Obstructive sleep apnoea and type 2 diabetes

Thesis submitted for the degree of Doctor of Medicine at the University of Leicester

Dr Sophie Diana West

MB ChB, MRCP (UK)

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Oxford Centre for Respiratory Medicine

Churchill Hospital, Oxford

ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

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Statement of personal contribution

I confirm that all the research described in this thesis was undertaken by myself.

Sophie West
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Abstract

Obstructive sleep apnoea and type 2 diabetes

Background

Obstructive sleep apnoea (OSA) is a common condition, caused by central obesity and characterised by recurrent upper airway obstruction, apnoeas, arousals and daytime sleepiness. Continuous positive airway pressure (CPAP) is an effective treatment. OSA is associated with glucose intolerance and insulin resistance, independent of obesity.

Aims

To establish the prevalence of OSA in individuals with type 2 diabetes, and whether treatment with CPAP improves glycaemic control and insulin resistance.

Methods and Results

A questionnaire was sent to 1682 men with type 2 diabetes from hospital and primary care databases. Fifty-six percent replied; 57% scored as 'high' and 39% as 'low' risk for OSA; 4% had known OSA. Overnight oximetry in 240 respondents from the 'high' and 'low' risk groups showed 31% and 13% respectively had significant OSA, verified by sleep studies. Extrapolation of oximetry data to the questionnaire respondent population suggests 23% have OSA. Comparison with a general population showed OSA prevalence to be significantly higher in the diabetes population ($p<0.001$). Multiple linear regression revealed diabetes was a significant independent OSA predictor after correction for BMI, explaining 8% of OSA variance ($p<0.001$). There was no correlation of OSA with HbA1c.

A double blind randomized controlled trial of CPAP in men with type 2 diabetes and newly diagnosed OSA was performed. Forty-two men attended for baseline investigations and then received either therapeutic or placebo CPAP for 3 months; baseline tests were then repeated. In the therapeutic group, significantly improved subjective and objective sleepiness were noted, however no significant improvement in HbA1c, euglycaemic clamp, adiponectin or HOMA-%S were found.

Conclusions

OSA is highly prevalent in men with type 2 diabetes; most individuals are undiagnosed. Diabetes may be a significant independent contributor to OSA risk. CPAP treatment of OSA does not improve insulin resistance or HbA1c in men with type 2 diabetes.

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Abbreviations

AHI	Apnoea-hypopnoea index
BMI	Body mass index
CPAP	Continuous positive airway pressure
CT	Computerised tomography
ESS	Epworth Sleepiness Score
EEG	Electroencephalogram
EMG	Electromyogram
EOG	Electrooculogram
HbA1c	Glycosylated haemoglobin
HDL	High density lipoprotein
IL6	Interleukin-6
LDL	Low density lipoprotein
NREM	Non rapid eye movement sleep
OSA	Obstructive sleep apnoea
OSAHS	Obstructive sleep apnoea/hypopnoea syndrome
PPARγ	Peroxisome proliferator-activated receptor γ receptors
RDI	Respiratory disturbance index
REM	Rapid eye movement sleep
SaO_2	Oxygen saturation
TNFα	Tumour necrosis factor alpha
VLDL	Very low density lipoprotein

Chapter 1

Introduction:

Obstructive sleep apnoea, type 2 diabetes and their interrelation

CHAPTER 1

INTRODUCTION: OBSTRUCTIVE SLEEP APNOEA, TYPE 2 DIABETES AND THEIR INTERRELATION

Hypotheses of this thesis

It was hypothesised that the risk of obstructive sleep apnoea (OSA) and the actual prevalence of OSA would be higher amongst men with type 2 diabetes than men in the general population, because of their levels of central obesity. Those men at high risk of OSA would have higher HbA1c levels, as the sleep disordered breathing would be associated with poorer diabetic control. It was also hypothesised that continuous positive airway pressure (CPAP) would improve HbA1c and insulin resistance in men with type 2 diabetes.

1.1 Obstructive sleep apnoea

Obstructive sleep apnoea (OSA) is a condition characterised by increasing upper airway resistance during sleep, leading to upper airway obstruction and apnoea with subsequent oxygen desaturation and increased respiratory efforts (Guilleminault 1976). A return to the awake/semi-awake state occurs in order to terminate the apnoea. This cycle of upper airway obstruction and arousal is repeated, often hundreds of times each night. Sleep fragmentation is caused by the recurrent arousals and this is thought to be the main cause of the daytime sleepiness associated with OSA (Stepanski 1984). Obstructive sleep apnoea/hypopnoea syndrome refers to the presence of at least five obstructed breathing events per hour of sleep on overnight monitoring, in association with the clinical syndrome of either excessive daytime sleepiness not better explained by other factors, or two of the following that are not better explained by other factors: choking or

gasping during sleep, recurrent awakenings from sleep, unrefreshing sleep, daytime fatigue, impaired concentration (American Academy of Sleep Medicine 1999).

1.1.1 Pathophysiology

The size of the upper airway during sleep is fundamental to whether a person will experience apnoeas and hypopnoeas or not. Airway patency is maintained during wakefulness by the action of pharyngeal dilator muscle activity (Mezzanotte 1996). Sleep causes muscle hypotonia, which can lead to pharyngeal collapse when the intraluminal pressure falls on inspiration (Mezzanotte 1992, Fogel 2005). If the pharyngeal size is small, then this pharyngeal collapse causes airway narrowing, inspiratory flow limitation, snoring, hypoventilation, and ultimately complete obstruction – apnoea (Deegan 1995). An apnoea is defined as a ten second breathing pause and a hypopnoea as a ten second event in which breathing continues, but there is at least a 50% reduction in the baseline ventilation (American Academy of Sleep Medicine 1999). During an apnoea, the pulse rate falls (Zwillich 1982). This mimics the diving reflex, activated in mammals by cold water diving and hypoxia, in order to prolong their diving time. In OSA, the apnoea is associated with frustrated inspiratory efforts, which cause pleural pressure swings and paradoxical movements of the rib cage and abdomen (Rees 1995). There is a fall in the oxygen saturation caused by the apnoea. At the onset of the arousal and the termination of the apnoea, the pulse and blood pressure rise and there may be associated body movement (Ringler 1990). Recurrent apnoeas lead to recurrent arousals, sleep fragmentation and subsequent daytime sleepiness (Bennett 1998). This pharyngeal hypotonia is particularly profound during the rapid eye movement (REM) sleep stage and some patients desaturate more during REM sleep (Pevernagie 1992, Loadsman 2000). It is recognised that arousals

can also occur in response to increased upper airway resistance and increased respiratory effort without apnoeas, the upper airway resistance syndrome. This causes daytime sleepiness in the same way as frank OSA (Guilleminault 2000, Rees 2000).

The pharyngeal size in OSA may be reduced for two main reasons: firstly, increased soft tissue surrounding the airway, and secondly a small bony compartment in which the airway is enclosed. The main cause of increased upper airway soft tissue is adipose deposits lateral to the pharynx, which contribute to an additional load on the pharynx during sleep (Horner 1989, Davies 1990). These adipose deposits are a reflection of increased overall body fat, particularly of the upper body. Obesity is the cause of OSA in most patients. The neck size is a valuable marker of upper body obesity and neck sizes of greater than 17" or 43cm are significant independent predictors of OSA (Stradling 1991). As men are more prone to upper body obesity (Larsson 2004, Regitz-Zagrosek 2006), OSA is more common amongst men (Young 1993). Other less common causes of increased soft tissue include large tonsils, hypothyroidism, acromegaly, mucopolysaccharidoses and oedema. A small bony compartment is due to facial bone structure abnormalities (Shepard 1991, Schwab 1995), with retrognathia being the most common. This causes pharyngeal narrowing, due to posterior displacement of the soft tissue and tongue (Jamieson 1986). Thin patients with OSA are more likely to have abnormal facial bone structure than obese people. A small amount of weight gain in someone with facial bone abnormalities may cause OSA to develop, even though they may not be obese or even overweight (Mayer 1996).

1.1.2 Genetics of obstructive sleep apnoea

The genetic influences on the development of OSA have been extensively studied. OSA is thought to be due to multiple interacting genes and environmental influences, including obesity, metabolism, upper airway anatomy and the neuromuscular control of the upper airway (Palmer 2003). There are a number of candidate genes for OSA and genome scanning of individuals with OSA, as well as neighbourhood controls, has been performed (Palmer 2003, 2004). These studies have shown that body mass index is linked to multiple chromosomal regions; in White Americans, the linkage to the apnoea-hypopnoea index was removed after adjustment for body mass, although in African Americans, the linkage to apnoea-hypopnoea index was only slightly reduced after this adjustment. Genetic pleiotrophy is clearly present, where one gene or set of genes result in a number of related phenotypes, and it is thought that 50% of the genetic susceptibility of OSA is derived from obesity components. Family aggregation of cases of OSA has been found: if three members of a family have OSA, the odds ratio is 4.2 for another family member having the disease (Redline 1995).

1.1.3 Prevalence of obstructive sleep apnoea

Population studies have estimated the prevalence of symptomatic OSA to be 2-4 % of adult men and 1-2% of women (Young 1993). It is still under diagnosed, although awareness amongst health professionals and the general public is increasing. As the number of people who are overweight and obese continues to rise, particularly in the West, OSA will increase in prevalence.

1.1.4 Clinical presentation

Patients with OSA typically snore and may have apnoeas and restless sleep witnessed by bed partners. The most common presenting symptom is daytime sleepiness and feeling unrefreshed when they wake from sleep (Whyte 1989). Cognitive function is often affected, affecting concentration and psychomotor vigilance when performing tasks such as driving (Engleman 1997). Quality of life can be significantly impaired (Jenkinson 1997). There may be a history of recent weight gain, with symptoms of unrefreshing sleep and daytime sleepiness since. Examination takes account of weight, neck size, facial and pharyngeal structure. The nose is also assessed, as nasal problems and blockages may lead to difficulties with the initiation of continuous positive airway pressure (CPAP) treatment.

1.1.5 Diagnosis

OSA is diagnosed by a clinical history, with an assessment of the severity of daytime sleepiness, and by an overnight sleep study. The Epworth Sleepiness Score (ESS) is an eight point self-administered questionnaire asking about a person's tendency to fall asleep in situations (Johns 1991, Appendix 1). This is commonly used to establish subjective daytime sleepiness, with a score of ten or more being regarded as pathologically sleepy. Objective tests of sleepiness, such as the multiple sleep latency test (Guilleminault 1988), the maintenance of wakefulness test (Banks 2004), the Oxford sleep resistance test (Bennett 1997) and driving simulators (Findley 1989, George 1996, Hack 2000) are not routinely used outside research settings. Sleep studies are performed primarily to diagnose and quantify the severity of sleep-disordered breathing. Along with the clinical assessment, they can also be used to evaluate whether the severity of a patient's daytime symptoms of sleepiness are likely to be attributable

to the amount of arousals and sleep fragmentation that result from an obstructed upper airway (Bennett 1998, Martin 1997). It may sometimes be difficult to correlate the degree of sleepiness a person is experiencing with the severity of OSA seen on their sleep study; it has been found that objective sleepiness is not significantly associated with the nocturnal variables of OSA (Cheshire 1992, Kingshott 1998). This is probably due to several factors. Firstly, there are night-to-night variations in sleep study indices, meaning that unless someone is studied for many nights, which is not usually feasible, the true level of their sleep disordered breathing is not accurately quantified (Stradling 2004). Secondly, multiple factors lead to a person feeling sleepy, or more non-specifically "tired", and it can be difficult to tease out which aspects of their symptoms may be amenable to treatment for OSA. Thirdly, the measures for both subjective and objective sleepiness are limited and even the objective tests do not correlate well with symptoms (George 1996, Guilleminault 1988, Olson 1998, Banks 2004).

Sleep studies have evolved over time as the understanding of the pathology of OSA has progressed, with different techniques of direct and indirect measurement being developed. The way in which OSA is investigated and diagnosed varies between centres. The current main types of sleep study performed are discussed below.

1.1.5.1 Polysomnography

Polysomnography was first used for the diagnosis of sleep disorders by neurologists and neurophysiologists (Benca 1992). Techniques used for the investigation of patients with neurological disorders were adapted for sleepy patients. Electro-physiological signals derived from the electro-encephalogram (EEG), electro-oculogram (EOG) and electro-myogram (EMG) are used to determine sleep onset, sleep stage and duration, as well as

sleep fragmentation, arousals and more recently, microarousals. Simple signal pressure transducers, such as oro-nasal thermistors and ribcage/abdominal mercury strain gauges, document irregular breathing. Obstructive apnoeas are counted to give an apnoea index per hour of sleep and oximetry has also been added. Polysomnography requires a sleep technician and a laboratory. It became established as the standard method of investigation of sleep patients, against which other techniques were judged (American Sleep Disorders Association Standards of Practice Committee 1997). Many of the variables measured however may not be the best, or only, way to determine sleep, wakefulness or arousals. There is no evidence that the diagnosis and management of OSA requires full polysomnography and it is not indicated for the vast majority of patients (West 2006).

1.1.5.2 Limited sleep studies

This term encompasses those sleep studies which do not record EEG/EOG/EMG, so therefore do not require a fully trained sleep technician. These simplified tests have evolved and been shown to be at least as good as polysomnography for the diagnosis of CPAP-responsive OSA (Bennett 1998, Choi 2000, Vazquez 1998). They can produce apnoea-hypopnoea indices (AHI), or respiratory disturbance indices, similar to those obtained by full polysomnography, but may also provide more sophisticated derivatives. Commonly, some or all of oximetry, snoring, body movement, heart rate, oro-nasal airflow, chest and abdominal movements and leg movements are monitored. Arousals are inferred from respiratory signals and autonomic indices, such as rises in heart rate and blood pressure or falls in pulse transit time (Pitson 1995). Estimates of sleep onset, sleep duration and awake time can be determined from body movements, measured with actigraphy, video or other devices.

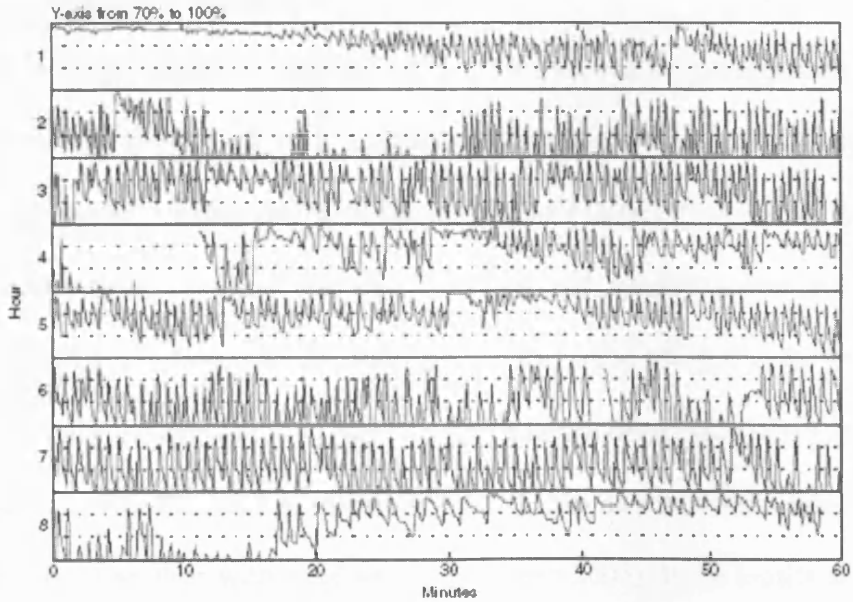
Many other limited sleep study systems have been devised for home use (Flemons 2003). They can be applied by the patient at home, following suitable instruction. They are relatively cheap and do not require patients to spend a night in a hospital bed. They can be difficult to set up correctly, and this may lead to sufficient data loss to preclude a confident diagnosis. This may be an area of future development by industry.

1.1.5.3 Overnight oximetry alone

Portable recording oximeters are now often used to perform simple sleep studies, usually in the patient's own home (Flemons 2003). Tracings of all-night oximetry and pulse rate are obtained. Algorithms count the number of hypoxic dips and, by inference, respiratory events. Recurrent pulse rate rises are usually indicative of recurrent arousal and help in the analysis (Pitson 1998). In those patients with symptoms suggestive of OSAHS, no reason to have central apnoeas and a baseline SaO_2 of greater than 92%, then more than 15 >4% SaO_2 dips per hour allows a confident diagnosis of OSAHS (Gyulay 1993) In one study of 240 out-patients, a negative home oximetry test result was helpful in ruling out the diagnosis of OSA in patients clinically suspected of having this syndrome, because a negative test result reduced the probability from 54.1% to 3.1% (Series 1993). A visual review of the overnight tracing is always recommended, particularly for negative studies, to ensure the characteristic subtle SaO_2 dipping of OSAHS is not missed (for example when many of the SaO_2 dips do not quite reach the 4% threshold for counting). The number of >4% SaO_2 dips has been found to correlate well with improvement in ESS following subsequent CPAP treatment (Choi 2000). In another study, clinicians correctly identified which patients would have a favourable outcome with CPAP based on clinical data and review of either polysomnography or oximetry, with no significant difference between the two diagnostic methods,

suggesting oximetry may be adequate at identifying CPAP-responsive OSA (Whitelaw 2005). Oximetry alone is clearly a limited study, but can be successfully used, with appropriate expertise, to identify moderate to severe cases of OSAHS (Figure 1), thus allowing rapid referral for a diagnostic sleep study and continuous positive airways pressure treatment (Golpe 1999). Measurements of SaO_2 correlate very well with the apnoea-hypopnoea index (Vazquez 2000). False positive oximetry can occur with Cheyne Stokes breathing (for example, in heart failure and post stroke), which also causes cyclical falls in SaO_2, and if there is a low awake baseline SaO_2 (for example, chronic obstructive pulmonary disease), where the nocturnal SaO_2 oscillates considerably with only small actual PaO_2 changes, due to the shape of the oxygen-haemoglobin dissociation curve. False negative oximetry can occur in younger and thinner patients, who can have frequent apnoeas and arousals without detectable desaturations (Sano 1998). Those with negative oximetry studies, but symptoms suggestive of OSAHS, should undergo further sleep study assessment.

Figure 1. *Severe OSA on overnight oximetry, with frequent regular desaturations throughout the night.*



1.1.6 Treatment of obstructive sleep apnoea

Treatment of OSA is aimed at reducing the number of episodes of airway obstruction and subsequent arousals, hence improving nocturnal sleep and decreasing daytime sleepiness. The severity of the patient's symptoms of daytime sleepiness influences the choice of treatment, more than the severity of OSA diagnosed on their sleep study. At present, excessive daytime sleepiness with OSAHS is the main indication for treatment, and the improvement of the sleepiness is the outcome used to measure the success of treatment. As the evidence for other conditions being associated with OSAHS increases (for example, hypertension), it is debated whether patients with OSA, but without excessive daytime sleepiness, should receive treatment to modify the associated conditions. At present, there is not enough evidence to support or justify this. Indeed, hypertension in non-sleepy patients with OSA has recently been found not to improve with CPAP (Barbe 2001, Robinson 2006) in the same way it does in sleepy patients (Pepperell 2002, Faccenda 2001).

There are several different options for the treatment of OSA.

1.1.6.1 Conservative management

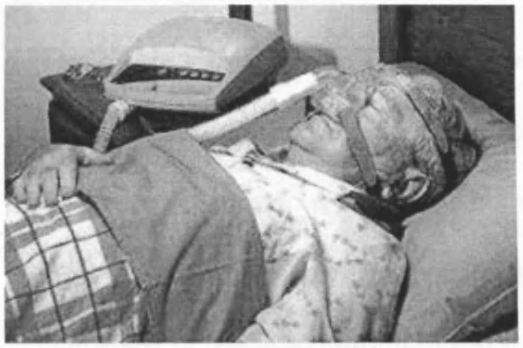
Simple treatment measures may be all that are required in patients with mild OSA or with more severe OSA but with minimal daytime sleepiness. Avoiding sleeping on the back will lessen snoring and apnoeas (Oskenberg 2006). Alcohol is associated with decreased muscle tone and will make snoring and apnoeas worse due to decreased pharyngeal muscle tone (Tassan 1981), and so should be avoided in the evening prior to bed. Similarly the avoidance of sedative drugs is recommended (Berry 1995). Sleeping propped up, with the head of the bed elevated, can help some (Skinner 2004), as can keeping the nose clear with nasal sprays (McLean 2005). If the tonsils are significantly

enlarged and likely to be contributing to airway obstruction, their removal should be considered; this may be pertinent particularly to people without significant upper body obesity (Moser 1987). Weight loss is likely to be beneficial, particularly in those with a history of OSA onset since recent weight gain, those with a body mass index (BMI) of greater than 25 kg/m^2, or with a neck size greater than 43 cm or 17" (Stradling 1991). The benefits of weight loss achieved after gastric surgery in patients with OSA has been shown (Spivak 2005, Lara 2005).

1.1.6.2 Continuous positive airway pressure (CPAP)

CPAP is the delivery of air to the upper airway non-invasively, via a nose or full-face mask and a positive pressure ventilator, which maintains airway patency during sleep by means of 'pneumatic splinting'. The use of CPAP for the treatment of patients with OSA was first described by Sullivan in 1981 (Sullivan 1981). He found that low levels of pressure (4.5-10cm H_2O), applied via a nasal mask, completely prevented upper airway obstruction during sleep. Dramatic effects after one night's use were noted, with improved daytime sleepiness and a shift from the lighter stages of NREM sleep to stages III and IV NREM sleep. It has been widely used since that time and randomised controlled trials have found it to be an effective treatment at improving both subjective and objective daytime sleepiness, self-reported health status, and cognitive function, measured by simulated steering performance (Jenkinson 1999, Engleman 1998, Hack 2000; Figure 2). Randomised controlled trials have also found improvements in blood pressure and cholesterol with CPAP (Pepperell 2002, Faccenda 2001, Robinson 2004).

Figure 2. *Photograph of patient using CPAP, with nasal mask, tubing and machine beside the bed.*



CPAP is the mainstay of treatment of people with significant symptomatic OSA. The best correlates of whether a patient is likely to have improved daytime sleepiness following a therapeutic CPAP trial are the number of >4% SaO_2 dips per hour, and the number of body movements (indicating arousals) (Bennett 1998, Choi 2000). There is considerable night-to-night variation in sleep study indices, which makes the use of thresholds to initiate treatment illogical. The sleep study needs to be interpreted to assess if there is sufficient evidence to explain the patient's symptoms of daytime sleepiness. If the severity of the OSAHS (and how much it may be affecting the patient) is unclear, then it is reasonable to undertake a diagnostic (as well as therapeutic) trial of CPAP, to determine whether the patient has sufficient clinical improvement to warrant continued treatment; giving rise to the concept of CPAP-responsive disease (Stradling 2004). Those with milder OSA may benefit from CPAP, but may find the side-effects intolerable for their level of sleep disturbance (Engleman 1999). Typical side effects experienced by patients starting CPAP are mask leaks, mouth leaks, claustrophobia, discomfort, sore nasal bridge, blocked or dry nose, sneezing and rarely abdominal bloating and vomiting (Hoffstein 1992).

The pressure required for effective CPAP is essentially the pressure at which most of the apnoeas, hypopnoeas and arousals are eliminated (Issa 1986). This pressure can be determined in several ways. Traditionally an overnight polysomnographic sleep study is performed, with technicians titrating CPAP pressure, until most of the apnoeas and arousals are abolished, as measured by concurrent polysomnography (American Sleep Disorders Association Standards of Practice Committee 1997). Autotitrating machines, which adjust pressure according to inspiratory flow limitation, snoring and apnoeas, are as effective as manual titration at performing overnight CPAP titration (Stradling 1997). They have been used to initiate CPAP treatment, either at home or in hospital (D'Ortho 2000, Planes 2003). A technician is not required to be present overnight. The results regarding airway pressure can be used to determine the effective level of CPAP required, then administered by a simpler fixed pressure machine. Alternatively, patients may use the autotitrating machines long-term, although these are more expensive than fixed pressure machines (Konnermann 1998, Gagnadoux 1999). Algorithm-based methods of determining a fixed CPAP pressure are also used, which predict the required CPAP pressure based on neck circumference/body mass index and oxygen desaturation/apnoea-hypopnoea index (Stradling 2004, Hoffstein 1994). This approach has given comparable pressures and patient outcomes to autotitrating machines in the limited studies done so far (Stradling 2004). Two recent studies compared three different methods of CPAP initiation and pressure determination for twelve weeks and six months respectively and found no difference in clinical outcomes with any of the methods (Masa 2004, West 2006).

1.1.6.3 Mandibular advancement device

These are dental appliances which are fitted over the patient's top and bottom teeth, and act to hold the lower jaw forward during sleep, thus increasing pharyngeal area and preventing upper airway obstruction (Schmidt-Nowara 1995). Mandibular advancement devices can be effective in treating snoring and OSAHS, mainly in those who have milder disease, retrognathia, postural OSAHS, or in those who are intolerant of CPAP; individual benefit is largely unpredictable (Ferguson 1996, Stradling 1998, Mehta 2001, Engleman 2002). Side effects include salivation, dry mouth, jaw discomfort and changes in teeth occlusion, although the latter two are said to be uncommon (Clark 1998).

1.1.6.4 Drugs

Drugs to increase respiratory drive during sleep, to suppress the rapid eye movement sleep associated with more severe OSA, to reduce airway resistance or to preferentially activate the upper airway dilator muscles have been postulated as a way in which OSA could be improved. A recent Cochrane review looked at studies involving trials of intranasal fluticasone, physostigmine, mirtazipine, topical nasal lubricant, paroxetine, acetezolamide, protriptyline and naltrexone; all had some effect on either AHI or subjective sleepiness, but as the studies were small and short term, drug treatments cannot be recommended on this level of evidence in the treatment of OSAHS (Smith 2006).

1.1.6.5 Surgery

Operations such as uvulo-palato pharyngoplasty (UPPP), in which the uvula, part of the soft palate and any residual tonsils are removed in an attempt to widen the retropalatal

airway, have been performed as a way to improve OSA. Studies have shown that these operations are not effective in the treatment of OSA and can be associated with significant complications, including post-operative pain and death (Sher 1996). They can make the future administration of CPAP more difficult, as it is harder to achieve a good seal between the palate and the tongue (Mortimore 1996). A recent Cochrane review concluded there was not enough evidence to support the use of surgery in OSA, as overall significant benefit has not been demonstrated (Sundaram 2005). Long term follow-up of patients who undergo surgical correction of upper airway obstruction was recommended in order to further evaluate surgical treatments. If the tonsils are significantly enlarged and thought to be contributing to airway obstruction, their removal should be considered and this may be beneficial to the OSA (Moser 1987). Tracheostomy is an effective way in which the upper airway obstruction of OSA is overcome (Katsantonis 1988). Its use has largely been replaced by CPAP, but it may still be indicated in patients with life threatening ventilatory failure, who are unable to tolerate nasal CPAP.

1.1.7 Conditions associated with obstructive sleep apnoea/hypopnoea syndrome

OSAHS is increasingly recognised to be associated with certain clinical conditions.

1.1.7.1 Hypertension and cardiovascular disease

OSAHS is now recognised to be a cause of systemic hypertension, independent of obesity, with rises in blood pressure at night and during the day (Davies 2000, Peppard 2000). The hypertension is likely to be due to both increased day-time and night-time sympathetic nervous system activity caused by either (or both) the hypoxia and sleep fragmentation found in OSA. Apnoeas and arousals are associated with profound

autonomic and cardiovascular changes (Somers 1995, Dimsdale 1997, Davies 1993), with systolic blood pressure falls of often more than 50mmHg due to the frustrated inspiratory efforts, and rises of more than 80mmHg with each arousal (Ringler 1990, Garpestad 1995). These may directly damage the arterial system, but the evidence is unclear. There may be cardiac arrhythmias associated with these arousals (Harbison 2000, Gami 2004). Randomised controlled trials of CPAP have found that hypertension improves following effective treatment of OSA (Faccenda 2001, Pepperell 2002, Becker 2003).

By extension, OSA is therefore likely to be indirectly or directly related to vascular disease, including coronary heart disease, arrhythmias, heart failure, transient ischaemic attacks and stroke (Parish 1990, Nieto 2000). An increased incidence of cardiovascular disease in patients with OSA was found in one cohort study of 182 men with or without OSA, followed over seven years (Peker 2002). At baseline, subjects were free of comorbid cardiovascular disease. Those with OSA had a higher risk of cardiovascular disease, but effective treatment with CPAP reduced this excess risk. The increased risk appeared to be independent of obesity on multiple logistic regression models. Another observational study performed polysomnography on 6424 people and quantified people according to their AHI (Shahar 2001). People were also stratified according to self reported cardiovascular disease, and it was found that the multivariable adjusted relative odds of cardiovascular disease increased with increasing AHI. A further observational study compared the incidence of fatal and non-fatal cardiovascular events in 377 simple snorers, 403 patients with untreated mild-moderate OSA, 235 with untreated severe OSA, and 372 with OSA treated with CPAP (Marin 2005). Patients with untreated severe disease had a higher incidence of fatal cardiovascular events and non-fatal

cardiovascular events than did untreated patients with mild-moderate disease, simple snorers, patients treated with CPAP and healthy participants ($p<0.0001$). Non-compliers with CPAP treatment are not however an ideal control group with whom to make this comparison, as they may well be non-compliant in other areas of their life (for example smoking, excess alcohol, failure to take prescribed drug treatment) and hence the cardiovascular risk of this group would be overestimated. In addition, the use of body mass index (BMI) is probably an inadequate measure of weight in the studies by Peker and Marin. Waist to hip ratio has been found to be more accurate at predicting cardiovascular risk than BMI (Yusuf 2005), as it takes account of visceral fat. Visceral fat is related to adipokine release and insulin resistance and is therefore more predictive of cardiovascular risk (see sections 1.2.6 & 1.2.7.1). Until there are controlled interventional studies to determine the effect of CPAP treatment on the modification of these risks, the true effect of OSA on cardiovascular risk cannot be determined. Also, studies of cardiovascular risk have traditionally not taken OSA into account; it is increasingly recognised that this possible risk factor needs accounting for (Garvey 2006).

1.1.7.2 Cognitive dysfunction

Some studies have shown changes in brain morphology in OSA, with grey matter loss in multiple sites (Macey 2002, Morrell 2003), although another study has shown no change in grey matter (O'Donoghue 2005). There is evidence of cognitive dysfunction in people with untreated OSA (Kingshott 1998, Twigg 2006) and possible residual decrements even after treatment. This may be due to nocturnal intermittent hypoxia, sleepiness or other effects of severe sleep fragmentation, and can be manifest as poor concentration, problems with vigilance or attention. One study of right handed men

with OSA has shown a loss of grey matter concentration within the left hippocampus and bilaterally in the parahippocampus, compared to healthy controls, as measured by magnetic resonance imaging of the brain (Morrell 2006). These areas are those in which cognitive processing occurs, suggesting that OSA causes a detectable neural deficit. The increased risk of motor vehicle accidents in people with untreated moderate to severe OSA, up to seven times higher than those in the general population, is well known (Findley 1988, George 1999). Cognitive performance, measured by a range of neuropsychological tests in patients with OSA, shows a relationship with AHI (Engleman 2000, Ferini Strambi 2003). Studies of CPAP therapy show trends towards better performance in attention and cognitive testing with CPAP compared to placebo (Engleman 2000). Cognitive impairment measured by simulated steering performance (as a surrogate for driving ability) also improves following therapeutic CPAP (George 1997, Hack 2000).

1.1.7.3 Insulin resistance

This will be discussed in more detail in section 1.2.6.

1.1.7.4 Other conditions

OSA has also been postulated to have effects on clotting factors, platelet activation and function, vascular endothelial function and may have a causative role in pre-eclampsia (Eisensehr 1998, Wessendorf 2000, von Kanel 2003, Edwards 2001, Ip 2004). The evidence for these areas is from small observational studies and there have been no controlled interventional trials.

1.2 Type 2 Diabetes

Diabetes is a condition of hyperglycaemia, caused by inadequate insulin levels. The World Health Organisation criteria for its diagnosis are a fasting blood glucose of greater than or equal to 7.0mmol/L, or a two hour blood glucose following a 75g oral glucose load of greater than or equal to 11.1mmol/L (Alberti 1998).

1.2.1 Pathophysiology

Type 1 diabetes is a condition of inadequate initial insulin production, due to autoantibody destruction of the beta cells of the pancreas. It typically occurs in children and young people, who are of normal body weight. There is a human leucocyte antigen (HLA) association, with environmental triggers (Atkinson 1991). Type 2 diabetes occurs when the beta cells of the pancreas are unable to produce enough insulin to maintain euglycaemia. This usually occurs in association with obesity and cellular insulin resistance, which leads to an initial increase in insulin secretion, followed by progressive beta cell failure (Dandona 2002, Reaven 1988). Insulin resistance is present at the pre-diabetic stage of impaired glucose tolerance (Goldstein 2002). Type 2 diabetes has been called maturity onset diabetes, reflecting the fact that it is predominantly seen in middle age onward. It has also been called non-insulin dependent diabetes, reflecting the fact that the initial treatment is usually not with insulin. These two names have largely been replaced by the term type 2 diabetes, to avoid confusion. Obese young people, including children, are increasingly being recognised as developing type 2 diabetes (Cara 2006, Weiss 2006) and many patients whose initial therapy is with diet or oral hypoglycaemic tablets go on to require insulin during the course of their treatment.

1.2.2 Prevalence

The prevalence of type 2 diabetes is increasing, as the number of people with obesity increases. One hundred and seventy million individuals worldwide have diabetes, with growth predicted to increase, particularly in Africa, Asia and South America. An estimated six percent of American adults have type 2 diabetes. Ninety percent of people with diabetes worldwide have type 2 diabetes (Stumvoll 2005).

1.2.3 Aetiology

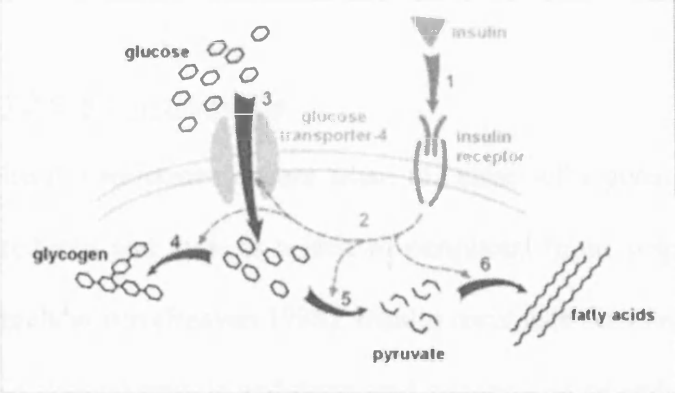
Type 2 diabetes is a heterogeneous disease, related predominantly to obesity, but also to genetic factors. Positive family history confers a 2.4 fold increased risk (Pierce 1995). Fifteen to 25% of first degree relatives of patients with type 2 diabetes develop impaired glucose tolerance or diabetes. It is likely that more than one abnormal gene is necessary for the development of type 2 diabetes (LeRoith 2002). Candidate gene analysis has shown the Pro12A1a polymorphism in the peroxisome proliferator-activated receptor γ (PPARγ) to be a single candidate gene variant (Hansen 2005). PPARγ is a transcription factor activated by certain fatty acids, prostanoids and thiazolidinediones (see section 1.2.9.3.4). One of the isoforms of the receptor has a key role in adipogenesis and this explains its causal relationship with type 2 diabetes and insulin resistance (Auwerx 1999). Research to identify other candidate genes is ongoing.

1.2.4 Normal glucose metabolism

Glucose is the major source of metabolic energy in humans. Normal blood glucose levels are tightly controlled, with a balance between glucose utilization and glucose intake and synthesis. Insulin is the key hormone for the regulation of blood glucose,

enabling it to be converted to the stored energy resources of glycogen and fat. Insulin is a 51 amino acid peptide produced by the beta cells of the islets of Langerhans in the pancreas. It is formed by the removal of the C chain from proinsulin (84 amino acids). Insulin contains two peptide chains, A and B, connected by two disulphide bonds (S-S bonds). It has a half life of 10-30 minutes and is mainly broken down in the liver and the kidneys. When blood glucose levels rise, following food ingestion and intestinal glucose absorption, insulin is released by the pancreas. Insulin binds to a specific plasma membrane receptor with tyrosine kinase activity (White 2002). The hormone-receptor complex is then internalised, binds to adaptor proteins and leads to a downstream signalling cascade (Figure 3). This is linked to the translocation of facilitative glucose transporters (the GLUTs) to the cell membrane. The GLUTs mediate glucose uptake by cells and tissues. They are present in all cell types and many different isoforms have been described. Their expression is cell-specific and subject to hormonal and environmental control, with substrate specificities of the different isoforms specifically suited to the energy requirements of the particular cell types. For example, GLUT 1, the erythrocyte transporter, is widely distributed, providing for the basal glucose needs of all cells. Its expression is increased by low ambient glucose concentrations and by cellular growth and division (Lancet 1991). Thyroid stimulating hormone, exercise and insulin like growth factor also have similar effects on the GLUTs.

Figure 3. *Effect of insulin on glucose uptake and metabolism. Insulin binds to its receptor (1), which in turn starts many protein activation cascades (2). These include: translocation of Glut-4 transporter to the plasma membrane and influx of glucose (3), glycogen synthesis (4), glycolysis (5) and fatty acid synthesis (6). (Diagram reproduced from Wikipedia).*



Insulin acts to convert glucose into a stored energy resource. Rises in glucose levels following food intake are rapidly lowered and a normal blood glucose level is maintained. Insulin secretion from the pancreas decreases glucose output by the liver, enhances skeletal muscle glucose uptake and suppresses fatty acid release from fat tissue. Insulin causes glucose to be converted to glycogen (glycogenesis), and it can then be stored in the liver and the muscle. Insulin causes decreased lipolysis, but increases lipogenesis, protein metabolism and sodium retention. There is hence a ready supply of stored glucose, which can be easily utilised, particularly by the brain and central nervous system, which are reliant on glucose for their metabolism. Glycogen can be converted back to glucose by the action of glucagon, a hormone produced by the alpha cells of the pancreas (glycogenolysis). The actions of insulin are antagonised by somatostatin, catecholamines, cortisol, and growth hormone. Raised catecholamine levels inhibit insulin action, ensuring adequate plasma glucose levels in order for "flight or fight". In OSA, plasma catecholamine levels are increased presumably due to the

recurrent nocturnal arousals; these have been found to decrease following effective CPAP therapy (Ziegler 2001, Mansfield 2004). It is hypothesised that these raised catecholamines are likely therefore to have effects upon insulin action in patients with OSA.

