Diagnosis

2.2.2.1 Diagnostic criteria

The diagnosis of SDB is made by the criteria of the International Classification of Sleep Disorders[29,30] formulated by the American Academy of Sleep Medicine (AASM). The most commonly used terms are tabulated below (table 2.1).

Apnoea	A complete cessation of breathing for ≥ 10 seconds
Hypopnoea	A partial reduction in breathing where the amplitude of a valid measure of breathing (e.g. air flow) is reduced - by more than 50% with an oxygen desaturation of 3% OR - by 30% with a 4% oxygen desaturation
AHI	Apnoea-hypopnoea index; the sum of apnoeas and hypopneas occurring per hour
RDI	Respiratory disturbance index; respiratory effort related arousals that are characterised by increasing respiratory effort leading to arousal from sleep (but do not meet the criteria for apnoea/hypopnoea)

Table 2.1 Common descriptions of SDB

The severity of SDB is classified by the apnoea-hypopnoea index (AHI), where an AHI of 0-4 is considered as normal, 5 to14 as mild, 15 to 30 as moderate and >30 as severe. SDB is considered to be clinically significant if the AHI is 15 or more, or greater than 5 with the presence of symptoms. Depending on the proportion of the type apnoea (e.g. central or obstructive), SDB is either defined as predominantly CSA or predominantly OSA. For example, typically when at least least 50% of apnoeas are scored as central events, the primary diagnosis is considered to be CSA.[31]

Criteria for the diagnosis of Cheyne-Stokes respiration have also been described by the AASM. They require 10 apnoeas or hypopnoeas per hour of sleep with the characteristic crescendo-decrescendo pattern of respiration, occurring as part of another medical illness such as heart failure or stoke and not explained by another sleep disorder or substance misuse.[29,32]

Criteria to diagnose OSA are shown in table 2.2.

OSA is diagnosed when criteria A and B, OR C are present
A. The presence of one or more of the following • The patient complains of daytime sleepiness, unrefreshing sleep, fatigue or insomnia symptoms • The patient wakes with breath holding, gasping or choking • The bed partner or other observer reports snoring, breathing interruptions or both during the patient's sleep • The patient has been diagnosed with hypertension, a mood disorder, cognitive dysfunction, coronary artery disease, stroke, congestive heart failure, atrial fibrillation or type 2 diabetes
B. Sleep recording (e.g. PSG/PG) demonstrates • 5 or more predominantly obstructive respiratory events per hour of sleep (i.e. obstructive and mixed apnoeas, hypopnoeas or respiratory effort-related arousals)
C. Sleep recording demonstrates • 15 or more predominantly obstructive respiratory events per hour of sleep (i.e. obstructive and mixed apnoeas, hypopnoeas or respiratory effort-related arousals)

Table 2.2 Criteria for the diagnosis of OSA

The criteria set by the American Academy of Sleep Medicine for diagnosing OSA. (Adapted from Zucconi et al.[33])

2.2.2.2 Sleep stages

Sleep consists of 4 stages: one stage of rapid eye movement (REM) sleep and 3 stages of non-REM sleep.[32] Non-REM consists of stages N1 (or NREM1), which is stage between wakefulness and sleep where the brain activity gradually slows down (characterised by brain activity of 'mixed' frequency with theta waves of 4-7 Hz), N2 is considered the first definite stage of sleep where any consciousness begins to cease (characterised by sleep spindles which are bursts of 12-14 Hz activity and 'K' complexes) and N3 is deep sleep with complete unawareness from external stimuli (characterised by delta waves of high amplitude and low frequency <4Hz). During REM sleep, the stage of sleep where dreaming is common, there are characteristic phasic rapid eye movements and 'sawtooth waves' (bursts of activity of 2-6 Hz) on the EEG. These stages are illustrated in figure 2.2.

An arousal is a rapid switch from sleep to wakefulness.[31] It is accompanied by a change in EEG frequency (>16 Hz) consisting of alpha and theta activity (but not sleep spindles) and lasting between 3 to 15 seconds, where at least 10 seconds of normal sleep should be recorded before and after the event.[34] An arousal is also not considered a state of wakefulness (because the patient is unconscious during that time), but a 'lighter' stage of sleep. Identifying these arousals are important in SDB because they are closely related to apnoeic events, usually occurring at the end of an apnoea.[35] While arousals can restore airflow by recruiting upper airway dilator muscles and opening the airway,[35] they can lead to sleep fragmentation, interfere with the progression to deep sleep stages and REM sleep and even facilitate repetitive apnoeas as a result of hyperventilation and

the consequent fall in $PaCO_2$ associated with arousals, leading to a reduction in the respiratory drive.[36] The enhanced sympathetic activity associated with arousals, such as the elevation of arterial blood pressure will be discussed later (section 2.2.4.3).

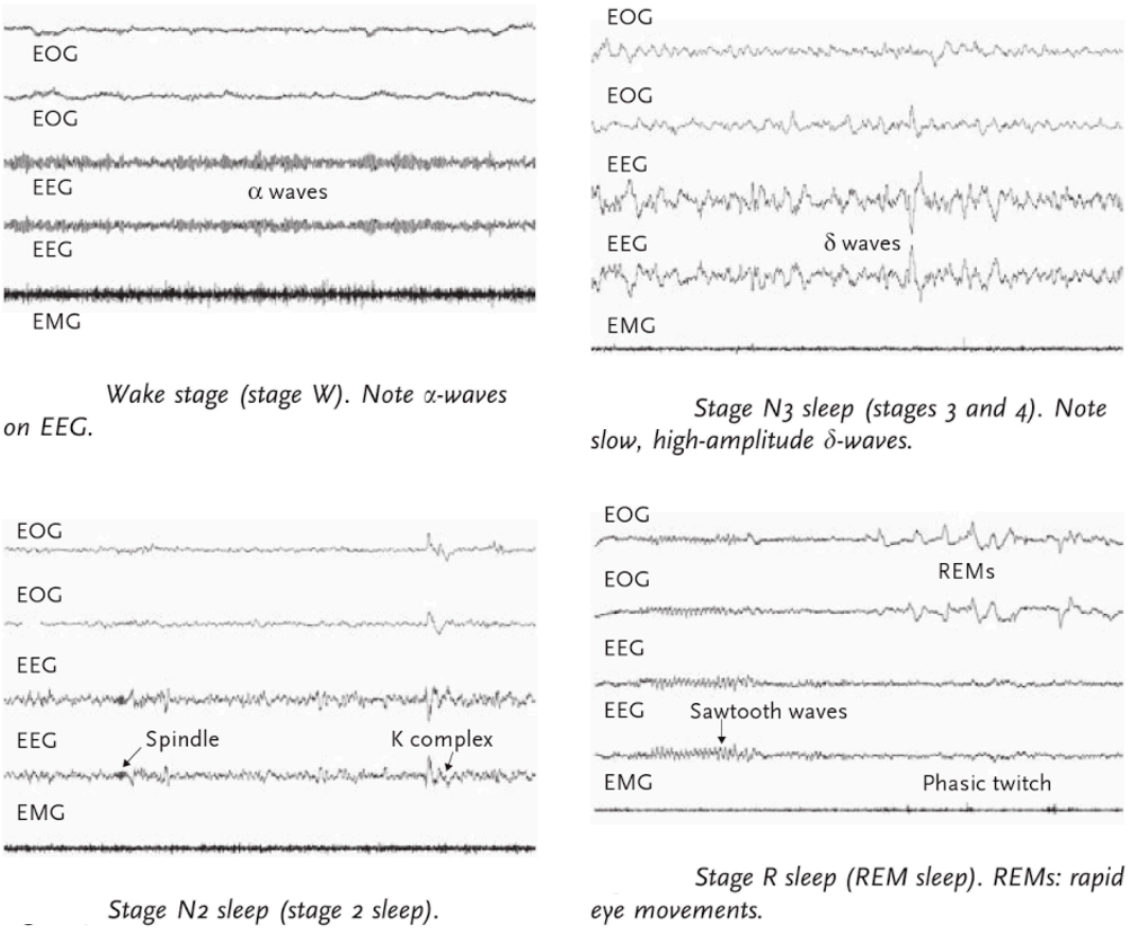


Figure 2.2 Sleep stages and their characteristic activity pattern

Different sleep stages and activity pattern recorded from EEG, EOG and EMG channels. Wake stage is characterised by alpha waves (top left). Stage 2 sleep is characterised by spindle and K complexes (bottom left). N3 sleep has predominant delta waves, which are slow, and has a large amplitude (top right). REM sleep has phasic rapid eye movements on EOG and 'sawtooth' waves on EEG (bottom right). (Adapted from ERS handbook of respiratory sleep medicine, page 123.[32])

2.2.2.3 History and clinical examination

SDB is characterised by sleep disturbance and deprivation, which leads to daytime somnolence and fatigue. However, most patients with SDB do not report daytime sleepiness. This is marked in CSA,[37] but even for OSA, in large population studies, daytime somnolence was only found in ~20% of patients who were diagnosed with SDB after polysomnography.[38,39] Some patients may also suffer from early morning headaches, due to raised CO_2 levels as a result of nocturnal hypoventilation.

Daytime sleepiness may lead to a poor quality of life and lack of concentration affecting daytime performance. One of the main areas this impacts is driving ability and road traffic accidents,[40] with ~20% of driving incidents are estimated to be due to excessive sleepiness.[41,42] In the UK, patients with SDB who experience symptoms are legally obliged to inform the Driver and Vehicle Licensing Agency (DVLA) and stop driving until the condition is treated, according to the guidance provided by the British Thoracic Society.[43,44] National Institute for Health and Clinical Excellence (NICE) also recognises the importance of this and recommends the assessment of vocational drivers to be expedited to allow driving again within four weeks following first referral.[45] The guidance also states that SDB patients who are asymptomatic or have their symptoms controlled with therapy can continue to drive without relinquishing their licence. Hack and colleagues, in a small study of 60 patients, randomised either to therapeutic or sub-therapeutic CPAP, showed that CPAP improves driver performance, measured by the reaction time and steering position on a driving simulator.[46]

A patient's bed partner can play an important role in elucidating apnoeas, periods often described by them as "stopped breathing", "gasping" or "choking". In addition, patients with obstructive sleep apnoea are usually snorers, which is commonly reported by their partners. Partners may suffer from sleep disturbance themselves, due to the noise generated by the vibration of upper airway respiratory structures, which can be in the order of 80-90 decibels.[47]

Physical examination mainly consists of measuring the patient's height, weight and calculating the body mass index (BMI). Neck circumference is also a risk factor for OSA, which is considered to be significant if it is greater than 43 cm (17 inches) in men and 37 cm (15 inches) in women. Upper airway scoring systems, such as the Mallampati score are useful, and can be an important predictor of OSA.[48] This classification system is based on the anatomic features of the upper airway (figure 2.3).

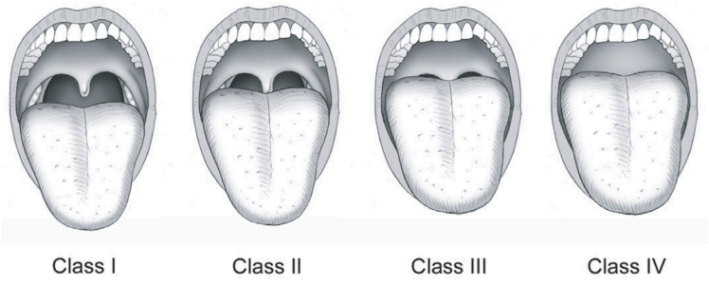


Figure 2.3. Mallampati score

A score of 1 is given when the soft palate and entire uvula visible, 2 when the soft palate and portion of uvula visible, 3 when the soft palate and only the base of uvula is visible and 4 when the soft palate not visible.
(Adapted from Nuckton et al.[48])

2.2.2.4 Screening for SDB

2.2.2.4.1 Questionnaires

Several questionnaires have been used to screen for SDB. The most commonly used ones are the Epworth Sleepiness Scale (ESS), Berlin Questionnaire (BQ), and the STOPBang questionnaire.[32] These questionnaires are presented in the Appendix. ESS consists of 10 items and a score 10 or more (from a total of 24) indicates a positive test; BQ has 10 items distributed across 3 categories and if two of these categories are positive it indicates an increased risk of OSA; and the STOP Bang questionnaire has 8 items, including BMI, age, sex and neck circumference, and is positive if the score is 3 or more. ESS is the most widely used, as it is perceived to be a simple, practical tool and has been in clinical practice for more than 20 years. However, ESS was initially developed to determine the likelihood of onset of sleep, rather than the likelihood of SDB.[49]

The clinical utility of these questionnaires has been studied in large studies. Pataka and colleagues,[50] retrospectively compared these questionnaires in 1853 patients, who underwent sleep studies between 2009 and 2012 at the Papanikolaou sleep clinic in Greece. In addition to the ESS, BQ and STOPBang, this study also included the 4-Variable Screening Tool (4-V), which is mainly used to screen for moderate to severe OSA.[51] A summary of their findings is shown in table 2.3. ESS, although used widely, in comparison to other questionnaires had the lowest sensitivity (50%) and the STOPBang questionnaire had the highest sensitivity (96%). All of these tools had similar positive predictive values (PPVs), exceeding 80%. Thus, if these tests were

positive there was a high likelihood of a patient having OSA. However, in this patient group the baseline BMI was ~33, the average age was 52 and 75% of participants were male. The higher prevalence of risk factors for OSA in this study could have been influenced the PPV, which depends on the prevalence of disease in the population. The negative predictive value of these questionnaires, which is the ability of the screening tool to exclude OSA (i.e. if negative the patient is less likely to have OSA), was comparatively poor (<50%). STOPBang questionnaire had the highest NPV (45%) compared to other tools. In summary, these questionnaires are helpful when positive (i.e. when OSA is very likely) but cannot be used to exclude SDB.

In a sub study of the Sleep Heart Health Study (SHHS), evaluating the predictive parameters of the questionnaires, showed similar results for ESS with sensitivities and specificities of 39% and 71%, respectively. STOPBang, however performed better with a specificity of 43%, compared to the above study (14%).[49]

Parameters	ESS	Berlin	STOPBang	4-Variable
				⩾11
Sensitivity	50%	84.4%	96.2%	78%
Specificity	67%	35.3%	14%	40.8%
PPV	86.6%	85.3%	83.3%	84.3%
NPV	24%	33.8%	45%	31.1%

Table 2.3 Properties of different screening tools for SDB

Comparison of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of various questionnaires such as Epworth Sleepiness scale, 4-Variable Screening Tool, Berlin and STOPBang questionnaires (Adapted from Pataka et al.)[50]

The main limitation of questionnaires is that they depend on the subjective reporting of symptoms related to sleep quality, fatigue and daytime sleepiness by the patient. Patients may fail to recognise the importance of these symptoms, and moreover, they may not volunteer symptoms such as snoring due to the attached social stigma. For example, patients who are in full-time employment as drivers may deliberately avoid revealing their symptoms due to the fear of loss of employment and income.[52] Therefore, better screening tools are needed which are independent of patient reporting.

Questionnaires, however, may still be useful. If used in combination, their specificity and sensitivity can potentially be improved. In the above study by Pataka and colleagues,[50] the specificity increased to 95% when 4-V, STOPBang, ESS and BQ questionnaires were used in series (i.e. the combination deemed 'positive' if all tests are positive). The sensitivity was 99% when all 4 questionnaires were used in parallel (i.e. the combination deemed negative if all tests are negative). For example, the likelihood of having OSA is higher if a patient scores highly in all 4 questionnaires and vice versa. However, the practicality of using all 4 questionnaires in the clinical settings is likely to be challenging and may not be very helpful as most patients would end up with a mixture of positive and negative questionnaires.

2.2.2.4.2 Pulse Oximetry

The pulse oximeter works by detecting the differences in absorbance between the wavelengths of oxygenated and deoxygenated blood.[53] The mean oxygen saturation (SpO_2) at night in healthy individuals is 96.5 % (± 1.5%) but in OSA

the dips in overnight SpO_2 can be much lower and more variable (65.9 % ± 22.6%).[54] The aim of using pulse oximetry in patients with SDB is to detect the frequency of this 'drop' in oxygen saturation of haemoglobin, which will occur repetitively throughout the night. Usually a 4% drop in the oxygen saturation from baseline (i.e. oxygen desaturation index [ODI]), is considered as clinically significant in the context of air flow limitation.

Pulse oximetry was an important tool in identifying patients with the Pickwickian syndrome in the 1960s, however, its use as the sole modality for diagnosing SDB has declined in the past two decades. As a screening tool, its properties are highly variable and the evidence for using pulse oximetry as a single-channel recording to screen for SDB is poor. A systematic review of published studies conducted by Netzer and colleagues in 2001,[54] reported that the sensitivity of pulse oximetry in OSA ranged from 31% to 98% and specificity from 41 to 100%.

Pulse oximetry has also been used to screen for SDB in patients with heart failure. A study carried out by Ward and colleagues[55] at the Royal Brompton Hospital involving 180 patients, showed that using a 3% oxygen desaturation index and a cut-off of 7.5 events/h, pulse oximetry had a high sensitivity (97%) and negative predictive value (94%). However, the specificity and the positive predictive value were low (32% and 53%, respectively). This suggests that pulse oximetry may be used to "rule out" SDB in heart failure patients (i.e. those patients who do not desaturate are unlikely to have SDB and in those who desaturate, although SDB is not diagnosed, are likely to be investigated further).

Pulse oximetry has several limitations. Its utility will depend upon having an adequate peripheral perfusion. Further, it cannot be used to differentiate between central and obstructive apnoeic events. Therefore, pulse oximetry is generally used, if at all, as a screening tool, but is more typically used in combination as part of multi-channel recordings in sleep monitoring devices (e.g. polygraphy and polysomnography) for the proper characterisation and detection of SDB.

2.2.2.5 Sleep monitoring devices

American Academy of Sleep Medicine[56] categorises 4 types of sleep monitoring devices depending on the number of channels for data recording. These include channels, which record:

1. Sleep wake activity
    a. Electrical activity of the brain using electroencephalography (EEG)
    b. Electrooculography (EOG) to record eye movements
    c. Electromyography (EMG) to record muscle activity from lower limbs and chin/jaw
2. Beat-to-beat cardiac activity (i.e. ECG)
3. Respiratory activity
    a. Airflow
    b. End-tidal CO_2
    c. Respiratory effort (chest and abdominal)
    d. Snoring
4. Pulse oximetry
5. Body position

Type I monitoring is conducted in a laboratory setting, attended by health care professionals such as sleep physicians or physiologists. The devices used for

these sleep studies gather information from 7 or more channels. Type II devices also have similar number of channels, but they are carried out in an ambulatory setting, usually in a patient's own home. Type I and II sleep monitoring are termed 'full' polysomnography (PSG), a comprehensive multi-channel recording of sleep conducted using EEG, EOG, EMG, ECG, respiratory activity and pulse oximetry. These studies are sometimes accompanied with video and audio recording. SOMNOscreen™ (SOMNOmedics GmbH, Germany) and Alice 6 LDx™ (Phillips Respironics™) are examples of commercially available PSG devices. PSG is the current 'gold standard' for the diagnosis of SDB. Full polysomnography is superior to other types of sleep devices, because they have the capability of determining sleep stages and arousals using EEG and EOG signals.[57] Further, these devices can quantify the amount and quality of sleep.[58] Additionally, Type I and II devices can also determine whether the arousals are respiratory effort related.[34]

Type III and IV monitoring or polygraphy (PG) is conducted using 'limited' channel devices. A type III device should have a minimum of 4 channels and Type IV device will have 2 channels where one of them will be pulse oximetry. The incentive and the drive for these devices comes as a result of the high costs and resources associated with carrying out inpatient or laboratory sleep studies. An example of a commercially available Type III device is an Embletta device™ (ResMed Inc., Australia) and it incorporates 4 channels: pulse oximetry (which also derives the heart rate), nasal pressure (which measures air flow and snoring), respiratory effort (which is measured by abdominal and thoracic movements) and body position. The Embletta system, has also been validated as

a diagnostic tool for diagnosing SDB. Ng and colleagues[59] explored this in 80 Chinese OSA patients, where the AHI obtained from the Embletta system strongly correlated with the AHI obtained from PSG. Sensitivity for detecting mild OSA (AHI>5) was 92% and the negative predictive value was 88%, suggesting that it was also acceptable in excluding patients without clinically significant SDB (AHI<15).

Type IV devices, such as the ApneaLink™ (ResMed Inc., Australia) and Alice PDx™ (Phillips Respironics™) have 3 channels consisting of pulse oximetry, nasal flow and respiratory effort. Newer version of these devices may also qualify as Type III devices as they have body position sensors. These devices have been validated for detection of both types of SDB. Weinreich and colleagues[60] showed that this device detected Cheyne-Stokes respiration at a sensitivity of 87.1% and a specificity of 94.9%. In a study of 50 patients using the ApneaLink device,[61] AHI obtained was comparable to PSG, with a correlation of r=0.98 ($p< 0.001$). The sensitivity (for detecting an AHI>5) and specificity (for detecting an AHI>15) was 100%.

Newer screening devices, based on oximeters attached to smartphones,[62] and 'Apps' which monitor the sleeping pattern using sound waves and vibrations from the mobile phone's inbuilt accelerometer and microphone,[63] have arrived on the market. These new technologies will be an asset to screening patients with SDB in an era of extensive pressure on sleep services. However, appropriate validation of these new technologies will be extremely important and has yet to be carried out robustly.

2.2.3 Epidemiology of sleep disordered breathing

SDB is common in the general population. The prevalence of symptomatic OSA is between 2-4% in adults.[64–66] Although CSA is less common, it is strongly associated with heart failure and can affect up to 50% of these patients.[37] Both types of SDB have a male predominance and the prevalence increases with age. Further, 16% of patients who suffer from SDB are found to have co-existing cardiovascular disease such as heart failure, stroke or coronary artery disease.[67]

2.2.3.1 Epidemiology of OSA

Several large population studies have demonstrated that when patients without symptoms are also considered the prevalence of OSA is likely to be much higher than 4%. Earlier studies[65] had estimated the prevalence of OSA syndrome, in patients who are both symptomatic (with hypersomnolence) and meet polysomnography criteria (having an AHI>5). However, many patients in recent studies did not report symptoms such as daytime somnolence, but were subsequently diagnosed with OSA after screening and polysomnography. The Vitoria Sleep Cohort, the largest of these,[39] conducted between 1993 and 1997, surveyed 2794 subjects between 30-70 years of age. A stratified random cluster sampling strategy by census areas was adopted in this study, where the sampling frame included all the eligible participants within a household. This sample reflected about ~1% of the population of Vitoria-Gasteiz in Spain. The study was done in two stages. The first stage consisted of screening for SDB using structured interviews based on the Nordic sleep questionnaire,[68] which is a 27-item standardised sleep questionnaire exploring the tendency to fall asleep during daytime based on a five-point quantitative scale, and home-polygraphy

using the MESAM™ IV portable recording, which consisted of 4 channels for monitoring heart rate, snoring, oxygen saturation and body position. A total of 2148 (1050 men) completed this stage and 442 subjects were positive for screening. 390 of these patients (82%), who had a 'potential diagnosis' of OSA, agreed to participate in the second stage. During the second stage laboratory polysomnography was carried out in all of these subjects and also on a random sample of 163 subjects with negative screening. When an AHI ≥10 on polysomnography was used as the cut-off, the false positive rate for MESAM IV was 45% for men and 65% for women and the false negative rate was 5.8% for men and 11.2% for women. After accounting for this, OSA prevalence for the whole sample was calculated based on age, sex and AHI category. The prevalence of mild OSA, defined as having an AHI ≥5, was 26% (95% CI: 20–32%) in men and 28% (95% CI: 20–35%) in women. Men had a higher prevalence of OSA compared to women for all age groups, apart from the women who are were aged between 50-59 years with an AHI ≥ 5. However, when clinically significant OSA (AHI ≥ 15) was considered, the prevalence in men was almost twice (14.2%; 95% CI: 10–18%) compared to women (7%; 95% CI: 3–11%). The prevalence of OSA also increased with age in both sexes, with an odds ratio of 2.2 (95% CI: 1.7–3.0) per 10-year increase in age. This was only 1.2 (95% CI: 0.7–2.0) once adjusted for BMI, suggesting that the effect of age is largely related to the increase in BMI with age.

Other population based studies, such as the Wisconsin[65] and Pennsylvania cohorts in the USA[69,70] have uncovered similar epidemiological patterns. The

prevalence of these studies, grouped according to gender, age and the severity of OSA, are summarised in Table 2.4.

	Prevalence (%)								
	AHI								
	>5			>10			>15		
Study	Vit	Wis	Penn	Vit	Wis	Penn	Vit	Wis	Penn
Age									
Male - ALL	26.2	24.0	17.0	19.0	15.0	10.5	14.2	9.1	5.6*
30-39	9.0	17.0	.	7.6	12.0	.	2.7	6.2	.
40-49	25.6	25.0	.	18.2	18.0	.	15.5	11.0	.
50-59	27.9	31.0	.	24.1	14.0	.	19.4	9.1	.
60-70	52.1		.	32.2		.	24.2		.
20-44	.	.	7.9	.	.	3.2	.	.	1.7*
45-64	.	.	19.7	.	.	11.8	.	.	6.4*
65-100	.	.	30.5	.	.	23.9	.	.	13.3*
Female - ALL	28.0	9.0	.	14.9	5.0	.	7.0	4.0	2.2
30-39	3.4	6.5	.	1.7	4.9	.	0.9	4.4	.
40-49	14.5	8.7	.	9.7	4.9	.	-	3.7	.
50-59	35.0	16.0	.	16.2	5.9	.	8.6	4.0	.
60-70	46.9		.	25.6		.	15.9		.
20-44	.	.		.	.		.	.	0.6
45-64	.	.		.	.		.	.	2.0
65-100	.	.		.	.		.	.	7.0

Vitoria (Vit); Wisconsin (Wis); Pennsylvania (Penn) sleep cohorts. Pennsylvania cohort is shown in grey as different age/AHI categories.*In these groups prevalence is for AHI>20

Table 2.4 Prevalence of OSA in cohort studies

An overview of prevalence rates of Vitoria, Pennsylvania and Wisconsin sleep cohorts, stratified according to gender, age and AHI.

In the Pennsylvania study (published in 1998), the prevalence of clinically significant SDB (AHI ≥ 15) was much lower compared to the Vitoria cohort (5.6% versus 14% and 2% versus 7%, for men and women, respectively). This could be explained by the differences in sampling and methodology of these studies: in the Pennsylvania study the screening process was carried out using telephone interviews of randomly selected households of two counties in Southern

Pennsylvania. 4334 men and 12,219 women were interviewed and stratified according to a pre-determined risk score, based on symptoms and risk factors for SDB (e.g. snoring, daytime sleepiness, obesity, and hypertension). Subjects with a higher risk score were over sampled. 745 men and 1000 women were then chosen to have laboratory polysomnography. Unlike the Vitoria study, Pennsylvania study did not use polygraphy in the screening process. Therefore, it could have underestimated the number of subjects with asymptomatic SDB. Similar methodology was used in the Wisconsin study, which could have accounted for the lower prevalence (9% versus 14% and 4% versus 7%, respectively for men and women with an AHI ≥ 15). In this study, which started in 1988, a random sample of state employees in Wisconsin were surveyed about their sleep patterns using a mailed-questionnaire. 3513 subjects completed the questionnaire and 602 of them had full polysomnography. The sample selection was not random: authors included all patients who were habitual snorers in the study and only included 25% of non-snorers, which similarly could have underestimated the subjects with asymptomatic SDB. Daytime hypersomnolence was reported in only 18% of subjects in the Vitoria study, although the prevalence of OSA (26-28%) was much greater. These findings also suggest that most patients with OSA in the community are likely to be asymptomatic.

The prevalence of SBD has likely increased over the past two decades.[71] Obesity, which is an important risk factor for developing OSA, is likely to be a contributory factor, as both obesity and OSA have increased in parallel during the same period.[72] This is also shown by a sub-study of the Wisconsin sleep cohort,[73] in which the prevalence of SDB was modelled as a function of age, sex,

and body mass index, using data extrapolated from the United States National Health and Nutrition Examination Survey. They analysed data from 1520 participants who had overnight polysomnography between 1988 and 2011. The estimated prevalence of SDB (defined as AHI ≥ 5) had increased from 26% (95% CI: 24–29%) to 34% (95% CI: 31–37%) in men and from 13% (95% CI: 11–15%) to 17% (95% CI: 15–20%) in women. SDB classified as severe (defined as AHI ≥ 15) also increased from 1998 to 2010 for both men and women.

In summary, men have a higher prevalence of OSA compared to women, by more than two-fold. In both genders, patients with OSA tend to be older and have a higher BMI and blood pressure. The prevalence of OSA is similar between different ethnic groups. Secondary analysis of the Sleep Heart Health Study conducted in 2010,[38] which included 5237 subjects, has shown that the prevalence was 17% in Caucasians, 19% in African-American and 17% in Hispanics, living in the USA.

2.2.3.2 Epidemiology of CSA

The prevalence of CSA is less than that of OSA. It is common in patients with heart failure – several studies have shown that the prevalence of CSA in this population is in the order of 30–50%. One of the early studies that explored this was carried out by Javaheri and colleagues in 1998.[74] This cross-sectional study included 81 heart failure patients with a reduced ejection fraction and stable disease, who were recruited from primary care and cardiology outpatient clinics over a 4-year period. Presence of SDB was defined as an AHI of ≥ 15 on polysomnography. 51 patients had some form of SDB and 32 of these patients

(40%) had CSA. In patients with SDB, the left ventricular ejection fraction (22±8% versus 27±9%, p<0.05) was significantly lower, and the prevalence of atrial fibrillation (22% versus 5%, p<0.05) and premature ventricular depolarisations (178±272 versus 34±58 per hour, p<0.001) was significantly higher, compared to patients without SDB. However, this study had several limitations. It did not include any female patients. Further, it is difficult to establish whether these patients were on 'optimal therapy' as per current guidelines: 73 patients were reported to be on ACE inhibitors but no data was presented for aldosterone inhibitors or beta-blockers. However, a large prospective study at a tertiary centre in Germany[37] carried out by Oldenburg and colleagues, addressed these limitations. This study included 700 consecutive stable heart failure patients recruited over 2 years with a reduced ejection fraction and a NYHA class ≥ 2, who had not undergone any form of previous screening for SDB. 139 patients (~20%) were female. Most patients in this study were on ACE inhibitors (>90%), beta-blockers (>80%) and spironolactone (>60%). Three quarters of patients had some form of SDB (when the AHI cut-off was >5) and a third had moderate to severe SDB (AHI≥15). 278 of the 700 patients (40%) in the study had CSA, and only 19% had OSA. In the CSA group, there was an increased prevalence of atrial fibrillation (35% compared to 21% in the OSA group). Their left ventricular ejection fraction (27.4±6.6% versus 29.3±2.6%, p<0.05), and both systolic (114.5±20.0 versus 121.0±17.7mmHg, p<0.05) and diastolic blood pressure (72.3±10.6 versus 73.7±9.7mmHg, p<0.05) was also significantly lower compared to the OSA patients. OSA patients on the other hand, had a higher BMI and a higher incidence of diabetes, compared to patients with CSA. Other patient characteristics were similar between both

groups. Both types of SDB had a male predominance, with 87% of patients with CSA being male.

Another study, which only studied patients with mild symptoms of chronic heart failure (i.e. NYHA class II), revealed similar findings. This study conducted by Vazir and colleagues at the Royal Brompton Hospital,[75] involved 55 male patients, who were recruited from a total of 517 patients from cardiology heart failure outpatient clinics between 2002 and 2004. All patients recruited had a left ventricular ejection fraction of <45% (with a mean of 30.6±10.1%) and stable symptoms, with no changes to their medications or hospitalisations prior to polysomnography. The aetiology of heart failure in patients was ischaemic and idiopathic with an equal distribution. 25% of the patients had atrial fibrillation. Most patients were on optimal therapy with 98% being on an ACE inhibitor or an Angiotensin receptor blocker, ~80% on a beta-blocker and ~50% on an aldosterone antagonist. The prevalence of CSA in this study was 38%. Although in patients with and without SDB, characteristics such as the left ventricular ejection fraction, blood pressure and parameters from the cardiopulmonary exercise test were similar, the BNP levels were higher in patients with SDB.

In summary, the results from the Pennsylvania, Wisconsin and Vitoria sleep cohorts highlight that a significant number of people in the community, possibly as much as 3-fold (as symptomatic OSA), do not experience symptoms related to their SDB. Most of the patients with CSA are also asymptomatic and up to a third of patients with heart failure suffer from CSA. Therefore, the burden of SDB in

the population is likely to be far greater than previously thought and reliance cannot be made solely on symptoms to raise the suspicion of SDB.

SDB is associated with other cardiovascular conditions, such as hypertension, stroke, ischaemic heart disease and atrial fibrillation and these associations will be discussed in detail in section 2.3. The prevalence of SDB in each condition[18] is shown in figure 2.4.

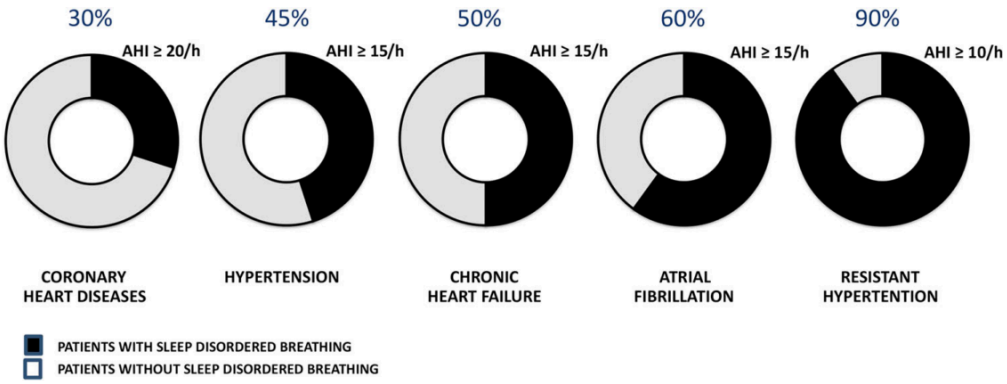


Figure 2.4 Prevalence of SDB in cardiovascular disease

The prevalence of SDB in coronary heart disease, heart failure, atrial fibrillation and hypertension.
(Adapted from Linz et al.[18])

2.2.4 Pathophysiology

SDB is characterised by repetitive cycles of either complete or partial cessation of breathing (i.e. apnoeas and hypopneas) during sleep, leading to a reduction in airflow and ventilation. As a consequence, periods of intermittent hypoxaemia and neurohormonal activation during arousals, will stress the cardiovascular system.[16] This cycle will persist throughout the night. Although, these features are common to both forms of SDB, OSA and CSA have two distinct pathophysiological mechanisms. OSA is manifested by an airflow limitation during sleep secondary to upper airway collapse, therefore, it is closely associated with patients with obesity who are at risk of upper airway obstruction. In OSA, the 'central' drive for respiration and the thoracic effort is still preserved. However in CSA, this central drive for breathing from the respiratory centre is diminished transiently[76] and usually there is no upper airway obstruction (Figure 2.1). Therefore, during a central apnoeic event, on PSG, both the naso-oral airflow and thoracic and abdominal movements will be absent. Heart failure patients with CSA normally display a characteristic cyclical breathing pattern, Cheyne-Stokes respiration.

In both types of SDB the common pathophysiological basis is intermittent hypoxaemia, which occurs due to complete cessation of airflow for at least 10 seconds (i.e. apnoea) or a reduction in airflow by about 50%.[32] This state of oxidative stress, which is associated with sympathetic nervous system activation, vasoconstriction, systemic inflammation and endothelial dysfunction, is potentially detrimental to the cardiovascular system.

2.2.4.1 OSA

The collapse of the upper airway in OSA is caused by the loss of pharyngeal muscle tone during sleep.[77] In normal individuals, the partial withdrawal of pharyngeal dilator muscle tone is insufficient to cause pharyngeal collapse. However in patients with OSA, this is altered as a result of risk factors such as age and obesity. Airway muscle tone gradually reduces with age and increased fat deposition in the neck, which narrows the pharyngeal lumen, further predisposes the airway to collapse.[16] Risk factors leading to upper airway collapse are listed in table 2.5.

Airway obstruction will lead to a reduction in the airflow, and if there is a complete cessation of airflow, an apnoea will occur, typically resulting in hypoxaemia. An apnoea will then terminate with an arousal, which is a transient period of awakening from sleep occurring as a result of the feedback received from chemoreceptors and thoracic stretch receptors.[77] The increased sympathetic outflow during an arousal will increase the pharyngeal muscle tone, restoring airflow and oxygenation. These repetitive cycles of airway obstruction, apnoeas and arousals will continue throughout the night, at a frequency depending on the OSA severity.

- Abnormal anatomy of the UA
  - Skeletal factors
    - Maxillary and/or mandibular hypoplasia or retroposition
    - Hyoid position (inferior displacement)
  - Soft tissue factors
  - Increased volume of soft tissues
    - Adenotonsillar hypertrophy
    - Macroglossia
    - Thickened lateral pharyngeal walls
      - Increased fat deposition
      - Pharyngeal inflammation and/or edema
      - Increased vascular volume
      - Increased muscle volume
- Pharyngeal muscle factors
  - Insufficient reflex activation of UA dilator muscles
  - Impaired strength and endurance of pharyngeal dilators
- Pharyngeal compliance
  - Increased UA collapsibility
- Sensory function
  - Impaired pharyngeal dilator reflexes
  - Impaired mechanoreceptor sensitivity
- Lung volume dependence of UA cross sectional area
  - Increased below functional residual capacity
- Ventilatory control system factors
  - Unstable ventilatory control
  - Increased ventilatory responses and loop gain
- Sex factors
  - Male influences
  - Centripetal pattern of obesity
  - Absence of progesterone
  - Presence of testosterone
- Weight
- Obesity causing peripharyngeal fat accumulation

Table 2.5 Factors predisposing to upper airway collapse

(Adapted from Verbraecken et al.[78]*)*

One of the other distinct pathophysiological consequences in OSA compared to CSA is the change in intrathoracic pressure.[79] The inspiratory effort against a closed airway results in a significant rise in the negative intrathoracic pressure. Although the rise in negative intrathoracic pressure can increase the venous return to the right ventricle, it also increases the left ventricular (LV) transmural pressure. This results in an increase in afterload, which outweighs the increase

in preload, impairs LV filling and leads to a reduction in the stroke volume. This was demonstrated in a small study carried out by Bradley and colleagues in 9 healthy subjects and 9 patients with heart failure.[80] They simulated a negative intrathoracic pressure of up to -30 cmH_2O, by asking the patients to carry out the Mueller manoeuvre. In both groups, the left ventricular transmural pressure during systole increased by almost 10 mmHg. The magnitude of the reduction in stroke volume index (–8.5 ± 1.8 ml/m^2 versus –4.1 ± 2.1 ml/m^2; $p<0.05$) and systolic blood pressure (–25 ± 3mmHg versus –11 ± 2mm Hg; $p<0.05$) was higher in patients with heart failure compared to healthy subjects. Increased LV afterload and wall stress can ultimately contribute to LV hypertrophy.[81]

2.2.4.2 CSA

CSA is characterised by a lack of central respiratory drive from the brain stem due to a temporary failure of the pontomedullary pacemaker and can occur as a result of multiple factors (table 2.5).[82] However, in this section only CSA due to heart failure will be discussed.

- Physiologic CSA
  - Sleep onset
  - Post arousal
  - Phasic REM sleep
- Non-hypercapnic (hypocapnic) CSA
  - **Systolic heart failure**
  - Idiopathic
  - pulmonary hypertension
  - High altitude
  - Post stroke
- Hypercapnic CSA
  - Alveolar hypoventilation with normal pulmonary function
    - Congenital central hypoventilation syndrome
    - Primary chronic alveolar hypoventilation syndrome
  - Brainstem and spinal cord disorders encephalitis; tumours; infarcts; cervical cordotomy; anterior cervical spinal artery syndrome; neurodegenerative disorders; amyotrophic lateral sclerosis; multiple sclerosis; Chiari malformation
  - Muscular disorders; myotonic and Duchenne dystrophies; acid maltase deficiency; Guillain-Barre´ syndrome
  - Opioids
- CSA with endocrine disorders
  - Acromegaly
  - Hypothyroidism
- CSA with OSA
  - A minor component of OSA
  - With CPAP therapy (complex sleep apnoea)
  - Post tracheotomy
- CSA with upper airway disorders

Table 2.6 Causes of central sleep apnoea

There are multiple causes of CSA. CSA occurring in heart failure is only one subtype of the CSA syndrome
(Adapted from Javeheri et al.[82])

CSA is strongly associated with heart failure. The severity of heart failure appears to directly correlate with the severity of CSA. A study conducted by Solin and colleagues,[83] showed that the pulmonary capillary wedge pressure (PCWP) was associated with the severity of CSA (figure 2.5). Of the 75 stable heart failure patients in the study who underwent invasive right heart catheterisation and polysomnography, 33 had CSA. These patients had a significantly higher PCWP (22.8±1.2 mmHg) compared to patients with no SDB (11.5±1.5 mmHg) or OSA (12.3±1.2 mmHg; $p<0.001$). 7 patients who had CSA underwent intensive medical (i.e. diuretic) therapy for ~4 months, and as a result their PCWP was reduced from 29.0±2.6 to 22.0±1.8 mmHg ($p<0.001$), which also resulted in a reduction in the frequency of central apnoea (AHI: from 38.5±7.7 to 18.5±5.3 events/hour; $p<0.01$). This also suggests the importance of optimisation of heart failure therapy in the management of CSA, where improving heart failure appears to also improve CSA. Pulmonary stretch receptors, which are activated due to pulmonary venous congestion, appears to contribute to reflex hyperventilation in CSA.

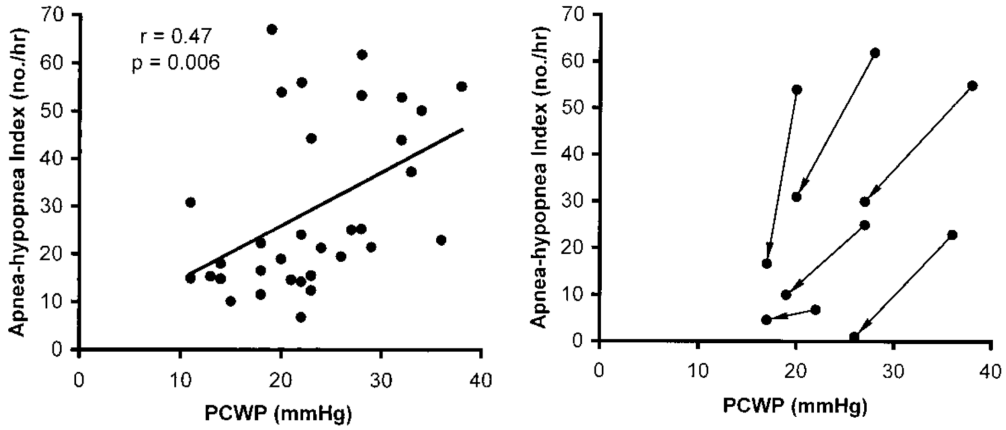


Figure 2.5 Relationship between PCWP and AHI

Pulmonary capillary wedge pressure (PCWP) and AHI correlated strongly (left panel) but once diuresis was commenced, both the AHI and PCWP were reduced (indicated by arrows in right panel). (Adapted from Solin et al.)[83]

In addition to the apnoeic episodes that occur due to the lack of central respiratory drive during sleep,[84] CSA in heart failure is usually characterised by a crescendo-decrescendo ventilatory pattern, a type of periodic breathing termed Cheyne-Stokes respiration.[85] The high ventilatory drive that is associated in heart failure, the increased circulatory time as result of systolic dysfunction and the impaired chemoreceptor sensitivity to $PaCO_2$, are factors that have been shown to promote Cheyne-Stokes respiration.[31]

Changes in $PaCO_2$ play a key role in sustaining this pattern of breathing. In normal breathing, the level of $PaCO_2$ increases as ventilation is reduced with the onset of sleep.[82] However, Naughton and colleagues[86] found that the transcutaneous CO_2 levels in sleep were significantly lower in patients with heart failure with CSA compared to heart failure patients without CSA (33.2 ± 1.2 versus 42.5 ± 1.2 mmHg, $p < 0.0001$), likely due to the high ventilatory drive due to increased chemosensitivity and pulmonary J-receptor stimulation in these patients. Heart failure patients have a higher respiratory drive and they commonly suffer from symptoms such as shortness of breath and paroxysmal nocturnal dyspnoea.

$PaCO_2$ in arterial blood is detected by central and peripheral chemoreceptors, located in the brainstem and carotid bodies, respectively. A rise in $PaCO_2$ leads to an increased respiratory drive, which will drive the $PaCO_2$ below the apnoeic threshold. This will then lead to hypoventilation and an apnoea, which will persist until $PaCO_2$ has risen above the apnoeic threshold.[76] Moreover, in heart failure patients with CSA, the difference between the apnoeic and circulating

$PaCO_2$ is shallow and chemoreceptors elicit an exaggerated ventilator response.[82] Thus, this cycle will continue because chemoreceptors will be activated again with the rising CO_2 levels, which in turn will result in hyperventilation and increased respiratory drive. These cyclical changes are illustrated in figure 2.6.

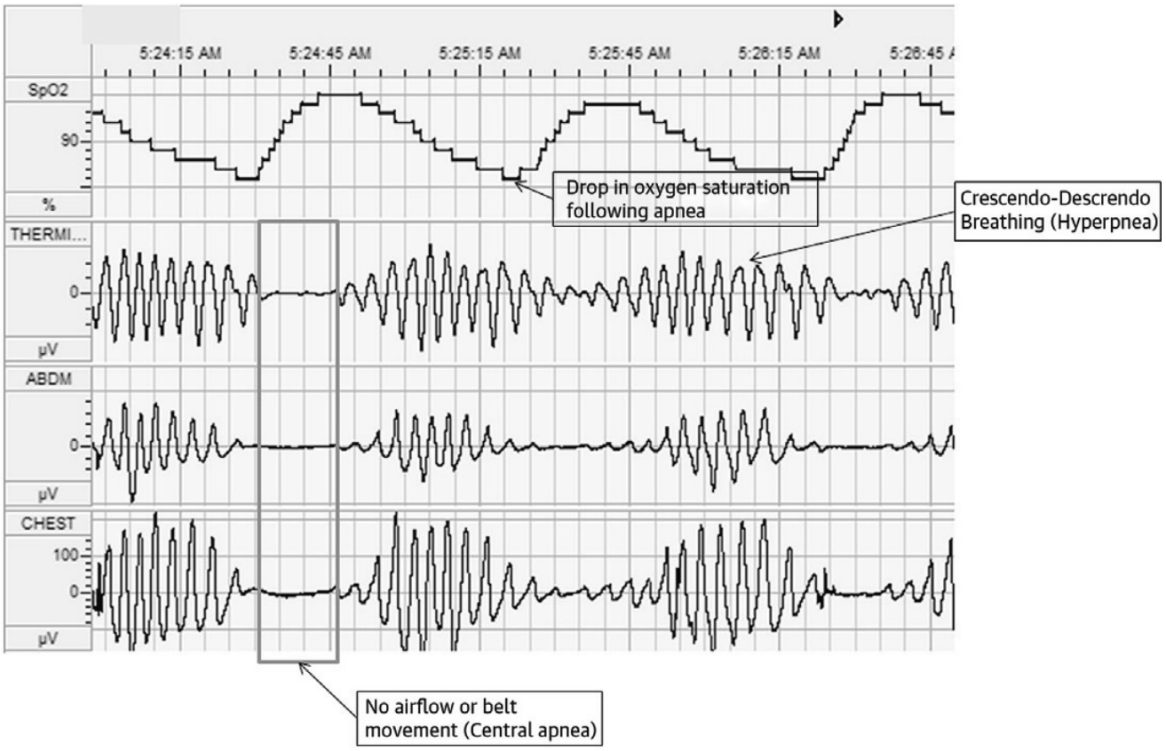


Figure 2.6 Cheyne-Stokes breathing pattern in CSA

This is a 30-second recording from a polysomnogram of a patient with CSA. The thoracic and abdominal effort corresponds with airflow – when there is no abdominal or chest wall movement the airflow is zero and vice versa. The oxygen saturation trace is out of phase (by approximately half a cycle) with chest, abdominal and thoracic gauges, where the peak oxygenation in blood occurs during the apnoea. This is due to the prolonged circulatory time in heart failure. (Adapted from Costanzo et al.)[87]

The low cardiac output state in advanced heart failure have been further suggested to perpetuate periodic breathing. Cardiac output is inversely proportional to the cycle length of periodic breathing and circulatory time, both

of which are elevated in patients with co-existing CSA and heart failure. Hall and colleagues[88] demonstrated this by comparing patients with CSA and heart failure and patients with idiopathic CSA without cardiac failure. In patients with heart failure, CSR cycle length was significantly higher (59.0 ± 4.9s versus 37.3 ± 3.0s; $p<0.005$) compared to patients without heart failure. The circulation time, calculated indirectly as the duration from an end of an apnoea to the time of lowest oxygen saturation (measured at the ear lobe), was also longer in these patients (24.3 ± 2.0 s versus 10.3 ± 1.0 s; $p<0.001$). This circulation time correlated directly with the cycle length ($r = 0.88$; $p<0.001$), hyperpnoea length ($r = 0.9$; $p<0.001$), but inversely with cardiac output ($r = –0.72$, $p<0.01$). This suggests that a low cardiac output will increase the circulatory time, delaying the transport of chemical signals such as the O_2/CO_2 level in blood from the lungs and peripheral tissues to central chemoreceptors, thus the central response to changes in $PaCO_2$ is delayed.

2.2.4.3 Sympathetic activation

Activation of the sympathetic nervous system is an evolutionary protective mechanism, which stimulates the body's fight-and-flight response, to maintain sufficient blood pressure by increasing the cardiac output and peripheral vasoconstriction during periods of stress. Sympathetic nervous system also activates the renin-angiotensin-aldosterone (RAS) system.[89] However, chronic activation is harmful to the cardiovascular system, leading to cardiac remodelling, left ventricular hypertrophy, increased myocardial oxygen demand and ultimately heart failure.[90]

An increase in sympathetic activity in SDB has been suggested because increased levels of plasma and urinary catecholamine were found in patients with OSA.[91] The increased sympathetic activity in SDB is likely due to the activation of chemoreceptor reflexes due to hypercapnia and hypoxaemia, and the excessive sympathetic nerve discharge during repetitive cycles of arousals. Increased sympathetic drive has also been shown to persist even during wakefulness.[92] Somers and colleagues[93] demonstrated this using intraneural recordings to measure muscle sympathetic activity in 10 patients with OSA. The sympathetic activity when awake was significantly higher in patients with OSA (59±14 bursts/min) compared to controls (34±3 bursts/min). An example of one of these traces is shown in figure 2.7. Sympathetic outflow increased even further during sleep, up to 141% in REM sleep and 300% during an apnoeic event. This study also showed the synchronous oscillations of blood pressure with sympathetic nervous activity, where the mean blood pressure increased by ~30 mmHg during sleep. 4 patients who had their OSA treated (with CPAP) had a reduction in their sympathetic activity. A randomised controlled trial (RCT) involving 102 patients,[94] further highlights this link between sympathetic activity and OSA, where treatment (using CPAP for 4 weeks), urinary catecholamine levels, which is a marker of sympathetic activity, decreased by 26%.

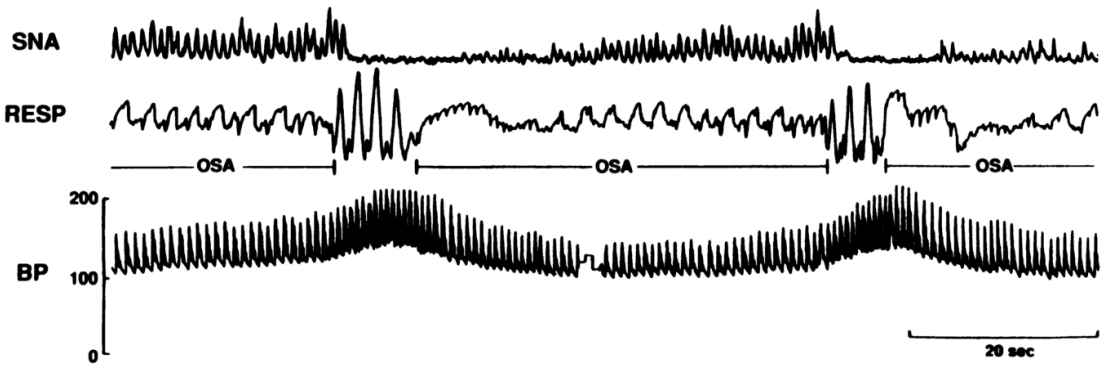


Figure 2.7 Increased sympathetic nervous activity in OSA

Muscle sympathetic nerve activity (SNA), measured as "bursts per minute", is increased during an obstructive apnoeic event (OSA), which is shown by the reduced respiratory effort (RESP). There was a corresponding rise in blood pressure (BP) towards the end of the apnoeic event.
(Adapted from Somers et al).[93]

Heart failure is a clinical syndrome characterised by a low cardiac output. This results in the activation of baroreceptors, and in turn the activation of the renin-angiotensin-aldosterone and sympathetic nervous systems.[89] Therefore, in patients with heart failure there is an elevated sympathetic drive at baseline, which may increase further during apnoeic events. In one study carried out in 60 heart failure patients with an ejection fraction of <45%,[95] the muscle sympathetic nerve activity was higher in patients with SDB compared to the heart failure patients without SDB (76±2 versus 63±4 bursts per 100 heartbeats; $p<0.01$). This was irrespective of the type of SDB (14 patients had predominant CSA). The increased sympathetic outflow may account for the adverse prognosis seen in patients with heart failure and co-existing SDB.