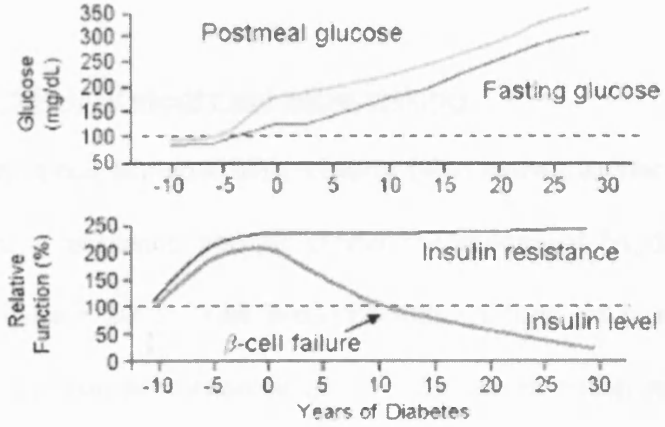
1.2.5 Insulin resistance

Insulin resistance occurs when the effect of a given amount of insulin upon a cell is reduced and there is a lack of peripheral tissue response to insulin-mediated glucose metabolism (Reaven 1988). Insulin resistance therefore causes reduced glucose disposal in skeletal muscle and decreased suppression of endogenous glucose production in the liver. Greater amounts of insulin therefore need to be produced by the pancreas to have the same effect on the cell, and higher insulin levels are required to maintain normoglycaemia (Dinneen 2002). In the fasting state, hepatic glucose production is not suppressed by insulin because of the insulin resistance, and hyperglycaemia results (Meyer 1998). Resistance to insulin is apparent with both endogenous and exogenous insulin (Goldstein 2002). Hyperinsulinaemia causes exaggerated responses in tissues which remain sensitive to insulin, for example the sympathetic nervous system, possibly contributing to hypertension (Kern 2005). Insulin resistance in fat cells leads to increased lipolysis, fatty acid release, subsequent dyslipidaemia and vascular abnormalities (Lewis 2002).

Over a period of time, usually years, the beta cells of the pancreas are unable to maintain the increased production of insulin, which leads to pancreatic dysfunction and failure (LeRoith 2002). Normoglycaemia then cannot be maintained, blood glucose levels rise and type 2 diabetes develops (Figure 4). Insulin resistance is therefore the

primary metabolic defect in type 2 diabetes, but can also be seen as a pre-diabetic stage, when glucose tolerance is impaired and fasting glucose is abnormal, but diabetic hyperglycaemia is not present (Unwin 2002). A proportion of people with insulin resistance go on to develop type 2 diabetes, approximately 11% in one study (Haffner 2000).

Figure 4. *Natural history of type 2 diabetes, showing insulin resistance, compensatory hyperinsulinaemia and beta cell dysfunction, with subsequent declining insulin secretion and worsening hyperglycaemia over time. Reproduced from LeRoith 2002.*



Insulin resistance is strongly associated with obesity and physical inactivity (Stumvoll 2005). The likely molecular mechanisms for insulin resistance all block the insulin signalling downstream cascade. Adipocytokines released from visceral adipose tissue adversely affect this insulin signalling cascade (Rajala 2003). This will be discussed further in section 1.2.6. Non-esterified free fatty acids originate in the adipocyte and modulate insulin action (Boden 2002). Lipolysis of the adipocytes leads to increased levels of circulating free fatty acids, which inhibit insulin-stimulated glucose metabolism in skeletal muscle and stimulate gluconeogenesis in the liver, so glucose

levels are raised (Boden 2002). Also, insulin is an anti-inflammatory hormone and an insulin-resistant state is therefore pro-inflammatory and potentially proatherogenic (Dandona 2002).

There are some conditions which are recognised as being associated with insulin resistance. These include: polycystic ovary syndrome, myotonic dystrophy, Cushing's disease, acromegaly, acanthosis nigricans, precocious pseudo-puberty, gestational diabetes, growth retardation and lipodystrophy (Shoupe 1983, Vialettes 1986, Wajchenberg 1984, Barbieri 1983, Matsuoka 1986, Ibanez 2004, Endo 2006, Klein 1992).

1.2.6 Role of obesity and adipocytokines

Centripetal or upper body obesity (also known as visceral obesity) is associated with insulin resistance, and the greater the abdominal fat, the greater the insulin resistance (Miyazaki 2002). This predominantly visceral fat is more resistant to the effects of insulin than subcutaneous fat. Weight loss in which subcutaneous fat is lost has little effect on insulin resistance; if visceral fat is lost (measured by CT), insulin resistance measures show significant improvements (Park 2005). This is because adipose tissue itself is recognised as being metabolically active, secreting a large number of factors with diverse functions. Increased amounts of stored triglyceride, especially in visceral or deep subcutaneous adipose tissue, lead to large adipocytes, which are resistant to the ability of insulin to suppress lipolysis. Therefore they release free fatty acids and glycerol which circulate, aggravate insulin resistance further and contribute to dyslipidaemia (low high density lipid (HDL) cholesterol, high triglycerides and small dense low density lipid (LDL) cholesterol particles, which are more atherogenic)

(Boden 1996). Adipocytes also produce a number of biologically active molecules, known as the adipokines or adipocytokines. These include tumour necrosis factor-α (TNF-α), interleukin 6, resistin, adiponectin, leptin and glucocorticoids and sex hormones. As well as causing insulin resistance, the adipocytokines also affect vascular endothelial function, linking the increased vascular risk found in the metabolic syndrome to cellular insulin resistance mechanisms. The adipocytokines also recruit and activate inflammatory cells, perpetuating a systemic inflammatory state, which also affects vascular function and atherogenesis (Wellen 2003).

1.2.5.1 TNF-α and interleukin-6

TNF-α is a pro-inflammatory cytokine produced by adipose tissue, which inhibits the tyrosine phosphorylation of the insulin receptor, leading to insulin resistance (Goldstein 2001, Pittas 2004). Expression in obesity, insulin resistance and type 2 diabetes is high, and weight loss decreases TNF-α levels. Interleukin-6 (IL-6) is secreted by many cell types, including adipose tissue, and is also a pro-inflammatory cytokine. Plasma IL-6 levels positively correlate with obesity and insulin resistance, with elevated levels predicting the development of type 2 diabetes (Vozarova 2001). Weight loss significantly decreases IL-6 levels. IL-6 increases circulating free fatty acid levels and decreases adiponectin (Pittas 2004). These seem likely to be the mechanisms by which it contributes to insulin resistance.

1.2.5.2 Resistin

Resistin is a hormone produced by adipose tissue. Levels are raised in diabetes and obesity. Its role in insulin resistance in humans is not clear.

1.2.5.3 Adiponectin

Adiponectin is a hormone produced by adipose tissue which has insulin sensitizing effects in the liver and muscle and may have anti-atherogenic and anti-inflammatory effects also (Kumada 2003, Dzielinska 2003). In contrast to the other adipocytokines, levels are low in visceral obesity, but levels are restored to normal after weight loss. Levels are inversely, but closely correlated with the degree of insulin resistance and hyperinsulinaemia (Hotta 2000, Weyer 2001, Tschritter 2003). High levels have also been found to be associated with a substantially reduced relative risk of type 2 diabetes after adjustment for age, sex, waist to hip ratio, BMI, smoking, exercise, alcohol and HbA1c (Spranger 2003). In lipoatrophic mice models, administration of adiponectin with leptin completely reversed insulin resistance (Yamauchi 2001). The mechanisms by which adiponectin affects insulin resistance are not clear.

1.2.5.4 Leptin

Leptin is a protein secreted by adipose tissue in response to satiety, which binds to leptin receptors (Ob-R) (Considine 1996). These provide feedback to the hypothalamus, to inhibit synthesis of neuropeptide Y, which has stimulatory effects on appetite (Pittas 2004). Genetically obese animal models which have the ob-ob gene, in which leptin is deficient or leptin or hypothalamic receptors are absent, are hyperphagic, obese and insulin resistant (Zhang 1994). Exogenous leptin administration reverses these abnormalities (Pelleymounter 1995). Leptin levels are low in starvation and levels increase with weight gain. It was thought that the discovery of leptin might represent a breakthrough in human obesity treatment, if therapeutically administered leptin could be used to induce satiety. It has since been discovered that the majority of obese humans have high, not low, levels of leptin, indicating a state of cellular leptin

resistance (Considine 1996). The mechanism for this is not clear. Leptin rises continuously with increasing adiposity (Ostlund 1996). Rarely patients have congenital leptin deficiency due to a gene mutation (Montague 1997) and leptin replacement is beneficial (Licinio 2004).

1.2.5.5 Visfatin

Visfatin is a newly discovered adipocytokine produced by adipose tissue, with insulin mimetic actions. Levels increase with induced hyperglycaemia in healthy individuals and this effect is suppressed by exogenous hyperinsulinaemia or somatostatin infusion (Haider 2006). Levels are significantly increased in people with type 2 diabetes compared to controls ($p=0.01$), but seem to be unrelated to insulin sensitivity (Dogru 2006). Its role has not been fully elucidated.

1.2.7 Metabolic syndrome

The clustering of closely related abnormalities, all related to insulin resistance and causing increased cardiovascular risk, is known as the metabolic syndrome, or syndrome X. This was first described by Reaven in 1988, who described a subset of patients with hypertension who had insulin resistance, hyperglycaemia, low HDL-cholesterol and raised very low density lipid (VLDL) triglycerides, persisting after the hypertension was controlled with treatment (Reaven 1988). Whilst the pathogenesis of the metabolic syndrome and each of its components is complex and not well understood, central obesity and insulin resistance are acknowledged as important causative factors (Carr 2004, Anderson 2001). Each of the components of metabolic syndrome is associated with increased cardiovascular risk; it is not known whether all the components together have simply an additive effect on cardiovascular risk, or

whether any of the components are synergistic in some way, causing an increase in cardiovascular risk greater than the sum total of the components. The importance of diagnosing metabolic syndrome probably lies in the effective treatment of all of the component parts individually, in order to maximally reduce cardiovascular disease risk. Some say, however, that the definition of metabolic syndrome is imprecise, as it is slightly different according to the three main organisations who define it (see below), which together with a lack of certainty about its pathogenesis and doubt regarding its value as a cardiovascular disease risk marker, make it an unhelpful syndrome to diagnose (Kahn 2005). Rather, clinicians should evaluate and treat all cardiovascular risk factors, regardless of whether they fulfil the criteria for this syndrome.

The World Health Organisation, the National Cholesterol Education Panel and the International Diabetes Federation have all issued definitions for the metabolic syndrome (WHO 1999, NCEP 2001, IDF 2005). The criteria differ slightly between each. The updated definition by the International Diabetes Federation is the most recently published and is shown here:

For a person to be defined as having the metabolic syndrome they must have:

- Central obesity (defined as waist circumference ≥94cm for Europid men and ≥ 80cm for Europid women, with ethnicity specific values for other groups),
- Plus any two of the following four factors:

• Raised triglyceride level: ≥ 150mg/dL (1.7mmol/L), or specific treatment for this lipid abnormality

• Reduced HDL cholesterol: < 40mg/dL (1.0mmol/L) in males and < 50 mg/dL (1.3mmol/L) in females, or specific treatment for this lipid abnormality

• Raised blood pressure: systolic BP ≥130 or diastolic BP ≥ 85 mm Hg, or treatment of previously diagnosed hypertension

• Raised fasting plasma glucose ≥ 100mg/dL (5.6mmol/L), or previously diagnosed type 2 diabetes.

The central obesity in this definition reflects high levels of visceral obesity, which is associated with insulin resistance, and therefore underpins many aspects of the syndrome. Visceral obesity is the most likely the causative factor for metabolic syndrome. Improving insulin sensitivity may limit the consequences of dyslipidaemia and alter visceral fat distribution, hence leading potentially to a modification of the risks associated with the metabolic syndrome (Reusch 2002).

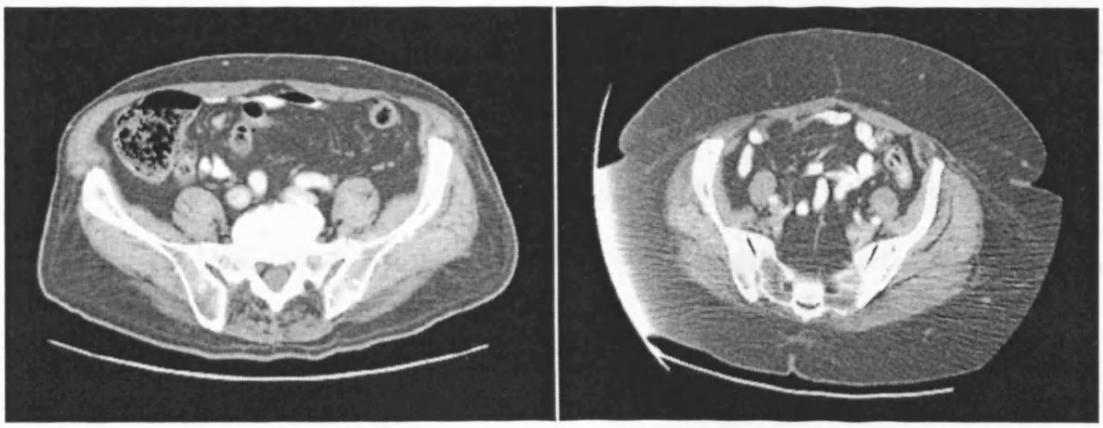
1.2.7.1 Measurement of visceral obesity

Visceral obesity is best measured on abdominal computerised tomography (CT) scans and these are regarded as the "gold standard" for quantifying abdominal fat, with waist and waist to hip ratio measurements being poorer correlates (Riberio-Filho 2003) (Figure 5). It is however impractical in large studies to perform CT scans on all participants and abdominal CT scanning also involves radiation exposure, which is difficult to ethically justify in a research study. BMI has traditionally been used to define obesity, but it takes no account of muscle and fat mass, or the all important fat distribution. Waist to hip ratio has been found to be superior to BMI at predicting cardiovascular risk in a large observational case control study of 27000 people in 52 different countries, and is the strongest anthropometric measure associated with risk of myocardial infarction (Yusuf 2005). In normal weight subjects, increased waist circumference has been found to be associated with increased cardiovascular risk (Bouchard 1993). Waist circumference has also been found to be a very good predictor of insulin sensitivity, with a waist circumference of less than 100cm excluding insulin resistance in both sexes (Wahrenberg 2005). Both waist circumference and waist to hip ratio take account of visceral fat, and as visceral fat is related to adipokine release and

insulin resistance, these are therefore far more predictive of cardiovascular risk than BMI alone. Neck circumference has been found not only to predict OSA, but also to correlate with the metabolic disorders associated with insulin resistance and with the metabolic syndrome (Laakso 2002, Ben-Noun 2003). This suggests neck circumference is also a useful measure of visceral obesity.

It is imperative that studies of cardiovascular risk, insulin resistance, the metabolic syndrome, type 2 diabetes and obstructive sleep apnoea all have measures of visceral fat performed in order to control for this variable and the associated insulin resistance, which is a very important potential confounder. This is the reason why cross sectional studies looking at OSA as a predictor of cardiovascular and cerebrovascular disease using BMI may be seriously flawed, as these potential confounders have not been fully allowed for or controlled for.

Figure 5. *Abdominal slice computerised tomography scans of two patients. One (left) has high amounts of visceral fat and one (right) has high amounts of subcutaneous fat. The one with the high amounts of visceral fat is likely to have a disordered metabolic profile with insulin resistance as a consequence, whereas the one with high amounts of subcutaneous fat is unlikely to have similar metabolic disorders.*



1.2.8 Complications of diabetes

Diabetes is associated with micro and macrovascular disease, including retinopathy, nephropathy, neuropathy and accelerated atherosclerosis causing cardiovascular and cerebrovascular disease (Stratton 2000, Klein 1998). Cardiovascular morbidity in people with diabetes is two to four times greater than that of non-diabetic people (Zimmet 2001). It has recently been reported that diabetes confers an equivalent cardiovascular risk to aging ten years (Booth 2006). There is now substantial evidence that improved glycaemic control decreases the incidence of complications associated with diabetes and reduces the progression of retinopathy, nephropathy and microalbuminuria (Stratton 2000, Ohkubo 1995).

1.2.9 Management of type 2 diabetes

1.2.9.1 Weight loss and exercise

Prevention of type 2 diabetes is the ideal management, with diet and exercise having been consistently shown to reduce the incidence of diabetes in large scale randomised controlled trials (Pan 1997, Diabetes Prevention Program Research Group 2000, Tuomilehto 2001, Abuissa 2005, Lindstrom 2006). For patients who do develop type 2 diabetes, the initial treatment for it, and the associated insulin resistance, is still weight loss and increased physical activity, in those who are overweight or obese (National Clinical Guidelines for Type 2 Diabetes). Small amounts of weight loss can improve insulin sensitivity (the reciprocal of insulin resistance) (Park 2005). Exercise can also increase insulin sensitivity, with moderate exercise such as brisk walking being found to improve insulin sensitivity (Krotkiewski 1985). A low sugar diet is recommended to try and maintain normoglycaemia.

1.2.9.2 Monitoring blood glucose

Optimising blood glucose control is the major goal of management in established type 2 diabetes, in order to reduce the likelihood of the long term complications of diabetes. The UK Prospective Diabetes Study showed a 25% risk reduction in microvascular end points (p=0.001) in patients with better glucose control achieved through intensive therapy (with sulphonylurea medication or insulin, compared to diet alone), although macrovascular disease was no different between the two groups (UKPDS group, 1998). The effects of treatments for type 2 diabetes are monitored in two main ways. The patient can monitor their blood glucose levels at home daily, by means of a finger prick blood test and portable blood glucose monitor. Alternatively a venous blood sample can be sent to measure the glycosylated haemoglobin value (HbA1c) every 3-12 months. Five percent of circulating haemoglobin is glycosylated with glucose. Glycosyation is the reaction of glucose with free amino acid groups on proteins. The extent of glycosyation depends on the average glucose concentration the protein is exposed to. As the half life of haemoglobin is 60 days, the HbA1c levels reflect the prevailing blood glucose concentration over the previous one to two months. This is hence a surrogate measure of the average concentration of plasma glucose.

HbA1c levels have been found to correlate with microvascular and arterial risk in patients with diabetes (Stratton 2000). In type 2 diabetes, target levels are set between 6.5 and 7.5%, often with an increase or change in treatment if these are not being achieved (National Clinical Guidelines for Type 2 Diabetes). Lower target HbA1c levels are preferred for those people at significant risk of macrovascular complications, with higher targets necessary for those at risk of iatrogenic hypoglycaemia. A 10% decrease in HbA1c leads to a 24% risk reduction in retinopathy (Molyneaux 1998).

1.2.9.3 Drug treatment

1.2.9.3.1 Biguanides (Metformin)

Biguanides inhibit gluconeogenesis in the liver, reduce blood glucose levels and improve hepatic and peripheral tissue sensitivity to insulin, but have no direct effect on pancreatic beta cell function. Metformin should be used as the first line glucose lowering therapy in people who are overweight with a BMI of >25 kg/m^2, and whose blood glucose is inadequately controlled using lifestyle interventions alone. Metformin should also be considered as an option for first line or combination therapy for people who are not overweight. It can be used in combination with a sulphonylurea. Treatment decreases HbA1c by 1 to 2% (De Fronzo 1995, 1999). It is not associated with weight gain and it does not cause hypoglycaemia. It is contraindicated in those with renal impairment and those at risk of sudden deterioration in renal function, due to problems with lactic acidosis.

1.2.9.3.2 Insulin secretagogues (sulphonylureas and meglitinides)

Sulphonylureas (such as gliclazide, glibenclamide) enhance basal and postprandial pancreatic insulin secretion. They interact with ATP-sensitive potassium channels on functioning pancreatic beta cells and cause hypoglycaemia. They have no effect on tissue insulin sensitivity. They decrease HbA1c by 1-2% (De Fronzo 1999). They should be used in combination with metformin in overweight or obese people when glucose control becomes unsatisfactory, or as a first line therapy if metformin is contraindicated, or if people are not overweight. As a monotherapy, they will not achieve glycaemic control in 75% of people. There is a risk of hypoglycaemia, of which patients should be made aware; this is more profound with the older drugs, which have long half lives. They can also cause weight gain.

Repaglinide is a meglitinide, which is indicated as an adjunct to diet and exercise. It can cause hypoglycaemia and weight gain and is not widely used.

1.2.9.3.3 α-Glucosidase inhibitors

Acarbose is one of the α-glucosidase inhibitors, which delays absorption of complex carbohydrates and lowers post-prandial hyperglycaemia. It can be used alone, or in combination with metformin, a sulphonylurea or insulin. Hypoglycaemia can occur when it is used in combination. It typically decreases HbA1c by 0.5-1% (De Fronzo 1999). It is associated with flatulence, which deters some from using it.

1.2.9.3.4 Thiazolidinediones

Thiazolidinediones (such as rosiglitazone, pioglitazone) are a new group of tablets used in type 2 diabetes. They increase insulin sensitivity in peripheral organs and improve peripheral glucose disposal, leading to decreased insulin levels and a range of resultant effects: hyperglycaemia and glycosylated haemoglobin are reduced, dyslipidaemia and visceral fat distribution are improved, thrombotic potential is decreased and endothelial-dependent vascular response to insulin is enhanced (Reusch 2002). One placebo controlled study of pioglitazone studied glucose and HbA1c levels before and after twenty-six weeks of therapy: significant improvements in fasting plasma glucose with piolitazone were seen at two weeks, became maximal at ten to fourteen weeks, and were sustained until the end of the study (Aronoff 2000). HbA1c also significantly improved. Thiazolidinediones also appear to have anti-inflammatory effects, which may modify atherosclerosis (Aljada 2001). They act by binding to peroxisome proliferator-activated receptor γ receptors (PPARγ) sites in adipose tissue and this in turn leads to

transcription of the genes controlling the synthesis of proteins involved in regulating adipocytes, changing their expression (Dandona 2002). Levels of circulating plasma free fatty acids are reduced, and insulin mediated glucose uptake by the skeletal muscle is therefore improved. HbA1c is decreased by up to 1.5%, although obese patients may demonstrate greater reductions (Raskin 2001). They are well-tolerated drugs, with a low risk of hypoglycaemia. It is recommended that liver function tests are measured periodically, as one drug in this class, troglitazone, was withdrawn due to hepatotoxicity. A side effect of the group is weight gain, related to the effects of the drugs on adipose tissue differentiation and triglyceride storage. They are effective when administered alone, but may be combined with metformin or sulphonylureas for greater effect. Insulin is not given in combination with the thiazolidinediones, due to an increased risk of oedema and cardiac failure. Suitable patients are those with newly diagnosed diabetes with mild to moderate fasting hyperglycaemia, or obese patients with predominant central adiposity (Weissman 2002).

1.2.9.3.5 Insulin

Exogenous insulin is necessary when circulating levels of insulin are inadequate, and hyperglycaemia persists, despite optimal doses of other treatments (Weissman 2002). Insulin is often given in conjunction with oral insulin sensitizers. Insulin is associated with hyperglycaemia and weight gain. Many patients with type 2 diabetes will eventually require insulin therapy.

1.2.9.3.6 Other drug treatments

In addition, lipid lowering, anti-hypertensive and antiplatelet drugs are likely to be required to modify the cardiovascular risks associated with type 2 diabetes. Anti-obesity drugs may be considered as part of a weight loss strategy.

1.2.10 Measuring glucose and insulin levels in research studies

Quantification of insulin resistance is important in studies assessing the effects of different therapies in type 2 diabetes. It is difficult however, as it cannot be measured in isolation and requires assessment of multiple physiological variables, including the pancreatic beta cell response to glucose and the sensitivity of body tissues to insulin. Beta cell response is measured by changes in plasma insulin concentration to changing glucose levels. Surrogate markers of insulin resistance, such as waist circumference have been used, with a quoted waist circumference of <100cm in both sexes excluding insulin resistance in one study (Wahrenberg 2005). These crude measures may be useful in large population studies, but they are not sensitive enough to assess changes in insulin resistance following an intervention, in which weight has not been the target for change.

All blood tests to assess glucose and insulin resistance should be performed in patients after an overnight fast and they should not have taken any unaccustomed exercise for the preceding 24 hours. They should avoid alcohol and not smoke on the day of the test. Results will be abnormal if patient is concurrently unwell or has an infection, as raised glucose levels may occur in response to this stress. Corticosteroid drugs and diuretics can also impair glucose tolerance and give falsely raised results.

1.2.10.1 Insulin concentration in plasma

Raised insulin levels occurring in association with normal glucose levels in the fasting state suggest a state of insulin resistance, if the pancreatic beta cell function is normal. These may therefore be used as a crude measure of insulin resistance, for example in population studies. Measures of glucose concentration should also be made, in order to interpret the insulin concentration appropriately. There is a wide range of glucose concentrations in normal and diabetic subjects, and healthy individuals may also have a degree of insulin resistance. There may also be considerable inter-laboratory variation in insulin assays and proinsulin may cross react in assays with partially processed proinsulin, and hence overestimate the level of hyperinsulinaemia.

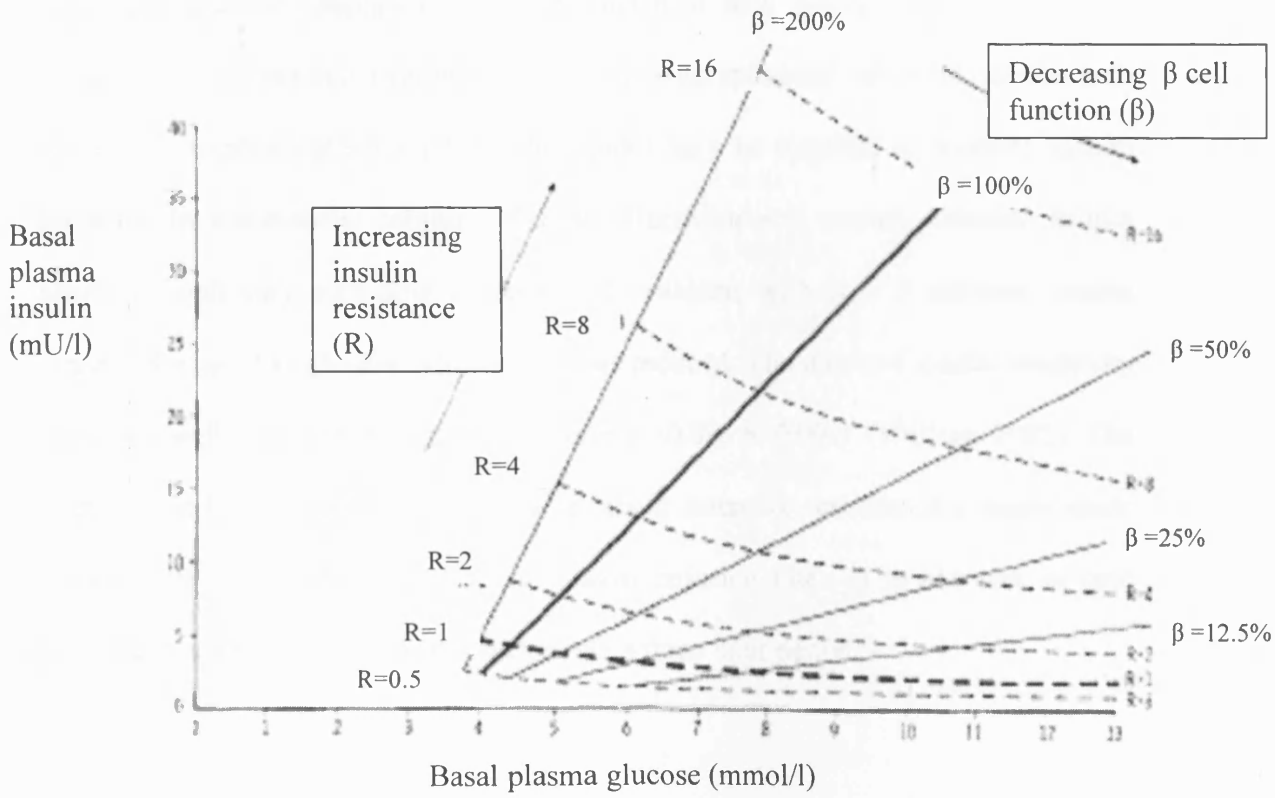
1.2.10.2 Model assessments of insulin resistance

1.2.10.2.1 Homeostatic model assessment (HOMA)

This was first described by Matthews et al in 1985 (Matthews 1985). Three fasting blood tests five minutes apart are taken, as basal insulin secretion is pulsatile every 3.8 minutes. The insulin and glucose values are inserted into a mathematical model and the evaluation of the concentrations of each in an individual allows an estimate of steady state beta cell function (%B) and relative insulin sensitivity (%S), as well as its reciprocal, insulin resistance (HOMA-IR) (Figure 6). The model estimates these values as percentages of a normal reference population. It gives a measure of basal (i.e. non-stimulated) insulin resistance. These figures correspond well with non-steady state estimates of beta cell function and insulin sensitivity derived from sensitivity models, such as the hyperinsulinaemic clamp, the hyperglycaemic clamp, the intravenous glucose tolerance test and the oral glucose tolerance test, although they are not necessarily equivalent to these. Correlation with the euglycaemic clamp is high (r=0.88,

p<0.0001) (Matthews 1985). The coefficient of variation (CV) for HOMA using specific insulin assays on large numbers of subjects is around 7.8 and 9.4% in diabetic and non-diabetic patients respectively (Bonora 2000). HOMA is useful for estimates of beta cell function and insulin resistance in large-scale epidemiological studies particularly, as it is simple, robust and can be used to assess changes in insulin resistance with time.

Figure 6. *Basal homeostatic model assessment (HOMA). Computer model predictions for the basal or fasting state in man. The grid shows the model prediction of the steady-state plasma glucose and insulin concentrations for a series of different beta cell functions (____) and insulin resistance values (----). Basal plasma glucose is on the x axis, and basal plasma insulin on the y axis. For any individual, fasting observations of plasma glucose and insulin may be centred on the grid and the estimated beta-cell function and insulin resistance obtained (Matthews 1985).*



1.2.10.2.2 Continuous infusion of glucose with model assessment (CIGMA)

This is a steady state mathematical model, in which a 60-minute low dose glucose infusion (5mg/kg ideal body weight/hr) is given, to stimulate endogenous insulin release, which is then measured at 50, 55 and 60 minutes (Hosker 1985). This test has not been widely used, although it appears to correlate well with the euglycaemic clamp ($r=0.87$, $p<0.0001$), but there is high day to day variability in the test, with a CV of 21%.

1.2.10.2.3 Frequently sampled intravenous glucose tolerance test (Minimal model of Bergman)

Based on the intravenous glucose tolerance test, this is a model assessment of glucose kinetics and insulin effects (Bergman 1989). Intravenous glucose is injected, followed by insulin, with frequent blood sampling to establish glucose and insulin levels and mathematically analyse these, in order to ascertain beta cell function and insulin resistance. Glucose concentrations are predicted at time points from the measured insulin levels and predicted values are compared with measured values. In patients with diabetes, a sulphonylurea (usually tolbutamide) may be required to promote insulin secretion. In non-diabetic subjects, glucose effectiveness is normal, although insulin sensitivity will vary according to obesity. In subjects with type 2 diabetes, insulin sensitivity as well as glucose effectiveness are reduced. The index of insulin sensitivity correlates well with the euglycaemic clamp ($r=0.89$, $p<0.001$) (Wallace 2002). The within subject CV is 20%. This is a less labour intensive test than the euglycaemic clamp, with no need for alteration in glucose infusion rates. It is however as time consuming, with 25 blood samples taken over a three hour period.

1.2.10.3 Clamp tests

These are highly reproducible physiological tests. They were first described by DeFronzo in 1979 and have been widely used since (DeFronzo 1979).

1.2.10.3.1 Euglycaemic clamp

The hyperinsulinaemic euglycaemic clamp is a method of quantifying tissue sensitivity to insulin. It is referred to as the "gold standard" method for the measurement of insulin resistance in a wide variety of circumstances (Wallace 2002). Other tests are evaluated against the euglycaemic clamp. It is usually performed in conjunction with a measurement of basal insulin secretion, such as HOMA (see 1.2.10.2.1), as the two tests are measuring different aspects of glucose uptake/metabolism. The plasma insulin concentration is raised by a fixed infusion rate, in order to inhibit hepatic glucose production. This infusion rate is calculated as a dose per unit of body surface area, rather than body weight, to avoid over-insulinisation of obese individuals. The investigator controls the plasma glucose, "clamping" it at a pre-determined level (for example, 6 mmol/l) by titration of a variable rate hypertonic glucose infusion. Blood glucose concentrations are checked every 3-5 minutes, with adjustment of the exogenous glucose infusion accordingly. The aim is to achieve steady state plasma glucose, when the glucose being infused is equivalent to that being metabolised. This may take several hours. At this point, the degree of insulin resistance can be calculated. The quantity of exogenous glucose required to maintain euglycaemia is a reflection of the net sensitivity of the target tissues to insulin (M). A reduced rate of insulin-mediated glucose disposal is regarded as being synonymous with insulin resistance. Hypoglycaemia should be avoided as this causes glucagon and sympathetic hormone secretion, and hyperglycaemia should be avoided as this results in increased urinary

glucose losses. Falling asleep or having excessive mental stimulation can affect the patient's glucose requirements and hence affect the results. This is a time-consuming and labour intensive test. It can be difficult to achieve steady state glucose levels. There is good intra-subject reproducibility, with a coefficient of variation (CV) of less than 5% (Bonora 2000), enabling repeat clamp testing after a therapeutic intervention, but the intersubject CV is 21% in normal volunteers and 46% in subjects with type 2 diabetes. This is particularly relevant to parallel or cross sectional studies.

1.2.10.3.2 Hyperglycaemic clamp

The hyperglycaemic clamp quantifies the beta cell secretory function and measures the amount of glucose metabolised by the body following a controlled hyperglycaemic stimulus. The early and late stages of insulin secretion can be examined also. Variable rate intravenous glucose is infused to "clamp" glucose levels at a predetermined hyperglycaemic level (for example, 12 mmol/l). Blood glucose concentrations are checked every 3-5 minutes, with adjustment of the exogenous glucose infusion accordingly. The glucose infusion rate is an index of glucose metabolism. There is an early burst of insulin release during the first six minutes, followed by a gradually increasing plasma insulin concentration. The plasma insulin response (I) to fixed hyperglycaemia is a measure of beta-cell response to glucose. Plasma insulin levels which are higher than predicted reflect insulin resistance.

1.2.10.4 Tests administering exogenous insulin

1.2.10.4.1 Insulin tolerance test

This is a simple test, in which a bolus of intravenous insulin is given, with blood sampling performed every two minutes for 15 minutes, after which the test is

terminated with a glucose bolus (Bonora 1989). The fall in blood glucose reflects the effect of the insulin on the liver and peripheral tissues. The log-linear decline of the glucose is plotted and insulin sensitivity is determined. If hypoglycaemia is induced, stress hormones are released which antagonise the insulin. The test has acceptable reproducibility, with a mean within subject CV of 13% and between subject CV of 26% in normal subjects (Wallace 2002).

1.2.10.4.2 Insulin sensitivity test

An intravenous infusion of fixed amounts of somatostatin, insulin and glucose is administered to the patient continuously over 150-180 minutes (Shen 1970, Harano 1977). The somatostatin suppresses hepatic insulin production and the insulin suppresses hepatic glucose production. Blood is measured every 30 minutes over a two hour period. The steady state plasma glucose concentration, derived from the last 30 minutes of the test, reflects the sensitivity of the tissues to insulin, with higher glucose levels reflecting lower insulin sensitivities (Yeni-Komshian 2000). Glucose clearance can be calculated by dividing the exogenous infusion rate by the steady state plasma glucose concentration. The metabolic clearance rate derived correlates well with that of the euglycaemic clamp (r=0.9) (Wallace 2002). It is a less labour intensive test than the clamp.

1.2.10.5 Oral glucose tolerance test (OGTT)

This is often used to establish a diagnosis of diabetes mellitus or of impaired glucose tolerance, for example in gestational diabetes. It has a possible role in the estimation of insulin resistance (Pontiroli 2004). The patient is given a 75g oral glucose load. Blood tests are performed before the glucose load and at 30-minute intervals afterwards for two hours. A normal response sees a rise in blood glucose at 30 minutes, which then

begins to fall by one hour. In patients with diabetes, there is a large rise in blood glucose at 30 minutes, which continues until 60 minutes and only slowly comes down after this. A two hour glucose level of 11.1mmol/l or greater is diagnostic of diabetes. The logarithm of the two hour plasma insulin has been shown to correlate with the hyperglycaemic clamp ($r = -0.67$, $p<0.05$), but has not been widely used (Wallace 2002).

1.3 The interrelation of obstructive sleep apnoea and type 2 diabetes

1.3.1 Overlap of OSA and type 2 diabetes

Both OSA and type 2 diabetes are conditions associated with obesity. The prevalence of each condition is increasing as the population level of obesity increases. It is therefore to be expected that the two conditions will overlap, with patients with OSA having type 2 diabetes and patients with type 2 diabetes having OSA. Increasing evidence points towards the association of OSA with fasting hyperglycaemia, insulin resistance and type 2 diabetes. Studies have sought to determine whether either disease is causative in the development of the other. These will be discussed further below.

1.3.2 Relationship of insulin resistance with OSA

There has been much interest over the past few years in the relationship of insulin resistance to sleep disordered breathing and OSA. In a small study of 50 people, insulin resistance and body mass were measured and polysomnography performed (Stoohs 1996). Insulin resistance increased as the breathing disturbance index increased in those with sleep disordered breathing After adjustment for potential confounding variables, however, it was found that the relationship was based entirely on body mass. This led to thinking that there was a common causal association of obesity in OSA with insulin resistance. Other work sought to establish a link between OSA and insulin resistance, independent of obesity. Tassone et al studied 30 obese people with OSA, 27 weight matched people without OSA and 15 normal weight subjects (Tassone 2003). He found that the insulin sensitivity index was significantly lower in those patients with OSA ($p<0.0001$), even after age, BMI and waist to hip ratio adjustment ($p<0.01$), suggesting OSA caused additional insulin resistance to that from obesity alone. As has been

discussed earlier (section 1.2.7.1), BMI matching alone is probably inadequate for the all important measure of visceral obesity, and this therefore may have accounted for the differences in insulin resistance between the two studies.

Two large population studies in Baltimore and Hong Kong, have been fundamental to our knowledge in this area. In Baltimore, 150 mildly obese healthy men were recruited via advert to have polysomnography, body composition measures (BMI, waist to hip ratio, hydrodensitometry) and HOMA performed (Punjabi 2002). It was found that an AHI of more than five/hour was associated with an increased risk of worsening glucose tolerance test, after adjustment for percentage body fat. If the population studied was stratified according to the severity of their AHI, it was found that insulin resistance significantly increased with increasing AHI ($p<0.05$). The impairment in glucose tolerance was also related to the severity of oxygen desaturation. These effects were independent of obesity, when adjusted for on multiple linear regression models. In Hong Kong, 270 people (197 men) were recruited via the sleep clinic and had polysomnography, body composition measures (BMI, waist circumference, waist to hip ratio) and HOMA tests performed (Ip 2002). Those people found to have OSA (AHI>5/hour) were significantly more insulin resistant than those without OSA ($p<0.001$). Obesity was the major determinant of insulin resistance, but when it was controlled for in regression models (using both BMI and waist to hip ratio), the AHI and minimal oxygen levels were still significant determinants of insulin resistance. The use of waist to hip ratio in both of these studies represents a measure of visceral obesity, which is essential. The Baltimore study however did not find waist to hip ratio significantly improved linear regression model prediction once BMI and percentage body fat had been allowed for (Punjabi 2001).