Like in OSA, treatment of CSA has been shown to reduce the sympathetic activity in small studies. A study conducted by Joho and colleagues, using similar intraneural recordings in 20 patients,[96] showed a significant reduction in muscle

sympathetic nerve activity (from 53±14 bursts/min to 41±15 bursts/min; p<0.001) after 3 months of treatment with adaptive servo ventilation (ASV). Heart rate variability parameters, such as the standard deviation of normal R-R intervals measured between consecutive sinus beats (SDNN), is another measure of sympathetic activity.[97] An observational study of 17 patients, using these methods, also showed an improvement in SDNN (71.5±31.1 vs. 80.4±36.1, p<0.01) with ASV therapy.[98]

This evidence suggests that sympathetic tone plays an important role in the pathophysiology of both OSA and CSA. However, it is difficult to establish whether this association between SDB and increased sympathetic activity is causal due to multiple reasons: firstly, there is no clear linear relationship with severity of SDB (i.e. AHI) and sympathetic activity.[93] Secondly, there was a great degree of heterogeneity in patient populations in these small studies. Finally, these studies also had shorter follow up periods, therefore, whether the reduction in sympathetic activity with treatment is clinically significant is debatable, particularly when long-term therapy has not been translated into mortality benefits,[99] and this will be discussed further in section 2.3.6.2.

2.2.4.4 Vascular and Inflammatory changes

The inflammatory process and the vascular changes that occur in SDB are likely to be driven by hypoxaemia and oxidative stress. The repetitive short cycles of desaturation and re-oxygenation can promote the production of reactive oxygen species (ROS). ROS damage the vascular endothelium and increase the expression of cell adhesion molecules promoting adherence of neutrophils and

monocyte. Further, hypoxia can induce angiogenesis via production of growth factors. These changes are the hallmark of atherosclerosis.[100] High levels of ROS in neutrophils,[101] vascular endothelial growth factors and cell adhesion molecules such as ICAM/VCAM[102] have been expressed in patients with OSA.

Endothelium has an important function regulating the blood flow by promoting vasodilation via nitric oxide (NO). Patients with OSA have low levels of plasma nitrite concentrations, suggesting the loss of endothelial-mediated vasodilation. A study carried out by Jelic and colleagues[103] found that in 32 patients with newly diagnosed OSA, when venous endothelial cells were harvested and immunohistochemistry conducted, the levels of endothelial NO was reduced by at least 60%, compared to patients with no OSA. Concurrent sympathetic activity during apnoeic events may further exacerbate this degree of vasoconstriction in SDB.

As atherosclerosis is a state of inflammation, inflammatory markers such as C-reactive protein (CRP) are elevated. Shamsuzzaman and colleagues[104] studied 22 patients with newly diagnosed OSA and free of any other disease. Plasma CRP levels were significantly higher in patients with OSA compared to healthy controls (0.33 versus 0.09 mg/dl, $p<0.001$) and, CRP levels were independently associated with OSA severity. Although, this evidence suggests that OSA may contribute to atherosclerotic plaque and thrombus formation, there is no direct evidence showing that SDB causes atherosclerosis. Further, small studies have shown that CPAP inhibit these changes by reducing ROS, improving endothelial

NOS and inflammation,[102] but these have not been reproduced in large randomised controlled trials.

2.2.5 Treatment modalities

The aim of treatment in SDB is to improve patient symptoms, mainly abolish daytime somnolence and tiredness, establish stable oxygenation and ventilation while also correcting associated pathophysiology where possible. Treatment of SDB can be classified into positive airway pressure treatment and non-positive airway pressure treatment (table 2.7).

Positive airway pressure treatment	Non-positive airway pressure treatment
• Continuous positive airway pressure (CPAP) • Bilevel Positive Airway Pressure (BiPAP)Adaptive servo ventilation (ASV)	• Conservative strategies – patient education and weight loss • Oral devices • Drug treatment • Administration of O_2 or CO_2 • Surgical treatment (upper airway surgery and bariatric sugery)

Table 2.7 Treatment modalities for SDB

A summary of different treatment modalities for SDB, which could be categorised into positive airway pressure (PAP) therapy and non-PAP treatment strategies

2.2.5.1 Positive airway pressure treatment

Positive airway pressure (PAP) has formed the mainstay of treatment of SDB, since the 1980s. CPAP was invented by Colin Sullivan, who first administered it to a patient with severe OSA[105] and demonstrated that obstructive apnoeic events could be terminated with PAP. PAP, essentially acts as a pneumatic splint to keep the airway open, counteracting the forces that promote airway collapse. Constant level of pressure, typically 5-10 cmH_20 but up to 20 cmH_20, is applied throughout the respiratory cycle.

Pressure is delivered via an 'interface', in the form of a mask. A variety of masks are available, such as nasal, oro-nasal or full-face masks. Nasal masks are less claustrophobic and allows speech, however, their major problem is flow leak via the mouth. On the contrary, in oro-nasal masks the leak is small and they offer more stable pressure, but are less well tolerated by patients. Teo and colleagues[106] showed that up to 79% of OSA patients preferred the nasal mask, although there was no difference between the mean pressure required for effective CPAP therapy.

There are different modalities of PAP, mainly continuous positive airway pressure (CPAP) and adaptive servo ventilation (ASV). Bilevel positive airway pressure (BiPAP) therapy (without adaptive pressure support), which is widely used in type II respiratory failure and chronic obstructive pulmonary disease (COPD), where there is CO_2 retention, is not routinely used in the management of OSA and CSA.

2.2.5.1.1 Continuous positive airway pressure

CPAP, in addition to splinting the airway, works by improving the functional residual capacity and cardiac afterload and reducing the work of breathing and oxygen consumption of respiratory muscles.[107] NICE guidelines have indicated CPAP as a treatment option for the management of patients with OSA.[108] CPAP has been shown to be effective in improving symptoms such as daytime sleepiness. One of the key early randomised controlled clinical trials was carried out by Jenkinson and colleagues,[109] who randomised 107 OSA patients and compared therapeutic versus sub therapeutic CPAP (positive pressure of 1

cmH_2O, which was unlikely to have any effect on splinting the airway). They showed that patients who received therapeutic CPAP had lower subjective sleepiness scores and wakefulness, which was objectively measured by a modified maintenance-of-wakefulness test, increased from 22.5 to 32.9 minutes ($p<0.01$).

In addition to reducing daytime symptoms, CPAP also reduces respiratory events at night by reducing or completely obliterating snoring and obstructive events and normalises the AHI. The earliest evidence comes from Berry and colleagues,[110] who administered CPAP in 9 patients, (AHI range from 18 to 29) and had their AHI reduced to 0. CPAP can reduce the AHI by ~60% in patients with severe OSA. This is demonstrated in an observational study by Clark and colleagues in 21 patients with OSA,[111] which reduced the baseline AHI of 33.86±14.30 to 11.15±3.93, after 2 weeks of CPAP treatment with pressures ranging from 4 to 10 cmH_2O. Overnight saturation also increased from 84% to 91%. In current practice, pressure therapy is titrated until the desired level of treatment is achieved. Auto-titrating algorithms have also been incorporated to CPAP machines, which have been shown to be equally effective in achieving this.[112]

Compliance in patients is an important aspect of treatment and achieving sufficient compliance is a significant problem in clinical practice. Adequate compliance has been defined as using CPAP treatment for more than 4 hours per night. Only about 50% of patients are known to adhere to therapy to this level,[113] and compliance has been shown to be similar among different populations.[114,115]

Further, this does not include patients who refuse therapy at the time of diagnosis. In one study involving 903 patients,[116] 255 patients refused therapy from the start. From the rest, only 326 were adherent to therapy after 12 months, thus an overall compliance rate of only 36%. It is likely that a compliance of at least 4 hours is required to have cardiovascular benefits. In a large RCT which studied the incidence of hypertension or cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, transient ischemic attack, hospitalization for unstable angina or arrhythmia, heart failure, or cardiovascular death),[117] in sub-group analysis, the composite event rate was significantly lower in patients who were compliant with CPAP for more than 4 hours per night (incidence ratio of 0.72; 95% CI: 0.52–0.98; P<0.05). The effect of CPAP will be explored further in relation to cardiovascular disease in section 2.3.

2.2.5.1.2 Adaptive servo ventilation

Compared to CPAP that delivers a constant level of pressure during the respiratory cycle, ASV like other bilevel devices applies two levels of pressure. ASV is the intended treatment for CSA. The ASV algorithms have the capacity to overcome the 'overshooting' and 'undershooting' of ventilation that occur in Cheyne-Stokes respiration, by delivering a higher inspiratory pressure during period of hypoventilation. In contrast, during hyperventilation, the difference between inspiratory and expiratory pressure is reduced.[118] In addition, ASV devices maintain the expiratory pressure to overcome obstructive events and apply mandatory breaths during central apnoeas. This is illustrated in figure 2.8.

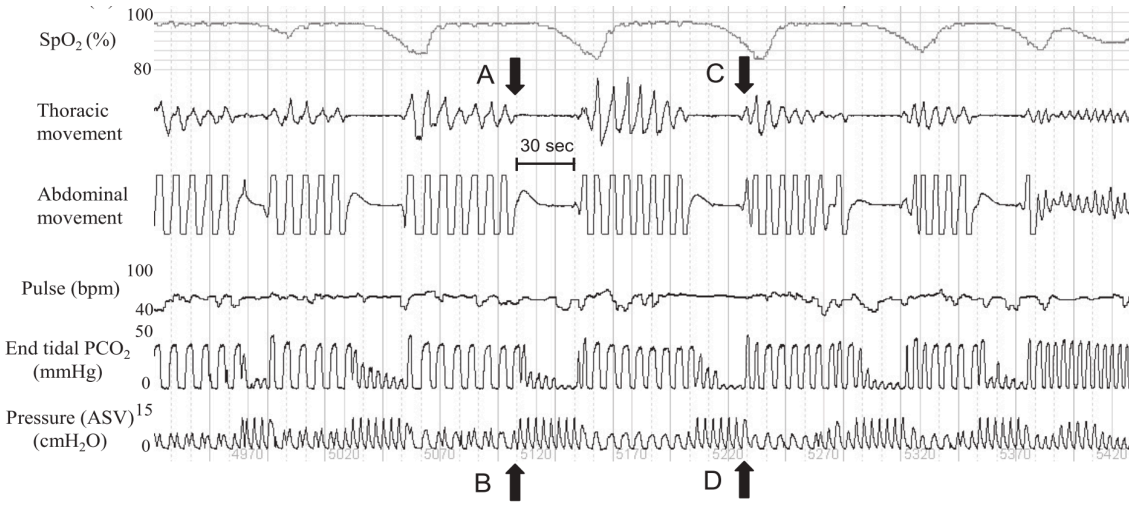


Figure 2.8 Adaptive pressure support in CSA

During apnoeas (black arrow A), the ventilator increases adaptive pressure support (black arrow B), and when breathing resumes (black arrow C) pressure output is decreased (black arrow D).
(Reproduced from Banno et.al [118])

Small clinical trials show that ASV therapy is superior to CPAP in the treatment of CSA. ASV therapy was first used as a novel mode of treatment for CSR in 2001 by Teschler and colleagues.[119] This was a small observation study with 14 stable heart patients (NHYA class III) with predominant CSA, comparing 3 modes of treatment (Oxygen, CPAP and BiPAP) against ASV. Each treatment was given to patients in random order, on 4 consecutive nights. ASV reduced central events, from a baseline value of 35.8±2.9/h to 3.3±0.5/h, much more effectively than oxygen (19.7±2.7/h) or CPAP (18.5±3.2). Similar findings have been repeated in other trials. In addition to improving the AHI, ASV has been shown to improve cardiac function and sympathetic activity. Kasai and colleagues[120] conducted a small prospective RCT, comparing ASV and CPAP, in 23 patients with systolic heart failure with an average ejection fraction of ~32%. In the ASV group, the ejection fraction improved by 6% over a follow up period of 3 months. BNP

levels were also reduced in this group. No changes in BNP or ejection fraction were seen in the CPAP group. Remarkably however, these physiological changes have not been translated to improvement in mortality. ASV was found not to be effective in improving mortality in the SERVE-HF trial[99] and this is discussed in section 2.3.6.

2.2.5.2 Other forms of treatment and management options

2.2.5.2.1 Patient education and weight loss

Patient education forms an integral part of SDB management. Most patients do not perceive symptoms associated with SDB, such as snoring and daytime sleepiness as important, and are unaware of the potential cardiovascular risk. Therefore, patients should be informed about the importance of SDB, potential treatment benefits and the avoidance of hypnotics such as alcohol and sedatives, which increase the likelihood of SDB.[32]

Obesity is the most important risk factor in OSA and ~60% of patients with OSA are obese.[121] In an epidemiological study, weight loss has been shown to reduce the AHI: each 10% decline in weight resulted in a 26% reduction in the AHI.[122] However, achieving weight loss in patients is challenging, as only 10-20% of patients lose and maintain a stable weight.[123] Therefore, weight loss, should only be offered as the primary treatment to patients with mild to moderate SDB.

As a management strategy, weight loss, could be challenging in patients with heart failure due to their poor exercise tolerance. Although, CSA and systolic heart failure is not typically associated with obesity, weight loss is still generally

considered important in patients with heart failure,[124] especially in heart failure with preserved ejection fraction. No study however has demonstrated the benefits of weight reduction on SDB in this population.

2.2.5.2.2 Mandibular advancement devices

The aim of mandibular advancement devices (MADs) is to widen the upper airway in patients with OSA, which reduces pharyngeal collapsibility due to the lateral movement of fat pads and anterior movement of basal tongue muscles. These can also reduce snoring. MADs are advocated for mild to moderate SDB and/or for patients who cannot tolerate positive airway pressures therapy.[125,126] A variety of MADs are available and their success is variable, potentially because of poor tolerability and dependence on good oral health. The compliance for these devices at 1-year is approximately 75%.[127]

Quinnell and colleagues[128] carried out a crossover trial comparing MADs against no treatment in 90 patients. It showed that MADs were effective in reducing the AHI by 26-36% with similar reductions in the oxygen desaturation index. However, the effectiveness of CPAP, compared to MADs is far superior. A Cochrane review carried out by Lim and colleagues,[129] showed that the pooled difference in the AHI between MADs and CPAP was ~8 events per hour (95% CI: 6.4–9.6/h), favouring CPAP.

2.2.5.2.3 Surgical treatment

The surgical treatment is mainly aimed for patients with OSA for two reasons. First is to correct any anatomical abnormalities in the upper airway that cause upper airway obstruction. Second is for bariatric surgery in patients with severe

obesity, who concurrently suffer from SDB. Common upper airway surgical approaches are nasal septoplasty in patients with nasal obstructions, uvulopharyngopalatoplasty (excision of the tonsils, posterior soft palate and uvula), adenoidectomy for adenoid hypertrophy, and maxillo-mandibular advancement (a multilevel invasive form of surgery that involves enlarging the oropharygeal airway). These surgical techniques can be effective as evidenced by a recent systematic review,[130] but most of the studies included in this were observational studies with marked heterogeneity. Further, their outcomes measures were compared to oral appliances rather than CPAP.

Bariatric surgery is an effective strategy for achieving weight loss but it is currently only indicated within the NHS for patient with an extremely high BMI (e.g. >40 or >35 with comorbidities) according to NICE guidance.[131] Large registry data suggest that it improves long-term cardiovascular outcome.[132] Although bariatric surgery is not directly indicated for the management of OSA, patients who have undergone this type of surgery have shown marked improvements in SDB, in some cases curing OSA.[127] Postoperatively the AHI has been shown to reduce by ~40 events per hour.[133]

Surgical management strategies should only be considered once other options have been exhausted. Also, they may not be appropriate in patients with cardiovascular disease, due to multiple cormobidities and increased anaesthetic risk, as the risk of surgery could be far greater than the benefits of improving SDB.

2.2.5.2.4 Pharmacological treatment

Tricyclic antidepressants such as Protriptyline, selective serotonin re-uptake inhibitors such as Paroxetine, Serotonin agonists such as Mirtazipine have been used in small studies for the treatment of OSA.[32] The pharmacological effects are likely to be mediated via serotonin by improving sleep quality, respiratory drive and upper airway muscle tone. In CSA, acetazolamide, which is a carbonic anhydrase inhibitor that promotes acidosis and theophylline, which is a phosphodiesterase inhibitor, are respiratory stimulants which has been shown to increase the respiratory drive. Javaheri and colleagues in 2006[134] showed that acetazolamide, in 12 patients with systolic heart failure patients, reduced the central apnoeic events by almost 20 events per hour compared to baseline. However, using pharmacological agents, in patients with cardiovascular disease could be harmful, as they may increase the risk of arrhythmias due to effects such as QTc prolongation,[135] and they are therefore, not recommended as routine treatment for SDB.

2.2.5.2.5 Administration of O_2 or CO_2

O_2 is administered with the aim of normalising oxygen saturation. This is a treatment option that has been attempted in CSA patients and has been shown to reduce central events. A small double-blind placebo-controlled crossover study involving 11 patients with systolic heart failure, conducted by Staniforth and colleagues,[136] showed that from baseline, compared to administration of air (i.e. placebo), administration of Oxygen at 2 l/min for 4 weeks, significantly reduced the frequency of central events (3.8±2.1 versus 18.4±4.1 events per hour; p=0.05) and the proportion of the time spent in Cheyne-Stokes respiration

(10.7±3.9% versus 33.6±7.4 %; $p<0.05$). In another study, in addition to administering oxygen, carbon dioxide was administered, with aim of obliterating Cheyne-Stokes respiration by raising the arterial carbon dioxide levels above the apnoeic threshold.[137] Carbon dioxide was given mixed with oxygen via nasal prongs, with its concentration altered according to the transcutaneous carbon dioxide tension measured by a sensor that was placed on the anterior chest, and the flow increased when Cheyne-Stokes respiration was present. Air (as placebo) was administered on the 2nd night. The duration of Cheyne-Stokes respiration, expressed as a percentage of total sleep time, decreased markedly from 48% to 7.4%. Despite this improvement, sleep quality in patients did not improve and plasma noradrenaline levels, a surrogate marker of the sympathetic activity, was worse with treatment, which is therefore not recommended.

Although some studies have shown oxygen therapy can be as effective as CPAP therapy, apart from reducing the frequency of central events, no direct cardiovascular benefits such as improvements in the cardiac function have been observed. Most of these studies with O_2 therapy had short follow up periods (e.g. 4 weeks) and have only recruited ~10-20 patients. Therefore, O2 therapy is not routinely recommended for treatment of SDB, as its long-term benefits are not yet known.

2.3 Association with cardiovascular disease morbidity and mortality

The repetitive oxidative stress and neurohormonal activation that occurs in SDB have been shown in small experimental studies to be detrimental to the cardiovascular system, but whether they translate into clinically significant patient outcome is controversial. CSA is closely associated with heart failure and it is likely to occur as a consequence, rather than causing heart failure. Having CSA is likely to reflect the severity of the disease process and these patients are known to have a poor prognosis.[138,139] OSA, in contrast, appears within the spectrum of metabolic syndrome and has been considered as an independent risk factor for cardiovascular disease.[140] It is also associated with hypertension, stroke, ischaemic heart disease and cardiac arrhythmia.

A recent meta-analysis[10] of 6 studies with a total of 11932 patients, showed that moderate to severe OSA is associated with an increase in all-cause mortality with a hazard ratio of 1.67 (95% CI: 1.25-2.23) and cardiovascular mortality with a hazard ratio of 2.21 (95% CI: 1.61-3.04). This association appeared to be greater with the increasing severity of OSA. One such study,[141] which was included in this meta-analysis, was an eighteen-year follow-up of 1522 subjects from the Wisconsin Sleep Cohort. It studied cardiovascular and all-cause mortality against the severity of SDB. Cardiovascular mortality accounted for 26% of all deaths in subjects without SDB and 39% of all deaths in moderate to severe SDB. A statistically significant mortality risk was only found in patients with severe OSA, with an AHI ≥30. After adjusting for variables such as age, gender and BMI, the hazard ratio for all-cause mortality was 3.0 (95% CI: 1.4-6.3). However, this association was slightly weaker (2.7; 95% CI: 1.3-5.7) after adjustments were

made for hypertension, diabetes, stroke and coronary artery disease. There was no significant association between the severity of SDB and cardiovascular mortality.

Marin and colleagues also conducted a similar prospective study[142] with 1651 patients and a mean follow-up of 10 years. Men who presented to a Spanish sleep clinic between 1992 and 1994 were recruited and divided into several groups: patients treated with CPAP (372 patients), who were untreated (a total of 638 patients where 235 had severe OSA with an AHI ≥30) and simple snorers (377 patients). 264 healthy men without SDB, who had polysomnography as part of another study, were used as matched-controls. The characteristics of the groups were similar, but patients with severe OSA and CPAP-treated group had a higher BMI and increased prevalence of hypertension. After adjusting for potential confounders, untreated severe OSA was significantly associated with an increased risk of cardiovascular death (odds ratio of 2.87, 95% CI: 1.17–7.51) and non-fatal cardiovascular events (odds ratio of 3.17, 95% CI: 1.12–7.51) compared to healthy participants. Patients with severe OSA who were treated with CPAP, had a similar outcome to healthy men, which suggests some potential for risk reduction with therapy.

The Sleep Heart Health Study (SHHS) is a large cohort study,[143] which was specifically designed to study the association between OSA with cardiovascular disease. It began in 1995 and has recruited nearly 6400 subjects (60%) as part of other cardiovascular cohort studies, which also included the Framingham study. Each subject in the study underwent home polysomnography to evaluate for

SDB. In a sub-study stemming from the SHHS,[144] patients with severe SDB (AHI ≥30) had a significantly higher all-cause mortality with a hazard ratio of 1.46 (95% CI: 1.14–1.86), even after adjustments were made for potential confounders such as hypertension, diabetes, and cardiovascular disease and increased BMI, neck circumference and waist size. This association was largely driven by men who were under the age of 70 with severe OSA (hazard ratio of 2.09; 95% CI: 1.31–3.33). In women however, the link between mortality and SDB was weak and not statistically significant in all groups.

It is important to emphasise these studies are observational studies, and have limitations. Although they have suggested that SDB may increase cardiovascular and all-cause mortality, it cannot be concluded that this association is causal. Multiple cofounders are likely to be influencing these results, because after correction for factors such as BMI, age, blood pressure, diabetes and stroke in multivariate models, this associated was found to be much weaker. However, it is likely that men with severe SDB are the ones with highest risk of mortality, a finding that has been consistent across all of these large observational studies. Further, as to what mechanisms drive these deaths and most importantly, whether treatment of SDB can reduce cardiovascular events remains to be unanswered. The data available so far have been inconclusive.

Thus far, several large RCTs have been conducted looking at cardiovascular outcomes in OSA.[117] One such RCT was a Spanish study conducted by Barbe and colleagues, which included 725 asymptomatic OSA patients, who were randomised to either CPAP therapy or no active intervention. It showed that

there was no difference in the composite endpoint, which included the incidence of hypertension and cardiovascular events such as nonfatal myocardial infarction, stroke, transient ischemic attack, hospitalization for unstable angina or arrhythmia, heart failure or cardiovascular death. There were a total 28 of cardiovascular events in the CPAP group and 31 in the control group (the incidence density ratio was 0.83; 95% CI: 0.63-1.1; p= 0.2). However, in patients who were compliant with CPAP (more than 4hrs per night) had a lower incidence compared to controls (incident ratio of 0.72; 95% CI: 0.52-0.98, $p<0.05$).

The Sleep Apnea Cardiovascular Endpoints (SAVE) study,[145] was a much larger international multi-centre RCT, with the primary composite endpoint being death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for unstable angina, heart failure, or transient ischemic attack. A total of 15,325 patients were initially assessed for eligibility, 5844 underwent a screening home sleep study (ApneaLink, ResMed) and 3246 entered a 1-week run-in phase with sham CPAP. After exclusion (of patients who had poor compliance or could not attend clinic or who had CSA-CSR) 2717 patients were randomised to either CPAP group (CPAP treatment plus usual care) or usual-care group (usual care alone/control group). These patients were between 45 and 75 years of age, having moderate to severe OSA (defined as an ODI of at least 12 determined by ApneaLink, ResMed) and co-existing CVD (either coronary or cerebrovascular disease). They were matched for characteristics such as age, sex, BMI, measures of severity of OSA (i.e. AHI and ESS scores) and the proportion of cardiovascular disease and risk factors such as hypertension. After a mean

follow-up of 3.7 years there was no difference in the primary end-point – the events rates were 17% and 15.4% in the CPAP and control groups, respectively (HR with CPAP: 1.10; 95% CI: 0.91– 1.32; p=0.34). This was despite CPAP therapy effectively suppressing OSA (residual AHI measured from the CPAP machine decreased from 29 events/h at baseline to 3.7 events/hr at follow-up; no p-value available), patients achieving a good compliance (mean adherence during follow-up, 3.3±2.3 hours) and a reduction in symptoms of daytime sleepiness (measured by the adjusted change in ESS score: -2.5; CI: -2.8 to -2.2; p<0.001) with an improved health-related quality of life measured by SF-36 and EQ-5D questionnaires. Further there was no influence on the systolic and diastolic blood pressure with treatment. These RCTs suggest that, CPAP therapy, although has been shown to be improve symptoms and cardiovascular indices (e.g. blood pressure, cardiac function and sympathetic activity) in small studies, it does not appear to translate to mortality benefit or reduction in 'harder' CV endpoints.

2.3.1 Metabolic syndrome

OSA is associated with the spectrum of diseases, which encompasses the metabolic syndrome. Metabolic syndrome (or "Syndrome x") is diagnosed in the presence of three of the following conditions; insulin resistance often leading to type II diabetes, hypertension, dyslipidaemia (either high triglycerides or low LDL) or obesity. It increases the cardiovascular risk disease by at least 74%.[146] Approximately 50 to 60% of patients with metabolic syndrome suffer from OSA and this combination has been named "Syndrome Z".[147] The prevalence of OSA is highly influenced by obesity, as it predisposes the individual to upper airway

narrowing and collapse due to fat deposition and also a reduces lung volumes due to the increased abdominal girth.

OSA can potentially worsen metabolic syndrome. This evidence comes from animal models, where OSA has been suggested to exacerbate hypoxia in adipose tissue leading to inflammation, adipocyte death, inhibition of adipogenesis and consequently increase circulating free fatty acids.[148] The same mechanism has been postulated for the development of insulin resistance due to pancreatic beta-cell dysfunction and development of fatty liver disease.

There are only limited data showing the direct link between OSA and metabolic dysregulation in humans. Polotsky and colleagues[149] conducted a small study whether nocturnal hypoxia in OSA predicted the severity of non-alcoholic steatohepatitis in patients presenting for bariatric surgery. 20 of the 90 patients who took part in the study had liver biopsies during bariatric surgery. They found that histologically, using semi-quantitative measures (such as ballooning of hepatocytes and pericellular fibrosis), hepatic inflammation was higher in patients with moderate to severe OSA who had an AHI of >15. In addition, one randomised cross-over study,[150] where 38 patients were randomised to CPAP or sham therapy, studied the effects of CPAP on postprandial lipid levels. CPAP reduced the mean triglyceride levels by 357 mmol/l(95% CI: 687.3 to 26.8; $p<0.05$). However, there were several limitations in this study: at the cross-over stage at 8 weeks, the number of subjects in the study had dropped to 29 and further, it is not clear whether subjects in each group were matched according to their characteristics.

The significance of metabolic syndrome is also relevant in cardiovascular remodelling, as hypertension and metabolic abnormalities can lead to arterial stiffness, increased after load and result in left ventricular hypertrophy.[151] These pathophysiological mechanisms can potentially lead to diastolic dysfunction and new phenotypic variants such as heart failure with preserved ejection fraction (HFPEF). Although currently CSA is not recognised as part of the metabolic syndrome, this is likely to change with more awareness of HFPEF.[124]

2.3.2 Hypertension

Up to 30% of hypertensive patients suffer from OSA and almost half of patients with OSA are hypertensive.[140] It is also recognised as an important cause of drug-resistant hypertension, where up to 64% of these patients have OSA.[152] Pathophysiological mechanisms such as repetitive cycles of hypoxia, sympathetic activation and vasoconstriction in SDB, are likely to interfere with the physiological nocturnal drop in blood pressure.

Population based studies have identified OSA as an independent risk factor for developing hypertension. Data from the Wisconsin sleep cohort,[153] in which 709 patients were followed up for 4-years (184 were followed-up for 8 years), indicated a dose-response relationship between the severity of OSA and the incidence of hypertension. It is important to note at the start of the study, patients with severe OSA had a higher baseline systolic and diastolic blood pressure compared to patients with mild OSA and almost 96% of patients had a blood pressure of >140/90. However, even after correcting for this baseline

blood pressure and other confounders such as age, sex, BMI, waist/neck circumference and alcohol/smoking use, a statistically significant relationship was observed. The risk of hypertension increased with the severity of OSA, where the odds ratios were 1.42 (95% CI: 1.13–1.78), 2.03 (1.29–3.17) and 2.89 (1.46–5.64) for AHI of <5, 5–14.9 & ≥15 events/h, respectively. Data from other population studies such as the SHHS[154] and Vitoria sleep cohort[155] do not provide such a strong association. In the SHHS, 2470 participants who did not have hypertension, nor who were taking anti-hypertensive medication at baseline, were followed-up for 5 years. The strength of the association between AHI and incident hypertension diminished once adjusted for BMI. This relationship was modest even in severe SDB (AHI ≥30) with an odds ratio of 1.51 (95% CI: 0.93–2.47). Similarly, in the Vitoria sleep cohort, which consisted of 1180 non-hypertensive subjects who were followed up for 7.5 years, after accounting for age, sex, BMI and neck circumference, there was no dose-response relationship between AHI and incidence of hypertension. This suggests that the association between OSA and hypertension may not be strong as previously thought.

Treatment of OSA with CPAP is likely to reduce the systolic and diastolic blood pressure by about 2-3 mmHg.[140] This effect is greater in patients with higher baseline blood pressure and who are compliant with therapy. This has been confirmed by large multicentre RCTs. In one such trial in 2010,[156] Barbe and colleagues randomised 359 patients to either CPAP or conventional treatment and followed-up for 1 year. Approximately 45% of patients in each arm were already on pharmacological antihypertensive treatment. The groups were well-

matched for their characteristics including the antihypertensive drug class. After 12 months, in the CPAP group, the systolic blood pressure had reduced by 1.89 mmHg (95% CI: -3.90, 0.11 mmHg; p=0.065) and diastolic blood pressure by 2.19 mmHg (95% CI: -3.46, -0.93 mmHg; p<0.001). In subgroup analysis, patients who had higher degree of compliance with CPAP therapy (>5.6 hours) had a statistically significant reduction in both systolic (by 3.73 mmHg; 95% CI: -7.02, -0.45) and diastolic blood pressure (by 3.51 mmHg; 95% CI: -5.57, -1.46; p<0.01). The RCT conducted by Martínez-García and colleagues[157] in 194 patients with resistant hypertension showed similar degrees of reduction. These patients had a good compliance with their medication (at least 80%) and all other causes of resistant hypertension such as renal artery stenosis or primary aldosteronism had been excluded. Blood pressure was evaluated by 24-hour ambulatory blood pressure measurements (ABPM), which was carried out at the start and at the end of the study at 3 months. CPAP group achieved a statistically significant decrease in the mean blood pressure by 3.1mmHg (95%CI: 0.6 to 5.6, p<0.05) and diastolic blood pressure by 3.2mmHg (95%CI: 1.0to 5.4, p<0.01), but not in systolic blood pressure (3.1mmHg, p= 0.10).

In an observational study carried out by Marin and colleagues,[158] CPAP was shown to reduce the incidence of hypertension. This study included 1889 patients without hypertension, who were followed-up for ~12 years and was sub-divided into controls (310 patients without OSA), ones on CPAP therapy (824 patients) and ones with OSA but who were not on CPAP (which included 195 patients who declined therapy and 462 patients who were ineligible for therapy). The hazard ratio for incident hypertension was found to be lower in

patients with OSA who were treated with CPAP therapy (0.71; 95% CI, 0.53-0.94) compared to controls. Hypertension was greater among the groups of patients with OSA who were ineligible for CPAP therapy 1.33 (95% CI; 1.01-1.75), those who declined CPAP therapy 1.96 (95% CI: 1.44-2.66) and those who were non-adherent to CPAP therapy 1.78 (95%CI: 1.23-2.58).

The magnitude of blood pressure reductions achieved by CPAP compared to pharmacological agents in combination is modest at least.[6] Further, these studies had shorter follow-up periods than that of RCTs of drug therapy. Therefore, whether these small changes will lead to clinically significant mortality and morbidity benefits over long period is as yet unproven.

2.3.3 Stroke

The central nervous system, mainly the brainstem, plays an important part in the regulation of breathing. Therefore, any vascular damage could potentially contribute to SDB, and CSA has been observed in the setting of a brainstem stroke.[82] A study conducted by Parra and colleagues, however,[159] showed that there was no difference in the number of central or obstructive events according the location of the lesion. This study prospectively studied 161 consecutive patients with new onset stroke or TIA events. 122 patients had a stroke (112 ischaemic) and in 97 of them the parenchymatous location of the vascular damage was established with MRI and CT. 13 had brainstem strokes, 3 cerebellar strokes and there were 81 hemispheric strokes in which the location was further divided into specific areas of the brain (such as frontal, parietal, temporal, occipital, internal capsule, base ganglia). However, none of the categories

showed a significant difference between central or obstructive events. Patients with hemispheric strokes had 6.9 ± 10.5 central events/hr compared to 6.6 ±11.2 events/hr for brain stem strokes and a third of patients in each group had Cheyne-Stokes respiration pattern. It is likely that the type of stroke plays a more important role than the location: haemorrhagic strokes (11.1 ± 15.1 central events/hr) had a higher rate of central events than ischaemic strokes (5.9 ± 10.1 events/hr), however this was not statistically significant. These central events however, reduced significantly after 3 months.

OSA has been recognised as an independent risk factor for incidence of stroke. A meta-analysis of 5 cohort studies,[160] which included a total of 8435 patients, found that OSA increases the risk of stroke significantly with an odds ratio of 2.24 (95% CI: 1.57,3.19), and a 10-unit increase in the AHI increased the relative risk of stroke by 36%. The SHHS study[161] is the largest cohort study that has investigated the incidence of stroke in patients with OSA. In this study, 5422 subjects who were stroke free at baseline were followed-up for a period of 8 years. After adjusting for confounders such as age, BMI, blood pressure and diabetes, men with an AHI>19 (i.e. the upper quartile) had a hazard ratio of 2.86 (95% CI: 1.10–7.39) of developing stroke. There was no statistical significance in the relationship between OSA and stroke in women.

It is important to highlight that these observational data did not adjust for atrial fibrillation, which is an important risk factor for stroke. In these studies, the rate of atrial fibrillation in patients with stroke was significantly higher compared to ones who were stroke-free. However, in the SHHS, after excluding these patients

the association remained statistically significant (for the same group of men above the hazard ratio was 2.70; 95% CI: 1.04–7.05), although residual confounding cannot be excluded.

The effect of CPAP on patient outcome in secondary prevention of stroke is unclear. A small study conducted by Parra and colleagues,[162] which included 140 patients having an AHI ≥20 and suffered their first ever episode of an acute stroke, who were randomised to either CPAP or standard treatment for 2 years, found that CPAP treatment did not improve survival. The event-free survival was 88% in both groups. The disability measures, however, after stroke (measured by the Rankin and Canadian scale) improved significantly in the CPAP group. There are no randomised data investigating the primary prevention of stroke with CPAP, however, in the subgroup analysis of the SAVE study,[145] in patients who were compliant with CPAP therapy (≥4 hours per night) had a lower risk of stroke (hazard ratio, 0.56; 95% CI, 0.32 to 1.00; p=0.05) compared to controls.

2.3.4 Cardiac arrhythmia

Cardiac arrhythmia associated with SDB can be classified into atrial and ventricular arrhythmia. Atrial fibrillation is the most significant atrial arrhythmia in SDB. Sudden cardiac death, related to ventricular tachycardia or ventricular fibrillation, has also been shown to be associated with SDB. A cross-sectional study[163] conducted in a subgroup of patients from the SHHS, who underwent simultaneous polysomnography and ECG recording, showed that the prevalence of both ventricular and atrial tachyarrhythmia were higher in the 228 patients with AHI ≥30, compared to the matched 338 subjects without SDB (AHI<5). The

prevalence of atrial fibrillation was 4.8% in the SDB group and 0.9% in the group without SDB. The odds ratio for incident atrial fibrillation and non-sustained ventricular tachycardia (NSVT), after adjusting for variables such as age, sex, body mass index, and coronary heart disease, was 4.02 (95% CI: 1.03–15.74) and 3.40 (95% CI: 1.03–11.20), respectively. However, in this study ECG data were only acquired during a single sleep study, it is likely for the prevalence of tachyarrhythmia, such as paroxysmal AF, to have been underestimated.

2.3.4.1 Atrial Fibrillation

Atrial fibrillation is characterised by fibrillatory atrial activity, which leads to an irregular ventricular response. The most important consequence of atrial fibrillation is the increase in stroke risk, which could be up to 14%.[164] Atrial fibrillation is the commonest arrhythmia in the population with a prevalence of about 1-2%, but in SDB this is ~3 to 4 times of the general population.[163,165] In patients with heart failure and co-existing SDB, this prevalence increases even further, up to 22% in OSA and 36% in CSA.[37]

OSA is common in patients with atrial fibrillation and could be present in ~30-50% of patients and can be an independent risk factor for developing atrial fibrillation. In a small study conducted by Porthan and colleagues,[166] in 59 patients with lone atrial fibrillation who underwent polysomnography, 32% of patients had clinically significant SDB (AHI≥15). Lone atrial fibrillation was defined as atrial fibrillation occurring without a known precipitant such as hypertension, ischemic heart disease, valvular heart disease, hyperthyroidism or any acute cause such as alcohol abuse. Further, in a large retrospective cohort

study conducted by Gami and colleagues,[167] which followed-up 3542 subjects who have had diagnostic polysomnography and were free of atrial fibrillation at baseline, after 4.7 years, the incidence of atrial fibrillation was found to higher in patients with OSA. OSA (defined as AHI ≥ 5) was a strong predictor for developing atrial fibrillation with a hazard ratio of 2.18 (95% CI: 1.34–3.54, $p<0.01$). A 10-unit increase in the AHI was associated with hazard ratio of 1.31 of developing AF (95% CI: 1.14–1.50, $p<0.001$).

A meta-analysis of 6 studies, which included a total of 3995 patients, also found that in patients with OSA, recurrence of atrial fibrillation was increased by 25% following catheter ablation[168] compared to patients without OSA. Catheter ablation is a technique that is used to restore sinus rhythm, usually by delivering radio frequency energy. The success of this procedure is variable, but is better for paroxysmal atrial fibrillation compared to non-paroxysmal (persistent) atrial fibrillation (success rate of 54% versus 42%) and with multiple procedures, the long-term success rate can be improved up to 80%.[169] The largest study[170] in this meta-analysis, which included 3000 patients, had 78% success in the non-OSA group compared with 73% in the OSA group ($p<0.05$). However, there was marked heterogeneity between the groups. OSA group had a higher proportion of non-paroxysmal (i.e. persistent) atrial fibrillation.

Non-randomised studies have shown that treatment of OSA with CPAP reduces the risk of atrial fibrillation recurrence. Fein and colleagues[171] studied 62 patients having OSA, out of 426 patients who underwent catheter ablation (with pulmonary vein isolation; PVI) between 2007 and 2010 at the Beth Israel

medical centre. 32 of these patients were on CPAP therapy. Two control groups were included in the study: one with 30 patients who underwent PVI but had no OSA and one which included 22 patients with atrial fibrillation and OSA who were on CPAP. These groups were well-matched according patient characteristics, such as left atrial size, LV function, hypertension and type of atrial fibrillation. Atrial fibrillation patients without OSA who underwent PVI had the highest atrial fibrillation-free survival after 12 months and the survival curves are shown in figure 2.9. CPAP appeared to have a protective effect on atrial fibrillation recurrence: patients who had OSA but treated with CPAP and underwent PVI had a similar survival to patients without OSA and undergoing PVI. This protective effect was lost in similar patients who did not have CPAP (where only 37% of patients with PVI/OSA/no-CPAP group were free of atrial fibrillation compared to 71.9% of patients in the PVI/OSA/CPAP group: $p<0.05$). Having OSA increased the risk of atrial fibrillation recurrence by 2-fold (hazard ratio of 2.15; 95% CI: 1.10 to 5.44; $p<0.05$) and CPAP reduced this risk by half (hazard ratio of 0.48; 95% CI: 0.22–0.91; $p<0.05$).

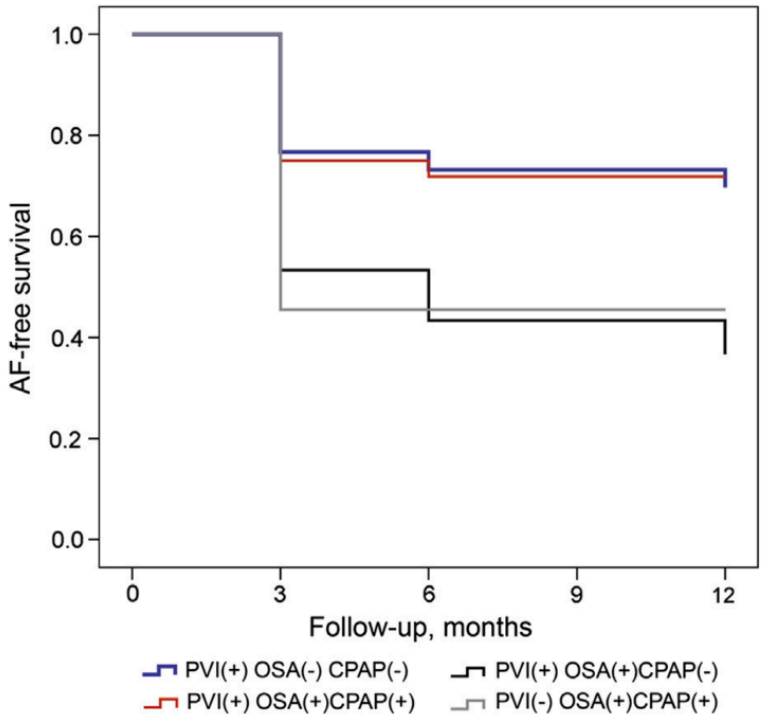


Figure 2.9 Effect of radiofrequency ablation and CPAP therapy in patients with OSA and Atrial Fibrillation

The highest AF-free survival was found in patients who underwent PVI for atrial fibrillation (AF), but this was only demonstrated in patients either without OSA or ones who had OSA but had treatment (blue and red lines). Having OSA without CPAP treatment appeared to reverse the protective effect of PVI (black line) (Adapted from Fein et al.[171]*)*

2.3.4.2 Ventricular tachyarrhythmia

SDB is an independent risk factor sudden cardiac death (SCD). In a longitudinal study conducted by Gami and colleagues,[172] 10701 patients who had polysomnography between 1987 and 2003 at the Mayo Clinic Sleep Disorders centre were observed for 5 years, for the incidence of resuscitated or fatal SCD. 6% and 14% of the study population had heart failure and coronary artery disease respectively. SCD was defined as death due to fatal cardiac dysrhythmia, cardiac arrest, cardiorespiratory arrest and myocardial infarction. In OSA patients having an AHI≥20, the risk of SCD was significantly increased with a

hazard ratio of 1.60 (95% CI: 1.14-2.24; p<0.01). In multivariate analysis, each 10-unit increase in AHI was associated with a hazard ratio of 1.06 (95% CI: 1.0–1.13; p=0.05) of developing SCD. Oxygen desaturation in OSA also predicted the risk of SCD.

It is likely that CSA, like OSA, is associated with SCD. Heart failure patients are at risk of ventricular arrhythmia and sudden cardiac death.[173] Whether CSA is an independent risk factor for SCD or whether it is just a marker of severe heart failure, remains to be established. The likely mechanism for SCD is ventricular arrhythmia. In a study conducted by Yamada and colleagues,[174] 50 patients with heart failure were monitored using a 24-hr ECG. NSVT was defined as more than 5 repetitive ventricular complexes with a heart rate >100 beats/min. The characteristics such as BNP and LV ejection fraction were matched. It showed that the prevalence of NSVT was higher in the group of patients with a RDI ≥20 events/h (46% versus 19%; p<0.05). The prevalence of NSVT in patients with predominant CSA was higher than in patients with OSA, but this difference was not statistically significant.

The relationship between life-threatening ventricular arrhythmia and SDB in patients with heart failure having an implantable cardioverter-defibrillator (ICD), has also been studied. In one study conducted by Staniforth and colleagues,[175] who followed up 101 patients with ICDs, reported no significant difference in the ICD discharge rates. In this study, there were 42 patients with a diagnosis of CSA with Cheyne-Stokes respiration, and only 26% had an ICD discharge compared to 25% in patients without CSR. In another study carried

out by Serizawa and colleagues,[176] in 47 of the 71 heart failure patients with ICDs who were followed up the incidence of appropriate ICD therapies was significantly higher in patients with SDB (43% versus 17%; $p<0.05$). SDB was also an independent predictor for appropriate ICD therapy with a hazard ratio 4.05 (95% CI: 1.20 to 13.65, $p<0.05$). Despite this potential increased risk of sudden cardiac death with SDB, the effect of positive airway therapy in these patients has not been studied.

2.3.5 Coronary heart disease

The prevalence of OSA in patients with IHD could be up to 70% and likely to be an independent risk factor for coronary artery disease[140] SDB can exacerbate myocardial ischaemia by direct hypoxia during apnoeas or as a consequence of poor coronary perfusion resulting from increased cyclical changes in ventricular afterload and increases in systemic blood pressure.[91]

To investigate the association between coronary artery disease and SDB, 308 patients of the Gothenburg sleep cohort,[177] who did not have prior coronary heart disease at baseline, were followed-up for 7-years. The relative risk of developing coronary artery disease was 4.60 (95% CI: 1.83–11.6, $p<0.001$). However, the baseline characteristics such as BMI and systolic and diastolic blood pressure of these patients were markedly different between patients with OSA and non-OSA. Data from large prospective cohort studies suggests that this association weakens when corrected for confounders. In the SHHS study,[178] 4422 subjects who were free of coronary artery disease and heart failure were also followed up for 8.7 years. A total of 454 men (24%) and 280 women (11%) had

at least moderate SDB (AHI≥ 15). The incident coronary artery disease was defined as the first occurrence of myocardial infarction, coronary artery disease death or having a coronary revascularization procedure. There were a total of 472 coronary events. The event rate increased with the severity of OSA measured by AHI, but the strength of this association diminished after correcting for confounders such as age, BMI, diabetes, hypercholesterolaemia and hypertension, for both men and women. The only statistically significant association was for men less than 70 years, where the hazard ratio for incident coronary artery disease was 1.1 (95% CI: 1.00-1.21) per 10-unit increase in AHI. In these patients who had AHI of ≥ 30, compared to patients with AHI<5, the adjusted hazard ratio for incident coronary artery disease was 1.68 (95% CI: 1.02 to 2.76). This suggests that risk of coronary artery disease in male patients with severe OSA is likely to be greater.

IHD is an important cause of systolic heart failure,[124] therefore, CSA can occur as a consequence of IHD. The incidence of CSA appears to be higher post myocardial infarction[179] and also have a higher mortality if the aetiology of heart failure is ischaemic in the presence of SDB.[180]

2.3.6 Heart failure

Heart failure can be defined as a clinical syndrome, manifested by an abnormality of cardiac structure and function leading to a failure of the heart to deliver oxygen to match the body's metabolic demand. It is characterised by neurohormonal abnormalities such as sympathetic and renin-angiotensin-aldosterone system activation and typical symptoms such as breathlessness,

ankle swelling and fatigue. Heart failure can be classified according to symptoms (such as the NYHA class I-IV classification), time course (either chronic or acute) and LV ejection fraction.[124]

Most recognised is heart failure with reduced ejection fraction (HFREF). In addition to the prognostic importance, where survival is negatively correlated with ejection fraction, robust therapeutic evidence exists only for these patients because the majority of clinical trials has been conducted in patients with ejection fraction <40%. Another group of heart failure patients have been recognised, who have signs and symptoms similar to HFREF, but do not exhibit systolic dysfunction. Their ejection fraction is preserved (i.e. >55%), therefore this group of patients have been classified as heart failure with preserved ejection fraction (HFPEF). The prevalence of both types are more or less equal but their aetiological profile differs.[181] The most common factors that are strongly associated with HFPEF are obesity, hypertension and diabetes.[182] Although, the most common cause of HFREF is coronary artery disease, this is much less in HFPEF. As part of a large study which recruited 4133 HFPEF patients,[183] the most common aetiology of heart failure was hypertension (64%), compared to ischaemic heart disease (25%).

Both CSA and OSA are likely to be independent risk factors for heart failure. SDB may worsen the progression of heart failure by mechanisms such as increasing oxidative stress leading to myocardial ischaemia, and sympathetic outflow causing further activation of the RAAS system during apnoeic periods. Also in

OSA, a high intrathoracic pressure is generated during apnoeas, which can lead to an increase in ventricular afterload.[184]

2.3.6.1 OSA and heart failure

OSA is present in both HFREF and HFPEF, but its more common in patients with HFPEF.[185] The same risk factors that are associated with OSA are also associated with HFPEF. Hypertension, diabetes and obesity are highly prevalent in both OSA and HFPEF. However, thus far the studies that have been conducted investigating HFPEF and SDB have focussed on establishing the prevalence rather than disease outcome. Moreover, these studies are smaller in size compared to that of HFREF.

In a study conducted by Herrscher and colleagues,[186] when 115 consecutive heart failure patients who presented to clinic were studied, 44 patients had HFPEF. 62% of these HFPEF patients were found to have OSA. There was a significant difference in the ejection fraction between the OSA and CSA groups (40.4±13.2% versus 34.0±12.5%; $p<0.05$). In a much larger study carried out by Bitter and colleagues,[185] 244 patients with a normal ejection fraction were chosen from a total of 878 heart failure patients who were admitted to a heart and diabetes centre in Germany. 97 patients (40%) with a normal ejection fraction had OSA and 60 of these patients (62%) had either moderate or severe OSA. Also, in the OSA group there was a high proportion of hypertension and diabetes compared to the CSA group. In both these studies, patients were selected and categorised using NT-proBNP, echocardiography and Embletta polygraphy.

Although these studies have suggested that OSA, HFPEF and metabolic syndrome could be linked, more evidence is needed to understand this association. This is likely to improve as our understanding and the awareness of diagnostic criteria for HFPEF increases.[187]

OSA also has an increased prevalence in HFREF (compared to the normal population). Hypertension and diabetes can also increase the risk of coronary artery disease and myocardial infarction. Thus, post-infarction, systolic dysfunction can occur leading to HFREF. The prevalence of OSA in patients with HFREF was 36% (when the presence of SDB was defined as AHI≥5) and 19% for moderate OSA (AHI ≥15). This was also demonstrated in a study by Oldenburg and colleagues, which explored SDB in 700 chronic heart failure patients with an ejection fraction ≤40%, and found the prevalence of OSA in HFREF to be 19% (section 2.2.3.2).[37]

OSA in patients with HFREF has been shown to increase mortality in observational studies. In the SHHS study,[178] the hazard ratio for developing heart failure was 1.13 (95% CI: 1.02—1.26) for every 10-unit increase in AHI. However, after adjusting for covariates such as BMI, age, diabetes, hypercholesterolaemia and hypertension, the association between risk of incident heart failure and OSA, was not statistically significant for either sex or AHI category. It is important to note that in this study BNP and echocardiography was not conducted in all patients and the diagnosis of heart failure was based on clinical history and supportive findings from chest radiographs. The authors also did not distinguish between HFPEF and HFREF.

However, in a small study carried out by Wang and colleagues[188] these issues were addressed. They recruited 164 patients with an ejection fraction ≤45%, which was measured either with echocardiography or radionuclide angiography. In addition, the groups were matched for NYHA class, type of medication, aetiology of heart failure, hypertension and diabetes. The mortality in the OSA group was almost twice has high compared to patients with either no OSA or mild OSA (AHI<5). When a multivariate model was applied, OSA increased the risk of death with a hazard ratio of 2.81 (95% CI: 1.11—7.10; p<0.05). Further, OSA patients who were untreated had a higher mortality compared to patients without OSA.

Although these studies suggest a mortality association between OSA and HFREF, there are no large well-controlled studies to suggest that OSA is an independent risk factor for heart failure. This association is likely to be confounded by factors such as BMI, which could be driving mortality. For example, in the Framingham study,[189] raised BMI was strongly associated with the risk of developing heart failure. Large data registries such as the SCHLA-HF,[190] which is collecting data related to risk factors and prevalence of SDB in HFREF, is likely to provide more insight about this association in the future.

CPAP therapy in heart failure has been shown to improve cardiac function in multiple small studies.[140] These studies, however, were limited by sample size (where most of these had less than100 patients) and very short follow-up periods (usually no more than 3 months). One such study conducted by Kaneko and colleagues,[191] which included 24 heart failure patients with LVEF<45% and

predominant OSA, were randomised to either medical therapy alone (control group) or the addition of CPAP (treatment group). In the CPAP group AHI was significantly reduced from 30.3±4.7 at baseline to 3.6±0.7 after 1 month ($p<0.001$). ODI was also reduced significantly (from 12.7±3.2 to 0.8±0.5; $p<0.001$). These improvements in OSA indices were associated with an improvement in left ventricular ejection fraction, which increased from 25.0±2.8% to 33.8±2.4% ($p<0.001$) and the left ventricular end-systolic dimension, which reduced from 54.5±1.8mm to 51.7±1.2 mm ($p<0.01$). In the control group however, no significant changes in the AHI, ODI and cardiac function was observed. In another study,[192] which randomised heart failure patients with a left ventricular ejection fraction <45% to either 3 months of CPAP (28 patients) or sham-CPAP (32 patients), similar improvements in cardiac function were reported. Most marked improvements were seen in the CPAP group in patients who had a left ventricular ejection fraction less than 30% and predominant OSA at baseline (difference of means between groups of 5.2%; 95% CI of 0.5 to 9.8%; $p<0.05$). Parallel improvement in AHI was also seen in the treatment group but none of these changes were seen in the sham-CPAP group.