The mechanism for the insulin resistance found in association with OSA is not known. It is hypothesised that the cycles of intermittent hypoxia, sleep fragmentation and arousals in OSA cause catecholamine release, which may lead to a state of glucose intolerance initially and later insulin resistance (Punjabi 2003). Cortisol released in response to the catecholamine release may cause changes in glucose metabolism, with a raised fasting glucose. The sleep deprivation also found in OSA may cause impaired glucose tolerance, as it has been found that minimal sleep deprivation in a small study of 11 healthy young men, of four hours per night for six nights, was associated with impaired glucose tolerance ($p<0.02$), which reverted to normal when normal sleep was resumed (Spiegel 1999). Sympathetic nervous system activation was also increased with the sleep deprivation and evening cortisol levels were raised.

1.3.3 Prevalence of type 2 diabetes in OSA

It is recognised that there is a high prevalence of impaired glucose tolerance and type 2 diabetes in patients with OSA. In one study, all men with a BMI <40kg/m^2 who were referred for sleep studies for possible OSA had a glucose tolerance test performed. Fifty percent of those with newly diagnosed OSA were found to have either type 2 diabetes or impaired glucose tolerance, compared to 28% of non-OSA unmatched patients (Meslier 2003). Another study sought to investigate the prevalence of type 2 diabetes in patients with sleep disordered breathing and to establish whether an independent relationship existed between them (Reichmuth 2005). One thousand three hundred and eighty seven participants from the Wisconsin Sleep Cohort had polysomnography and assessment of whether they had type 2 diabetes: either by physician-diagnosis or by fasting blood glucose. The cumulative prevalence of type 2 diabetes in the sample was 4.2%. There was a greater prevalence of diabetes in subjects with increasing levels of

sleep disordered breathing. Fifteen percent of subjects with an AHI ≥ 15 had a diagnosis of diabetes, compared to 2.8% of subjects with an AHI <5. Following adjustment for body habitus (using waist circumference), the odds ratio for having diabetes was only significant in those with an AHI ≥ 15 (OR 2.30, 95% CI 1.28-4.11, p=0.005). No statistically significant independent causal effect in the development of type 2 diabetes was found, but had other measures of visceral obesity been used, such as waist to hip ratio, these results may have been different.

1.3.4 Effect of OSA/sleep disordered breathing on glucose metabolism

Insulin resistance is the precursor to type 2 diabetes, and OSA appears to be associated with insulin resistance; it has been questioned therefore whether OSA itself might be an independent risk factor for developing diabetes. Elmasry et al studied a cohort of 2668 men by means of a postal questionnaire on two occasions, 10 years apart (Elmasry 2000). Questions were asked regarding habitual snoring and whether the respondent had diabetes. Habitual snorers had a significantly higher prevalence of diabetes on both occasions. The incidence of new diabetes after 10 years was higher amongst habitual snorers (p<0.001). Multiple logistic regression analysis to determine the risk factors for the development of diabetes over the 10 year period showed obesity alone (measured by self reported BMI) and obesity with habitual snoring were independently associated with the development of diabetes. Habitual snoring without obesity was not a risk factor for the development of diabetes. The authors concluded that men who habitually snore have a more than twofold higher incidence of diabetes than non-habitual snorers in the same age group, with the risk largely attributable to obesity. A similar study sent two questionnaires 10 years apart to 69,852 female nurses in the USA asking about snoring patterns and development of diabetes, as well as self-reported BMI and waist and hip

measurements (Al Delaimy 2002). Following adjustment for age and body mass index in a multivariate analysis, snoring was independently associated with elevated risk of type 2 diabetes ($p<0.0001$). Further adjustment for waist to hip ratio as well as BMI and age slightly attenuated the risk of diabetes among regular snorers, but it remained significant compared to occasional snorers. This demonstrates the importance of using a measure of central obesity in any study examining the risk of a variable associated with visceral fat. These studies appear to suggest that diabetes is more likely to occur in people who habitually snore, due to the insulin resistance caused presumably by untreated OSA.

Obesity and body fat distribution are significant confounders in studies of type 2 diabetes and obstructive sleep apnoea and it is therefore often difficult to determine whether the sleep apnoea itself causes insulin resistance and diabetes independent of obesity, or whether obesity is the main mediating factor. These studies do however raise the concept of OSA exerting a possible causal effect on the impairment of glucose and insulin homeostasis, predisposing to type 2 diabetes.

1.3.5 Prevalence of the metabolic syndrome in OSA

OSA has been found to be independently associated with the metabolic syndrome in one study (Coughlin 2004). Sixty-one men with newly diagnosed OSA and 43 unmatched controls had their body composition, blood pressure, fasting glucose, lipids and insulin resistance measured, along with polysomnography. Eighty seven percent of those with OSA were diagnosed with the metabolic syndrome (determined on National Cholesterol Education Programme criteria), compared to 35% of the controls ($p<0.0001$). Following regression analysis controlling for BMI, it was determined that

metabolic syndrome was nine times more likely to be present in subjects with OSA. This was the first time the clustering of risk factors found in the metabolic syndrome were studied together in association with OSA, raising the question of whether OSA promotes components of the metabolic syndrome via recurrent hypoxia or whether OSA should be regarded as another component of the metabolic syndrome (Wilcox 1998, Vgontzas 2005). Specific effects of OSA may further increase the cardiovascular consequences of people with metabolic syndrome.

1.3.6 Prevalence of OSA in type 2 diabetes

The prevalence of OSA in patients with established type 2 diabetes has not been studied previously. It has been established in two studies that OSA is commoner in patients with diabetes with associated autonomic neuropathy. One of these studies found 6 out of 23 patients (26%) with autonomic neuropathy had OSA and none of the 25 patients without autonomic neuropathy had OSA (Ficker 1998). OSA was defined as an apnoea-hypopnoea index of $\geq$10/hour. Autonomic neuropathy was determined by screening using a computer system, measuring heart rate variation supine and standing. In the other study of 26 non-obese people with diabetes, autonomic neuropathy was found to increase the likelihood of OSA, independent of the severity of neuropathy (Bottini 2003). Possible mechanisms causing OSA to occur with autonomic neuropathy are dilator muscle neuropathy in the pharynx, leading to upper airway collapse; or problems in controlling the upper airway muscles at the level of the brainstem, due to abnormalities in autonomic regulation. No larger studies have been performed to further investigate this.

1.3.7 Effect of CPAP treatment on insulin resistance and OSA

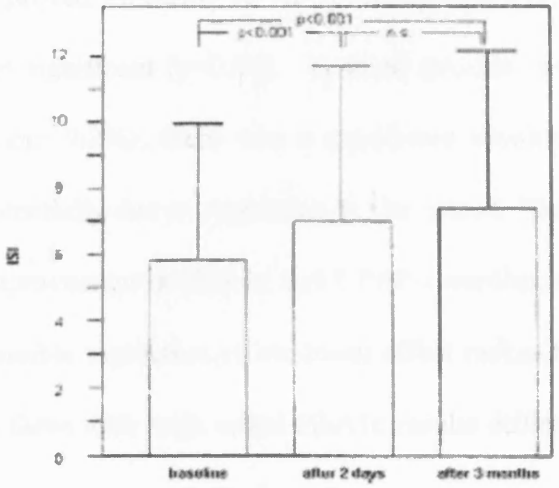
There have been several small studies to date which have assessed whether insulin resistance or glycaemic control in type 2 diabetes is improved by CPAP treatment in patients with OSA. The studies are discussed below, but have different findings. Different methods of measuring insulin resistance were used, with not all using the euglycaemic clamp, making the results of the studies difficult to compare. The studies have used small numbers of patients, and data on CPAP compliance is lacking, which makes conclusions difficult to draw. Also, none of the studies have used a control group. Insulin resistance is subject to change by many variables, including weight loss, body fat distribution and exercise, making a control group essential. A control group is also crucial to allow the significance of positive results to be interpreted. CPAP treatment is a physical therapy and therefore will have a placebo effect. Placebo CPAP has been found to improve subjective sleepiness and quality of life scores (Jenkinson 1999). Therapeutic CPAP not only improves daytime sleepiness, but can have other associated effects, for example, improving activity due to loss of fatigue, and these may influence study results. The effect of being in a study leads to changes in behaviour which can influence results. Regression to the mean can affect result interpretation. A control group is mandatory with any studies of this kind.

1.3.7.1 Studies showing insulin resistance or glycaemia is improved by CPAP

Harsch *et al* in Germany have performed two uncontrolled studies looking at the effect of CPAP on insulin resistance. In the first, 40 patients with OSA, but not with diabetes, had a euglycaemic clamp performed before commencing CPAP, following two nights of CPAP therapy and again after three months of CPAP (Harsch 2004). They found mean insulin resistance was significantly improved at two days (from 5.75 ± 4.20 to

6.79 ± 4.91 μmol/kg.min, p=0.003). They studied 31 of these patients at three months, and found no further improvement in insulin resistance, but the changes were sustained, and were statistically significantly different from baseline values (from 5.75 ± 4.20 to 7.54 ± 4.84 μmol/kg.min, p <0.001) (Figure 7). There were no significant changes in BMI or body fat mass (measured by bioimpedance) during the three months of CPAP, but activity levels were not assessed. There was no correlation between improvement in insulin resistance and CPAP compliance, which is surprising as one would expect the greater the treatment of apnoeas and the associated catecholamine release, the greater the improvement in insulin resistance, if this is the mechanism. Mean BMI was 32.7 kg/m^2. In patients with a BMI of more than 30 kg/m^2, there was no significant change in insulin resistance at two days, but the change of insulin resistance at three months was significant when compared to baseline. Lower obesity levels were the main predictor of an improvement in insulin sensitivity following CPAP, with the people with BMI < 30 kg/m^2 having a significantly greater improvement in insulin sensitivity at all time points. They postulated that changes in sympathetic hormone activation following successful CPAP treatment may be responsible for the change in insulin resistance after two days, but changes in visceral fat distribution due to lifestyle changes may have contributed to the changes in insulin resistance seen at three months. The need for a control group is hence emphasised.

Figure 7. *Improvement in the insulin sensitivity index at baseline, 2 days and 3 months after onset of CPAP treatment in 32 patients. The insulin sensitivity index (ISI) is given in µmol/kg.min (Harsch 2004).*



In their second uncontrolled study, nine patients with type 2 diabetes (controlled by diet or tablets) and OSA had a euglycaemic clamp performed before commencing CPAP, following two nights of CPAP therapy and again after three months of CPAP (Harsch 2004). Insulin resistance was unchanged after two days of CPAP treatment, but was significantly improved after three months ($p=0.02$). The improvement in insulin resistance was greater in those patients with lower BMI than in more obese patients. There were no significant changes in body weight or body fat mass (measured by bioimpedance) during the three months of CPAP. The mean BMI of participants was 37.3 kg/m^2.

Babu *et al* in Chicago studied 25 patients with type 2 diabetes (insulin, tablet or diet controlled) and OSA (Babu 2005). Seventy two hour continuous glucose monitoring was performed before and after a mean of 83 days of CPAP treatment, and again there

were no controls. The continuous glucose monitoring system is a device which measures interstitial glucose subcutaneously, every five minutes, providing 288 glucose levels per day. Seventy two hour continuous glucose monitoring was significantly improved following CPAP (p=0.05). Mean HbA1c fell from 8.3 to 7.9%, but this was not significant (p=0.06). In those patients with an initial HbA1c of greater than 7% (mean 9.2%), there was a significant absolute reduction of 0.6% (to 8.6%, p=0.02, potentially due to regression to the mean). There was a significant correlation between improvement in HbA1c and CPAP compliance of more than four hours per night. The possible regression to the mean effect makes the statistically significant fall in HbA1c in those with high initial HbA1c results difficult to deem clinically significant without comparison to a control group.

1.3.7.2 Studies showing insulin resistance is not improved by CPAP

Brooks *et al* in Sydney studied 10 patients with type 2 diabetes (insulin, tablet or diet controlled) and OSA (Brooks 1994). She performed euglycaemic clamps before and four months after CPAP treatment, but had no control group. Insulin resistance was improved by 28%, but this was not significant (p=0.06). BMI was not significantly changed during the study period. The mean BMI of participants was 42.7 kg/m^2. The exclusion of one of the study participants who was non compliant with CPAP treatment meant the results became statistically significant.

Saarelainen *et al* from Finland studied 10 people with OSA and normal glucose (no controls) (Saarelainen 1997). A euglycaemic clamp was performed before and after three months of CPAP treatment. Completion data was available on seven patients, which showed the insulin resistance was unchanged.

Smurra *et al* from France studied 10 people with glucose intolerance found to have sleep disordered breathing and six people with sleep disordered breathing without glucose intolerance (Smurra 2001). The 10 patients with glucose intolerance had an oral glucose tolerance test (GTT) performed before and after two months of CPAP therapy, and the six patients without glucose intolerance had a euglycaemic clamp performed at the same time intervals. Both the GTT and the clamp were not significantly changed after three months.

In a case control study, Davies *et al* from Oxford studied 15 men with OSA, 18 men who snored and 33 sex, age, BMI and smoking and drinking habit matched controls (Davies 1994). Each patient had fasting insulin measured at baseline and after three months. In those with OSA, CPAP was commenced after baseline blood tests. There was no difference in insulin levels between patients with OSA, snorers or controls and there was no significant difference in the three month insulin results, including those being performed after CPAP. It may be that insulin levels alone were not sensitive enough to demonstrate a difference in insulin resistance between the groups.

Punjabi *et al* reviewed nine studies of the effect of CPAP on glucose tolerance and /or insulin resistance in sleep disordered breathing, including those studies listed here. The studies had between five and 31 participants. Eight of the studies, all in patients without diabetes, did not produce any significant improvement in insulin or glucose measures (Punjabi 2003).

1.3.8 Summary

OSA is common in the general population, with a strong causal relationship with obesity. It is associated with daytime sleepiness, poor vigilance, decreased quality of life and hypertension, all of which can be improved with CPAP treatment. Type 2 diabetes is a condition of disordered glucose metabolism and insulin resistance caused by obesity. Insulin resistance also occurs alongside OSA, partly independent of obesity (simply measured by BMI and neck circumference) and correlates with the severity of the OSA. It certainly seems therefore that OSA can be viewed potentially as a contributor to the metabolic syndrome. It is not yet clear whether CPAP improves the metabolic indices of glucose and insulin resistance.

Chapter 2

Questionnaire survey of men with type 2 diabetes to assess the risk and prevalence of obstructive sleep apnoea and its correlation with glycaemic control

CHAPTER 2

Questionnaire survey of men with type 2 diabetes to assess the risk and prevalence of obstructive sleep apnoea and its correlation with glycaemic control

2.1 Introduction

As there is a causal relationship of both OSA and type 2 diabetes with central or visceral obesity, it is expected that there must be a significant overlap between these two conditions. The likely risk of OSA and its prevalence amongst patients with type 2 diabetes has not been investigated previously. We hypothesised that the risk of OSA would be higher amongst men with type 2 diabetes than men in the general population because of their levels of central obesity and that those men at high risk of OSA would have higher HbA1c levels, as the sleep disordered breathing would be associated with poorer diabetic control. We therefore performed a study in men with known type 2 diabetes, to establish the likely risk of OSA in this population by means of a screening questionnaire. Risk of OSA was used as a surrogate for prevalence. We also sought to establish whether there was any correlation of risk of OSA with diabetic control, measured by the glycosylated haemoglobin (HbA1c).

2.2 Methods

2.2.1 Subjects

All men with type 2 diabetes, aged 18-75, on the databases of a tertiary specialist hospital centre (the Oxford Centre for Diabetes, Endocrinology and Metabolism), and five local primary care centres (non-specialist, family doctor), were sent a questionnaire and an explanatory letter about the study. The letters were sent from either the diabetes

centre or their primary care practitioner on our behalf, explaining the nature of the study and what their involvement would entail (see Figure 1, Appendix 1). Type 2 diabetes was a primary care practitioner diagnosis, based on raised fasting blood glucose levels ≥7.0 mmol/l or a two hour glucose of 11.1 mmol/l following a glucose tolerance test. The questionnaires asked for permission from the subjects to have their results passed to the Oxford Sleep Unit. There was some overlap, with some subjects on both databases. A second letter and questionnaire was sent to those who did not respond. The response rate of the questionnaire was optimised using information from a systematic review designed to increase response rates to postal questionnaires (Edwards 2002). This study found that shorter questionnaires, personalised questionnaires and letters, stamped return envelopes, follow up contact and providing non-respondents with a second copy of the questionnaire, all increased the odds of a response. The majority of subjects lived in Oxfordshire, although some people from the hospital database were from other local counties. The study was approved by the local ethics committee (C03.091).

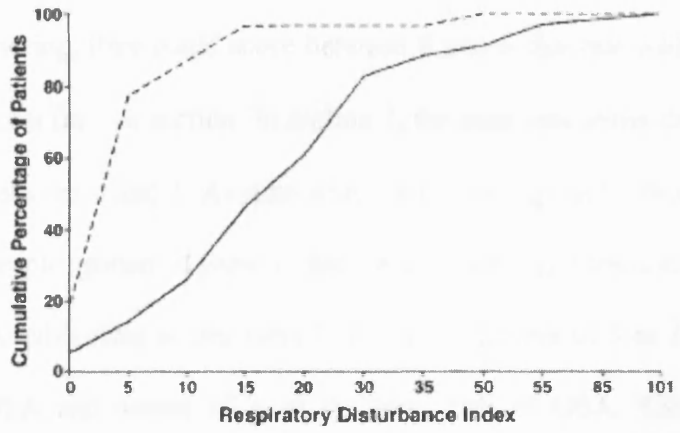
2.2.2 Questionnaire

The questionnaire is shown in Figure 2, Appendix 1. It asked demographic questions: age, height and weight (so that body mass index could be calculated) and neck size (for this a tape measure was included with instructions for the respondents on how to measure their necks, just below their larynx) to give information regarding upper body obesity. Information was asked for regarding duration of diabetes and whether they were diet, oral hypoglycaemic, or insulin treated. They were also asked whether they had previously been diagnosed with OSA and if so, whether they were receiving any treatment for this.

The questionnaire contained questions regarding symptoms associated with obstructive sleep apnoea. These questions were those in the Berlin questionnaire, a questionnaire designed to screen for OSA, by determining whether people were 'high' or 'low' risk for OSA, according to their answers. The Berlin questionnaire was published by Netzer *et al* in 1999 (Netzer 1999). Sleep and primary care physicians selected a series of questions to predict the likelihood of OSA. In the questionnaires, five questions are asked about snoring, volume of snoring and witnessed apnoeas and three about daytime sleepiness, including one about sleepiness behind the wheel. There are also questions regarding body weight, height and history of hypertension. In the paper first published regarding the use of the Berlin questionnaire, it was given to 1008 consecutive unselected people attending primary care centres in Cleveland, Ohio, USA (Netzer 1999). Of the 744 respondents, 44.5% of men and 33% of women scored as being 'high' risk of OSA. The 'high' risk subjects were more likely to have a higher body mass index, to be male, to have a history of hypertension, to snore loudly and have observed apnoeas, to have gained weight recently, to be tired during waketime and to fall asleep at the wheel. Thirteen percent of questionnaire respondents went on to have multichannel sleep studies performed with a home sleep monitor in order to validate the results. People with RDIs of five and above per hour met the criteria for obstructive sleep apnoea-hypopnoea syndrome. The mean respiratory disturbance index (RDI) of subjects in the 'high' risk group was 21.1 +/-18.5 (range 0-101) per hour, with a mean oxygen desaturation index of 19.4 +/-19.5 (range 50-97). The mean RDI in the 'low' risk group was 4.7 +/-7.0 (range 0-37) per hour, with a mean oxygen desaturation index of 5.9 +/- 7.6 (range 0 to 35). There was a significant difference in the RDI between the groups ($p<0.001$) (Figure 1). Risk grouping resulted in a post-test probability of 85% for both high and low risk groups. The fact that the features used in the Berlin

questionnaire as an OSA screening tool have been rigorously evaluated added weight to its usefulness for our purposes. We decided that this would be a good questionnaire to use for screening our study population of men with type 2 diabetes.

Figure 8. *The respiratory disturbance index in a subset (13%) of 744 Berlin questionnaire respondents. The cumulative distribution of the respiratory disturbance index for patients at high risk (n=69; solid line) and those at lower risk (n=31; dashed line) for sleep apnoea is shown. The groups differed significantly (p<0.001) (Netzer 1999).*



We omitted one question from the original Berlin questionnaire, namely "Have you ever nodded off or fallen asleep while driving a vehicle?" We performed two previous community studies several years apart to investigate predictors of OSA and nocturnal blood pressure falls (Stradling 1991, 2000). A marked change was noted in the answers given to questions regarding sleepiness when driving between the two studies, thought to be due to increased population awareness of the dangers of sleepiness whilst driving, which perhaps decreased their willingness to admit to this in the later study. We

therefore thought that this question was unlikely to be answered accurately, could deter some respondents from answering the questionnaire at all and hence bias results.

2.2.2.1 Scoring the questionnaire

Questionnaires were returned to the study investigators, who manually scored them as per the Berlin scoring criteria (see Figure 3, Appendix 1). Responses to the three symptom categories (snoring and apnoeas, daytime fatigue, hypertension or body mass index of greater than 30kg/m^2) determined whether subjects were 'high' or 'low' risk for OSA. If a patient answered "yes", or answered in the top two categories to two or more questions in a section, they gained one point. In section 1, the questions about snoring, they could score between 0 and 5. Anyone with a score of 2 or more gained a point for that section. In section 2, the questions about daytime fatigue, they could score between 0 and 2. Anyone with a score of 2 gained a point for that section. In section 3, people gained a point if they either had hypertension or had a BMI of >30mg/kg^2. Possible final scores were 3, 2, 1 or 0. Scores of 3 or 2 were counted as 'high' risk of OSA and scores of 1 or 0, 'low' risk of OSA. The omission of the question on sleepiness whilst driving did not alter the scoring, which was comparable to that used previously. This question on driving was only one of six questions in section one of the original questionnaire, and its omission therefore made it potentially harder for people to score two points in section one in our questionairre, hence leading to a possible underestimation of men at 'high' risk for OSA. In reality it seems unlikely that men would have answered that they were sleepy when driving and not answered affirmatively to at least two of the other questions, so underestimation of OSA risk is unlikely to have been a major issue in this study.

2.2.2.2 Other clinical prediction models for OSA evaluated

Other studies have been performed to determine whether people with OSA have clinical features which would allow them to be accurately identified, when compared to people without OSA. This screening could then be used to try and prioritise investigation with sleep studies in those likely to have OSA and obviate the need for investigation in those unlikely to have OSA. The Berlin questionnaire is just one of these studies, which was clearly questionnaire based. We chose to use it after evaluating other published studies in this area. Some of these are described briefly here.

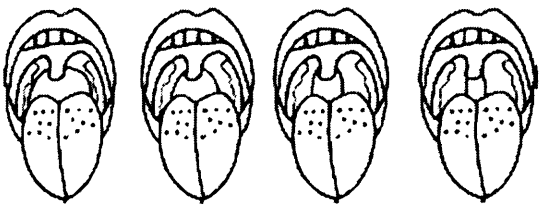
Flemons et al used multiple linear and logistic regression models to determine which features of patients' histories in patients referred for sleep studies predicted a high likelihood of OSA (Flemons 1994). Using a 36 question seven item Likert response questionnaire asking how frequently patients experienced various symptoms, along with polysomnography of 200 patients seen in their sleep clinic, they identified increased neck circumference, hypertension, habitual snoring and bed partner reports of nocturnal gasping/choking respirations. A sleep apnoea clinical score of less than 5 had a likelihood ratio of 0.25 (95% CI: 0.15 to 0.42) and a corresponding post test probability of 17%, while a score of greater than 15 had a likelihood ratio of 5.17 (95% CI: 2.54 to 10.51) and post test probability of 81%. They proposed clinical prediction rules to generate a sleep apnoea clinical score, in order to prioritise patients for further investigation of OSA.

Rodsutti et al evaluated 837 patients referred for polysomnography for suspected OSA (Rodsutti 2004). Increasing age, male sex, BMI >25kg/m^2, snoring and apnoeas were significantly associated with OSA, defined as an apnoea hypopnoea index of >5. They developed a scoring scheme based on regression coefficients, allowing patients to be

stratified into high, moderate or low risk of OSA, with prevalence figures of 82%, 51% and 8% respectively.

Further work from Flemons' group identified age, snoring, apnoeas and hypertension as predictive of OSA in a further group of 75 patients referred for assessment for OSA (Tsai 2003). They also identified three physical examination based predictors: a cricomental space of 1.5cm or less, a pharyngeal grade of more than two (Figure 2) and the presence of overbite. In patients with all three of these predictors, there was a positive predictive value of 95% and a negative predictive value of 49%, giving a simple and reliable possible tool for predicting OSA in patients referred to a unit. We did not seek to use any of these factors in our questionnaire, as it was being conducted by post, with no clinical interaction.

Figure 9. *Pharyngeal grading system. Class I = palatopharyngeal arch intersects at the edge of the tongue. Class II = palatopharyngeal arch intersects at 25% or more of tongue diameter. Class III = palatopharyngeal arch intersects at 50% or more of tongue diameter. Class IV = palatopharyngeal arch intersects at 75% or more of tongue diameter (Tsai 2003).*



In another study, four different clinical prediction models were evaluated and their usefulness assessed regarding the diagnosis of OSA in patients referred to a sleep centre for assessment (Rowley 2000). They did not however find the clinical prediction models tested were sufficiently accurate to discriminate between patients with or without OSA, although they may have a role in prioritising patients for investigation.

Clearly, the work already performed in this area highlighted that no prediction model, questionnaire or physical examination features were sufficiently sensitive or specific to diagnose OSA without further investigation, although it did seem possible to either ascribe people to risk groups or priority groups based on their scores in any of these models. We chose to use the Berlin questionnaire for the purposes of this study. We included a measurement of neck circumference to gain more information about the upper body obesity of respondents, as this was indicated as a useful predictor in one of the studies above (Flemons 1994), but as this was not in the original Berlin questionnaire, it was not used to define high/low risk status. It was used to define the population characteristics and to allow comparison of this population with a previously studied population (see Chapter 4).

2.2.3 Glycosylated haemoglobin

The most recent glycosylated haemoglobin (HbA1c) result was recorded for all questionnaire respondents. This was obtained by either accessing the hospital pathology database, or by contacting the primary care practitioner. Subjects who did not have an HbA1c result recorded within three months of completing their questionnaire were contacted to ask if they would have this performed.

2.2.4 Analysis

All the results were entered onto a spreadsheet, from which statistical analysis was carried out using SPSS version 12.0. Data are expressed as mean (standard deviation, 0-100% range). Comparison of multiple groups was performed with one-way analysis of variance (ANOVA), with Duncan's multiple ranging for post hoc analysis. This explores which groups are different to which, within a dataset with more than two groups being compared. Differences between the 'high' and 'low' risk groups, and the two different study populations (hospital vs. primary care), were assessed with unpaired t-tests and chi-square when comparing proportions. Data were tested for normal distribution with the Shapiro-Wilk test of normality and where the data were shown to be not normally distributed, analysis was repeated using non-parametric tests (Kruskal-Wallis if there were more than two groups and Mann-Whitney to compare two independent groups).

2.3 Results

2.3.1 Questionnaire response rate

Questionnaires were sent to a total of 1433 men from the Oxford Centre for Diabetes, Endocrinology and Metabolism database and to 243 men from primary care databases (1676 men total). Sixty-five men were on both databases, but they were only contacted from the hospital centre. The population of Oxfordshire is of mixed ethnicity, but is predominantly Caucasian. There were 793 replies in total from the hospital database (55%) and 145 from the primary care databases (60%), representing a 56% overall response rate (Figure 3). Sixty-three percent of the hospital database replies and 45% of the primary care database replies were received after the first mailing. In a few cases, whole sections of the questionnaire had been left blank. These were returned to the person concerned, asking them to complete the missing sections. Some of these were not then sent back to us. There were no data available on men who did not respond to the questionnaire, so we were unable to classify these non-responders.

2.3.2 Questionnaire responses: demographics and diabetes

Table 1 shows the physical characteristics of the questionnaire respondents. The hospital and primary care database groups did not differ in their characteristics, other than the mean duration of diabetes and the treatment taken for this. This was not an unexpected difference between the two groups, as the hospital database is likely to reflect those with more severe disease, who have been referred for specialist consultant diabetes input. All the data collected from the questionnaires, with the hospital and primary care groups combined, are shown in Table 1, Appendix 2.

Table 1. Physical characteristics (Mean (SD)) of the questionnaire respondents.

	Hospital database N = 793	**Primary care database N = 145**
Age (years)	61.0 (9.9)	62.2 (8.6)
BMI (kg/m^2)	29.7 (5.4)	29.3 (5.3)
Neck size (cm)	42.9 (2.9)	42.9 (1.2)
Duration of diabetes (years)	12.0 (8.5)	7.0 (6.8)
Treatment with:		
Insulin	32%	4%
Insulin & oral hypoglycaemics	22%	4%
Oral hypoglycaemics	41%	77%
Diet alone	5%	14%
HbA1c (%)	8.4 (1.6)	7.9 (1.6)

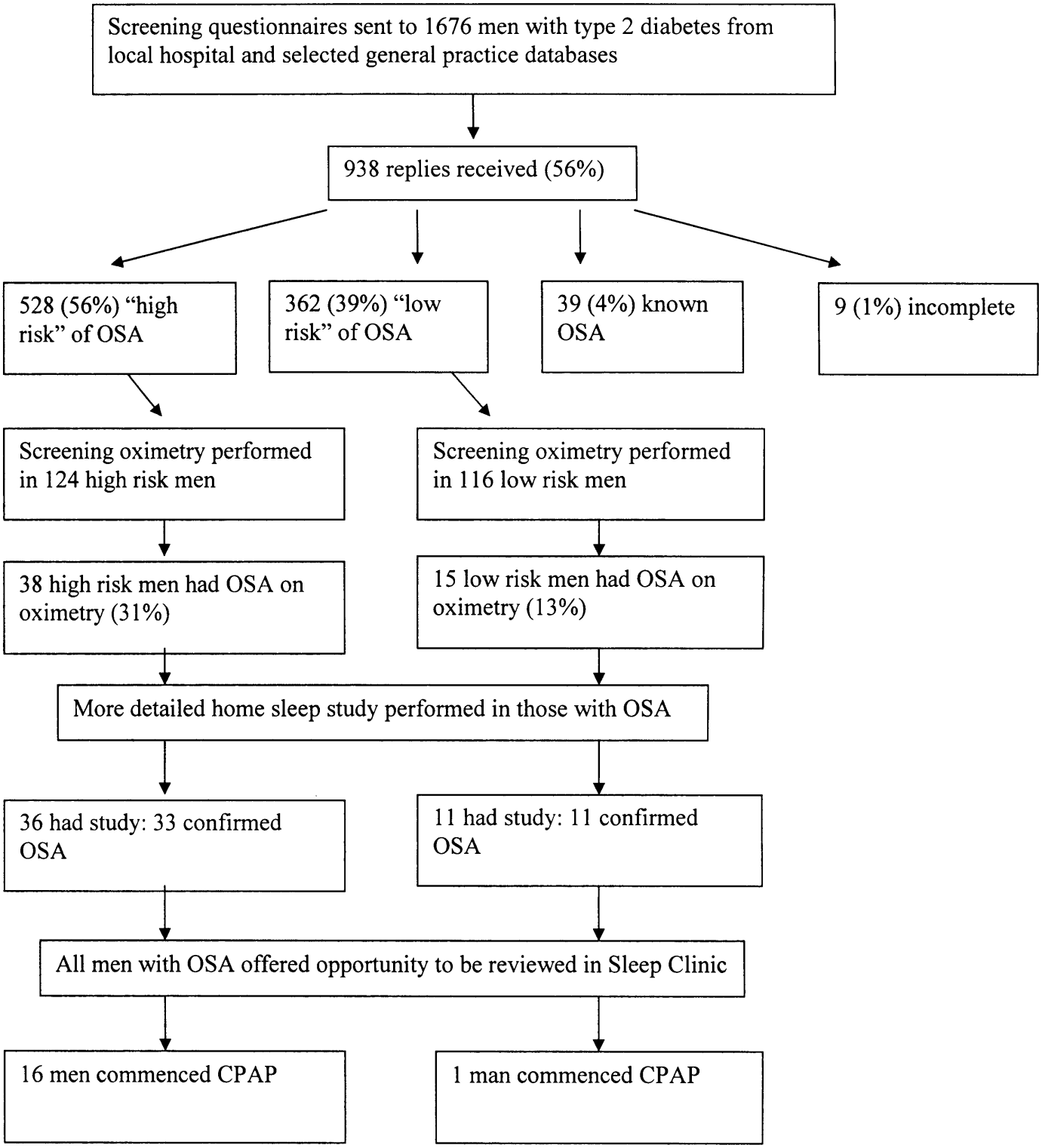
2.3.3 Questionnaire responses: snoring, daytime sleepiness, hypertension

Both the hospital and primary care database groups did not differ significantly in their responses to the questions regarding snoring, daytime sleepiness and hypertension. The answers to these questions allowed them to then be scored as being at 'high' or 'low' risk of OSA. These results are shown in Table 2. Those people who answered that they had previously diagnosed OSA did not complete any further questions. For each database group, a small number of people did not fill in all the sections correctly and therefore the percentages do not add up to 100.

Table 2. Responses to the questions regarding snoring, daytime sleepiness and hypertension by database group

	Hospital database N = 793	**Primary care database N = 145**
Known OSA	34 (4.3%)	5 (3.4%)
CPAP treatment	26 (3.3%)	4 (2.8%)
Section 1: Snoring Mean score	2.7	2.5
No scoring 0	191 (24.0%)	42 (29.0%)
No scoring 1	93 (11.7%)	15 (10.3%)
No scoring 2	107 (13.4%)	18 (12.4%)
No scoring 3	66 (8.3%)	16 (11.0%)
No scoring 4	101 (12.7%)	15 (10.3%)
No scoring 5	99 (12.5%)	16 (11.0%)
Scores of 2 and above gain a point for this section		
Section 2: Daytime tiredness Mean score	0.84	0.94
No scoring 0	386 (48.6%)	66 (45.5%)
No scoring 1	103 (13.0%)	16 (11.0%)
No scoring 2	266 (33.5%)	58 (40.0%)
Scores of 2 gain a point for this section		
Section 3: Hypertension No with known hypertension	522 (65.7%)	79 (54.5%)
No on anti-hypertensive medication	511 (64.4%)	78 (53.8%)
Hypertension or BMI of >30 m/kg^2 gain a point for this section		
RISK SCORE: **High**	449 (56.5%)	85 (58.6%)
Low	308 (38.8%)	55 (37.9%)

Figure 10. *Flow diagram of study*



2.3.4 Risk of OSA

As the two database groups did not differ significantly in their characteristics other than duration of diabetes and treatment type, their results have been analysed together. From the 938 total questionnaire responses, 528 men (56.2%) scored as being 'high' risk of OSA, 362 men (38.6%) scored as 'low' risk and 39 men (4.1%) stated that they had already been diagnosed with OSA, with 30 of them (3%) receiving treatment for this with CPAP. Nine questionnaires were incomplete and prevented assignment to a risk group. The physical characteristics of these groups are shown in Table 3, along with the HbA1c.

The 'high' risk group had significantly higher BMIs and neck circumferences than the 'low' risk group, indicating more obesity and specifically, more upper body obesity. The 'known OSA' patients had significantly larger BMIs and neck circumferences than the 'high' risk group, indicating a likely correlation of increasing upper body obesity and increased risk of OSA or actual OSA. As this data were shown to not be normally distributed, analysis was repeated with the Kruskal-Wallis test. The results showed BMI and collar remained significantly different between the groups (both $p<0.001$), and HbA1c and age were not significantly different between the groups ($p=0.1$ and 0.06 respectively).

Table 3. Characteristics of 'high' and 'low' risk and known OSA questionnaire respondents. Results are shown as mean (SD). Comparison of the groups is by one-way ANOVA, with Duncan's multiple ranging for post hoc analysis. Groups with different superscript numbers are significantly different from each other.

	Known OSA n=39	'High' risk n=528	'Low' risk n=362	P value between groups
Age (years)	61.1 (10.5)[1]	60.5 (9.7)[1]	62.3 (9.5)[1]	0.03
BMI (kg/m^2)	34.9 (5.8)[1]	30.8 (5.6)[2]	27.5 (3.9)[3]	<0.001
Neck size (cm)	45.5 (3.6)[1]	43.4 (3.0)[2]	41.7 (2.8)[3]	<0.001
HbA1c (%)	8.1 (1.9)	8.3 (1.5)	8.3 (1.7)	0.9

2.3.5 Correlation of risk of OSA with HbA1c

The HbA1c results for the two database groups, and for the subdivisions of 'high' and 'low' risk of OSA categories, as well as known OSA, are shown in Table 4, along with the comparison of the two groups. As this data were shown to not be normally distributed, analysis was repeated with the Kruskal-Wallis test. HbA1c overall was significantly different between the two groups ($p<0.001$), as was the HbA1c in the 'high' and 'low' risk groups ($p=0.03$ and 0.002 respectively). HbA1c was not significantly different between the two known OSA groups ($p=0.1$).

Table 4. Mean (SD) HbA1c results for the two population groups. Comparison of the groups was by one way ANOVA.

	Hospital database N = 793	**Primary care database N = 145**	**P value**
HbA1c overall	8.4 (1.6)	7.8 (1.6)	<0.001
HbA1c 'low' risk	8.4 (1.7)	7.9 (1.6)	0.09
HbA1c 'high' risk	8.3 (1.5)	7.9 (1.7)	0.2
HbA1c known OSA	8.3 (2.0)	7.1 (0.8)	0.2

The HbA1c overall was significantly higher in the hospital group than the primary care group. As those people on the hospital database were more likely to have more severe or poorly controlled diabetes, necessitating their referral to hospital, this may be the reason for the higher values in this group and this is not a surprising finding. The HbA1c was significantly higher in the hospital database 'low' and 'high' risk groups compared to the primary care database groups. There was no significant difference between the hospital and primary care database HbA1c results in the 'known OSA' group. When comparing the HbA1c of people in the 'high' risk group from the hospital and primary care databases together, with those in the 'low' risk group, there was also no significant difference ($p=0.8$, results not shown).

2.3.6 Diabetes medication

We wanted to establish the types of treatment that men in each risk group were receiving for their diabetes, and whether this could have affected the HbA1c values, which were not statistically significantly different between the two risk groups. HbA1c is potentially subject to practitioner intervention; if it is high, suggestive of inadequately controlled diabetes, the type of treatment the person is receiving for their diabetes is increased. Therefore possible high HbA1cs in the high risk group may have been brought under control by increased amounts of hypoglycaemic medication, meaning no significant difference in HbA1c between the two risk groups existed, but the medication requirements might be significantly different, in order to achieve this.

The percentages of men receiving different types of medication for their diabetes are shown in Table 5. A chi-square test of the proportions of people receiving each type of medication was performed. This showed that significantly more people in the 'high'

risk group were receiving treatment with insulin and oral hypoglycaemic tablets, and, conversely, significantly more people in the 'low' risk group were receiving treatment with oral hypoglycaemic tablets or diet alone (p=0.008). Performing univariate analysis of variance allowing for obesity, however, showed no significant difference between high and low risk groups (p=0.8), using type of treatment as the dependent and BMI and risk as the independent factors. In a questionnaire/observational study of this sort, any correlation between HbA1c and risk of OSA may be negated by practitioner intervention regarding the HbA1c, for example with increased treatment in the high risk group. This explanation is not however supported by the treatment types in the two groups, which were not significantly different once obesity was allowed for.

The mean BMI increased across treatment groups, with those on diet only having a mean BMI of 28.2, those on tablets having a mean BMI of 29.2 and those on insulin having a mean BMI of 29.8. Although the likely explanation for this is that those men with higher BMIs are more insulin resistant, with worse diabetes control, hence requiring more medication, the confounding problem is that people with type 2 diabetes commencing insulin usually experience weight gain.

Table 5. Medication for diabetes by risk group. Results are shown as percentages.

	High risk (%) N=528	**Low risk (%) N=362**
Insulin alone or insulin and oral hypoglycaemics	51.2	42.0
Oral hypoglycaemics	44.1	49.7
Diet alone	4.7	8.3

Chapter 3

Study to perform home sleep studies on a selection of men with type 2 diabetes scored as being 'high' and 'low' risk of OSA from the previous questionnaire study in order to validate the questionnaire

CHAPTER 3

Study to perform home sleep studies on a selection of men with type 2 diabetes scored as being 'high' and 'low' risk of OSA from the previous questionnaire study in order to validate the questionnaire

3.1 Introduction

In the previous chapter, a questionnaire study to establish the likelihood of OSA in a population of men with type 2 diabetes was described. Five hundred and twenty eight men (56.2%) scored as being 'high' risk of OSA and 362 men (38.6%) scored as being 'low' risk. In order to establish the validity of the questionnaire at allocating risk of OSA, overnight screening home sleep studies were performed in a selection of men, from both the 'high' and 'low' risk groups. This was to determine whether they had evidence of OSA, which had not previously been diagnosed. Those people found to have OSA were then seen by a doctor in the Oxford Sleep Clinic, to assess whether they needed definitive treatment for the OSA. From this data regarding confirmed OSA in both the 'high' and 'low' risk groups , we would be able to estimate the true prevalence of OSA in men with type 2 diabetes, by extrapolation to the questionnaire responses of the group as a whole.

3.2 Methods

3.2.1 Subjects

A sample of subjects found to be at both 'high' and 'low' risk for OSA from their questionnaire answers were written to, inviting them to participate in further studies for

OSA (Figure 4, Appendix 1). They were then contacted by telephone to see if they agreed and if so, to arrange a time for one of the study investigators to visit. Subjects who could not be initially contacted by telephone were tried on a number of occasions. If they could not be contacted, another letter was sent asking them to telephone us. Subjects were selected on the basis of their postcodes, with those with postcodes within 20 miles of the base hospital being preferred, for ease of equipment delivery. Subjects were contacted until the numbers required for studies had been reached. The number of studies performed was determined by the research personnel and resources available: as it was not possible to study all the questionnaire respondents, approximately 25% were studied, in order to give a representative sample. As no studies of this sort had been performed previously in people with type 2 diabetes, a power calculation could not be performed to determine the number studied. (In the original Berlin questionnaire study by Netzer et al, 13% of their questionnaire respondent population were investigated for OSA, in order to validate the questionnaire (Netzer 1999)). Both questionnaire respondents from the hospital and primary care databases were selected.

3.2.2 Epworth sleepiness score and overnight oximetry

Subjects were visited at their homes. When they were visited, a consent form and an Epworth Sleepiness Score were completed, an eight point questionnaire assessment of the tendency to fall asleep during various daytime situations (Johns 1991, Figure 5, Appendix 1). Initial overnight oximetry studies were performed with a small portable battery operated wrist worn monitor and attached finger probe (Pulsox-3i, Konica Minolta, Japan). This measures the oxygen saturation of arterial blood and the pulse rate, and stores this data. A normal overnight oximetry tracing has been found in a systematic literature review of home diagnosis of sleep apnoea to substantially reduce

the probability of OSA in the majority of patients (Flemons 2003). Measurements of SaO_2 correlate very well with apnoea-hypopnoea index (AHI) (Vazquez 2000). The oximeter was left with them, with instructions on how to use it for one night. Subjects were provided with a padded envelope to return the oximeter the next day.

3.3.3 Oximeter analysis

When the oximeter was received back, it was downloaded via a computer and automatically analysed (Download, Stowood Scientific Instruments, Oxford, UK). Those subjects who had normal oximetry studies were written to and reassured. Those subjects who had more than ten, > 4% oxygen saturation dips per hour, or an oximetry trace with less than ten, > 4% oxygen saturation dips per hour but with significant nocturnal dipping compatible with a diagnosis of OSA when manually reviewed by a sleep expert (John Stradling), were classified as having OSA (usually occurring when SaO_2 dips were repeatedly a little less than 4%). Evidence of 4% dips in oxygen saturation occurring at a rate of more than 10 per hour is an accepted cut off for the diagnosis of OSA (Choi 2000). These are associated with a rise in pulse rate and increased movement, secondary to arousals.

3.3.4 Unattended portable monitor home sleep study in those with OSA on oximetry

Those subjects who were classified as having OSA following their overnight oximetry test were contacted in order to perform an unattended sleep study with a portable multi-channel home sleep monitor, to confirm the diagnosis of OSA, and to verify that abnormal oximetry traces were due to obstructive apnoeas, not central apnoeas. The equipment for the sleep study was delivered to the subject by one of the investigators, who fitted it and explained how to use it on that night. Full written instructions were

also provided. The sleep study equipment was collected by the investigators the following day and downloaded by computer. The sleep study equipment measured body position via an in-built sensor, body movement via internal actigraph, nasal pressure via nasal cannula, oximetry, pulse rate, plus respiratory effort via thoracic and abdominal bands (Embletta PDS 3.0, Flaga Medical, Iceland). From these measurements, a validated apnoea-hypopnoea index and oxygen desaturation events per hour were automatically calculated (Dingli 2003), with manual review and editing. As oximetry is relatively simple for patients to perform at home, this was our primary screening tool for OSA. The more complicated Embletta studies were performed essentially for validation of the oximetry findings.

3.3.5 Correlation of OSA with glycosylated haemoglobin

A correlation between the glycosylated haemoglobin and the severity of OSA was performed, to determine if there was any relationship between the two.

3.3.6 Follow-up of subjects found to have OSA

Those subjects who were identified as having OSA based on their sleep studies were offered a clinic appointment at the Oxford Sleep clinic, in order to discuss their results and determine whether they were sufficiently symptomatic with daytime sleepiness to require treatment.

3.3.7 Analysis

Statistical analysis was carried out using SPSS version 12.0. Data are expressed as mean (standard deviation, 0-100% range). Comparison of groups was performed with one-way analysis of variance (ANOVA). Differences between the 'high' and 'low' risk

groups, and the two different study populations, were assessed with unpaired t-tests and chi-square when comparing proportions. Data were tested for normal distribution with the Shapiro-Wilk test of normality and where the data were shown to be not normally distributed, analysis was repeated using non-parametric tests (Kruskal-Wallis if there were more than two groups and Mann-Whitney to compare two independent groups).

3.3 Results

3.3.1 Overnight oximetry

Overnight oximetry recordings were performed in 124 subjects in the 'high' risk group and 116 subjects in the 'low' risk group. Ninety further men who were contacted refused to have overnight oximetry performed. Comparison of the characteristics of those individuals selected for oximetry, to their risk group as a whole, showed no significant differences (Table 1). As this data were shown to not be normally distributed, analysis was repeated with the Kruskal-Wallis test. This also showed no significant differences.

There was no data available for the ethnicity of this sub-group, or their socio-economic status or level of education, as this was not collected. Clearly if a particular socio-economic group or ethnic population was overrepresented in this sample, it may have introduced bias, with an over or under estimate of OSA levels according to the men selected. As the subjects were selected on the basis of their postcodes, most of the subjects lived near the city centre. They therefore represented an ethnically diverse group of men, of mixed socio-economic status and so this potential source of bias is likely to be minimal.

Table 6. Mean characteristics of the high and low risk groups in the questionnaire population as a whole and of the oximetry sub-groups. Comparison is by one-way ANOVA.

	High risk questionnaire population overall	**High risk oximetry sub-group**	P value	**Low risk questionnaire population overall**	**Low risk oximetry sub-group**	P value
Age	60.5	60.9	0.5	62.3	62.3	0.8
BMI (kg/m^2)	30.8	30.5	0.4	27.5	27.0	0.6
Collar (cm)	43.4	43.2	0.3	41.7	41.1	0.2
Duration of diabetes (yrs)	11.1	9.8	0.1	11.6	11.5	0.9
HbA1c	8.3	8.1	0.2	8.3	8.2	0.5

In the 'high' risk group, 38 of 124 people (31%) had traces consistent with a diagnosis of OSA (29 with >10, >4% SaO_2 dips/hour; 9 with <10, >4% SaO_2 dips/hour, but oxygen saturation tracing consistent with a diagnosis of OSA), and 36 went on to have a portable monitor home sleep study. In the 'low' risk group, there were 15 of 116 people (13%) with oximetry traces consistent with OSA (11 with >10, >4% SaO_2 dips/hour; 4 with <10, >4% SaO_2 dips/hour, but oxygen saturation tracing consistent with a diagnosis of OSA), and 11 proceeded to have a portable monitor home sleep study. Those who did not have portable monitor sleep studies declined consent. These results are shown in Table 2.

Table 7. Table showing sleep study results according to questionnaire risk group. Results are shown as mean (SD) and are compared with an unpaired t-test, with χ^2 of percentage with OSA on oximetry.

	'High' risk (n=124)	**'Low' risk (n=116)**	P value
Epworth Sleepiness Score	9.8 (4.5)	6.2 (3.7)	<0.001
>4% SaO_2 dips per hour	9.1 (12.8)	4.3 (4.7)	<0.001
Mean SaO_2 (%)	93.9 (3.0)	94.9 (1.6)	0.002
Min SaO_2 (%)	79.9 (12.4)	84.0 (8.3)	0.003
No with OSA on oximetry	38 (31%)	15 (13%)	<0.001

As this data were shown to not be normally distributed, analysis was repeated with the Mann-Whitney test. The results remained statistically significant (ESS $p<0.001$, >4% dips $p<0.001$, mean SaO_2 $p=0.009$, Min SaO_2 $p=0.009$).

3.3.2 Unattended portable monitor home sleep study

In the 'high' risk group, automatic analysis and manual review of the portable monitor home sleep studies confirmed that 33 of the 36 people agreeing to be studied (of the original 124 subjects who had oximetry performed) had confirmed OSA (27%). Two of these 33 also had some central sleep apnoea and one of the 33 had OSA with obesity hypoventilation. The three people who did not have OSA are as follows: one had only central sleep apnoea, dying soon after taking part in the study from a myocardial infarction and may have had left ventricular failure at the time of the study; one had low baseline oxygen saturations known to be due to concurrent chronic obstructive pulmonary disease, with little evidence of OSA; one had difficulty performing the portable monitor home sleep study and the recording was inadequate - this was not repeated. These three people who did not have confirmed OSA have been excluded

from further analysis. In the 'low' risk group, the portable monitor home sleep study showed all 11 people had confirmed OSA (9%). These results are shown in Table 3.

Table 8. Table showing portable monitor home sleep study results on those with positive oximetry according to questionnaire risk group. Results are shown as mean (SD).

	'High' risk subgroup n=33	**'Low' risk subgroup n=11**	P value
AHI from portable monitor sleep study	32.2 (23.1)	26.2 (22.3)	0.5

As this data were shown to not be normally distributed, analysis was repeated with the Mann-Whitney test. There was no significant difference between the two groups (p=0.8).

3.3.3. Epworth Sleepiness Score

The mean ESS was significantly higher in those people who had oximetry performed in the 'high' risk group compared to those in the 'low' risk group (mean (SD) 9.8 (4.5) vs. 6.2 (3.7), p<0.001) (Table 2). Surprisingly, there was no significant correlation between ESS and 4%SaO_2 dip rate in either risk group (High risk: r=0.07, p=0.4. Low risk: r=-0.7, p=0.5).

3.3.4 Correlation of OSA indices with HbA1c

There was no significant correlation in the hospital and primary care groups combined between the 4% SaO_2 dip rate per hour and HbA1c in either the 'high' or 'low' risk group (n=240, r=0.11, p=0.1). If the hospital and primary care groups were analysed

separately, however, there was a small positive correlation in the hospital group (r=0.2, p=0.006), but not in the primary care group. A multiple linear regression model, using HbA1c as the dependent variable, showed the strength of this correlation decreased when allowing for BMI, although it remained statistically significant (p= 0.03).

3.3.5 Number of men found to have OSA starting CPAP treatment

Of the 33 subjects found to have OSA on their portable monitor sleep studies in the 'high' risk group, 16 of the 33 were symptomatic with daytime sleepiness and were commenced on continuous positive airway pressure (CPAP) treatment following clinic review. In the 'low' risk group, of the 11 people found to have OSA on their portable monitor sleep studies, 1 of the 11 was symptomatic and commenced CPAP. Chi square analysis showed the proportions starting CPAP in the two groups were significantly different, $p<0.001$.

Chapter 4

Comparison of screening oximetry results in men with type 2 diabetes with a previous primary care population and discussion of the prevalence of OSA in men with type 2 diabetes

CHAPTER 4

Comparison of screening oximetry results in men with type 2 diabetes with a previous primary care population and discussion of the prevalence of OSA in men with type 2 diabetes

4.1 Introduction

Previous studies have been performed to assess the prevalence of OSA in different populations. We wanted to compare the prevalence of OSA in a control population with the prevalence in our current study population of men with type 2 diabetes. In a previous study performed by our own department, 275 men were recruited randomly from a primary care population in Bicester, Oxfordshire (Stradling 2000). These men had a range of tests performed at home, including overnight sleep studies, to primarily determine which aspects of breathing during sleep influenced overnight changes in blood pressure. These sleep studies were performed with RM50 portable monitors (Parametric Recorders, London UK) and the data have already been published. The men came from the general primary care population and diabetes was not an inclusion or exclusion criterion. We therefore regarded this "normal" population as a reasonable control population with which to compare the prevalence of OSA with that in our current study population of men with type 2 diabetes.

4.2 Methods

We needed first to establish the equivalence or otherwise of the >4% oxygen desaturation dip rate per hour of the two oximeters which had been used in each study (RM50 and Pulsox-3i). Although the SaO_2 dip counting computer algorithm was

identical, the actual oximeter devices came from different manufacturers. We performed overnight oximetry studies using both oximeters on the same night, mostly in patients with confirmed OSA of variable severity from the Oxford Sleep Clinic. The recordings were downloaded and scored automatically, with manual review. This was exactly the same as the analysis performed in both the current and previous studies. The results of the two readings were then compared and correlated. Linear regression was performed to calculate a conversion factor to enable direct comparison of results from the two oximeters. The recordings from the diabetes population and the previous general practice population could thus be directly compared, in order to compare the prevalence of OSA in the two populations.

4.2.1 Subjects

Most of the subjects who participated in this part of the study were recruited from the Oxford Sleep Clinic. In addition some normal subjects from within the hospital were recruited to provide the full spread of data. Subjects from the clinic had confirmed OSA of differing severity and were awaiting CPAP treatment. Subjects were selected across a range of OSA severity, from mild to severe, in order to compare the two oximeters at different oxygen saturation dip rates. Subjects were either recruited in the clinic or they were written to and then contacted by telephone to arrange a time for one of the researchers to visit them and deliver the oximeters.

4.2.2 Oximeters

Subjects wore both oximeters on the same night. Both had finger probes which were secured in place by tape. One was small and attached to the wrist by means of a Velcro strap (Pulsox-3i); the other was larger and was placed near the pillow (RM50). The

recordings from both were downloaded by computer and scored automatically. Both oximeters were set to count the number of 4% oxygen desaturation dips per hour, as per the original studies. Manual review was performed to ensure the same hours on each were being studied, and that the probe was in place throughout the recording. The results of the readings were then compared.

4.2.3 Analysis

The Pulsox-3i and RM50 monitor SaO_2 results were compared and correlated. Linear regression was performed to calculate a conversion factor to enable direct comparison of results from the two oximeters. A multiple linear regression analysis was performed, using the two different study populations (Diabetes vs. Bicester), to determine predictors of >4% SaO_2 dips per hour. A p-value of <0.05 was considered to be statistically significant.

4.3 Results

4.3.1 Comparison of the readings of the two oximeters

Twenty-eight separate individuals, (26 from the Oxford Sleep Clinic and 2 normals), completed overnight oximetry studies with both the Pulsox-3i and RM50 recorders, to investigate equivalence. Table 2, Appendix 2 shows the results from the two recordings. There was a close positive correlation of the >4% SaO_2 dip rate from the Pulsox-3i with the RM50 ($r=0.97$, $p<0.0001$) (Figure 1). Both recorders were processed using the same algorithm for calculating the >4% SaO_2 dips per hour, and the small differences are presumably due to hardware differences in the oximeter boards. A small conversion factor was calculated to allow direct comparison of the previous primary care populations' RM50 oximetry recordings with the current Minolta oximetry recordings

(Minolta reading =1.26 x RM50 reading -2.56, where 1.26 is the slope and -2.56 is the intercept) (Figure 1b).

4.3.2 Comparison of prevalence of OSA in men with type 2 diabetes (current study) and men from primary care population (Bicester study)

Having established the conversion factor needed to allow direct comparison between the RM50 and Pulsox-3i overnight recordings, we were able to apply this conversion factor to the RM50 oximetry results from the previous population study of men from the primary care study in Bicester. The results of the two study populations are shown in Table 1. A threshold diagnosis of OSA was based solely on >10 >4% SaO_2 dips/hour i.e. without expert visual review of borderline traces, because this had not been done in the original Bicester study and we were unable to obtain the oximetry printouts for further analysis. This meant a purely objective comparison was performed.

Figure 11a. *Graph of overnight oximetry results from the Pulsox-3i compared to the RM50 (n=28).*

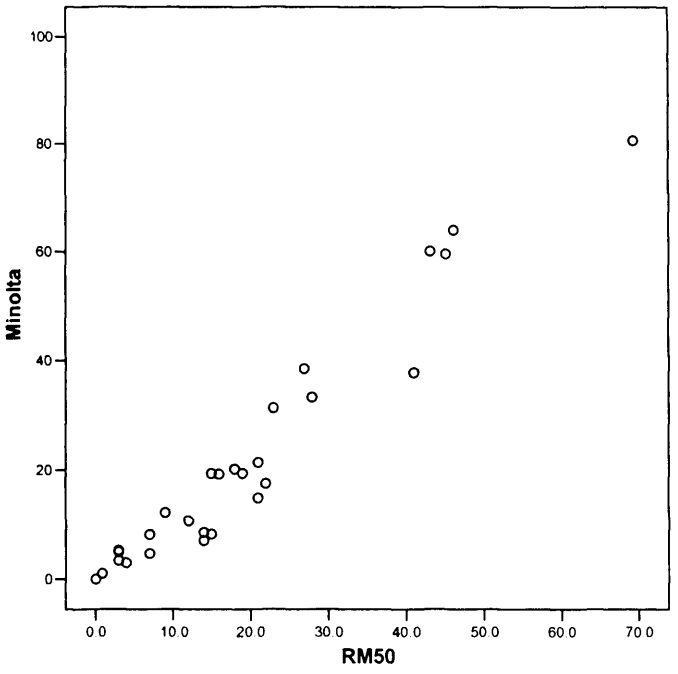
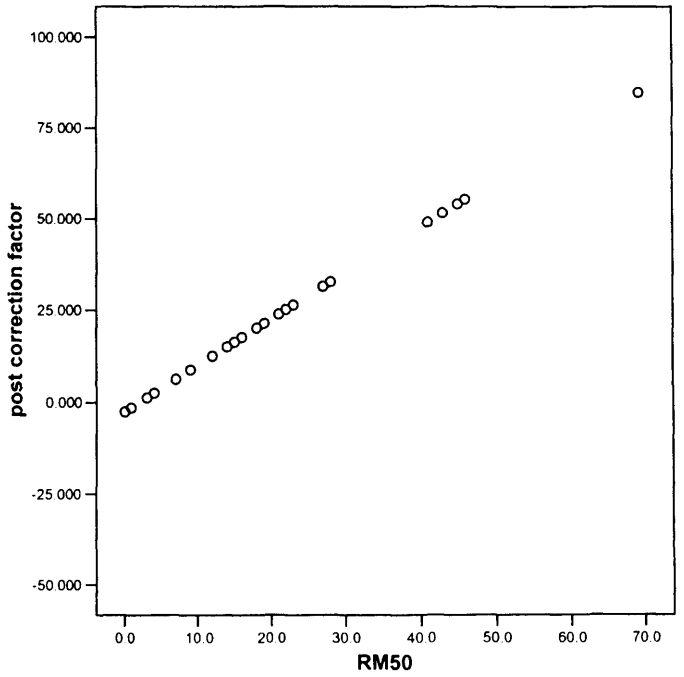


Figure 11b. *Graph of overnight oximetry results from the Pulsox-3i compared to the RM50 after correction factor applied to the Pulsox-3i to allow direct comparison of the two oximeters.*



Multiple linear regression modelling was performed on all the men from the two populations, to allow for the fact that the two groups in their entirety were not matched and had different characteristics. The models of the two populations used >4% SaO_2 dips per hour as the dependent variable, and it was found that significant predictors for this were BMI and diabetes status (having or not having diabetes). Once BMI was allowed for, the neck size and age were not significant predictors. Neck size may not have been a significant predictor because the patients in the diabetes study measured their necks themselves and this may have therefore been subject to some inaccuracy. Diabetes status gave an additional small increase in the R^2, after correction for BMI. (R^2 = 0.13 (13%) for BMI, and 0.21 (21%) for diabetes status in addition). This shows that 13% of the variance in >4% SaO_2 dips per hour can be explained by BMI, but an additional 8% is explained by diabetes status. The β coefficients of SaO_2 for BMI and diabetes status were 0.6 and 5.2 respectively ($p<0.001$). Thus, for every 1 point increase in BMI, the >4% SaO_2 dips per hour rose by 0.6, and having type 2 diabetes increased the >4% SaO_2 dips per hour on average by 5, independent of body mass index, neck size and age (table 2).

Table 10. Multiple linear regression results for >4% SaO_2 dips per hour of the two populations (primary care population and current diabetes study)

	Uncorrected (single regression)		Corrected (multiple regression)	
Predictor variable	**r**	**R^2**	**r**	**R^2**
Age	0.2**	0.04	0.09	n.s.
BMI, kg/m^2	0.35**	0.12	0.36**	0.13
Neck size	0.19**	0.04	0.04	n.s.
Diabetes status	0.36**	0.13	0.29**	0.09
Model			0.46**	0.22

Dependent = >4% SaO_2 dips per hour, ** = $p<0.001$, n.s. = not significant

On a second alternative analysis, subjects from the type 2 diabetes and the Bicester populations, who had all had overnight oximetry performed, were case matched for BMI. One hundred and seventy four subjects from each group were individually case matched on the basis of BMI alone. One way ANOVA showed no significant difference between BMI or neck size following this matching, but there was a significant difference between the two groups in the 4% SaO_2 dip rate/hour and ESS (Table 3). This confirms, along with the larger multiple linear regression analysis, that there is a significant independent association of diabetes status with >4% SaO_2 dips per hour. As this data were shown to not be normally distributed, analysis was repeated with the Kruskal-Wallis test. The results were unchanged (BMI p=0.9, neck size p=0.1, 4% dip rate p<0.0001, ESS p=0.02).

Table 11. Subjects from the type 2 diabetes and the Bicester population case matched on the basis of BMI. Data are shown as mean (SD). Analysis is by one way ANOVA.

	Type 2 diabetes population N=174	**Bicester population N=174**	P value
BMI (kg/m^2)	27.5 (3.7)	27.5 (3.7)	1.0
Neck size (cm)	40.7 (6.8)	39.8 (2.8)	0.1
4% SaO_2 dips/hour	5.9 (8.5)	0.1 (4.7)	<0.0001
ESS	7.7 (4.3)	6.7 (3.9)	0.02

4.4 Discussion of chapters 2, 3 and 4

4.4.1 Prevalence of OSA in men with type 2 diabetes

This study in three parts (a questionnaire study, targeted sleep studies and comparison of these results to a previously studied control group) has shown that obstructive sleep apnoea is common in this population of men with type 2 diabetes. Based on answers to the Berlin questionnaire, 56% of men scored as being 'high' risk of OSA and 4% stated they had known OSA. Of the subset of both 'high' and 'low' risk men studied, 22% had an overnight screening oximetry study compatible with a diagnosis of OSA. Diagnostic home monitor sleep studies largely confirmed these findings. If the results of the home monitor sleep studies are extrapolated proportionally to the whole questionnaire respondent population, and added to those with known OSA, then 213 men of the 938 respondents (23%) would be expected to have OSA.

The number of men with type 2 diabetes scoring as 'high' risk of OSA (56%) was higher than in the original Berlin questionnaire study, in which 45% of 741 men scored as 'high' risk (Netzer 1999). The number of men with type 2 diabetes in our study confirmed as having OSA on oximetry was much higher than the number of men found to have OSA in a control primary care population in Bicester, Oxfordshire: 6% of 275 men in Bicester had overnight oximetry compatible with a diagnosis of OSA (based on >10, >4% SaO_2 dips/hour alone), compared to 17% of our diabetes population diagnosed on these criteria (Stradling 2000). These results therefore show that OSA is highly prevalent in men with type 2 diabetes, with estimated prevalence rates of 17-23% and it is more common than in previously studied control populations, even when matched for obesity.

4.4.2 Type 2 diabetes as an independent risk factor for OSA

Although body mass index was the best predictor of OSA, we found that having type 2 diabetes conferred a significant extra increase in the likelihood of having OSA, after allowing for body mass index, age and neck size. Having type 2 diabetes was found on average to increase the >4% SaO_2 dips per hour by five. A separate analysis using cases matched on the basis of BMI also confirmed a significant difference between the two populations in the 4% SaO_2 dip rate/hour. Although the comparison of the previous primary care and the diabetes populations was not ideal (different selection criteria, neck size and weight measured by nurse or individual, different oximeters requiring correction factor to be applied, studied at different times, and the possibility of some men in the Bicester sample having type 2 diabetes), we regard the results as informative. The population with type 2 diabetes studied here were predominantly hospital treated, which may add some bias to the sample. A high proportion were using insulin (44%), which causes weight gain, although this would have been taken into account by both the paired and the multiple linear regression analysis. Thus OSA may be a particular problem in men with type 2 diabetes. The reasons for this are not clear. There may an aspect of central obesity in type 2 diabetes that contributes to the OSA, which is not captured in BMI or neck size; despite the fact that neck size itself is a significant independent predictor of the rate of overnight hypoxic dipping in OSA (Stradling 1991). It could be that OSA is a close correlate of the same central obesity distribution that also predisposes to insulin resistance. It is accepted that computerised tomography is the gold standard method of quantifying abdominal fat; BMI, waist and waist to hip measurements are poorer correlates (Riberio-Filho 2003). Using these indirect measurements to allow for this important central obesity distribution is probably not adequate (Yusuf 2005, Romero-Corral 2006). Alternatively it may be that

diabetic autonomic neuropathy causes increased OSA, and this has been noted in other studies (Ficker 1998, Bottini 2003). This study shows that whatever the mechanism, OSA is extremely common in men with type 2 diabetes, more so than entirely predictable from their usual extra weight, and may well be under diagnosed. Women were not included in this study, and the gender differences in body fat distribution mean that further studies would be needed to gain an estimate of the prevalence OSA in women with type 2 diabetes.

4.4.3 Use of the Berlin questionnaire as a screening tool for OSA

The Berlin questionnaire was used to classify people as being at 'high' or 'low' risk of OSA. The results were then validated by performing oximetry sleep studies on respondents from each risk group. We found that the questionnaire was not particularly sensitive or specific, with people in both risk groups being found to have a spectrum of OSA severity, from none to severe. The 'high' risk group did however have a significantly higher mean SaO_2 >4% dip rate/hour than the 'low' risk group (9.8 vs. 6.2 dips/hr, $p<0.001$). The questionnaire was useful in differentiating patients who were likely to require CPAP, evidenced by significantly more of the 'high' risk patients found to have OSA commencing CPAP, than the 'low' risk patients with OSA ($p<0.001$). This is because the questionnaire contained two questions about daytime sleepiness, which if both answered affirmatively, contributed to the scoring of someone as 'high' risk. As daytime sleepiness is a key factor for determining whether a person with OSA warrants CPAP treatment, it is not surprising that the risk group allocation was significant in differentiating who required CPAP. Therefore although the questionnaire was unable to exclude OSA in 'low' risk respondents, the likelihood of them subsequently requiring CPAP was low. It was interesting that we found no

correlation between 4% SaO_2 dip rate/hour and ESS in either of the two risk groups. It may be that this unselected community population, who have not sought help for sleep apnoea symptoms, have a different subjective experience of sleepiness than the patients attending the sleep clinic with OSA, who often have an ESS of ten or more, suggesting they have significant daytime sleepiness, and this has led them to seek help. It was however discussed in section 1.1.5 that sleep study indices of OSA and objective sleepiness do not correlate well (Cheshire 1992, Kingshott 1998).

It is not clear why we found the prediction ability of the questionnaire to be less good than when it was originally used by Netzer et al, where a post-test probability of 85% was achieved (Netzer 1999). It was used in an American primary care population in the original study and it may be that it worked less well out of this setting. The questionnaire has been used and validated with sleep studies in only two other small studies, but with high positive predictive values in both (Gami 2004, Sharma 2006). These studies were performed in America in 44 patients attending for electrical cardioversion for atrial fibrillation and in India in 104 people seemingly from the general population. It is therefore difficult to compare these settings and applications with our study. There were more men who scored as 'high' risk in our diabetes population than in the original study (56% vs. 45% respectively), although it is not clear that this would affect the results. In the original study, confirmatory sleep studies were performed in only 13% of questionnaire respondents; 69% of these were in 'high' risk respondents and 31% in 'low' risk respondents. We performed sleep studies in 25% of our sample (52% of these were 'high' risk) and our threshold for the diagnosis of OSA was higher, with >10 >4% SaO_2 dips/hr being necessary for diagnosis, as opposed to an

RDI of 5/hour. These factors may have all affected the sensitivity of the questionnaire at diagnosing OSA in our hands.

4.4.4 Correlation of OSA with HbA1c

We found no correlation between indices of sleep disordered breathing and HbA1c in the diabetes group as a whole, but the men with type 2 diabetes recruited from the hospital database did show a low but significant correlation when analysed separately ($r=0.2$, $p=0.006$). We postulated the sleep fragmentation of OSA would lead to more disordered glucose metabolism, resulting in worse diabetic control. This was not the case overall, and may reflect the fact that HbA1c level was closely controlled by physician intervention with extra hypoglycaemic treatment, thus masking any effect. This explanation is not however supported by examination of the proportions on diet versus oral hypoglycaemics versus insulin: there being no difference between high and low risk groups after allowing for obesity. This does not therefore support the idea that OSA caused worse glycaemic control, but that this had been treated at the expense of high medication requirements. The fact there was a low but significant correlation within the hospital population alone is interesting, and that this remained significant after correction for BMI ($p=0.03$). It may be that the people with type 2 diabetes on the hospital database had more severe and perhaps less well controlled diabetes, with OSA making a small contribution. This would be supported by the finding of higher mean HbA1c in the hospital group compared to the primary care group (8.4 vs. 7.8, $p=0.001$). There would however be other potential explanations.

4.4.5 Clinical relevance of these findings

Clinicians who manage patients with type 2 diabetes must be aware of the increased likelihood of OSA, routinely asking about habitual snoring, witnessed apnoeas, nocturnal choking and daytime sleepiness as part of their patient assessment, or using the Epworth sleepiness score (Johns 1991). If OSA is considered likely, referral to the local sleep service for a diagnostic sleep study is appropriate. It may be difficult without a sleep study to differentiate sleepiness due to OSA from fatigue and tiredness associated with diabetes and comorbid disease. As we have shown, screening questionnaires can predict risk, but have poor sensitivities and specificities. Daytime sleepiness contributed to a 'high risk' score on the questionnaire, and this is one of the main factors which determines whether someone is likely to receive and benefit from CPAP therapy. The benefits of CPAP to people with OSA are clear: improvements in daytime sleepiness, cognitive function, driving ability and blood pressure (Jenkinson 1999, Hack 2000, Pepperell 2002). Improvements in blood pressure are likely to translate to improved cardiovascular risk, particularly important in a diabetes population (Wei 1998). It is not known whether CPAP improves glycaemic control in people with OSA and type 2 diabetes, as adequately controlled studies have not previously been performed; this is the subject of the next section in this thesis.

4.5 Conclusion

Men with type 2 diabetes have a very high prevalence of obstructive sleep apnoea, much higher than that of men in the general population, even allowing for the extra obesity usually seen in patients with type 2 diabetes. Recognition and treatment of this is likely to be beneficial to them if they are symptomatic with excessive daytime sleepiness.

Chapter 5

The effects of CPAP on glycaemic control and insulin resistance in men with OSA and type 2 diabetes: a randomised controlled trial

CHAPTER 5

The effects of CPAP on glycaemic control and insulin resistance in men with OSA and type 2 diabetes: a randomised controlled trial

5.1 Introduction

There has been interest in whether the treatment for OSA, continuous positive airway pressure (CPAP), can improve the insulin resistance found in OSA. If the hypoxia, arousals and increased sympathetic drive found in OSA were adequately treated, would the cellular insulin resistance improve and thus glycaemic control? Several studies have been performed to try to answer this question, some in people with OSA only, and some in people with OSA and type 2 diabetes, but none have included a control group (Brooks 1994, Saarelainen 1997, Smurra 2001, Harsch 2004). These studies have found differing results of the effect of CPAP on longitudinal change in insulin resistance from baseline; the significance of the changes cannot be assessed without a control group, due to the many confounders of insulin resistance, such as weight change and exercise. Thus far, the available data has not led to a conclusive answer. We hypothesised that CPAP would improve insulin resistance and HbA1c in men with type 2 diabetes and have therefore performed a randomised controlled trial, using therapeutic and placebo CPAP, to assess the effect of CPAP on insulin resistance (homeostatic model assessment and euglycaemic clamp) and glycaemic control (HbA1c) in men with established type 2 diabetes and newly diagnosed OSA.

5.2 Methods

5.2.1 Subject selection

Subjects were recruited via the Oxford Sleep Clinic between June 2004 and August 2005. Eligible subjects were men aged between 18 and 75, with established type 2 diabetes (on diet, oral hypoglycaemic agents or insulin therapy), which was stable, with no treatment changes anticipated. They had excessive daytime sleepiness (ESS $\geq$ 9) and were due to start CPAP for proven OSA. Some subjects were those diagnosed with OSA through the questionnaire part of the study (see chapters 2 and 3) and otherwise were from the Oxford Sleep Clinic. Patients were excluded if they required urgent CPAP due to respiratory failure or to prevent job loss due to excessive daytime sleepiness, or if they had unstable diabetes (requiring an escalation in treatment), as well as any other disease likely to influence diabetic control, such as uncontrolled cardiac failure or untreated hypothyroidism.

5.2.2 Diagnosis of OSA

The diagnostic criteria for OSA were either greater than ten, oxygen saturation (SaO_2) dips of greater than 4% per hour on a one-night hospital respiratory polysomnography sleep study, or an apnoea-hypopnoea index (AHI) of $\geq$ 15 per hour on an unsupervised one-night home sleep study. The hospital sleep study took place in a hospital room decorated and furnished to resemble an ordinary bedroom. Subjects' body movements, heart rate and pulse transit time (PTT) changes were recorded as measures of arousal from sleep. The PTT signal and body movements derived from video are robust markers of arousal (Bennett 1998). Arterial oxygen saturation measurements, snoring and increases in the respiratory effort (from the PTT) were used as markers of breathing pattern and respiratory effort (Win-Visi monitoring system, Stowood Scientific

Instruments, Oxford UK). The PTT swing is a sensitive index of respiratory effort that accurately predicts change in pleural pressure and differentiates between central and obstructive apnoeas (Argod 1998). The results of the sleep study were scored automatically, with manual review to ensure accuracy of the data. OSA was diagnosed from a review of all the data. The severity of the sleep apnoea was quantified as the number of dips in oxygen saturation of greater than or equal to 4% for every hour of the study, confirmed as being caused by upper airway obstruction. This index is one of the best predictors of therapeutic response to nasal CPAP (Bennett 1998) and a recent study has also shown oximetry to be as good as conventional EEG-based polysomnography at predicting response to CPAP (Whitelaw 2005). In the home sleep study, body position, body movement, nasal pressure via nasal cannula, oximetry, pulse rate, plus respiratory effort via thoracic and abdominal bands were measured to give a validated AHI and automatic calculation of oxygen desaturation events per hour (Embletta PDS 3.0, Flaga Medical, Iceland). Areas of artefact were manually edited. Good agreement between Embletta home sleep studies and in hospital polysomnography has been shown previously in the diagnosis of OSA (Dingli 2003).

5.2.3 Study design

5.2.3.1 Baseline assessment

Eligible subjects were seen for their baseline study visit 10 days prior to commencing CPAP. They attended hospital having fasted and omitted their morning diabetes medications. A medical history was obtained, including questions regarding duration of diabetes, complications of diabetes and current medication. Home blood glucose records were reviewed in order to ensure stable glucose control. Patients were examined to ensure they were clinically stable, with no uncontrolled heart failure, requiring

changes to medication. Their primary care physicians were asked not to change their medications during the three month duration of the study, unless it was essential, because of a change in diabetic control. A range of blood tests and assessments, described below, were completed. Subjects were asked not to change their diet or exercise habits for the duration of the study.

5.2.3.2 Randomisation

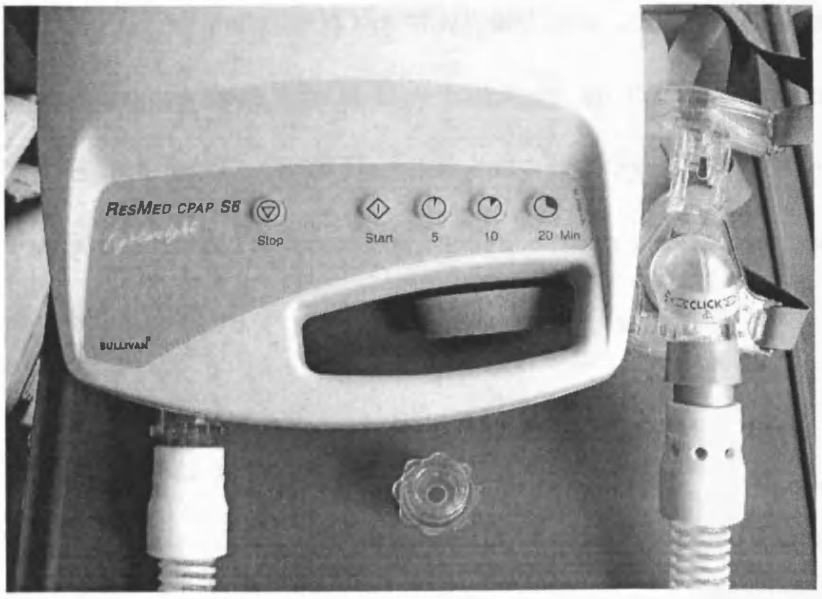
Following baseline studies, each subject was randomised to receive either therapeutic or placebo CPAP for three months in a double blind fashion. It was explained to the subjects that the CPAP provided would either be therapeutic or non-therapeutic. They were aware they were randomised in a double blind fashion to either treatment. Randomisation was by means of a balanced computer programme, with the randomisation criteria selected being 4% SaO_2 dip rate/hour, BMI, HbA1c and age (MINIM version 1.5, Evans S).