A meta-analysis which included a combination of smaller studies involving both OSA and CSA,[193] showed that the left ventricular ejection fraction may be improved by about 5 % (95% CI: 3.72 to 6.38%) with CPAP therapy. Whether this potential improvement in cardiac function will lead to a reduction in 'hard' endpoints (such as mortality) in patients with OSA needs to be established. Ongoing randomised trials, such as the ADVENT-HF trial (NCT01128816), which

studies the effect of Adaptive Servo Ventilation (ASV) in heart failure patients with either OSA or CSA, may provide more evidence to answer this question.[194]

2.3.6.2 CSA and heart failure

CSA and CSR occur predominantly as a consequence of HFREF. The prevalence and severity of CSA increase with worsening cardiac function and symptoms.[195] Whether CSA/CSR is an independent risk factor for adverse patient outcomes in heart failure or whether it is merely an epiphenomenon of the natural disease progression is a question that remains to be answered. In small studies, CSA has been shown to increase heart failure hospitalisations and mortality.[139] A study conducted by Javaheri and colleagues,[11] followed up 88 male heart failure patients with an ejection fraction ≤45% for 51 months, who were recruited from an outpatient clinic setting. They had overnight polysomnography and the presence of CSA was defined when the AHI was ≥5. They found that the survival of patients having CSA was significantly worse (hazard ratio of 2.14; $p<0.05$). In another study conducted by Lanfranchi and colleagues,[138] the duration of CSR, in addition to the AHI, was associated with higher mortality in a dose-response manner.

Small published clinical trials have shown that positive pressure ventilation, such as CPAP and ASV, are effective in heart failure, leading to an improvement in left ventricular ejection fraction, improved oxygenation, exercise tolerance, sleep quality, quality of life and reductions in plasma BNP and noradrenaline levels.[184] In a study conducted by Sin and colleagues,[196] 66 heart failure patients (with NYHA class III or IV symptoms) were randomised to either medical

therapy alone or the addition of CPAP. These patients were further stratified according the to the presence of CSA and Cheyne-Stokes respiration, which included 15 patients in the control group and 14 patients in the CPAP group. All groups were matched for age, sex, medical treatment and left ventricular ejection fraction, but not for BMI. At 3 months CPAP significantly improved left ventricular ejection fraction by ~8% (±2%) in patients with both CSA and Cheyne-Stokes breathing compared to control, however, this effect diminished when the whole group was included. This group was followed up further, where one final telephone follow up was carried out at 1.5 years (median, 2.2 years; maximum, 4.8 years after initial randomisation). This showed that patients with CSA and Cheyne-Stokes respiration had a higher mortality (RR of 2.53; 95% CI: 1.08-5.94; $p<0.05$) independent of other factors including the use of CPAP. The effect of CPAP on mortality, even in patients with Cheyne-Stokes respiration, was modest but was significant when non-compliers were excluded (RR reduction of 81%; 95% CI: 26%-95%; $p<0.05$).

ASV is another mode of positive airway therapy that has been used to treat CSA in heart failure. Uniquely, compared to CPAP, ASV delivers servo-controlled inspiratory pressure support on top of expiratory positive airway pressure. One small study carried out by Philippe and colleagues,[197] showed that ASV may be marginally better in reducing sleep apnoea and improving cardiac function. They randomised 25 heart failure patients (with a left ventricular ejection fraction less than 35% and NYHA class II-IV), who were matched for age, sex, BMI, medical therapy, NYHA class, ejection fraction and AHI, to either ASV or CPAP. Both CPAP and ASV reduced the AHI significantly, however, ASV induced a greater decrease

in AHI (by almost twice; absolute values were not available). ASV also improved the left ventricular ejection fraction at 6 months compared to the CPAP group, although echocardiographic data was only available in 7 patients with ASV and 6 with CPAP. In a similar study carried out by Pepperell and colleagues,[198] the effects ASV in 30 heart failure patients (NYHA class III or IV) with CSA were investigated. Patients were randomised to either therapeutic ASV or sub-therapeutic ASV (15 patients in each arm), and were matched for age, BMI, left ventricular ejection fraction, NYHA class, AHI and ESS, and followed up for 1 month. Therapeutic ASV was delivered at the default settings (expiratory pressure of 5 cm H_2O and inspiratory pressure support between 3 and 10 cm H_2O) of an Autoset CS machine and sub-therapeutic ASV was delivered from an identical machine, delivering only a pressure of 1.75 cm H_2O and with little pressure support (minimum, 0.75; maximum, 2.75 cm H_2O). The primary outcome (duration of wakefulness measured by the Oslers test), improved significantly in the therapeutic group compared to the sub-therapeutic group (difference of 8.9 min; 95% CI: 1.9–15.9 minutes; $p<0.05$). Secondary outcomes such as BNP levels (median reduction in BNP was 56 pg/ml; interquartile range, -238 to -16 pg/ml) and urinary catecholamine levels (metadrenaline but not metnoradrenaline) also improved in this group (difference of 19.2 nmol per mmol of creatinine; 95% CI: 3.5–35.0; $p<0.05$) compared to the sub-therapeutic group. However, these modest findings in these smaller clinical trials using PAP therapy have not been translated to improvements in mortality in large randomised controlled trials, discussed below.

2.3.6.2.1 Randomised controlled trials evaluating PAP therapy in heart failure

The largest study that evaluated the use of CPAP in patients with heart failure is the CANPAP trial.[199] This multicentre trial, randomised 258 stable heart failure patients with left ventricular ejection fraction <40% and central sleep apnoea to either CPAP (128 patients) or no CPAP (130 patients) and followed up for 2 years. There was no significant difference in the baseline values between the two groups, such as NYHA class, left ventricular ejection fraction, disease-modifying heart failure medications and AHI values. The average CPAP use was ~4 hours and the average positive airway pressure was ~8 cm of water. There were statistically significant improvements in physiological parameters with CPAP: reduction in the AHI by 21±16 events/hr, the mean oxygen saturation by 1.6±2.8 %, reduction in plasma noradrenaline concentration by 1.03±1.84 nmol/l and a small improvement in left ventricular ejection fraction by 2.2±5.4%. However, this did not translate to benefits in mortality: there was no difference in the primary outcome, which was defined as the combined rate of death from all causes and heart transplantation. The hazard ratio for transplantation-free survival was 1.1 (95% CI: 0.65—1.88; p=0.714). Further, no statistically significant difference was found for cardiovascular mortality (73% in the control group versus 85% in the CPAP group; p=0.33). An early divergence in the survival rates between the control and CPAP groups was also observed and this favoured the control arm (hazard ratio 1.5; p<0.05). One potential reason for this early harm with CPAP therapy could have been the acute effect of positive airway pressure, which can interfere with ventricular filling pressure (i.e. preload) in these heart failure patients, leading to a reduction in the cardiac output. This difference diminished when patients who dropped out of the study

were excluded. A higher rate of mortality was observed in these patients compared to the ones that completed the study. Nevertheless, whether these patients dropped out because they became too unwell to participate in the study soon after being initiated on CPAP, is difficult to establish, as the authors have not stated the reasons for their dropout. In addition, CPAP did not make any significant difference to health-related quality of life, which was assessed by the Chronic Heart Failure Questionnaire.

The effectiveness of ASV in HFREF was evaluated in the SERVE-HF trial,[99] the largest multicentre RCT conducted in patients with SDB. In this study, a total of 1325 patients with an ejection fraction of ≤40% having CSA (with an AHI≥15) were randomised to either ASV and standard heart failure therapy based in current heart failure guidelines or standard heart failure therapy alone. These patients were followed up for 31 months (median; range: 0-80). All patients recruited for this study had severe heart failure according to the NYHA class (70% in both groups were class III). The baseline characteristics (such as AHI, oxygen desaturation index, BMI, blood pressure, diabetes, renal function, haemoglobin, left ventricular ejection fraction, atrial fibrillation, type of disease modifying cardiac drugs and device implantation) were similar between the ASV and standard treatment arms. Primary endpoint was defined as the first event of death from any cause, any lifesaving cardiovascular intervention (such as cardiac transplantation, implantation of a ventricular assist device, resuscitation after sudden cardiac arrest, or appropriate lifesaving shock) or unplanned hospitalization for worsening heart failure.

There was no difference in the primary end-point where the event rates were 54.1% and 50.8%, in the ASV and control groups, respectively (hazard ratio of 1.13; 95% CI: 0.97—1.31; p=0.10). Alarmingly, both all-cause mortality and cardiovascular mortality were significantly higher in the ASV group: hazard ratio for death from any cause was 1.28 (95% CI: 1.06—1.55, p<0.01) and for cardiovascular death it was 1.34 (95% CI: 1.09—1.65; p<0.01). Similar to the CANPAP trial, there was no difference in quality life measures and the 6-minute walk test. Further, the sub-group with the highest mortality were patients with severe left ventricular dysfunction, with an ejection fraction of <30% and having >50% CSR. This was despite a good therapy compliance (where 60% of patients used ASV for more than 3 hours per night), good control of SDB (the mean AHI at 12 months was ~6 events/h compared to ~31 events/h at baseline) and correction of oxygen desaturation index (this was ~8 events/h compared to ~32 events/h at baseline in the ASV group).

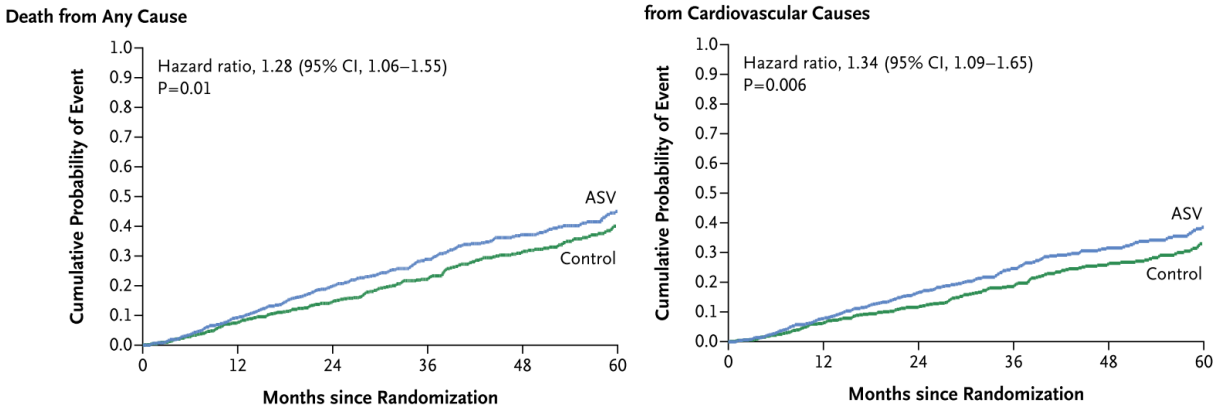


Figure 2.10 The effect on mortality in patients with CSA from ASV

The Kaplan-Meier curves showing the significant increase in death from any cause and death from cardiovascular causes in heart failure patients who were treated with ASV, compared to the control group who were on optimal heart failure therapy in the SERVE-HF trial.
(Adapted from Cowie et al.)[99]

These findings are contradictory to most of the small clinical trials that have been conducted thus far in patients with heart failure using PAP therapy. The most common explanation for this is the potential bias associated with these studies, as they were largely underpowered (small studies with <100 patients), single-centre or had very short follow-up periods (usually no more than 6 months). Further the measures used to evaluate primary or secondary outcomes in these studies, such as markers of sympathetic nerve activity, blood pressure and heart rate reduction, burden of Cheyne-Stokes respiration, arousals and AHI, although associated with SDB, may not be causal. Publication bias could also be a factor, where authors and journals alike are unlikely to write up or publish data which are negative, or findings that do not show a statistical significance.

The deleterious effects of ASV in the SERVE-HF study could have been driven by multiple pathophysiological mechanisms. In a literature review, Naughton[200] has suggested that CSA and Cheyne-Stokes respiration could be a compensatory mechanism and is potentially beneficial in heart failure. Potential 'protective' mechanisms have been hypothesised:

1. *Reduction of hypercapnic acidosis*

   Acidosis is harmful to the myocardium and has been shown to depress myocardial contraction in in-vitro human myocardial cells because the pH can modify cellular and ionic interactions involved the excitation-contraction coupling pathway.[201] Acidosis could also be arrythmogenic.[202]

   Hyperventilation during Cheyne-Stokes respiration leads to hypocapnia, which results in respiratory alkalosis, which may protect against these

changes in pH. Further, alkalosis can promote oxygen extraction from cardiac muscle and reduce lactate production.

2. *Increased lung volume leading to an increase in 'intrinsic' PEEP*

   Cyclical hyperventilation in CSA and longer expiratory time has been shown to increase lung volume by up to 500ml,[203] which could result in an increase of 'intrinsic' positive end-expiratory pressure (PEEP) by 5-10mmHg. This would ultimately reduce airway collapse and increase oxygen availability to tissues.

3. *Increased stroke volume*

   The intrathoracic pressure swings in that occur in CSA is much lower than in OSA (<25mm Hg compared to 30-120mm Hg),[204] thus unlikely to attenuate cardiac output by obstructing venous return. But these pressure swings during hyperventilation can act as a cardiac pump, reducing the afterload.

4. *Attenuation of the sympathetic drive*

   In CSA there is sympathetic over activity[95,96] and increase sympathetic drive is harmful to the cardiovascular system and perpetuate heart failure.[124] However, in CSA associated hyperventilation, large tidal breaths may promote the activation of the vagus nerve and counterbalance the increased sympathetic nerve activity. An inverse correlation between tidal volume and muscle sympathetic nerve activity has been observed.[205]

   Further, the elevated sympathetic nervous activity in CSA is deemed to be associated with arousals, which also leads to sleep fragmentation[36] and increased nocturnal blood pressure.[17] However, heart failure patients with CSA do not suffer from daytime sleepiness.[37,75] Thus the elevated sympathetic

activity may be unrelated to arousals but may correlate with the severity of the clinical heart failure syndrome.[206]

5. *Cyclical respiratory muscle rest*

   Intermittent work followed by rest or recovery is more advantageous than continuous work, a concept similar to reconditioning training in athletes.[207] Therefore, during apnoeas, respiratory muscles could be considered as having a period of 'rest' preventing respiratory muscle fatigue.

Since the CANPAP trial there have been concerns that certain patients could be more sensitive to the positive airway pressure and reduce the cardiac output, especially in the background of poor left ventricular function. In the SERVE-HF trial an excess mortality was observed in this patient group with a left ventricular ejection fraction <30%. However, the magnitude of positive airway pressure used in this study was quite modest (~5 and 10 cm H_2O for expiratory and inspiratory pressure, respectively), which may not be enough to inhibit cardiac function. Further, it also seems that patients with left ventricular systolic dysfunction behave differently to patients with normal cardiac function. An early study carried out Bradley and colleagues[208] showed that in 11 patients with a high PCWP (i.e. patients with pulmonary oedema due to left ventricular dysfunction), CPAP of 5 cm H_2O, lead to a significant increase in the cardiac output (from 4.75 ± 0.55 to 5.37 ± 0.55 l/min; $p<0.01$) compared to matched 11 patients with low PCWP (from 5.58 ± 0.31 to 5.14 ± 0.39 l/min; $p<0.05$) and 3 control patients with EF>55%). The authors hypothesise that this could be due to the application of PAP leading to an increased raised intrathoracic pressure,

which in turn leads to a reduction the transmural LV pressure, thus reducing the afterload. This effect of PAP on cardiac output in left ventricular systolic dysfunction has been repeated in other studies.[209] Further in the large multicentre 3CPO trial of 1069 patients, which explored whether PAP (either CPAP of NIPPV) can reduce mortality in acute pulmonary oedema compared to oxygen therapy, did not show any adverse events related to PAP. The pressures used in this study ranged from 5 to 15 cm H_2O for CPAP and inspiratory pressures of 8 to 20 cm H_2O and expiratory pressures of 4 to 10 cm H_2O for NIPPV.

Another potential mechanism for the increased mortality in the ASV arm is ventricular arrhythmia. From a post-hoc analysis of the SERVE-HF study using multistate modelling,[210] the mechanism of harm in the ASV group was found to be cardiovascular death without preceding hospitalisation, likely sudden cardiac death. In patients allocated to ASV, the risk of cardiovascular death without a previous hospital admission for worsening heart failure or a life-saving event (defined as cardiac transplantation, implantation of a ventricular assist device, resuscitation after sudden cardiac arrest, or an appropriate life-saving shock) was significantly higher compared to the control group (HR of 2.59, 95% CI of 1.54–4.37, $p<0.001$). In addition, the rate of cardiovascular death after a lifesaving event was also higher in the ASV group (HR of 1.57, 95% CI of 1.01–2.44, $p<0.05$). The strength of these associations persisted after adjusting for the presence of an ICD. The risk of cardiovascular death without prior hospital admission was most pronounced in patients with a left ventricular ejection fraction ≤30% with an HR of 5.21 (95% CI of 2.11-12.89, $p<0.05$) in the ASV

group. The lack of an ICD at baseline further increased this risk of death (HR of 24.08, 95% CI of 3.14–184·46, p<0.01) in these patients. This post-hoc analysis shows that patients had an increased risk of death without an admission to hospital or after a lifesaving event, which suggest the mechanism of harm is likely due to sudden death. A significant increase in death in patients without an ICD, further suggests that sudden death is likely to be cardiac arrhythmia related.

Another possible mechanism is the suppression of ventricular ectopic activity by ASV. Small clinical studies[174,211] have shown that premature ventricular complexes are higher in patients with CSA and that ASV therapy reduces the frequency of these.[212] Suppression of premature ventricular complexes with antiarrhythmic therapy lead to an increased mortality in the CAST trials,[213] and potentially ASV could have a similar effect.

The use of antiarrhythmic medications was significantly higher in the ASV group. Antiarrhythmic medication can potentially be pro-arrhythmic and may be associated with an excess mortality as shown by a recent Cochrane systematic review of antiarrhythmic drug use in atrial fibrillation.[214] However, this alone is unlikely to explain such a profound increase in sudden death in the ASV group, and the increase in cardiovascular and all-cause mortality persisted despite adjusting for borderline difference in antiarrhythmic use.

Considering these findings, it is likely that CSA and CSR pattern is a manifestation of the severity of heart failure, and is a prognostic marker, rather

than a separate disease process that requires intervention. A complete transformation of our understanding of SDB is now necessary.

The improvement in CSA with optimal heart failure therapy, such as with cardiac resynchronisation therapy (CRT),[215] also strengthens this argument. CRT has been shown to improve mortality in patients with heart failure. For example, in the CARE-HF trial,[216] which included 813 heart failure patients (who were NYHA class III-IV and had a LVEF <35% and a QRS duration of at least 120ms), CRT significantly reduced deaths (HR 0.64; 95% CI: 0.48 to 0.85; P<0.002) compared to the medical therapy group (both groups were on optimal medical therapy with 95% of patients were on an ACE inhibitor or angiotensin receptor blocker, ~70% on beta-blockers and ~55% on spironolactone). The mortality benefits gained with CRT is independent of having an implantable cardioverter–defibrillator device (ICD).[217] There are no large randomised trials carried out exploring the effects of CRT on sleep apnoea, however small studies (controlled before-and-after studies) indicate that there could be benefits with CRT in CSA. Oldenburg and colleagues[218] studied the effects of CRT in patients with heart failure and SDB. The study included 77 patients with NYHA class III or IV, left bundle branch block with a QRS duration of ≥150ms, a left ventricular end diastolic diameter of ≥60mm and a LVEF of ≤35%. Before the CRT device was implanted, multiple lead positions were tested to obtain the maximal haemodynamic response. Sleep studies carried out using an Embletta™ device identified 36 patients with CSA (i.e. if the cessation of airflow was ≥10s, without any abdominal or thoracic efforts), 26 patients with OSA and 15 patients with no SDB, when a cut-off AHI of 5 events/h was used. There were no significant

differences in the baseline characteristics of these groups (such as age, sex, aetiology of heart failure, NYHA class and the proportion of patients on heart failure medical therapy). After ~5 months of follow-up, the NYHA class, 6-min walk test and LVEF significantly improved in all groups. However, SDB was improved only in the CSA group (where the AHI decreased from 31.2± 15.5 to 17.3±13.7; p<0.001) and not in OSA group (from 18.2±13.3 to 14.6±9.8; no statistical significance). The improvement was more marked in CRT responders (figure 2.11). The increase in cardiac output (because of the improvement in LVEF) has been suggested as the primary mechanism, leading to a reduction of lung to chemoreceptor circulation time and pulmonary venous pressure, which in turn may reduce hyperventilation and hypocapnia.[215]

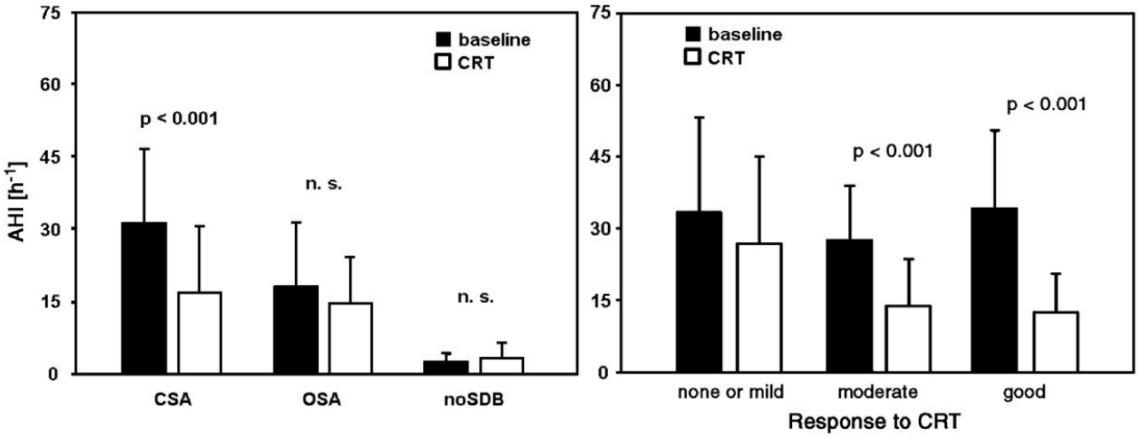


Figure 2.11 The effect of Cardiac resynchronisation therapy on CSA

After 5 months, SDB was improved in patients with CSA only with a statistically significance reduction in AHI. This was despite CRT improving measures and symptoms of heart failure such as NYHA class (3.1±0.3 to 2.4±0.6, 3.0±0.2 to 2.0±0.4 and 2.9±0.2 to 2.2±0.6 in CSA, OSA and no SDB respectively), 6-min walk distance (328±121 390±108m, 377±94 to 443±125m and 343±123 to 423±47m in CSA, OSA and no SDB respectively) and LVEF (25.2±6.1 to 29.1±7.3%, 26.3±5.7 to 30.9±6.7% and 24.9±5.9 to 31.8±6.1% in CSA, OSA and no SDB respectively). The figure on right shows that AHI did not improve in patients who did not respond to CRT. (Adapted from Oldenburg et al.[218])

2.4 Current guidelines and the level of evidence for management of sleep disordered breathing

Clinical guidelines are a perceived to be a systematic synthesis and a critical evaluation of the evidence, based on the available literature at a particular point in time. They provide a framework for the clinician for decision-making about the best management strategy for patients. One of the key features of clinical guidelines is that they take into account of the quality of clinical trials and aims to offer recommendations based on this strength of evidence. An illustration of how evidence and recommendations are graded is shown below in table 2.7. The best level of recommendation of a particular type of treatment in the current hierarchical approach is 'IA'. Level 'C' generally includes data only from observational studies.

Level	Evidence
A	Data from multiple randomised controlled trials or meta-analyses
B	Data derived from a single randomized clinical trial (or large non-randomized studies)
C	Consensus of opinion of the experts and/ or small studies, retrospective studies, registries

Class	Recommendation
I	General agreement that a given treatment or procedure is beneficial, useful, effective *(i.e. it is indicated or recommended)*
II	Conflicting evidence about the usefulness or efficacy of the given treatment or procedure *(i.e. it should or may be considered)*
III	Evidence that the given treatment or procedure is not useful, nor effective, and in some cases may be harmful *(i.e. it is not recommended)*

Table 2.8 The level of evidence and classes of recommendation adopted in clinical guidelines

The level of evidence is based on the current literature from the literature. Based on these, recommendations are made for patient management.
Adapted from ESC Heart failure guidelines.[124]

A variety of specialist bodies, including both cardiovascular and respiratory societies, have issued guidance on the management of SDB.

2.4.1 UK guidelines

The National Institute for Health and Care Excellence (NICE) in England is the main organisation in the UK offering recommendations for the treatment of a variety of clinical conditions. None of the NICE guidelines related to cardiovascular disease such as heart failure,[219,220] acute coronary syndromes,[8,221] atrial fibrillation[222] and hypertension,[223] comment on the association with SDB. The only guidance that is related to SDB from NICE (excluding the guidance for soft-palate implants) is the CPAP technology appraisal for the treatment of OSA, published in 2008.[108] This guidance states that CPAP therapy is recommended for patients with moderate or severe OSA (if AHI ≥15) or for patients with mild OSA (AHI between 5–14) having symptoms affecting their quality of life and when life style modifications or other treatment options have failed. The primary aim of treatment, is to reduce daytime sleepiness and address its consequences such as the effect on driving ability. The 23 RCTs identified in this guidance, showed a significant reduction in daytime sleepiness measured by the ESS, where the weighted mean difference in ESS score was −2.7 (95% CI: −3.5 to −2.0). However, little emphasis is given on the potential impact of CPAP on cardiovascular risk factors and its effect on mortality. This is possibly because of the lack of robust randomised controlled trial data in the literature at that time. Only one paragraph is devoted to the effect of CPAP on blood pressure; in the 6 RCTs that were analysed in the preparation of these guidelines, there was a 2.1mmHg drop (95% CI: −4.3 to 0.0 mmHg) in daytime blood pressure, which

was likely to be driven by patients with severe OSA who had a statistically significant drop (−4.2 mmHg; 95% CI: −6.4 to −2.0 mmHg). Further, this document does not comment on the study quality of these RCTs, particularly, whether they were blinded or if ambulatory blood pressure was used to measure blood pressure.

The Scottish Intercollegiate Guidance Network (SIGN) published guidance for OSA in adults in 2003,[125] which has been recognised by the British Thoracic Society (BTS). This guidance offers a 'level A' recommendation for CPAP as the treatment of choice for moderate to severe OSA in adults. However, this evidence is based on a RCT consisting of only ~100 patients, conducted at a single-centre and the primary outcome being measured on the basis of ESS.[46,109] Further, this guidance document is no longer available on the SIGN website as it is more than 10 years old. Specific guidelines on the management of SDB (either OSA or CSA), is not available on the BTS website,[224] however, a position statement supporting the current UK DVLA guidance in relation to driving and OSA syndrome has been published.[44]

2.4.2 European guidelines

In Europe, guidelines for the management of cardiovascular disease, such as heart failure, coronary artery disease and atrial fibrillation, are primarily set by the European Society of Cardiology (ESC). The most up-to-date guidance in each subject area, which reported on SDB, is presented below.

Topic	Summary
Hypertension (2013)	Offers no formal guidance (page 2199). Acknowledges the lack of well-designed large-scale controlled therapeutic studies and the lack of evidence whether SDB potentiates the CV risk of hypertension and whether correction of OSA with CPAP therapy reduces BP and CV events.[225,226]
Acute & Chronic heart failure (2012)	Offers no formal guidance (page 1824). Recognises SDB is common among patients with heart failure and that positive airway therapy may be used to treat nocturnal hypoxia. Refers to Canadian heart failure guidelines (focus on sleep apnoea) for screening, diagnosis and treatment.[124]
Acute & Chronic heart failure (2016)	The updated guidance[227] also recognises SDB in heart failure has important prognostic implications. For treatment of OSA (with an AHI>30) it suggests that any of CPAP, BiPAP, ASV and nocturnal O_2 supplementation can be effective mode, although they have not been shown to be beneficial on major outcomes in HFrEF. For CSA, these guidelines highlight the important findings of the SERVE-HF[99] trials (neutral primary endpoint but an increase in both all-cause and cardiovascular mortality with ASV in patients with HFrEF) and recommends against using ASV in HFrEF patients with CSA (IIIB recommendation).
Stable coronary artery disease (2013)	Only recognises sleep apnoea as a risk factor, which increases CV mortality and morbidity (page 2976).[228]
Atrial Fibrillation (2016)	Compared to the 2012 guidelines,[229] latest guidelines recognises OSA as an important risk factor in the pathogenesis of AF and recurrence of AF after catheter ablation. Screening for OSA in patients with AF and optimisation of treatment for OSA in these patients to prevent recurrence has been recommended (IIaB).[230]
CRT therapy (2013)	Not addressed.[231]
Acute Coronary syndrome (STEMI, 2012 & NSTEMI, 2015)	Not addressed.[232,233]

Table 2.9 Summary of guidelines from the European Society of Cardiology and the focus on SDB

2.4.3 North American guidelines

The most recognised cardiovascular guidelines in North America is usually set jointly by the American College of Cardiology (ACC), which is the professional association of cardiologists in United States and the American Heart Association (AHA), which is a non-profit voluntary organisation whose mission is to reduce deaths and disability due to cardiovascular disease. The ACC and AHA have partnered to develop standards, performance measures and clinical guidelines for both inpatient and outpatient care. Similar to the ESC, they have provided guidance on various areas in cardiology such as hypertension, coronary artery disease and arrhythmia management. Summary of these in relation to SDB is shown in Table 2.9. In addition, the focussed update of the heart failure management guidelines related to sleep apnoea, provided by the Canadian Cardiovascular Society provided in 2011, was also included.

Topic	Summary
Hypertension (2014 & 2015)	Neither the American society of hypertension (ASH) nor the Canadian hypertension education programme (CHEP) recognises SDB.[234,235]
Heart failure (2013)	ACCF/AHA[236] offers Class IIa recommendation for the use of CPAP in patients with heart failure and SDB. It states that CPAP has been shown to improve LV function, reduce sympathetic activity and AHI. However, the basis of these recommendations are debatable – for example the CANPAP trial, in which most of the evidence is based on, was carried out in patients with CSA, not OSA as stated in this document. Further studies are included in a data supplement. It recognises that patients with heart failure rarely reports symptoms, however, the decision to refer patients for sleep studies to be based on clinical judgement.
(2011)	Canadian heart failure guidelines with a focus on sleep apnoea[237] states that CPAP can be used for symptom relief in heart failure patients with OSA, having daytime somnolence (strong recommendation) or arrhythmias including AF (weak recommendation). They also recommend that treatment of CSA by CPAP should only be considered at experienced centres (Strong)
Stable coronary artery disease (2012)	The joint AHA/ACC guidelines[238] on the management of sleep apnoea recognises OSA as a potential cause of hypoxia, leading to angina (e370)
Atrial Fibrillation (2014)	Recognises OSA as a risk factor for developing AF and that a sleep study may be useful if sleep apnoea is suspected (e210)[239]
Device therapy (2008)	The joint AHA/ACC guidelines for device-based therapy for cardiac rhythm abnormalities[240] states that atrial overdrive pacing has been shown to reduce events of SDB, however, this not validated by randomised trials and is less effective than CPAP. This section further states that CRT therapy reduced CSA in heart failure patients with ventricular conduction delay (e363)
Acute Coronary syndrome	The joint AHA/ACC guidance on both the STEMI (2013) and NSTEMI (2014) management do not refer to sleep apnoea[241,242]

Table 2.10 A summary of ACC/AHA and Canadian cardiovascular society guidelines with a focus on SDB

2.4.4 Respiratory guidelines

The British Thoracic Society is one of the leading organisations in the UK, providing guidance on the management of respiratory diseases. It does not offer guidance specifically for SDB, however it refers to the 2003 SIGN guidance.[243] Guidelines issued by the BTS for other respiratory conditions such as asthma highlights the importance of recognising SDB.

A key document issued by the European Respiratory Society related to SDB and CVD, is the joint ERS/ESH task force report offering recommendations for the management of OSA and hypertension.[226,244] Nevertheless, this document does not provide an official guidance for the management of hypertension and OSA, but provides a diagnostic algorithm for the investigation of patients with a high pre-test probability of OSA, mainly ones with refractory hypertension.

The guidelines from the American Thoracic Society have published statements over the past decade about SDB. However, they are not directly related to CVD, and mainly focuses on areas such as driving risk in sleep apnoea,[245] ambulatory management of adults with OSA and the use of CPAP adherence tracking systems[246] and portable monitoring equipment.[247] Comprehensive guidance for management of SDB comes from the Canadian Thoracic Society published in 2006 and 2011.[126,248] The key difference of this guidance compared to others is that each statement is supported by the level of evidence available in the literature. Selection of key recommendations of this document and its corresponding level of evidence is shown in the table below.

Management criterion	Level of evidence
Criteria for diagnosis of OSA (e.g. presence of excessive daytime sleepiness *and* sleep monitoring demonstrating an AHI>5)	D
Assessment of daytime sleepiness using Epworth Sleepiness Scale	D
Definition of apnoea/hypopnoea event (for both OSA and CSA)	D
Classifying the severity of OSA (mild/moderate/severe) using symptoms such as sleepiness *or* AHI (AHI: 5-14,15-30 & >30)	D & B respectively
Diagnostic criteria for CSA and/or Cheyne-Stokes breathing	D
The use of laboratory polysomnography as the gold standard (level 1 device) for investigation of SDB	C
The use of Level II (full ambulatory polysomnography) or level III devices (i.e. portable multichannel recording) to confirm the diagnosis of patients with a moderate to high pre-test probability of SDB (but limited use in comorbid disease)	C
Increased risk of motor vehicle collisions in patients with OSA and a treatment trial to improve symptoms	B
Weight loss in patients with OSA	B
Treatment of asymptomatic patients with abnormal sleep studies	C
CPAP therapy at fixed pressure as the primary treatment for OSA	B
Titration polysomnogram as the standard for determining the optimal CPAP pressure	D
Oral appliances are a first-line therapy for patients with mild-moderate OSAHS with minimal daytime symptoms	A

Table 2.11 Level of evidence for different management strategies in SDB

Most guidance related to the management of SDB is not supported by a high level of evidence (adapted from 2006 Canadian respiratory guidelines[126]*)*

It is clear from the review of the clinical guidelines from both cardiology and respiratory societies, that no robust guidance for the management for SDB is available. Broadly, the use of diagnostic criteria, screening questionnaires and PSG/PG only carries level C or D evidence and level B is the highest level of evidence for treatment of SDB with positive airway therapy. The use of oral adjuncts, which aims to support the airway, in patients with mild to moderate

OSA is the only management strategy in this document carrying level A evidence. The important areas in the 2011 guideline update[248] from the Canadian Respiratory Society includes treatment of asymptomatic adult OSA, CPAP use in patients with heart failure and CSA and evaluation of the different positive airway pressure therapies available. Again, all of these recommendations are based on limited evidence (level C), formulated from expert opinions and non-RCTs.

2.5 Summary

SDB is extremely common; 1 in 5 people in the general population could be affected with OSA and 1 in 3 patients with heart failure have CSA. Observational studies have suggested that both CSA and OSA could potentiate cardiovascular risk and increase cardiovascular death, but this strength of association may not be profound as previously thought. Treatment of SDB with positive airway pressure therapy has been shown to improve cardiovascular endpoints in small studies, however, these have not been reproduced in large randomised controlled trials. Identification and diagnosis of SDB is still important for two reasons: 1) the presence of SDB may indicate a phenotype of high-risk cardiovascular patients, 2) therapy is likely to improve quality of life, daytime sleepiness and driving safety in patients with OSA.

Clear and comprehensive guidelines are needed to help guide healthcare professionals in screening, diagnosis and treatment of SDB. Large randomised controlled such as the SERVE-HF trial[99] highlights the importance of carrying out adequately powered studies with randomisation and longer follow-up. This trial has provided a paradigm shift in our understanding of SDB treatment using positive airway therapy. Large randomised trials that are currently undergoing will also undoubtedly make a huge impact in changing clinical practice and influencing future guidelines.

Chapter 3: Epidemiology, trends and variation in screening of sleep disordered breathing in the UK

3.1 Aims

The aim of this chapter is to

a) explore the epidemiology of SDB in the UK, using public data sources such as the Health Survey for England (HSE) and
b) explore the trends and variation in screening and diagnosis of SDB in the UK, using the data from Hospital Episode Statistics (HES) and NHS atlases of Variation.

3.2 Background

Large population studies, such as the Vitoria sleep chort,[39] have demonstrated that the prevalence of OSA may be higher than previously perceived, because most patients with OSA are asymptomatic (section 2.2.3). Similar large-scale studies, exploring the UK prevalence of OSA, were not identified from literature search carried out as part of this thesis. The only relevant large cross-sectional study that has been published, was carried out by Wall and colleagues in 2012.[249] It estimated the prevalence of OSA in people aged 50 and above in UK primary care. The data were derived from The Health Improvement Network (THIN) database,[250] which is a longitudinal computerised primary care database containing electronic medical records of about 11 million patients (representing about 6% of the population). These data were routinely collected as part of usual clinical practice. Prevalence of OSA was determined by identifying all the patients who had a diagnosis of OSA recorded in their medical record (on the 1st

of July 2005) and capturing patients who were aged 50 years or older (i.e. born before 30th June 1945). There were 1,073,116 patients (47% men) who were above the age of 50 years and the total number of patients who had a diagnosis of OSA were 6527, equivalent to 0.6% of this sample. This was 1% for men and 0.24% for women. For the 50-69 age group, which included 66% of the total number of patients and 83% of the OSA patients, the prevalence was 0.76%. These estimates are far less than the prevalence estimates found by the large population studies for this age group (table 2.4 in section 2.2.3.1). For example, in the Wisconsin study, the prevalence of asymptomatic OSA in men and women aged between 50 and 70, was 9% and 4%, respectively. This study was not a controlled observational study, thus there are likely to be several limitations, as these data, which was derived retrospectively, were not collected specifically for the purposes of research and could have had data recording errors. Nevertheless, this difference of up to 20-fold, suggests that OSA in the UK primary care could be hugely 'underdiagnosed'.

Applying the 2001 prevalence estimates from the Vitoria study (~14% in men and ~7% in women)[39] for clinically significant asymptomatic OSA (defined as an AHI ≥15),[251] to the UK population, suggests that there could potentially be up to a total of ~6.5 million people suffering from OSA (4.3 million men and 2.2 million women). Further, as there are around 800,000 people with chronic heart failure in the UK,[252] and assuming a prevalence of 35% in this population, there could be ~300,000 patients with CSA. Therefore, the total burden of SDB would be significant, as these conservative estimates suggest that the total number of patients having from both types of SDB could be ~7million. It appears that this

burden of SDB continues to be underestimated – for example, even in a recent report from the British Lung Foundation (BLF),[13] which explored and mapped the relative predicted prevalence estimates of OSA in the UK, could have underestimated the prevalence of OSA in their calculations by almost 3 times (as only symptomatic OSA was included in these calculations). Identification of this increased prevalence of SDB, particularly because most patients are asymptomatic, could be an 'epidemiological time bomb' and potentially put enormous pressure on diagnostic sleep services.

3.2.1 Sleep services in the UK

Sleep services are a key component of the patient pathway that ultimately leads to the investigation and treatment of patients with SDB. The capacity of sleep services needs to be matched according to the population demand, so an understanding of its provision is required. The sleep service can vary due to a number of factors such as the geographical location, characteristics and expectations of the patient population, and local expertise. Further, each sleep service may offer different levels of service ranging from screening of OSA with pulse oximetry to full polysomnography with initiation and titration of PAP therapy. Although, all diagnostic services are not expected to be identical, large variations in service delivery may affect patient care.

'The NHS Atlas of Variation in Healthcare' was first published in 2010[253] by the NHS Right Care programme (part of NHS England), with the aim of identifying and reducing unwarranted variation in healthcare. This was set up, so that the

resources can be invested to increase the value and quality of healthcare for the local population.[254]

The variation in sleep studies was first explored in the 2011 atlas.[255] This showed that the magnitude of variation in the rate of sleep studies carried out in 2010/11 was 60-fold (range: 0.1 to 7.8 per 1000) between the 151 primary care trusts (PCTs) that existed during that time. Further, even when the five PCTs with the highest and the lowest rates were excluded there was a 27-fold variation (range: 0.2 to 6.0 per 1000). This variation in 2011/12 was similar at 57-fold,[256] however, in 2012/13 this variation increased further to 79-fold between the 151 PCTs (range 0.1 to 7.6 per 1000).[257] The latest Right Care Atlas,[258] which was published in September 2016 (which includes data from 2013/14), shows that this variation has increased even further, as there was an 88-fold variation (range 0.1 to 8.8 per 1000) between the 211 clinical commissioning groups (CCGs). However, after the exclusion of the CCGs with the 5 highest and the 5 lowest rates (to exclude extreme outliers), this variation was comparatively similar (23- to 30-fold). These data are summarised in Table 3.1.

Year	Variation (x fold)	Range (sleep studies per 1000 population)	Variation (*when top 5 and bottom 5 are excluded*) [x fold: range]
2010/11	60[$]	0.1 to 7.8[$]	27 (0.2 to 6.0)
2011/12	57	0.2 to 8.6	24 (0.3 to 6.2)
2012/13	79	0.1 to 7.6	23 (0.2 to 4.9)
2013/14*	88	0.1 to 8.8	31 (0.2 to 5.8)
* This is variation between 211 CCGs. Other periods include variation among 151 PCTs $ Variation and upper range as presented in NHS Right Care publication.			

Table 3.1 Variation in sleep services between PCTs

The rate of sleep studies conducted between PCTs and CCGs in England since 2010 shows marked variation (between 60 to 88-fold) and even after exclusion of the five top and bottom PCTs, the variation was still significant (up to 30-fold)

NHS RightCare has also published the degree of variation for other diagnostic and therapeutic services related to cardiology. In 2012/13,[257] the variation between PCTs for echocardiography, was shown to be 34-fold (range of 1.2 to 42.0 per 1000) but 3.7-fold when the five PCTs with the highest rates and lowest rates were excluded. The 2010/11 NHS RightCare atlas,[255] included data related to the variation in the implantation of pacemakers, ICD and CRT devices (which was 5-, 17- and 68-fold, respectively and after exclusion of the five PCTs with the highest rates and lowest rates, these were 2.3-, 4- and 6-fold) and the provision of angioplasty (34-fold and 8-fold variation between PCTs for the percentage of patients receiving primary angioplasty and rate of admissions to hospital for elective angioplasty, respectively). The latest atlas[258] shows the variation in the rate of mortality from CVD (in patients under 75) to be 5.3-fold (22 to 113 per 100,000) between CCGs (and 2.4-fold variation when the seven CCGs with the highest rates and lowest rates were excluded). This was 3-fold in 2006 (and 2-fold variation when the five PCTs with the highest rates and lowest rates were excluded). These data suggest that, although there is variation between PCTs and

CCGs in the cardiology diagnostic and therapeutic services, the magnitude of this variation is much less compared to the number of sleep studies conducted.

In summary, the data from NHS RightCare suggest that across the NHS, the variation in diagnostic sleep studies carried out is high and appears to have increased since 2010. This is despite a 70% increase in the total number of sleep studies conducted in the UK.[258]

Some variation could be attributed to the geographical redefinition of 'health areas' as a result of the introduction of the CCGs, where 151 PCTs were replaced under the Health and Social Care Act in 2012 to form 211 CCGs.[259] CCGs are NHS organisations which are defined by a geographical area for the commissioning and delivering of healthcare services for that region. In addition, the differences in symptom recognition, the lack of appropriate referrals to sleep services, and the lack of availability of sleep services within the PCTs/CCGs (which could potentially result in areas with large centres carrying out more sleep studies by accepting referrals from other surrounding areas), could contribute to this observed variation.

To further our insight about trends and variation of sleep services in the UK, the data from Hospital Episode Statistics (HES) and NHS RightCare, will be explored in this Chapter. In addition, as there are no large-scale studies exploring the epidemiology of SDB in UK, this will be evaluated using the data from the 2010 Health Survey for England (HSE). As these publicly available data sources will be analysed in parallel, the overall aim of this chapter is to improve the

understanding of the epidemiology of SDB in the UK and then to identify the pressures on the provision of sleep services in the UK against the population demand.

3.3 Methods

Health survey for England (HSE) 2010, hospital episode statistics (HES) data and rate of sleep studies undertaken for each PCTs/CCGs (from NHS RightCare), were downloaded from the Health and Social Care Information Centre (HSCIC), available at http://www.hscic.gov.uk (now NHS digital; https://www.digital.nhs.uk). This is a publicly available data source and this website was searched carefully. Source data related to SDB was identified (using the search term "sleep", a total of 107 items were found and each file was examined carefully). Only files that contained continuous numerical data (for example in *.xls or *.csv formats) were included and other items such as audit reports etc. were excluded. Monthly diagnostic data from NHS England was download from https://www.england.nhs.uk/statistics/statistical-work-areas/diagnostics-waiting-times-and-activity/monthly-diagnostics-waiting-times-and-activity/. The HSE raw data were downloaded from the UK Data Service website (https://www.ukdataservice.ac.uk/) in SPSS file format.

3.3.1 Health Survey for England

HSE which started in 1991, is an annual statistical survey that is conducted to assess the health of people living in England, with the aim of monitoring health, lifestyles and specific conditions within the population. These data are used by institutions such as Department of Health and Public Health England to target and implement national health policies.[260]

HSE was carried out by NatCen Social Research (http://natcen.ac.uk/), on behalf of the HSCIC. Briefly, this was a survey representative of the population living in

private households in England, where the subjects were selected randomly by their addresses. Every address in England was included in this selection process, thus, had an equal chance of being included in the survey each year. The survey consisted of two stages: the first being a health interview, which included questions about health and lifestyle behaviours such as diet, smoking and alcohol intake, mental health and wellbeing (question from GHQ-12 or General Health questionnaire[261]), social care and living conditions (e.g. type of accommodation, heating), education, employment and income. The second stage was a nurse visit (if the subject had consented after completing the first stage). This included physical measurements (e.g. height, weight, blood pressure), recording of prescribed medication and taking biological samples (to assess renal function, hyperglycaemia and hyperlipidaemia). ~1600 variables were generated from the questions of this survey.

HSE 2010, had a household response rate of 66% and included a total of 14112 participants (this included 5692 children aged 2-15). 6914 (~50%) completed the nurse visit (this also included 1,327 children). The HSE theme in 2010 was respiratory health,[262] therefore included multiple questions related to SDB which are presented in the box below.

Questions related to SDB in the HSE (2010)

- Have you ever been told that you snore heavily or loudly?
- In contrast to just feeling tired, how likely are you to doze off or fall asleep during the day?
- Has anyone ever told you that you stop breathing during your sleep?
  (if the answer was YES, following question was asked)
    - Have you ever been investigated (or assessed) for a sleep related breathing problem?

  (if the answer was YES, following question was asked)
    - Are you receiving treatment from the NHS for a sleep related breathing problem?

  (if the answer was YES, following question was asked)
    - Are you being treated with a machine you use at home called CPAP, or something else?

Questions related to shortness of breath were also included in the survey. From these questions MRC breathlessness scale[263] was calculated using the SPSS syntax.[264] For example, individuals who reported to have breathlessness while dressing and/or were too breathless to leave the house were classed as MRC scale 5, those who reported to have breathlessness on walking on level ground or stopping due to breathlessness were grouped to MRC scale 3 or 4, and those who stated they were having breathlessness on walking uphill was classed as MRC scale 2. Only one question related to having a diagnosis of heart failure, and this question was only presented to individuals who reported a diagnosis of obstructive airways disease (either COPD, emphysema or Bronchitis).

Questions related to symptoms of Shortness of breath (2010)

- Apart from strenuous exercise, had SOB, breathlessness or DIB in last 12 months?
- Troubled by SOB when hurrying on level ground or walking up a slight hill?
- Do you get SOB walking with other people of your own age on level ground?
- Do you have to stop for breath after walking at your own pace on level ground?
- Are you ever too breathless to leave the house?
- Are you ever breathless when dressing or undressing?
- Has the doctor ever told you that you had chronic bronchitis, emphysema or COPD?
    - Have you ever been told by a doctor that you also have heart failure?

Further questions were asked related to cardiovascular risk factors such as diabetes, hypertension and hypercholesterolaemia are presented below.

Questions related to cardiovascular risk factors in the HSE (2010)

- Do you now have, or have you ever had, diabetes?
- Were you told by a doctor that you had diabetes?
- Have you ever had diabetes apart from when you were pregnant?
- Are you currently taking any medicines, tablets or pills for diabetes?
- Do you have or have you ever had high blood pressure (hypertension)?
- Were you told by a doctor/nurse that you had high BP?
- Have you had high BP apart from when pregnant?
- Are you receiving any other treatment/advice for high BP?
- Are you currently taking any medicines, tablets or pills for high BP?
- Do you still have high blood pressure?
- Have you ever taken medicines, tablets, or pills for high BP?
- Are you taking statins (drugs to lower cholesterol), bought over the counter?

During the nurse visit, BMI of individuals were calculated from the height and weight that were measured, blood pressure was measured using an OMRON HEM BP monitor and blood samples were taken for glycated Hb (HbA1c), and cholesterol (HDL and total cholesterol).

3.3.2 Hospital Episode statistics (HES) and NHS rightcare data

The HES data is a hospital records-based system that covers all NHS trusts in England, and includes details of all admissions, outpatient appointments and A&E attendances, (approximately 125 million records per year). All sleep apnoea episodes from 1999/2000 were included in the analysis. An 'episode' was defined as an admitted patient record for a continuous period of care, administered at a single hospital provider (i.e. a consultant) as part of a particular specialty. 'Sleep apnoea' was coded using the ICD-10 classification "G47.3" and included both obstructive and central sleep apnoea.[265] Waiting times and the proportion of patients admitted from a waiting list for sleep studies, were also explored. The 'waiting time' was defined as the time (which was measured in days) between the date on which it was decided to admit the patient and the actual admission date. Sleep studies were coded using the generic clinical code "A84.7". However, this code did not differentiate between different types of sleep investigations, such as pulse oximetry, full polysomnography (which consisted of EEG, EOG, EMG), multiple sleep latency test or maintenance of wakefulness test (MWT).[266] The code "U33.1", which was intended specifically to code for cardiopulmonary sleep studies, have been used from 2008/09, but only infrequently.[267]

It should be noted that this analysis does not include the 'patient-level' HES data, but the sum of all admissions across the NHS Trusts in England coded as having a primary diagnosis of SDB (i.e. the collection of records for each period of care). The patient level data are not publicly available and requires special authorised access with a subscription fee.

Monthly diagnostic data related to waiting times and activity is recorded by NHS England. These report the total activity of key diagnostic tests, which includes the actual number of sleep studies carried out each month. This data was available from Jan 2006 and presented up to the end of 2016.

In addition, NHS RightCare contained data related to the number of sleep studies carried out annually in the UK at trust level. The rate of sleep studies that were carried out, per 1000 weighted population, at each health area were available for 2012,2013 (PCT level) and for 2014 (CCG level).

3.3.3 Statistical analysis

Data analysis from the HSE was carried out in SPSS statistical software package (IBM Corp © SPSS Statistics, Version 24). HES and NHS RightCare data were available to download in MS Excel file format, therefore, descriptive statistics were carried out in MS Excel (Microsoft ®).

Independent samples t-tests (or Student's t-tests) were used to determine the difference in means between groups and analysis of variance (ANOVA) to determine the difference between multiple groups. The Chi-square test was used to determine the association between categorical variables. A p-value of 0.05 was used as the cut-off for statistical significance.

3.4 Results

3.4.1 Health Survey

The total number of adults (age≥18) in the survey was 8196. A summary of the descriptive statistics is shown in table 3.2. 46% reported that they snore, 57% that they are likely to fall asleep during the day and 7% that they snore heavily or stop breathing at night (which may signify a possible apnoeic episode). 74% had at least one symptom and 21% had all 3 symptoms.

Of all the 4656 patients who reported possible daytime sleepiness, 47% had at least a moderate chance of 'dozing off' (this was 27% of the total subjects). 208 individuals from the survey (2.5%) had all 3 symptoms (if patients having at least moderate daytime sleepiness were included with snoring and possible apnoeic episodes). 75% of all these were male.

Only 17% (i.e. 97 out of the 565 subjects who reported to stop breathing at night) said that they had been investigated for sleep related breathing problem. Further, only 14 of them had some form a treatment and 12 of these patients were on CPAP.

	Questions about sleep disordered breathing	Total (after exclusion of missing or invalid data)	YES	
Q1	Have you ever been told that you snore heavily or loudly?	8162	3765	46%
Q2	In contrast to just feeling tired, how likely are you to doze off or fall asleep during the day?	8189	4656	57%
	Slight chance of dozing	*2471*		
	Moderate chance of dozing	*1136*	2185	27%
	High chance of dozing	*1049*		
Q3	Has anyone ever told you that you stop breathing during your sleep?	8175	565	7%
3a	*Have you ever been investigated (or assessed) for a sleep related breathing problem?*	565	97	17%
3b	*Are you receiving treatment from the NHS for a sleep related breathing problem?*	97	37	38%
3c	*Are you being treated with a machine you use at home called CPAP, or something else?*	37	29	78%

* Total number of adults responding to the survey was 8196. In Q2, 3533 responses to "would never doze".

* Q3a was asked from individuals who responded "YES" to Q3 & Q3b from individuals responding "YES" to Q3a. Similar for Q3c.

Table 3.2 Responses to questions related to SDB from HSE 2010

46%, 57% and 7%, respectively, reported that they snore, were likely to fall asleep during the day and have possible witnessed apnoeic episodes at night. 27% had an at least moderate chance of dozing. Only 97 subjects stated that they have been investigated for SDB, however, this question (3a) was not presented to all the subjects in the survey, only to the 565 subjects who answered "yes" to Q3.