5.2.3.3 CPAP

CPAP was first used overnight at home, following an afternoon training and induction session, which is standard practice in the Oxford Sleep Unit. Two weeks after CPAP initiation, all patients were seen in the nurse-led CPAP clinic. If the patients had problems before or after this two-week visit, they were instructed to telephone the sleep nurses for advice. The nurses involved in the randomisation, CPAP initiation and ongoing CPAP care were separate to the study investigators. Those subjects receiving therapeutic CPAP had autotitrating machines (Autoset Spirit, ResMed UK). Autotitrating machines adjust pressure according to inspiratory flow limitation, snoring and apnoeas, and are as effective as polysomnography at performing overnight CPAP

titration (Stradling 1997). They have been used to initiate CPAP treatment, either at home or in hospital, or for long-term therapy (Planes 2003, Berry 2002, Konermann 1998, Gagnadoux 1999). Those receiving placebo CPAP had the same machines, set to their lowest pressure, with a flow-restricting connector inserted at the machine outlet and six extra 4mm holes inserted in the collar of the main tubing to allow air escape and to prevent rebreathing of carbon dioxide (Figure 1). A pressure of <1cm H_20 but >0 was delivered, which is insufficient to hold open the pharynx. These methods of placebo CPAP provision have been described previously (Jenkinson 1999, Hack 2000, Pepperell 2002). The data from the CPAP machines were downloaded at the second study visit to give the usage (hours CPAP used per 24 hours, measured as mask-on time, on nights worn, and number of nights used) and treatment pressure (over the time period during mask-on time).

***Figure 12**. Photograph showing placebo CPAP. A restrictor valve in the outlet port is visible, as well as 6 extra 4mm holes in the rubber collar of the connecting tube at the mask end, to allow more air to escape. The machine is set at its lowest pressure.*



5.2.3.4 Study visit following CPAP treatment

After three months of CPAP treatment, the baseline studies were repeated. Details of any medication changes were noted. The studies were performed at the same time of day as the pre-treatment measures, in order to reduce any unnecessary variation in the measures. All the studies were performed by the same two investigators (SW & DN). The investigators performing the repeat tests were unaware of the patients CPAP treatment group and were not involved in the set-up or maintenance of the machines. Therefore despite the physical nature of the treatment, the study was effectively double blind. At the end of the study, all subjects were informed of their treatment group and those receiving placebo CPAP were changed to therapeutic CPAP.

5.2.3.5 Ethics

As the waiting list to commence CPAP treatment for National Health Service patients at the Oxford Sleep Unit was five months at the time of this study, we were able to ethically justify administering placebo CPAP for three months, as subjects taking part in the study commenced CPAP within one to two weeks. Participants who received placebo CPAP completed the study and then commenced therapeutic CPAP and this took no more time than if they had been on the routine waiting list. Subjects gave written informed consent and the study was approved by the local ethics committee (04/Q1605/5). All subjects were given written information about the study (Figure 6, Appendix 1).

5.2.4 Measures of sleepiness

Subjective sleepiness was measured by the ESS (Johns 1991), and objective sleepiness was measured once, using a modification of the Maintenance of Wakefulness test

(OSLER), a behavioural sleep resistance challenge, where the patient is required to stay awake in a darkened sound protected room, responding to a regularly flashing light by pressing a sensor (Bennett 1997). The test terminates when the patient fails to respond to seven flashes in a row (21 seconds, or assumed sleep), or after 40 minutes.

5.2.5 Measures of self reported health status

The Sleep Apnea Quality of Life Index (SAQLI) questionnaire is a disease specific quality of life measure, recording the key elements of sleep apnoea which are important to patients. It has been used as a measure of outcome in clinical trials related to sleep apnoea (Flemons 1998, 2002). The Short SAQLI has been devised and validated by the same authors and as it is more straightforward to administer and use, was selected for use in this study. The Short Form-36 (SF-36) was also completed. The SF-36 questionnaire has been used to measure decreased quality of life in several disorders, including OSA, and shows large improvements following CPAP therapy, especially the Energy and Vitality dimension (Jenkinson 1997, 1999). These variables were measured to confirm patients were responding to therapeutic CPAP, compared to the placebo group.

5.2.6 Measures of insulin resistance

Insulin resistance was assessed by both a homeostasis model assessment (HOMA) and euglycaemic hyperinsulinaemic clamp on a single day. Studies were carried out after an overnight fast. Baseline blood samples were collected for the determination of glucose and insulin for HOMA. An antecubital vein was cannulated for blood sample collection. The contralateral antecubital vein was cannulated for glucose and insulin infusions. The arm from which blood samples were taken was heated to obtain arterialized samples.

Three basal blood samples were obtained at five minute intervals for glucose and insulin determination (Abbott Aeroset Analyser, UK, insulin respectively).

5.2.6.1 Euglycaemic clamp

Following the basal sampling, subjects underwent a hyperinsulinaemic euglycaemic clamp (DeFronzo 1979) (discussed in section 2.10.3.1). Blood glucose was measured every three minutes by HemoCue Glucose 201 (HemoCue AB, Sweden). A priming insulin infusion (Human Actrapid 100iμ/ml, NovoNordisk, Denmark) of 600mU min^{-1} m^{-2} for 10 minutes was followed by a maintenance infusion at a rate of 100mU min^{-1} m^{-2} into a peripheral vein. Body surface area was determined using height, weight and the formula from DuBois (DuBois 1988). A variable rate glucose infusion (glucose intravenous 20% w/v, Fresenius Kabi, UK) was administered to maintain euglycaemia (6.0mmol/l) via a peripheral vein. Blood glucose sampling was performed every three minutes from a contralateral vein, which was cannulated and warmed to provide an arterialised sample. The infusion rate was adjusted at three minute intervals on the basis of blood glucose concentrations which were entered into an iterative computer programme (Matthews 1989). The programme assembled an array of changes in the glucose concentration according to certain infusion rates running at the time and predicted the infusion rate required to achieve a given change of concentration. Some people have used algorithms based on preconceptions of body functions to predict glucose infusion rates in the euglycaemic hyperinsulinaemic clamp, but these can give inflexible infusion rates. Others prefer subjective determination of infusion rates, but this can lead to observer bias. The euglycaemic clamp was continued for 150 minutes to achieve steady state. Plasma samples were collected at five minute intervals for the last 30 minutes of the clamp for determination of insulin concentrations. Subjects who were

more insulin resistant required less exogenous glucose to maintain their blood glucose at 6 mmol/l and *vice versa*. Subjects were kept awake for the duration of the clamp, in order to avoid any confounding effects of sleep on glucose metabolism, as sleep is recognised to decrease glucose uptake (verbal communication, David Matthews). Plasma glucose and HbA1c were analysed fresh. Other blood samples were placed on ice immediately and, following centrifugation, plasma samples were stored at -70°C.

5.2.6.2 Homeostasis model assessment (HOMA)

HOMA is a structural mathematical model which interrelates fasting plasma insulin and glucose to derive measures of beta-cell function (%B) and insulin sensitivity (%S) from basal plasma glucose and insulin (or c-peptide) concentrations (Matthews 1985). Using a computer model, HOMA-%B and HOMA-%S are calculated (Levy 1998). The model is adjusted to yield median 100%B and 100%S in normal subjects. It has been discussed further in section 2.10.2.1. The %B cannot be assessed from insulin and glucose measurements alone in subjects who are receiving exogenous insulin for diabetes (Wallace 2004). We did not use it therefore in this study on any of the subjects as a proportion was receiving insulin.

5.2.7 Other blood tests

HbA1c (Menarini 8140 Analyser, UK), adiponectin (AutoDelfia 1235 Analyser, Perkin Elmer, Finland), fasting lipids (cholesterol, HDL-cholesterol, triglycerides) (Abbott Aeroset Analyser, UK), highly sensitive CRP (Dade-Behring BN II Analyser, Germany), free fatty acids (Wako NEFA C enzyme assay, Wako Chemicals) and platelet catecholamines (Spectra Physics SP 4290 integrator) were measured at baseline and at the end of the study.

5.2.7.1 HbA1c

HbA1c is discussed in section 2.9.2. Essentially, the HbA1c level reflects the prevailing blood glucose concentration over the previous 1 to 2 months and is hence a surrogate measure of the average concentration of plasma glucose. A change in HbA1c following a therapeutic intervention of 0.5% or more would be regarded as clinically significant (verbal communication, David Matthews).

5.2.7.2 Adiponectin

Serum adiponectin is discussed in section 2.5.3. Adiponectin is an adipocyte derived peptide with insulin sensitizing properties. It is decreased in adiposity and increases after weight reduction and higher levels correlate with increased insulin sensitivity (Tschritter 2003).

5.2.7.3 Lipids

Fasting lipids were measured because a collective analysis of blood from several randomised trials performed by our unit had shown a clinically and statistically significant fall in cholesterol following CPAP treatment (Robinson 2004). We wanted to determine whether this fall was replicated in this study.

5.2.7.4 HS-CRP

C-reactive protein (CRP) is a non-specific marker of inflammation. Highly sensitive CRP has been found to be a marker of sub-clinical atherosclerosis and raised levels provide a sensitive predictor for cardiovascular mortality (Pearson 2003). Sleep deprivation has been found to cause raised HS-CRP in healthy subjects (Meier-Ewert 2004), leading to hypotheses that the sleep loss associated with OSA may cause

increased systemic inflammation, atherosclerosis and subsequently increase cardiovascular disease. OSA is associated with higher CRP levels than controls, with the severity of the OSA being proportional to the level of the CRP (Shamsuzzaman 2002, Minoguchi 2005, Zouaoui 2005). One month of treatment with CPAP significantly decreased HS-CRP levels (Yokoe 2003), leading to speculation that CPAP may improve cardiovascular risk in people with OSA. HS-CRP concentrations have been found to be raised in obese individuals and in those who are insulin resistant (McLaughlin 2002). People with metabolic syndrome, with or without type 2 diabetes, have also been found to have higher HS-CRP levels than people without metabolic syndrome (Frohlich 2000, Rodilla 2006), with abdominal obesity being the feature of metabolic syndrome most closely related to the CRP levels. Weight loss from calorie restriction causes a significant fall in CRP levels and improvement in insulin resistance in those who are insulin resistant, independent of obesity (McLaughlin 2002).

5.2.7.5 Free fatty acids

Free fatty acids are metabolised in the cellular mitochondria along with glucose and lactate for adenosine triphosphate (ATP) production. People with diabetes are known to have increased fatty acid oxidation and decreased glucose and lactate oxidation in the cardiac mitochondria, which is less energy efficient (Stanley 1997). The increased levels of fatty acids in type 2 diabetes have been found to negatively correlate with cardiac muscle energy metabolism, measured by magnetic resonance spectroscopy (Scheuermann-Freestone 2003). Treatment with rosiglitazone significantly decreased free fatty acid levels and improved cardiac muscle energy metabolism (Scheuermann-Freestone 2006, submitted). We chose to measure free fatty acid levels to determine whether they were decreased by CPAP treatment. A sample of venous blood was taken

in an EDTA tube and centrifuged at 4000 rpm for 10 minutes, after which the plasma was removed and frozen at -70°C prior to analysis of all the samples collectively.

5.2.7.6 Platelet catecholamines

Platelet catecholamine levels are a novel technique of measuring circulating catecholamines. They have not been used previously in studies of OSA; however, it is known by the traditional techniques of urinary catecholamine measurement that both noradrenaline and adrenaline levels are increased in OSA and these levels decrease with CPAP treatment (Mansfield 2004). Catecholamines are known to be concentrated and retained within platelets after plasma catecholamine concentrations have returned to normal. The retention half life is 23 and 44 hours for adrenaline and noradrenaline respectively (Pierce 1999). Hence the platelet catecholamine levels reflect the ambient catecholamine concentration during the life of the platelet, which is approximately 10 days. A rise in circulating catecholamines, as occurs with the repeated apnoeas and arousals in OSA, would mean platelet catecholamine levels would be expected to be raised in people with untreated OSA and decrease following CPAP treatment. To assess this, a sample of venous blood was taken in an EDTA tube and centrifuged slowly at 1100rpm at 4°C for 10 minutes, in order to obtain a sample of platelet rich plasma. This had EGTA preservative added. An aliquot of platelet rich plasma was removed and stored, and the remaining plasma was centrifuged again for 10 minutes at 3000 rpm, to yield a sample of platelet free plasma and a platelet pellet. These were separated and stored frozen at -80°C for later analysis. On the same day as the study visit, a full blood count was analysed and a plasma platelet count was obtained from a sample of the platelet rich plasma. All the samples were sent to the University of Nottingham for catecholamine extraction at the end of the study. Platelet concentrations were based on

the concentration of catecholamines in the platelet rich plasma and the platelet count per ml of platelet rich plasma. As exercise can affect platelet catecholamine levels, subjects were asked not to undertake strenuous exercise for 24 hours prior to their study visits.

5.2.8 Measures of body composition

Subjects had their height and weight recorded, body mass index (BMI) calculated and neck, waist and hip measurements made. The waist was measured half way between the lower ribs and the iliac crest and the hips at the level of the greater trochanter. The same person performed the measurements at each visit. Body composition was measured using bioelectrical impedance analysis (Bodystat 1500, UK). This is a non-invasive simple technique which gives a complete analysis of body fat and lean mass (Lukaski 1985). It involves attaching four self-adhesive electrodes to the reclining subject's right hand and foot and connecting them to the analyser. Information regarding the subject's gender, age, weight and height were inputted prior to impedance measurement. The average activity was set at 'medium' for all subjects. A small electric current is passed through the body and an impedance value is calculated, which relates to the subject's body fat and lean proportions. The lean compartment (everything which is not fat, including bone, muscles, viscera) is a good conductor of current due to its high water content, whereas fat is a poor conductor with high impedance.

5.2.9 Measures of activity

Activity was quantified using wrist worn actiwatches (Cambridge Neurotechnology Ltd, UK). These are compact electronic devices containing accelerometers, which measure and record intensity, amount and duration of physical movement. Actigraphy has been recognised as being an important tool in sleep research over the last decade,

particularly for documenting sleep-wake patterns and hence diagnosing some sleep disorders (Sadeh 2002). Actiwatches have been used in the diagnosis of OSA (Elbaz 2002, Ayas 2003). There is, as yet, no published work of actigraphy performed before and after the treatment of OSA. The actiwatches were set for one minute epochs. Subjects were asked to wear the actiwatches for the whole of a nine day period, taking them off only for washing or swimming, and they were asked to press the event marker button on the front of the actiwatch to mark the times they took the watch off and put it on and also to mark the times they went to sleep at night and when they arose in the morning. Subjects wore the same actiwatch on each of the two monitoring periods. The actiwatches were returned at the end of the nine day period and were automatically downloaded via a computer reader. Automatic activity analysis using software was completed for seven consecutive days (of the nine days recording) following both the baseline tests and the second study visit after three months of CPAP (Actiwatch Monitoring System, Cambridge Neurotechnology Ltd, UK). The same weekdays were analysed in each seven day period (for example, Wednesday to Tuesday on both recordings). We opted to use the average activity as one measure, calculated from the seven consecutive days and nights displayed on the actogram (Figure 2). This activity analysis included sleep and wake times and gave a mean 24 hour activity score. Then, via the non-parametric circadian rhythm analysis, we obtained an average score for the most active 10 consecutive hours/day (M10) over the preceding week and the least active 5 consecutive hours/day (L5) (Figure 3). L5 is presumed to represent sleep.

5.2.10 Twenty-four hour blood pressure

Subjects were fitted with an ambulatory blood pressure monitor to wear for 24 hours as an outpatient during normal activities (TM2420, 2421, Takeda A&D, Japan). It was

programmed for cuff inflation measurements every 30 minutes throughout the 24-hour period, including sleep time. By averaging the 48 readings a 24-hour mean systolic and diastolic pressure was obtained. A single mean blood pressure was calculated from this (one third of the systolic pressure plus two thirds of the diastolic pressure).

5.2.11 Analysis

The primary end point was the change in HbA1c measured after 3 months of therapeutic or placebo CPAP. Secondary end points were changes in insulin sensitivity measured by euglycaemic clamp and HOMA. Differences between groups (using the change from baseline as the outcome variable) were assessed with unpaired student's t-tests. A Chi-squared test was used to compare the proportions in each group on different diabetes therapy. Non-normally distributed data were logarithmically transformed before applying parametric statistical tests and data are reported as geometric means. Activity data was analysed using non-parametric tests. A p value of <0.05 was considered to be statistically significant. Analysis was performed with SPSS version 12.0.

5.2.12 Study size

The study was powered not to miss a difference of 0.8 in HbA1c (assuming a within subject SD of 0.8) (Phillips 2003) at a significance level of 5% and with a power of 90%, which required 20 subjects in each treatment group.

Figure 13. *Actogram showing measures of activity as vertical black lines, with higher lines representing more activity. Sleep is shown in the areas of minimal black lines. The box on the right shows the automatic calculation for the average 24 hour total activity score, calculated from a seven day period.*

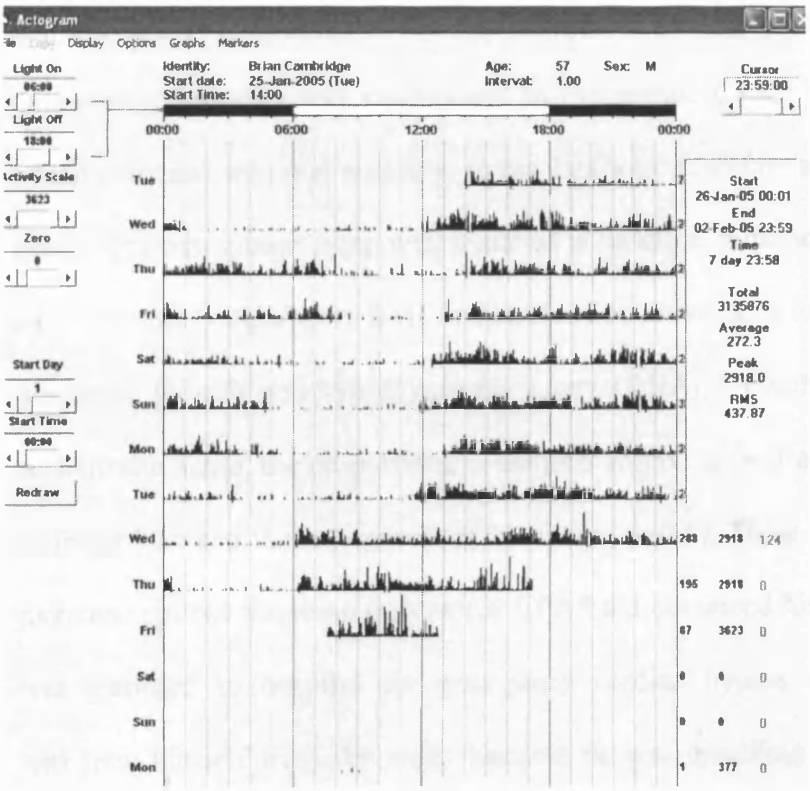
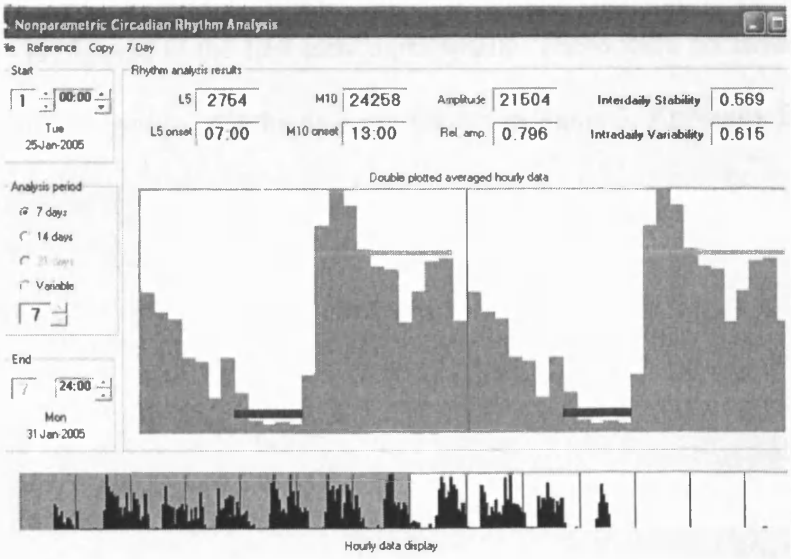


Figure 14. *Nonparametric circadian rhythm analysis showing automatic calculation of the most active 10 consecutive hours/day (M10) (higher bars) over the preceding week and the least active 5 consecutive hours/day (L5) (lower bars).*



5.3 Results

Figure 4 shows a flow chart of the study. Forty-eight men were considered for entry to the study: four declined entry and two were unsuitable, so 42 were enrolled. Twenty-one men were randomised to receive therapeutic CPAP, 21 to receive placebo CPAP. One patient however was randomised to therapeutic CPAP had a defective machine which delivered minimal pressure, so his data were therefore analysed with the placebo group. The two groups were well matched at baseline, with no significant difference in age, >4% SaO_2 dips/hour, BMI or HbA1c. For diabetes, 5 subjects were treated with diet only, 23 with oral hypoglycaemic agents (OHA), 23 with insulin and OHA and 4 with insulin alone; the proportions of subjects receiving treatment were not significantly different between the two groups (Chi-square, p=0.6). There is completion data on 40 men: one patient receiving therapeutic CPAP did not attend his second study visit, as he was admitted to hospital for emergency cardiac bypass surgery and one patient withdrew himself from the study because he was unwilling to continue using CPAP (randomised to placebo). Patients who attended and had poor or negligible CPAP usage were included and analysed on an intention to treat basis. Further per protocol analysis was performed, with these poor compliers excluded. Euglycaemic clamps were performed on 33 of the study participants; technical difficulties meant these were not performed in the first nine participants. There were no adverse events reported in either of the groups. All the data are shown in Table 3, Appendix 2.

Figure 15. Flow diagram of randomised controlled trial

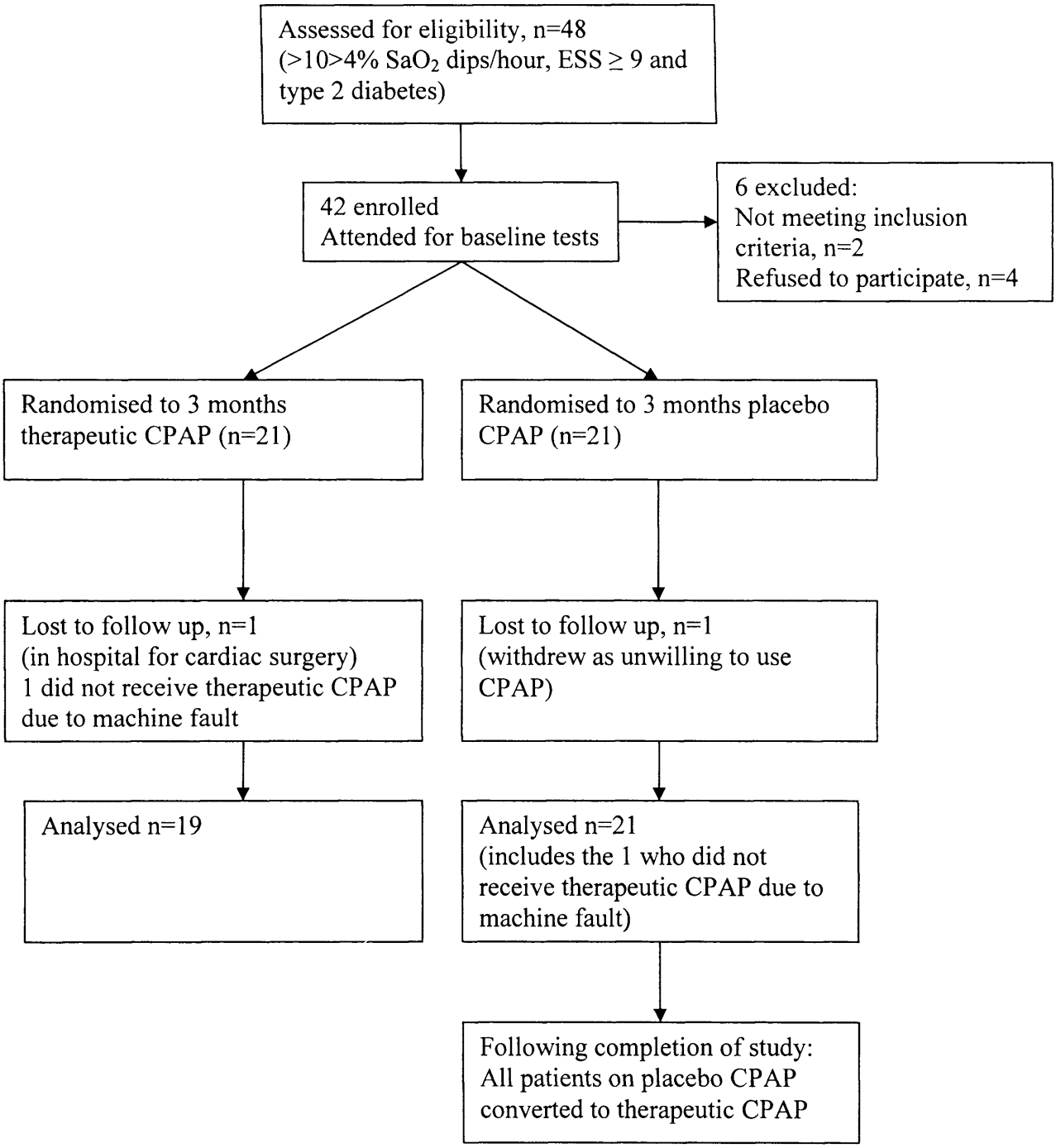


Table 12. Baseline measurements and changes from baseline in subjects randomised to therapeutic and placebo CPAP. Data are shown as mean (SD), †geometric mean (SD).

	BASELINE		**CHANGE FROM BASELINE (Δ)**		
	Therapeutic CPAP n=20	**Placebo CPAP n=22**	**Therapeutic CPAP n=19**	**Placebo CPAP n=21**	P (for Δ)
Age (years)	57.8 (10.4)	54.5 (9.4)			
>4% SaO_2 dips/hr	31.7 (19.6)	39.2 (23.6)			
ESS	14.7 (3.5)	13.6 (3.5)	-6.6 (4.5)	-2.6 (4.9)	0.01
MWT (Osler) (mins)	21.9 (12.8)	32.0 (10.8)	+10.6 (13.9)	-4.7 (11.8)	0.001
BMI (kg/m^2)	36.6 (4.9)	36.8 (4.6)	-0.2 (1.0)	-0.2 (1.1)	1.0
SAQLI	4.3 (1.1)	4.4 (0.9)	+0.8 (1.1)	+0.03 (1.2)	0.04
Neck size (cm)	46.2 (2.6)	47.0 (2.6)	+0.04 (1.2)	-0.06 (1.4)	0.8
Waist to hip ratio	1.0 (0.06)	1.1 (0.06)	0 (0.3)	0 (0.4)	0.5
Impedance	426.4 (91.3)	404.9 (39.5)	-3.8 (28.4)	+9.3 (31.2)	0.2
Fasting glucose (mmol/l)	10.1 (3.6)	10.0 (4.5)	+0.3 (2.1)	-0.2 (2.1)	0.5
HbA1c (%)	8.5 (1.8)	8.4 (1.9)	-0.02 (1.5)	+0.1 (0.7)	0.7
Fasting plasma insulin (pmol/l)	93.3 (1.7)†	100.0 (1.8)†	+1.3 (1.6)	+1.1 (1.7)	0.4
HOMA-%S	47.9 (1.6)†	44.7 (1.7)†	-1.5 (2.3)†	-1.1 (1.8)†	0.2
M/I: euglycaemic clamp ($l/kg/min^{1000}$)	26.5 (14.4)	27.8 (17.9)	+1.7 (14.1)	-5.7 (14.8)	0.2
Adiponectin ug/ml	3.7 (2.2)†	2.8 (1.5)†	-1.1 (1.2)†	-1.1 (1.3)†	0.2

There was no significant difference in any of the baseline data between the groups (p range 0.3 to 0.9), except for MWT, $p<0.01$ and adiponectin, $p=0.05$.

5.3.1 HbA1c

HbA1c did not change significantly following CPAP treatment in either of the groups (therapeutic -0.02 (1.5), placebo +0.1 (0.7), 95% CI -0.6% to +0.9%, p=0.7) (Table 1). Per protocol analysis with the non and poor CPAP compliers removed remained non-significant for change in HbA1c between groups (Therapeutic n=14, -0.1 (1.1), placebo n=18, -0.07 (0.7), 95%CI -0.7% to +0.6%, p=0.9). The changes in HbA1c and adiponectin were found to be not normally distributed and therefore the two groups were recompared with the Mann-Whitney test, but this made no difference and the results remained non-significant (p=0.3 and 0.4 respectively).

5.3.2 Measures of daytime sleepiness

Subjective sleepiness, measured by the ESS, improved in both groups following CPAP treatment (Table 1), but the change was significantly greater in the group receiving therapeutic CPAP ($p<0.01$). Objective sleepiness, measured by the modified MWT, improved significantly in the group receiving therapeutic CPAP, by a mean of 10.6 minutes ($p<0.001$). This change in MWT was similar to Oxford's previous randomised controlled trial in this area (+7.0 mins), and the change in ESS was of an effect size (1.9) nearly as large as this previous study (2.2), in which the patients had less comorbidity (Jenkinson 1999). The SF-36 and SAQLI data are shown in Tables 4 and 5 respectively, Appendix 2.

5.3.3 Insulin sensitivity

Results are shown in table 1. The clamp characteristics are as follows: the mean (SD) blood glucose concentrations over the last 20 minutes of baseline euglycaemic clamp were 5.9 (0.5) mmol/l in the therapeutic CPAP group and 5.9 (0.5) mmol/l in the

placebo group (p=0.8); and in the repeat clamp were 6.1 (0.8) mmol/l and 5.9 (0.5) respectively (p=0.5). This shows that the subjects in both groups were effectively "clamped" to the same level, with a steady blood glucose and steady glucose infusion. Comparison between the two groups is therefore possible.

There was no significant change in insulin sensitivity in either the therapeutic or placebo CPAP groups after three months of treatment. The plasma insulin concentrations during the baseline and final euglycaemic clamps were not significantly different. The geometric mean (SD) plasma insulin concentrations over the last 30 minutes of the baseline clamp were 1412 (7) pmol/l in the therapeutic CPAP group and 1445 (1) pmol/l in the placebo group (p = 0.6); and in the repeat clamp geometric mean (SD) plasma insulin concentrations were 1445 (1) pmol/l and 1479 (1) pmol/l respectively (p=0.8). Insulin sensitivity (M/I) is expressed as the quantity of glucose metabolised (M) per unit of plasma insulin concentration (I), data obtained from the euglycaemic clamp. At the end of the study, M/I had changed by +1.7 (14.1) in the therapeutic CPAP group compared with -5.7 (14.8) in the placebo CPAP group (p=0.2, 95% CI -1.8 to +0.3 l/kg/min^{1000}). A positive change indicates an improvement in insulin resistance. HOMA-%S, changed by -1.5 (2.3) in the therapeutic group and -1.1 (1.8) in the placebo group (p=0.2, 95% CI -0.3 to +0.08%). There was no correlation between change in M/I with change in weight, BMI, waist to hip ratio, bioelectrical impedance, HbA1c, %S, adiponectin or change in physical activity.

5.3.4 Adiponectin

Adiponectin did not change significantly following CPAP treatment in either of the groups (therapeutic -1.1 (1.2), placebo -1.1 (1.3), p=0.3, 95% CI -0.7 to +0.6 ug/ml) (Table 1).

5.3.5 Lipids

There was no significant change in HDL cholesterol, cholesterol or triglycerides following CPAP treatment in either of the two groups (table 2).

5.3.6 HS-CRP

There was no significant change in HS-CRP following CPAP treatment in either of the two groups (table 2).

5.3.7 FFA

There was no significant change in FFA following CPAP treatment in either of the two groups (table 2).

Table 13. Lipids, HS-CRP and free fatty acids baseline measurements and changes from baseline in subjects randomised to therapeutic and placebo CPAP. Data are shown as mean (SD).

	BASELINE		**CHANGE FROM BASELINE**		
	Therapeutic CPAP n=20	**Placebo CPAP n=22**	**Therapeutic CPAP n=19**	**Placebo CPAP n=21**	P (for Δ)
Total cholesterol (mmol/l)	4.2 (1.0)	4.17 (1.25)	0.2 (0.8)	-0.2 (1.1)	0.2
HDL-cholesterol (mmol/l)	1.04 (0.3)	1.0 (0.2)	0.2 (0.2)	0 (0.2)	0.8
Triglycerides (mmol/l)	1.9 (1.1)	2.4 (1.9)	-0.005 (0.7)	+0.3 (1.8)	0.4
HS-CRP (mg/l)	2.4 (2.5)	2.5 (4.5)	+0.6 (2.5)	+2.5 (6.7)	0.2
FFA (mmol/l)	525.6 (164.3)	520.2 (258.6)	+76.7 (179.4)	+64.4 (72.4)	0.9

5.3.8 Platelet catecholamines

Overall, there was no significant change in any of the measures used to calculate the circulating platelet catecholamine levels and no change in the circulating platelet catecholamine levels themselves following CPAP treatment in either of the two groups (table 3). Although there was a significant change in the adrenaline level in the platelet rich plasma in the placebo group, this did not contribute to a significant overall change in the platelet adrenaline levels following the final calculations.

Table 14. Platelet catecholamine baseline measurements and changes from baseline in subjects randomised to therapeutic and placebo CPAP. Data are shown as mean (SD).

	BASELINE		**CHANGE FROM BASELINE**		
	Therapeutic CPAP n=20	**Placebo CPAP n=22**	**Therapeutic CPAP n=19**	**Placebo CPAP n=21**	P (for Δ)
Platelet free plasma					
Noradrenaline (nmol/l)	2.5 (1.1)	2.3 (1.1)	-0.04 (1.3)	+0.08 (1.6)	0.8
Adrenaline (nmol/l)	1.4 (0.9)	1.2 (0.6)	+0.03 (1.2)	-0.08 (1.1)	0.8
Platelet rich plasma					
Noradrenaline (nmol/l)	3.5 (1.6)	3.6 (1.2)	+0.2 (1.4)	-0.2 (1.8)	0.4
Adrenaline (nmol/l)	0.1 (0.1)	0.2 (0.3)	+0.04 (0.1)	-0.07 (0.2)	0.05
Platelet pellet					
Noradrenaline (nmol/l)	1.01 (0.8)	1.0 (0.9)	-0.2 (0.8)	-0.2 (0.7)	0.9
Adrenaline (nmol/l)	0.04 (0.05)	0.04 (0.06)	+0.2 (0.9)	+0.3 (0.7)	0.9
Plasma platelet count $x10^9$/L	351 (100)	338 (110)	-22 (84)	+11 (112)	0.3
Overall platelet catecholamines					
Noradrenaline (nmol/l)	3.5 (2.6)	3.2 (3.2)	+0.04 (2.4)	-0.6 (3.5)	0.5
Adrenaline (nmol/l)	0.3 (0.7)	0.07 (0.3)	-0.06 (0.3)	-0.2 (0.6)	0.4

5.3.9 Measures of body composition

There was no significant change in any of the measures of body mass index, waist to hip ratio, neck size or bioelectrical impedance over the 3 month period in either of the two groups (table 1).

5.3.10 Actigraphy

There was no significant difference in any of the baseline activity data between the groups (p range 0.1-0.8).There was an increase in M10 (the most active 10 consecutive hours/day over the preceding week) in both groups following CPAP treatment, but this was much higher in the group receiving therapeutic CPAP. The activity levels were highly variable however and these changes did not reach statistical significance (Table 4).

Table 15. Mean 24 hour activity, measured by actiwatches, baseline measurements and changes from baseline in subjects randomised to therapeutic and placebo CPAP. M10 represents the most active 10 consecutive hours/day and L5 the least active 5 consecutive hours/day, most likely sleep. Data are shown as mean (SD). Units are arbitrary.

	BASELINE		**CHANGE FROM BASELINE**		
	Therapeutic CPAP n=20	Placebo CPAP n=22	Therapeutic CPAP n=19	Placebo CPAP n=21	P (for Δ)
Average activity over 24 hours	161.3 (68.3)	179.1 (59.5)	-30.0 (75.2)	-5.2 (69.1)	0.3
Least active 5 hours (L5)	1208 (750)	1799 (1464)	-289 (846)	-354 (1640)	0.9
Most active 10 hours (M10)	16555 (7218)	17007 (5937)	+13273 (68264)	+683 (5940)	0.4

5.3.11 Twenty-four hour blood pressure

There was no significant change in either the mean 24 hour blood pressure, or the day or night time blood pressure following CPAP treatment in either of the two groups (table 5). Based on the data from a previous study, the sample size was too small in this study to detect a change in 24 hour blood pressure following CPAP (Pepperell 2002).

Table 16. Twenty-four hour blood pressure baseline measurements and changes from baseline in subjects randomised to therapeutic and placebo CPAP. Data are shown as mean (SD).

	BASELINE		**CHANGE FROM BASELINE**		
	Therapeutic CPAP n=20	**Placebo CPAP n=22**	**Therapeutic CPAP n=19**	**Placebo CPAP n=21**	P (for Δ)
Mean BP (mmHg)	91.5 (6.2)	95.4 (6.5)	-0.3 (4.5)	+0.3 (4.7)	0.7
Daytime BP (mmHg)	94.4 (7.4)	98.1 (7.0)	+0.7 (4.9)	-0.2 (6.6)	0.7
Night time BP (mmHg)	85.8 (6.0)	89.6 (9.7)	-1.1 (5.1)	-2.0 (6.0)	0.7

5.3.12 CPAP use

There was no significant difference in the mean number of hours for which CPAP was used on the nights it was actually used, between the two groups (table 6). Three subjects in the placebo CPAP group (14%), and five in the therapeutic CPAP group (26%), had on average below one hour per night of CPAP use per night worn over the last one month of the study period (effectively non-users). In the therapeutic CPAP group, there was no correlation between the hours of CPAP usage per night and the change in M/I, %S or HbA1c. Per protocol analysis with the non and poor CPAP compliers removed showed significant improvements in ESS and MWT favouring therapeutic CPAP, but remained non-significant for all the other variables measured, with no suggestion of an improvement in the therapeutic group. With all the poor compliers removed, CPAP usage was a mean of 5.4 hours per night in the therapeutic group (n=14) and 5.6 hours per night in the placebo group (n=18).

Table 17. CPAP use in all patients. Data are shown as mean (SD).

	Therapeutic CPAP n=19	Placebo CPAP n=21	P value
Mean hours on nights used over last month	3.6 (2.8)	3.3 (3.0)	0.8
% nights used over last month	74.8 (30.2)	65.4 (28.5)	0.4
Mean hours on nights used over last 3 months	3.3 (2.6)	3.5 (2.8)	0.9
% nights used over last 3 months	74.5 (29.3)	69.3 (26.6)	0.6
% with compliance <1 hour/night used	26	14	
Mean hours on nights used in those with >1hour/night compliance over last month	4.8 (2.3)	4.1 (2.7)	0.4
Mean hours on nights used in those with >1 hour/night compliance over last 3 months	4.4 (2.0)	4.2 (2.6)	0.8

5.3.13 Measures of self reported health status

The mean short SAQLI score improved following CPAP treatment in both groups, but the change between the groups was significant, in favour of therapeutic CPAP, p=0.04 (Table 7).

In the SF-36, the mean scores for the energy and vitality and mental component summary domains of the SF-36 improved in both groups following CPAP treatment, but the improvements in the two groups compared were not significant. The mean score for the physical component summary decreased in both groups, but again, this was not statistically significant (Table 7).

Table 18. SF-36 baseline measurements and changes from baseline in subjects randomised to therapeutic and placebo CPAP. Data are shown as mean (SD).

	BASELINE		**CHANGE FROM BASELINE (Δ)**		
	Therapeutic CPAP n=20	**Placebo CPAP n=22**	**Therapeutic CPAP n=19**	**Placebo CPAP n=21**	P (for Δ)
SAQLI	4.32	4.30	+0.8	+0.03	0.04
Energy and vitality	49.0 (22.8)	52.0 (21.3)	+11.8 (14.5)	+8.9 (15.8)	0.6
Physical component summary	136.5 (216.4)	121.8 (204.3)	-75.4 (209.6)	-63.2 (200.0)	0.9
Mental component summary	57.9 (22.4)	60.0 (19.7)	+8.7 (25.1)	+2.7 (18.0)	0.4

5.4 Discussion

5.4.1 Overall findings in HbA1c and insulin resistance

This double blind randomised controlled trial, using therapeutic and placebo CPAP for three months, in men with type 2 diabetes and obstructive sleep apnoea, has not shown any significant improvement in glycosylated haemoglobin or insulin resistance measured by euglycaemic clamp and HOMA. This suggests that CPAP has no significant effect on glycaemia or insulin resistance in this setting. As anticipated, subjects receiving therapeutic CPAP experienced significant improvements in their subjective and objective sleepiness and sleep apnoea quality of life scores, similar to our previous studies (Jenkinson 1999, Pepperell 2002), indicating that CPAP was effectively treating their OSA, but this was not accompanied by improvements in glycaemic control or insulin resistance.

There were no significant changes in any of the other variables which were measured, despite the clinical response of improvement in OSA. In comparison, a previous study showed large and significant changes in adiponectin, along with significant changes in M/I, following treatment with 45mg pioglitazone (Wallace 2004). Following three months of pioglitazone treatment, HbA1c significantly improved (-0.3%, p=0.003), as did HOMA-%S (+25%, p=0.02), M/I (+15 l/kg/min^{1000}, p=0.009) and adiponectin (3.9μg/ml, p=0.00004). These results demonstrate that large, significant improvements in all these measures are achieved with pioglitazone, whereas the small improvements in HbA1c and M/I found in the CPAP group in our study are not statistically significant and are unlikely to be clinically significant. The validity characteristics of the euglycaemic clamp (mean and SD of the measures of blood glucose concentrations over the last 20-30 minutes and SD of M/I) in this pioglitazone study were comparable to

those in our study. Adiponectin is therefore another marker, along with %S and M/I, which can be used to determine if there is a change in insulin resistance, but in this study, it did not significantly change. The fact that neither the primary outcome measure of HbA1c, nor any of the other variables associated with insulin resistance changed, adds validity to the consistent findings of this study.

This study was powered not to miss a difference of 0.8 in HbA1c (based on a within subject SD of 0.8). This was a large change and it may have been more appropriate to power the study not to miss a difference of 0.4 in the HbA1c. In this case 60 people would have been required in each group at a significance level of 5% and with a power of 80%. This study was not powered to find significance for each of the secondary end points.

5.4.2 Overall findings of other variables measured

Many of the variables were measured in this study in order to further investigate potential mechanisms of improvement in insulin resistance following CPAP, if this had occurred.

5.4.2.1 Blood pressure and SF-36

Blood pressure and SF-36 domain scores have been shown in other randomised controlled studies to improve with CPAP treatment (Pepperell 2002, Jenkinson 1999). These studies were however powered so as not to miss any changes in these variables and the numbers recruited were much higher than in this study. As this study was designed not to miss any changes in HbA1c, it is therefore not surprising that significant changes were not seen in these variables. It is not clear why the physical component

summary of the SF-36 decreased following CPAP treatment in both groups, but these changes were not statistically significant.

5.4.2.2 Lipids

Cholesterol has previously been noted in randomised placebo controlled trials to significantly decrease following CPAP treatment (Robinson 2004). There were 108 patients who received therapeutic CPAP in this study and clearly the power of this study to detect this change was much greater.

5.4.2.3 HS-CRP

We did not find any improvement in HS-CRP following CPAP in this study, but again, the study was not powered to assess change in HS-CRP. The previous study published in this area which found HS-CRP decreased following CPAP treatment recruited 30 patients with OSA, but had no controls (Yokoe 2003).

5.4.2.4 Free fatty acids

There have been no studies published which have measured free fatty acids in OSA. Although it has been found previously that rosiglitazone treatment for type 2 diabetes improves free fatty acids in 12 patients in a randomised controlled trial (Scheuermann-Freestone, submitted), we did not find a similar effect with CPAP. It is difficult to know whether we failed to detect a change due to the sample size, or whether CPAP does indeed not change free fatty acid levels. A further study would need to be performed to determine this.

5.4.2.5 Platelet catecholamines

No previous studies have been performed on platelet catecholamine levels in OSA. Plasma catecholamine levels decrease following therapeutic CPAP treatment, and it was hypothesised that platelet catecholamine levels would also decrease following treatment. Whether this change occurs in OSA is not known however, and again, we cannot be sure whether we failed to detect a change due to the sample size, or whether CPAP does indeed not change platelet catecholamine levels. This also needs further study.

5.4.2.6 Body composition

No significant changes in body mass index, neck size, waist or hip measurements or bioimpedance were noted. Subjects had been asked not to change their diet or activity for the duration of the study, as weight gain or loss would have been a confounder for changes in insulin resistance. Clearly these instructions were well adhered to.

5.4.2.7 Activity

Activity measurements with actiwatches have not previously been reported in the context of a randomised controlled trial, before and after CPAP. We hypothesised that activity would increase following therapeutic CPAP, as people were less sleepy. This increased activity might decrease insulin resistance. People with untreated OSA have increased activity at night due to sleep disturbance compared to people without OSA; this therefore leads to some difficulties with the interpretation of the data, as effective treatment for OSA may decrease nocturnal activity, increase daytime activity, but not lead to any change in total activity. The most active 10 hours (M10) in a 24 hour period, reflecting isolated daytime activity, did increase much more following treatment in the

therapeutic CPAP group compared to the placebo group, although the results were not statistically significant. This suggests daily activity is increased following CPAP, but an adequately powered randomised controlled study would need to be performed to confirm this.

5.4.3 Patients selected and CPAP duration

The patients studied all had well established type 2 diabetes. The development of type 2 diabetes reflects progressive decline in pancreatic beta-cell function rather than increasing insulin resistance (UKPDS 1995). Studies of drug therapy in patients with type 2 diabetes receiving different therapies have shown significant improvements in insulin resistance, typically within three months (Miyazaki 2001, Yamasaki 1997). The use of CPAP for three months would therefore seem to be long enough for any changes in insulin resistance or glycaemic control to occur. It would be difficult to ethically justify giving placebo CPAP for longer than three months in this symptomatic group. It is possible that CPAP might be effective in a pre-diabetic group, by improving the activity of the still functioning beta-cells and hence improving insulin resistance.

5.4.4 The importance of the control group and discussion of other studies

The inclusion of a control group treated with placebo CPAP is particularly important in a study of insulin resistance. Glycaemic control and insulin resistance may be influenced by taking part in a study, regardless of the intervention, as people are more likely to modify their behaviour, knowing they are being monitored. It would be impossible in an uncontrolled study to attribute any changes purely to the intervention concerned.

There have been several studies published assessing the effect of CPAP on insulin resistance. These have been discussed previously in section 1.3.7. None of these studies used a control group, which leads to concern regarding the interpretation of the results. Without a control group, it is difficult to attribute any changes in glycaemic control solely to CPAP and not to the effect of being monitored in a study. Insulin resistance is subject to change from many possible confounding variables. Not only this, but it has also been noted previously that the clamp procedure itself increases sympathetic nervous system activity, presumably because patients are uncomfortable and anxious, and this is likely to increase insulin resistance (Moan 1995). Control patients who underwent a clamp procedure, but received only saline, had increases in plasma norepinephrine similar to the increases found in patients undergoing a euglycaemic clamp with insulin and glucose. By a second clamp, patients are likely to have acclimatized to the situation, and insulin resistance is hence reduced (Punjabi 2004), and by the third clamp this acclimatization would be greater. This effect makes the inclusion of a control group mandatory, so that changes in insulin resistance are not falsely attributed to the intervention concerned (Moan 1995). One study, assessing change in insulin resistance in people with type 2 diabetes commenced on either pioglitazone or placebo, showed that insulin resistance (measured by euglycaemic clamp) was improved in both groups after three months, although the improvement was greater and statistically significant in the pioglitazone group (41% vs. 10% in the controls) (Wallace 2004). The control group improvement was likely to be due at least in part to acclimatization to the clamp procedure itself, as well as other factors such as better adherence to diet and medication, or increased exercise. We did not see such improvements in either group in our study, but it could be questioned whether the 18% and 31% improvement found in insulin resistance by Harsch *et al* (Harsch 2004) after 2

days and 3 months respectively is not in fact due to CPAP, but due to clamp acclimatisation or study effect and confounding variables.

5.4.5 CPAP compliance

It could be argued that the mean CPAP compliance figures of less than 4 hours use per night in our study might account for the lack of improvement in glycaemic and insulin resistance variables. If subjects had used their CPAP for longer, decreasing the number of apnoea-related arousals and the resultant sympathetic nervous system activation, would they have improved their insulin resistance? We do not think this is the case. Firstly, the mean CPAP compliance was clearly great enough in the therapeutic group to improve their OSA, by making a significant difference to sleepiness and symptoms as measured by ESS, MWT and SAQLI, whereas the placebo group experienced no significant improvement. If the sleepiness had improved, the number of apnoea-related arousals were likely to have decreased, along with the associated sympathetic nervous system hormone surges. Secondly, there was a range of mean compliance over the preceding month, from zero use to 9.1 hours per night, with poor and good compliers being found in both the therapeutic and placebo groups. We could find no correlation between any of the measures of insulin resistance or HbA1c and CPAP compliance. We would have expected positive correlations if improvements in insulin resistance were associated with compliance. Indeed, even the study by Harsch at al showed no correlation between CPAP use and the improvements in insulin resistance (Harsch 2004). This is surprising, given the treatment of OSA was thought to have led to the improvements in insulin resistance found, via decreased sympathetic nervous system activation. Thirdly, per protocol analysis with the poor compliers excluded also showed

no significant improvement in any of the study outcome measures, except for ESS and MWT. So we are clear that the outcome of our study is not due to lack of CPAP use.

It is interesting that the CPAP usage in hours per night is lower than previous studies performed by the Oxford group (Jenkinson 1999, Hack 2000, Pepperell 2002). In these studies, all the patients were recruited via the Oxford Sleep Clinic, to which they had been referred because of symptoms of sleepiness. In this study, most patients were recruited in this manner (n=30, 71%), but the remainder were recruited via the prevalence study described in chapters 2, 3 and 4. These men had newly diagnosed symptomatic OSA but had not sought help for their symptoms and had not been referred to the Sleep Clinic. They may therefore have represented a slightly different group of patients, and as they had not sought help, perhaps they were less willing to use CPAP and this brought the overall compliance figures of the group down. The compliance figures for the men recruited via clinic however were not significantly different to those of the men recruited via the prevalence study (3.6 and 3.2 hours/night respectively, Chi square p=0.6). There were also no significant differences in compliance for either population group when analysed according to whether they received therapeutic or placebo CPAP.

5.4.6 Ethics of using placebo CPAP

It has been thought in the past that as CPAP is a physical therapy, a truly double blind randomised controlled trial of its effects would be impossible. An identical placebo device delivering an ineffective pressure to the upper airway, about which the patient is unaware, was an important development in randomised controlled trials of CPAP (Davies 1993). Placebo CPAP made no difference to polysomnographic variables in 10

patients with confirmed OSA (Farre 1999). Several large studies have now used placebo CPAP, with the observers carrying out investigations being blinded to the treatment groups (Jenkinson 1999, Hack 2000, Dimsdale 2000, Barbe 2001, Ziegler 2001, Pepperell 2002, Becker 2003, Arias 2005). The use of placebo CPAP in other studies has been found to be associated with a significant improvement in the ESS and in some domains of the SF-36 and even changes in hormone levels, such as aldosterone and insulin growth factor-1 (Jenkinson 1999, Meston 2003). Objective sleepiness, measured by the maintenance of wakefulness test, does not change, however, as was seen in this study. Overall, this indicates a positive placebo effect and that effective blinding is possible. Hence the effects of CPAP can be studied and compared to placebo CPAP in a methodologically rigorous way.

In this study, it was important that an appropriate control group was used, as we wanted to try and obtain conclusive data regarding the effects of CPAP on insulin resistance, because the existing research in this area has not used any control groups. Results could therefore be affected by a number of different confounding variables. We therefore obtained ethics committee permission to use placebo CPAP for three months in half the trial participants. As there was a long NHS waiting list for CPAP of more than five months, the trial was felt to be ethically justifiable in this context. It would be difficult to justify placebo CPAP for three months in these symptomatic patients if this was delaying their treatment overall. The use of people who were non-compliant with CPAP as a control group would not have been appropriate as it is recognised that non-compliers in any area of medicine do not tend to be representative of the group as a whole.

5.5 Conclusion

This is an important area of research, as OSA, insulin resistance and type 2 diabetes are all increasing in prevalence as the population obesity levels increase. It is essential that well-conducted studies using control groups are performed in order to draw valid conclusions. Our randomised placebo controlled study adds evidence that CPAP is not effective in improving insulin resistance and glycaemic control in men with established type 2 diabetes and obstructive sleep apnoea. Routine treatment of OSA in patients with type 2 diabetes is unlikely to result in improved diabetic control through a direct effect on insulin resistance.

Chapter 6

Final discussion and future work

Chapter 6

Final discussion and future work

6.1 The findings of this research

In the first part of this thesis, a questionnaire study with targeted sleep studies showed OSA to be highly prevalent in men with type 2 diabetes, with estimated prevalence figures of between 17 and 24%. This is much more common than the prevalence of OSA in the general population shown in previous studies, or the prevalence of OSA in a control group of men from Oxfordshire (4% and 6% respectively) (Young 1993, Stradling 2000). Diabetes was found to be an independent risk factor for OSA, with concurrent type 2 diabetes increasing the 4% SaO_2 dip rate on average by five per hour. Much of the OSA in people with type 2 diabetes is caused by obesity, but this study shows that diabetes itself confers an additional risk of OSA.

In the second part of this thesis, a randomised controlled study established that the treatment of OSA with three months of CPAP in men with type 2 diabetes made no significant difference to measures of glucose control, insulin resistance and other metabolic variables. As a blinded placebo CPAP control group was used, we can be confident that these results are reliable, and not subject to bias or confounders. The fact that there was consistency across the changes found in many different variables adds validity to this study.

6.2 Relevance of this research to the field of OSA and type 2 diabetes

The prevalence of obesity is increasing worldwide. As more people become overweight and obese, the prevalence of obstructive sleep apnoea and type 2 diabetes will increase.

Following the described prevalence study, increased recognition of individuals with type 2 diabetes and previously undiagnosed OSA is likely. Health care planners will need to allocate sufficient resources to OSA management, in order to manage these increased demands.

CPAP is an effective treatment for OSA and relieves the associated symptoms of daytime sleepiness, snoring and apnoeas. As recognition of the conditions associated with OSA (such as hypertension, increased cardiovascular risk, insulin resistance) has increased, so clinicians have considered whether CPAP might be an effective way to treat not only OSA, but also the associated conditions. The question has been raised as to whether individuals, who are asymptomatic from OSA and would not usually receive CPAP treatment, should receive CPAP in order to treat the associated condition. It is crucial that these questions are answered with robust evidence from well-conducted randomised controlled trials, in order for patients to be treated optimally and for resources to be used appropriately. As the evidence for the association of insulin resistance with OSA has increased (Punjabi 2002, Ip 2002), and the large number of patients with OSA and type 2 diabetes has been recognised (Meslier 2003), it has been discussed whether treatment of OSA with CPAP would improve the associated insulin resistance and if so, whether CPAP may be an effective primary treatment for insulin resistance. A small number of uncontrolled studies did show an improvement of insulin resistance with CPAP (Harsch 2004, Brooks 1994), but these did not take account of all the possible confounders of insulin resistance. Following the randomised controlled trial discussed in this thesis, CPAP has not been shown to be an effective treatment for insulin resistance or glycaemic control in men with established type 2 diabetes. CPAP is not therefore an appropriate additional therapy for type 2 diabetes in patients with OSA.

6.3 Future research

The possible reasons as to why type 2 diabetes confers an additional risk of OSA in people are an area of interesting future research. It would be important to establish whether the upper body obesity distribution is different firstly in an individual with type 2 diabetes compared to an individual without type 2 diabetes and secondly in someone with type 2 diabetes and OSA compared to someone with type 2 diabetes without OSA. Comparing pharyngeal area with magnetic resonance imaging in these study groups would be a valuable measurement tool, to establish whether their upper airways are different, causing predisposition to OSA. Finding suitable controls with which to match the cases is often difficult in these studies, as matching based on body mass index, waist to hip ratio or even abdominal slice visceral fat measured by computerised tomography can be difficult. Controls are often found to have either type 2 diabetes or OSA and adequate screening for each of these two conditions with fasting blood glucose tests and overnight oximetry would be necessary.

Daytime sleepiness is one of the key symptoms in people with untreated OSA, which improves with CPAP. This is regarded differently to symptoms of fatigue and tiredness by sleep physicians. Fatigue and tiredness are usually thought not to be caused by OSA, but are multifactorial and do not change with CPAP. Fatigue and tiredness are reported to be highly prevalent in people with type 2 diabetes (thought to be due to the type 2 diabetes per se, personal communication, David Matthews). A study of the symptoms of OSA in patients with type 2 diabetes could therefore be performed. Participants could be recruited from the hospital clinic and would all perform overnight oximetry. They would also complete an Epworth sleepiness score, as well as questionnaires evaluating fatigue and tiredness. It would be important to determine whether those with OSA on

oximetry had higher levels of fatigue and tiredness compared to OSA patients without type 2 diabetes. The response of these symptoms to CPAP would also be relevant. It may be that people with type 2 diabetes and OSA manifest fatigue rather than daytime sleepiness, perhaps due to their comorbidity and OSA may therefore be under recognised.

At present, the evidence of whether CPAP improves insulin resistance in people who do not have established pancreatic beta cell failure is lacking. It may be that those with insulin resistance but without type 2 diabetes do have an improvement in insulin resistance following CPAP, as they may be more responsive to possible change. It will be important to repeat the randomised controlled trial of three months of CPAP in a group of pre-diabetic men, who have documented insulin resistance. As yet the question of whether CPAP affects insulin resistance in people with OSA has only been answered for people at one end of the beta cell failure spectrum. This question needs answering adequately with controlled trials, particularly in light of the current conflicting published trial data.

Following the research described in this thesis, the relationship between OSA and type 2 diabetes has been further delineated. The findings that OSA is highly prevalent in men with type 2 diabetes, and that CPAP does not improve the insulin resistance or glycaemic control of men with OSA and type 2 diabetes, are important in the light of the current epidemic of obesity. As the prevalence of both OSA and type 2 diabetes increases, clinicians need to be increasingly aware of the relationship between obesity, OSA and insulin resistance and detect and treat these conditions appropriately.

Appendix 1

Figure 1. Initial letter sent to patients with the questionnaire

The Oxford Centre
for Diabetes, Endocrinology and Metabolism

(Incorporated within the Nuffield Department of Medicine of the University of Oxford)

Professor David R Matthews MA (Oxon) DPhil FRCP
Chairman of the Oxford Centre
Consultant Physician
University of Oxford Professor in Diabetic Medicine

Oxford Centre for Diabetes, Endocrinology & Metabolism
Churchill Hospital
Headington
Oxford
OX3 7LJ

April 2004
OCREC 03.091

Dear Sir

Study of Obstructive Sleep Apnoea in people with type 2 Diabetes

The Sleep Unit at the Churchill Hospital has recently asked us to undertake a joint research project. They want to find out more about a common condition called Obstructive Sleep Apnoea in people with diabetes.

You are being invited to take part in the research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends and relatives if you wish. Ask us if there is anything that is not clear, or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

What is Obstructive Sleep Apnoea?
People with Obstructive Sleep Apnoea (OSA) tend to snore and stop breathing whilst they are asleep. This causes a disturbed night's sleep, and therefore people can often be sleepy in the daytime. When OSA is diagnosed in patients, effective treatment is available, in the form of a mask to wear at night, attached to a machine (called CPAP).

What is the purpose of the study?
The Sleep Unit is interested in finding out how common it is for people with diabetes to have OSA, as it may be a particular problem affecting the control of their blood sugar levels.

Why have I been chosen?
As you have Type 2 (adult onset) diabetes, you have been selected from the list of all the people with this condition held by OCDEM or your GP.

Do I have to take part?
It is up to you to decide whether or not to take part. If you do decide to take part you can keep this information sheet and you are still free to withdraw at any time and without giving a reason. This would not affect the standard of care you receive.

What would happen to me if I take part?
We would be grateful if you would complete the enclosed questionnaire about yourself and your sleep habits and send it back in the envelope provided. It should take less than 10 minutes of your time. We would like you to fill in the questionnaire even if you don't think you have Obstructive Sleep Apnoea, or if you already know that you do. Your answers will be kept confidential. We will pass the questionnaire on to the doctors at the Sleep Unit to look at. They would like to look at your notes to look at your current diabetes treatment and your last blood sugar result.

From the answers you give in your questionnaire, you may be selected for some further tests, to see if you have any OSA. The first test would involve wearing a simple sensor on your finger overnight whilst you sleep at home to measure your oxygen levels. If this test were normal, they would not suggest any further tests. If the test were to show a suggestion of OSA, they would then arrange for you to have a more detailed diagnostic sleep study. This would involve wearing a belt and a recording device during sleep at home, to measure your heart rate and breathing patterns. This would give them a better understanding of your sleep patterns. They would ask for you to sign a consent form before they did these tests. A doctor or nurse would visit you at home with the equipment and could answer any of your questions. They would then arrange for this equipment to be collected from your house and they would give you clear written instructions on how to use it.
If your sleep studies were normal or negative, they will write and let you know.
If they found from your sleep studies that you did have some OSA, they would invite you to attend their clinic to discuss whether you would need or want any treatment for this.

What are the possible benefits of taking part?
OSA is a common condition and it is important to diagnose it if you have it. The treatment for it can improve your sleep quality and feelings of daytime sleepiness. It has recently been found out that treatment can improve your blood pressure as well. People with diabetes have not been looked at in detail before to see whether and how OSA affects them.

What are the possible disadvantages of taking part?
It will take about 10 minutes to fill in the questionnaire. If you are selected for overnight studies, these will be in your own home to minimize any inconvenience for you. The sleep studies are easy to perform, but you would need to wear some simple monitoring equipment to bed, and this can sometimes be slightly uncomfortable.

Who should I contact for further information?
Dr Sophie West from the Sleep Unit is running the study. You can contact her at the Churchill hospital on 01865 225227.

Thank you for reading this.
Yours faithfully

Professor David Matthews, OCDEM

Figure 2. Questionnaire sent to patients with type 2 diabetes

The Oxford Centre
for Diabetes, Endocrinology and Metabolism

Questionnaire for people with Diabetes taking part in Obstructive Sleep Apnoea Research

OCREC No. C03.091

ABOUT YOU

Name: .....
Date of Birth: .....
Address: .....
.....
.....

How tall you are? _____feet/m

How much do you weigh? _____lbs/kgs

What is your collar size? _____inches/cm

Please can you measure round your neck with the enclosed tape measure, just below your Adam's apple, onto your skin. Don't worry if you can't do this.

YOUR DIABETES

1. **When did you develop diabetes?** Year _____

Is your diabetes treated with: Insulin
Diabetes tablets
Diet
Please tick all that apply

YOUR SLEEPING HABITS

Please tick the boxes for the appropriate answers.

2. Have you ever been diagnosed with Obstructive Sleep Apnoea? Yes
No

If yes, do you have treatment for this? Yes No
Please tick: CPAP Jaw device

Now please go to Q.11

3. **Do you snore?** Yes
No
Don't know

If you do snore, is your snoring :
Slightly louder than breathing
As loud as talking
Louder than talking
Very loud. Can be heard in adjacent rooms

YOUR SLEEPING HABITS (continued)

4. **How often do you snore?**
Nearly every night
3-4 times a week
1-2 times a week
1-2 times a month
Never or nearly never

5. **Has your snoring ever bothered other people?** Yes No

6. **Have people who have shared your bedroom told you that you snore?**
Nearly every night
3-4 times a week
1-2 times a week
1-2 times a month
Never or nearly never

7. **Has anyone ever noticed that you stop breathing during your sleep?**
Nearly every night
3-4 times a week
1-2 times a week
1-2 times a month
Never or nearly never

8. **Have other people told you that you gasp, choke or snort while you are sleeping?**
Nearly every night
3-4 times a week
1-2 times a week
1-2 times a month
Never or nearly never

9. **How often do you feel tired or fatigued on waking in the morning?**
Nearly every day
3-4 times a week
1-2 times a week
1-2 times a month
Never or nearly never

10. **When you are awake, do you feel tired, fatigued, or not up to par?**
Nearly every day
3-4 times a week
1-2 times a week
1-2 times a month
Never or nearly never

11. **Are you known to have high blood pressure?** Yes No
If yes, are you taking medication for this? Yes No

THANK YOU VERY MUCH FOR YOUR TIME.

Figure 3. Score sheet for Questionnaire

SLEEPING HABITS

3. **Do you snore?**	Yes	1
	No	0
	Don't know	0

If you do snore, is your snoring :	Slightly louder than breathing	0
	As loud as talking	0
	Louder than talking	1
	Very loud. Can be heard in adjacent rooms	1

4. **How often do you snore?**	Nearly every night	1
	3-4 times a week	1
	1-2 times a week	0
	1-2 times a month	0
	Never or nearly never	0

5. **Has your snoring ever bothered other people?**	Yes	1
	No	0

6. **Has anyone ever noticed that you stop breathing during your sleep?**

Nearly every night	1
3-4 times a week	1
1-2 times a week	0
1-2 times a month	0
Never or nearly never	0

(The next two questions were not in the original Berlin questionnaire)

7. **Have people who have shared (or are sharing) your bedroom told you that you snore**?

Nearly every night	1
3-4 times a week	1
1-2 times a week	0
1-2 times a month	0
Never or nearly never	0

8. Have other people told you that you gasp, choke or snort while you are sleeping?

Nearly every night	1
3-4 times a week	1
1-2 times a week	0
1-2 times a month	0
Never or nearly never	0

Section 1 total /5 (plus score for additional 2 questions)

9. **How often do you feel tired or fatigued on waking in the morning?**

Nearly every day	1
3-4 times a week	1
1-2 times a week	0
1-2 times a month	0
Never or nearly never	0

10. **During your waketime, do you feel tired, fatigued, or not up to par?**

Nearly every day	1
3-4 times a week	1
1-2 times a week	0
1-2 times a month	0
Never or nearly never	0

Section 2 total /2

---

11. **Are you known to have high blood pressure?** Yes 1
No 0

If not hypertensive, score 1 if BMI 30kg/m

Section 3 total /1

Figure 4. Letter sent to patients regarding sleep studies

The Oxford Centre for Diabetes, Endocrinology and Metabolism

Oxford Centre for Diabetes, Endocrinology & Metabolism
Churchill Hospital
Headington
Oxford
OX3 7LJ

PA: (01865) 857312
Facsimile: (01865) 857313
E-Mail: david.matthews@ocdem.ox.ac.uk

Dear Sir

You recently kindly completed a questionnaire about yourself and your sleep habits. You may remember we are working with the OCDEM doctors to investigate Obstructive Sleep Apnoea (OSA) in people with diabetes. OSA is often found in people who snore and stop breathing at night.

From the answers you gave in your questionnaire, we would be interested to carry out some further tests on you, to see if you have any OSA.

The first test would involve wearing a simple sensor on your finger overnight at home whilst you sleep to measure your oxygen levels. If this test were normal, we would not suggest any further tests and we would write to you to let you know.
If the test were to show a suggestion of OSA, we would then arrange for you to have a more detailed diagnostic sleep study at home. This would involve wearing a belt and a recording device to bed, to measure your heart rate and breathing patterns. This would give us a better understanding of your sleep patterns. These tests are part of our usual clinical practice. They cause minimal discomfort or disruption.

One of the researchers, Dr Sophie West, would like to contact you by telephone in the next few days, to see if you would be willing to have these further tests. If so, she will then arrange a time for her or a colleague to visit, to deliver the overnight sensor and answer any questions you may have. She will also fill in a consent form with you, agreeing to have these tests done.

If you would like to contact her, or have further questions, please ring 01865 225227.

Yours sincerely

Dr Sophie West Professor John Stradling

Sleep Unit, Oxford Centre for Respiratory Medicine, Churchill Hospital, Oxford

Figure 5. Consent form for men having sleep studies performed

The Oxford Centre for Diabetes, Endocrinology and Metabolism

OCREC03.091

Professor David R Matthews MA (Oxon) DPhil FRCP
Chairman of the Oxford Centre
Consultant Physician
University of Oxford Professor in Diabetic Medicine

Oxford Centre for Diabetes, Endocrinology & Metabolism
Churchill Hospital
Headington
Oxford
OX3 7LJ

PA: (01865) 857312
Facsimile: (01865) 857313
E-Mail: david.matthews@ocdem.ox.ac.uk

Version 1, October 2003

Consent form (C)

Study of Obstructive Sleep Apnoea in people with type 2 Diabetes

Researchers: Dr Sophie West and Professor John Stradling

	Please initial box Yes	No
1. I confirm that I have read and understand the information sheet dated October 2003 about the above study of overnight sleep. I have had the opportunity to ask questions.	☐	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐	☐
3. I understand that sections of my medical notes may be looked at by responsible individuals from the Sleep Unit. I give permission for them to have access to my records.	☐	☐
4. I agree to take part in the above study.	☐	☐

Name of patient	Date	Signature
Name of person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature

Figure 6. Epworth Sleepiness Score

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 have not 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 = no chance of dozing
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

SITUATION	CHANCE OF DOZING
Sitting and reading	_____
Watching TV	_____
Sitting inactive in a public place (e.g a theater 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 traffic	_____

Consultant/Director:	Prof John Stradling	
Secretary:	Denise Roberts	01865 225236
Consultant:	Dr Rob Davies	
Secretary:	Nicky Richards/Amanda Brewerton	01865 225230
Consultant:	Dr Maxine Hardinge	
Secretary:	Jenny Lay	01865 225223
Consultant:	Dr Lesley Bennett	
Secretary:	Navraj Cooper	01865 225234
Sleep Clinic Nurses:	Debby Nicoll, Debbie Smith, Joy Crosby Beverly Langford-Wiley, Jo Williams, Tara Harris, Kate Mutendera	01865 225959
Research registrar:	Dr Sophie West	01865 225227

Sleep Unit, Oxford Centre for Respiratory Medicine
Churchill Hospital
Old Road
Headington
Oxford
OX3 7LJ

Fax: 01865 225221

Oxford REC:04/Q1605/5

12/05/2007

Dear Patient

Obstructive Sleep Apnoea in patients with type 2 diabetes: a double blind randomised controlled trial of the effect of therapeutic and sub-therapeutic CPAP on diabetic control, insulin resistance and blood pressure

You should have by now had the CPAP treatment explained to you by the doctor you saw in the clinic. It involves wearing a mask over your nose during sleep, which slightly raises the pressure at which you breathe and stops both heavy snoring and stopping breathing episodes, and thus prevents transient awakenings. As you are due to receive treatment with CPAP, we are inviting you to participate in a research study. We are investigating the effect of CPAP for Obstructive Sleep Apnoea in people with diabetes.

Before you decide whether you want to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

What is the purpose of the study?
We are interested in whether the CPAP treatment makes any difference to your sugar control, the diabetic medication you need, your insulin levels or your blood pressure. We are going to give half the people in the study the standard CPAP treatment and the other half will have sub-therapeutic CPAP, set at a pressure well below that normally used for treatment, which may not relieve all the symptoms of Obstructive Sleep Apnoea (but may be equally effective or ineffective in influencing your diabetes). A computer will select the groups randomly. Patients in each group having each different treatment can be compared. Neither you nor the research doctor will know which treatment group you are in.

Why have I been chosen?
You have because you have type 2 (maturity onset) diabetes and sleep apnoea. We are recruiting 40 patients in total.

Do I have to take part?
Taking part in the research is entirely voluntary. It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?
Before you start on CPAP, we will arrange another visit to the hospital. This will involve you seeing one of the researchers, Dr West and one of the sleep nurses. They will record details about your medical history and what medications you are taking. It would be useful to bring them or a list with you. They would also like to look at any recent records of what your sugars have been, if you check them at home. They will measure your weight, height, neck, hip and waist size. They would like to measure your ability to stay awake for 40 minutes, by lying down in a quiet darkened room, responding to a dim flashing light in front of you.

They would then perform some blood tests. These involve putting a small needle/cannula in both arms. One of these can then be used to take blood samples from. Through the other you will be given a drip of glucose and insulin for 2 hours. Blood tests to monitor your sugars will be performed regularly during this. This is to assess your body's insulin resistance levels. To do these blood tests accurately, it is important for you to be starved from midnight before the tests. Whilst you are having the drip, we will ask you to fill in some simple questionnaires about your symptoms. At the end of the drip test, we will give you lunch and make sure your sugars are stable. The study visit will take about 5 hours and we will perform it in the morning.

We will then ask you to have your blood pressure measured over a 24-hour period at home, with a standard system, which consists of a cuff worn around the upper arm that inflates every 30 minutes and takes a reading. We will also give you a device called an Actigraph to wear for the next week. This is a small device, worn like a wristwatch, and measures movement. It is used to measure how many hours each day you are asleep and how many you are active for. If you agree, we will let your GP know that you are participating in the study after your first study visit.

What happens after the first study visit?
You will be given a date after this to attend the Sleep Unit to learn about CPAP and to try the CPAP equipment. You will be given equipment to take home and use. After 2 weeks the sleep nurses will see you in their clinic to see how you are getting on. This is the same as you would receive even if you were not in the study.

After 3 months of using CPAP, we would like to see you again for a second study visit. We will repeat all the tests that we did at the first visit. We would also like to see if any of your medications have changed in this time, so please bring them with you. At this point, all patients on the sub-therapeutic low pressure CPAP will be changed onto standard pressure CPAP. We are also planning to store the blood samples we collect, so that we can perform further hormonal analysis on them in the future. You can say if you don't want us to do this.

All information collected about you during the course of the research will be kept strictly confidential. We will pay any travel expenses you incur from the study and provide you with a lunch voucher on the study days.

What are the potential risks and/or disadvantages of taking part?
Before you start on the CPAP treatment, and again after 3 months of treatment, you will be seen at the hospital for some extra tests, which will take most of a morning. These will include blood tests, which may cause some discomfort and occasionally bruising. There are no risks associated with this study.

Who is organising and funding the research?
The research is being organised by the Sleep Unit at the Churchill Hospital. They are being funded by the charity Diabetes UK. The Oxford Research Ethics Committee has reviewed the study. We hope to publish the results in Sleep and Diabetes journals.

Thank you for taking part in this study.

Yours faithfully,

Dr Sophie West	Debby Nicoll	Professor John Stradling
Oxford Sleep Unit	Oxford Sleep Unit	Oxford Sleep Unit
01865 225227	01865 225227	01865 225236

SPECIAL NOTE

This item is tightly bound and while every effort has been made to reproduce the centres force would result in damage.