There were significant differences in cardiovascular risk between the people who reported to have all 3 symptoms of snoring, possible daytime sleepiness (having at least a moderate chance of dozing off) and witnessed apnoeas, compared to people who did not have these symptoms. The presence of all 3 of these symptoms could potentially indicate the presence of SDB. These subjects were significantly hypertensive (this included individuals who had already been diagnosed and/or established on medication or anyone who had a measured SBP of ≥140mmHg and/or DBP of ≥90mmHg as part of the health visit), diabetic (this included individuals who already had a diagnosis of diabetes or anyone having a HBA1c ≥6.5% measured from laboratory test as part of the survey) and obese (individuals having a BMI≥ 30). There was no difference between the groups for

hypercholesterolaemia (having a plasma cholesterol level ≥5mmol/l). These data are summarised in table 3.3.

	Subjects with all 3 symptoms (i.e. SDB likely)	Subjects NOT having all 3 symptoms	P-value	Chi^2
	[Risk factor (e.g. hypertension) present vs not present] *observed (expected) % of total*			
Hypertension	1.6% (1.0%) vs 0.9% (1.5%)	37.3% (38.0%) vs 60.2% (59.5%)	<0.001	26.3
Diabetes	0.6% (0.2%) vs 1.9% (2.3%)	7.6% (7.9%) vs 89.9% (89.5%)	<0.001	29.1
Obesity	1.4% (0.7%) vs 1.1% (1.8%)	26.6% (27.2%) vs 70.9% (70.3%)	<0.001	60.5
Hypercholesterolaemia	1.3% (1.5%) vs 1.2% (1.1%)	56.6% (56.5%) vs 40.8% (41.0%)	0.16	2.0

* The 3 symptoms include witnessed snoring, stopping breathing at night and having atleast a morderate or high chance of dozing off

Table 3.3 Prevalence of cardiovascular risk factors in subjects with possible SDB

Data from the HSE 2010 demonstrates that the prevalence of hypertension, diabetes and obesity was significantly higher in subjects with possible SDB. (i.e. those who had all 3 symptoms: at least a moderate chance of daytime sleepiness, snoring and possible apnoeas).

Similarly, the BMI (31.3 ± 6.7 versus 27.6 ± 5.3; p<0.001), waist/hip ratio (0.95 ± 0.08 versus 0.88 ± 0.09; p<0.001) and HbA1c (6.0 ± 1.0 versus 5.7 ± 0.7; p<0.01) were also significantly higher in this group. When the ratio of total cholesterol and HDL cholesterol (TC/HDL) was calculated, ones with possible SDB, had a higher TC/HDL (4.2 ± 1.4 versus 3.8 ± 1.3; p<0.01). Both SBP (129.7 ± 18.0 versus 127.3 ± 17.5 mmHg) and DBP (73.8 ± 12.6 versus 73.4 ± 10.9 mmHg) were marginally higher but this was not statistically significant. It is important to note that the data did not differentiate between people who were already on

anti-hypertensive treatment and untreated when BP was measured. Patients having all 3 symptoms were also significantly older (58 ± 15versus 50 ± 18; p<0.001). This is presented in table 3.4.

	Individuals having all 3 symptoms	Individuals NOT having all 3 symptoms	P-value
BMI	31.3 ± 6.7	27.6 ± 5.3	<0.001
Waist/Hip Ratio	0.95 ± 0.08	0.88 ± 0.09	<0.001
HbA1c	6.0 ± 1.0	5.7 ± 0.7	<0.01
Total Cholesterol/ HDL ratio	4.2 ± 1.4	3.8 ± 1.3	<0.01
Blood Pressure (SBP/DBP)	129.7 ± 18.0 73.8 ± 12.6	127.3 ± 17.5 73.4 ± 10.9	0.138 0.726
Age	58 ± 15	50 ± 18	<0.001

* The 3 symptoms include witnessed snoring, stopping breathing at night and having atleast a morderate or high chance of dozing off

Table 3.4 Association between of cardiovascular risk factors and possible SDB

The BMI, waist/hip ratio, HbA1c and a total cholesterol to HDL ratio was higher in subjects with possible SDB (i.e. those who had all 3 symptoms: at least a moderate chance of daytime sleepiness, snoring and possible apnoeas). Although BP was also higher in this group, there was no statistical significance for measured blood pressure.

436 people in the survey responded that they had obstructive airways disease (either COPD, emphysema or Bronchitis). Out of these, 40 patients had a diagnosis of heart failure and 77% of them reported having at least one of the above three symptoms related to SDB and 10% to having all 3 symptoms. Nevertheless, it was also observed that individuals who reported having symptoms of severe SOB also experienced more symptoms possibly related to

SDB. 7% and 10%, respectively, experienced all 3 symptoms related to SDB for MRC scales 3/4 and 5, compared to only 2-3% for MRC scales 1 and 2. This is presented in table 3.5.

MRC Scale		Total in Survey	%	Possibly SDB related symptoms			
				All 3 symptoms	%	At least 1 symptom	%
1	*Not troubled by breathlessness except on strenuous exercise*	5978	73	94	1.6%	3136	52%
2	*Short of breath when hurrying on the level or walking up a slight hill*	966	12	33	3.4%	684	71%
3 or 4	*Walks slower than most people on the level OR stops after walking atleast a mile OR stops after 15 minutes walking at own pace*	502	6	35	7.0%	393	78%
5	*Too breathless to leave the house, or breathless when undressing*	294	4	29	9.9%	253	86%

Table 3.5 Relationship between breathlessness and symptoms related to SDB in the HSE (2010)

3.4.2 NHS RightCare data

The rate of sleep studies carried out between 2012 and 2013 was explored at PCT level. There was no significant difference in the average rate of sleep studies carried out between 2012 and 2013, which was 1.9±1.6 and 1.8 ±1.4 per 1,000, respectively (p=0.67). However, when the 151 PCTs were divided into quartiles (ranked by the rate of sleep studies conducted in 2012) and a head-to-head comparison between each trust was carried out, there was a statistically significant difference (ANOVA: F-statistic 3.4; $p<0.05$). The middle two quartiles had an increase in the number of sleep studies conducted from 2012 to 2013 (6% and 15% respectively). In contrast, the top quartile that showed a reduction of 10%. In the bottom quartile, this increase was small (3%). This is summarised in figure 3.1.

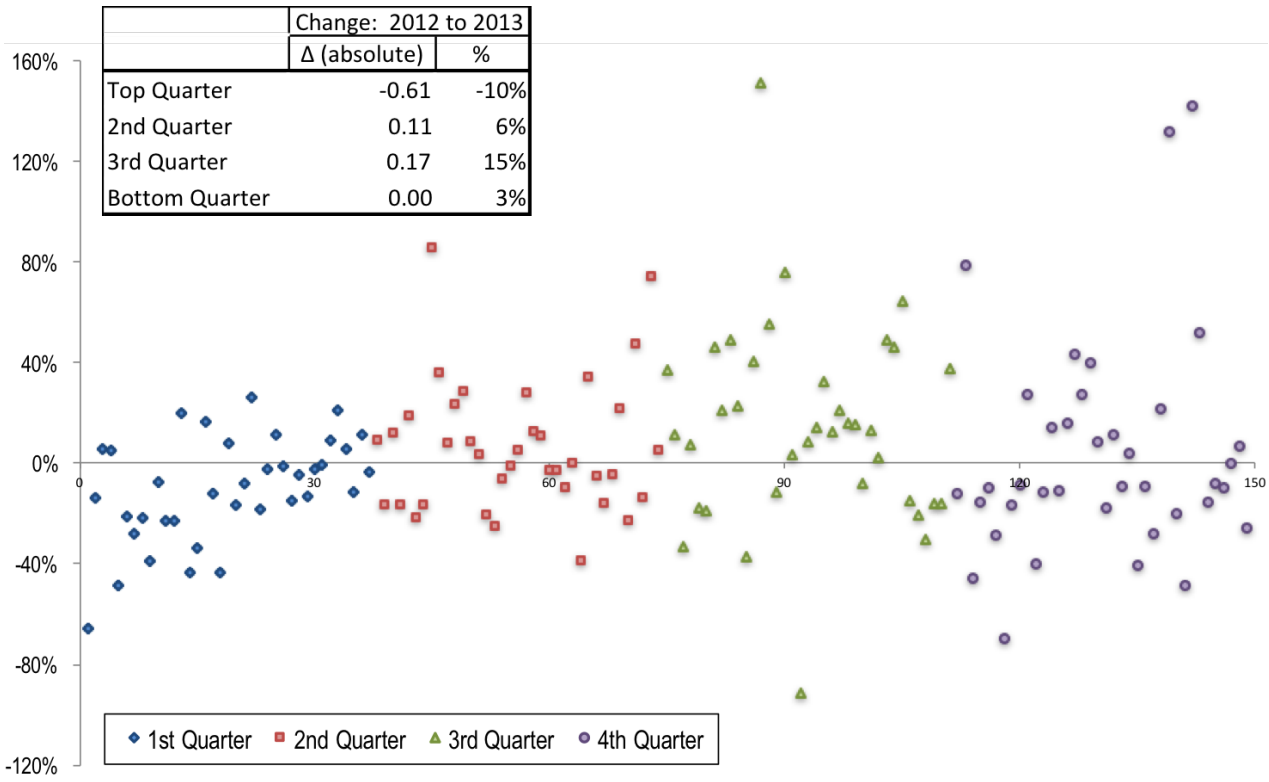


Figure 3.1. The change in the sleep studies conducted between 2012 and 2013 for each PCT

On the x-axis, the PCTs are ranked according to the rate of sleep studies carried out in 2012. The y-axis shows the percentage change in the rate of sleep studies carried out between 2012 and 2013. The PCTs divided in to 4 quartiles are shown in 4 different colours. (Of the 151PCTs, 3 were excluded as they fell beyond two SDs from the mean)

In 2014, the variation in sleep studies were categorised according to the CCGs, so direct comparison could not be made. The mean rate (1.8±1.5 per 1,000), however, was similar to 2012 and 2013. In London CCGs, this was 1.6±1.2 and was also no different to rates in 2012 and 2013 (1.6±1.2 and 1.6±1.4, respectively).

3.4.3 HES data

In HES data, when sleep apnoea was coded as the primary diagnosis for an 'inpatient episode', the mean length of stay was 2 days (median 1 day), suggesting that a sleep study was likely to have been conducted in hospital overnight. 66% of the patients were coded as being admitted as part of an elective admission from a waiting list.

The number of sleep apnoea episodes over the past decade has been increasing (see figure 3.2). There has been a 2.3-fold increase in sleep apnoea inpatient episodes from 2003 to 2013, with a steep increase between 2007 and 2009. This increase also coincides with a sharp drop in the mean waiting time for a sleep study, which has been reduced from 85 days in 2007 to 36 in 2009 (Figure 3.1). Mean age across this period (2003-13) ranged between 42 to 45 and 70 to 77% were male.

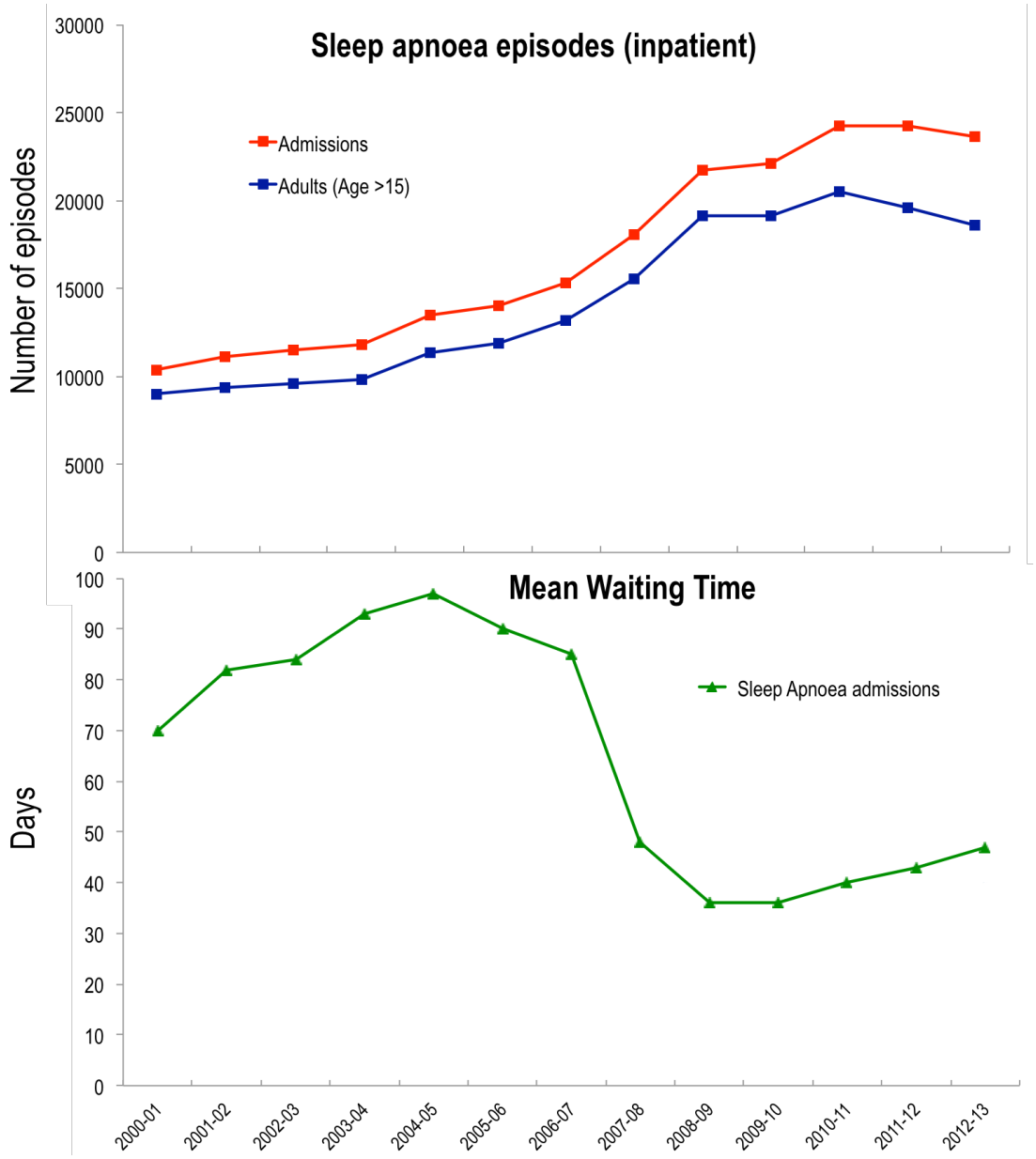


Figure 3.2. Annual trends in the number of sleep apnoea episodes and the mean waiting time from HES data

One sleep apnoea episode denotes one inpatient admission for a sleep study. This has steadily increased over the years with most significant change between 2006-2009 (top). During same period, there was a parallel decrease in the waiting time for sleep studies, however, this has continued to increase since then (bottom).

The diagnostic sleep studies carried out each month show a similar trend to the inpatient sleep apnoea episodes (figure 3.3). In comparison to 2006, in 2016 the number of sleep studies carried out was ~2 to 3-fold higher. Moreover, 75% of the sleep studies were from patients who were on a waiting list. Similar to inpatient episodes, a sharp spike in the number of sleep studies was seen in June 2008 (from 6107 to 11747 sleep studies), however, an additional, small spike was also observed at the end of 2015 (from 11456 to 13941 sleep studies). After 2008, the waiting times also appeared to improve, with the proportion of patients who were waiting for a sleep study for more than 6 weeks were reduced from more than 61% to 2%, and those waiting more than 13 weeks from 59% to <1%.

Although the pattern was similar between the total number of sleep studies and the inpatient sleep apnoea episodes, the absolute size of these differed markedly. For example, the number of inpatient episodes related to the spike in 2008 (~22000 episodes), which was significantly lower compared to the sum of the sleep studies carried out in from Jan to Dec 2008 (~82000 sleep studies over the 12-month period). Therefore, it suggests that the total number of sleep studies is likely to include non-inpatient activity, such as carrying out ambulatory sleep studies (i.e. PG using Embletta™ devices), however, differences in the coding process may also be a factor (section 3.5.4).

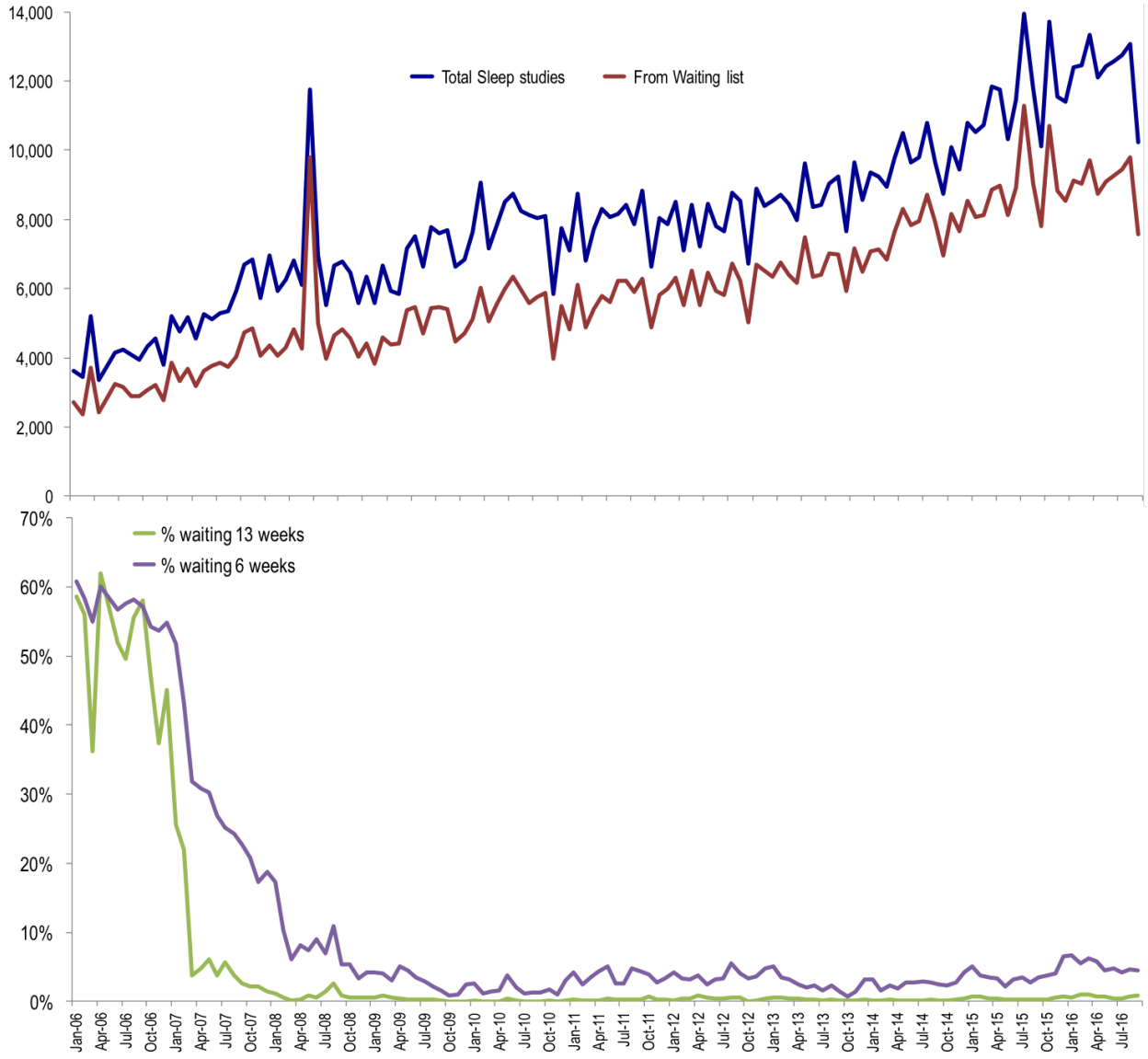


Figure 3.3. Monthly trends in the number of sleep studies carried out and the proportion of patients who had waited for more than 6 or 13 weeks for a sleep study

The total number of sleep studies carried out each month is presented from Jan 2006 to Dec 2016 (top). The bottom figure shows the proportion of patients having sleep studies, who had been either waiting for more than 6 weeks or 13 weeks (from the total number of sleep studies that month). This sharply declined after 2008 with a correspondingly sharp increase in number of sleep studies conducted.

Outpatient (OP) HES data for sleep apnoea showed similar trends. The activity before 2008 was low which was followed by a marked increase, by almost 24-fold, from 2008 to 2012. This increase was 79-fold for outpatient polysomnography episodes for same period (figure 3.4). However, the significance of these OP data, particularly in the relation to coding of OP activity to IP activity and whether they signify sleep studies conducted in an outpatient setting (e.g. portable sleep studies such as Embletta) was not clearly defined.

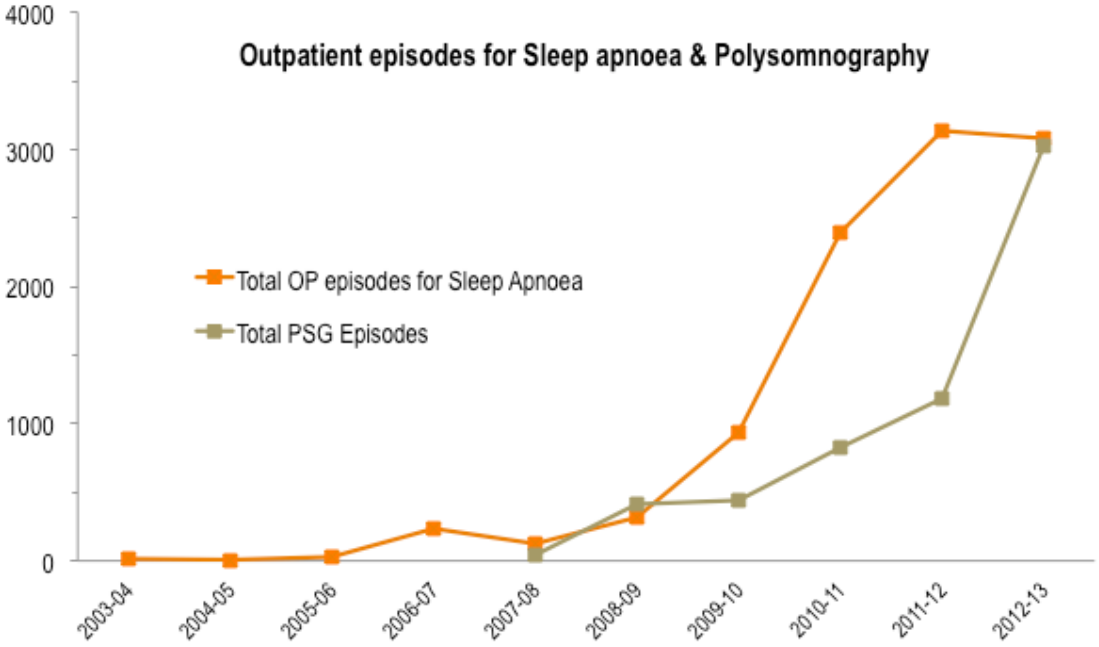


Figure 3.4 Annual trends of outpatient activity for SDB

3.5 Discussion

This chapter analysed publicly available data sources such as the Health Survey for England (2010), Hospital episode statistics and NHS RightCare. The important findings were related to the prevalence of possible SDB in the UK and their associated CV risk, trends in the number of sleep studies carried out in the past 15 years and the variation in sleep services in the UK.

3.5.1 Prevalence of SDB and the cardiovascular risk

The data from the HSE 2010 suggests that the prevalence of possible symptomatic SDB in UK adults is likely to be ~2.5%. This is an indirect estimation from the reported symptom profile of the subjects who participated in the survey. Although this prevalence estimate was not based on a diagnosis confirmed with polysomnography, a subject who experiences all three symptoms related to SDB (i.e. daytime somnolence, apnoeic episodes and snoring) are highly likely to suffer from SDB. Moreover, the questions related these symptoms, form an integral part of the STOP Bang Questionnaire, which has a high sensitivity for identifying SDB (section 2.2.2.4). This prevalence estimate is also similar to findings from previous population studies carried out, where the prevalence for symptomatic OSA has been shown to be 2-4%.[64] As mentioned above, no UK study has thus far explored the prevalence of SDB at the population level. Due to these reasons, findings from the HSE 2010 is likely to be significant and could reflect a close approximation of the prevalence of SDB in UK.

Further, no large-scale population studies have explored the associated between cardiovascular risk factors and SDB in the UK. Individuals who had possible OSA,

had a significantly higher cardiovascular risk-factor profile than those who did not report these symptoms in the survey (tables 3.3 & 3.4). The proportion of diabetes, hypertension and obesity was significantly higher in this group. This increased risk was further illustrated with biochemical (HbA1c and total cholesterol/HDL ratio), body habitus (BMI and hip/weight ratio) and blood pressure (SBP and DBP) measurements, which was higher in the group with all three symptoms, compared to the individuals who did not have all 3 symptoms (statistical significance for all apart from SBP and DBP). These factors such as obesity, dyslipidaemia, hypertension and impaired glycaemia are also important components of the metabolic syndrome, suggesting that SDB is may be associated with this clinical syndrome. In addition, most of these individuals who suffered from these symptoms were men. Similar trends were observed in large population studies and registries, such as the Sleep Heart Health Study and its substudies,[143,154] which were designed specifically to study the cardiovascular risk associated with SDB, including metabolic syndrome, were discussed in section 2.3.

In addition to exploring the prevalence and association of SDB with CV risk, these data also demonstrated that the patients with possible SDB had more symptoms related to breathlessness measured according to the MRC scale (Table 3.4). This suggests that these patients may also have had lung disease such as COPD, or heart failure. However, a prevalence estimate could not be calculated as the denominator (i.e. the total number of subjects who reported a diagnosis of heart failure in the survey) was unknown.

No study has previously explored the rates of underdiagnosis and undertreatment of SDB at a population level. HSE 2010, only revealed 97 subjects who had been previously investigated for a sleep related breathing problem (and this figure could have also included investigations for sleep disorders other than SDB). This reflected only 17% of the 565 subjects who reported symptoms consistent with possible apnoeic episodes. The exact number investigated for possible symptomatic SDB cannot be calculated from the survey data because the survey question which asked about previous sleep investigations was only available to subjects who reported possible apnoeic episodes (table 3.2). Nevertheless, these data from the HSE 2010 suggest that a large proportion of patients with possible SDB were likely to be underdiagnosed. Furthermore, only a third of the patients investigated were on treatment for SDB. There are likely to be multiple factors associated with initiating treatment for SDB, such as patient choice and 'negative' sleep studies, however, it is likely that underdiagnosis is accompanied by undertreatment.

3.5.2 Variation in sleep services

This chapter also explored the changes in the rate of sleep studies carried out in 2012 and 2013, at the PCT level. From the previous NHSRightCare publications, the respective geographical variation for this period was found to be 79- and 88-fold, respectively.[258] Although, trust-level data were available for only two consecutive years (i.e. a change between 2012 and 2013) and may not be generalised to explain current patterns, it provides an insight into the observed variation seen in NHS atlases. Although, there was no significant change between the sleep studies (i.e. rate per 1000) conducted between 2012 and 2013 among

the 151 PCTs, when these were divided into quartiles and then the percentage change between 2012 and 2013 was calculated for each trust, this change was significant (figure 3.1). The data suggests that this difference is likely to be driven by the trusts in the mid-quartiles, which showed an increase (6% and 15%) from 2012. The difference in the bottom quartile was small, however the top quartiles showed a 10% decrease in the number of sleep studies carried out from 2012 to 2013. Further, the NHS trusts in the mid quartiles, in addition to increasing their activity, could have absorbed some burden from trusts having a high activity. This could potentially be explained by the geographical proximity of the boundaries of PCTs – for example a decrease in activity in Oxfordshire (-91%) and Buckinghamshire (-70%), was associated with an increase in activity in Hertfordshire (151%), Bedfordshire (74%) and Northamptonshire (76%).

It is important to note that these data were only limited to a comparison between 2 consecutive years and multiple factors such as change in population dynamics (e.g. immigration) and economic factors (e.g. funding), could have impacted the outcome. Similar data for treatment rates of SDB with non-invasive positive pressure ventilation, were not available and have not been published in the literature. Therefore, we do not know whether a regional variation in the treatment of SDB exists and how many patients are initiated on therapy, after having a sleep study.

One possible explanation for this variation is the lack of availability of sleep services in the UK, which was also highlighted by the recent audit that was conducted by the British Lung Foundation (BLF).[13] Although the main aim of this

work was to improve the awareness of OSA in the UK, it also created a map of the relative predicted prevalence estimate of OSA based on risk factors such as obesity, age, sex diabetes and hypertension. This map included 238 NHS organisations in the UK defined geographically (which consisted of the 211 CCGs in England, 14 NHS Health Boards in Scotland, 7 Local Health Boards in Wales and the 6 Health and Social Care Trusts in Northern Ireland). This project also explored the current sleep services in UK, where a total of 289 sleep centres were identified as part of this work and superimposed on the same map (see figure 3.5). However, only 50 of these 'health areas' (21%) had sleep centres that offered full polysomnography and had capacity of providing a full diagnostic sleep service. Alarmingly, 66 areas (28%) did not have access to a sleep centre. Further, in 76 health areas, the type of diagnostic modality could not be confirmed and therefore, we do not know whether these sleep centres used basic screening tools such as pulse oximetry or other sleep monitoring devices such as polygraphy for diagnosis of SDB.

Comparison of the maps from NHS RightCare and BLF (see figure 3.5) highlights a 'gap' between the estimated population risk of OSA against the rate of sleep studies conducted. Alarmingly, areas that could potentially have the highest predicted risk of OSA (e.g. dark blue areas of the map on left) appear to correspond to areas with the lowest activity (e.g. areas in the lightest shade represent the lowest quartile in terms of rates of sleep studies). For example, this is more prominent for the East Midlands and Yorkshire/Humberside regions of the UK ('boxed area' in figure 3.5). Statistical comparisons however, could not be made, as numerical data of predictive risk for each CCG were not available.

Although this publication provides us with a general insight into the number of sleep centres in the UK, making any inferences about services and pressures at local level is difficult, because data such as population density and the number of sleep studies carried out in each area were not included in the publication.

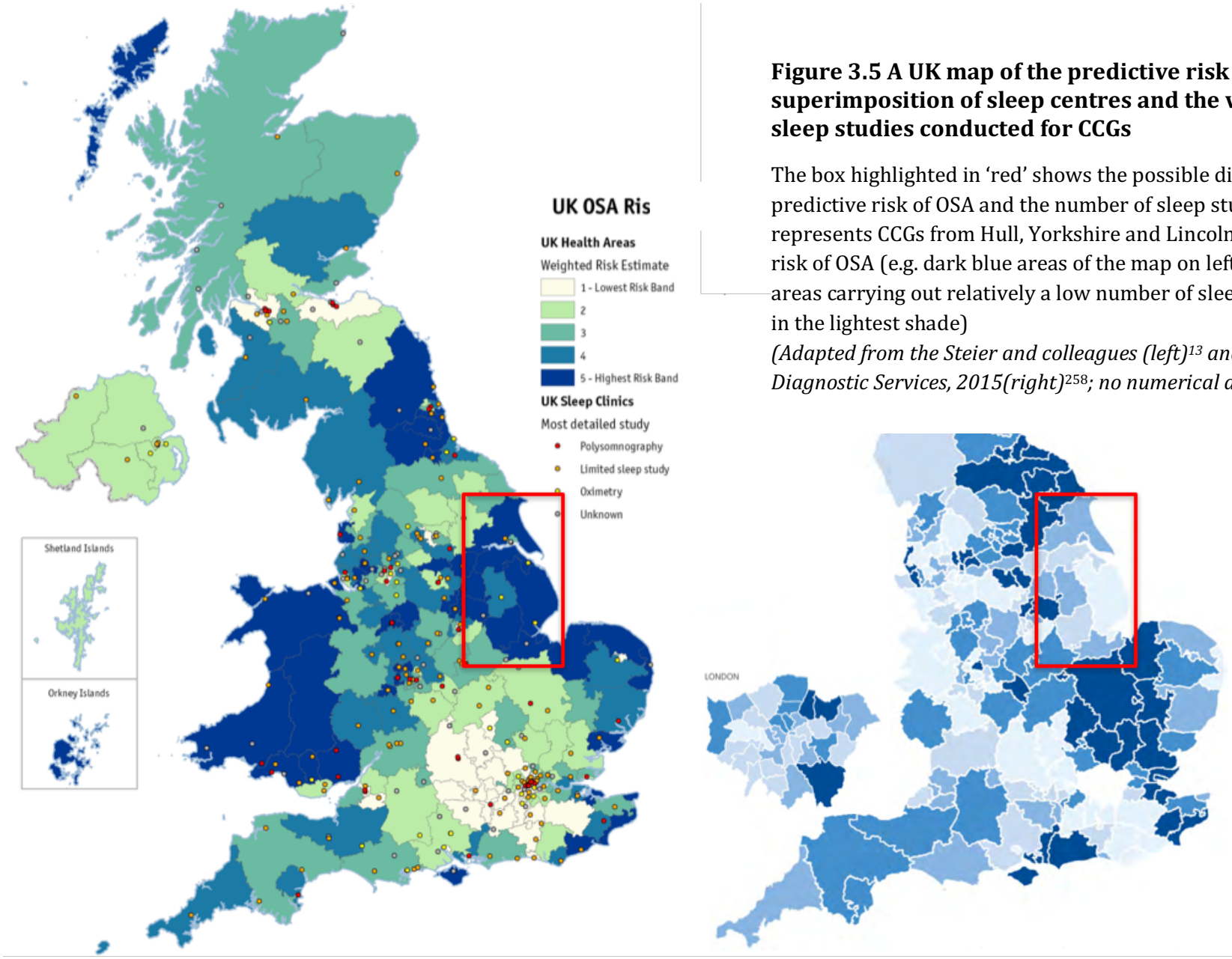


Figure 3.5 A UK map of the predictive risk for OSA with the superimposition of sleep centres and the variation in the number of sleep studies conducted for CCGs

The box highlighted in 'red' shows the possible differences between the predictive risk of OSA and the number of sleep studies conducted – this area represents CCGs from Hull, Yorkshire and Lincolnshire. The highest predictive risk of OSA (e.g. dark blue areas of the map on left) appear to correspond to areas carrying out relatively a low number of sleep studies (e.g. areas depicted in the lightest shade)

(Adapted from the Steier and colleagues (left)[13] and The NHS Atlas of Variation in Diagnostic Services, 2015(right)[258]; no numerical data available)

3.5.3 Demand for sleep studies and NICE guidance

HES (both IP and OP activity) suggest that the number of sleep studies carried out has increased since the records began in early 2000. Further, both data sets show a sharp increase in the activity between 2007 and 2008. During the same period, there was also a sharp decrease in the waiting time for a sleep study (from 85 days in 2006-06 to 36 days in 2008-09 according to data from inpatient sleep apnoea episodes). Further, according to monthly sleep activity (figure 3.3), the proportion of patients who had been waiting for a sleep study for more than 6 weeks also reduced from 52% in Jan 2007 to 10% in Feb 2008. These changes appeared to have coincided with the publication of the NICE technology appraisal for CPAP in 2008.[108] It is likely that these changes increased awareness about SDB and the importance of prompt investigation. But most importantly the NICE publication would have supported supply and commissioning of sleep services in England. The purpose of NICE guidelines is to help CCGs/PCTs deliver higher quality care.[268,269]

Since 2006, the proportion of patients waiting for more than 6 weeks for a sleep study has also reduced significantly (from ~60% in 2006 to ~2% in 2016) and the number of sleep studies has also increased steadily overtime. Thus, it suggests that the demand for sleep services has also increased in parallel, likely related to the increased awareness and a lower threshold for referral by healthcare professionals. This is illustrated from the monthly sleep activity (figure 3.2), which shows a sharp increase in the number of sleep studies carried out towards the end of 2015. During this period, toolkits and leaflets aimed at

healthcare professionals in primary care[42] and commissioners[269] related to OSA were published by the British Lung foundation, which could have further raised the awareness of SDB. In addition, the results of the ground breaking SERVE-HF trial was published around the same period.[270]

3.5.4 Limitations

Although the HES is a large database with nearly 125million patient records per year, and can provide useful insights into clinical practice within the NHS, there are many limitations. The data collection is based on routine coding in hospital clinical practice and is usually coded retrospectively once the patient has been discharged. The process of coding rarely receives input from trained medical professionals such as doctors or nurses who have patient contact; thus, the clinical diagnosis could be potentially misinterpreted or missed, leading to further error. Further, the coding process is unlikely to have the same stringent data quality measures such as a large clinical trial or well-maintained clinical registry. Recent reports have highlighted inaccuracies in data derived from the HES database, such as missing data, errors in coding and data linkage.[271] Moreover, during the analysis of HES data, 96-98% of records for outpatient activity were found to be coded as "unknown" or having an "unspecified cause of morbidity", suggesting that a large proportion of data may not have been included.

Another limitation of the HES data is the way sleep studies were coded, because in 2008 a new coding classification was introduced for sleep studies and polysomnography. The usage and differences in the adoption of these codes, is

unlikely to fully account for the large increase in the number of sleep studies and the fall in waiting times (e.g. compared to introduction of NICE guidelines, service expansion, improved awareness and socioeconomic impact), but should be considered during the interpretation of these data, as it could be a potential confounder. Further, some of the effect could also reflect a lag in the adoption of this new coding system that could have contributed to the low rates seen during the early years and soon after 2008. However, since the new coding system began for polysomnography in 2008, the number of admissions has also increased steadily, up to 5-fold from 2008 to 2013. The waiting time for polysomnography also increased in parallel during this time and approximately 80% of the patients were admitted from a waiting list for polysomnography. These follow similar patterns to the data coded using the previous coding classification.

HES data do not clearly define or distinguish the difference between OP and IP sleep apnoea episodes. Although, an IP episode could be inferred as an admission to hospital for 1 night for overnight polysomnography (suggested by the median length of admission for these episodes being 1 day), making such an inference for OP episodes is difficult. The coding and HES data dictionary do not provide details whether these OP episodes relate to routine clinic appointments for SDB assessment by physicians, sleep studies conducted in an OP setting (e.g. home polygraphy using Embletta devices) or patient visits for titration of therapy/masks. However, HES data has given a valuable overview of the variation and the demands on the sleep service in England, over the past decade, but these findings should be interpreted with caution.

HSE 2010, although it had a respiratory focus, was not designed to study SDB specifically. In addition, the main aim of the HSE is to understand the general health of people of England and the influence of socioeconomic impact. Therefore, the data obtained from the HSE related to SDB is very limited (which only included 3 questions), and the validity of these questions in relation to a potential diagnosis of SDB has not been determined. The data collection is also retrospective. Although quality control measures are adopted for the HSE, they could be less rigorous than some of the large studies carried out in the US, such as the Sleep Heart Health Study. In addition, subject responses (e.g. whether they have been investigated for SDB or undergoing treatment for SDB) were not checked against their GP record, however, this reflects the inherent reporting bias of surveys. The limitations of surveys are discussed in section 4.5.

3.6 Conclusion

The data from the HSE 2010, HES and NHS RightCare, revealed important factors related to the epidemiology of SDB and the provision of sleep services in the UK. There was a large geographical variation in the sleep service in the NHS, and most alarmingly, there appears to be a mismatch between the provision of these services and both the likely prevalence and population risk for cardiovascular disease and SDB. This suggests a considerable underdiagnosis and undertreatment of SDB. The subsequent chapters will explore these concepts and any additional barriers to diagnosis and treatment of SDB.

Chapter 4: Management of sleep disordered breathing in primary care in the UK

4.1 Aims

The aim of this chapter is to understand the factors affecting the diagnosis and management of SDB in primary care, using surveys of GPs and patients

4.2 Background

Significant variations in service provision, such as the variation of sleep services in the NHS described in Chapter 3, is likely to have a significant impact on the management of SDB in primary care. Primary care accounts for a large proportion in the NHS, both in terms of the number of patients seen and funding. 90% of all patient interactions in the UK are in primary care,[272] and as of April 2016, ~58 million patients were registered with General Practitioners (GPs).[273] CCGs (which replaced Primary Care Trusts in 2013), are also allocated 60% of the total NHS budget of ~£116 billion.[274] Moreover, GPs in primary care play a significant role in delivering care to the UK population. Therefore, an understanding of the management of SDB in primary care is important.

GPs, in addition to being the first point of contact for most patients with undiagnosed health problems in the community, are responsible for controlling patient access to specialist care, especially when patients require further assessment of their conditions. As such, they serve a 'gate-keeper' function. Patients can also access healthcare care privately (either self-pay or via medical insurance), but this only accounts for a small proportion of all consultations. For example only 3% of GP consultations are private.[275] Under the NHS rules,

patients do not have direct access to either secondary or tertiary centres, and as a rule cannot be seen in those settings without a formal GP referral.[276] Although some primary care services offer limited specialist services, such as the management of chronic heart failure[277] or diabetes, for most patients requiring specialist advice, a GP referral to secondary or tertiary care is necessary.

SDB is also a condition that requires input from specialist services for both diagnosis and treatment. Although some GPs with a special interest work in conjunction with tertiary centres and conduct basic screening using pulse oximetry,[278] currently, diagnostic sleep services are not routinely and widely available directly through primary care.[269]

4.2.1 Identification of patients with SDB in primary care

GPs have an important responsibility to identify patients with SDB in the community and to promptly refer them for assessment. This particularly applies to the people who present with symptoms but conceivably also to people who are asymptomatic but have an increased cardiovascular risk. A recent publication from the British Lung Foundation (BLF) reported that up to 80% of patients with OSA could be undiagnosed and untreated,[13] and as discussed in section 2.2.2.3 (using the prevalence estimates for asymptomatic OSA), this figure could easily be ~5 million.

Several studies have demonstrated a difference between the rate of diagnosis of SDB and the presence of symptoms. In 2002, a sub study of the Sleep Heart Health Study (SHHS) involving 15699 subjects,[279] found that the mismatch

between the diagnosis of OSA by physicians, and the presence of symptoms as reported by patients, could be up to 3-fold. Surveys were conducted as part of this large study and subjects were divided into 3 groups: people who reported symptoms related to SDB such as snoring and daytime sleepiness (self-reported group), subjects who had been told by their physician that they had OSA (physician-diagnosed group) and subjects who reported that they had previously been both diagnosed and treated with either O_2, PAP therapy or surgery (diagnosed & treated group). The prevalence for each group was 4.1%, 1.6% and 0.6%, respectively. Only a tenth (68 out of 650 subjects) from the self-reported group (i.e. subjects with possible OSA) had their OSA either investigated or diagnosed by a physician. Only 14 patients from this group (2.2%) had their OSA both diagnosed and treated.

Similar results were found as part of the French cross-sectional survey (ESPS; Enquête Santé et Protection Sociale or French health, health care, and insurance survey).[280] The 2008 survey consisted of questions related to sleep disorders including OSA and included 12203 adults, who were a random sample of the French population insured under the French health insurance companies (this covers 96.7% of the French population). Patients were asked about symptoms related to SDB, and daytime sleepiness was also assessed using the Epworth sleepiness scale (ESS) as part of this survey (Table 4.1, A). The presence of symptoms that were highly suggestive of OSA was used to define patients who were at risk of having OSA, using an algorithm.

Questions asked in the Survey			
1	Do you have non-restorative sleep? (i.e. poor quality sleep)	3	Have you been told that you stop breathing during your sleep?
	yes		*yes*
	at least three nights/week		*no*
	yes, one or two nights/week		
	yes, less than one night/week		
	no		
2	How do you feel after a typical sleeping night?		
	completely rested	4	Do you snore?
	refreshed		*no*
	slightly tired		*rarely*
	very tired		*often*
5	Epworth Sleepiness scale (ESS)		*almost every night*
	(see Appendix for questions)		*do not know*

(A)

Diagnostic algorithm to define symptoms highly indicative of OSA	Prevalence (95% CI)
Frequent snoring (almost every night) plus (witnessed apneas or ESS >10).	4.9% (4.5–5.3)
Frequent snoring plus (witnessed apneas or non-restorative sleep at least three nights a week)	4.1% (3.7–4.4)
Frequent snoring plus (witnessed apneas or feeling tired after a typical sleeping night)	5.7% (5.3– 6.2)
Self-reported Diagnosis and treatment	
Has a medical doctor ever told you that you had OSA?	2.4% (2.1–2.6)
Have you previously undergone sleep recording performed at the hospital or at your home?	2.6% (2.3–2.9)

(B)

Table 4.1 French cross-sectional survey (2008)

Questions related to OSA (A) and the criteria in which the algorithm was based on to define patients with possible OSA (B)
Adapted from Fuhrman et al[280]. Items from the Epworth Sleepiness scale (ESS) is not shown here as it is included in the Appendix.

Using these different algorithms (table 4.1, B), the estimated prevalence of OSA was ~5%. In comparison, the prevalence of self-reported OSA (i.e. people who have been told by their doctor to have OSA) was 2.4%. In addition, 2.6% have had some form of sleep study or monitoring. Only 15% of patients with possible OSA, had any form of sleep monitoring.

These two surveys suggest that only 10–15% of people who report symptoms consistent with OSA, have any form of investigation. An accurate measure of the rate of underdiagnosis cannot be obtained reliably from these data, due to reasons such as self-reporting bias and that the prevalence of OSA represented in these study cohorts is purely defined by the presence of symptoms and not based on PSG/PG, thus the actual prevalence of OSA may differ. However, these studies clearly demonstrate the significant difference between the proportion of subjects who report symptoms consistent with SDB and the patients who were diagnosed after clinical assessment. This highlights the problem of poor recognition and screening of patients who are at risk of OSA in the community. Underdiagnosis of SDB has not been formally studied in the UK primary care.

The aim of this chapter is to understand the diagnosis and treatment of SDB in the UK primary care setting, by analysing surveys that had been previously carried out in primary care. Two were conducted in primary care (in 2009 and 2011) and one in patients who were part of ResMed's "RealSleep" programme.[281] These surveys were initially conducted with the aim to explore views about SDB and included multiple-choice questions (MCQs) but also had the facility of acquiring free-text responses. The aim was to explore the dynamics of the GP–patient relationship, circumstances surrounding the patients' initial presentation to their GP, and highlight both physician and patients' views about the recognition of the initial symptom profile, potential underdiagnosis and delays to diagnosis and treatment.

4.3 Methods

4.3.1 GP Surveys

Two GP surveys had been carried out by Doctors.net in 2009 & 2011 to explore the attitudes of GPs towards sleep apnoea.

4.3.1.1 Participants

This survey included ~1000 GPs who were part of the Doctors.Net register, which consisted of a total of 22 000 'active' GPs. This is a third of the total number of GPs (~67000) registered in the UK.[282] The GPs were considered 'active' if they had logged into the Doctors.Net website at least once during the preceding 90-day period. The 1000 GPs who responded were from a group of self-selected GPs – a subset of the GPs registered with Doctors.Net who were happy to be surveyed and had previously expressed an interest in participating in research, when they initially signed up to the Doctors.Net website. These doctors were contacted via email with clinical bulletins and promotional campaigns and the survey was conducted online.

The survey ran until 1000 responses were obtained from this subset of the self-selected GPs. The 1000 GPs were a geographically representative sample; a quota was allocated to each region based on population and GP density according to NHS workforce statistics.[283] The number of GPs who participated in the survey from each Strategic Health Authority (SHA) is presented in figure 4.1. The highest participation was from Northwest of England, London and Scotland with ~11% representation from each of those SHAs. Further, 30% of the GPs described that they were practicing in a 'rural' area, the rest in an 'urban' area.

Strategic Health Authority (SHA)	No of GPs in survey
Northern Ireland	30
North East SHA	45
Wales	47
East Midlands SHA	65
South Central SHA	65
South East Coast SHA	67
Yorkshire & Humber SHA	83
West Midlands SHA	84
East of England SHA	88
South West SHA	94
London SHA	108
North West SHA	110
Scotland	114

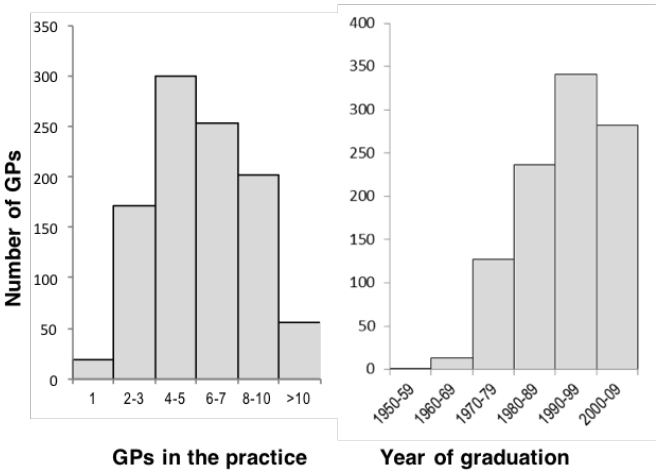


Figure 4.1 Characteristics of GPs who participated in the 2009 survey

Representation of the 1000 GPs by the size of practice, year of graduation and the number of GPs in the survey belonging to each strategic health authority (SHA)

Most of these GP practices (55%) had around 4-7 GPs practicing within the surgery. There were also larger GP practices, where 26% of them having more than 8 GPs, and 2% were single-handed GP practices. This group included GPs from a variety of background and roles; 63% were GP principals, 24% were salaried GPs, 5 % were GP registrars and a small proportion were locum GPs (7%). There were no doctors from secondary care (i.e. non-GPs). The distribution of year of qualification is also shown in figure 4.1. 589 of the GPs were Male (59%).

4.3.1.2 Survey design

The two surveys conducted in 2009 and 2011 were cross-sectional surveys. The survey questionnaire included MCQs and it also had the facility to include free-text responses. The survey questions were designed to explore the attitudes of GPs towards the diagnosis and treatment of SDB (mainly OSA). The questions were written by a medical writer and peer-reviewed by 2 doctors (a consultant/professor of respiratory and sleep medicine and one GP).

A full list of questions from the survey is shown in Table 4.2. In summary, this included questions about the GPs role in the practice, their experience, the size (i.e. number of patients seen each month) and the geographical area of the practice, their understanding of risk factors (e.g. Type II DM, heart failure) and the management strategies of SDB (e.g. advice given to patients and referral to specialist services). The questions with free-text responses enabled the GPs to express any additional comments such as reasons for not referring patients with SDB to specialist services or any other management strategies they used (these free-text responses are analysed in Chapter 5).

1	Overall, how many patients do you see in a typical month (not just those you see for Obstructive Sleep Apnoea)?
2	And of these patients you see in a typical month, how many have Obstructive Sleep Apnoea (OSA)?
3	How likely are you to consider OSA in your overall management of the following patient groups (Diabetes and Heart failure)? *□Not at all likely □Not very likely □Somewhat likely □Very likely □Don't know*
4	Which, if any, of the following types of advice do you give to your patients who you suspect of suffering from sleep apnoea? *□Lose weight □Give up smoking □Avoid alcohol □Keep a sleep diary □Sleep on your side & not back □Use decongestant drops, capsules or tablets □Other (please specify) □Do not offer any advice*
5	How many suspected sleep apnoea patients would you refer in a typical month?
6	To which of the following would you refer your sleep apnoea patients to? *□A Sleep Centre □Weight loss clinic □A cardiologist □A Care of the Elderly specialist □An endocrinologist □Other (please specify)*
7	Why would you not refer patients you suspect of OSA to specialist care?
a	Which of the following best describes your role in the practice? *□GP Principal □Salaried GP □GP Registrar □Locum GP*
b	Where are you currently practising?
c	Please write in the number of GPs working in your practice (including yourself).
d	Is your practice based in a*...(Urban/Rural)* area?
e	Are you*...(M/F)*?
f	When did you qualify as a doctor?

(A)

1	What do you look for when identifying obstructive sleep apnoea? *□Excessive daytime sleepiness □Snoring □Obesity □Repeated complaints from patient □Depression □None of the above*
2	What action do you take if you suspect obstructive sleep apnoea? *□Refer to a sleep centre □Provide lifestyle advice □Refer to a specialist weight loss clinic □Refer to a cardiologist □Refer to an endocrinologist □Refer to a Care of the Elderly specialist □Other (please specify) □Would never refer patients for OSA*
3	Why would you NOT refer a patient with suspected obstructive sleep apnoea to a sleep centre? (Verbatim/Free-text responses)
a	Which of the following best describes your role in the practice? *□GP Principal □Salaried GP □GP Registrar □Locum GP*
b	Where are you currently practising?
c	Please write in the number of GPs working in your practice (including yourself).
d	Is your practice based in*...(Urban/Rural)* area?
e	**Is your practice a dispensing practice?** *(Yes or No)*
f	Are you*...(M/F)*?
g	When did you qualify as a doctor?
h	**Are you**...(AGE)**?**
i	**How many patients do you have on your practice list? ……**

(B)

Table 4.2 Questions from the GP survey in 2009 (A) and 2011 (B)

Questions listed numerically (e.g. 1,2,3) inquired about the GP experience and views about OSA and Questions listed alphabetically inquired about characteristics of GPs (questions in bold are new questions that were introduced as part of 2011 survey)

4.3.2 Patient survey

The "RealSleep" survey was a survey of 753 patients carried out by ResMed in 2010. These patients were part of the "RealSleep" programme of ResMed (UK).[281] The RealSleep programme is a paid-membership offered by ResMed for the ongoing care of patients who are on treatment for SDB and it consists of ~6000 patients. These patients were approached via e-mail, and the survey was conducted through an online questionnaire (www.surveymonkey.com), which had a series of multiple choice questions and free-text responses. The full list of questions is included in Table 4.3. 48% who responded to this survey had been on CPAP therapy for more than 5 years.