Table 1: Questionnaire and sleep study data from hospital and primary

No	Age yrs	BMI kg/m2	Collar cm	DM yrs	Treatment	HbA1c	median	1	2	Known BP	BP treatment	Risk score	RISK	Known OSA	Treatment	Oxim 4%dip/hr	Mean SaO2	Min SaO2	ESS	Embletta AHI	Outcome
1	73	28.4	41.91	17	ins tab	7.6	0	0	y	y	1	L	n		2.3	94.9	86	10		
2	70	34.6	46.99	7	ins	9.1	4	2			3	H	n							
3	75	25.7	39.37	11	tab	7.5	2	0	n		1	L	n							
4	61	30.8	40.64	29	ins tab	8.8	0	2	y	y	2	H	n							
5	60	30.4	43.18	17	ins	7.9	3	1	y	y	3	H	n							
6	59	43.5	46.99	19	ins	8.7	2	1	n		3	H	n		5.5	93.5	84	9		
7	57	40.8	45.72	6	ins tab	8.9	4	2	n		3	H	n		3.3	95.4	84	17		
8	56	26.9	43.18	11	tab	8.2	4	1	n		2	H	n							
9	63	28.1	43.18	12	tab	8.2	4	2	y	y	3	H	n							
10	44	27.8	40.64	5	tab	11.2	4	0	n		1	L	n		2.8	95.6	89	13		
11	45	30.5	43.18	16	ins tab	11.4	2	0	y	y	2	H	n							
12	58	33.4	45.72	1	tab	9.9	0	0	n		1	L	n		4.2	97	89	3		
13	66	23.8	38.1	7	ins	7.3	6	1	n	y	2	H	n		16.8	92.9	76	8	12.3	No CPAP
14	40	36.7	43.18	3	tab	10.2	7	2	y	y	3	H	n							
15	68	36.1	35.56	8	tab	6.4							yes	n	2.3	94.4	90	12		
16	65	25.1	40.64	20	tab	7.3	1	0	n	y	1	L	n							
17	50	27.8	41.91	1	tab	9.8	2	0	y	y	2	H	n							
18	51	21	36.83	20	tab	10.1	0	0	n		0	L	n							
19	66	27.3	39.37	13	tab	8.4	6	2	n		2	H	n							
20	51	32.5	44.45	15	ins tab	11	7	0	y	y	2	H	n							
21	66	20.3	36.83	13	diet	6.3	2	2	n		2	H	n		0.04	95.6	90	10		
22	66	28.1	40.64	11	tab	6.8	5	1	y	y	3	H	n							
23	68	35.9	44.45	3	tab	7.5							yes	n						
24	71	26.5	40.64	2	ins tab	6.4	2	0	n		1	L	n							
25	58	23.1	40.64	29	ins	7.1	0	0	n		0	L	n							
26	49	25.7	39.37	8	ins tab	8.9	0	0	n		0	L	n		1.4	95.3	90	8		
27	57	36.9	43.18	1	tab	8.1	4	2	n		3	H	n							
28	43	34.1	50.165	3	tab	6.2	0	2	n		2	H	n							
29	54	26.5	35.56	2	tab	6.7	3	0	y	y	2	H	n		4.6	95.6	77	7		
30	61	25	40.64	8	ins tab	8	2	0	y	y	2	H	n							
31	64	35.2	45.72	22	ins tab	10.2	0	2	y	y	2	H	n		36.7	94.2	84	7	65	No CPAP
32	61	26.1	40.005	7	ins	8.3	0	2	y	n	2	H	n							
33	72	30.8	45.72	14	tab	8.7	0	2	y	y	2	H	n							
34	62	23.8	38.1	5	tab	12.5	2	2	n		2	H	n							
35	73	26.2	41.91	17	tab	6.6	0		y	y	1	L	n							
36	67	27	39.37		Diet	6.6	3	2	y	y	3	H	n		4.3	93.3	87	0		
37	46	26.2	39.37	3	tab	7.1	4	0	n		1	L	n							
38	59	21.8	41.91	3	tab	8.7	0	0	n		0	L	n							
39	65	33.6	43.815	12	ins	7.9	1	1	y	y	2	H	n							
40	70	32.2	45.72	35	ins	10.9	0	0	y	y	1	L	n							
41	51	26.2	39.37	6	tab	7.8	2	0	y	y	2	H	n							
42	75	26.4	41.91	8	tab	9.4	0	0	y	y	1	L	n							
43	67	21.5	40.64	26	diet	7.7	0	0	y	y	1	L	n							
44	65	29.9	41.91	5	tab	5.9	7	2	y	y	3	H	n		5.2	90.1	62	6		
45	66	36	44.45	4	tab	7.3	1	0	y	y	1	L	n							
46	50	26.5	40.64	16	tab	7	2	0	y	y	2	H	n							
47	64	34.2	45.72	23	ins	12.3	0	2	y		2	H	n		37.9	92.8	70	12	4	CPAP

Table 1. Questionnaire and sleep study data from hospital and primary care databases combined

No	Age yrs	BMI kg/m2	Collar cm	DM yrs	Treatment	HbA1c	section 1	2	Known BP	BP treatment	Risk score	RISK	Known OSA	Treatment	Oxim 4%dip/hr	Mean SaO2	Min SaO2	ESS	Embletta AHI	Outcome
48	46	30.5	41.91	31	ins	11.5	6	0	y	y	2	H	n		3.4	96	90	13		
49	47	36.7	44.45	3	tab	7.4	7	2	n		3	H	n							
50	65	22	41.91	24	ins	10.5	0	2	n		1	L	n							
51	67	26.1	43.18		ins	11.9	0	0	y	y	1	L	n							
52	53	31.8	43.18	3	tab	6.3	6	2	y	y	3	H	n							
53	59		44.45		ins	7.1	2	2	y	y	3	H	n							
54	75	27.1	40.64	9	tab	8.7	3	0	y	y	2	H	n							
55	56	23.8	38.1	26	ins	9.3	6	0	y	y	2	H	n							
56	56	21.9	40.005	7	ins	11	2	2	n		2	H	n							
57	74	27.8	41.91	22	ins	10.9	1	0	y	y	1	L	n							
58	50	32.6	44.45	4	ins tab	9.7	6	2	y	y	3	H	n		4.1	93.8	86	10		
59	50	27.1	39.37	4	tab	8.7	2	0	y	y	2	H	n		0.4	96.5	92	0		
60	66	34.7	48.26	16	ins	12	4	1	n		3	H	n							
61	55	26.2	40.64	9	ins tab		4	1	y	y	3	H	n							
62	70	23.6	43.18	15.5	tab	6.6	0	0	n	n	0	L	n							
63	51	33.2	43.18	12	tab	10.4	4	0	n		2	H	n							
64	39	27.5	40.64	17	ins	8.8	6	2	y		3	H	n							
65	54	33.2	46.99	5	ins tab	6.8	4	0	y	y	2	H	n							
66	74	22	40.64	20	tab	5.9	5	1	n		2	H	n		1.1	96.1	87	8		
67	51	28.3	44.45	8	tab	7.9	4	0	y	y	2	H	n							
68	56	27.4	44.45	20	ins	12	1	2	y	y	2	H	n							
69	70	39.4	50.165	20	ins tab	8.3							yes	CPAP						
70	73	25.1	41.91	22	ins tab	7.9	1	0	y	y	1	L	n		0.5	96.1	90	5		
71	52	25.4	40.64	17	ins	8.4	5	2	y	y	3	H	n							
72	67	32.3	46.99	9	tab	7.5							yes	CPAP						
73	66	25.2	41.91	31	ins	10	4	0	y	y	2	H	n							
74	53	29.5	40.64	13	ins tab		5	0	n		1	L	n							
75	59	30.2	43.815	5	ins	6.9	5	0	y	y	2	H	n							
76	49	38.2	50.8	1	diet	7.6	7	0	y	y	2	H	n							
77	59	28.8	43.18	25	ins tab	6.4	2	0	y	y	2	H	n							
78	69	28.1	45.085	2	diet	9.5	5	0	y	y	2	H	n		1.6	92.8	88	7		
79	63	24.7	39.37	14	tab	9.1			y	y			no							
80	62	29	43.18	3	tab	6.9	5	2	n		2	H	n							
81	73	27.3	40.64	8	diet	6.2	5	0	y	y	2	H	n		2.5	95.2	89	1		
82	71	37.2	50.8	10	ins tab	10.9	1	2	y	y	2	H	n							
83	67	27.1	45.72	9	ins	7.6	3	2	y	y	3	H	n							
84	75	29.2	40.64	8	ins	8.4	5	2	n	n	2	H	n							
85	58	28.9	44.45	1	tab	10	0	0	y	y	1	L	n							
86	64	26.5	43.18	10	ins	7.7	0	0	y	y	1	L	n							
87	66	30.2	40.64	2	tab	7.1	1	2	y	y	2	H	n		6.2	94.1	87	17		
88	74	32.2	44.45	10	tab	7.2							yes	CPAP						
89	70	24.1	40.64	19	ins	7.2	2	0	y	y	2	H	n							
90	54	27.8	41.91	8	tab	6.1	3	0	n		1	L	n		1.3	95.8	92	13		
91	41	28	38.1	7	tab	10.2	2	0	y	y	2	H	n							
92	60	33.5	45.72	4	tab	7.2	7	2	y	y	3	H	n		4.1	94.2	87	11		
93	56	28.1	43.18	13	ins	10.7	2	0	y	y	2	H	n							
94	66	24.7	40.64	23	ins	7.7	0	0	y	y	1	L	n							

Table 1: Questionnaire and sleep study data from hospital and primary care databases combined

No	Age yrs	BMI kg/m2	Collar cm	DM yrs	Treatment	HbA1c	section 1	2	Known BP	BP treatment	Risk score	RISK	Known OSA	Treatment	Oxim 4%dip/hr	Mean SaO2	Min SaO2	ESS	Embletta AHI	Outcome
95	66	30	41.91	6	tab	7.9	2	0	y	y	2	H	n		2.2	94.7	89	5		
96	68	34.3	43.18	9	tab	8.3	2	2	y	y	3	H	n							
97	53		43.18	12	ins	10.6	1	0	n	y	0	L	n							
98	47	32.6	44.45	5	ins tab	10.3	4	2	y	y	3	H	n							
99	55	36	46.99	12	tab	9.3	4	2	y	y	3	H	n							
100	59	31.4	44.45	9	tab	6	5	0	y	y	2	H	n							
101	73	33	43.18	14	ins tab	9.5	0	2	y	y	2	H	n							
102	57	41.7	45.72	3	diet	6.9	2	0	n	n	2	H	n							
103	75	24.9	41.91		tab	7.8	0	1	n	y	2	H	n		1	97.1	89	9		
104	73	23.4	38.1	36	diet	7.5	0	0	n		0	L	n							
105	64		0			9.1							no							
106	65	29.7	44.45	8	tab	8.6	0	0	y	y	1	L	n							
107	71	24.8	39.37	1	tab	10.7	0	0	n		0	L	n		13.1	94.7	82	2		refused
108	43	33.3	50.8	8	ins	10.3	3	1	n	n	3	H	n							
109	45	37	45.72	5	ins	6.9	5	2	y	y	3	H	n							
110	53	31.3	43.18		ins	9.3	0	0	n		1	L	n							
111	63	33	41.91	20	ins tab	9.7	0	0	n		1	L	n							
112	72	31.2	43.18	20	tab	8.5	5	2	y	y	3	H	n							
113	73	31.6	43.18		tab	6.5	1	0	y	y	1	L	n		19.6	93.3	86	1		Refused
114	73	24.7	39.37	10	tab	6.5	0	0	y	y	1	L	n		5.8	95.8	54	5		
115	43	30.4	44.45	3	tab	7.9	4	2	n		3	H	n							
116	76	34	48.26	9	ins tab	9.2	6	2	y	y	3	H	n							
117	64	25.4	39.37	14	ins tab	11.2	0	2	n		1	L	n							
118	57	26.4	53.34	10	ins tab	7	7	2	y	y	3	H	n							
119	44	33.3	43.18	2	diet	6.7	1	2	y	y	2	H	n							
120	49	29.7	45.72	4	ins tab	8.3	7	2	y	y	3	H	n		35.8	91.5	64	12	19.6	CPAP
121	61	25.2	39.37	2	diet	6.6	6	0	y	y	2	H	n							
122	75	25.2	39.37	16	tab	9.7	0	0	n		0	L	n							
123	61	37.9	48.26	12	ins	7.6	5	0	y	y	2	H	n							
124	75	25.1	43.18	22	tab	7.9	7	0	y	y	2	H	n							
125	54	29.4	43.18	14	ins	9.9	0	0	n		0	L	n							
126	53	31.8	41.91	4	tab	6.7	0	2	y	y	2	H	n							
127	64	24.9	35.56	16	ins	8.1	5	2			2	H	n		2.8	93.8	87	13		
128	71	24.1	39.37	10	tab	7.3	0	1	n	y	1	L	n							
129	60	35.6	46.99	11	ins tab	12	0	0	y	y	1	L	n							
130	63	37.3	46.99	24	ins tab	7.4	5	2	y	y	3	H	n							
131	62	33.2	45.72	20	ins tab	10.7	5	2	n		3	H	n							
132	72	44.3	53.34	8	tab	9.1							yes	CPAP						
133	53	24.1	40.64	8	ins	9.4	2	0	y	y	2	H	n							
134	66	26.5	42.545	7	ins tab	8.1	3	2	n		2	H	n							
135	75	24.7	40.64		ins	7.2	3	0	y	y	2	H	n							
136	57	22.5	41.91	10	tab	8.3	2	2	y	y	3	H	n							
137	47	30.9	43.18	2	tab	8.9	1	0	y	y	1	L	n							
138	50	35.7	48.26	6	ins tab	9.6	7	2	y	y	3	H	n							
139	73	28.7	43.18	20	ins	10.8	1	0	y	y	1	L	n							
140	69	34	45.72	5	diet	6.6							yes	n						
141	49	33.8	46.355	10	tab	8.1	3	1	y	y	3	H	n							

No	Age yrs	BMI kg/m2	Collar cm	DM yrs	Treatment	HbA1c	section 1	2	Known BP	BP treatment	Risk score	RISK	Known OSA	Treatment	Oxim 4% dip /hr	Mean SaO2	Min SaO2	ESS	Embletts AHI	Outcome
142	72	31.9	41.91	21	ins	7.6	0	2	y	y	2	H	n							
143	56	26.6	43.18	8	tab	5.8	4	0	n		1	L	n		0.5	95.3	88	8		
144	70		43.18	10	tab	7.8	0	2	y	y	2	H	n							
145	65	33.9	45.72	24	ins	8.5	7	2	y	y	3	H	n		15.2	94.4	54	9	31.3	no CPAP
146	68	20.2	41.91	21	tab	10.2	2	0	y	y	2	H	n							
147	64		0	5	tab	11.9	0	0	n	n	0	L	n							
148	57	23.7	38.1	7	ins	6.5	2	0	y	y	2	H	n							
149	72	27.5	44.45	22	ins tab	8.6	2	2	y	y	3	H	n		1.5	95.5	91			
150	65	22.6	39.37	6	diet	6.4	0	0	y	y	1	L	n							
151	75	26	41.91	1	tab	7.6	5	2	n		2	H	n		14	95.2	82	12	0	no CPAP
152	45	31.7	44.45	4	tab	6.5	3	2	y	y	3	H	n		0.3	96.4	88	8		
153	61	24.6	38.1	4	tab		0	0	n		0	L	n		4.4	96.5	87	13		
154	73	30.7	43.18	8	ins	6.1							yes	n						
155	52	29.1	43.18	8	tab	7.7	1	1	y	y	2	H	n							
156	64	23.7	39.37	12	ins tab	8.5	3	2	y	y	3	H	n							
157	75		0	8	tab	7.7							yes	CPAP						
158	65	26.6	41.91	20	ins	10	0	2	y	y	2	H	n							
159	62	23	38.1	12	tab	7.2	5	0	n		1	L	n							
160	75	28.6	43.18	11	ins	7.9	0	0	y	y	1	L	n							
161	53	34.5	44.45	8	ins	10.1	1	0	y	y	1	L	n		13.2	94.2	76	12	46.2	CPAP
162	33	46.1	50.8	3	ins	10.3	7	2	y	y	3	H	n							
163	71	32.1	45.72	22	ins	10.7	5	0	n		2	H	n							
164	44	21.1	38.1	9	ins tab	8.1	5	0	n		1	L	n							
165	58	44.25	49.53	12	ins tab	11.2	5	2	y	y	3	H	n		19.9	87.8	48	17	35.1	CPAP
166	57	30.4	40.64	24	tab	7.3	1	0	y	y	1	L	n							
167	62	30.4	40.64	25	tab	9.9	6	2	y	n	3	H	n							
168	61	22.9	38.1	5	tab	7.1	1	0	n		0	L	n							
169	71	32	41.91	4	ins	11	0	0	n		1	L	n							
170	56		40.64	13	ins	8.1	0	2	y	y	2	H	n							
171	75	26.4	44.45	18	tab	8.8	5	2	y	y	3	H	n		0.7	95.8	92	1		
172	62	28	41.91	18	tab		6	2	y	y	3	H	n							
173	64	27.7	43.18		tab	7.9	1	0	y	y	1	L	n							
174	67	25.6	36.576	44	tab	9	0	0	n		0	L	n		0.2	95.6	92	5		
175	52	39.3	48.26	4	ins tab	10.2	4	2	y	y	3	H	n							
176	61	25.2	40.64	20	tab	7	1	2	y	y	2	H	n							
177	59	24.4	40.64	32	ins	10.7	0	2	y	y	2	H	n							
178	65	30.6	41.275	2	tab	6.5	0	0	y	y	2	H	n							
179	68	24.6	41.275	3	tab	6.7	4	0	y	y	2	H	n							
180	66	27.7	41.91	12	tab	8.7			n				no							
181	73	35.7	41.91	14	tab	7.7	2	0	y	y	2	H	n							
182	54	27.9	43.18	13	tab	7.7			y	y			no							
183	53	25.9	36.83	23	ins	8.5	0	0	y	y	1	L	n		0.8	96.4	86	2		
184	54	37	45.72	14	ins tab	10.6	4	2	y	y	3	H	n							
185	55	34.9	45.72		diet	6.3	5	2	n		3	H	n		2.4	95.2	89	8		
186	58	28.5	43.18	4	tab	8.4	4	1	y	y	3	H	n							
187	35	22.8	41.91	3	tab	6	0	0	n		0	L	n		0.9	96.2	90	12		
188	73	31.6	43.18	3	ins	8.4	2	1	y	y	3	H	n							

Table 1: Questionnaire and sleep study data from hospital and primary care

No	Age yrs	BMI kg/m2	Collar cm	DM yrs	Treatment	HbA1c	section 1	2	Known BP	BP treatment	Risk score	RISK	Known OSA	Treatment	Oxim 4%dip/hr	Mean SaO2	Min SaO2	ESS	Embletta AHI	Outcome
189	57	34.5	45.72	22	ins	8.5	3	0	y	y	2	H	n							
190	66	33.5	43.18	5	tab	7.6	3	1	y	y	3	H	n							
191	55	28.6	40.005	3	tab	6.2	3	0	y	y	2	H	n							
192	60	32.6	45.72	6	ins	9.6							yes	n						
193	66	39.7	44.45	7	tab	7.9	2	1	y	y	3	H	n							
194	60	26.6	40.64	5	diet	6.6	0	2	y	y	2	H	n		1.3	95.1	89	6		
195	69	30.1	0	20	ins	6.9	4	1	y	y	3	H	n							
196	55	29.6	43.18		diet	7.2	4	0	n		1	L	n							
197	69		44.45		ins tab	9.6	0	0	n		0	L	n							
198	63	26.5	40.64	24	tab	9	7	0	y	y	2	H	n							
199	67	38.8	46.99	9	tab	7	2	0	n		2	H	n							
200	66		39.37	3	tab	7.3	3	0	y	y	2	H	n							
201	65	34.1	45.72	3	tab	8.1	6	2	y	y	3	H	n		3.5	94.6	89	12		
202	48	29.3	41.91	8	tab	9.8	6	2	n	n	2	H	n		1.8	95.08		16		
203	65	25.3	41.91	25	tab	7.1	0	0	n		0	L	n							
204	74	29.38	43.18	18	tab	7.3	4	0	n		1	L	n							
205	69	29.9	44.45		tab	8.1	5	0	y	y	2	H	n							
206	48	29.2	39.37	7	tab	7.3	3	1	y	y	3	H	n							
207	64	27.6	43.18		tab	12.3	3	0	n		1	L	n							
208	75		41.91	10	ins tab	8.2	2	1	y	y	3	H	n							
209	60	37	46.99	7	ins tab	7.1	7	2	n		3	H	n		15	92.9	51	21	41.2	CPAP
210	72	32	40.64	27	ins tab	8.7	0	2	y	y	2	H	n							
211	63	28.4	43.18	2	ins	7.5	0	0	y	y	1	L	n							
212	47	37.4	44.45	9	tab	7.6	0	0	y	y	1	L	n							
213	70	24.5	38.735	29	tab	7	5	2	n		2	H	n							
214	64	31.9	46.99	5	tab	6.9	3	0	y	y	2	H	n							
215	41	34.1	45.72	6	tab	6.6	4	1	y	y	3	H	n							
216	59	26.9	40.64	0.5	tab	9.9	2	0	n		1	L	n		1.4	96.3	92			
217	56	27.46	43.18	6	tab	7.5	1	0	y	y	1	L	n							
218	57	23.3	41.656	2	ins tab	7.2	1	0	n		0	L	n							
219	64	32.9	44.45	3	tab	6.9	2	0	y	y	2	H	n							
220	69	28	39.37	20	ins	6.4	2	0	y	y	2	H	n							
221	66	32.3	43.18	18	tab	10.8	0	0	y	y	1	L	n							
222	73	22.8	41.91	30	tab	7.6	4	0	n		1	L	n		2.8	95.3	88	7		
223	75	34.6	45.72	7	ins	8	7	2	y	y	3	H	n							
224	73	26.8	41.91	25	ins	8.2	2	2	y	y	3	H	n							
225	61	26.9	41.91	18	tab	6.8	1	0	n		0	L	n							
226	51	27.9	43.18	24	tab	6.4	0	0	y	y	1	L	n		2.2	94.5	87	2		
227	54	28.8	43.18	7	ins		5	0	n		1	L	n							
228	65	30.1	39.37	24	ins tab	7	7	0	n		2	H	n							
229	48	35.1	45.72	5	tab	7.8	0	1	n		2	H	n							
230	60		46.99	1	tab	6.2	5	0	y	y	2	H	n							
231	58	28.5	40.64		ins	7.3	2	0	y	y	2	H	n							
232	66	34.3	43.18	5	ins tab	6.7	0	2	y	y	2	H	n							
233	75		41.91	8	tab	7	6	1	y	y	3	H	n							
234	71	36.3	41.91	10	tab	10.9	0	0	y	y	1	L	n		2.6	94.7	85	9		
235	66	28.9	41.91	24	ins tab	7.5	0	0	n		0	L	n							

Table 1: Questionnaire and sleep study data from hospital and primary

No	Age yrs	BMI kg/m2	Collar cm	DM yrs	Treatment	HbA1c	section 1	2	Known BP	BP treatment	Risk score	RISK	Known OSA	Treatment	Oxim 4%dip/hr	Mean SaO2	Min SaO2	ESS	Embletta AHI	Outcome
236	71	22.5	36.83	11	ins	6.9	0	0	n		0	L	n							
237	66	40	53.34	19	ins	8.6							yes	CPAP						
238	44	22.2	38.1	4	ins	6.9	5	2	y	n	3	H	n		1.6	96.7	77	11		
239	62	37.9	45.72	3	ins	8.2	1	0	y	y	1	L	n							
240	63	26.3	38.1		ins	7.4	0	0	y	y	1	L	n							
241	48	31.4	44.45	4	tab	8.4	2	0	y	n	2	H	n							
242	73	29.2	41.91	4	Diet	6.2	6	2	y	y	3	H	n		4.9	93.4	84	17	47.3	RIP
243	71	30	43.18	12	tab	7.1	1	0	y	y	1	L	n							
244	52	26.6	39.37	3	tab	6.7	5	0	y	y	2	H	n							
245	56	28.6	0	0.5	tab	6.9	0	2	y	y	2	H	n							
246	64	25.3	40.64	27	ins	6.6	2	2	y	y	3	H	n		2.8	93.5	83	8		
247	73	23.2	39.37	8	tab	8.6	0	0	y	y	1	L	n							
248	59	24.9	43.18	23	ins	8.4	4	0	y	y	2	H	n							
249	55	35.2	45.72	7	ins tab	8	5	1	y	y	3	H	n							
250	75	30.6	41.91	15	ins	7.2	5	2	y	y	3	H	n							
251	52	37.8	50.8		ins	7.4	1	2	n		2	H	n							
252	47	35.5	44.45	5	tab	9.4	3	0	y	y	2	H	n							
253	58	35.5	45.72	12	ins	7.4	5	0	y	y	2	H	n							
254	54	23	38.1	4	tab	6.6	0	0	n		0	L	n							
255	71	26.5	43.18	6	tab	7.3	5	0	y	y	2	H	n							
256	71		0	5	tab	9.2	2	2	n		2	H	n		0.3	95	88	13		
257	67	27.5	41.91	16	ins tab	8.6	0	0	n		0	L	n		0.3	97.2	93	5		
258	72	25.3	44.45	27	tab	7.4	0	0	y	y	0	L	n							
259	67	24.4	39.37	6	tab	9.8	0	0	y	y	1	L	n							
260	62	29.1	41.275	18	ins tab	7.3	3	2	n		2	H	n							
261	61	30	44.45	8	ins	9.1	4	2	n		3	H	n							
262	63	28.6	41.91	4	tab	7.1	1	0	y	y	1	L	n		5.3	91.6	82	5		
263	67	23.4	0	14	ins	8	0	0	n		0	L	n		1.1	95.1	69	3		
264	39	28.9	40.64	8	ins	7.6	3	1	n		2	H	n							
265	74	23.8	40.64		tab	5.9	0	0	y	y	1	L	n		17	95.5	77	3	66.5	no CPAP
266	55	42.1	46.99	6	ins	8.4	5	0	y	y	2	H	n							
267	37	41.1	0		tab	9	0	0	y	y	1	L	n							
268	59	32.2	44.45	4	ins	6.5	4	0	n		2	H	n							
269	64	30	43.18	24	ins	7.9	0	0	y	y	1	L	n							
270	55	22.6	36.83	17	ins	10.5	3	0	y	y	2	H	n							
271	53	21.9	43.18	15	ins	10.9	3	2	n		2	H	n							
272	73	50	52.07	1	tab	7.6							yes	CPAP						
273	64	21.7	39.37	12	tab	5.3	6	2	y	y	3	H	n							
274	62	26.1	41.91	14	ins tab	8.4			n	y			no							
275	42	31.1	44.45	9	ins tab	7.4	0	2	n		2	H	n							
276	54		43.18	7	tab	6	2	0	y	y	2	H	n							
277	75	24.5	39.37	35	ins	7.6	0	1	y	y	2	H	n		8.6	93.2	85	6		
278	51	25.8	0	9	tab	7.4	1	2	n		1	L	n		0.3	97.6	94	6		
279	62	27.6	40.64	14	ins	8.1	0	0	y	y	1	L	n							
280	63	28.3	43.18	16	ins	8.1	6	2	y	y	3	H	n							
281	65	37.2	43.18	21	tab	6.7	5	1	y	y	3	H	n							
282	39	33.3	43.18		ins tab	12	0	2	y	y	2	H	n							

Table 1: Questionnaire and sleep study data from hospital and primary care databases combined

No	Age yrs	BMI kg/m2	Collar cm	DM yrs	Treatment	HbA1c	section 1	2	Known BP	BP treatment	Risk score	RISK	Known OSA	Treatment	Oxim 4% dip/hr	Mean SaO2	Min SaO2	ESS	Embletta AHI	Outcome
283	73	26.4	38.1	15	ins tab	9.6	3	2	n		2	H	n							
284	56	27.3	43.18	22	ins	6.3	5	0	n		1	L	n							
285	60		44.45	4	tab	8.1	1	0	y	y	1	L	n							
286	59	25.1	40.64	15	tab	9.8	3	2	n		2	H	n		1.8	94.1	82	14		
287	72	27.4	43.18	30	ins tab	6.6	3	0	y	y	2	H	n							
288	65	26.1	41.91	28	diet	7.7	5	0	y	y	2	H	n							
289	56	28.7	41.91	14	tab	10.2	0	0	n		0	L	n		5.7	95	78	3		
290	58	24.6	40.64	12	tab	11.6	4	0	n		1	L	n							
291	52	38.7	45.72	18	tab	7.3	1	1	y	y	2	H	n							
292	63	25	41.91	3	diet	6.4	6	0	y	y	2	H	n							
293	63	28.3	40.64	17	ins	8.6	4	2	y	y	3	H	n							
294	61	29.1	43.18	14	ins	8.6	5	2	n		2	H	n							
295	56	36.9	48.26	14	ins	9.5	0	2	y	y	2	H	n							
296	64	31.8	45.72	14	ins tab	8.3	6	0	y	y	2	H	n							
297	37	28.7	41.91	2	tab	7.7	5	2	n	n	2	H	n							
298	54	26.3	40.64	6	tab	8.6	3	0	n		1	L	n		2.9	95.3	85	0		
299	55	26.5	41.91		tab	10.5	0	0	n		0	L	n							
300	68	35.4	45.72	26	ins tab	7.6	0	2	y	y	2	H	n		6.7	95.9	87	11	72.9	ENT ref
301	60	26.4	40.64	8	ins tab	10.5	2	0	n		1	L	n							
302	74	25.1	40.64	14	tab	7.8	1	0	y	y	1	L	n		1.8	94.2	88	5		
303	68		41.91	4	tab	7.5	0	0	n		0	L	n		0.4	94.9	91	10		
304	75	28.9	43.18		diet	7.6	0	0	y	y	1	L	n							
305	64	30.1	40.64	6	ins tab	8.4	3	1	y	y	3	H	n							
306	73	43.2	55.88	11	ins	8.4	5	0	y	y	2	H	n							
307	68	25.9	41.91		ins	8	6	2	y	y	3	H	n		26.9	94.4	80	11	63.3	no CPAP
308	68	29.4	45.72	7	tab	6.7	4	0	y	y	2	H	n							
309	66	32.1	41.91	9	tab	7.1	2	0	y	y	2	H	n							
310	42	35.11	46.99	3	tab	9	4	2	y	y	3	H	n							
311	65	29.7	41.91	10	ins	7.6	4	0	y	y	2	H	n							
312	73	20.9	44.45	19	ins tab	6.7	0	1	y	y	2	H	n							
313	63	32.2	44.45	14	ins tab	8.3	5	2	n		3	H	n							
314	71	28.5	43.18	6	ins	9.4	6	2	y	y	3	H	n		5.7	94.9	68	3		
315	68	26.3	41.91	6	ins tab	8.3	2	0	n	n	1	L	n							
316	72	42.9	45.72	8	tab	10.1	3	0	n		2	H	n							
317	59	28.4	43.18	2	tab	7.8	2	0	y	y	2	H	n							
318	75	32.7	39.37	6	tab	6.6	0	0	y	y	1	L	n		1.2	92.8	88	7		
319	72	27.7	43.18	23	ins	9.1	0	0	n		0	L	n							
320	60	23.9	40.64	7	tab	6.9	4	0	n		1	L	n							
321	52	29.6	43.18	12	tab	7	1	2	n		1	L	n							
322	59	30.4	41.91	6	tab	8.9	1	1	y	y	2	H	n							
323	47	47.9	45.72	8	tab	7.7	2	2			3	H	n							
324	35	32.5	43.18	2	tab	6.9	4	2	n		3	H	n		1	95.8	91	10		
325	55	32.7	41.91	10	ins tab	8.3	7	1	y	y	3	H	n							
326	72	32.4	45.72	28	ins	12	4	0	n		2	H	n							
327	54	24	38.1	8	ins tab	11.8	4	1	n		2	H	n							
328	59	36.2	44.45	10	diet	6.9	7	0	n		2	H	n		46.1	88.3	60	2	Refused	
329	70		43.18	27	tab	9.3	1	0	y	y	1	L	n		5.1	92.7	85	1		

Table 1. Questionnaire and sleep study data from hospital and primary care databases combined

No	Age yrs	BMI kg/m2	Collar cm	DM yrs	Treatment	HbA1c	section 1	2	Known BP	BP treatment	Risk score	RISK	Known OSA	Treatment	Oxim 4%dip/hr	Mean SaO2	Min SaO2	ESS	Embletta AHI	Outcome
330	68	46.8	40.64		ins	9.5	0	2	n		2	H	n		0.5	96	88	6		
331	63	19.6	36.83	8	ins	9.3	4	2	y	y	3	H	n							
332	65	37.6	45.72	25	ins tab	8	6	2	y	y	3	H	n							
333	67	25.1	40.64	4	tab	8.7	5	0	y	y	2	H	n							
334	66	24.4	40.64	14	tab	8.7	0	0	n		0	L	n							
335	54	24.9	40.64	6	tab	8	0	0	y	y	1	L	n		0.6	94.5	88	0		
336	66	27.2	44.45	12	tab	9.1	0	0	n	y	0	L	n							
337	61	28.2	38.1	7	tab	6.8	4	0	n		1	L	n		1.1	96	92	6		
338	71	27.1	40.64	10	tab	8	4	0	y	y	2	H	n							
339	48		40.64	8	tab	8.8	6	2	y	y	3	H	n							
340	61	44.54	49.53	15	ins	9.3	3	2	y	y	3	H	n							
341	75		40.005		diet	7.1	0	0	n		0	L	n		17	94	88	5	43.8	no CPAP
342	58	28.4	43.18	4	tab	6.1	2	0	y	y	2	H	n							
343	57	25.8	41.91		diet	5.9	3	0	n		1	L	n		1.6	94.2	89	6		
344	45	27.9	45.085	10	ins	8.9	0	0	n		0	L	n		2.2	95.9	88	8		
345	62	29.3	41.91		ins tab	9.1	2	2	n		2	H	n							
346	67	24.4	36.83	2	tab	7.3	2	0	n		1	L	n							
347	62	23.7	39.37	25	ins	11.4	0	0	y	y	1	L	n							
348	36	36.2	46.99	8	tab	7.9							yes	CPAP						
349	69	32.3	41.91	6	tab	6.4	4	0	n		2	H	n							
350	57	24.5	39.37	9	ins	8	7	2	y	n	3	H	n							
351	71	31.1	43.18	22	tab	7.3	1	0	y	y	1	L	n							
352	66	20.5	43.18	20	ins	7.7	3	0	y	y	2	H	n							
353	75	28	43.18	6	ins tab	7.3	1	1	y	y	2	H	n							
354	71	30.4	44.45	8	tab	7.1	0	0	y	y	1	L	n		5.5	93	82	0		
355	40	34	43.18	10	ins	9.7	4	1	y	y	3	H	n							
356	67	25.9	38.1	8	tab	6.5	0	0	n		0	L	n							
357	72	29	43.18	6	tab	6	0	0	n		0	L	n							
358	63		40.64	6	tab	8.7	3	0	y	y	2	H	n		23.3	93.4	84	8	39.8	CPAP
359	70	26.5	44.45	18	ins	10.9	0	0	y	y	1	L	n		1.9	94.7	84	9		
360	44	29	43.18	6	ins	8.7	0	0	y	y	1	L	n							
361	63	21.5	39.37	12	tab	7.4	2	0	y	y	2	H	n							
362	57	27.7	40.64	8	tab	6.8	5	2	y	y	3	H	n							
363	70	38	49.53	28	ins tab	9.1	5	2	y	y	3	H	n							
364	41	24.5	39.37	1	diet	6	2	2	n		2	H	n							
365	56	20	38.1	6	ins	9.4	2	2	n		2	H	n							
366	54	30.4	40.64		diet	7.2	6	2	y	y	3	H	n							
367	67	31	44.45	13	ins tab	6.1	6	2	y	y	3	H	n							
368	71	29.3	45.72	17	tab	8.1	0	2	n		1	L	n							
369	53	29.4	44.45	8	tab	7.5	2	2	n		2	H	n							
370	67	22.9	35.56	0.5	tab	8.6	4	2	n		2	H	n							
371	31	30.8	43.18	5	tab	10.6	1	0	n		1	L	n							
372	65	29.8	43.18	6	tab	8.8	3	0	y	y	2	H	n							
373	59	37.9	46.99	28	ins	8	0	0	y	y	1	L	n							
374	74	19.4	41.91	10	ins tab	8.4	0	0	y	y	1	L	n							
375	67	34.1	43.18	2	ins tab	6.3	0	0	y	y	1	L	n							
376	62	24.6	43.18	10	tab	12.4	0	1	y	y	2	H	n							

Table 1: Questionnaire and sleep study data from hospital and primary care database combined

No	Age yrs	BMI kg/m2	Collar cm	DM yrs	Treatment	HbA1c	section 1	2	Known BP	BP treatment	Risk score	RISK	Known OSA	Treatment	Oxim 4%dip/hr	Mean SaO2	Min SaO2	ESS	Embletta AHI	Outcome
377	47	35.5	45.72	3	tab	7.3	1	0	y	y	1	L	n		6.7	93.6	81	5		
378	69	24.5	41.91	24	ins	9.4	0	0	n		0	L	n		4	96.1	86	3		
379	64	27.3	41.91		tab	6	2	1	n		2	H	n							
380	69	43.3	53.34	11	ins tab	8.9	7	2	y	y	3	H	n							
381	65	22.7	40.64	3	tab	11.5	1	2	n		1	L	n		2.1	96.3	87	5		
382	69	22.5	0	10	ins	7.6	5	0	n		1	L	n							
383	71	26.8	44.45	27	ins	7.5	6	2	n		2	H	n							
384	56	27.3	41.91	5	tab	8.4							yes	CPAP						
385	75	23.4	39.37	14	tab	8.1	0	0	n		0	L	n		1.7	95.7	88	8		
386	69	25.6	40.64	5	tab	6.5	2	0	n		1	L	n							
387	67	35.3	45.72	6	tab	6.7	0	2	y	y	2	H	n		12.8	88.6	73	13	4.1	no CPAP
388	56	29.4	45.72	14	tab	7.5	6	2	y	y	3	H	n							
389	75		41.91	27	ins	7.7	3	0	y	y	2	H	n							
390	66	36	44.45	49	ins	9.6							yes	n						
391	63	31	44.45	6	tab	7.1	5	0	y	y	2	H	n							
392	43	38.6	45.72	4	ins	8.5	4	2	y	y	3	H	n							
393	65	35.5	50.8	17	ins	7	1	0	n	y	1	L	n							
394	53	33.2	44.45	5	ins tab	7.8	1	1	y	y	2	H	n							
395	50	28.5	43.18	3	diet	7.9	5	1	n		2	H	n							
396	71	24.5	38.1	13	ins	8.2	1	0	n		0	L	n		3.8	97.1	86	5		
397	75	29.3	43.18	17	tab	8	2	0	y	y	2	H	n		1.9	93.1	87	3		
398	75	30.7	43.18	24	ins	8.8	0	0	y	y	1	L	n							
399	73	28.5	44.45	3	diet	6.8	0	0	y	y	1	L	n							
400	70	29.1	44.45	13	ins tab	7.2	4	0	y	y	2	H	n							
401	64	32.4	44.45	13	ins	7.9	2	2	y	y	3	H	n							
402	65	25.2	39.37	4	ins	7.7	1	1	y	y	2	H	n							
403	71	26.8	38.1	2	diet		4	0	y	y	2	H	n		0.7	94.3	91	2		
404	40	37.5	40.64	8	ins	8.8	7	1	y	y	3	H	n							
405	58	24.2	36.83	4	diet	7.3	0	0	n		0	L	n							
406	59	23.2	39.37	10	tab	11	3	0	y	y	2	H	n							
407	70	19.8	38.1	20	ins tab	10.5	0	0	y	y	1	L	n							
408	71	28.4	41.91	10	ins	10.4	2	2	y	y	3	H	n		7.6	95.3	88	10		
409	57	30.4	41.91	7	tab	9.7	0	0	y	y	1	L	n							
410	59	33.9	45.72	15	ins tab	12.8	0	0	n		1	L	n							
411	57	26.8	38.1	2	tab	5.2	4	2	y	y	3	H	n							
412	71	24.9	40.64	8	ins tab	8.5	0	2	y	y	2	H	n							
413	60	34.7	46.99	35	ins	7.5	5	2	y	y	3	H	n		1.6	95.1	91	17	5.3	no OSA
414	75	26.8	39.37	9	tab	7.2	5	1	n		2	H	n							
415	50	31.4	43.18	6	tab	8.6	7	1	y	y	3	H	n							
416	59	24.2	40.64	8	tab	10	0	0	y	y	1	L	n		2.4	94.7	90	4		
417	60	32.2	46.482	25	ins	8.5			y	y			no							
418	73		44.45	19	ins tab		4	0	y	y	2	H	n							
419	61	27.3	39.37	2	diet	6.5	3	1	n		2	H	n		2.8	93.8	87	4		
420	62	36.1	49.53	4	tab	6.2							yes	CPAP						
421	72	25.2	40.64	3	tab	7	5	2	n		2	H	n		1.7	94.5	88	9		
422	56	43.9	45.72	4	tab	6.7	5	2	y	y	3	H	n		1.5	95.8	90	13		
423	61	31.3	43.18	22	tab	7.8	1	0	y	y	1	L	n							

Table 1: Questionnaire and sleep study data from hospital and primary care databases combined