How long have you been on CPAP? (Please select only one answer)
☐Less than a year ☐1-2 years ☐ 2-4 years ☐5+ years
What symptoms did you have that took you to your GP? (Tick all that apply)
☐ Tiredness or sleepiness ☐ Snoring ☐ Witnessed stopping breathing at night (apnoeas) ☐ Choking episodes at night
Other (please specify)
When you first described your symptoms, did your GP recognise you may have OSA?
Yes
No
Don't know
Did you suggest the diagnosis of OSA to your GP?
Yes
No
If 'Yes', where did you learn about OSA? (Open-Ended Response)
Did your GP refer you immediately to a sleep centre to be tested for OSA?
Yes / No
If you answered 'No'
**** How many visits did it take to the GP before you were referred?***
**** If you were not referred at the first visit, what was the outcome of that first visit? (Select all that apply)***
☐ Told to lose weight ☐ Advised to stop smoking ☐ Referred to ENT for possible surgery ☐ Treated for depression
Other (please specify)
How long was it before you were seen at the sleep centre after referral by your GP?
☐ 0-6 months ☐ 6 months – 1 year ☐ 1-2 years ☐ 2+ years
Other
Did you obtain treatment via the NHS?
Yes / No
**** If you answered 'No', was it because:***
☐ Waiting list too long ☐ No local sleep unit ☐ GP advised that NHS treatment was not possible
Other (please specify)
In which area is your sleep clinic located? (Open-Ended Response)
Do you continue to receive care/replacements parts at your sleep centre?
Yes / No
**** If you answered 'Yes', do you receive follow up care/replacements:***
☐ Regularly ☐ As required ☐ Phone advice only
Other (please specify)
**** If you answered 'No', is that because:***
☐ No funding available ☐ Service not offered ☐ Chose not to attend further follow up
Other (please specify)
Questions that were present in the survey but not analysed
When was your treatment last reviewed by a doctor or specialist nurse/physiologist?
When did you last replace your mask or its cushion/headgear?
Did you receive replacement masks, mask parts and filters via the NHS?
Did you receive replacement masks, mask parts and filters via the NHS? - Other (please specify)
We are constantly working to deliver high standards of customer service at ResMed to meet the needs of patients. How would you rate the customer service level provided by ResMed?
We are constantly working to deliver high standards of customer service at ResMed to meet the needs of patients. How would you rate the customer service level provided by ResMed? - Other (please specify)
To help us better understand your experience during OSA diagnosis and CPAP treatment, please add any other comments you feel are applicable. Your feedback is valuable to us (Open-Ended Response)

Table 4.3 Questions from the patient survey

4.4 Results

4.4.1 GP survey

Data from the MCQs, were related to the number of patients seen by GPs, their perceptions about the relationship between OSA and other cardiovascular disease such as diabetes and heart failure, different management options for OSA and the referral of patients to specialist sleep services. The data presented in this chapter are quantitative (analysis of free-text responses from the surveys are presented in Chapter 5).

4.4.1.1 Number of patients seen per month

The majority of GPs (70%) saw approximately 200-600 patients per month (median and mode = 400 patients) and these figures are similar to the national average.[284] However, most GPs (55%) stated that they were seeing ~1–2 patients with OSA each month (median = 2; mode = 1). This distribution appears to be resemble a 'bi-modal distribution' pattern with two peaks: one for GPs seeing 1-2 patients and the other for GPs seeing 5 patients with OSA per month (Figure 4.2). This pattern was observed irrespective of region and characteristics of GP (e.g. sex, year of graduation or type of GP).

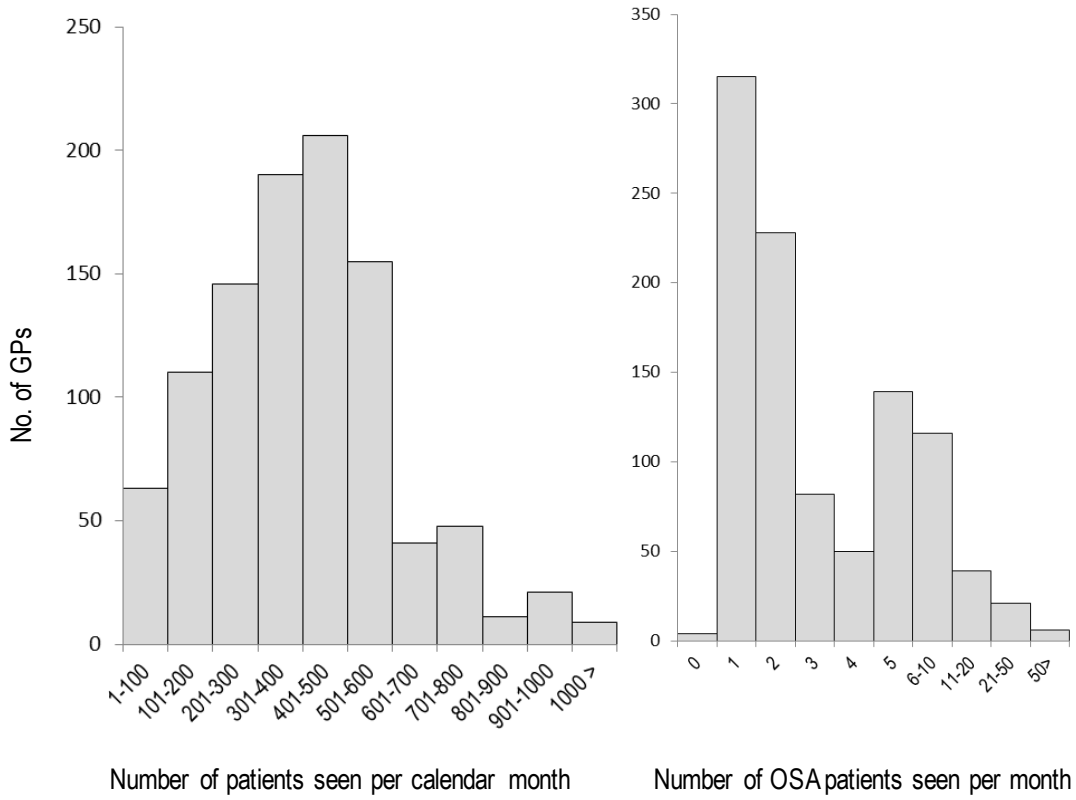


Figure 4.2 The number of patients seen by GPs

Total number of patients seen by GPs (on left) and the number of OSA patients seen by GPs (right)

4.4.1.2 Associations of OSA with heart failure and type II DM

The GPs were asked whether they would consider OSA in the management of patients with heart failure and type II diabetes from the following options; *Not at all likely, Not very likely, Somewhat likely, Very likely or Don't know*. Majority of the GPs (47% for heart failure and 49% for Type II Diabetes) mentioned that they would consider OSA in both conditions as "*Somewhat likely".* However, the proportion of GPs who considered the options "*Not at all likely" or "Not very likely"* were higher compared to the GPs who considered "*Very likely",* for both heart failure and Type II Diabetes (28% versus 20% and 25% versus 23%, respectively). This pattern was again observed across all GP demographics (sex,

year of graduation, and type of GP) and was statistically significant ($p<0.05$). Moreover, 4% (39 GPs) answered this question as "*Don't know".*

4.4.1.3 Management of sleep disordered breathing

Nearly all the GPs (98%) identified losing weight as an important management strategy for patients with SDB. A high proportion of GPs also identified giving up smoking and alcohol as important aspects of managing these patients (93% and 88%, respectively). More conservative management strategies were also considered, such as keeping a sleep diary (55%) and patient sleeping on their side (i.e. not on their back) (46%) as part of the management of SDB. Further, 20% of GPs considered the use of decongestant drops, capsules or tablets as part of their management plan. A similar pattern was observed regardless of the GP demographics.

4.4.1.4 Referring patients to specialist sleep services

61% of GPs (614) responded that they would refer at least one patient with SDB every month to specialist services (this included 48% of GPs referring one patient and 13% referring 2 or more patients in a calendar month). Of the 614 GPs who said that they would refer, further attempts were made to explore which specialist services they would choose when referring these patients. 78% of these GPs said that they would refer the patients to a sleep centre. However, the rest of the GPs suggested other options such as referring patients to a weight loss clinic, a cardiologist, elderly care specialist or an endocrinologist. Referring SDB patients to these specialist services are not routinely considered as the primary management strategy as part of the referral pathways for investigation of patients with SDB.

386 GPs (39%) said that they would not refer patients presenting with sleep apnoea at least once within a calendar month. However, 99% of the GPs reported to have seen at least 1 patient with OSA in a calendar month. This suggests that considerable number of GPs may not refer patients to specialist services who presents to them with OSA. Again, this pattern was repeated and was not related to the GP demographics. These GPs, answering this option (i.e. if they answered "0" to the question "*How many suspected sleep apnoea patients would you refer in a typical month?*"), had the opportunity to express their reasons for non-referral using free-text responses, which is explored later in chapter 5 (section 5.4.1).

4.4.2 Results of the 2011 GP survey

The characteristics of the GPs from the 2011 survey did not differ significantly from 2009. The size of practice (the average number of GPs working in a practice was 6), sex distribution (58% were male) and their role in the practice (GP principals and salaried GPs were 64% and 25%, respectively) were similar to the 2009 survey. The year of qualification was almost identical to the 2009 survey, despite a small increase (by 3%) in the GPs graduating between 2000 and 2010 and a small decrease in the GPs who qualified in 1970-1979 and 1980-1989 (by 2% and 1%, respectively). Location of practice, as determined by the SHA was also similar, despite a proportional increase in the number of GPs from Northern Ireland and a decrease in GPs from Scotland and North West.

Three additional questions were asked in the 2011 survey, which inquired about the age of GPs, the number of patients registered in the practice and whether it had the capacity to dispense. Most GPs (43%) were between the ages of 30 and

39, and only 6% were above the age of 60 and 3% were under the age of 30. Almost two thirds of the GP surgeries (61%) had more than 6000 patients registered and only 8% had less than 2000 patients. Almost all the practices (84%) did not have the capacity to dispense.

Two questions were asked about the GPs' understanding of OSA, where one of these questions was related to symptom recognition and the other was related to management of SDB. Almost all GPs (93-97%) responded that they would enquire about symptoms such as excessive daytime sleepiness, snoring and obesity when seeing patients with OSA. In relation to management options, ~80% of GPs answered that they would refer the patients to a sleep centre and offer lifestyle advice.

4.4.3 Results of "RealSleep" patient survey

Data were available for 753 patients, who were enrolled in the ResMed patient support programme and undergoing treatment for OSA. 98% (737 patients) reported having at least one symptoms related to SDB (either tiredness or sleepiness, snoring, witnessed apnoeas or choking episodes at night). 51% (385 patients) had at least three of these symptoms, which may be strongly indicative of having SDB. The data are summarised in table table 4.4.

No. of symptoms	No. of patients having symptoms	Not 'recognised' by GP		Not referred Immediately		Taking 3 or more visits to GP for referral		Waiting longer than 6 months to be seen at a sleep centre	
4	97	37	*38%*	42	*43%*	27	*28%*	17	*18%*
3	288	96	*33%*	93	*32%*	30	*10%*	52	*18%*
2	203	78	*38%*	83	*41%*	38	*19%*	36	*18%*
1	149	59	*40%*	58	*39%*	28	*19%*	22	*15%*
	737	**270**	***37%***	**276**	***37%***	**123**	***17%***	**127**	***17%***

Table 4.4 Summary of findings from the RealSleep patient survey

30-40% of patients having symptoms consistent with SDB (as reported by patients), were not recognised by GPs, and a similar proportion were also not referred to a sleep centre immediately. ~20% of patients reported to visiting their GP more than 3 times or taking more than 6 months, to be ultimately seen at a sleep centre. Patients with either 3 or more symptoms (grey area) are likely to have a high suspicion of SDB

4.4.3.1 Recognition of OSA by GPs (as perceived by patients)

Of the 737 patients who reported symptoms, 37% stated that GPs did not recognise that they may have OSA, and a similar proportion reported that they were not referred to a specialist sleep centre 'immediately'. Even in patients having strong suspicion of SDB (i.e. having 3 or more symptoms), lack of recognition of OSA and lack of referral was 34% (133 patients) and 35% (135 patients), respectively. Further, 14% (55 patients) reported that their OSA was neither recognised nor they were referred to specialist services.

A third of patients (238 patients) stated that they had themselves raised the possibility of having OSA. However, despite suggesting the diagnosis, ~50% of them (115 patients) reported that their OSA was not 'recognised' and more than

a third (90 patients) felt that they were not referred promptly to specialist sleep services.

Of the patients having symptoms and who were not referred to a sleep centre during the first visit, in 45% (123 patients) it took 3 or more visits to the GP to be ultimately referred. 17% (127 patients) waited for more than 6 months for a sleep study. In patients having 3 or more symptoms related to OSA, the proportion requiring more than 3 visits to GP or waiting more 6 months, was also 17%.

4.4.3.2 Delays experienced by patients for diagnosis and treatment

Of the 288 patients who stated that they were not referred to specialist services during their 1st visit, it took an average of 2.9 visits to the GP (SD: 1.45; median = 3) to receive specialist input. Nearly half the patients reported that they had to see their GP at least 3 times before they were referred to specialist services.

75% who responded to this survey (568 patients), reported that they were seen at the specialist sleep centre within 6 months of the referral being made. 17% of patients waited longer than 6 months, further, a small proportion of patients (~4%) waited more than 2 years to be assessed at sleep centre from the time of referral. Of the patients who had at least 3 symptoms, the proportion who required 3 or more visits to their GP or waited for longer than 6 months for an assessment at a sleep centre, were both 17%.

4.5 Discussion

Data from both the GP and the patient surveys highlight the potential underdiagnosis of SDB and underreferral of patients with SDB to specialist sleep services in UK primary care.

4.5.1 Underdiagnosis and Underreferral of SDB

The number of patients with OSA seen in a calendar month, as reported here by GPs, were less than the epidemiological estimates. For example, a GP seeing ~400 patients in a month, assuming a prevalence estimate of 4% for symptomatic OSA and that the patients are seen at the same rate, should be seeing at least 16 OSA patients with symptoms per month, or more if asymptomatic OSA is considered (which could be up to 30 patients per month). However, most GPs (55%) stated that they were seeing only 1 or 2 patients per month, a difference of up to 30-fold. These statistics cannot be generalised due to many other variables, for example many patients with symptomatic OSA may not present to their GPs, however, it suggests that the underdiagnosis of SDB in primary care is likely to be significant. This observation is further strengthened by the data from the patient survey. As reported by patients, only a third of them were 'recognised' to have OSA. This even applied to patients having multiple symptoms which could be highly indicative of SDB.

Even lower rates have been reported in the literature.[285] A study designed specifically to explore this question by Reuveni and colleagues,[286] found that only 10% of sleep related symptoms were recognised. This study was carried out using an actor, who simulated a 26-year-old woman suffering from OSA. She

randomly took part in consultations with 30 physicians and these sessions were incorporated into the physicians' routine clinical practice. The consultation was standardised, where the presentation of the case history and responses to physician questions were carried out in a systematic and an identical manner. However, physicians were 'blinded' to this clinical scenario but were expected to take a history from patients with suspected SDB, and then their performance was evaluated against a predetermined checklist of 15 questions. The study found that only 3 of the 30 primary care physicians who participated asked 3 or more of these questions. 50% of them did not ask relevant questions about OSA such as daytime sleepiness and snoring. At the end of the simulated consultation (after the diagnosis had been revealed), primary care physicians were asked 3 further questions about their self-awareness and knowledge about OSA. 90% of them responded that they would consider further assessment of OSA at a sleep laboratory and only 50% identified that OSA was associated with an increased cardiovascular risk.

The GP survey also showed a difference between the number of patients seen and the number of patients referred to specialist services for assessment. ~40% of the GPs said they do not refer any patients with sleep apnoea in a calendar month. Even accounting for patients who may be already on treatment and had sleep studies, the underreferral is likely to be significant as 99% of the GPs who reported that they see at least 1 patient with OSA in a calendar month. In addition, only 2% of the GPs participating in the survey expressed a sleep study as a suitable management option. The patient experience also demonstrates the problem of underreferral and delayed referral for sleep studies. ~40% of

patients reported that they were not referred to a sleep centre when they presented with symptoms related to SDB on their first visit to the GP. In ~20% of patients, it took them 3 or more visits to the GP to be ultimately referred and in a similar proportion, it took more than 6 months from the referral to be assessed at a sleep centre.

4.5.2 Understanding the factors responsible for underrecognition of SDB

The poor awareness among primary care physicians when seeing patients with possible OSA and their lack of understanding of its potential risks, have been proposed as one of the potential factors for lack of recognition and management of SDB.[285] This has been attributable to the lack of emphasis and the limited number of topics that are taught related to SDB in the medical school curriculum.[287] However, it is unlikely that a lack of GP knowledge about SDB could solely be responsible for the underdiagnosis of SBD in primary care. Nearly half the GPs in the survey demonstrated that SDB can be associated with cardiovascular risk factors such as diabetes. Further, the 2011 GP survey showed nearly all GPs (~97%) stated that they would look out for symptoms such as excessive daytime sleepiness, snoring and obesity, when seeing patients with OSA. In addition, ~80% of GPs were aware that referral to a sleep centre was an important management option, which is similar to the findings of the study carried out by Reuveni and colleagues (section 4.5.1).[286]

The concept that a potential lack of physician knowledge is likely to be responsible for the underdiagnosis of SBD, is explored by a US study carried out by Grover and colleagues.[288] It included 249 consecutive patients from two

family practices in Arizona (this was equivalent to approximately two thirds of all patients seen during a 6-week period between 16th March to 30th April 30 in 2009). Patients who had a prior diagnosis of SDB were excluded. Before the appointment, all patients were asked to complete the Berlin questionnaire, which was used as a screening tool and a surrogate for determining the risk of OSA. Physicians however, were not given the results of the Berlin questionnaire. Patients were also required to complete another questionnaire which included two questions related to sleep (e.g. "are you tired much of the time?" and "do you frequently have trouble sleeping?"). At one site this completed questionnaire was used during the consultation, however on the other site, the physicians were expected to ask these questions related to sleep during the consultation. Overall 82 patients in the study, answered "yes" to at least one of the above questions related to sleep, but only 9 patients (11%) had their sleep complaints formally investigated. Despite use of this questionnaire, about two-thirds of patients did not have their sleep complaints addressed. In a second stage of this study, knowledge and attitudes of primary care physicians about SDB were assessed using the OSAKA questionnaire.[289] This is a validated questionnaire which consists of 18 items testing the knowledge of OSA and 5 items inquiring about the importance, and the ability to identify and manage patients with OSA. 22 of the 25 primary care physicians who participated in the study completed the OSAKA questionnaire. 70% scored at least 13 of the 18 items correctly and 80% considered that identification of OSA was either 'extremely important' or 'very important'. Despite the wide perception that primary care physicians may lack the appropriate knowledge and understanding of SDB, findings from this study shows that most physicians recognised the importance of SDB. Therefore, it is

unlikely that the knowledge of physicians about SDB to be the primary cause for the poor identification and treatment of patients with SDB.

As described in Chapter 2, most patients with SDB are asymptomatic and they are unlikely to volunteer symptoms, which makes identifying SDB a significant challenge. Further, once patients with SDB have been identified, they require evaluation for SDB and need to be directed to specialist sleep centres with appropriate resources. This referral process, however, may not be straightforward due to the variation in sleep services, as discussed in the chapter 3, where many health areas within the UK did not have access to a sleep centre. Thus, physicians may face additional challenges in obtaining the appropriate diagnosis and treatment for their patients, potentially contributing to the lack of diagnosis and treatment of SDB in primary care. Lack of an onward-referral pathway is also likely to be major barrier to appropriate diagnosis and treatment. Specific barriers will be further explored in the next chapter.

4.5.3 Limitations

The 1000 GPs were from a pool of self-selected GPs, from the 22000 GPs who were on the Doctors.Net register and had previously expressed an interest in participating in surveys. The raw numerical data of the survey was not known (e.g. the number of GPs who replied to this survey), thus, a 'return rate' could not be calculated as the denominator was unknown. We also do not know the duration in which the survey portal was active. Both ResMed and personnel who ran this survey at Doctors.Net were contacted but could not provide these data.

The surveys were carried out by selecting 1000 GPs, which was geographically representative (based on population and GP density of each SHA), however, there appears to be differences in the selection of GPs between 2009 and 2011. Although the proportion of GPs for each SHA generally stayed the same in both surveys, there was a small increase in the number of GPs from Northern Ireland and a decrease in the number of GPs from Scotland and North West in the 2011 survey, compared to the 2009 survey. This suggests a variation in the geographical representation between the two GP surveys.

Some questions in the GP survey were poorly phrased and could lead to biased answers. For example, in the 2009 survey, a GP answering "0" to the question, "How many suspected sleep apnoea patients would you refer in a typical month?", lead to a subsequent question, "Why would you not refer patients you suspect of OSA to specialist care?". A GP, not seeing a patient with symptoms consistent of SDB in a calendar month, does not necessarily mean that they would not refer to specialist services if clinically appropriate. 13 GPs who participated in this survey also highlighted this problem.

The RealSleep patient survey was conducted on patients who were part of the RealSleep programme, which included a subscription. Most patients who responded have had private consultations and funded their treatment either with medial insurance or self-funding, due to the long waiting times under the NHS. Therefore, this sample of patients may not reflect the typical patient population in the NHS. Further, there was a considerable gap between the time when the survey was carried out and when the patients presented to their GPs

with symptoms. This is evidenced by the fact that most of the patients who responded had been on CPAP therapy for more than 5 years. Therefore, the validity of these responses could be limited by the ability to recollect these events by patients.

One of the inherent limitations of non-systematically sampled surveys is self-selection bias.[290] The GPs who participated were self-selected, as they expressed an interest in participating in surveys when registering to Doctors.Net. Further, it is difficult establish whether, the views expressed by the GPs in this study could represent the views of GPs who did not participate or the ones who were not on the Doctors.Net register. In addition, it is possible that the GPs who responded were more interested in the topic of recommended diagnosis and treatment of OSA than a typical GP, so the survey results may provide an overtly optimistic impression of GP awareness compared to common clinical practice.

4.6 Conclusion

In this chapter, the quantitative analysis of the primary care surveys revealed an underrecognition, underdiagnosis and underreferral of SDB in primary care in the UK. In patients presenting with possible OSA, the rate of referral to a specialist sleep centre is likely to be no more than 17%. Although a lack of GP awareness about SDB has been suggested as a possible factor, it is likely that many barriers interact and contribute. Therefore, I set out to gain a deeper understanding of these barriers using qualitative methodology. This will be explored in Chapter 5.

Chapter 5: Identification of potential barriers to diagnosis and treatment of sleep disordered breathing in UK primary care

5.1 Aims

The aim of this chapter is to identify potential barriers to diagnosis and treatment of SDB in primary care, using content analysis of free-text responses of the GP/patient surveys (that were presented in the previous chapter).

5.2 Background

The lack of diagnosis, investigation and treatment of SDB has been recognised in the literature.[285,286,288] This is also a likely to be a common problem in UK primary care, which has been highlighted in previous chapters. However, the specific factors that could contribute to this have not been formally described. Identification of these 'barriers' to optimal patient care, is difficult to accomplish using quantitative methodology alone because of the complex interactions between patients, primary care physicians and the health service. Thus, exploratory research[291] is required for hypothesis generation and to gain an in-depth understanding of these barriers.

5.2.1 Qualitative research and content analysis

Qualitative research uses an interpretive, naturalistic approach to explore and understand the question of interest using various data collection techniques such as interviews, and open-ended survey responses. Quantitative methods require a more precise definition of the hypothesis, which is usually generated using pre-

existing concepts that can be easily quantified.[292] Due to the lack of prior research on this topic, quantitative methods cannot be used to fully explore the barriers related to diagnosis and management of SDB. However, the use of qualitative methodology in this setting will help to explore physician and patient beliefs, attitudes and their experiences, and help to define these healthcare barriers. Content analysis is such a technique that incorporates qualitative methodology. Doctors.Net GP surveys and RealSleep patient survey (which were presented in Chapter 4), in addition to having multiple-choice questions (MCQs), had the capacity to acquire free-text responses. These text responses or 'statements' from physicians and patients allowed a more in-depth analysis using these methods.

Content analysis is a technique that is used to analyse data, such as text from surveys and transcripts from interviews, in a systematic and reproducible manner, which enables the description of both form and content.[293] It uses a structured coding scheme, which reduces many words of texts into fewer content categories, and provides a more objective description and understanding of the data.[294] This method is beyond a 'simple word count', but can provide a novel insight about the data and can help the interpretation of the research question in detail.[295]

Content analysis is a type of mixed-methods research, as it combines aspects of both quantitative and qualitative methodology.[296] It consists of three distinguishing features: objectivity (i.e. development of a systematic coding scheme using qualitative methodology), organisation (defining and organisation

of categories within the data)[297] and quantification (where descriptive statistics such as the frequency count of those categories, is carried out using quantitative methods).[298] Thus, integrating both these methods can represent a broad overview of the data, with qualitative text interpretation whilst preserving the advantages of quantitative content analysis. This may also reduce researcher bias.[299]

Content analysis has been previously used in cardiovascular research. A French study carried out by O'Brien Cherry[300] used content analysis to explore the beliefs of primary care physicians about CVD risk factors and their perceived best practices for managing CVD. A web-based survey was emailed to 1200 physicians practicing across France, who were members of the French Society of General Medicine. This survey consisted of 45 MCQs and 3 questions with the facility of acquiring "free-text" responses, which were related to physician views about the quality of health care, perceived success factors for managing patients with CV risk, and the reasons for lower death rates in France (compared to the US). 656 physicians returned the survey and the free-text responses were collated to a spreadsheet and coded into categories. The codes were initially generated by recognising key words, which were often repeated. A codebook was developed based on these, and when new themes emerged they were adopted into the coding process. An example of these codes and the frequency of the success factors perceived by physicians for managing CVD, is shown below (table 5.1). A total of 10 themes were identified for this question and the most prominent theme was related to the doctor-patient relationship (which was represented in more than half the responses). This theme was further divided

into 6 sub-themes. It is also important to highlight that the total number of codes were 832, which was far greater than the number of participants. This is because a single response could have multiple codes.

N (%)	I believe I am successful managing patients with CVD risk factors because:		
89 (14)	1	Guidelines or recommendations	Treatment in accordance with established guidelines and recommendations
41 (6)	2	Prevention	Stresses preventive rather than only curative practices
21 (3)	3	Monitoring	Regular measurement and biomonitoring, computerized med records
90 (14)	4	Motivation of doctor	Persistence and commitment
58 (9)	5	Motivation of patient	Follow recommendations; be active participant in care; attend appointments and follow-up
106 (16)	6	Doctor knowledge	Expertise and training
21 (3)	7	Patient diet/lifestyle	Patient knowledge of importance of diet/lifestyle changes
66 (10)	8	Patient health coverage	Access to paid drugs and care
9 (1)	9	Group care	Doctor works with other doctors; nurse involvement
331 (51)	Doctor–patient relationship		
	Sub code		
8%	10	Trust	Patient trusts doctor, doctor trusts patient, bilateral respect, shared responsibility
7%	20	Communication	Nonverbal, verbal, listening
6%	30	Understanding	Patient understands doctor and doctor understands patient
30%	40	Education	Doctor gets patient to understand suggestions, treatment, and biology of diagnosis and disease
14%	50	Social	Doctor is aware of patients' family, financial, work, life goals, and cultural context
35%	60	Time	Length of time in relationship between doctor and patient, time spent with patient

Table 5.1 An illustration of the codebook used in the French study.

A total of 10 themes were identified and their description is shown on the right. On the left (in grey box) the frequency of those themes and sub-themes are presented.

Two methods of content analysis, inductive or deductive, have been described.[294] A deductive analysis is conducted based on prior knowledge, such as after a literature review, and the purpose of the research is to test a hypothesis. On the contrary, an inductive approach is used if sufficient information is not known about the subject prior to answering the research question. The main purpose of inductive analysis is hypothesis generation, where a more general overview will be presented. An inductive approach was used in the French study presented above. Both methods have similarities in their stepwise approach[294] as shown in figure 5.1.

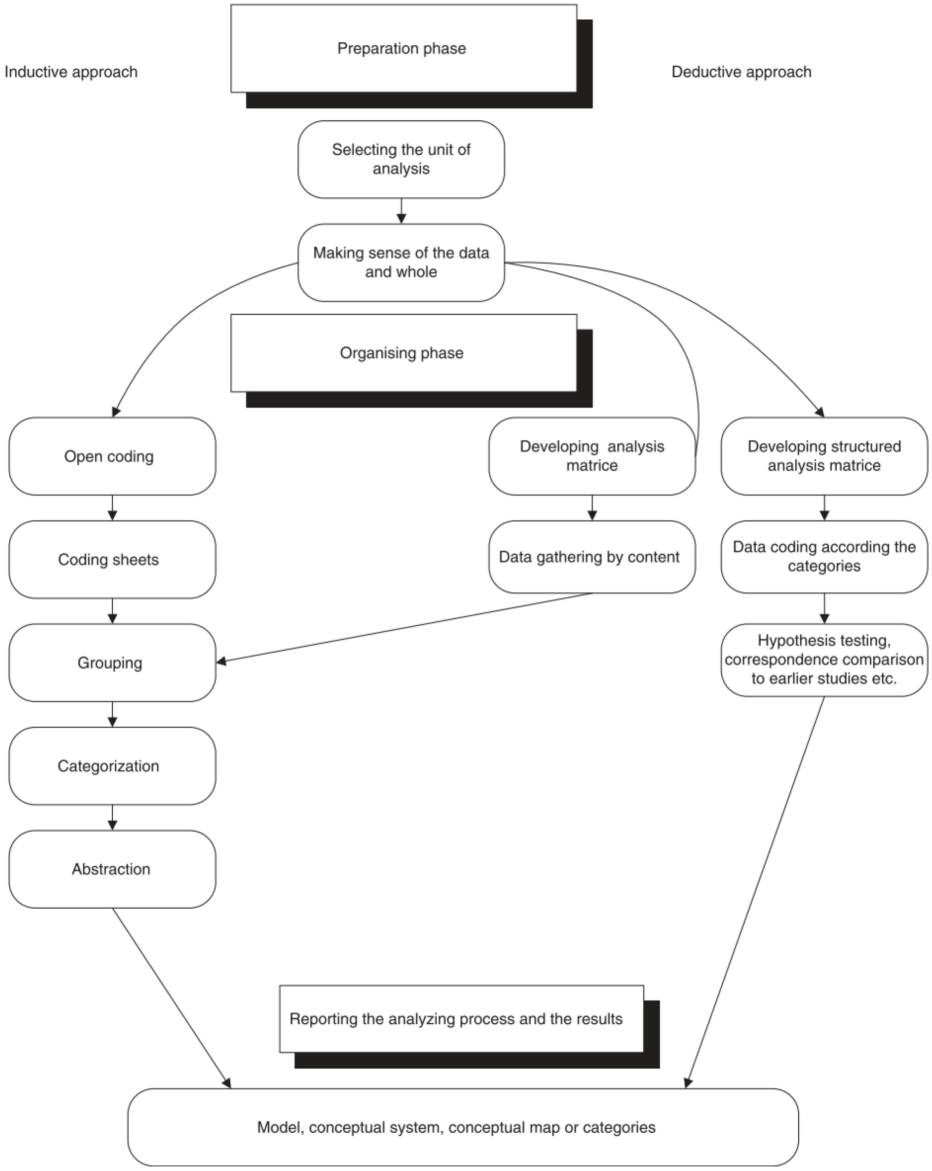


Figure 5.1 The stepwise approaches of content analysis

Inductive approach is shown on the left and deductive approach on the right but both share common features
(Adapted from Elo et al.[294]*)*

An inductive approach was used to analyse the free-text responses from the primary care surveys in this study. This is because as described above, although the underdiagnosis of SDB in primary care has been described (section 4.2.1), thus far, no study has formally explored these barriers to management of SDB, either in primary or secondary care.

5.3 Methods

The methodology described here is related to the analysis of the free-text responses from these surveys. These free-text responses were systematically analysed using content analysis.

5.3.1 Developing the methodology to analyse primary care surveys

The first step is defining the population or the sample from where the data is drawn. As described above, the data are extracted from the free-text responses of the previously carried out primary care surveys, involving GPs (section 4.2.2) and patients (section 4.2.3). In summary, the GP survey included a sample of 1000 GPs from the 22,000 GPs who were registered with Doctors. Net. The patient survey included 800 patients who had been registered with the "RealSleep" programme of ResMed (UK).

5.3.1.1 Unit of analysis

The most important step in content analysis is selecting the unit of analysis.[294] This could be a word, theme, phrase, sentence or a portion of pages or words. However, more precisely it is considered as a 'unit of meaning' used in context during the analysis process.[301] It also has a clearly defined length to maximise data capture and description, for example, the unit of analysis cannot be too narrow (e.g. a single word), which may result in fragmentation of the understanding of the data. On the contrary, a long phrase having several meanings may make the analysis process more challenging. A free-text response that belonged to each subject from the GP/patient surveys, was chosen as the unit of analysis in this study.

A total of 611 free-text responses from the GP surveys and 308 free-text responses from the patient survey were chosen for content analysis. 452 text-responses were from the 2009 survey, where 386 responses were generated from the question, "*why would you not refer patients to sleep services?*", which was available to the GPs who had not referred a patient in the preceding month (i.e. answered "0" to this question; section 4.2.2.3.4). The remaining 73 responses were in reply to the question "*Which, if any, of the following types of advice do you give to your patients who you suspect of suffering from sleep apnoea?*", where one of the options to this question was a free-text entry. In the 2011 GP survey, 152 free-text responses were generated from the question, *"What action do you take if you suspect obstructive sleep apnoea?"*, which included an option to capture any additional comments. Of the 308 free-text responses in the patient survey, 147 responses were related to the question "*If you were not referred in your 1st visit, outcome of 1st visit*?" and 161 were generated as a result of patients answering 'NO' to the question *"Did you obtain treatment via the NHS?"*, which enabled them to express any further remarks.

5.3.1.2 Analytical process and coding

The main objective of analysis was organisation and "making sense of the data".[294] This was achieved by becoming 'immersed' in the data, after carefully reading through the free-text responses multiple times.[295] This process was also coupled with coding, which was central to the process of content analysis.[302] Coding divided the data into categories, which made the management of the dataset much easier. A 'category' was essentially a group of words with a similar underlying meaning,[293] which either repeated or overlapped. Coding and the

development of categories was a dynamic process, where categories with similar meanings or duplicates were combined, the existing ones were changed and/or new discrete groups described. The list of categories was comprehensive, describing the entire dataset and subsequently were merged to form themes.

For each survey, all the text responses were collated into one worksheet managed in MS Excel (MS Excel, Microsoft). Each free-text response was read multiple times and was then coded in the adjacent column next to each response. When coding, key descriptive words from the text-responses were used to build codes. For example, to describe the responses from GPs that related to the lack of diagnostic sleep services, such as "*no local access*", "*limited availability*" or "*No local centre*", the code "access", was used. If one response included two or more mutually exclusive concepts these were coded appropriately with multiple codes. However, a code was not applied multiple times to an individual response.

Finally, these identified categories were reduced to broader themes by grouping the ones that related to each other. Themes where then summarised using descriptive statistics. The number of times that a particular code or a theme was repeated, indicated the number of individuals who expressed that particular view. All the free-text responses and the attached codes are available in the Appendix.

5.4 Results

5.4.1 Themes from free-text responses from GP surveys

The analysis of 73 free-text responses unearthed new themes related to patient management (in addition to the options listed in the survey), such as advising patients to stop driving, completion of the ESS, upper airway interventions such as the use of mandibular devices and obtaining a collateral history from a spouse/partner. Although, this question was available to all 1000 GPs who participated in the survey, and they had facility to enter additional comments, only 23 GPs stated that referring patients to sleep services was an appropriate management step. Further, only 1 GP recognised the importance of checking cardiovascular risk in these patients. Lifestyle management strategies, such as exercise and offering patient information were also listed, in addition to the ones that were already part of the survey (e.g. losing weight and avoidance of smoking and alcohol). The frequency of each of these categories is shown below (table 5.2). Further, 4 GPs described unconventional approaches to managing sleep apnoea: *"fan", "raise head of bed, use fewer pillows"*, "*spouses to try ear plugs*" and *"stay awake in the day".*

Which, if any, of the following types of advice do you give to your patients who you suspect of suffering from sleep apnoea?			Responses (n)
Survey Question Options	Lose weight		985
	Give up smoking		927
	Avoid alcohol		884
	Keep a sleep diary		552
	Sleep on your side/not back		459
	Use decongestant drops/tablets		199
	Do not offer any advice		1
	Other (please specify)		73
Categories from Content Analysis	Stop Driving		9
	ESS Completion		9
	Upper Airway (UA) interventions	Mandibular/UA devices	7
		Treat UA inflammation	3
	Collateral History		6
	Exercise		7
	Referral to Sleep Services		23
	Check CV risk		1
	Patient Information		3
	Unconventional Approach		3

Table 5.2 Management options of sleep apnoea considered by GPs

In addition to the options listed in the 2009 GP survey (in grey box), additional management strategies were generated from the 73 free-text responses after content analysis.

The themes unearthed from the 538 free-text respones from both GP surveys (about the referral for sleep studies), are presented together (Table 5.3). These themes represent the barriers that the GPs potentially experienced in the management of patients with SDB in primary care. 3 major themes were found: poor access to sleep services, GP beliefs and patient factors. The lack of a local sleep service (86 responses) or difficulty in accessing sleep services in either secondary or tertiary care (4 responses), were likely to be the primary reasons that the GPs could not refer patients for sleep studies (as it accounted for ~17% of all GPs who responded). Further, the variation in local policy such as restrictions from PCTs (10 responses), lack of funding for sleep studies and PAP therapy (7 responses) and complicated referral pathways involving either

multiple specialities such as ENT (10 responses) or the lack of awareness of local pathways (3 responses), were other important barriers. 22 GPs however, stated that although they were not able to access sleep services directly, they were able to refer to local respiratory specialists for further assessment.

From the data, it is also evident that most GPs (~16%) were prepared to adopt a conservative management strategy in the first instance, such as weight loss and lifestyle modifications (86 responses). Few GPs did not consider SDB to be a priority, either in terms of cost or clinical importance (5 responses). 13 GPs acknowledged that their self-awareness about SDB was limited, particularly when considering SDB as a potential differential diagnosis when seeing patients. Further, it was also apparent that a few GPs did not perceive that treatment with PAP therapy (4 responses) or input from specialists (3 responses) to be either effective or successful when managing patients with SDB.

26 responses from GPs were related to patient factors. Some GPs believed that patients themselves should be taking responsibility for improving their own health (8 responses). They stated that factors such as lack of motivation in engaging with lifestyle intervention, patient refusal for further investigation (15 responses) due to reasons such as restrictions on driving, and poor compliance with PAP therapy, could affect the management of SDB.

2009 - *Why would you not refer patients you suspect of OSA to specialist care?* **2011** - *Why would you NOT refer a patient with suspected obstructive sleep apnoea to a sleep centre?*				
			Responses (n)	Examples of responses from GPs
Themes from Content Analysis	**Poor Access to sleep services**	Lack of a local service	86	*"We don't have an nhs service for this in my area", "No sleep lab available in area, sadly"*
		Lack of funding	7	*"The local sleep centre can investigate but funds very limited for treatment", "not funded by local LHB"*
		Local policy	10	*"I know our sleep clinic will refuse the referral...pts have to score highly before we can refer"*
		Referral pathway	35	*"We are not allowed to by our PCT, we can only refer to ENT who can then refer on!"*
		Difficult access to 2' or 3' care	4	*"We don't have anyone in 2ary care in our LHB who provides a service and were told not to send any more referrals"*
		Waiting time	9	*"little funding for care, waiting lists years", "lack of appointments in 3 care"*
	GP beliefs	Perception about therapy	4	*"No point. Weight loss is the only cure and wearing crap on your face at night is pathetic"*
		Conservative approach 1st	86	*"treatment is lifestyle changes whether to refer or not", "lifestyle changes first are better"*
		Self-awareness	13	*"Not a disgnosis on the forfront of my mind so probably under refer/diagnose"*
		Priority	5	*"Too many other complex medical problem. Patients not interested."*
		Value of specialist input	3	*"managed by self in my own ENT GPwSI clinic"*
	Patient factors	Perceived poor compliance	3	*"Rx usually uncomfortable/unacceptable (CPAP)", "We do need a motivated patient if CPAP is to work..."*
		Patient choice	15	*"because they usually baulk at the prospect of losing their driving licence"*
		Responsibility	8	*"if they are keen on improving their condition, they should at least try to work on some of the interventions that will help"*

Table 5.3 Potential barriers to diagnosis and treatment of OSA in primary care

3 major themes were identified after content analysis. These were generated from the 538 free-text responses that were related to two the questions about referring patients to specialist sleep services. The frequency that these subthemes were repeated and example of quotes from GPs are also listed.

5.4.2 Themes from free-text responses from patient survey

2 major themes, which were related to patient perceptions about the diagnosis and treatment of SDB, were found from the analysis of free text responses from the patient survey (Table 5.4). Most responses reflected the difference between the expectations of patients and the care delivered by GPs (as perceived by patients). Patients expressed concerns because their condition was either misdiagnosed (69 responses) or were offered 'inappropriate' treatment options (28 responses). Furthermore, they were dissatisfied, as patients perceived that GPs predominantly used a conservative approach in the management of SDB (13 responses) and had a lack of initiative when referring them to specialist services for further investigation (9 responses). In some patients, this led to delays in receiving treatment (16 responses).

The patient survey also highlights the poor of access to sleep studies for GPs. Lack of local funding (13 responses), long waiting lists (18 responses) and restrictions from the local PCTs (19 responses), were listed as possible contributory factors for this lack availability of sleep services. Due to these reasons, some patients who participated in this survey reported that they had obtained treatment privately. Such patients may be over-represented in the survey due to sampling frame of a company patient-support network.

	Q1) Did you obtain treatment via the NHS? *(Available if answered'NO' to this question)*		Q5) Did your GP refer you immediately to a sleep centre to be tested for OSA? *(Available if answered'NO' to this question)*	
Survey Question Options		Responses (n)		Responses (n)
	Waiting list too long	*103*	Told to lose weight	162
	No local sleep unit	*21*	To stop smoking	34
	GP advised that NHS treatment was not possible	*45*	ENT for possible surgery	109
			Treated for depression	37

	Patient expectations	Responses (n)	Examples of responses from Patients
Themes from Content Analysis	Perceived misdiagnosis	69	*"Actually, my GP never diagnosed it even though my wife mentioned it to him. I was referred to a consultant regarding muscle pain"*
	Perceived Inappropriate	28	*"Dentist teeth brace £150.(had fitted,useles) ENT surgery. Fortunately not actioned. Eventually sent to Sleep Clinic"*
	Perceived lack of action	9	*"I never actually got referred. After three visits, I referred myself on my wife's advice to a snoring clinic where I was diagnosed"*
	Use of conservative approach	13	*"have hot milky drink before bedtime", "wife told to use ear plugs! we were at the point of near devorce"*
	Concerns for wellbeing	28	*"Was told my driving licence would be taken away and the wait for NHS could be over a year so we went private"*
	Ease of access	9	*"I was feeling so poorly, i wanted immediate relief"*
	Persistence	9	*"I insisted on being referred and took completed Epworth scale with me."*
	Delay in treatment	16	*"sent to dentist for mandibular device. Complete waste of time 2years", "only referred after complaining that I was going to sleep whilst driving. This was on the third GP visit."*
	Healthcare factors		*"Did Epworth Sleepiness scale and did not score high enough first time around. Family had noticed my condition and confirmed it to me. Also, I was getting more and more tired! Went back to GP, did scale test again and this time I got the required score!"*
	Strict Diagnositc criteria	4	
	Lack of funding	13	*"No funding for cpap therapy in my area when diagnosed just before the N.I.C.E guidelines came out on cpap."*
	Local access	7	*"There was no sleep unit initially there is now."*
	Long waiting list	18	*"75 people on waiting list some had been waiting 2 years"*
	Local/NHS policy	19	*"Told that CPAP device not available on NHS via local unit, but would have to go on waiting list for London clinic."*

Table 5.4 Patient perceptions about diagnosis and treatment of their OSA

In addition to the number of responses received for the list of options available to Question 1 & 5, two themes were identified from content analysis of the 308 free-text responses from the RealSleep patient survey.

5.5 Discussion

The analysis of the primary care surveys using content analysis has produced additional insight into the potential barriers that may exist in the management of SDB. The major barrier appears to be the lack of access to sleep services, which was evident from both the patient and GPs surveys. The other major themes that were revealed in both surveys were the service delivery factors, such as the long waiting time for sleep studies and the restrictions by local PCTs leading to difficulties within referral pathways, and physician factors, such as the lack of awareness about SDB and the predominantly conservative strategies that were adopted by GPs when managing patients with SDB.

The poor awareness and lack of recognition of SDB by GPs, as perceived by patients, led to a delay in their diagnosis and treatment. Patients also stated that they were either misdiagnosed with depression, asthma, rhinitis, reflux disease and lethargy or offered 'inappropriate' or conservative treatment options mainly involving lifestyle changes. The lack of awareness or failure to consider SDB as a potential differential diagnosis, when seeing patients who present with symptoms such as daytime sleepiness, tiredness and snoring, was also evident from the quantitative analysis of both the GP and patient surveys (Chapter 4).

GPs stated that their familiarity of care pathways of SDB was limited. Both patients and GPs perceived that involvement of multiple specialities, for example ENT surgeons managing sleep services, delayed treatment. Some patients expressed that they had undergone 'inappropriate' invasive surgical intervention

to the upper airway (e.g. removal of nasal polyps and septoplasty), prior to having a trial of PAP therapy.

Content analysis of both GP and patient surveys suggest that GPs were more inclined to adopt a conservative strategy first, before referring patients for specialist advice. Most GPs used conservative measures such as weight loss and exercise, life style changes (e.g. reducing stress and alcohol intake), nasal sprays or upper airway adjuncts such as mandibular devices and nasal clips. Although weight loss has been shown to improve sleep apnoea by reducing the AHI,[303] no more than 20% manage to maintain a stable weight loss despite intensive weight loss programmes.[123] This is because the success of weight loss depends on other factors such as motivation and diet. Therefore, the primary management strategy of SDB should include both lifestyle changes and treatment with PAP in parallel, if clinically indicated. Further, life style interventions should not delay screening and diagnosis of SDB.

GP responses also indicate that they perceived PAP and mask therapy to be an uncomfortable and an invasive form of treatment. A few GPs also suggested that PAP therapy may not offer the intended treatment benefits. They did not provide explicit reasoning for this, as these were short text responses. Therefore, it is likely that their beliefs and perceptions were influenced at least in part by their previous experience, such as encountering patients who may have declined PAP therapy. However, none of the patients stated that treatment was difficult to tolerate, but the RealSleep patient questionnaire did not directly explore patients' views about mask or PAP therapy, and was a self-selected group of

patients many of whom tolerated CPAP for some years and were also willing to answer a questionnaire.

The most consistent and recurring theme in all 3 surveys was the lack of access to sleep services. The major contributory factor for this was the lack of a local sleep service or an efficient referral pathway, which was illustrated by ~25% of all responses. My data also confirm the findings of the BLF[13] and RightCare[257] reports, which also showed a large variation in the sleep services in the UK (Chapter 3). This was further complicated by local service barriers, such as the variation in local policies and a lack funding for CPAP therapy by health authorities. Some PCTs had a set of strict criteria for management of SDB, for example restrictions were placed when referring patients to diagnostic sleep services, such as having a 'high symptom threshold' in order to warrant screening. Some GPs even stated that they were actively discouraged from referring patients to the local sleep service (table 5.3). Due to these service pressures and variation in the health delivery, both patients and primary care physicians stated that there was a long waiting time for sleep studies. With the advent of the choose-and-book system, it has been possible to access services beyond their locality,[277] however, some patients experienced significant difficulties, as they had to travel a long distance to undergo a sleep study. This could be even more demanding for patients who are already established on mask therapy, if frequent visits are required for therapy titration.

5.5.1 Limitations

The primary surveys were conducted between 2009 and 2011 and it is likely that the provision of sleep services in the UK has since changed. Especially after

the publication of the NICE technology appraisal for OSA in 2008,[108] the waiting time for a sleep study was reduced as the number of sleep studies carried out in the UK increased (Chapter 3). Therefore, these surveys may not reflect the clinical practice due these changes. For example, some patients of the RealSleep survey stated that they received treatment privately, because they were not able to have CPAP treatment through the NHS, as it wasn't funded. However, since the publication of this NICE appraisal, PCTs have recognised the importance of SDB and have now commissioned these services.[278] Further, NHS trusts have begun to set-up diagnostic sleep services as results of this. Despite this, some of the themes found are still applicable to current clinical practice. Poor access to sleep services, which was found to be the major barrier to management of SDB from this survey, was also raised in the recent publication from the BLF.[13]

The RealSleep patient survey was conducted in patients who were part of the RealSleep programme. Almost half the patients who responded to this survey had been on CPAP therapy for more than 5 years. Therefore, these patients were likely to be highly compliant with CPAP therapy. The RealSleep programme is a subscription service that includes offers and discounts for masks and devices, which could have further promoted CPAP use. These factors may explain the positive perceptions towards CPAP therapy by these patients, in contrast to GPs.

Another limitation of surveys is self-reporting bias.[304] Self-reporting bias was present in both patient and GP survey. For example, the misdiagnosis and the inappropriate treatment by GPs, which was highlighted by patients, could have been influenced by their frustration due to delays in diagnosis and treatment. In

addition, patients were not medically qualified, therefore, their self-interpretation of symptoms and their expectation of the most suitable treatment options, could be different to the clinical assessment performed by physicians. Further, we do not have details of the GP consultation notes or the presenting complaints of patients, to check whether GPs had formulated an appropriate management plan. Similarly, the views of GPs could also have been biased, only reporting about the poor compliance with PAP/mask therapy in patients.

5.6 Conclusion

In summary, the content analysis of these surveys unearthed the potential barriers in to screening, diagnosis and treatment of SDB in the primary care setting. The major barrier was shown to be the perceived lack of access to sleep services locally. In addition, lack of awareness and a mismatch between patient expectations and care delivery by GPs, particularly related to conservative management strategies, were also contributory factors. These results were also invaluable in consolidating the qualitative methodology and helped to formulate the questions for the semi-structured interviews of healthcare professionals. Further exploration of barriers to management of SDB, especially in the secondary and tertiary care setting, will be carried out in the next chapter.

Chapter 6: Exploring barriers to diagnosis and treatment of sleep disordered breathing in hospital care

6.1 Aims

The aim of this chapter is to identify potential barriers to diagnosis and treatment of SDB in secondary and tertiary care. Qualitative methodology was adopted using semi-structured interviews of a purposeful sample of healthcare professionals.

6.2 Background

SDB is widely perceived as a subspecialty interest within respiratory medicine and the diagnostic and therapeutic services are managed predominantly by respiratory physicians.[305] However, various healthcare professionals (HPs) are involved in delivery of care at different points of the pathway for patients who may have SDB. For example, cardiologists and other medical specialities, primary care physicians and specialist nurses such as heart failure nurses, provide care for a large proportion of patients with CVD and SDB. The GP-patient interaction was explored in previous chapters using primary care surveys and this highlighted a significant level of underdiagnosis and undertreatment of SDB in primary care. However, whether the interactions between specialities affect patient management, has not been previously explored in patients with SDB and CVD in UK.

A qualitative study carried out in North America[306] explored the interaction between specialities in the management of generic sleep disorders (which

included OSA). The study included 401 participants, a combination of generalists (e.g. primary care physicians) and specialists (e.g. family physicians, neurologists, respiratory and internal medicine physicians with a sub-speciality interest in sleep). Purposive sampling was used to ensure that the sample was representative of the target audience and participants were selected from multiple centres around the US (for example in association with American Thoracic Society, University of Virginia School of Medicine, New Jersey Academy of Family Physicians & Public Health Office of Continuing Professional Development). However, it is important to note that financial compensation was provided to participants in this study, which may have had an influence on their responses. The study adopted a mixed-method analysis and most participants took part in the 'survey' component of the study, which explored the confidence levels of physicians, when dealing with the screening, diagnosis and treatment of the sleep disorders. 32 (20 generalists and 12 specialists) participated in 5 group discussions and 24 (16 generalists and 8 specialists) were interviewed. The main themes from these data were related to lack of knowledge of diagnostic testing, lack of prioritisation of sleep disorders and the attitudes towards the value and role of each speciality. It reported a lack of interdisciplinary communication and a lack of definition of clear roles and responsibilities in the management of sleep disorders between healthcare professionals. The lack of coordination between specialities were likely due the contrasting views expressed by the generalists and specialists. This is illustrated from the quotes below.

"I don't think they [generalists] see sleep as a unifying subspecialty. Someone may have snoring, they don't see it as a referral to a sleep lab as they would for someone with insomnia or restless leg syndrome." — Specialist

"It seems that the emerging group of sleep specialists are more than willing to do the test and make the diagnosis, but not to follow with the treatment, compliance, etc. Specialists make the money and leave the hard stuff for the primary care physician."—Generalist

A close relationship between different specialities is vital to providing the holistic care needed for these patients.[307] A lack of "cross-talk" between cardiologists and sleep services may contribute to a delay in the diagnosis and treatment of patients at risk of CVD.

In addition, to managing the sleep services, the guidance for the management of SDB is predominantly driven by Respiratory Societies,[244,248] although SDB was mentioned in the guidelines for management of hypertension,[225] atrial fibrillation,[229] and heart failure.[124] In addition, the potential adverse effects of SDB on the cardiovascular system have been well documented and recognised (chapter 2).[184] However, as discussed in section 2.4, the specific details and indications for diagnosis and treatment of SDB in these clinical guidelines is lacking. This could potentially impact the clinical practice of healthcare professionals managing SDB,[308] particularly if they focus more on cardiovascular risk management.

The primary care surveys analysed in previous chapters revealed potential barriers that could influence the management of SDB. For example, there was a poor access to sleep studies in primary care, which was potentially due to the lack of availability of sleep centres locally. Similarly, large variations in the UK

sleep service was also demonstrated in Chapter 3. The content analysis of primary care surveys suggested that patient factors, such as patient choice and lack of treatment compliance influenced the optimal management of SDB. Compliance with mask therapy and positive airway pressure (e.g. CPAP) in OSA patients is a major problem that has been described, where only about 50% of patients are known to adhere to therapy,[113] which has been consistent among different study populations.[114,115]

Although the primary surveys presented a broad overview of different management aspects of SDB in primary care and views of GPs and patients, they were not designed specifically to explore barriers to diagnosis and treatment of SDB, across the care pathway. Therefore, specific barriers need to be explored, especially in relation to the interaction of multiple specialties. Thus, in this chapter, qualitative techniques such as semi-structured interviews, were adopted to formally explore the perceptions, experiences and beliefs of healthcare professionals (HPs) managing patients with SDB and cardiovascular disease.

6.3 Methods

6.3.1 Study design

A background to qualitative research was presented in section 5.2.1. This chapter also adopted qualitative methodology, using semi-structured interviews of purposefully-selected HPs.

6.3.2 Participants

16 HPs were interviewed in the study. These HPs were purposefully selected from a range of health service settings in the NHS (e.g. tertiary, secondary and primary care) and geographical locations in England. Qualitative research, in contrast to quantitative methods where sampling is typically generalised, typically involves purposely selecting the sample to explore the research question.[309] The sample of HPs chosen were 'homogenous' (i.e. they are similar characteristics, because they worked for the NHS and managed patients with CVD and SDB), however, to ensure maximum variability within the data, HPs from different levels of care, specialties and regions were selected.[310,311]

There were 6 Cardiologists, 4 heart failure nurses, 3 respiratory physicians and 3 general practitioners (GPs). All GPs and physicians (apart from one cardiologist who was a specialist trainee registrar) had completed their speciality training. Healthcare professionals were approached via e-mail communication and all healthcare professionals who gave their consent were interviewed. Their characteristics are shown in table 1.

Sampling was carried out until saturation was reached in the dataset. This is defined as the point when further coding is no longer possible, as new additional information is not generated during the data collection process and that sufficient information has been attained to reproduce the study.[312] Saturation was reached after 13 (of the 16) interviews (i.e. no new themes were unearthed from further interviews).

Health Professional	Speciality	Sex	Type of Hospital	Area
C1	Cardiology	M	DGH/Tertiary	Greater London
C2	Cardiology	M	Tertiary	Central London
C3	Cardiology	M	DGH	Greater London
C4	Cardiology	F	DGH	Greater London
C5	Cardiology	M	DGH	Greater London
C6	Cardiology	M	DGH & Tertiary	London/South
R1	Respiratory	M	Tertiary	Central London
R2	Respiratory	M	Tertiary	Out of M25
R3	Respiratory	M	DGH	Greater London
N1	HF Nurse	F	Tertiary	Central London
N2	HF Nurse	F	Tertiary	Central London
N3	HF Nurse	F	DGH	Greater London
N4	NIV Nurse	F	DGH	Greater London
G1	GP	M	Primary care	Middlesbrough
G2	GP	M	Primary care	Durham
G2	GP	M	Primary care	Gloucestershire

Table 6.1 Characteristics of interview participants

6.3.3 Interviews

The semi-structured interviews of HPs were informed by an interview guide from the results of the primary care surveys (which were discussed in chapters 4 and 5) and advisory board meetings on SDB. A variety of open-ended questions were used to structure these interviews (e.g. "*What is your experience of managing patients with sleep disordered breathing*?" and "*What role does the*

patient play in sleep apnoea?"). At the same time, it was ensured that the questioning style was adaptable for further open discussion. The views expressed by HPs were probed without making them feel coerced or influenced by the interviewee.

The interviews were conducted one-to-one and in a comfortable environment where the healthcare professional would normally practice (e.g. consultation room). The average duration of the interview was 30 minutes (with a range of 15-68 minutes). The interviews were pre-arranged and conducted privately without any interruptions. The interviews were carried out by myself (AM).

The interviews were recorded on a digital voice recorder (Olympus WS-200S). Once the interviews were conducted the audio files were handled securely and transcribed verbatim by experts in typing (i.e. cardiology secretaries). Each interview was listened to repeatedly where the transcripts were re-read and checked (by AM and Dr Jillian Riley, Honorary lecturer, Imperial College London).

6.3.4 Analysis

The transcripts were managed using a qualitative data analysis package (NVIVO 10; QSR International Pty Ltd., Doncaster, Victoria, Australia). Codes were attached to phrases or sentences in each interview transcript and organised into provisional 'themes' and 'sub-themes'. A schematic of this is shown in figures 6.1 below.

A thematic analysis of the data was then carried out with a process of constant comparison, where the broader patterns in data were unearthed. A theme can be defined as common recurring pattern within the data, which are linked and describes similar concepts.[313] Both a deductive (where explanations were derived from pre-existing knowledge and literature) and an inductive approach (where the understanding of data was derived by carefully reading the transcripts without relating to pre-existing concepts) was adopted when analysing themes.[314] Generation of themes was a "fluid" iterative process with continuous comparison and contrast. Where necessary new themes were created and similar ones were merged together. Each transcript was analysed and coded before the subsequent interview, so the interview technique and questions could be modified to improve data collection, with further understanding of the data. This process was carried out by myself (AM) and to ensure rigour it was reviewed by an expert in qualitative methodology (JR). A summary of codes generated is illustrated in figure 6.2.

6.3.5 Ethical considerations

All HPs consented to participate in the study. Consent was also obtained to publish their quotations from interviews. Patient and professional confidentiality was maintained during interviews. The local NHS Research and Development (R&D) department at the Royal Brompton Hospital and the Joint Research Compliance Office, Imperial College, London gave approval for this study.

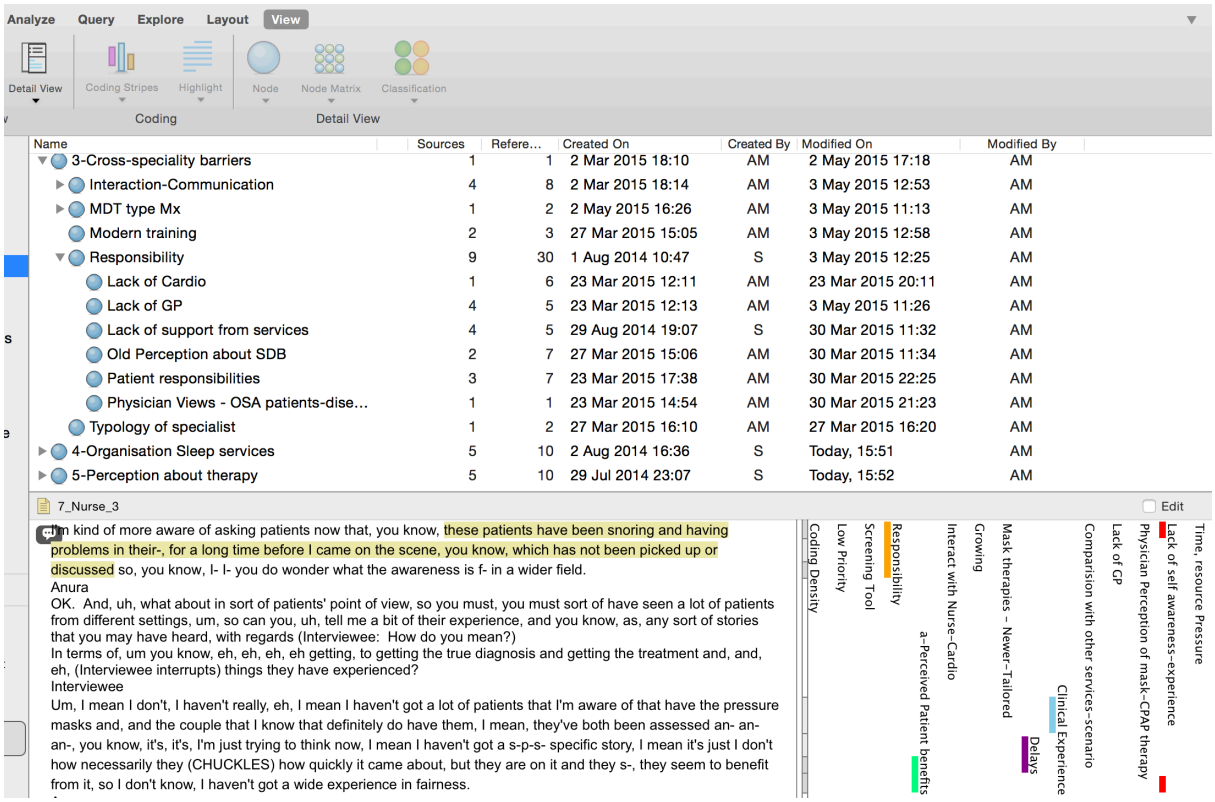


Figure 6.1 Typical analysis window of NVIVO

Each transcript was exported on to NVIVO and coded (e.g. the highlighted text is related to coding under "responsibility". Other codes from this transcription is also shown on right and colour coded). A summary of all codes and its subcategories are shown above. NVIVO had the capacity to link similar codes and their respective sections of text (from all transcripts) which enabled data management easier.

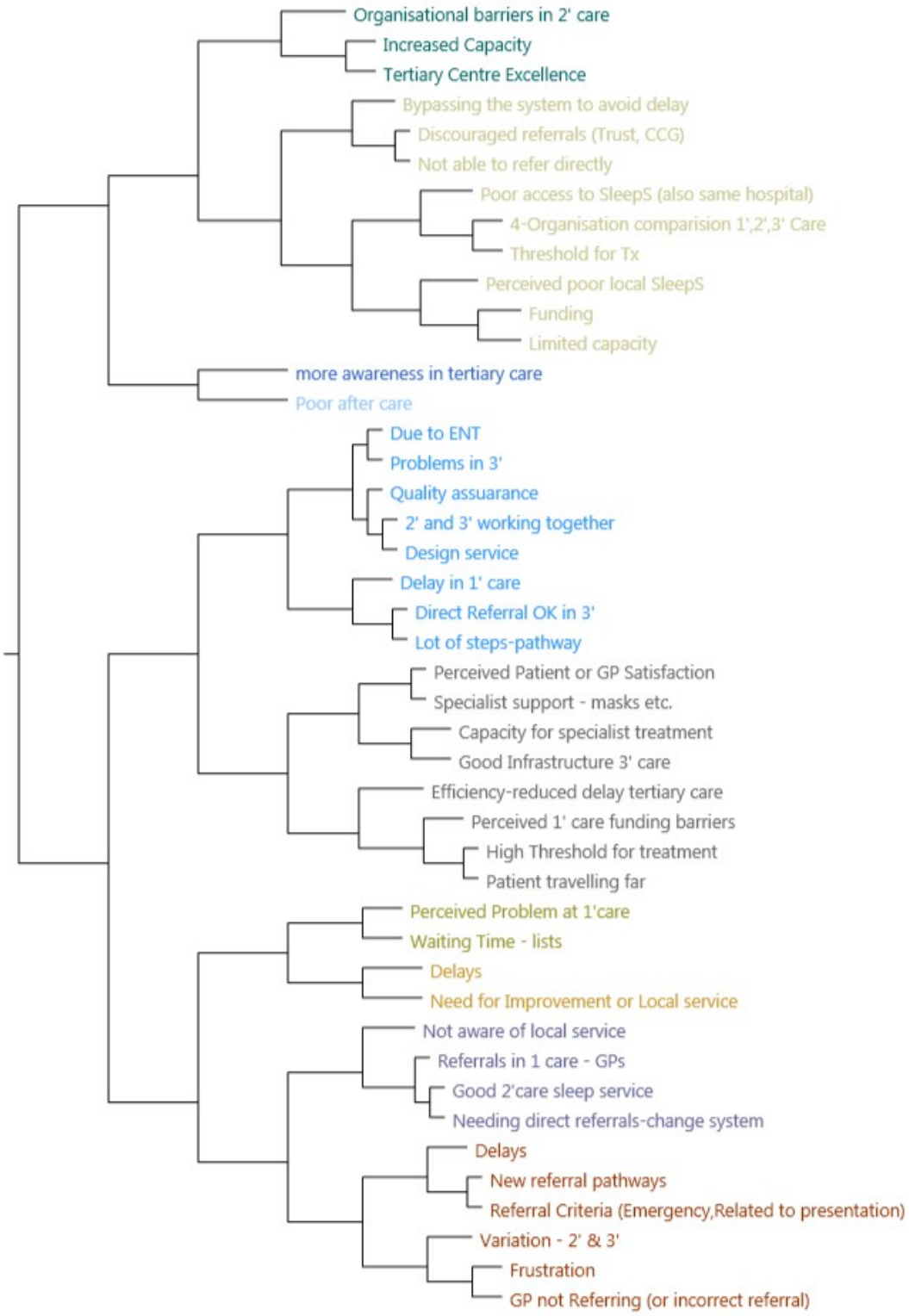


Figure 6.2. A 'code-tree' representing the data from all transcripts

The codes were generated during data analysis and managed using NVIVO. This shows how the themes and sub-themes are interlinked.

6.4 Results

5 major themes were identified in this study: varying awareness of SDB, low priority in clinical practice, variation in the local sleep service provision, variable perception of responsibility for patients with SDB, and varying perceptions about therapy for SDB. Each theme and its sub-themes are discussed below.

6.4.1 Awareness of SDB

Cardiologists, nurses and GPs acknowledged that their awareness of SDB was low. Further, most of their patients with SDB had OSA, and the healthcare professionals' understanding and experience of managing patients with CSA was limited. This was emphasised by a cardiologist at a District General Hospital (DGH) in London with a catchment population of around 350 000, when asked about his experiences in managing patients with CSA, who stated:

> *"I don't know what central sleep apnoea is…I mean, we just treat the heart failure, basically"*
>
> Cardiologist (C5)

Further, one of the nurses (N4) managing the sleep service at a district general hospital with almost 900 patients on CPAP therapy stated that there were "*virtually no centrals*".

At least 6 healthcare professionals said that they had difficulty in identifying patients with CSA compared to OSA, as it was perceived as a "*different kettle of fish*" (R2). The characteristic features in the history (e.g. snoring, daytime somnolence) and "*classic Mr Pickwick*" type phenotypic features with high BMI

and large collar size, made it easier to identify patients with OSA (C3). They also relied on the history from patients' partners who were concerned about symptoms such as snoring. However, eliciting features of CSA or asymptomatic OSA was more challenging.

"it's often difficult to differentiate between people whose habitus actually means that they got it"

Nurse (N1)

6.4.1.1 Lack of hard end-point data

Lack of mortality benefits in the treatment of CSA was another factor that influenced the practice of healthcare professionals. Some found that the lack of guidelines was a barrier to optimal patient management, particularly during discussions with patients about treatment benefits. One respiratory physician stated that without this lack of "*hard evidence*", the treatment of CSA is unlikely to have an economic benefit, particularly due to the low prevalence of CSA.

"you could talk about patient satisfaction, quality of life and all the rest of it, but if you're [not] going to show that the patients are not going to die…you will still sit on the fence"

Respiratory physician (R2)

6.4.1.2 Ineffective screening tools

The difficulty in diagnosing SDB was further complicated by lack of effective screening tools. Most healthcare professionals used questionnaires such as Epworth Sleepiness Scale (ESS) to screen patients with suspected SDB, however, they raised its validity as a screening tool. ESS was ineffective in identifying patients even with severe SDB.

> *"He's not sleepy, his Epworth sleepiness score was 6 when he came to see me. So, I did an Embletta on him, he had an AHI of 55, desaturation index of something like 50"*
>
> Respiratory physician (R2)

6.4.2 Low Priority

SDB received a low priority in clinical practice as it was perceived to be a non-urgent, non-life threatening condition. On GP stated that it was "*a Cinderella topic*" (G2), at the "*bottom on the list*" of clinical priorities. In addition, one cardiologist (C4) considered SDB to be *"at number 10 or 15",* in the hierarchy of comorbidities affecting a patient with heart failure. When cardiologists assessed patients with heart failure, symptom control and drug titration got precedence. Further, healthcare professionals perceived that the investigation and treatment for SDB was considered as a "*last resort*", after other treatment strategies had failed (N4). Some HPs regularly experienced delays in diagnosis and assessment of patients with SDB, compared to other disorders which were thought to be more 'significant'.

"like a lot of things that aren't cancer, it tends to take a bit longer, perhaps it'll be four, five, six months before they eventually end up on a C-PAP machine"

GP (G1)

6.4.2.1 Time-pressure

All HPs interviewed were part of busy clinical services. Therefore, to meet the demands of clinical practice, they were regularly pressured for time which was a key contributory factor for SDB receiving a low priority. One cardiologist (C4) described that their "*time's not limitless*" and they may not have the capacity to undertake the added responsibility of managing patients with SDB as there was "*enough to keep us all busy to start with"*. They also highlighted that the current duration allocated for patient consultations was limited, and as a result sufficient time was not spent on assessing patients with SDB, particularly if they presented with multiple medical problems.

"*they can come in with four or five things and we got 10 minutes"*

GP (G1)

Both primary and secondary care settings appeared to be demanding environments. However, the hospital setting was likely to be more challenging compared to the primary care setting. For example, a GP with a specialist interest (GPSI) in heart failure had more time to assess patients.

"as a GPSI have half an hour and I can take a m- a much more detailed history"

GP (G1)

The hospital setting was a "*more pressurised*" environment, because the staff experienced difficulties such as poor staffing levels and staff shortages. In a large DGH in London, the cardiologist (C6) described himself as "*singlehanded"* in his hospital with multiple responsibilities of daily cardiology ward rounds, the general medical take, teaching and reporting cardiac investigations. As a result, he stated that SDB received a "*very low priority*". In addition, at another large DGH in London, all the duties of the heart failure service were assumed by a single nurse (N3). Within this environment undertaking new responsibilities such as screening for SDB within the existing heart failure management plan, was found to be overwhelming.

"Well [laughs], yet another, yet another thing we have to do"

Nurse (N2)

Moreover, the referral process to book a sleep study took a significant proportion of the clinician's time. For example, a referral to a respiratory physician responsible for the sleep service involved dictating and sending a

letter, which added to their workload. This was perceived to be a significant barrier, taking up valuable time allocated for patient assessment.

"if I'm going to refer them, because of the process of referring takes between 5 and ten minutes most of your consultation's taken up by that time"

GP (G3)

6.4.3 Variation in sleep service

The data demonstrates that in DGHs, especially without a diagnostic sleep service, the access to sleep studies was more limited. The waiting times were longer and obtaining a diagnostic sleep study within 18-weeks, the minimum delay recommended in the NHS from referral to treatment,[315] was challenging. Physicians expressed their frustration about the significant delays in diagnosis and treatment of SDB in patients in secondary care.

"by the time they get there, they're either doubled in size or they're better"

Cardiologist (C3)

In contrast, within tertiary care, physicians found it much easier to access the sleep service and there was no apparent delay in getting patients to have diagnostic sleep study and initiate them on therapy.

"We don't bother to see them in clinic, we just book a sleep study…they get the treatment the next day"

Respiratory physician (R1)

A cardiologist, who had experience in working in both tertiary and secondary care, described this mismatch between these two settings further. He was unable to offer the optimum treatment recommended for patients, when he was working within a secondary care setting.

"having worked here [tertiary hospital], you are aware of what a sleep and ventilation service potentially can offer…all I can literally do is flag this up to the GP as an issue"

Cardiologist (C6)

6.4.3.1 Referral pathways

In tertiary care, the referral pathways were much simpler, which was a main factor for the ease of access to sleep services. In addition to adopting strategies such as using e-mail communication to book sleep studies to minimise administrative delays, healthcare professionals in tertiary care had the independence to carry out consultant-to-consultant referrals. Cardiologists were able to 'bypass' the primary care setting and directly consult respiratory physicians (who managed the sleep service).

"they come in for primary PCIs and they do have barn-door sleep apnoea, yes, we, we do have direct referrals"

Respiratory physician (R2)

Although the referral process was straightforward in tertiary care, in contrast, it was more complicated in secondary care. These patient pathways included multiple steps, potentially leading to delays.

"we can do all sorts of measurements, but…to refer for any form of sleep study… I have to then refer that back to the GP, for the GP to refer back in"

Cardiologist (C4)

A heart failure specialist nurse (N3) from secondary care considered that this "*circle*" of referrals was a "*delaying process*" and a "*significant barrier*" in the management of patients with SDB. A cardiologist (C5) felt that, they would be more "*empowered*" if they were allowed to refer patients directly to diagnostic sleep centres and request a sleep studies similar to other diagnostic tests such as an echocardiogram or a cardiac MRI scan. The current payment structure within

the NHS Clinical Commissioning Groups (CCGs) was perceived as the primary reason why diagnostic sleep studies were not considered within the same pathway as other routine cardiology investigations.

6.4.3.2 Sleep service capacity

Tertiary centres provided specialist services, which were accessible both regionally and nationally, and patients travelled over long distances to use these services. One tertiary centre cared for approximately 7000 patients on CPAP therapy and had extensive resources with 12 technicians, a 24 hour service with trained nurses having the ability to support patients on CPAP therapy, quality control measures which ensured diagnostic sleep studies were appropriately conducted and analysed, and the ability to provide a variety of masks of different types and sizes. This increased capacity in tertiary care meant that the sleep and ventilation team could *"spend a lot of time"* with patients to optimise their treatment (R1).

However, in contrast in the DGH setting this capacity was limited. The NIV specialist nurse from a Greater London DGH (N4), which consisted of ~900 patients on CPAP therapy, stated that there was only one part-time sleep technician and all sleep studies that were carried out (which was approximately 20 studies a week) were analysed by the single consultant who was responsible for the sleep service. DGHs also lacked infrastructure, as perceived by a cardiologist about their own sleep service:

> *"it, it's a very sort of basic assessment that's done, they have a little sleep laboratory"*
>
> Cardiologist (C3)

Therefore, all DGH cardiologists used a variety of strategies to access this "*large volume and high-quality service"* provided by tertiary centres. Their participation in research studies linked to these tertiary centres, enabled them to "*bypass*" their local NHS referral system. This way the process of obtaining a sleep study for their patients was much quicker.

> *"when the [large randomised] study was running we managed to get people who had obstructive sleep apnoea, which wasn't the main focus of the study,…established onto CPAP"*
>
> Cardiologist (C4)

6.4.3.3 Treatment threshold

The specialised care provided by tertiary centres resulted in improved patient management. In secondary care, usually there was a higher threshold for initiating patients on treatment, where healthcare professionals believed that "*mild or sort of moderate sleep apnoea wouldn't necessarily need CPAP*" (N4). However, tertiary care physicians believed that current guidelines such as the NICE guidelines were "*too much down the conservative side*" and did not reflect the treatment need of some patients. They also had a very low threshold for treatment where treatment was initiated based with the intention of improving patient's symptoms rather than solely relying on arbitrary cut-offs.

> *"we can think about the bigger picture...even if it's under 15...we generally would be much more readily, uh, start CPAP than other centres do"*
>
> Respiratory physician (R1)

Healthcare professionals in secondary care were also extremely happy with the services patients received from these tertiary hospitals. This was due to a variety of factors such as timely assessment, excellent on-going care after been established on treatment and sufficient time being spent with patients. The treatment was tailored individually to reflect each patient's needs by using different types of masks such as lighter nose-only masks. Most importantly, this also led to perceived patient satisfaction.

"patients, certainly come away from there feeling very happy…adjustments that need to be made to masks, for both making them…nose-only or lighter, And I think that is very much appreciated"

Cardiologist (C1)

6.4.4 Responsibility

Cardiovascular patients with SDB were perceived to have multiple comorbidities, needing the input and interaction of multiple specialities such as cardiologists, heart failure nurses, respiratory physicians, GPs, ENT specialists and dieticians. With multiple teams, HPs from both hospital and primary care settings believed that there was a tendency to lose continuity of care. No single speciality seemed to be responsible for managing SDB in patients with cardiovascular disease:

"these patients have been snoring and having problems in their-, for a long time before I came on the scene"

Nurse (N3)

6.4.4.1 Cross-speciality barriers

The interaction between respiratory physicians and cardiologists in secondary care was shown to be poor. The two specialities appeared to have little interest about each other's roles.

"obviously they drive it [the sleep service], not us - it's their baby, not mine"

Cardiologist (C3)

This poor communication and the lack of coordination between the cardiology and respiratory teams, especially when multiple services of different hospital were involved, resulted in substandard treatment.

"they've [patients] come here saying, "I've not been using it for weeks because I've not managed to get hold of someone to reset my settings"... there's the continuous loop of trying to find the right person"

Cardiologist (C4)

The relationship between primary care and hospital based HPs were also found to be poor. 4 hospital based HPs, both cardiologists and respiratory physicians, were critical of GPs, who stated that "*nothing happens*" if a referral was made to GPs for the assessment of SDB (C5). However, GPs believed that diagnostic sleep studies should be conducted within the same patient pathway and they had no hesitation in referring patients for further investigation if it was appropriate. There was clear evidence of a 'blame culture' in the management of these patients, in both the hospital and primary care setting.

"What would be even better if they sent the letter and we'll just sign it. That, would solve the problem…GPs get annoyed at being treated like foundation doctors"

GP (G1)

The heart failure nurses stated that they had a close relationship with cardiologists when managing patients. This was established by constant communication during MDTs and one-to-one meetings with the cardiologists. However, despite this close rapport between cardiologists and heart failure nurses, they failed to define and identify their roles and responsibilities clearly in the management of SDB, amid the increased workload.

"I'm sorry to be horrible from my point of view if a nurse picks it up it's going to be my problem"

Cardiologist (C3)

A close relationship between specialities was key to running a good service. The key success factors (as perceived by healthcare professionals) were: specialities being concentrated at a close distance, good communication, flexibility, simpler care pathways and having a sleep centre with multidisciplinary teams with input

from both cardiology and respiratory teams. 2 healthcare professionals gave an example of such a local service, which had the input of multiple specialities. This made it easier for healthcare professionals to access these services.

"it has a multidisciplinary input...it's all triaged at the point of the secondary care clinic, so I don't have to then make a re-referral...it's a common pathway for me"

GP (G1)

6.4.4.2 Multiple specialities running the sleep service

The interviews found that, although sleep services were mainly managed by respiratory physicians, in some areas (historically), these were run by ENT surgeons. Respiratory physicians believed that this led to a degree of confusion among clinicians, especially in primary care. Their experience was that a considerable number of GPs, to investigate suspected SDB in adults who had symptoms of tiredness and snoring, made the initial referral to ENT services. In some cases, this led to a significant delay because patients underwent multiple 'cycles of referrals' until they were appropriately assessed and treated. This led to a degree of frustration among healthcare professionals.

"One other thing which I must mention is there are still these remnants of patients who are referred to the ENT services…I do have patients who have taken about six extra months"

Respiratory physician (R2)

6.4.4.3 Perceived accountability of patients

HPs stated that obesity was highly prevalent among patients with SDB, especially in OSA. GPs adopted a more conservative approach to manage these patients, for example trying out strategies such as weight loss at first instance. This was likely because, OSA secondary to obesity was perceived "*as a disease of self indulgence*"

(R2), and most physicians highlighted the responsibility of patients themselves in managing their disease. Moreover, one cardiologist debated the cost-effectiveness of treating these patients within the remits of the NHS.

"People might consider it to be their own fault if they're massively obese…should we be spending on people who've decided to become massively obese"

Cardiologist (C5)

6.4.5 Perception about therapy

6.4.5.1 Perceived treatment benefits

All HPs recognised SDB as a significant disorder affecting the cardiovascular system. They identified obesity as an important risk factor for OSA and that there is a strong association between SDB and cardiovascular disease such high blood pressure, ischaemic heart disease and heart failure. Being familiar with the published literature and having experience in participating in clinical research enabled them to have a good understanding about SDB and identify patients at risk. All HPs also believed that not treating SDB would have detrimental effects on the cardiovascular system, for example potentially leading to a rise in blood pressure.

"those periods of apnoea you release massive amounts of adrenaline… I'm aware that it is, it's not a good thing to have"

GP (G1)

Therefore, healthcare professionals seemed to adopt a more aggressive approach when treating patients with SDB who had coexisting cardiovascular disease. They found that in patients with SDB, it was "*difficult to bring blood pressure under control*". Healthcare professionals prioritised these patients with resistant hypertension and referred them for diagnostic sleep studies much earlier.

"I would go with little suspicious of sleep apnoea…patients who are chronically tired and also difficult-to-treat hypertension"

Cardiologist (C1)

Most healthcare professionals observed that patients experienced benefits with treatment, predominantly due to an improvement in quality of life and daytime energy. After receiving treatment with CPAP, one patient seen by a respiratory physician (R2) had described himself as a "*changed man*". In addition, healthcare professionals also saw that there was a clinically significant reduction in blood pressure in patients after treatment of SDB.

"we do have a few, then it is one of those things, you, get on it [CPAP] and you may find that you don't need to take so much medication"

Nurse (N4)

6.4.5.2 Perceived poor patient compliance and understanding

HPs perceived that poor patient compliance with CPAP and mask therapy as a barrier to optimum treatment. One cardiologist (C2) from tertiary care stated that one of his heart failure patients couldn't "*stand her C-PAP"* and failed to gain the potential benefits of therapy. This was also a common theme among cardiologists in both tertiary and secondary care.

"I had somebody...to be honest with you I think he probably tried [the CPAP mask] for 10 minutes, either he just didn't engage with it or he didn't understand"

Cardiologist (C3)

Lack of patient understanding was seen as an important factor contributing to poor patient compliance. One respiratory physician (R1) believed that patients had "*no clue"* about SDB, and they were unaware of the detrimental effects of SDB on the cardiovascular system and unable to recognise its key symptoms. Most HPs agreed that patient education, in addition to improving adherence to

treatment, were also likely to empower patients to interact better with their medical professionals, potentially to leading to earlier diagnosis and treatment.

"you see patients coming in who say, "I've been like this for so many years and…if I [knew] there was this thing I would have obviously, chased a referral earlier or considered it before"

Respiratory physician (R1)

This lack of understanding was further complicated by the lack of certified educational material such as patient information leaflets about SDB.

"It's easy to talk about heart failure because we have…guides, and you explain what it is…that's easier for us, It's a little bit harder because we don't possess a lot of literature about it [SDB]"

Cardiologist (C3)

To overcome this barrier and to improve patient understanding, some healthcare professionals used online resources such as "*patient.co.uk*". Having these patient leaflets made patient management much easier for healthcare professionals and helped in their discussions with patients.

Respiratory physicians believed that achieving symptomatic benefits in patients in the early phases of treatment was a main factor for improving compliance with CPAP/mask therapy. Therefore, spending sufficient time during the first patient visit to improve patient understanding, establishing patients on suitable masks and optimally titrating pressure therapy to a level that is comfortable for

patients were perceived to be pivotal in achieving a good patient compliance with treatment.

6.4.5.3 Perceived impact on patient's lifestyle

Some HPs perceived that, in some patients, there was a degree of stigma attached to being diagnosed with SDB. This was marked in patients who had a fear of losing their driving licence, particularly if this was their livelihood. One respiratory physician stated that sometimes patients failed to inform the DVLA about their SDB.

"*there's one group who's denied the fact that they have it…driving is a sticking point in some patients*"

Respiratory physician (R2)

Further, 4 healthcare professionals stated that patients who were young or middle-aged, were likely to refrain using the CPAP machine at night because the noise generated from the machine interfered with the sleep pattern of their partners. CPAP/mask therapy was also perceived to contribute to problems in marital relationships.

"he's had problems with his wife because she then had to sleep in a different room and there been all sorts of issues there"

Nurse (N3)

6.4.5.4 Differences in perceptions about therapy

Cardiologists and heart failure nurses perceived that non-compliance among patients on CPAP therapy was common, and that mask therapy was an invasive and uncomfortable form of treatment. Frequent complains they received from

patients were, CPAP machines being "*too noisy*", masks being "*uncomfortable*" and causing "*a dry mouth*". These side effects were perceived as a barrier to optimal treatment.

"a recurrent complaint that some patients have is, um, is feeling rather claustrophobic with a mask tied to their face. So, this is clearly a significant, problem"

Cardiologist (C1)

Respiratory physicians however, did not recognise patient compliance to be a considerable problem. One respiratory physician stated that patient compliance with CPAP and mask therapy could be as high as 90%. On the contrary, respiratory physicians stated that some patients 'got attached' to their machines even without a clinical need.

"you have patients post-bariatric surgery who no longer have CPAP, but they want to keep the machine"

Respiratory physician (R1)

6.5 Discussion

In this study, the semi-structured interviews that were carried out explored the experiences and perceptions of HPs when managing patients with SDB. The important barriers that were revealed after thematic analysis were lack of awareness of SDB; the lack of hard end-point data and effective screening tools (which complicated management); low priority for SDB in clinical practice due to factors such as time pressure; variation in service provision due to factors such as limited capacity for sleep studies and availability of resources in secondary care; complicated referral pathways; lack of responsibility for patients with SDB due to cross-speciality barriers (because multiple specialities were managing these patients and sleep services); and patients factors such as (perceived) poor compliance with SDB treatment. All of these barriers likely impacted the quality of patient care.

6.5.1 Importance of making the distinction between CSA and OSA

All healthcare professionals in this study appropriately identified that cardiovascular disease and SDB had a strong association and in addition, most believed that treatment of OSA with CPAP lead to patient benefit. This is partly because they observed their patients achieving a symptomatic improvement, better quality of life and an improvement in the general wellbeing. For example, a respiratory physician from tertiary care expressed having a low threshold for therapy initiation in patients with symptoms but a low AHI, a decision based purely on symptoms. However, healthcare professionals should be more cautious about treating patients with SDB solely based on symptoms, particularly if the distinction between CSA and OSA is not made.

It is important to make the distinction between the two types of SDB when assessing these patients. OSA and CSA are likely to occur as the result of two entirely separate pathophysiological mechanisms.[76,77] A thorough clinical assessment of patients is important before therapy initiation, because the treatment for OSA (i.e. CPAP) and CSA (i.e. ASV) are mechanistically different. Until recently non-invasive positive pressure ventilation had been perceived as a safe form of treatment, as most research published had showed improvement in quality of life measures, cardiovascular measures and short-term mortality. No research study conducted thus far had reported on its long-term safety. However, a paradigm shift of our understanding and management of SDB is now necessary in view of the findings of the SERVE-HF trial.[99] It found that ASV therapy, despite eliminating the Cheyne-Stokes breathing pattern and apnoeas in patients with CSA, significantly increased all-cause and cardiovascular mortality (discussed in section 2.3.6.2). CANPAP trial,[199] studied the effect of CPAP therapy in heart failure, and although there was no difference in mortality, there were signs of harm during the early part of the trial. Therefore, initiating PAP therapy in patients with heart failure without making the distinction between CSA and OSA could be deleterious.

In this study, only 4 healthcare professionals (2 respiratory physicians and 2 cardiologists) made that clear distinction of OSA and CSA. HPs had a poor awareness of CSA compared to OSA. This reflects a greater need for the education of HPs and improving their awareness about SDB. This should be incorporated into the curricula of all HP training programmes, not merely respiratory. Some clinicians in the study however, due to the lack of hard end-

point data showing benefits of positive pressure therapy, appeared to be more reserved in initiating treatment in patients with CSA. This careful approach adopted by healthcare professionals (i.e. not initiating treatment in patients with CSA without conclusive evidence) is likely to be now justified considering the results of the SERVE-HF trial. As healthcare professionals, the primary goal is to minimise 'harm' to patients and this trial showed the importance of having reliable evidence prior to a treatment being widely adopted.

Despite there is no safe and effective form of treatment for CSA currently, screening for SDB in patients with cardiovascular disease is still vital because, it identifies a group of patients who at a higher risk of mortality (section 2.3.6). Cheyne-Stokes respiration in CSA is likely to be a manifestation of the severity of heart failure, therefore, further optimisation of the heart failure treatment in these patients should form as the mainstay in management. For example, cardiac resynchronisation therapy could be considered in these patients, as it has shown to improve SDB by reducing AHI.[215] However, further understanding of the pathophysiology of CSA is necessary if newer therapies are to be successfully directed.[316]

Under the current NHS tariff system the reimbursement cost of sleep study is ~£700,[267] therefore, hospital trusts are likely to be encouraged to set up sleep services based on monetary interests without the necessary expertise. However, a diagnostic sleep service should have the suitable resources to conduct sleep studies (e.g. PSG/PG) to obtain adequate information and the expertise to analyse and interpret these results, with the primary aim being identification of

the type of SDB. For example, a diagnostic sleep service based entirely on pulse oximetry could potentially put patients at risk, if positive pressure ventilation is initiated solely based on the oxygen desaturation index and proper characterisation of the SDB is not carried out. The expansion of sleep services is necessary but it's a process that should be carried out with good quality control measures ensuring patent safety, additionally initiating and supporting patients on CPAP.

6.5.2 Lack of evidence for management of SDB

HPs in this study also struggled to recognise SDB in patients due to the lack of appropriate screening tools. Two healthcare professionals stated that the Epworth sleepiness scale (ESS) (which is widely used as a screening tool for SDB), did not successfully identify these patients. ESS and other questionnaires have been reported to have a poor correlation (section 2.2.2.4), particularly in patients with CSA who typically do not experience symptoms of sleepiness during daytime.[317]

Clinicians who were interviewed in the study considered that the lack of hard-end-point and guidance for the management of SDB was a major barrier. Further, most of the current guidelines for the management of SDB[108,125] are more than 10 years old and therefore may not reflect current practice and evidence from the latest clinical trials. These also primarily focus on the management of OSA and use of different diagnostic modalities, but not on guidelines for the management of CSA. Moreover, the strength of evidence that these current guidance is based upon is poor as none of the treatment recommendations have

a level 1 (1a or 1b) indication,[126] as they are mainly based on observational studies, registry data or expert opinion. This was discussed in section 2.4. For example, the evidence for the widely accepted practice of treating symptomatic OSA patients,[125] is based on a RCT that included improvements in the measures of sleep related symptoms, as the primary outcome.[109] Therefore, even in OSA, we still do not know whether there are mortality benefits treating patients with symptomatic OSA. A recent randomised controlled trial[117] in patients without daytime sleepiness also showed no change in the composite cardiovascular end point. The outcome of these large clinical trials not only emphasises the importance of the strength of evidence obtained from a well-designed, high-quality large RCT, their findings are also likely to impact the formulation of future clinical guidelines on the management of SDB.

6.5.3 Differences in access to sleep studies

The data also highlight the gap between tertiary and secondary care sleep services. Tertiary care specialist centres had more expertise and the capacity to address challenging clinical problems in patients with SDB – they offer patients a greater choice of different types of masks and titrated positive pressure levels to achieve maximum patient comfort. This also resulted in improved patient compliance with mask therapy. On the contrary, the sleep service in secondary care was further complicated by the increased time and resources pressures, which also resulted in SDB receiving a low priority in clinical practice. With the diagnosis and the treatment of SDB becoming more challenging, these tertiary centres with both specialist cardiology and respiratory teams, are likely to be in

the best position to address the complex clinical problems in these high-risk patients with CVD.

HPs in this study found it difficult to directly access sleep services, which resulted in delays in the diagnosis and treatment of patients with SDB. The referral pathways were complicated involving multiple steps, sometimes up to six separate patient journeys converging back at the level of primary care – particularly if a primary care physician first refers a patient to ENT specialists and subsequently requires the input of specialist respiratory sleep services. Some healthcare professionals also found it difficult to access sleep services within their own hospital, a factor determined by the financial resources of the NHS Trusts and the current payment structure for diagnostic tests. This lack of direct referrals has been also shown in the literature to delay patient care.[318] Some of the HPs however, performed direct consultant-to-consultant referrals to overcome this barrier. Having a common care pathway for assessing patients with SDB that includes diagnostic sleep studies or effective screening tools, could make the referral process much more efficient. Care pathways could be an effective as a quality improvement tool (this is discussed further in Chapter 7) and pathway re-design in SDB may improve patient care.

6.5.4 Care coordination

The semi-structured interviews highlighted a lack of communication between healthcare professionals involved. Moreover, no one speciality appeared to take the exclusive responsibility for the management of SDB and there was a lack of coordination in the overall clinical care of these patients. Up to 7 different

specialities could potentially be involved in the care of these patients, such as cardiologists, heart failure nurses, respiratory physicians, general practitioners, dieticians, ENT and general surgeons, which made this process more challenging. All these healthcare professionals involved in patient care should have a thorough understanding of the symptoms, pathophysiology and the evidence for diagnosis and treatment of SDB. Considering the current challenges of treating SDB – the importance of identifying patient cohorts that will benefit and exclusion of groups of patients who may be harmed from therapy – these multiple specialities need better coordination, communication and common ground for decision making. Potentially, concepts similar to the 'dedicated NHS worker' for the management of patients with dementia[319] or having a 'responsible physician' who is accountable for the overall management, continuity and delivery of all patient care,[320] could potentially improve the management of SDB.

6.5.5 Patient compliance with therapy

HP, excluding respiratory physicians, perceived that mask therapy was an invasive form treatment and that poor compliance with PAP/mask therapy was a barrier to treatment. Therapy compliance in OSA patients presents a major problem. Only about 50% of patients are known to adhere to therapy[113] which have been consistent among different populations.[114,115] This does not include patients who refuse therapy at the time of diagnosis – in one study involving 903 patients,[116] 255 patients refused therapy from the start and from the rest only 326 were adherent to therapy after 12 months, thus an overall compliance rate of only 36%. A Canadian qualitative study,[321] which carried out 4 focus group

interviews of 22 OSA patients who were using CPAP, explored barriers for poor compliance. They unearthed themes such as direct side effects of CPAP (e.g. discomfort, dry mouth, claustrophobia and noise from machine), effectiveness of treatment and the stigma of having to wear a mask.

Recently however, therapies for SDB have improved significantly with much quieter machines with humidification capability and more comfortable masks,[322] such as nose masks or full facemask with reduced contact force. The perceptions of HPs about mask and CPAP therapy could potentially influence patient compliance, thus, HPs have an important role to play in educating patients and shared decision-making. Further, improving patient understanding about treatment has shown to improve patient compliance in the long-term.[323] Improved compliance could be important as it may improve these cardiovascular outcomes[158] – in the in sub-group analysis of the large OSA trial conducted by Barbé and colleagues[117] showed an improvement in the incidence of hypertension or cardiovascular events in patients using CPAP more than 4 hours per night.

6.5.6 Limitations

Purposive sampling technique used for selecting the HPs for semi-structured interviews was a subjective process based on the researcher's judgement. Therefore, it carries a some degree of bias and does not necessarily represent the population and the findings may not be generalisable. Further, the findings are dependent upon the knowledge of the interviewees. However, this technique has advantages in choosing a random sample of interviewees, because if the subjects

do not possess knowledge about the research question, the findings may not be relevant to the research question studied, which would have been a poor use of resources.

The findings of this qualitative study are based on 16 interviews, which is relatively a small number of subjects. Although, the possibility of having gaps in our understanding of the data cannot be completely excluded, the data collection was not stopped due to lack of time or resources, but once the saturation of data was reached (i.e. when no new insights in the data has been observed). Data saturation is different for each study, which can depend on the quality of participant selection, richness of data produced by interviewees, interview technique and data analysis. Saturation of the emerging themes prior to the end of the interview programme suggests that most of the key themes have been unearthed, although the relative importance of each is likely to vary overtime and by geography.

6.6 Conclusion

Our study showed that healthcare professionals experience a variety of barriers in the management of patients with CVD and SDB. In light of recent evidence treatment of SDB should be considered carefully and patient selection and risk stratification is extremely important. However, SDB is perceived to have a low priority in clinical practice, potentially due factors such the increased time-pressure this has made this even more challenging. Shared responsibility between different healthcare professionals and simpler pathways with easy access to specialist services that have the capacity and expertise will likely better management in SDB.

Chapter 7: Systematic review of the use of quality improvement tools in the management of cardiovascular disease, with relevance to improving care of SDB

7.1 Aims

The aim of this chapter is to

- summarise the history of quality improvement (QI) and different types of QI tools used in the management of CVD.
- systematically review the literature on their impact on CV outcomes in various healthcare systems.

7.2 Background

'Quality' in healthcare is a multifaceted concept based on the key concepts of patient safety, access, capacity, patient-centeredness, equity, efficiency and effectiveness.[324,325] Usually healthcare organisations are large and complex, such as the NHS. Therefore standardising practice and delivering quality is difficult due to multiple barriers such as local variation in service and availability of resources,[257] communication and cultural barriers between healthcare professionals,[306] and patient expectations and need, which has been demonstrated and discussed in previous chapters. A variety of quality improvement (QI) tools can be adopted to address these issues. There has been a widespread use of quality improvement strategies in healthcare on a global scale in the past few decades.[324] However, which of these tools have the greatest impact on healthcare outcomes is still not conclusive and it is an important

question that needs to be explored. Most of the studies conducted using these tools have been observational, rather than randomised.

7.2.1 QI Definitions

Quality improvement can be defined as making changes that will improve or better outcomes or performance in healthcare 'quality' measures.[326] It is based on the seven pillars defined by Donabedian in 1990.[327]

- Efficacy—the ability of care to improve health
- Effectiveness—how well care achieves improvement in health in the circumstances of everyday practice
- Efficiency—the cost of any given improvement in health
- Optimality—the point at which incremental increases in care begin to diminish in their return on investment (health may be improved, but in a less efficient manner)
- Acceptability of care to patients—accessibility, the practitioner-patient relationship, amenities of care, patient valuation of care outcomes
- Legitimacy—consideration of the value of care by others than the patient receiving that care (i.e. societal valuation)
- Equity—the balance between what individuals and what society consider appropriate distribution of care and resources

Further, it is important to make the distinction between QI 'tools' and 'approaches'. A quality improvement *tool* is a technique used for improvement, which could be used alone or in combination, but an *approach* includes the use of a variety of different tools at specific points along a methodological road map (i.e. more philosophical approach).[15] Therefore, for clarity, in this systematic review the term quality improvement 'methods' will be used, encompassing both these concepts. For example, one could use a specific quality improvement tool such as statistical process control (section 7.2.3.5) to identify variation in care (e.g. time to diagnosis and treatment of sleep disordered breathing in heart failure

patients), reduce this variation with a quality improvement approach (e.g. introduction of a patient pathway), and further continuous improvement can be made with other tools discussed in section 7.2.3 (e.g. plan-do-study-act approach [PDSA], and clinical audit). These quality improvement tools/approaches can be used concurrently and may complement each other.

7.2.2 History of Quality Improvement

Approaches that were similar to the clinical audit process have been used on a smaller scale in clinical practice as early as 1916, by the surgeon Ernest Codman to assess outcome based patient care.[15] However, the roots of formal quality improvement (as currently practiced), first originated in the manufacturing industry and these methods were later adopted by healthcare.[328] For example at Toyota, QI improvement tools were used to optimise production and reduce variation in the car manufacturing process. Toyota consulted Kaoru Ishikawa (who introduced the 'fishbone' tool to explore cause and effect),[329] Edwards Deming (who focused on continuous quality management and introduction of the PDSA cycle),[330] and Joseph Duran (who pioneered the use of statistical processes in quality improvement),[331] during the post-World War II reconstruction in Japan. Further, Feigenbaum at General Electric (GE) was the architect of 'total quality control',[332] a concept where improving quality is a responsibility of everyone in the organisation. Later, these tools that were successfully employed in industry, were applied to healthcare by individuals such as Don Berwick.[333] Concepts such as measurement of quality, team-work and patient centeredness and safety, were introduced with the principal aim of improving quality in healthcare.

7.2.2.1 Quality Improvement in the NHS

The NHS, the largest publicly funded healthcare system in world, was formed in 1948 with the aim of providing a healthcare free-of-charge at the point of usage for UK residents. The formation of the NHS was expected to reduce the variation in healthcare delivery in the population, previously dependent upon the patient's ability to pay. There have been major transformations in the NHS in the past two decades, with the main emphasis being concentrated on improving the quality of care provided to patients. Between 2000 and 2008, under a Labour government, large scale modernisation plans for the NHS were unveiled and *The new NHS*[334] focussed on rebuilding capacity and improving access to healthcare to all communities, with the aim of reducing variation in the delivery of care. The improvements in quality as part of these modernisation plans were primarily focused on quantitative measures such as waiting time targets (e.g. 4-hour A/E waiting time and the minimum 2-week wait for suspected breast cancer) and increasing in capacity of the NHS by increasing the staffing levels, to that perceived to be the basic acceptable standards in the healthcare system. The report by Lord Darzi in 2008, "High quality care for all",[14] underlines these objectives further and the strategic direction for the NHS. This report also formally laid the foundation and set the comprehensive strategy for quality improvement in the NHS.

Quality improvement is continuing to be a key agenda in ongoing NHS reforms. The recent Keogh Report[335] also underlines the importance of quality improvement with a considerable emphasis on patient safety. This report included reviews of 14 NHS Trusts that persistently had high mortality rates in

the UK, which was conducted after public enquires into the failures of the Mid Staffordshire NHS trust.[336] These Trusts failed to deliver good quality patient care and inadequacies in all three dimensions of quality – clinical effectiveness, patient experience and safety – were underlined.[337] Patient safety, which is a key indicator of quality of care, was measured in these trusts using National indicators such as the NHS safety thermometer,[338] and infection and pressure ulcer rates.[339] One of the contributory factors that compromised patient safety in these NHS Trusts was highlighted as the lack of drive for quality improvement. For example, the cause of certain serious clinical incidents (such as retained foreign objects after operation) were not explored and "root cause analysis" (e.g. using fishbone diagrams) was not carried out, and as a result, incidents on similar themes were repeated. In addition, lack of clear and efficient patient pathways in emergency and acute medical care was also identified as a key factor in increased patient mortality. Sir Bruce Keogh also recognised that the hospital leadership and commissioners did not appear to act on the data available to drive quality improvement and did not show a comprehensive and consistent approach to learning from quality and safety reviews.

7.2.2.2 Quality Improvement in CV disease

Cardiovascular care was one of the first area in medicine to adopt QI tools. Many of these projects were initiated in the United States (Figure 6.1) and were mainly based on measuring process of care against evidence-based guidelines (rather than outcome).[340] One such exercise was the quality assurance in the Medicare programme (i.e. the social medical insurance scheme in the US) in cardiovascular conditions such as heart failure, stoke and adherence to thrombolytic/aspirin

therapy in acute myocardial infarction. A national heart failure project in 1999[341] was also conducted in the US looking at measures such as the rate of prescription of ACE inhibitors and measurement of LV function. These objectives were mainly achieved by establishing national data registries to compare quality measures such as patient outcome across various hospitals (e.g. the National Cardiovascular Data Registry; 1997).[342]

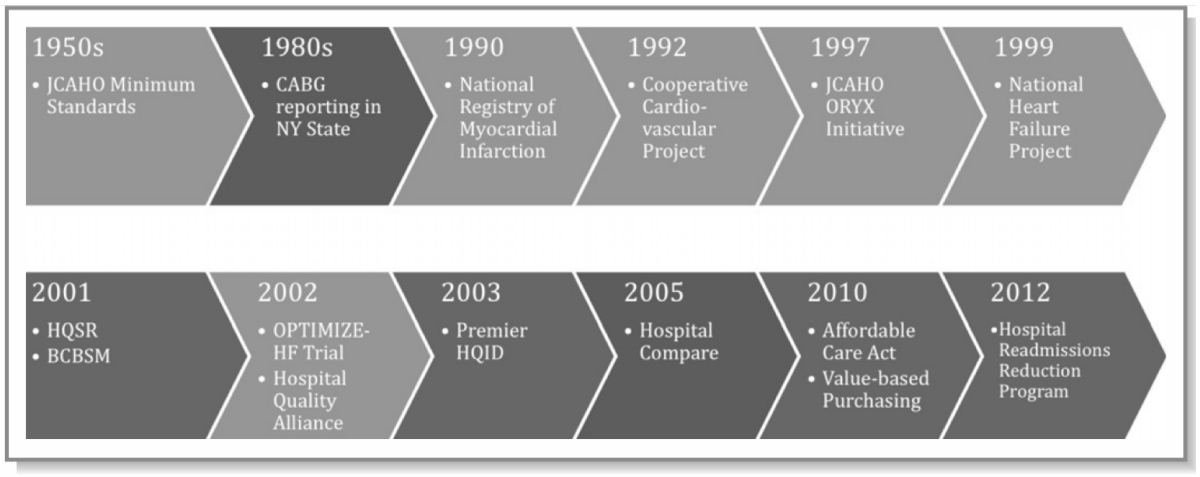


Figure. Timeline of quality improvement programs in cardiovascular care. Green: quality measurement programs; red: public reporting; purple: pay-for-performance programs. BCBSM indicates Blue Cross Blue Shield of Michigan Participating Hospital Agreement Incentive Program; CABG, coronary artery bypass graft; HQID, hospital quality incentives demonstration; HQSR, Hawaii Medical Service Association Hospital Quality Service and Recognition Pay-for-Performance Program; JCAHO, Joint Commission on Accreditation of Healthcare Organizations; OPTIMIZE-HF, Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure.

Figure 7.1 Timeline of different US quality improvement programmes in CVD

(Reproduced from Chatterjee et al.)[340]

Similar registries have also been initiated in the UK under the National Institute for Cardiovascular Outcomes Research (NICOR) programme,[343] such as the Myocardial Ischaemia National Audit Project (MINAP),[344] which is a national database of the management of ST elevation myocardial infarction and the National Heart failure Audit,[345] where the aim is to "drive up the quality of the diagnosis, treatment and management of heart failure by collecting, analysing

and disseminating data, and eventually to improve mortality and morbidity outcomes for heart failure patients", have been commenced.

QI measures to systematically deliver cardiovascular care have also been widely used in the NHS. The first large scale quality improvement project in the UK was the National Service Framework for Coronary Heart Disease,[346] published in March 2000, and initiated as part of NHS modernisation. The main aims of this programme were to have a systematic approach to the delivery of cardiovascular disease management and to reduce any variations and inconsistencies in service delivery. Although this national framework focussed mainly on the prevention and treatment of coronary heart disease (acute coronary syndrome, coronary revascularisation, management of angina), it also highlighted the standards for heart failure, such as in cardiac rehabilitation, conducting appropriate investigations such as echocardiography[124] and treatment with ACE inhibitors[27] and beta-blockers,[26] the measures that have been shown to improve survival in heart failure patients. As a part of this programme, quality improvement approaches such as clinical audit tools were utilised and performance measures were established, to ensure services were delivered according to nationally acceptable standards. In parallel, the setting up of the National Institute for Clinical Excellence (NICE) and its issuance of guidance facilitated improvement in care. NICE was established by the Secretary of State for Health (in April 1999),[347] to ensure that the most clinically and cost effective drugs and treatments were made available accross the NHS in England and to end the 'postcode lottery of healthcare' (where available treatments were dependent on the NHS Health Authority the patient resided). It also created a generally

accepted set of evidenced-based standards for clinicians in disease management and treatment.

7.2.3 Quality Improvement methods

Numerous QI approaches have been described in the literature.[348] The core concepts and the main QI tools used in clinical practice are discussed below.

7.2.3.1 Care pathways

Care pathways (CP), also known as patient pathways, clinical pathways, care maps or integrated care pathways,[349] are structured multidisciplinary management plans which list the essential steps of care in patients with a specific clinical problem. First introduced in 1985 by Zander,[349] care pathways are one of various multifaceted interventions of quality improvement interventions in healthcare.[350] They aim to improve healthcare delivery by translation of clinical guidance into local practice and to standardise the process of care delivery,[351] reducing variation and improving resource utilisation by mapping the ideal processes for specific care.[352] There has been wide utilisation of care pathways in many specialties such as surgery,[353,354]cancer[355] and airways disease such as COPD.[356] Care pathways have also been introduced widely in the management of cardiovascular diseases in conditions such as heart failure,[357] management of myocardial infarction,[358] stroke[359] and atrial fibrillation.[360]

A Cochrane review of 28 studies by Rotter and colleagues[361] suggests that the effect of CPs may be variable. A study conducted by Kim and colleagues,[362] in 2002, involving 18 patients with low-risk uncomplicated atrial fibrillation, evaluated the impact of an accelerated emergency department based strategy

that included early cardioversion with low molecular heparin, versus usual care involving hospital admission. It demonstrated a significant improvement in length of stay (<1 day for all patients with new pathway versus 2.1±2.3 days [range 1 to 8 days] for usual care), time to cardioversion (4.8 hours versus 29.8 hours; p<0.05) and time to sinus rhythm (4.5 hours versus 15 hours; p<0.05). An example of this pathway that was used is illustrated below (figure 7.2).

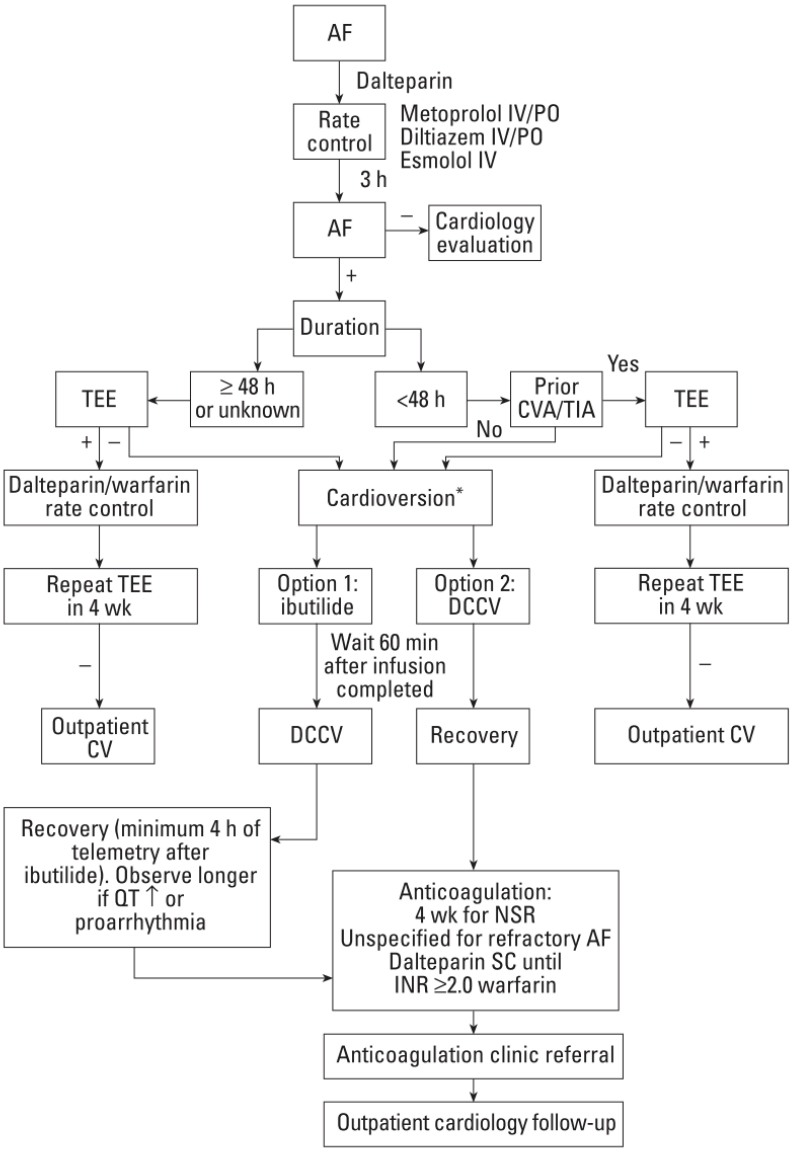


Figure 7.2. An example of a clinical care pathway

Pathway to optimise the management of atrial fibrillation involving DC cardioversion in patients presenting to hospital
(Adapted from Kim et al.[362]*)*

In a study carried out by Sulch,[363] which explored the effects of a new CP for stroke management, found an increase in length of stay compared to control (the length of stay was 50±19 days versus 45±23 days; p=NS), and mortality in the two groups also did not show any statistical difference at 26 weeks (13% versus 8%; p=NS). 3 other studies in this Cochrane review (not relating to CVD), which compared in-hospital mortality rates also did not find significant improvement in mortality but did improve procedure related complications (e.g. fractured neck of femur and GI surgery), and lead to improvements in documentation. From these data, it is not possible to conclusively determine that CPs are effective when evaluated against hard outcome measures, however, it may be successful in the correct setting which may depend on factors such as establishing a clear patient journey and appropriate objectives.

7.2.3.2 Pay for performance

Pay-for-performance (P4P) is the introduction of financial incentives to clinicians and commissioners to better health outcome. The Quality and Outcomes Framework (QOF) introduced in 2004 in the NHS is one the largest P4P programmes, where GPs are rewarded for good practice,[364] determined by a set of targets (currently based on 121 quality indicators). 93 of these are across 20 clinical areas including heart failure and hypertension and a further 9 indicators are related to public health and encompass cardiovascular prevention. Points are awarded (from a maximum of 900 points) for meeting these targets and for each point achieved an incentive of ~£150 is paid to the GP practice.[365] Despite its use for the past 10 years there is still no conclusive evidence that it improves patient mortality. A recent systematic review found that the

improvements in quality of care could be modest, with the most impact seen during the 1st year of its introduction,[366] however, this study was carried out in non-CVD.

Large scale P4P schemes have been introduced for cardiovascular disease in the US.[340] Centre for Medicare and Medicaid Services in the US organised the Hospital Quality Incentives Demonstration (HQID) programme, which offered payment bonuses to hospitals based on their performance in the management of acute myocardial infarction (AMI), cardiac bypass surgery (CABG) and heart failure. These hospitals were already part of an alliance that encouraged hospitals to collect and report data on quality measures such as the proportion of patients who were prescribed aspirin, beta-blockers and ACE inhibitors and had an assessment of their LV function. These hospitals were already linked to Medicare reimbursement and hospitals performing in the top 10% were given a bonus of 2% and the next 10% received a bonus of 1% on top of this reimbursement. Their outcome has been evaluated in multiple observational studies. Lindenauer and colleagues[367] found that after 2 years in the scheme, the 255 hospitals which were part of this P4P scheme, the calculated performance score (a measure of the percentage of patients who received the recommended treatment), was higher compared to matched controls (absolute change of 4.3% [CI: 2.5 – 6.1; p<0.001] for AMI and 5.2% [CI: 2.8 – 7.7; p<0.001] for heart failure). This study also found that the baseline performance of the hospital was inversely proportional to the degree of improvement. For heart failure, the difference in improvement was 1.2% for hospitals with the highest baseline performance and 9.6% for the hospital with the poorest performance. After

adjustment for this baseline performance, effect of P4P decreased but was still statistically significant (absolute change of 2.6% [95% CI: 1.3–3.9; p<0.001] for AMI and 4.1% [95% CI: 2.6–5.5; p<0.001] for heart failure). However, in another study carried out by Jha and colleagues,[368] when hard outcome measures, such as the mortality rate over a 6-year period (from 2003 to 2006) was studied, there was no significant difference between the P4P and control hospitals. Whilst there was no difference at baseline (measured as 30-day mortality) in the management of patients with heart failure and myocardial infarction, this persisted throughout the study period: the change in mortality per quarter (difference of −0.02% [95% CI: −0.05 to 0.01] for myocardial infarction and 0% [95% CI: −0.02 to 0.02] for heart failure) and the rate of mortality at the end of study was similar (difference of −0.18% [95% CI: −0.97 to 0.61] for myocardial infarction and 0.22% [95% CI: −0.28 to 0.71] for heart failure). These results suggest that P4P, although it may have short-term effects such as adherence to guideline quality measures, it is unlikely to affect mortality over the long-term. This is likely due to multiple factors such as baselines performance and capacity and the inherent ability of the hospital to respond to such incentives and the sustainability of any process changes.

7.2.3.3 Clinical Audit and feedback

NICE defines clinical audit as "a quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change".[369] Its importance was further recognised when clinical audit was included as one of the six pillars in the NHS clinical governance umbrella,[334] but has been formally endorsed since the 1980s,

with the publication of the White Paper 'Working for Patients', by the Department of Health.[369]

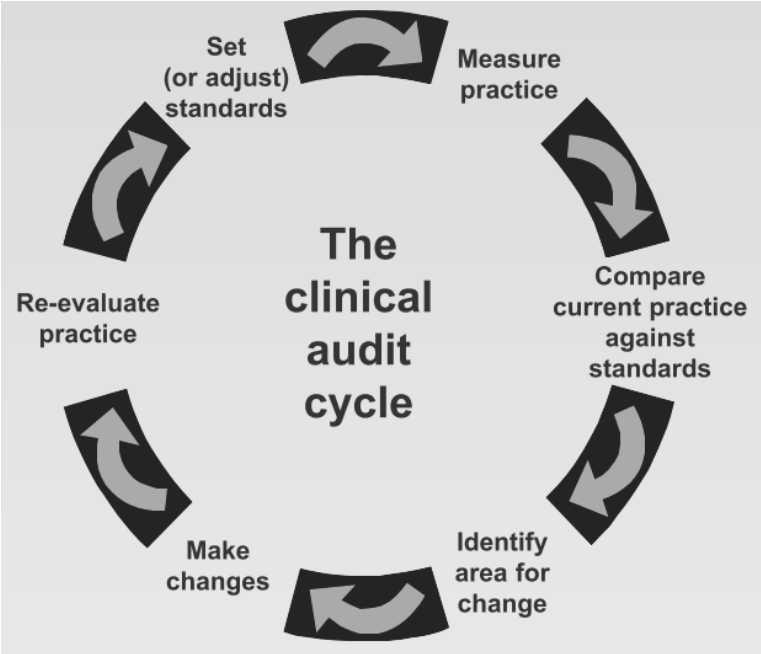


Figure 7.3 Six stages of the Audit cycle

(Adapted from Guide to Using Quality Improvement Tools to Drive Clinical Audits by Dixon et al.[370])

The audit cycle usually consists of 6 stages (figure 7.3).[370] For the audit tool to be useful and effective in improving clinical practice, it is imperative that the re-audit or the re-evaluation stage is carried out in an audit cycle. The audits are usually conducted on a small scale to determine the local practice against either local or national guidance. However, large scale clinical audits such as the National Heart Failure Audit,[345] which was instigated to help highlight clinical practice and outcomes that do not meet optimal standards in NHS hospitals, in the different aspects of heart failure management measured against NICE standards, are also in progress.

The effectiveness of audit and feedback seems to be small but depends on the baseline clinical performance. A recent systematic review of randomised controlled trials of audit and feedback[371] found that, compared to usual care, it improved the healthcare professionals' compliance with guideline-based clinical practice (in 49 studies after exclusion of studies with bias, the weighted median adjusted risk difference was 4.3%; interquartile range (IQR): 0.5% to 16%). 34 studies focused on management of patients with cardiovascular disease (which included risk factors such as diabetes). However, there was no significant effect on patient outcome measures such as improvement of blood pressure, glucose control or smoking cessation (in 6 studies the weighted median risk difference was -0.4%; IQR: -1.3% to 1.6%). In a study carried out by Peters-Klimm and colleagues,[372] in 168 patients with heart failure, which randomised 37 GPs to either a multifaceted intervention involving audit and feedback (that included four interactive educational meetings and a pharmacotherapy feedback) or to usual care (a lecture on guidelines adherence), showed improved prescription rates. This was related to an improvement in prescription of aldosterone antagonists (OR: 3.5; 95% CI: 1.1–11.1; p<0.04) and use of ACE inhibitors (OR: 3.3; 95% CI: 1.0–10.2; p<0.04). There was no significant difference between the rates of prescription at baseline and these findings were observed despite high rates of prescription for ACE inhibitors (91% versus 88%) and beta-blockers (78% versus 80%) at the start of the study. However, in another study carried out by Sauaia and colleagues (2000),[373] which compared the effect of feedback delivered either via on-site presentations or via mailed-written feedback (control group), about the management of patients with acute myocardial infarction admitted to hospital, showed no difference in quality measures, such

as prescription rates for aspirin, beta-blockers and ACE inhibitors at discharge, or rate of reperfusion within 12 hours of arrival at hospital. This study also evaluated the effect on mortality: there was no statistically significant difference in mortality between the intervention and control groups (19% versus 17% at baseline [p=0.21] and 15% versus 22% after 1 year [p=0.25], respectively).

Studies carried out in a primary care or outpatient settings also show mixed results in the management of high blood pressure[374] and diabetes. In a cluster randomised study of 417 patients carried out by Weitzman,[375] comparing the effect of a combined patient/physician intervention (where patients received a letter encouraging them to remind their doctors to address essential aspects of diabetes care) against physician only intervention (who received diabetes related quality performance feedback only), found that after 1 year, there was no difference in the SBP or HbA1c levels. However, in another study carried out by Phillips,[376] which randomised 4138 patients to different management strategies during clinics that included either computerised reminders with patient-specific management recommendations or individual face-to-face feedback on performance or both, found an improvement in HbA1c but not in blood pressure. Both these studies found improvements in lipid management. These findings suggest that the effect of audit and feedback in clinical practice may be variable.

7.2.3.4 PDSA

PDSA or the plan-do-study-act approach, was first developed by Deming in 1986, to improve processes in quality and changing the organisational culture in the manufacturing industry. PDSA has since been adopted in healthcare in re-design initiatives such as the Cancer Services Collaborative in the NHS.[348] It may be described as continuous iterative improvement approach, which involves important steps such as continuously testing out the ideas for change and modifying them from the results obtained (figure 7.4).

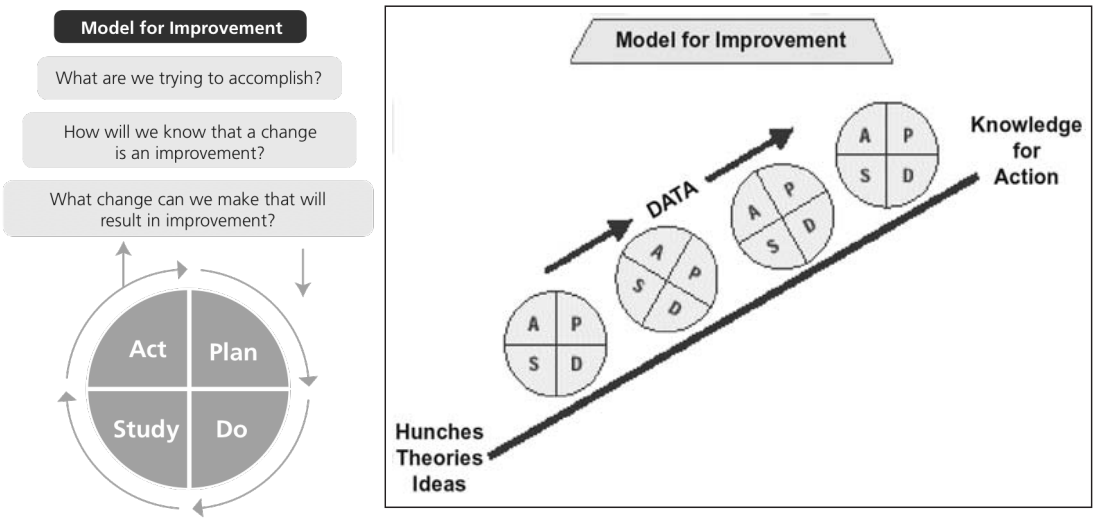


Figure 7.4 A schematic of a PDSA cycle and its model for improving quality

It has been difficult to establish the success of PDSA, mainly because its effectiveness has been affected by the lack of adherence and poor application of the tool. A systematic review carried out by Taylor,[377] exploring the application of the PDSA tool in healthcare to improve quality, found a poor understanding and inconsistent use of its methodology. Of the 73 studies included in this review, only 47 applied the PDSA tool that complied with the primary features of the method. Further, only 14 of them fully documented the application of a

sequence of iterative cycles and only half of them (7 of 14) reported the use of quantitative data at frequent data intervals to modify the progression of cycles. These are key features of PDSA cycles. PDSA has been used in the management of diabetes. An Australian study,[378] which carried out a retrospective analysis of 807 medical records of GPs over a 3-year period, found a significant improvement in the proportion of patients achieving lipid management targets (OR of 4.4, $p<0.001$). However, this association declined for blood pressure (OR of 0.68, $p=0.08$) and HbA1c (OR of 0.81, $p=0.3$). This study also did not provide details of how the PDSA cycle was during the study, particularly the changes made after each of the 3 cycles audited.

7.2.3.5 Statistical process control

Statistical Process Control (SPC), which is similar to PDSA, originated in manufacturing industry. It explores the difference between common cause variation (the natural variation that cannot be controlled) and special cause variation (the variation that can be controlled). SPC uses control charts which shows the variation of processes over time and consists of control limits (usually between 3 SDs from the mean in both directions), where data points appearing outside these limits are likely to exhibit special cause variation.[379] These control charts (figure 7.5) can be used to monitor a process in real time, detect trends and deteriorating performance. This method has been used for monitoring complications in cardiac surgery[380] and PCI procedures.[381]

Reading number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
Systolic blood pressure (mmHg)	169	172	175	174	161	142	174	171	168	174	180	194	161	181	175	176	186	166	157	183	177	171	185	176	181	174
Moving range		3	3	1	13	19	32	3	3	6	6	14	33	20	6	1	10	20	9	26	6	6	14	9	5	7

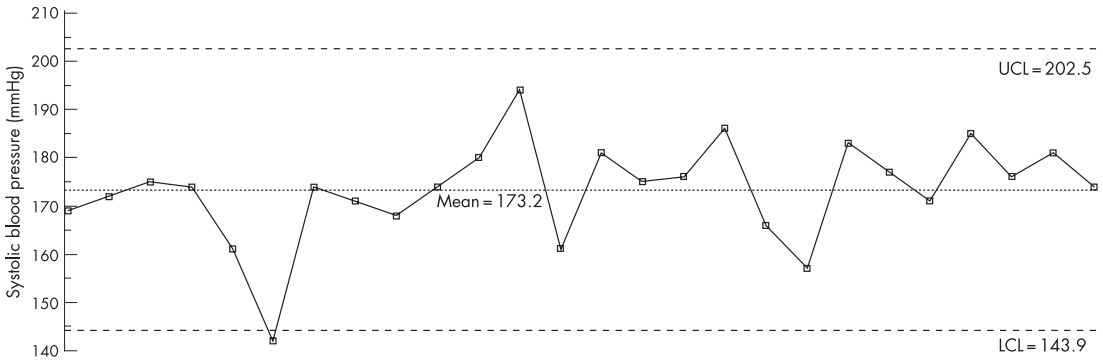


Figure 7.5 Use of statistical process as a QI tool

The use of the statistical process control tool is illustrated by 24hr systolic blood pressure readings from a patient
(Adapted from Mohammed et al.[379])

A systematic review conducted by Thor,[382] found benefits in the use of SPC in healthcare on themes such as identification of areas of improvement and assessing the impact of change, quantification of variation and improving communication. However, this review did not include studies which evaluated the effectiveness of the SPC tool quantitatively.

7.2.3.6 5S, Lean and six-sigma tools

The 5S strategy is normally used in combination with other approaches and forms an integral part of the Lean tool (i.e. adopted as Lean-5S).[383] 5S consists of five strategies; *sort* (sorting items in the immediate work area and keeping only those that are needed frequently and remove what is not used), *simplify or straighten* (set out work items in order to optimise the efficiency of the workflow), *shine* (cleaning the workplace and inspecting equipment to look for abnormal wear), *standardise or stabilise* (adopt standards for the workflow process), *sustain and self discipline* (on-going improvement and sustaining the

gains made from the previous 4 steps such as housekeeping audits). This approach is also sometimes termed 6S, with the addition of 'safety'.

"Lean" is a quality improvement approach that was developed in industry, originally evolved from Toyota,[384] to improve their flow of production and eliminate sources of waste. The Lean approach is a cyclical improvement process, which complements the use of the 5S tool.[385] This approach also recognises the importance of the customer, a concept that can also be applicable and translated to healthcare, particularly in improving patient satisfaction. Lean tool has been widely used in healthcare, especially improving surgical practice.[386] These improvements have been related to reduction in length of stay, improving efficiency in the theatre, reduction in infection and compliance with antibiotic and DVT prophylaxis use. One study relating to the management of patients with neck of femur fracture, reported improvements in mortality in a retrospective analysis after the introduction of the Lean tool (30-day mortality from 11.7% to 6.7%; $p<0.05$).[387] The Lean tool has also been used to restructure the patient journey at a tertiary diabetic day centre in Ireland,[388] in which the intervention included an introductory seminar on 'lean thinking' and moreover, patient journeys were also mapped and quantified. This exercise led to a significant improvement in journey time (from 118.13 ±38.02 minutes to 58.15 ±18.30; $p<0.001$) compared to baseline.

Six-sigma is a product improvement or redesign QI approach that was developed by Motorola (in 1986) and General Electric (in 1995s) with the aim of reducing product defects and improving their new products and services.[389] The sigma, 'σ',

indicates standard deviation, which is a measure of variation in the product from the mean. It uses a structured method of process improvement called the DMAIC process; define, measure, analyse, improve and control.[15]

Both six-sigma and lean are usually adopted together as a common approach (Lean Six-Sigma). Similar to Lean, 6-sigma has been mainly adopted in surgical specialities to reduce length of stay and improve efficiency in the operating theatre.[386] This tool was also used in cardiac intensive care to optimise the management of glycaemic control using an insulin protocol.[390] This is carried out because only 10% of patients who were admitted had a glucose level of <200mg/dl (~10mmol/dl). Therefore, the team carried out the DMAIC process:

1. *define the goal*: improve glucose control following admission
2. *measure*: glucose values at different time points and deviation from protocol was measured and this is an iterative process with discussion at monthly QI meetings
3. *analyse*: identification of key factors that impact glucose control
4. *improve*: based on above processes the insulin protocols were modified periodically
5. *control*: finally, to maintain continued improvement, education about glucose control was incorporated to the induction of new staff

These resulted in more than 90% patients achieving good glycaemic control. Lean-5S and six-sigma tools could potentially be applied for practical procedures such as cardiac surgery and the cardiac catheter lab to improve efficiency. However, there is likely to be a high risk of bias in these studies, as most of these studies were not randomised. Therefore due to this lack of evidence in its

adoption in clinical care it is difficult to conclusively judge the impact and the effectiveness of these tools.[391]

7.2.3.7 Total quality management

Total quality management (TQM) is a concept which recognises that the continuous improvement of quality of processes within an organisation is the responsibility of everyone within that organisation who delivers services, including the management workforce and patients.[392] The term TQM is used interchangeably with continuous quality improvement, which also signifies continuous effort by all members of the organisation. TQM has been used to improve outcomes of CABG surgery in a multicentre study of more than 6000 patients, where data were collected 3 years prior and 2 years following the intervention in 1990.[393] This intervention involved training of both the executive committee members and other staff, site visits to observe practice, and feedback of outcome data, which was distributed three times a year to individual physicians. This resulted in a mortality reduction of 24% (standardised mortality ratio of 0.76; 95% CI: 0.67 to 0.90; $p<0.01$). This was despite patients in the post-intervention period were older and more likely to have comorbid conditions.

In a systematic review carried out by Shortell and colleagues, TQM was found to reduce hospital length of stay and cost of care.[393] However, this review showed that only 13 studies were multi-site, and only 2 had a randomised design. Therefore, the effectiveness of TQM is debated due to the lack of appropriately controlled studies, and the doubts related to the cost of implementation versus benefit.[394]

7.2.3.8 Fishbone

The fishbone diagram introduced by Ishikawa (also termed 'cause and effect' diagrams), facilitate the identification of factors contributing to outcomes. The diagram, which looks like a skeleton of a fish, where the 'spines' represent causes and 'head' the effect, is useful for identifying and analysing multiple causes of a problem. This can be used together with root cause analysis with five "whys".[348,395] The fishbone tool has been used to identify causes of guideline non-adherence in the treatment of upper respiratory tract infections, as in figure 7.6, where all the possible causes were explored.[396]

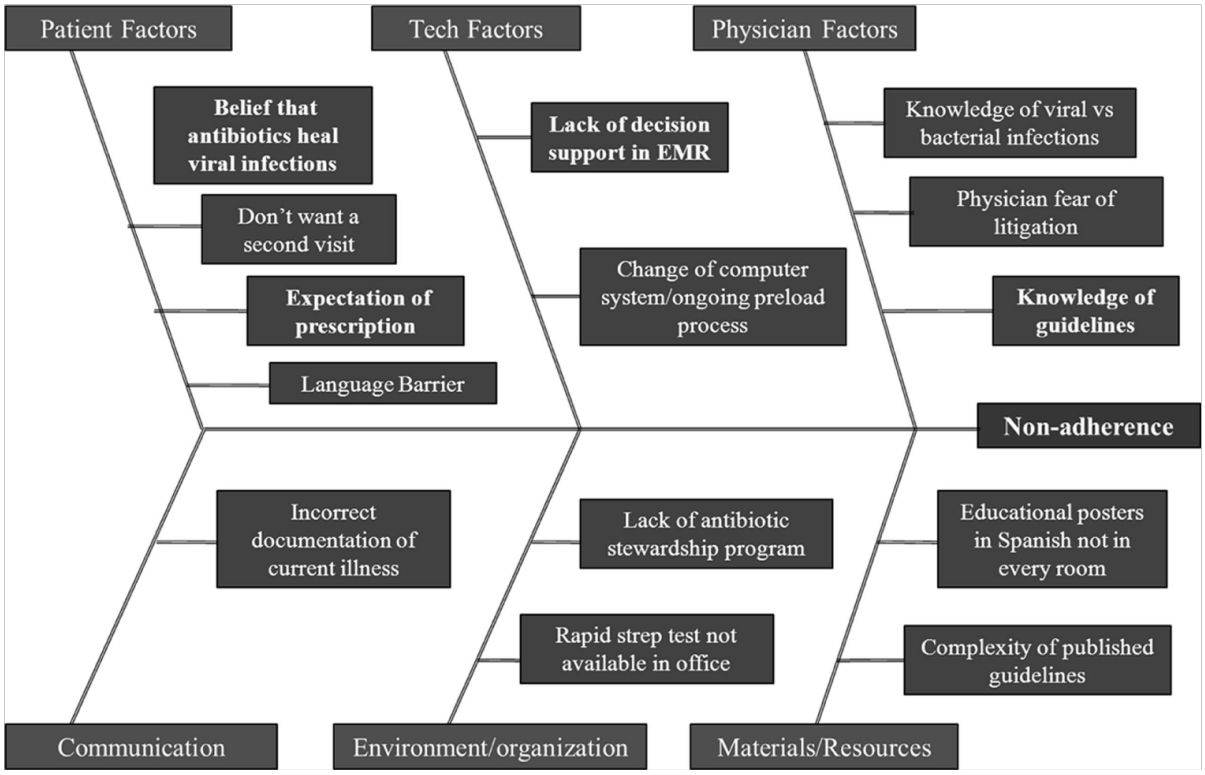


Figure 7.6 An illustration of the Fishbone method

All the potential causes or barriers in a pathway can be explored using this method (Adapted from Alweis and colleagues)[396]

7.2.3.9 Theory of constraints

This tool is based on the concept that an organisation will have at least one constraint and this acts as a 'bottleneck', a rate-limiting step in the workflow, setting the rate for the whole process. The first step is the identification of these rate-limiting factors and these tools have been used to solve issues such as bed-blocking in a Dutch hospital.[397]

7.2.3.10 Experience based design

Experience based design uses the patient experience (and of their carers) to improve healthcare. This involves using patient feedback, exploring patient stories and collaborative work with patient groups and communities. The use of this tool in the literature of is limited, however this method has been used in childcare services to improve access to healthcare.[398] The use of this tool in health care is limited or in combination of other tools such as audit.

Cardiovascular medicine has been in the forefront in the adaptation of QI tools. However, in the literature the effectiveness of these different QI tools in CVS disease management (including the management of cardiovascular risk factors such as risk factors such as DM and HTN), has not been explored. In this systematic review, we aim to study the impact of different QI methodologies used in CV disease management.

7.3 Methods

The systematic review has been performed under the Cochrane Handbook for Systematic Reviews of Interventions.[399] We searched databases Pubmed/Medline databases, NHS online libraries and the Cochrane Databases.

7.3.1 Search strategy

We used standard MESH terms that were already available on Pubmed such as "quality improvement", "clinical pathway", "clinical audit", "pay for performance", "total quality management", "continuous quality improvement", "root cause analysis".

Also, each quality improvement tool was also searched using search terms "care pathway", "patient pathway", "pathway redesign", "PDSA or plan-do-study-act", "statistical process control", "lean", "5S or 6S", "six sigma", "experience based design", "theory of constraints", "fishbone", and "cause and effect", to broaden the search.

7.3.2 Inclusion criteria

- All studies conducted during a 10-year period (from 2004 to 2014)
- Studies in which quality improvement methods or a programme have been used to change practice
- Studies where these quality improvement methods had been introduced in the management of cardiovascular disease and risk factors in the following areas
    - Heart failure
    - Ischaemic heart disease including acute myocardial infarction, acute coronary syndrome, angina

    - Stroke
    - Diabetes Mellitus (both type I and II)
    - Hypertension
    - High cholesterol or dyslipidaemia
    - Atrial fibrillation
    - Sleep disordered breathing
    - Coronary artery bypass graft surgery
- Only studies which were randomised: either randomised controlled trials (RCTs) or cluster randomised controlled trials (CCTs).
- All studies that have been published in peer-reviewed journals

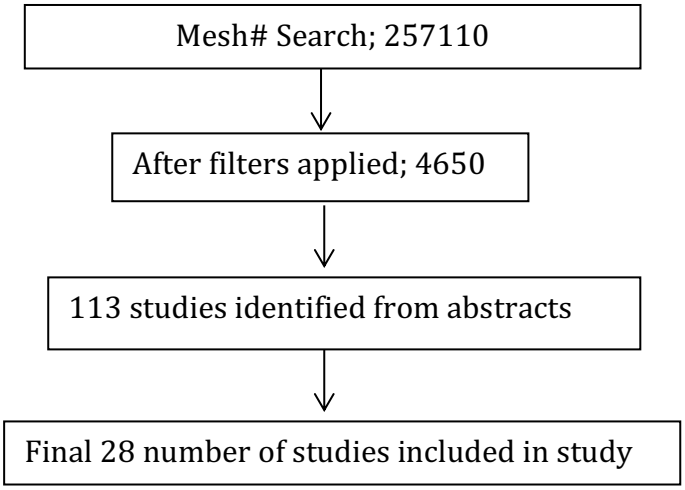
7.3.3 Exclusion criteria

- Studies not in English
- Studies pertaining
    - paediatric management (e.g. paediatric cardiology)
    - Obstetrics (e.g. pre-eclampsia or hypertension in pregnancy)
    - Peripheral vascular surgery
    - Management of cardiopulmonary resuscitation
- Studies without "full text" access to journal articles (after attempted access via the Imperial College UK access management federation)
- Any non-randomised study (e.g. studies which were observational, case studies, letters or opinion pieces or qualitative)
- The quality improvement method used is not clearly described

The selection of suitable articles was done in a two-step process. First, all the abstracts identified were screened manually to identify the relevant articles which met the exclusion and inclusion criteria. The second stage was narrowing down these articles further by reading the abstracts and closely checking the type of quality improvement method used and the strength of study design. We used standard filters within the search engines (e.g. date; from 2004 onwards, type of study; RCTs, language; English) to narrow the search.

7.4 Results

The initial search yielded 257110 studies, and after filters applied this was narrowed to 4650. Then after screening the abstracts using the inclusion/exclusion criteria this was narrowed to 113. Finally, 28 studies were identified for this systematic review.



The results have been categorised and presented by each quality improvement method. 3 studies were in heart failure, 4 in stroke, 5 in acute coronary syndrome, 15 in management and prevention of cardiovascular risk factors such as diabetes, hypertension and dyslipidaemia and 1 study in sleep disordered breathing. Half the studies (14/28) of these studies were exclusively conducted in primary care. Most commonly used methodologies were care pathways, audit and feedback, and education on clinical practice guidelines. The range of follow up periods in these studies was 1 to 36 months.

7.4.1 Multi-level, large scale quality improvement project (2)

CV risk factor	Country	Setting	Duration (F/U)	Sample Size & Design	Outcome/Improvement	Summary
ACS	Brazil	Hospital	30 days	1150 patients Cluster RCT (n=34)	Yes; improved use of evidence-based ACS therapy (aspirin, clopidogrel, statin and heparin); 68% vs 50% in the 1st 24hrs. No effect on 30-day mortality or CV events.	BRIDGE-ACS trial; comparison of usual care against a multifaceted QI initiative with reminders, checklists, case management, training, education material (e.g. pocket guidelines) and risk stratification algorithm[400]
ACS/ NSTEMI	Europe	Hospital	7 months (3 of 7 months were post QI)	2604 patients Cluster RCT (n=38)	Yes; improved quality indicators (OR 1.66, 95% CI 1.43–1.94; p<001) recommended by ESC (e.g. use of risk stratification, coronary angiography, use of ACS therapy). Effect on mortality not commented.	EQUIP-ACS trial; 38 centres in Europe randomised to QI initiative vs Non-QI. Centres with QI initiatives had multidisciplinary QI team meetings, QI tools to analyse local processes and used PDSA cycles to overcome barriers.[401]

7.4.2 Total quality management (2)

CV risk factor	Country	Setting	Duration (F/U)	Sample Size & Design	Outcome/Improvement	Summary
CVS risk factors	US (NY)	Primary care	12 months	727 patients RCT (2 sites)	Yes; Improvement in BP, lipid & HbA1c. Effect on mortality not commented.	This study evaluated a new QI initiative of concurrent peer review visits (a semi structured patient care visits conducted by a clinician) aiming to minimise clinical inertia[402]
CVS risk	Canada	Primary care	6 months	2344 Cluster RCT (122 GPs)	Yes; improved adherence to CPGs. Effect on mortality not commented.	GP education with workshops on CPGs Also included nurse visits once a month to screen medical records of patients who gave, prompts to physicians (by placing a label in front of the chart & enclosing a checklist)[403]

7.4.3 Care pathways (8)

CV risk factor	Country	Setting	Duration (F/U)	Sample Size & Design	Outcome/Improvement	Summary
Stroke	China	Hospital	90 days	758 patients RCT (n=5 sites)	Yes; reduction in length of hospital stay (21±6 vs 18±6.35 days) No change in stroke/ functional scale.	Use of a 11-step clinical pathway (spanning 2 days) for the management of transient ischaemic attack and intra cerebral haemorrhage patients[404]
Stroke	Italy	Hospital	6 months	4895 patients Cluster RCT (n=30)	Yes; improved referral to stroke unit (24% vs 13%) & rates of thrombolysis (8.6% vs 1.7%). Effect on mortality not commented	Evaluation of an emergency clinical pathway for stoke; comparing emergency care HPs trained in the clinical pathway (training by a facilitator in identifying stroke symptoms) against usual care[405]
Stroke	Italy	Hospital	6 months	476 patients Cluster RCT (n=14)	Yes; lower risk of mortality at 7 days (OR of 0.10; 95% CI: 0.01–0.95) and rate of adverse functional outcome (OR of 0.42; 95% CI: 0.18–0.98). No effect on primary outcome: 30-day mortality	Comparison of usual care against instigation of clinical pathway for stroke developed over 6 months. HPs in the intervention arm received training in clinical pathway and QI methods and used a standardized package which included evidence-based key interventions and indicators[406]
ACS	NZ	Hospital	30 days	544 patients RCT (single centre)	Yes; improved early discharge (within 6 hours; 19%vs 11.0%; OR ratio of 1.92; 95%CI: 1.18–3.13). No change in major adverse cardiac events (at 30-days only 1 MACE)	Comparison of an existing chest pain pathway of the hospital to a novel pathway based on an accelerated diagnostic protocol (e.g. risk stratification with TIMI score, ECG, 2-hr Troponin testing)[407]
ACS	China	Hospital	12 months	3500 patients Cluster RCT (n=70)	No; No improvement in measures (e.g. proportion receiving combined medical therapy, PCI/angiography, door to balloon time, hospital stay) but in one (proportion of patients on appropriate medical therapy). Improvement in death (OR 1.4; 95% CI: 0.7–2.8) & MACE (1.6; 95% CI: 0.9–3.0) but not statistically significant	The implementation of clinical care pathways in management of ACS (which included risk stratification, management of STEMI, and of NSTEMI). This pathway was based on AHA/ACC and Chinese society of cardiology guidelines and adopted locally with Chinese context.[408] Barriers for the lack to successful implementation of these pathway were also explored[409]

ACS	Australia	Hospital (A/E)	3 months (timeline unclear)	108 patients Cluster RCT (n=6)	No; No difference in door-to-needle time (29 mins vs 29mins) or proportion receiving thrombolytic therapy (78% vs 84%; p=0.7)	Implementation of a five-step clinical pathway including engaging clinicians, development of pathway using Australian heart foundation guidelines, reminders, education, audit & feedback) in 3 hospitals, compared.[410] **Allocation of 108 patients to each group was not blinded
Heart Failure	Italy	Hospital	6 months	429 patients Cluster RCT (n=14)	Yes; reduction in in-hospital death (5.6% vs 15.4%; p<0.01; OR of 0.18; 95% CI: 0.07–0.46) & readmissions (OR of 0.42; 95% CI: 0.20–0.87). Improved use of diagnostic procedures & medical treatment	Implementation of a clinical pathway over a 6-month period based on European HF guidelines but adapted locally. Involved clinical pathway training, analysis of care processes, detailing the results into protocols and documentation[411]
Sleep Apnoea	US (FL)	Hospital	6 weeks	106 patients RCT Single centre	No; No difference in two pathways in relation to CPAP adherence (5.20± 0.28 versus 5.25 ± 0.38 h/night) and improvement in scores for sleep questionnaires (e.g. ESS; −6.50 ± 0.71 versus −6.97 ± 0.73)	Study comparing a clinical pathway using portable monitoring (PM) for diagnosis (home sleep study) & optimising treatment (use of autotitrating positive airway pressure device) and a pathway using polysomnography (PSG) and CPAP with the presence of a technician.[412] **4 patients crossed over from PM to PSG group

7.4.4 Pay for performance (1)

CV risk factor	Country	Setting	Duration (F/U)	Sample Size & Design	Outcome/Improvement	Summary
CVS risk factors	US	Primary care	12 months	297720 patients Cluster RCT (n=42)	Yes; improvement in performance measure for BP control (5.5% 95% CI:1.6%–9.3%), aspirin therapy in CVD (6.0%; 95% CI: 2.2%–9.7%), smoking cessation (4.7%; 95% CI: −0.3%–9.6%), but no difference for cholesterol measures against control. Absolute levels of BP/cholesterol reduction and effect on mortality unknown	Evaluation of a pay-for-performance incentive in small practices looking at improvement of cardiovascular risk factor management, looking at proportion of patients on Aspirin, BP & cholesterol control within target[413] ** Patients were age and sex matched and included all patients of practices

7.4.5 Audit and feedback (8)

CV risk factor	Country	Setting	Duration (F/U)	Sample Size & Design	Outcome/Improvement	Summary
HTN	Denmark	Primary care	24 months	2646 patients Cluster RCT (n = 124)	No; no change in BP reduction between groups (i.e. measured change between 2007 and 2009) but BP was reduced in all groups (p<0.001)	Study evaluated giving feedback to GPs on their practice on BP management. Compared 3 groups; moderately intensive group (feedback information & 1-day meeting results presented), intensive group (similar to moderate group but with access to a cardiologist & clinical decision support system) or control group[414]
HTN/ Cholesterol	Norway	Primary care	12 months	Cluster RCT (n=146) Number of patients not included**	Yes; improvement in prescription of Thiazides (relative increase of 1.94; 95% CI: 1.49–2.4; p<0.001). But no significance in achieving treatment goals (0.98; 95% CI: 0.93–1.02; p=0.330.	Study comparing a multifaceted intervention (educational outreach visit with audit and feedback, and computerised reminders) to control [415]. ** Analyses were carried out by intention to treat. 3 different sample sizes (patients) were used for to assess each outcome.
CVS risk factors	Canada	Primary care	24 months	4617 patients Cluster RCT (n=14)	No; no change in the adjusted mean difference for SBP (−0.05; 95% CI: −2.11–2.02), DBP (−0.72; 95% CI: −2.18–0.75) or LDL values (0.04; 95% CI: −0.02–0.10)	Comparison between usual care and feedback against feedback + a work sheet for action planning and goal setting, sent 6 monthly. This also included documents such as clinical recommendations, a self-reflection survey, and explanations [416]
Stroke	US (multi state)	Hospital	6 months	3311 patients ** Cluster RCT (n=13)	No. No change in stroke performance measures (e.g. thrombolytic therapy in 1hr, dysphagia screening)	Comparison of audit feedback alone versus audit feedback plus site-specific interventions (with a toolkit having reminder systems, literature synthesis, individualized data analysis/suggestions and identification of potential barriers)[417] ** Sample sizes & statistics do not match in text/tables

DM	US (CA)	Out Patient	12 months	2007 patients Cluster RCT (n=22)	No; no improvement in clinical quality (HbA1c, LDL or BP change scores) or costs **primary outcome not defined and presented	Evaluation of audit and feedback (of practice patterns of physicians) and a diabetic resource nurse. Consisted of 3 groups; group 1: audit & feedback (from patient data on Medicare claims only), group 2: group 1 + medical records based & group 3: group 2 + nurse coordination[418]
DM	US (MN)	Out Patient	12 months (lipid control)	483 Cluster RCT (n=78)	No; No differences in BP (-0.02 vs -0.01; p=0.83), LDL (-0.02 vs -0.01; p=0.83) or HbA1c levels (-0.02 vs -0.01; p=0.83) nor the number patients of achieving targets. No of patients who had HbA1c (62% vs 48%) and LDL (76% vs 64%)monitoring was significantly improved (p<0.05)	Evaluation of a registry-generated audit, feedback, and patient reminders with information organised by evidence based guidelines given to resident doctors in a community clinic compared to a control group with usual education[419]
Diabetes + Heart Disease	Canada	Primary care	7 months	789 patients Cluster RCT (n=32)	Yes; outcome was the number of chronic disease prevention and screening actions (e.g. BP, glucose, LDL, BMI screening/monitoring, smoking/alcohol cessation) that were met. This was higher in PF+PP group (5.3±2.6), compared to PP (4.7±2.7), PF (2.6±2.3) or control (1.9±1.8), groups (p<0.001).	BETTER trial aimed to improve preventative care of heart disease, diabetes and cancers (breast/cervical/colonic). A multifaceted, evidence-based, intervention with a practice facilitator (PF) and audit & feedback tool was introduced. It also had a with a patient-level intervention (one-hour visit with a prevention practitioner; PP) with 4 comparator groups (control, PF, PP, PF + PP)[420] **Effect on mortality or other hard endpoints not included.
HTN in CKD	UK	Primary care	Yes (ABE)	23311 Cluster RCT (n=93)	Yes; increased odds (1.24; 95% CI: 1.05–1.45) of achieving a <5mmHg BP reduction. Reduction in BP was 0.96mmHg in audit based education group (0.4–1.4)	Study to see whether audit based education of clinical guidelines lowers BP. Had 3 arms; Audit based education (had a feedback loop, print aids, education about evidence base), guidelines & prompts or usual care.[421] ** Marked heterogeneity of baseline characteristics of patient population

7.4.6 Education on clinical practice guidelines (CPGs); 7

CV risk factor	Country	Setting	Duration (F/U)	Sample Size & Design	Outcome/Improvement	Summary
CVD in DM	Canada	Primary care	10 months	933789 patients Cluster RCT (n = 4007)	No; No significant improvement in mortality compared to control (MI occurred at 2.5% in both groups; p=0.77). The use of medications was also not significant (p=0.26). BP/LDL and HbA1c targets were also not met	Study designed (2 parts) to see an educational cardiovascular disease toolkit (summary of guidelines, algorithm for CVS risk assessment) improves 1. CVS outcome including all cause and CVD mortality (administrative component) 2. Use of statins, ACE inhibitors and achieving BP/LDL targets (clinical data study component)[422]
Cholesterol	US (NC)	Primary care	36 months	5057 patients Cluster RCT (n=61)	No; no change in primary outcome (appropriate prescription of LLT; net difference of +7.2%; p=0.37)	Comparing the lipid lowering therapy (LLT) using National Cholesterol Education Program Adult Treatment Panel guidelines (received guideline recommendations and Framingham risk scores via a personal digital assistant), with Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) guidelines[423]
Diabetes	Australasia	Primary care	12 months	386 patients Cluster RCT (n=99)	No; no change in HbA1c levels (primary outcome) with -0.11% in intervention group vs -0.22% in the control group (p=0.34).	GIANT study conducted in Asia-Pacific region, evaluated whether education of regional diabetes management guidelines (education meetings, reminders and medical record summary sheets) will improve diabetes management (measured as reduction in HbA1C) compared to control[424]
Diabetes	Spain	Primary care	12 months	5886 patients Cluster RCT (n=103)	No; No improvement in compliance indicators for HbA1c (OR 1.1; 95% CI: 0.8–1.4); p<0.6), BP (OR 1.2; 95% CI: 0.9–1.8); p<0.2) or LDL (OR 1.2; 95% CI: 0.9–1.6); p<0.12) measurement	OBTEDIGA project; Physicians randomised to educational intervention (e.g. feedback, on-line course, workshops) and control groups. Several indicators of good clinical practice in diabetes were explored (e.g. BP, LDL, Glycated Haemoglobin, micro-albumin measurements, eye exam)[425]

Diabetes	France	Primary Care	24 months	1832 patients Cluster RCT (n=257)	Yes; SBP and DBP reduction (by 4.8 mmHg and 1.9 mmHg, respectively, p<0.0001) with more patients achieving BP targets in the intervention group compared to usual care (OR 2.03; 95% CI: 1.44–2.88, p<0.0001)	ESCAPE trial,[426] was an educational intervention (with one day training on therapeutic targets from French national guidance on management of BP, summary leaflet and feedback) compared to usual care. **Proportion achieving therapy target was high in intervention group
Heart Failure	Germany	Primary care	7 months	168 patients Cluster RCT (n=37)	No; no change in primary outcome (change in SF-36 scale: -3.3; 95% CI: -9.7–3.1, p=0.3) or in most secondary outcome measures (apart from improved Spironolactone prescription)	Study looking at the adherence to evidence based guidelines in HF management. An intervention group (educational meetings addressing CPGs and feedback about pharmacotherapy) was compared to usual care. Primary outcome was quality of life measures (SF-36) and secondary outcomes were other questionnaires (Kansas, PHQ-9, European HF self-care behaviour), improvement of heart failure (in NT-proBNP-levels) and drug (ACE inhibitors etc.) prescriptions[427]
Heart Failure	USA (MA)	Hospital (rural)	6 months	591 patients Cluster RCT (n=23)	No; no significant change between groups in the HF compliance measures	Study evaluating the effect a quality collaborative and organizational context intervention (evidence based educational HF toolkit, onsite meetings, and teleconferencing calls) on 4 HF core compliance measures (LVEF assessment, ACEi/ARB use, discharge instructions, and delivery of smoking cessation counselling) according to national quality forum[428]

7.5 Discussion

7.5.1 Effectiveness of quality improvement methods in CVD

In this chapter, the published evidence (only from controlled clinical trials) in relation to the application of quality improvement (QI) methodologies in CVD management was reviewed. This included education of clinical practice guidelines (CPGs) (7 studies), care pathways (8 studies), audit and feedback (8 studies), total quality management (2 studies), pay-for-performance (1 study) and large-scale quality improvement programmes using two or more tools (2 studies).

Care pathways was the most frequently used QI method. Moreover, it was the most effective tool with 5 of the 8 studies showing an improvement in the outcome measures. This included 3 studies showing improvement in mortality and hospital re-admissions. In comparison, the results of using tools such as audit and feedback and education of CPGs were highly variable. These did not show the same degree of improvement: only 3 out of the 15 studies achieved the primary outcome. Further, these improvements were modest, related to improvement in soft endpoints such as in rates of prescription and meeting targets such as BP reduction.

Two large-scale multi-level QI programmes included in this review, the EQUIP-ACS[401] and BRIDGE-ACS trials,[400] which utilised a number of tools in as part of their quality improvement initiative showed a significant improvement in the primary endpoint (although no effect was seen on mortality). A range of QI tools

was adopted at different stages of the process, such as reminders and checklists, training and education material with CPGs, risk stratification algorithms, multidisciplinary QI team meetings, analysis of local processes and the use of 'PDSA' cycles to overcome barriers. This suggests that having a quality improvement strategy that adopts more than one tool is likely to be more advantageous, possibly due to the additive effects of the individual methods themselves. Most of these tools when used in parallel, have been shown to complement each other, and also have had their successes demonstrated in the manufacturing industry.[15,348] QI methodologies used in isolation however, may not achieve similar results.

Total quality management is another QI methodology that has shown improvement in primary outcome as evidenced by 2 studies. TQM, by definition, requires a cultural change within the organisation with participation of all members and disciplines to drive the quality improvement process. This further suggests that to achieve benefits, quality improvement approaches should be a multidisciplinary collaborative, implemented with the input of all specialities within an organisation. The importance of the harmony between the management, clinical leadership and other healthcare professionals was also highlighted in the Keogh Report, published in 2013,[335] where the disconnection between staff was seen as a factor for failure in the NHS.

7.5.2 Lack of evidence for effectiveness of using QI methodology in CVD

This review shows that the number of clinical trials (either RCTs or CCTs) that have been conducted to test the effectiveness of quality improvement

methodology in cardiovascular disease is small. Although there was extensive evidence in the literature of adopting quality improvement methodology in cardiovascular disease, this was largely in the form of small, 'before and after' observational studies or descriptive studies conducted at single sites. Further, out of the tools described in this review, only a few have been used in quality improvement in cardiovascular disease in RCT/CCTs. There was no high-quality evidence in the literature related to the use of QI tools such as such as statistical process control, lean, 5S, six sigma, theory of constraints, experience based design and fishbone tools. This lack of studies using QI tools could further explained by publication bias. It is likely that significant number of studies are conducted every year, particularly in the NHS, where QI initiatives such as Audit and Feedback is one of the key elements of clinical governance.[369] However, these studies are unlikely to be published due to a variety of factors such as negative or equivocal findings, small sample size and poor design, where most of them are likely to be case-control studies conducted on a local scale usually without a comparator arm, and of little interest to editors of scientific journals.[429]

In the few RCTs where quality improvement methodologies were used, only 4 studies considered outcome measures such as mortality or rate of hospitalisations (i.e. 'hard endpoints') and only 5 studies were multicentre trials. It appears that there is a large variation in how the outcomes of these trials are defined to assess the degree of 'improvement. In comparison to the above studies, the 3 studies using audit and feedback that had a positive outcome, used measures such as rates of prescription and meeting particular targets in BP reduction. None of the other studies using this tool had a positive outcome where

no significant improvements were seen in the reduction of BP, cholesterol and HbA1c levels. It suggests that there is likely to be a variation in different QI approaches and the study outcome may change depending on the outcome measures and the QI tool chosen.

One of the other major challenges in testing the effectiveness of these tools has been a lack of an approach to evaluate its effectiveness. The use of RCTs to test the effectiveness of QI methodology has been debated, as quality improvement strategies are seen as a complex social intervention having contextual dependent variables and components. It has been suggested that application of RCTs in this context may not be ethical[430] and may in fact impede the process of quality improvement because it does not promote continuous learning, because RCTs test conceptually 'neat' components of clinical practices (e.g. use of a test, effectiveness of a drug or a procedure).[431] Further, some have also suggested that these QI tools should be applied with the premise that they are already effective because of its success in industry, and to question whether these QI tools are effective may not be the right approach.[432] However, rigorously conducted large RCTs provide the highest level of evidence for effective patient treatment strategies (e.g. level 1 evidence) and application of QI methodology in healthcare, which ultimately impacts patient care should arguably undergo the same level of scrutiny.[433] Testing the efficacy of QI tools using RCTs could be compared to the evaluation of procedural techniques such as coronary intervention, EP ablation and surgical techniques, which also depend upon these 'contextual' variables, such as the skills of the operator and differences in local practice. Moreover, the value of QI tools has been tested widely in before-after observational studies;

therefore, there is no reason why RCT/CCTs could not be conducted or their design and findings less valuable in evaluating these tools. Observational studies may not be the best way to check the effectiveness of these tools, in the absence of a comparator group the changes could merely be the temporal changes reflecting the national trend.[340]

Despite this lack of evidence from RCTs healthcare systems around the world are continuing to adopt QI methodologies, including the NHS. In the NHS, although there has been a greater emphasis of quality improvement in the past two decades, the efforts in checking the effectiveness of these tools or adopting the tools that are effective, has been thin. The evidence showing the success of using these tools in the NHS is mainly anecdotal and in the form of small case studies.[348] However, when implementing quality improvement programmes more effective strategies are needed to maximise and justify the use of public resources. One potential approach could be forming a national registry collecting data of the use QI tools in the NHS and evaluating their effectiveness to provide a publicly available body of evidence.

7.5.3 Barriers to implementation of quality improvement methodology

The Keogh Report,[335] identified the limited understanding of healthcare commissioners and local NHS management in driving quality improvement, where they lacked "the high-level skills and sophisticated capabilities necessary at Board level to draw insight from the available data". He also highlighted that, although a rich set of data on quality improvement is available for the NHS, these data are highly fragmented and therefore difficult to use. Even when undertaking

this literature review I found that the NHS over time, has published significant literature on quality improvement tools but these are scattered over many sources. For example, NHS improving quality (www.nhsiq.nhs.uk), established in 2013, is driving quality improvement in the NHS, but there still seems to be a degree of repetition in the themes of various agendas and very little coordination between them (e.g. Quality, Innovation, Productivity and Prevention: https://www.evidence.nhs.uk/qipp; NHS right care, Healthcare Quality Improvement Partnership: www.hqip.org.uk). In addition, organisations that drove quality improvement within the NHS previously have now been decommissioned,[434] without little accountability and clear transfer of roles.[435] Although there are strategies to drive quality and safety in the NHS at each level of health care, no specific organisation seems to be responsible for setting the agenda: currently these are carried out by different bodies such as the government, local services, health care professionals and patient and charity groups. Therefore, a discussion of a more structured evidenced-based quality improvement approach is extremely important. This is necessary if the NHS is to cater for increasing demand within the current financial and workforce constraints.

Lack of education and understanding about QI methodology among healthcare professionals is also a potential barrier for implementing these strategies. One contributory factor for this is that medical professionals are not formally taught (or assessed) about QI tools in their undergraduate curricula.[436] For example, even during clinical practice junior doctors are only required to carry out one clinical audit per year. Medical professionals involved in management have been

shown to achieve better clinical outcome.[437] Therefore, it is important that medical professionals are at the forefront of driving quality improvement and improving their understanding about effective quality improvement methodology is vital.

In addition to healthcare professionals, care quality managers many also have a poor understanding about using QI approaches. It was highlighted in the Keogh Report that Board and clinical leaders were not driving QI approaches effectively. Although QI approaches such as the audit tool were adopted and 'failures' in practice were identified in these NHS trusts that were reviewed in this report, no steps were taken to abolish these. Therefore, aims of QI initiatives should be cleared defined, not only to identify failures but also to maintain patient safety and improve clinical practice. Further using the appropriate tool for the pre-defined objectives of the QI initiative is also important as some tools are probably more geared to identifying failure or inadequacies (e.g. audit, statistical process control) whilst others may drive change to improve patient safety and incorporated in to treatment algorithms (e.g. patient pathways).

Keogh Report also highlighted the failures in communication between the leadership and the clinical staff practicing at ground level leading to a disconnection amongst the workforce. Conflicts of interest between healthcare commissioners, managers and HPs can have a severe impact and lead to failures in patient care. In such a scenario using an approach such as TQM, which assumes a degree of responsibility by staff at all levels including heath care professionals and the management to continually improve quality processes,

may help to overcome these cultural barriers. Avid participation of physicians and supportive management are critical success factors for driving quality improvement.[15]

7.6 Conclusion

The effect of QI tools on patient outcome in the management of CVD is mixed. This is largely due to lack of credible evidence in the form of RCTs. Further there is a lack of use of many quality improvement tools in CVD. However, from the limited evidence we can suggest that to gain benefit and maximise its success, quality improvement methods should be used in combination and involve the participation of all HPs within organisation. However, more robust evidence is needed to establish the most effective quality improvement methodologies prior to its widespread adoption in healthcare.

Chapter 8: Clinical implications

This thesis explored the prevalence of SDB in CVD and the provision of sleep services in the UK, the barriers to its management using mixed-methods and the use of quality improvement tools in CVD that may to improve patient care.

8.1 Triangulation of findings

8.1.1 CV risk and estimated prevalence

SDB is important from a cardiology perspective because it is strongly associated with cardiovascular disease. OSA is linked to metabolic syndrome (obesity, hypertension, diabetes and dyslipidaemia) and could also be associated with HFPEF. CSA on the other hand is found in up to 40% of patients with HFREF and is associated with a ~2-fold increase in mortality.[11]

In Chapter 3, using the data from the Health Survey for England (HSE) in 2010, it was demonstrated that the prevalence of possible symptomatic SDB in the UK is likely to be ~2.5%. This is consistent with the studies carried out in the 1990s, which have also shown that the prevalence of symptomatic OSA is ~2-4%.[65] However, no studies have yet been published that have systematically surveyed symptoms related to SDB and CV risk factors in the UK at a population level. Further, those subjects with possible OSA, had a higher CV risk with an increased prevalence of diabetes, hypertension and dyslipidaemia.

Large population studies from the US, such as the Sleep Heart Health Study[143] and the Wisconsin sleep cohort,[153] have demonstrated that prevalence of

asymptomatic OSA was ~20%. However, similar population studies exploring the epidemiology of asymptomatic SDB in the UK have not been published.

8.1.2 Underdiagnosis, underreferral and undertreatment

Despite the high prevalence and increased CV risk, a large proportion of patients with SDB remain undiagnosed. The data from the HSE showed that there was a 6-fold difference between the proportion of people having possible SDB and the ones who have been investigated. This was further illustrated from the quantitative analysis of primary care surveys (chapter 4), where there was a significant difference (~30-fold) between the number of patients seen by GPs and the number of patients referred for diagnostic sleep studies. The patient experience highlighted similar problems: ~30-40% of patients reported that their SDB was not recognised by GPs. A similar proportion reported that they were not referred to specialist sleep services during their first visit and it took them at least 3 visits to their GP to be eventually referred for a sleep study. Further, 17 % of patients experienced a delay of more than 6 months to be assessed at a specialist sleep centre. Research exploring the underdiagnosis of SDB in the UK was not identified in the literature search carried out, and it is likely that this is first piece of work presenting such data.

The surveys also highlighted that primary care physicians were likely to adopt a more 'conservative' approach when managing patients with SDB. The content analysis (Chapter 5) suggested that GPs were inclined to use management strategies involving lifestyle modifications such as weight loss or changing sleep patterns before referring for sleep studies (as evidenced by 86 responses

derived from content analysis; e.g. *"Not until initial lifestyle measures had been tried"*). Patients also reported a similar experience (13 responses; e.g. "*Change my lifestyle*") and in addition, they perceived that their condition was misdiagnosed or being offered inappropriate treatment by doctors (97 responses; e.g. "*1. snoring is only social problem put up with it 2. referred to ENT for possible throat surgery - not carried out*").

Underdiagnosis and undertreatment of SDB could have economic and clinical implications. CV disease is still the most common cause of death worldwide. Because patients with SDB have an increased CV risk profile, lack of recognition of SDB may also reflect the lack of awareness of CV risk in these patients. Therefore, early identification of SDB is important in the primary and secondary prevention CV disease and risk factors. As a result, it could potentially reduce healthcare costs associated with long-term disease management and hospitalisation. In addition, undertreatment of symptomatic OSA could have direct economic impact by poor productivity of workers and an increase in road traffic accidents due to daytime sleepiness.[438]

8.1.3 Barriers to diagnosis of SDB

The key barriers to management of SDB in UK that was uncovered from the content analysis of primary care surveys (Chapter 5) and the semi-structured interviews of HPs (Chapter 6), and their potential clinical implications are listed below.

8.1.3.1 Poor patient compliance

Some GPs (from the surveys and semi-structured interviews) and cardiologists perceived that patients had a poor compliance to mask therapy and that it was an 'uncomfortable' form of treatment. They expressed that there was a certain stigma attached to being diagnosed with SDB (e.g. patients fear of losing their driving licence) or being on CPAP/mask therapy (e.g. noise generated from the machine causing the partner or spouse to sleep separately). These aspects that impacted patients' lifestyle could have reduced therapy compliance. Studies have shown that that patient choice plays a significant role in compliance, with approximately 30% of patients refusing therapy after a sleep study.[116]

In comparison however, respiratory physicians believed that compliance could be improved by spending more time with patients. Mask related side-effects have been identified as a factor for therapy withdrawal.[439] Therefore, dedication of resources to patient education, appropriate titration of PAP therapy and customising masks according to patient requirements, could potentially improve compliance. Healthcare professionals' beliefs about mask therapy may be vital to the shared decision making with patients about CPAP/mask therapy.

8.1.3.2 Lack of responsibility

Multiple specialities were involved in the management of patients with SDB. These included GPs who were responsible for the overall care of patients, cardiologists (as these patients have an increased CV risk), specialist nurses (such as heart failure nurses), respiratory physicians (who primarily run diagnostic sleep services and initiate and titrate therapy) and surgical

specialities (e.g. ENT or bariatric surgeons). The thematic analysis of semi-structured interviews revealed numerous cross-speciality barriers such as poor communication and the lack of coordination between the cardiology and respiratory teams, and hospital and primary care physicians. Data also suggest that no one speciality was responsible for managing SDB in patients with cardiovascular disease. Due to the 'silo-mentality' of these specialties, there was a tendency to lose the continuity of patient care.

The key success factors that improved patient care, as perceived by healthcare professionals were good communication and close relationship between the different specialities. Potentially, multidisciplinary team meetings particularly between cardiology, heart failure, endocrine and respiratory teams, could be a strategy that can be used to manage patients effectively with SDB and CVD. Feedback from these MDTs to GPs could also ensure continuity and coordination of care.

8.1.3.3 Referral pathways

Content analysis of primary care surveys and the thematic analysis of semi-structured interviews of healthcare professionals revealed 'multi-step' referral pathways, which delayed the diagnosis and treatment of patients with SDB. This also included patients with SDB being referred 'back to their GP' with recommendation for further specialist input, because due to local rules consultant-to-consultant referrals were not carried out, despite the availability of 'in-house' sleep services. All healthcare professionals from secondary care considered this was a "*significant barrier*" in the management of SDB and

suggested that this was an extremely inefficient process (as illustrated by one cardiologist from secondary care; "*to refer for any form of sleep study… I have to then refer that back to the GP, for the GP to refer back in")*. Patient pathways should be simpler and contain the least number of steps as possible, avoiding any unnecessary delays, so the patient journey is uncomplicated.

35 responses derived from content analysis of the GP survey were related to problems within referral pathway for SDB, which included referrals to ENT specialists (e.g. *"we can only refer to ENT who can then refer on"*). This was likely because traditionally some sleep units were managed by ENT surgeons. Although they subsequently directed patients to respiratory services for assessment of SDB, this had created an 'additional step' in the patient pathway, which led to delays in the management of SDB. Some patients also reported having been offered atypical management strategies such as invasive surgery, prior to having a trial of PAP therapy. Ideally non-invasive treatments options should always be considered first, because the proportion of OSA caused by structural abnormalities requiring corrective surgery is small compared to OSA caused by a collapsible airway (e.g. due to increased neck adiposity), which can be easily 'splinted' using PAP.

8.1.3.4 Lack of effective screening tools

Many patients with SDB, particularly if they have heart failure, are asymptomatic, which makes the diagnosis more difficult. Widely used screening tools such as ESS are dependent on patient symptoms, which makes these less effective. Respiratory physicians also experienced that there was a poor

agreement with the Epworth score and the severity of SDB. However, this was used in the referral pathways (as reported by GPs from the primary care surveys), which could have delayed or even prevented the assessment of patients (e.g. "*have to fill in epworth score… pts have to score highly before we can refer*"). HPs stated that the lack of screening tools was a barrier to identify patients with SDB.

8.1.3.5 Variation of health services

Data from NHS Rightcare (Chapter 3) showed that the variation in sleep services (as measured by the number of sleep studies carried out per 1000) among PCTs/CCGs in UK, was ~60-80-fold, which was consistent between 2010 and 2014. One possible explanation for this is likely to be the lack of availability of sleep centres in certain health areas in UK.[13] Both patients and GPs also highlighted this lack of availability of local sleep services. 28 and 90 responses (derived from content analysis), from patient and GPs respectively, were related to this geographical limitation.

In addition, these surveys highlighted the variation in local policies such as having strict criteria for referral to sleep centres (14 responses from both GPs and patients) and a lack of availability of local funding for CPAP therapy (20 responses). These factors could have further restricted patient management, however, the funding model in PCT/CCGs is likely to have now changed since these primary care surveys were conducted.

The qualitative analysis of semi-structured interviews highlighted a difference between the capacity of sleep services, particularly between secondary and tertiary care. Sleep services attached to tertiary care hospitals had more sleep technicians carrying out sleep studies and less service pressures (for example, one tertiary centre had 7000 patients on CPAP therapy managed by 12 technicians, compared to 900 patients on CPAP therapy being managed by part-time sleep technician at a DGH), more consultants specialising or having an interest in SDB, more capacity to offer a variety of masks and full polysomnography. Thus, these centres could spend more time with patients, which led to increased patient satisfaction.

This variation could have important consequences in patient management and could even affect patient mortality. BLF report[13] found that only 50 centres offered full polysomnography and others only offered limited respiratory studies such as pulse oximetry screening. Further, in 76 centres, the diagnostic modality used was not recorded. Pulse oximetry is a screening modality with low sensitivity in patients with AHI of <15.[54] Therefore, having a 'diagnostic' sleep service that is serving a population based solely on this modality will fail to identify these patients. Moreover, pulse oximetry does not have the capacity to differentiate between OSA and CSA and risk stratify patients.[440] A diagnosis of SDB based on pulse oximetry alone could potentially put patients at risk, for example if PAP therapy is inappropriately initiated for patients with CSA without this differentiation. Stratification of SDB is extremely important in selecting the correct patient populations for treatment and then directing suitable therapy,

particularly considering the findings of the SERVE-HF trial.[99] Therefore, expansion of sleep services should be done carefully, with appropriate diagnostic tools, otherwise more harm could be done to patients.

8.1.3.6 Lack of hard outcome data

HPs stated that their self-awareness of SDB was limited, which was demonstrated from both the interviews and surveys. The lack of clear clinical guidelines and the lack of patient information material related to the management of SDB, were highlighted by HPs as potential contributory factors. Clinical guidelines could improve awareness and patient management. This was evidenced by the HES data (chapter 3), where a sharp ~2-fold increase in the number of sleep studies carried out and a reduction in the waiting time for a sleep study by a half, coincided with the publication of the NICE technology appraisal for CPAP therapy in 2008. Further, a respiratory physician who was interviewed, stated that the timing of the NICE publication facilitated his 'business case' to set up the local sleep service.

Some HPs in comparison, found it difficult to influence health commissioners to fund the expansion sleep services or widen treatment indications due to the lack of substantial evidence (e.g. PAP therapy for asymptomatic OSA). A review of the literature in Chapter 2 (section 2.4) showed that the most management strategies for SDB did not have a strong evidence base, where the level of evidence of most strategies were Level B, C or D. Thus far, no large randomised controlled trials have shown significant improvements in hard outcomes with PAP therapy for either OSA or CSA.

All HPs expressed that SDB has a significant impact on CVD such as hypertension, ischaemic heart disease and heart failure, and that PAP therapy had made a significant symptomatic improvement to patients. However, they were uncertain about the mortality benefits of PAP therapy. This also affected the management of patients with SDB, particularly in relation to patient education about the definitive benefits of treating SDB. Some HPs exercised caution about initiating treatment for SDB for weak indications (e.g. PAP for CSA) because of this lack of data on hard CV end-points. Due to these reasons, SDB was a perceived as a 'low priority' in clinical practice in the hierarchy of the multiple medical conditions of patients, particularly during outpatient consultations, which already had time constraints.

During the write-up of thesis, the SERVE-HF trial, which the largest RCT carried out in patients with SDB and heart failure, was published. Its results are discussed in detail section 2.3.6.2. In summary, it found that that PAP therapy (i.e. ASV) did not affect the primary endpoint, but significantly increased all-cause and cardiovascular mortality in the therapy group. Thus, HPs who had reservations about initiating treatment in patients with CSA and heart failure without the hard outcome data, likely adopted the correct management approach. CV disease management usually is supported by multiple large clinical trials, which may explain why PAP therapy was not adopted and initiated widely in patients with heart failure without substantial evidence. There were similar findings in the SAVE trial, which studied the CV outcome in patients with asymptomatic OSA, where PAP therapy did not affect the primary composite

endpoint (death from cardiovascular causes, myocardial infarction, stroke, or hospitalisation for unstable angina, heart failure, or transient ischemic attack).

It is still important however, to recognise patients with SDB. As we do not have an effective mode of treatment for these patients, it could be argued that healthcare resources should not be allocated for the diagnosis and recognition of SDB, which are already constrained, particularly in the NHS due to austerity measures. However, as discussed before patients with SDB and CVD reflects a cohort of patients who are at high risk of mortality, therefore, its recognition is vital because treating their CVD and risk factors could improve SDB. For example, effective treatment and optimisation of the heart failure has been shown to improve CSA. In addition, in patients with daytime sleepiness due to OSA, diagnosis and therapy could improve their quality of life and potentially reduce road traffic accidents.

8.1.4 Effective QI tools for service improvement

One potential mechanism to overcome barriers in clinical practice is to use quality improvement methods. However, there are numerous QI tools, which have been used mainly in the manufacturing industry (e.g. Toyota). From the literature search it was also evident that no single body as part of the NHS has been solely responsible for driving QI. The QI initiatives appear to occur in 'pockets' at various levels and regions in the NHS. The reporting of the use of on QI methodology within the NHS was also not systematic and the availability of these data appear to be fragmented, with many different non-NHS bodies such as health care charities (e.g. King's fund) publishing these changes.[15,318,441] In

addition, the Keogh Report,[335] which is was a review of patient safety and quality of care, found that the knowledge of QI methods among managers and clinical staff was lacking and that poor communication and cultural barriers between them led to failures in patient safety.

Chapter 7 evaluated the strength of these tools in the management of CV disease in clinical practice. When search criteria were applied, the number of well-designed randomised (or cluster controlled) studies were limited. Further, most studies that were included did not use hard end-points to evaluate the intervention and had short study durations. Nevertheless, the most effective tools were the use of care pathways and multi-level large QI programmes, which showed improvement in outcomes such as reduction in hospital re-admission, length of stay and short-term mortality rates.

8.2 Model patient pathway

An ideal patient pathway should be simpler and have the least number of steps to avoid unnecessary delays. Each step in the pathway should serve a purpose. Figure 8.1. shows a proposed model pathway, constructed after consideration of barriers to management of SDB uncovered in this thesis.

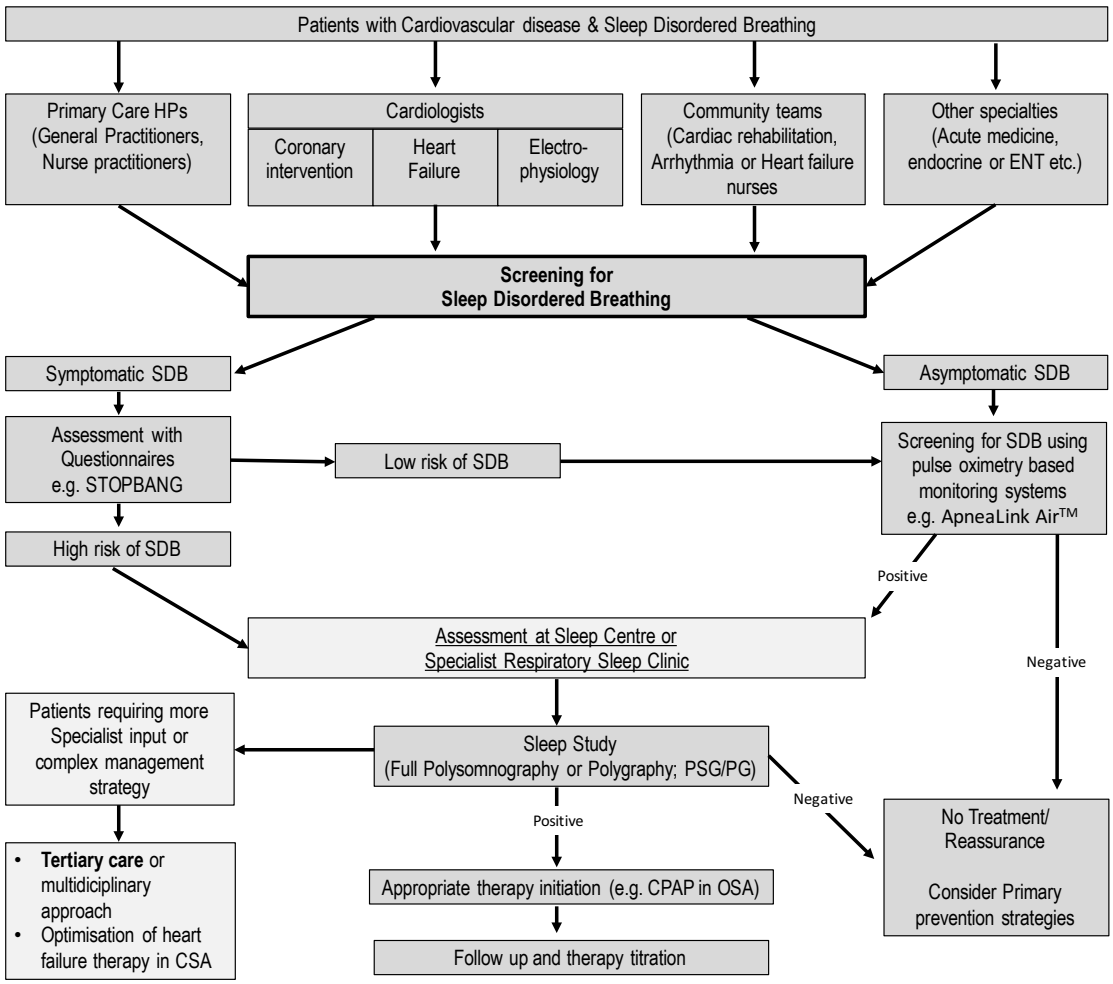


Figure 8.1. Model patient pathway for managing patients with CVD and SDB.

This pathway does not include referrals between specialties (e.g. cardiology to GP). The focus of this pathway is screening for SDB, for example, a combination of the STOPBANG questionnaire and devices based on pulse oximetry could be used for screening. This can be initiated by any HP looking after the patient, converging with a referral to a sleep centre/clinic for further assessment. Diagnosing SDB should ideally be done after full polysomnography or polygraphy. Complex patients should be managed in tertiary centres.

8.3 Limitations

Limitations of the methodology and findings were discussed in each chapter but the important aspects are discussed here. The main findings of this thesis are based on the mixed-methods analysis of primary care surveys and qualitative analysis of semi-structured interviews. Survey methods contain inherent limitations. How questions are phrased and survey design could influence the validity of the data collected from surveys. In the 2009 GP survey, a lack of clarity in the questions led to a degree of confusion among GPs (section 4.3.2). For example, the question, "*Why would you not refer patients you suspect of OSA to specialist care?",* which had the option of providing free-text responses, was only available to the 386 GPs who answered "0" to the question, "*How many suspected sleep apnoea patients would you refer in a typical month?*". This resulted in not capturing the views of other GPs who could have faced barriers when referring patients. In addition, not referring patients to a sleep centre in one calendar month, does not imply that a GP would not strictly refer a patient in their routine practice, if clinically indicated. Furthermore, once the survey has been implemented and running, further changes are difficult to introduce unless an entirely new survey is conducted. In comparison, in the 2011 survey this question was available to all GPs who participated in the survey and was phrased in a much more 'open-ended' manner.

Both the GP and the patient surveys were carried out online and the participants were 'self-selected' (i.e. GPs or patients themselves decided to participate in a survey) and their interest in taking part may be driven by interest in the subject or incentives. This also introduces reporting bias, where the views of

participants who are not surveyed are underrepresented or unexplored, compared to the ones who take part. For example, the patients who took part in the Realsleep survey were part of a paid membership of a ResMed sponsored patient programme and most of them had sought treatment privately. Therefore, their views and experiences may not necessarily represent the patients who receive treatment in the NHS. In addition, the primary care surveys were carried out more than 5-7 years ago and some patients could have presented to their GPs with symptoms at least 10 years earlier. Healthcare and clinical practice in the NHS is likely to have changed considerably since. For example, GPs and patients reported that CPAP therapy was not available and funded by their local health authority/NHS, an aspect of practice that has now changed. Therefore, some findings may not be applicable to current practice.

Qualitative methodology also consists of several limitations. The quality of research depends on the skills of the researcher and the findings could be influenced by their personal views and biases.[442] This is, to a degree, unavoidable and represents the uniqueness of qualitative research, where the aim is to explore a wide range of views without being restricted to stringent set of rules. However, the data analysis and the interview technique was supervised by two more senior researchers with experience in qualitative research (Prof MC & Dr JR), so that the data gathering was systematic. This helped to avoid individual bias and a common consensus was reached when themes were generated. Further, in comparison to quantitative data (e.g. findings of large randomised controlled trial for a treatment), the qualitative data cannot be generalised to the patient population, because statistical significance cannot be established.[443]

Qualitative data enables an explanation of topics in health care that haven't been researched previously, such as the barriers to the diagnosis and treatment of patients with SDB and CVD, and enable a more holistic understanding on this topic. Moreover, solely quantitative methods are difficult to adopt in research studying healthcare processes, and provide only limited insight into the underlying issues.

Finally, the data such as the hospital episode statistics (HES) and HSE, which were obtained from publically available UK data archives (ww.data.gov.uk or NHS digital under the remit of Department of Health), is primarily carried out by the UK government to observe annual trends in service provision and to facilitate an understanding of the health and lifestyle of people in the UK. These were not designed to collect data specifically on SDB. For example, the HSE 2010 which had a focus on respiratory disease, only included a handful of questions about SDB (a total of 6 variables out of ~1600). Moreover, the HSE estimates are inevitably subjected to sampling error, as the data are based on a sample of the population (i.e. rather than a census of the population).[444] In addition, concerns regarding the quality of data collection of HES have also been highlighted previously, particularly due to the inaccuracy in data coding.

8.4 Future research

Systematic research about identification of barriers and overcoming them in CVD is limited in the literature. Therefore, this thesis, using mixed-methods, was compiled as a piece of 'exploratory research' to obtain an understanding of the potential barriers that may affect the optimum management of patients with SDB and CVD. As there have been no studies published specifically related to this topic, further research is needed to confirm the findings of this thesis. In addition, research using qualitative methodology should be directed in other areas of service, such as to explore

- the barriers experienced by different stakeholders (e.g. commissioners, clinical managers, patient groups and GPs) during organisation and provision of local clinical services
- the cultural barriers between hospital management and HPs in the NHS during clinical practice, which may affect patient care
- the barriers experienced by patients with CVD who travel through the diagnostic and treatment pathways
- the management barriers in other areas in cardiology such as the potential lack of implantation of devices such as ICD/CRT in heart failure management and the lag in introducing novels oral anticoagulants (NOACs) for stroke prevention in AF

This thesis demonstrated that population studies exploring prevalence of SDB in the UK were limited. Although designing such novel studies may not change clinical practice, maintaining an accurate clinical coding system (e.g. registries about SBD) is important for CV disease prevention and planning.

One of the major barriers experienced by HPs was the lack of treatment guidelines for the management of treatment of SDB. This was directly as a result of the lack of high quality RCTs (which were adequately powered with longer follow-up) in SDB. More evidence is needed to optimally tailor therapy for both OSA and CSA. The recent large trials such as the SAVE trial,[145] which explored the effect of CPAP on CV outcome in OSA, the CANPAP[199] and SERVE-HF trials,[99] which explored the effect of PAP therapy (CPAP and ASV respectively) in heart failure, have not shown significant mortality benefits in patients (despite symptomatic benefits), and the current guidelines have not been yet updated to reflects these findings. Moreover, there are no 'safe' treatment strategies for the management of CSA in heart failure, as shown by the SERVE-HF trial, which demonstrated a signal of harm in these patients with ASV. New therapy options such as phrenic nerve stimulation could be potential therapies, however, robust RCTs demonstrating patient safety should be conducted before its widespread adoption in clinical practice. Currently, more large randomised control trials are underway in OSA exploring its efficacy in CVD.[140,445]

Chapter 7 demonstrated that, although several studies using QI have been published in the literature, the number of high quality controlled trials were limited. Thus, more evidence is needed before QI tools are widely adopted to redesign clinical practice in the NHS. The effect of QI tools in isolation is likely to be small, therefore future studies should ideally be designed with the use of multiple QI tools.

The fragmentation of responsibilities for improving standards, safety, variation in care, across the NHS is also detrimental to patient outcome and experience of care. Therefore, future QI programmes in the NHS should be driven in a coordinated manner with the involvement of all levels within the organisation, and adopting a more evidence-based approach with the use of effective QI tools.

8.5 General Conclusion

The current evidence suggests that treating patients with SDB using PAP therapy may not have strong CV benefits as previously thought, furthermore it could be harmful in patients with heart failure. However, the diagnosis of SDB is still important in these patients because it reflects a group with higher CV risk. There are a variety of barriers that could delay the diagnosis and treatment of SDB, such as the lack of local access to sleep studies, lack of guidelines and hard outcome data, patient perceptions and cultural barriers between HPs. QI methods can be used to potentially overcome these barriers and care pathways seems to be the most effective tool. This can be used to optimise the diagnosis and treatment of these high-risk patients and improve the patient journey.

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Appendix

Sleep Questionnaires

Epworth Sleepiness Scale

Name: _____ Today's date: _____

Your age (Yrs): _____ Your sex (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

0 = would **never** doze
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each question as best you can.

Situation	**Chance of Dozing (0-3)**
Sitting and reading	
Watching TV	
Sitting, inactive in a public place (e.g. a theatre or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in the traffic	

THANK YOU FOR YOUR COOPERATION

From http://epworthsleepinessscale.com/about-the-ess/

STOP Bang QUESTIONNAIRE

Snoring - *Do you Snore Loudly (loud enough to be heard through closed doors or your bed-partner elbow you for snoring at night)?*	o Yes o No
Tired - *Do you often feel Tired, Fatigued, or Sleepy during the daytime (such as falling asleep during driving)?*	o Yes o No
Observed - *Has anyone Observed you Stop Breathing or Choking/Gasping during your sleep?*	o Yes o No
Pressure - *Do you have or are being treated for High Blood Pressure?*	o Yes o No
Body Mass Index - *more than 10% over ideal range.*	o Yes o No
Age - *Older than 50?*	o Yes o No
Neck Size - *(Measure around Adams apple) Male is your shirt collar 17" or larger? Female, is your shirt collar 16" or larger?*	o Yes o No
Gender = Male?	o Yes o No

After you have completed the STOP-BANG questionnaire, please return it to the front desk for a quick risk assessment of possible sleep apnea.

From http://www.stopbang.com/stop-bang-desktop-screener/replacement-tear-off-notepads

All the free-text responses and the attached codes

Access to secondary care / sleep services	A	2'3'			
do not have non emergency referral rights	A	Pol		137	Acess Dif
dont see many - lack of appointments in 3 care	A	W, 2'3'		86	Lo
Excessive waiting times	A	W		4	Diff access 2'/
if i wasn't aare of facilities and pathways for referral that were locally available	A	Path		10	po
if they did not fit local referral guidelines	A	Pol		9	wa
lhb will not fund any service	A	Fun		7	Fun
little funding for care, waiting lists years	A	Fun, W		35	path
Little local option, case not severe enough to require onward care	A	Pol			
long waiting list, patients not keen on CPAP etc	A	W		23	Resp
long waiting lists - service not funded	A	Fun, W		10	Ent
long waits, sometimes patients don't want referral	A	W			
no good local service	A	Lo		151	
no local service	A	Lo			
no local service	A	Lo			
no local service	A	Lo			
no local specialist	A	Lo			
pct	A	Pol			
PCT does not fund one	A	Fun			
poor local services	A	Lo			
The local sleep centre can investigate but funds very limited for treatment	A	Fun			
Too few patients identified, unsure about local specialist services available.	A	Lo			
very difficult to access, unsure about diagnosis	A	A			
We don't have an nhs service for this in my area	A	Lo			
We don't have anyone in 2ary care in our LHB (Cardiff) who provides a service and were told not to	A	2'3'			
When I know our sleep clinic will refuse the referral We have to fill in epworth score and Berlin que	A	Lo			
1) I said i see nil in a typical month 2) No sleep lab available in area, sadly	A	Lo			
distance to travel	A	Lo			
No one in area with an interest Most patients can help by losing weight first	A & C	Lo			
don't very often think of diagnosis also no readilly available service	A & K	Lo			
I do not suspect many & the local services are not good	A & K	Lo			
there are various reasons- I have seen very few pts who have presented to me with severe sympto	A & K & LN	Path, Lo			
not a common presenting complaint, not aware of local service	A, K & LN	Lo			
access	A				
availability in region	A	Lo			
availability/locality of sleep centre	A	Lo			
Because we are not able to refer directly anymore	A	Pol			
because we don't have a "sleep centre" locally - but we do have a specialist sleep clinic	A	Lo			
because we don't have one near by	A	Lo			
blocking of referrals by local health board, have to refer to local resp consultant 1st	A, Resp	Path, Lo			
Do not have any in location	A	Lo			
don't have any - our service is ENT or respiratory who can do overnight pulse oximetry	A	Lo			
don't have one locally. distance is a major problem for this service, so it is undertaken by respirato	A	Lo			
don't know where the nearest one is	A	Lo			
have not got one	A	Lo			
I would, if we had one.	A	Lo			
If not commissioned or available locally	A	Lo, Pol			
it's run by our ENT dept	A, ENT	Path			
limited availability	A	Lo			
local availability	A	Lo			
local availability and lack of specialist service	A	Lo			
LOCAL GUIDANCE	A	Pol			
local policy	A	Pol			
long waiting list and we have our own service to refer to	A	W			
nearest sllep centre in birmingham- too far away	A	Lo			
nil available	A	Lo			
no able to refer directly from primary care	A	Lo, Pol			
no available	A	Lo			
No direct access (via local respiratory clinic)	A	Lo			
no local access	A	Lo			
No local centre	A	Lo			
No local centre	A	Lo			
no local dedicated facility	A	Lo			
no local provision	A	Lo			
No local sleep clinic	A	Lo			
None available in our area	A	Lo			
None available locally	A	Lo			
none available locally	A	Lo			

none avialable in our area							A	Lo			
None local							A	Lo			
none locally to refer to							A	Lo			
None locally.							A	Lo			
Not able to refer directly							A	Lo			
not avaialbe locally							A	Lo			
not available							A	Lo			
Not available							A	Lo			
not available							A	Lo			
Not available							A	Lo			
not available							A	Lo			
not available locally							A	Lo			
not available locally							A	Lo			
Not available.							A	Lo			
Not aware of a local specialist sleep centre							A	Lo			
not aware of any in my area							A	Lo			
not aware of centres in my area							A	Lo			
not aware of local service							A	Lo			
not aware of services							A	Lo			
not aware of there being one locally							A	Lo			
not directly as we now have the facility to do pulse oxcimetry study							A	Lo			
not readily available							A	Lo			
Service not available in area							A	Lo			
there is no local direct access service							A	Lo			
There is not a local sleep centre							A	Lo			
There isnt a dedicated 'Sleep Centre' near here							A	Lo			
THERE ISN'T A SLEEP CENTRE IN OUR AREA							A	Lo			
there isn't one locally							A	Lo			
unavailablity							A	Lo			
very long waiting list							A	W			
We don't have a local sleep centre							A	Lo			
we dont have one							A	Lo			
we haven't got one							A	Lo			
very long waiting times would only refer if symptoms severe and not motivated to lose weight etc							A & C	W			
Not familiar with the referral pathway for this							A & K	Path			
Not nearby. Not much information about the service							A & K	Path, Lo			
Potentially would if (1) No improvement with lifestyle and (2) if service was available							A & K	Lo			
not funded by local LHB							A & M	Fun			
not much access - expensive, need to exclude other diagnosis, wt loss and lifestyle first							A & M	Fun, Lo			
after assessment by local hospital ent/resp team							A & Resp	Path			
around here - goes to respiratory drs in their specialist seep apneo clinic							A & Resp	Path			
Because there is no nearby designated sleep centre to my knowledge, - although our Chest Physici							A & Resp	Lo, Path			
Because there is not one locally. The Respiratory physicians do run a sleep clinic though							A & Resp	Lo, Path			
I refer to a combined ENT /Respiratory physician run clinic at Frimley Park Hospital							A & Resp	Path			
I think we cannot directly refer from primary care							A & Resp	Path			
It is run jointly by Resp/ENT but all referral go to Respiratory							A & Resp	Path			
lack of access, nearest sleep centre is in many miles away, local respiratory department handles O							A & Resp	Lo, Path			
local access is through the respiratory department.							A & Resp	Path			
local protocol							A & Resp	Pol			
local sleep studies carried out by chest clinic hence ref there first							A & Resp	Path			
locally sleep service is run by resp consultants							A & Resp	Path			
locally sleep studies via respiratory physicains							A & Resp	Path			
nil in current area- resp clinic does sleep studies and diagnosis of OSA							A & Resp	Lo, Path			
no direct referal pathway available							A & Resp	Path			
No local sleep centre clinic. Local Consultants often refer on to a regional sleep centre clinic.							A & Resp	Lo			
No sleep centre avaliable in Northern Ireland - advice is to refer to local respiratory medicine consu							A & Resp	Lo, Path			
REFERRALS IN AREA GO TO RESPIRATORY CLINIC FOR ASSESSMENT (SLEEP STUDIES) AND TREATME							A & Resp	Path			
Send to a respiratory unit							A & Resp	Path			
The local respiratory clinic provides a very good sleep apnoea service							Resp	Path			
unavailable for GP's.access through resp physicians.							A & Resp	Path			
we refer to a res[iratory cosultant in secondary carebut cannot directly refer to a tertiarty sleep ap							A & Resp	Path, 2'3'			
ENT run apnoea clinic in this locality							A, ENT	Path			
not allowed - all have to go via ENT							A, ENT	Path			
Sleep studies undertaken via ENT in our area							A, ENT	Path			
Unable to refer directly from primary care - all referrals via ENT							A, ENT	Path			
Usually treated by ENT locally							A, ENT	Path			
we are expected to refer to ent in first instance via choose and book and local referal pathway/refe							A, ENT	Path			
we are not allowed to as has to go via a ent surgeon							A, ENT	Path			
We are not allowed to by our PCT, we can only refer to ENT who can then refer on!							A, ENT	Path			
We have to refer to ENT first							A, ENT	Path			

Why would you NOT refer a patient with suspected obstructive sleep apnoea tc		106	A	Acess Dif
access	A	24	C	conservative
availability in region	A	8	P	Pt factors
availability/locality of sleep centre	A	2	K	Knowledge
Because we are not able to refer directly anymore	A	4	M	Money
because we don't have a ''sleep centre'' locally - but we do have a specialist sleep clinic	A	23	Res	Respiratory con
because we don't have one near by	A	9	ENT	ENT conduct
blocking of referrals by local health board, have to refer to local resp consultant 1st	A			
Do not have any in location	A	1	NR	No Referral - no
don't have any - our service is ENT or respiratory who can do overnight pulse oximetry	A	14	R	Refer
don't have one locally. distance is a major problem for this service, so it is undertaken by	A			
don't know where the nearest one is	A	191		
have not got one	A			
I would, if we had one.	A			
If not commissioned or available locally	A			
it's run by our ENT dept	A			
limited availability	A			
local availability	A			
local availability and lack of specialist service	A			
LOCAL GUIDANCE	A			
local policy	A			
long waiting list and we have our own service to refer to	A			
nearest sliep centre in birmingham- too far away	A			
nil available	A			
no able to refer directly from primary care	A			
no available	A			
No direct access (via local respiratory clinic)	A			
no local access	A			
No local centre	A			
No local centre	A			
no local dedicated facility	A			
no local provision	A			
No local sleep clinic	A			
None available in our area	A			
None available locally	A			
none available locally	A			
none avialable in our area	A			
None local	A			
none locally to refer to	A			
None locally.	A			
Not able to refer directly	A			
not avaialbe locally	A			
not available	A			
Not available	A			
not available	A			
Not available	A			
not available	A			
not available locally	A			
not available locally	A			
Not available.	A			
Not aware of a local specialist sleep centre	A			
not aware of any in my area	A			
not aware of centres in my area	A			
not aware of local service	A			
not aware of services	A			
not aware of there being one locally	A			
not directly as we now have the facility to do pulse oxcimetry study	A			
not readily available	A			
Service not available in area	A			
there is no local direct access service	A			
There is not a local sleep centre	A			
There isnt a dedicated 'Sleep Centre' near here	A			
THERE ISN'T A SLEEP CENTRE IN OUR AREA	A			
there isn't one locally	A			
unavailability	A			
very long waiting list	A			
We don't have a local sleep centre	A			
we dont have one	A			
we haven't got one	A			

Not familiar with the referral pathway for this	A			
Not nearby. Not much information about the service	A			
Potentially would if (1) No improvement with lifestyle and (2) if service was available	A & C			
not funded by local LHB	A & M			
not much access - expensive, need to exclude other diagnosis, wt loss and lifestyle first	A & C			
after assessment by local hospital ent/resp team	A & Resp			
around here - goes to respiratory drs in their specialist seep apneo clinic	A & Resp			
Because there is no nearby designated sleep centre to my knowledge, - although our Che	A & Resp			
Because there is not one locally. The Respiratory physicians do run a sleep clinic though	A & Resp			
I refer to a combined ENT /Respiratory physician run clinic at Frimley Park Hospital	A & Resp			
I think we cannot directly refer from primary care	A & Resp			
It is run jointly by Resp/ENT but all referral go to Respiratory	A & Resp			
lack of access, nearest sleep centre is in many miles away, local respiratory department h	A & Resp			
local access is through the respiratory department.	A & Resp			
local protocol	A & Resp			
local sleep studies carried out by chest clinic hence ref there first	A & Resp			
locally sleep service is run by resp consultants	A & Resp			
locally sleep studies via respiratory physicains	A & Resp			
nil in current area- resp clinic does sleep studies and diagnosis of OSA	A & Resp			
no direct referal pathway available	A & Resp			
No local sleep centre clinic. Local Consultants often refer on to a regional sleep centre cli	A & Resp			
No sleep centre avaliable in Northern Ireland - advice is to refer to local respiratory medi	A & Resp			
REFERRALS IN AREA GO TO RESPIRATORY CLINIC FOR ASSESSMENT (SLEEP STUDIES) AND	A & Resp			
Send to a respiratory unit	A & Resp			
The local respiratory clinic provides a very good sleep apnoea service	A & Resp			
unavailable for GP's.access through resp physicians.	A & Resp			
we refer to a res[iratory cosultant in secondary carebut cannot directly refer to a tertiarty	A & Resp			
ENT run apnoea clinic in this locality	A, ENT			
not allowed - all have to go via ENT	A, ENT			
Sleep studies undertaken via ENT in our area	A, ENT			
Unable to refer directly from primary care - all referrals via ENT	A, ENT			
Usually treated by ENT locally	A, ENT			
we are expected to refer to ent in first instance via choose and book and local referal pat	A, ENT			
we are not allowed to as has to go via a ent surgeon	A, ENT			
We are not allowed to by our PCT, we can only refer to ENT who can then refer on!	A, ENT			
We have to refer to ENT first	A, ENT			
1.carry out history taking, examination assessment and investigation in primary care 2.ini	C			
because obesity/alcohol/social causes remain the main etiology	C			
because the majority need to lose weight and are obese ++++	C			
first diagnosis-try wt loss first, referral to sleep centre if severe symptoms, secondary mo	C			
i might do if they were very severe, but most just need to lose wt	C			
I would but was not able to click more than one option - would also provide lifestyle advi	C & R			
I would encourage weight loss first or try a respiratory clinic first	C			
I would try advise first	C			
if wt loss is a real possiilty	C			
It's a matter of degree. Lifestyle advice first. I would not rule out referral	C			
lifstyle causes are dominent--esp obesity	C			
need to do some things in 1' care first by way of investigations and management	C			
need to sort out respiratory and ent problems too	C			
Needs various investigations first - including Epworth sleepiness scale, ECG, wt loss, jaw a	C			
Not until initial lifestyle measures had been tried	C			
suspect other causes eg structural abnormality	C			
Try lifestyle advice first	C			
try lifestyle issues first	C			
treatment is lifestyle changes whether to refer or not	C & K			
I would try initially to address obvious causes such as weight We do need a motivated pa	C & P			
mild symptoms, patient request, to try weight loss etc first	C & P			
diagnosis does not really change the management of this condition	T			
If caused by e.g. rhinitis and treated successfully, why refer?	LN			
poor results	T			
Cost	M			
Cost Definitive diagnosis first	M			
Too costly	M			
i wouldn't	No			
I believe that if they are keen on improving their condion, yhey should at least try to worl	P			
If patient declined referral	P			
If patient declined.	P			
If the patient refused referral	P			
patient declines	P			
they initially prefer not to go	P			

Because I seek more diagnostic certainty first = then refer according to score	R				
clicked wrong i would	R				
i do	R				
I would on occasion	R				
If I hadn't completed the appropriate questionnaires - eg epworth sleepiness scale etc	R				
if their epworth score was too low	R				
My only local facility is a sleep breathing disorder clinic which provides a diagnostic and t	R				
No I would	R				
no reasons not to	R				
our local hospital has a clear pathway for ssuch referrals	R				
we can perform sleep study in the practice, will need to be ref after positive sleep study	R				
We have facilities in the practice to do an overnight oximetry, if this is positive, I would th	R				
we do not have a sleep centre in our area i will refer if he fits the criteria on the epworth	R & A				
well I might ...	R & K				
because we have a local consultant with an interest in sleep apnoea	Resp				
n/a	n/a				
n/a	n/a				
not immed	N/a				
qw	n/a				

No one in area with an interest Most patients can help by losing weight first	A & C					
very long waiting times would only refer if symptoms severe and not motivated to lose weight etc	**A & C**		86	C	conservative	
Not familiar with the referral pathway for this	**A**		25	P	Pt factors	
Not nearby. Not much information about the service	**A**		13	K	Selfaware-Knowledge	
Potentially would if (1) No improvement with lifestyle and (2) if service was available	**A & C**		3	S	Spciality Value	
don't very often think of diagnosis also no readilly available service	A & K		5	Imp	Priority	
I do not suspect many & the local services are not good	A & K		4	T	Percept Therap	
there are various reasons- I have seen very few pts who have presented to me with severe symptoms to want to be	A & LN		3	C	Compliance	
not funded by local LHB	**A**		15	Ref	Refusal	
not much access - expensive, need to exclude other diagnosis, wt loss and lifestyle first	**A & C, Im**		8	Res	Pt responsibility	
long waiting list, patients not keen on CPAP etc	A & P	Comp				
long waits, sometimes patients don't want referral	A & P	Ref				
not a common presenting complaint, not aware of local service	A & LN					
1st line therapy tried 1st in 1ary care	C					
advise weight loss first	C					
Depends on their weight	C					
first ask to loose weight and then review	C					
get better	C					
Good response to lifestyle changes.	C					
I usually wait for a while untill lifestyle has improved then refer	C					
I will try and address any underlying problems first e.g ENT problems, weightetc first before referring so will average	C					
I would initially advise about weight loss before considering referral	C					
I would refer if I felt that our management had failed	C					
I would try weight loss etc first before referring	C					
if i felt that the patient would make lifestyle changes which would help first	C					
If little symptoms and very overweight	C					
If patients are symptomatically better with management then I dont refer.	C					
if symptoms are mild and can responsible simple measures ie weight loss	C					
If the patient was determined to loose weight I would consider helping them with that for a 3 month period, but i us	C					
initial advice to see if imps	C					
Initially try simple methods first, but primarily try to get them to lose weight. Giving the patient ownership of the pr	C					
lifestyle changes first are better	C					
lifestyle changes initially	C					
lifestyle interventions first	C					
Manage conservatively first	C					
manage our selves	C					
no point. weight loss is the only cure and wearing crap on your face at night is pathetic	C, T					
not tried any measures first	C					
possibly suggest trial of self management first	C					
Simple self help measures first	C					
smoking and weight loss first	C					
these patients will need life style intervention and follow up before referring the patient	C					
Trial of first line advice first	C					
try basic measures first	C					
Try conservative measures first.	C					
try conservative methods first - not seen that many at all	C					
try home remedies first.	C					
try self help first	C					
try self help remedies first- ie, wt loss, alcohol reduction.	C					
try simple steps first before ref	C					
try to manage locally then refer	C					
usually advice is all that i s required I wouiold refer if they returned	C					
Where lifestyle issues can be addressed first.	C					
would try once tried 1st measures	C					
would try self management options available in primary care first - ie weight loss smoking cessation	C					
if mild symptoms	C					
if terminal illness	C					

1.carry out history taking, examination assessment and investigation in primary care 2.initial management in prin	**C**	
because obesity/alcohol/social causes remain the main etiology	**C**	
because the majority need to lose weight and are obese ++++	**C**	
first diagnosis-try wt loss first, referral to sleep centre if severe symptoms, secondary morbidity, unclear diagnosi	**C**	
i might do if they were very severe, but most just need to lose wt	**C**	
I would but was not able to click more than one option - would also provide lifestyle advice	**C**	
I would encourage weight loss first or try a respiratory clinic first	**C**	
I would try advise first	**C**	
if wt loss is a real possiilty	**C**	
It's a matter of degree. Lifestyle advice first. I would not rule out referral	**C**	
lifstyle causes are dominent--esp obesity	**C**	
need to do some things in 1' care first by way of investigations and management	**C**	
need to sort out respiratory and ent problems too	**C**	
Needs various investigations first - including Epworth sleepiness scale, ECG, wt loss, jaw advancement device	**C**	
Not until initial lifestyle measures had been tried	**C**	
suspect other causes eg structural abnormality	**C**	
Try lifestyle advice first	**C**	
try lifestyle issues first	**C**	
treatment is lifestyle changes whether to refer or not	**C & T**	
I would try usual advice first. I dont see one a month on avg so put 0	C & LN	
see very few and generally advise as above	C & LN	
I think I would have to be happy it seemed like an OSA problem, rather than just snoring/insomnia	C & LN	
I would try initially to address obvious causes such as weight We do need a motivated patient if CPAP is to work A	**C & P**	Comp
mild symptoms, patient request, to try weight loss etc first	**C & P**	Res
May delay referal with trial of weight loss if seems appropriate	C & R	
I would refer patients if I was suspecting OSA but may give them a trial of weight loss first to see if this helps	C & R	
if totally unwilling to make lifestyle changes	C & R	
Usually already seen by specialist care.	C & R	
Able to offer advice. DO refer patients but not monthly	C & R	
They can be managed in primary care	C & S	
managed by self in my own ENT GPwSI clinic	C & S	
Too many other complex medical problem. Patients not interested.	Im & P	Ref
lack of local knowledge	K	
Not a disgnosis on the forfront of my mind so probably under refer/diagnose	K	
probably not recognising enough	K	
rare need to do so	K	
Very rarely make the diagnosis	K	
I wouldn't, if suspected it, but perhaps I'm not suspecting it often enough?	K	
diagnosis does not really change the management of this condition	**T**	
poor results	**T**	
There are probably cases of OSA who have not come to my attention. I would normally encourage 'lifestyle' changes	K & C	
i do occassionally but don't see many - probably not identifying them	K & LN	
Rarely suspect this diagnosis	K & LN	
See too few patients. Perhaps I need to ask more regarding these symptoms	K & LN	
If mild, with minimal impact on day to day functioning (eg. job, driving, etc) + very likely to improve through simple l	LN & C	
Cost	**Im**	
Cost Definitive diagnosis first	**Im**	
Too costly	**Im**	
1. they decline referral 2. they have already been referred	P	Ref
because they usually baulk at the prospect of losing their driving licence	P	Ref, Res
depends on sx	P	Ref
do not see these patients that often as they seldom come back and give feed back	LN	
If patient did not wish referral	P	Ref
if they were resistant to the idea	P	Ref
Patient not suitable for or not keen on intervention	P	Ref
Patient symptoms, motivation, patient opinion	P	Ref
I believe that if they are keen on improving their condion, yhey should at least try to work on some of the interve	**P**	Res
If patient declined referral	**P**	Ref
If patient declined.	**P**	Ref
If the patient refused referral	**P**	Ref
patient declines	**P**	Ref
they initially prefer not to go	**P**	Ref
Quite rare and Rx usually uncomfortable/ unacceptable (CPAP)	P & LN	Comp
I do refer them if simple measures have not worked	R & C	
I would if I suspected it, however I would also advise on the lifestyle issues.	R & C	
It is only the ones with resistant symptoms that we refer, or a high Epworth score, or who need earlier intervention	R & C	
i would refer if truely symptomatic	R & C	
I would refer if patient requested	R & C & P	Res
well I might ...	**R & K**	
I do refer if patient prepared to try CPAP	R & P	Res
i would refer all suspected cases if they were happy to go	R & P	Res
I WOULD unless they objected.	R & P	Res
I would usually refer, unless adament would not attend	R & P	Res
Do refer for diagnosis - several patinets have refused this. Do not see patients presenting with this frequently.	R & P	Ref
I would, just don't have many - badly worded questionnaire.	R, LN, & B	
my practice has its own sleep apnoea testing service	S	