No	Age yrs	BMI kg/m2	Collar cm	DM yrs	Treatment	HbA1c	section 1	2	Known BP	BP treatment	Risk score	RISK	Known OSA	Treatment	Oxim 4%dip/hr	Mean SaO2	Min SaO2	ESS	Embletta AHI	Outcome
424	74	30.2	40.64	7	diet	5.8	2	0	y	y	2	H	n							
425	74	24.8	39.37	13	tab	6.9	0	1	y	y	2	H	n							
426	70		42.545	7	ins	7.1							yes	CPAP						
427	70	24.6	43.18	22	tab	10.4	1	0	n		0	L	n		0.8	92.1	82	4		
428	75	28.6	43.18	28	ins	11.3	2	1	y	y	3	H	n							
429	51	24.4	38.1	4	tab	9.1	1	0	y	y	1	L	n							
430	70	30	44.45	19	ins tab	7.2	0	2	n		2	H	n							
431	71	23.8	41.91	43	ins	10.1	0	0	n		0	L	n							
432	63	38.8	49.53		tab	7	5	2	y	y	3	H	n							
433	73	28.7	41.91	19	tab	8.1	0	2	y	y	2	H	n							
434	56	29.3	0	7	tab	5.4	7	2	y	y	3	H	n		8.6	92.5	75	15		CPAP
435	72	34	40.64	10	ins	7.1	2	1	n		3	H	n							
436	44		0	12	tab	11.5	0	0	y	y	1	L	n							
437	71	25.8	43.18	18	tab	7.4	2	2	y	y	3	H	n							
438	58	29.4	45.72	9	tab	6.1	4	2	n		2	H	n		13.1	95.6	72	12	21.9	no CPAP
439	62	23	39.37	15	ins	9.3	4	2	n		2	H	n		8.2	96.4	86	6	42.8	No CPAP
440	47	26.4	39.37	3	tab	13.2	5	2	n		2	H	n							
441	64	20.3	39.37	6	tab	7.3	2	2	y	y	3	H	n		4.2	96.2	79	13		
442	70	28.6	41.91	5	tab	7	0	0	y	y	1	L	n		3.5	92	81	8		
443	69	29.3	46.99	13	ins tab	9	2	0	y	y	2	H	n		4.7	95.1	82	15		
444	65	24.5	41.91	10	tab	7.8	5	2	y	y	3	H	n							
445	65		45.72	4	tab	7.7	2	0	y	y	2	H	n		3.2	94.1	89	5		
446	73	19.2	36.83	10	ins tab	9.5	4	2	n		2	H	n		0.8	97	92	10		
447	73	27.6	43.18	10	tab	7.2	2	0	y	y	2	H	n							
448	71	26.4	38.1	7	tab	7.4	0	0	n		0	L	n							
449	66	29.7	40.64		diet	6.7	7	2	y	y	3	H	n		40.8	91	40	9	20.8	No CPAP
450	57	32.8	46.99	11	tab	7.3	6	2	n		3	H	n		4.1	92.8	87	16		
451	52	30.1	41.91	3	tab	6.8	1	0	y	y	1	L	n		2.2	95.7	87	3		
452	66	31.8	43.18	5	ins tab	8	1	0	y	y	1	L	n							
453	71	34	48.26	21	ins	8.8	0	0	y	y	1	L	n							
454	65	27	40.64	14	ins tab		2	1	y	y	3	H	n							
455	43	23.1	39.37	7	ins tab	8.3	0	0	y		1	L	n		1.8	94.6	80	11		
456	69	26.6	44.45	16	tab	8.6	0	0	n		0	L	n							
457	62	30.8	43.18	0.5	tab	8.7	1	0	y	y	1	L	n		8.6	95.2	71	11		
458	67	30.3	45.72	20	ins	8.1	4	0	y	n	2	H	n		7.2	95.8	82	3		
459	73	28	45.72	33	ins	7.6	7	2	y	y	3	H	n							
460	60	29.7	45.72	31	ins	10.1	6	2	y	y	3	H	n							
461	73	36.7	41.91	41	ins	10	4	2	n		3	H	n							
462	68	29.3	45.72	22	ins tab	9	2	0	y	y	2	H	n							
463	71	27	43.18	8	tab	9.9	1	0	y	y	1	L	n							
464	74	28.3	44.45	10	tab	6.9	0	1	n	y	1	L	n							
465	75	29	44.45	11	ins tab	6.3	0	0	y	y	1	L	n							
466	73	27.6	44.45	12	ins	9.7	6	2	n		2	H	n							
467	73	34.1	43.18	20	tab	7.2	2	0	y	y	2	H	n		4.6	90.9	71	5		
468	74	31.1	45.72	11	ins	10.8	0	0	y	y	1	L	n							
469	73	26.8	44.45	22	ins tab	8.9	1	0	y	y	1	L	n							
470	56	28.3	35.56	6	ins tab	12.5	2	0	n		1	L	n		0.7	97.2	91	1		

Table 1: Questionnaire and sleep study data from hospital and primary

No	Age yrs	BMI kg/m2	Collar cm	DM yrs	Treatment	HbA1c	section 1	2	Known BP	BP treatment	Risk score	RISK	Known OSA	Treatment	Oxim 4%dip/hr	Mean SaO2	Min SaO2	ESS	Embletta AHI	Outcome
471	74	30.7	41.91	11	ins	8.2	6	2	y	y	1	L	n							
472	56	33.9	44.45	9	tab	8.4	7	2	n		3	H	n		19.6	92.8	82	12	19.9	CPAP
473	40	26	43.18	3	tab	10.9	0	2	n		1	L	n							
474	59	23	38.1	9	tab	12.1	3	1	n		2	H	n							
475	65	31	43.18	2	tab	8.1	2	0	y	y	2	H	n		0.6	95.8	93			
476	75	29.3	41.91	15	ins	8.8	0	0	n		0	L	n		3.8	96.5	90	4		
477	62	21.9	39.37	20	ins	6.2	1	2	y	y	2	H	n							
478	67	26.7	40.005		diet	7.5	0	0	y	y	1	L	n							
479	69	25.3	43.18	14	ins	7.7	4	0	y	y	2	H	n							
480	69	39.5	45.72	5	tab	6.8	3	2	y	y	3	H	n							
481	37	39.9	48.26	4	ins	11	6	2	n		3	H	n							
482	54	30.3	44.45	17	ins tab	7.4	1	0	y	y	1	L	n		3.1	95	83	12		
483	53	36.1	44.45	3	tab	8.1	4	1	n		3	H	n							
484	49	23.9	38.1	14	ins tab	8	4	2	n		2	H	n		5.7	85.4	25	5		
485	55	27.8	39.37	9	tab	9.5	0	0	n		0	L	n		12.8	93.4	56	7	refused	
486	52	24.9	40.64	5	tab	7.6	6	0	y	y	2	H	n							
487	51	25.9	38.1	6	ins tab	10.8	4	2	n		2	H	n							
488	63	30.1	39.37	9	tab	9.2	5	2	y	y	3	H	n		4.4	96.1	88			
489	71	32.8	43.18	14	tab	7.2							yes	n						
490	66		0	20	ins tab	10.1	5	2	y	y	3	H	n							
491	68		0	14	ins	8.4	5	2	y	y	3	H	n							
492	56	31.3	44.45	17	ins	9	2	2	y	y	3	H	n		18.1	94.8	76	11	21.4	no CPAP
493	56	38.6	48.26	16	ins	11.2							yes	CPAP						
494	71	27.8	40.64		tab	8.1	4	1	y	y	3	H	n							
495	60	35.2	45.72	4	tab	7.2	0	0	y	y	1	L	n		4.4	93.8	79	4		
496	53	47.3	53.34	10	ins	10.6	4	2	y	y	3	H	n							
497	64	26.2	39.37	4	diet	7.3	5	0	y	n	2	H	n							
498	62	28.9	44.45	5	tab	7.2	4	2	y	y	3	H	n							
499	63	37.1	43.18	17	ins	7.7	0	1	n	n	2	H	n							
500	64	27.1	40.64	12	tab	6.1	6	2	y	n	3	H	n							
501	64	25.9	41.91	17	ins tab	8.7	4	2	y	y	3	H	n							
502	69	53.2	43.18	10	tab	7.7	5	2	n		3	H	n							
503	55	30.5	38.1	12	tab	8.4	1	0	n		1	L	n							
504	33	26.6	40.64	2	tab	11.5	2	2	n		2	H	n							
505	50	31.6	48.26	12	ins tab	7.7	6	2	y	y	3	H	n							
506	60	43	46.99	7	ins	8	6	2	y	y	3	H	n							
507	36		45.72	6	tab	8.8	4	0	y	y	2	H	n							
508	71	28.8	44.45	16	ins	6.5	2	1	y	y	3	H	n							
509	65	30.8	43.18	7	ins	8.5	5	1	y	y	3	H	n							
510	48	26.5	0	2	tab	6.8	1	2	y	n	2	H	n		27.4	83.7	50	3	refused	
511	59	23.8	39.37	5	ins	8.3	5	2	y	y	3	H	n		6	95.7	69	8		
512	61	23.4	38.1	16	ins	8.2	1	0	n		0	L	n							
513	71	31.1	44.45	3	ins	6.8	0	1	n		2	H	n							
514	63	28	39.37	6	ins	7.6	3	0	y	y	2	H	n		29.9	92.5	81	5	Yes	refused
515	55	28.4	40.64	3	tab	6	1	0	n		0	L	n							
516	66	27.8	41.91	23	ins	7.7	4	2	y	n	3	H	n							
517	56	26.9	43.18	14	ins	9.2	1	0	y	y	1	L	n		15.6	93.8	81	4	Refused	

No	Age yrs	BMI kg/m2	Collar cm	DM yrs	Treatment	HbA1c	section 1	2	Known BP	BP treatment	Risk score	RISK	Known OSA	Treatment	Oxim 4%dip/hr	Mean SaO2	Min SaO2	ESS	Embletts AHI	Outcome
518	70	25.92	41.91	10	tab	7	2	2	y	y	3	H	n							
519	65	30.4	38.1	6	tab	10.9	3	1	n		3	H	n							
520	70	29.7	41.91	10	tab	8.1	5	1	n		2	H	n							
521	74		40.64	29	ins	5.9	0	1	n		1	L	n							
522	52	25.5	39.37	12	ins tab	10.6	3	2	n		2	H	n							
523	68	23.9	39.37	20	ins tab	9.1	6	0	y	y	2	H	n		37.5	93.5	58	13	46.6	DNA
524	63	38.1	50.8		tab	7.5	6	2	y	y	3	H	n		57.6	91	56	11	70.1	CPAP
525	75	31.4	45.72	32	ins tab	7	0	0	y	y	1	L	n		20.7	92.2	72	6	37.2	No CPAP
526	57	27	41.91	1	diet	6.6	2		n		1	L	n		0.6	96.3	92	6		
527	56	29.4	33.02	15	ins	9.7	3	0	n	n	1	L	n							
528	63	27	41.91	4	tab	6.2	5	2	y	y	3	H	n		4.2	95.4	88	7		
529	51	29	43.18	15	tab	8	0	0	n		0	L	n							
530	65	26.2	38.1	5	diet	7.2	0	0	y	y	1	L	n							
531	57	21.9	40.64	24	ins	8.8	0	0	n		0	L	n							
532	53	42.6	46.99	14	tab	11.8	1	0	y	y	1	L	n							
533	59	25	39.37	42	ins	10.7	2	2	y	y	3	H	n							
534	66	26	39.37	2	tab	6.8	3	0	n		1	L	n		8.7	93.7	68	10	10.3	No CPAP
535	66	35.2	45.72	7	ins tab	8.8	0	2	y	n	2	H	n							
536	68	22.5	36.83	20	ins	7.4	0	0	y	y	1	L	n							
537	57	28.7	41.91	3	tab	6.9	0	0	n	n	0	L	n							
538	60	26.1	41.91	6	tab	6.9	5	0	y	y	2	H	n		1.1	96.7	87	7		
539	65	38.2	50.8	2	ins	6.8	0	1	y	y	2	H	n							
540	40	30.9	43.18	4	tab	7.8	4	2	y	y	3	H	n							
541	62	26.5	40.64	24	ins tab	8.3	5	2	y	y	3	H	n							
542	65	31.7	0	10	ins tab	9.8	1	0	y	y	1	L	n							
543	51	23.8	44.45	9	tab	8	4	0	y	y	2	H	n							
544	69	29.4	43.18	8	tab	7.8	2	2	y	y	3	H	n							
545	51	29.5	44.45	10	tab	8.5	2	0	y	y	2	H	n							
546	73		48.26		tab	7.8	4	2	n	n	2	H	n							
547	76	28.8	45.72	22	ins	8	3	0	y	y	2	H	n							
548	48		0	2	tab	6.3	4	2	n		2	H	n							
549	56	31.4	48.26	7	ins tab	10.1	4	2	y	y	3	H	n							
550	59	32.5	49.53	12	ins	7.8							yes	CPAP						
551	59	22.8	40.64	14	ins	9.2	1	0	n		0	L	n							
552	68		43.18	8	tab	6.5	4	2	y	y	3	H	N		0	96.1	93	14		
553	47	25.1	41.91	2	diet	5.7	6	2	y	y	3	H	n		3.9	95.3	91	8		
554	66	27.2	41.91	2	tab	7.9	1	0	y	y	1	L	n		1	94.1	83	7		
555	51	32.7	41.91	6	tab	8.8	7	2	n		3	H	n							
556	30	22.8	43.18	3	ins	9.6	3	2	n		2	H	n							
557	39	28.6	42.545	6	ins tab	12.4	6	2	y	y	3	H	n		10.1	95.4	76	10	1.7	No CPAP
558	59	28.4	41.91	1.5	tab	7.8	1	1	y	y	2	H	n		2.1	95.5	83	2		
559	74	33.3	44.45	16	ins tab	7.1	0	1	y	y	2	H	n							
560	69		40.64	17	tab	7.6	4	0	y	y	2	H	n							
561	54	32.3	45.72	20	ins tab	9.5	6	2	y	y	3	H	n		27.2	93.7	68	13	48.8	CPAP
562	51	30	41.91		tab	7	2	0	n	y	2	H	n							
563	74	25.5	40.64	29	ins	10.4	0	0	n	n	0	L	n							
564	68	33.5	43.18	12	ins	10.2	2	0	n		2	H	n							

Table 1. Questionnaire and sleep study data from hospital and primary care database

No	Age yrs	BMI kg/m2	Collar cm	DM yrs	Treatment	HbA1c	section 1	2	Known BP	BP treatment	Risk score	RISK	Known OSA	Treatment	Oxim 4%dip/hr	Mean SaO2	Min SaO2	ESS	Embletta AHI	Outcome
565	56	30.6	43.18	11	ins	10	3	0	n		2	H	n							
566	73	29	43.18	3	tab	6.1	4	0	y	y	2	H	n							
567	65	27.4	40.64	10	diet	8.8	1	0	n		0	L	n		0.8	96.5	91	4		
568	58	33.3	45.72	5	tab	7	3	0	y	y	2	H	n							
569	72	31.8	43.18	20	tab	8.6	2	1	y	y	3	H	n							
570	64	31.4	43.18	6	tab	6.9	5	2	n	n	3	H	n							
571	65	28.6	43.18	14	tab	9.1	6	2	n		2	H	n							
572	33	27.5	41.91	8	tab	6.3	1	0	n		0	L	n		0.6	96.2	91	9		
573	58	30.9	43.18	12	ins tab	8.8	6	2	y	n	3	H	n							
574	54	27	40.64	5	tab	6.3	3	1	n		2	H	n							
575	64	29.4	43.18	4	ins tab	8.5	6	2	y	n	3	H	n							
576	72	17.4	36.83		ins	11.5	2	2	n		2	H	n							
577	68	39.4	45.72	31	ins	12.1	5	2	y	y	3	H	n							
578	46	23.5	38.1	6	tab	10	0	0	n		0	L	n							
579	34	27.3	43.18	9	tab	13.3	1	2	n		1	L	n		1.4	95	88	2		
580	58	27.6	40.64	6	tab	6.6	1	0	y	y	1	L	n							
581	60	42	42.545	9	tab	6.8							yes	CPAP						
582	60	28.8	46.99	1	tab	8	0	0	y	y	1	L	n							
583	56	36.6	48.26	8	tab	6.7							yes	CPAP						
584	46	27.6	41.91	17	ins	8.4	4	2	n		2	H	n							
585	56	28.9	41.91		Diet	6.7	5	1	n		2	H	n		0.7	96.6	88	4		
586	74	50	46.99	20	ins	7.5	1	2	y	y	2	H	n							
587	64	26.1	39.37	3	tab	7.2	1	1	y	y	2	H	n		10.2	95.8	71	3	6.7	no CPAP
588	56	32.5	41.91	6	tab	8.1	2	0	n		2	H	n							
589	50	21.8	38.1	8	ins	8	2	2	y	y	3	H	n		3.1	95.7	89	12		
590	48	31.8	41.91	2	ins tab	8	7	2	y	y	3	H	n							
591	68	36.9	50.8	20	tab	7.8	0	0	y	y	1	L	n							
592	39	28.9	40.64	6	tab	8.7	3	2	n		2	H	n							
593	67	25.5	38.1	34	ins	10.8	0	2	n		1	L	n							
594	68	27.5	43.18		ins	6.8	0	1	y	y	2	H	n							
595	54	27	39.37	8	ins	9.8	5	2	y	y	3	H	n		6.3	94.2	85	12	36.2	no CPAP
596	65	24.7	41.91	13	ins	9.3	2	0	y	y	2	H	n							
597	54	28.8	41.91	4	tab	7.1	5	0	n		1	L	n							
598	75	29.7	41.91	5	diet	7	1	0	y	y	1	L	n		7.1	94.3	73	8	15.3	no CPAP
599	52	20.5	48.26	2	tab	8.5	7	0	n		1	L	n							
600	52	41.3	50.8	23	ins tab	11.4	5	0	y	y	2	H	n							
601	56	27	43.18	7	diet	6.7	0	0	y	y	1	L	n							
602	56	26.4	46.99	4	tab	7	6	2	y	y	3	H	n							
603	74	20.7	39.37	18	ins tab	9.7	1	2	y	y	2	H	n							
604	69	18.1	38.1	5	ins	9.7	0	0	y	y	1	L	n							
605	71	31.9	41.91	9	ins	8	0	0	y	y	1	L	n							
606	73	21.7	38.1	7	ins	7.3	0	0	y	y	1	L	n							
607	71		44.45	13	ins tab	9.8	1	0	y	y	1	L	n		7.8	95.7	80	3		
608	75	22.3	39.37	10	tab	7.2	0	0	n		0	L	n							
609	67	36.4	44.45	1	tab	6	4	0	y	y	2	H	n		0.3	95.4	92	4		
610	69	28.3	41.91	6	ins tab	6.1	2	2	n		2	H	n		3.7	94.6	88	4		
611	48	32.7	40.64	3	ins tab	10.6	4	0	n		2	H	n							

Table 1. Questionnaire and sleep study data from hospital and primary care database

No	Age yrs	BMI kg/m2	Collar cm	DM yrs	Treatment	HbA1c	section 1	2	Known BP	BP treatment	Risk score	RISK	Known OSA	Treatment	Oxim 4%dip/hr	Mean SaO2	Min SaO2	ESS	Embleta AHI	Outcome
612	75	30	44.45	24	ins	8.2	5	2	y	y	3	H	n		5	91.8	69	11		
613	71	23.1	39.37	4	tab	8.4	5	0	n		1	L	n		4.5	96.7	90	4		
614	58	27	41.91	6	tab	6.4	0	2	y	y	2	H	n							
615	69	30.8	49.53	6	ins	9.7	7	1	y	y	3	H	n							
616	56	27.4	44.45	10	tab	6.6	2	0	n	y	0	L	n							
617	63	29.2	41.91	17	ins tab	9.7	0	1	y	y	2	H	n		18.5	91.7	82	6	45.8	no CPAP
618	57	25.5	38.1	4	diet	6.6	0	0	y	y	1	L	n							
619	68		46.99	6	ins tab	8.1	4	2	y	y	3	H	n							
620	44	24.6	43.18	12	ins	8.6	5	2	n		2	H	n							
621	44	27.8	43.18	2	tab	7.3	0	0	y	y	1	L	n							
622	60	28.8	43.18	17	ins	9.8	3	0	n		1	L	n							
623	50	22.7	0	18	tab	7	0	0	n		0	L	n		0.9	95.8	89	8		
624	66	25.7	43.18	19	ins tab	9.9	6	1	y	y	3	H	n							
625	43	34.1	44.45	6	tab	7.3	5	1	y	y	3	H	n							
626	69	33	43.18	33	ins	8.3	7	2	n		3	H	n							
627	60	22.8	38.1	4	tab	8.4	1	0	y	y	1	L	n							
628	36	46.3	50.8	12	tab	7.1	7	0	y	y	2	H	n							
629	66	29.7	44.45	8	diet	6.6	5	0	y	y	2	H	n							
630	64	34	52.07	8	tab	10.2	3	2	y	y	3	H	n		12.7	88.9	74	11	43.5	CPAP
631	71	26.4	44.45	38	ins	8.8	7	2	y	y	3	H	n							
632	58	31.2	45.72	7	ins	8.2	7	2	y	y	3	H	n							
633	60		44.45	19	ins	7.8	7	0	y	y	2	H	n		5.2	94.4	86	8		
634	71	33.8	44.45	6	tab	6.8	0	2	n		2	H	n		3.8	89.8	76	13		
635	53	25.4	41.91	7	ins	7.9	0	0	n		0	L	n							
636	68	33.2	45.72	13	tab	7.7	4	1	n		3	H	n							
637	60	26.2	41.91	3	tab	5.2	0	0	n	n	0	L	n							
638	55	32	48.26	5	tab	5.5	3	2	n		3	H	n							
639	73	26.2	41.91	5	diet	9.8	1	0	y	y	1	L	n							
640	57	28.1	44.45	8	tab	6.5	6	0	n		1	L	n							
641	33	51	48.26	2	tab	6.8	4	2	y	y	3	H	n							
642	66	38	44.45		tab	9.7	3	0	y	y	2	H	n							
643	50	35.9	45.72	3	ins tab	10.4	6	2	n		3	H	n							
644	55	30	43.18	4	tab	6	4	0	y	y	2	H	n							
645	57	30.2	44.45	25	ins	11.4	4	2	y	y	3	H	n							
646	65	34.1	44.45		tab	6.9	2	0	y	n	2	H	n							
647	55	29.5	43.18	15	ins	10.6	6	0	y	y	2	H	n							
648	67	38.2	45.72	8	tab	8.4	6	2	y	y	3	H	n							
649	66	20.4	38.1	18	tab	7.5	4	0	n		1	L	n		0.1	96.9	93	8		
650	55	23.3	35.56	10	tab	7.9	0	0	y	y	1	L	n							
651	62	28	41.91	5	tab	7.3	5	0	y	y	2	H	n							
652	47		41.91	5	ins tab	11.2	6	1	y	y	3	H	n							
653	74		45.72		tab	8.3	6	1	y	y	3	H	n							
654	61	26	41.91	18	tab	7.7	1	0	n		0	L	n							
655	52	30.1	40.64	15	ins	9.1	5	0	n		2	H	n		2.4	95.4	89	8		
656	44	28.3	43.18	5	tab	6.7	2	1	y	y	3	H	n							
657	52	24.4	38.1	4	tab	10	2	2	n		2	H	n							
658	51	26.6	43.18	12	tab	7.4	1	0	y	y	1	L	n		1.9	94.7	87	11		

Table 1. Questionnaire and sleep study data from hospital and primary care databases combined

No	Age yrs	BMI kg/m2	Collar cm	DM yrs	Treatment	HbA1c	section 1	2	Known BP	BP treatment	Risk score	RISK	Known OSA	Treatment	Oxim 4%dip/hr	Mean SaO2	Min SaO2	ESS	Embletta AHI	Outcome
659	58	30	44.45	16	tab	7.7	3	0	y	y	2	H	n							
660	64	21.2	38.1	6	ins	8.8	2	0	n		1	L	n							
661	70	31.1	41.91	4	tab	7.6	2	2	y	y	3	H	n							
662	61	30.8	41.91	8	tab	7.1	1	0	n		1	L	n							
663	52	23.1	36.83	4	ins tab	5.8	1	2	n		1	L	n							
664	59	32.3	43.18	4	tab	8.1	1	2	n		2	H	n		4.2	94.6	90	4		
665	74	25.2	38.1	13	tab	9.9	2	0	n		1	L	n		1.5	95.6	91	4		
666	65	30.2	43.18	10	tab	7.4	4	0	y	y	2	H	n							
667	66	27	41.91	10	tab	7.3	6	0	y	y	2	H	n		4.7	95.8	78	2		
668	59	32.8	45.72	29	tab	9.1	0	2	n		2	H	n							
669	57	24.1	38.1	1	tab	7.1	1	0	y	y	1	L	n		0.2	96.1	92	8		
670	70	33.8	44.45	9	ins tab	9.3	4	2	y	y	3	H	n							
671	75	36.1	45.72	23	ins tab	8.1	2	2	y	y	3	H	n							
672	39	30	41.91	5	diet	6	1	1	n		2	H	n		3.8	94.6	87	2		
673	68	25.8	0	49	tab	7.9	1	2	y	y	2	H	n							
674	65	26.48	43.18	11	tab	9.1	4	2	y	y	3	H	n							
675	73	27.9	43.18	32	ins	10.2	6	2	n		2	H	n		2.4	95.9	53	16		
676	75	24.8	40.64	12	ins tab	6.7	2	0	y	y	2	H	n		2.2	97.1	75	6		
677	66	31.8	45.085	20	ins tab	7.8	2	0	y	y	2	H	n							
678	49	33.2	43.18	10	tab	10.5	0	0	y	y	1	L	n		4.5	95	85	12		
679	59	37.2	50.8	8	tab	7.9	5	1	y	y	3	H	n							
680	61		46.99	16	tab	7.3	1	2	y	y	2	H	n		3.6	94.1	82	7		
681	45	32.3	38.735	8	ins tab	9	4	2	y	y	3	H	n		2.1	95	89			
682	70	25.9	41.91		tab	8.4	0	2	y	y	2	H	n							
683	45	32.2	40.64	4	ins	7.2	0	0			0	L	n		2.2	94.6	84	6		
684	69	29.7	43.18	28	tab	6.8	7	1	y	y	3	H	n							
685	55	27.2	41.91	2	tab	6.7	6	2	y	y	3	H	n							
686	70	27.6	40.64	7	tab	8.7	0	1	y	y	2	H	n		8.2	92.3	70	7		no CPAP
687	75	30.8	44.45	8	tab	5.8							yes	CPAP						
688	68	37	50.8	25	ins tab	7.6	4	2	y	y	3	H	n							
689	66	25.2	43.18	3	tab	7.9	2	0	n		1	L	n							
690	56	29.2	43.18	3	tab	7.2	0	1	y	y	2	H	n		2.9	94.5	86	5		
691	65	21.2	38.1	17	ins	7.6	3	0	n		1	L	n		5.8	90.9	61	3		
692	60	24	44.45	8	ins tab	11.4	2	1	y	y	3	H	n		0.7	94.9	83	11		
693	62	24.6	40.64		tab		0	1	n		1	L	n							
694	54	32.2	44.45	12	ins tab	13	7	2	y	y	3	H	n		61.3	84.2	55	11	77	CPAP
695	69	24	39.37	11	ins tab	8.3	3	1	y	y	3	H	n							
696	67	32	45.72	16	ins tab	7.4	1	0	y	y	1	L	n		5.9	94.4	77	9		
697	45	32.6	44.45	4	ins	7.9	3	1	y	y	3	H	n							
698	58	25.3	40.64		tab	6.6	7	0	y	y	2	H	n							
699	53	31.3	43.18	5	ins	7.6	4	0	y	y	2	H	n							
700	66	29.4	43.18	2	tab	14.7							yes	CPAP						
701	64		40.64	20	ins tab	10	2	1	y	y	3	H	n							
702	65	21.8	38.1	17	ins	10	2	1	y	y	3	H	n							
703	74	29.2	44.45	22	ins tab	9.9	4	0	n		1	L	n		7.8	92.8	85	15	1	no CPAP
704	52	31.4	44.45	1	diet	6.8	4	0	n		2	H	n							
705	67	29	41.91	50	ins tab	7.6	4	1	y	y	3	H	n							

Table 1. Questionnaire and sleep study data from hospital and primary care databases combined

No	Age yrs	BMI kg/m2	Collar cm	DM yrs	Treatment	HbA1c	section 1	2	Known BP	BP treatment	Risk score	RISK	Known OSA	Treatment	Oxim 4%dip/hr	Mean SaO2	Min SaO2	ESS	Embletta AHI	Outcome
706	67	29.1	43.18	2.5	ins tab	9.8	0	2	n		1	L	n							
707	56	31.7	44.45	23	ins tab	13.1	0	0	n		0	L	n							
708	69	39.7	48.26	30	ins tab	7.8	5	2	y	y	3	H	n							
709	61	29.2	43.18	7	ins	8.7	0	1	y	y	2	H	n							
710	30	28.5	45.72	12	ins	12.9							yes	CPAP						
711	65	23	38.1	23	ins tab	9.7	3	0	y	y	2	H	n							
712	63	25.7	36.83	15	ins	6.9	0	0	n		0	L	n		0.6	96.4	92	8		
713	45	30.8	43.18	4	tab	5.9	3	2	n		3	H	n		0.1	97.5	93	15		mild PMLS
714	66	42.5	53.34	1	tab	6.3	5	2	n		3	H	n		70.7	76.5	56	15	56.5	CPAP
715	73	31.6	44.45	6	tab	8.4	2	0	y	y	2	H	n							
716	64	25.8	40.64	19	ins	9	2	0	n		1	L	n		0.5	96.3	92	1		
717	72	27.5	40.64	24	ins	10.5	3	0	n		1	L	n		0.2	97.5	88	3		
718	74	35.2	43.18	10	tab	7.7	4	0	n		2	H	n							
719	64	30.5	45.72	5	tab	9.3	3	1	n		3	H	n							
720	74		40.64		ins tab	10.4	2	0	n		1	L	n		15.6	92.6	77	1	Refused	
721	48	24	39.37	6	tab	7	4	0	n		1	L	n							
722	64	21	39.37	12	tab	6.7	3	2	y	y	3	H	n		0.6	95.2	90	13		
723	43	36.8	43.18	12	ins tab	8.3	6	2	n		3	H	n							
724	68	24.9	41.91	7	ins tab	8.5	0	1	y	y	2	H	n							
725	51	26.5	44.45	1	tab	6.2	0	0	n		0	L	n							
726	64	28.4	43.18	1	ins tab	5.6	3	1	y	y	3	H	n							
727	73		48.26	2	ins	7.1	5	2	y	y	3	H	n							
728	51	24.8	39.37	4	tab	7	0	0		n	0	L	n							
729	65	34.6	43.18	9	ins tab	8.5	7	2	y	y	3	H	n							
730	70	24.3	40.64	3	tab	5.6	0	0	n		0	L	n							
731	54	28.3	50.8	6	ins	7.1	6	1	y	y	3	H	n							
732	59	33.3	0	10	ins tab	8.4	1	0	y	y	1	L	n							
733	71	26.4	39.37	7	tab	6.9	0	0	y	y	1	L	n							
734	65	25.7	41.91	11	tab	9	3	1	n		2	H	n							
735	58	30.8	39.37	5	tab	5.9	0	0	y	y	1	L	n							
736	66	31.5	43.18	16	ins tab	8.7	3	2	y	y	3	H	n							
737	68	28.5	43.18	27	ins tab	8.1	0	0	y	y	1	L	n							
738	63	30.1	41.91	26	ins	7.6	6	2	y	y	3	H	n							
739	68	28.8	45.085	6	tab	5.1	6	0	y	y	2	H	n							
740	75		44.45		tab	7.2	0	1	n		1	L	n		4.1	92.6	85	10		
741	56	34.9	44.45	8	ins tab	8.1	6	2	y	y	3	H	n		13.9	92.8	76	13	2.1	CPAP
742	54	28.4	45.72	10	ins		0	2	y	y	2	H	n							
743	64	28.6	40.64	21	ins	8.5	1	1	y	y	2	H	n							
744	66		41.91	8	ins	9.3	5	1	y	y	3	H	n							
745	70	26.2	39.37		ins	9.7	4	1	n		2	H	n		0.4	96.3	91	10		
746	45	35.3	45.72	3	tab	8.2							yes	CPAP						
747	63	42.6	0	6	ins	6.9	5	2	n		3	H	n							
748	70	29.2	40.64	10	ins tab	10.3	1	2	n		1	L	n							
749	63	39.7	45.72	4	tab	6.9	4	2	n		3	H	n		8.4	96.7	69	6		
750	70	29.1	48.26	27	ins	9.9	0	0	n		0	L	n							
751	64	23.6	40.64	2	tab	9	0	2	n		1	L	n							
752	70	26.2	39.37	17	ins tab	10.8	3	0	y	y	2	H	n							

No	Age yrs	BMI kg/m2	Collar cm	DM yrs	Treatment	HbA1c	median		Known BP	BP treatment	Risk score	RISK	Known OSA	Treatment	Oxim 4%dip/hr	Mean SaO2	Min SaO2	ESS	Embletta AHI	Outcome
							1	2												
753	71	24.4	41.91	15	tab	6.6	0	0	n		0	L	n		3.9	93.9	82	3		
754	52	32.8	45.72	6	tab	8.8	5	0	n		2	H	n		8.4	95.6	83	15	10.8	CPAP
755	54	26.5	41.91	6	ins	10	2	2	y	y	3	H	n							
756	62	44.4	50.8	13	ins tab	7.9	2	2	y	y	3	H	n							
757	46	23.9	38.1	2	ins tab	9.6	3	0	n		1	L	n		4.3	93.2	86	2		
758	68	32.1	44.45	3	tab	8.7	2	0	n	n	2	H	n							
759	73	28.9	39.37	4	tab	8.9	6	2	y	y	3	H	n		3.3	94.6	87	14		
760	72	25.8	41.91	18	tab	8.3	0	0	y	y	1	L	n							
761	72		45.72	13	ins tab	11.1	2	2	y	y	3	H	n		9	92.7	74	10	7.7	no CPAP
762	54	34.4	45.72	10	ins tab	9.3	1	2	y	y	2	H	n							
763	65	31.5	43.18	10	ins tab	7.1	2	0	y	y	2	H	n		10.4	90.7	74	6	10	No CPAP
764	53	37.4	46.99	12	ins tab	7.9	7	2	y	y	3	H	n							
765	56	22	39.37	6	diet	7.5	5	1	n		2	H	n							
766	61	26.6	41.91	6	tab	6.9							yes	CPAP						
767	45	26.2	0	22	ins tab	9.5							yes	n						
768	53	35	41.91	7	tab	7.2							yes	CPAP						
769	47	35	46.99	6	ins tab	6.5	5	2	y	y	3	H	n							
770	58	47.8	52.07	2	tab	7.1	6	2	y	y	3	H	n		28.1	91.5	67	2	58.9	no CPAP
771	44	37.9	50.8	3	tab	8.9	2	0	n		2	H	n							
772	50	35.5	42.545	2	ins	12.3							yes	CPAP						
773	65	24	41.91	15	tab	8.2							yes	n						
774	55	24.2	39.37	14	ins tab	8.3	0	0	n		0	L	n		1.3	96.3	89	9		
775	57	30.5	39.37	5	ins	6.9	2	0	y	y	2	H	n							
776	45	37.4	46.99	4	tab	6.8	5	2	y	y	3	H	n		4.8	96.2	87	13		
777	59	45.5	45.72	14	ins tab	8.5							yes	CPAP						
778	56	30.05	44.45	9	tab	6.3							yes	CPAP						
779	69	34	43.434	3	tab	8.7	0	2	y	y	2	H	n		6.5	88.7	79	21	15.2	CPAP
780	51	27.2	41.91	8	tab				y	y			n							
781	61	20.15	38.1	10	ins tab	7.4	0	2	n		1	L	n		0.1	96.8	93	4		
782	70	52	43.18	30	tab	7.4	2	0	n		2	H	n							
783	61	26.2	41.91		ins tab	8.4	4	2	y	y	3	H	n							
784	65	25.3	40.64	13	ins	10.5	0	2	n	n	1	L	n							
785	48	29.6	43.18	3	diet	6.8	2	0	n		1	L	n		4.2	94.9	84	8		
786	54	24.4	38.1	1	tab	9.2	0	0	y	y	1	L	n							
787	70	24.5	41.91	12	ins	8	2	2	n		2	H	n		7.8	95.7	88	12		
788	62	29	44.45	9	tab	7.3	2	0	y	y	2	H	n		11.2	93.9	85	11	Refused	
789	63	32.4	44.45	24	ins	11.5	1	0	y	y	1	L	n							
790	60	35.7	44.45		ins tab	8.8	4	0	y	y	2	H	n							
791	71	28.7	38.1	22	ins	8.4	5	2	y	y	3	H	n							
792	58	36.9	44.45	16	ins tab	9.7	4	2	y	y	3	H	n		1.8	95.7	88	8		
793	39	24.8	43.18	4	tab	due	3	0	y	y	2	H	n		3.9	96	81	7		
794	43	36.2	45.72	20	ins	12.4	6	1	y	y	3	H	n							
795	51	31.9	44.45	11	ins	8.8	2	0	y	y	2	H	n		3.2	93.5	86	10		
796	54	37.4	45.72	7	ins	7.9	4	2	y	y	3	H	n							
797	67	31.8	45.72	39	ins	7.8	0	0	y	y	1	L	n		9.4	91.2	80	6		
798	69	28.1	40.64	13	tab	5.6	0	0	y	y	1	L	n		0	96	94	3		
799	71		40.64	3	tab	9.5	5	2	n		2	H	n		9.5	95.5	63	11	13.7	Refused

Table 1: Questionnaire and sleep study data from hospital and primary care

No	Age yrs	BMI kg/m2	Collar cm	DM yrs	Treatment	HbA1c	section 1	2	Known BP	BP treatment	Risk score	RISK	Known OSA	Treatment	Oxim 4%dip/hr	Mean SaO2	Min SaO2	ESS	Embletta AHI	Outcome
800	74	21.5	38.1	32	ins	8.7	0	0	y	y	1	L	n		4.1	95.5	84	6		
801	68	30.4	41.91	4	diet	6.9	0	1	y	y	2	H	n		1.3	95.9	89	13		
802	56	27.2	44.45	9	tab	7.1	5	2	n		2	H	n		2.3	96.9	91	13		
803	74	30.04	45.72	5	tab	6.9	5	0	n		2	H	n							
804	69	29.3	41.91	12	tab	6.6	1	0	y	y	1	L	n		9.5	94.3	62	6	Refused	
805	46	25.5	42.545	2	ins	9	0	2	y	y	2	H	n							
806	59	35.1	45.72	23	ins	8.5	4	2	y	y	3	H	n							
807	49	30.9	40.64	16	tab	7	4	2	y	y	3	H	n							
808	57	36	43.18	0.5	diet	10.2	3	0	y	y	2	H	n							
809	53	23.4	36.83	5	tab	6.2	0	0	n		0	L	n		1.8	95.2	81	1		
810	63	27.1	43.18	11	tab	6	2	0	y	y	2	H	n							
811	65	31.1	45.72	34	ins	9.7	0	0	n		1	L	n		3.1	93.7	82			
812	72	25.9	41.91	5	tab	6.2	0	0	n		0	L	n							
813	40	25.4	39.37	3	tab		0	2	y	y	2	H	n							
814	53	31.6	44.45	1	tab	6.3	5	2	y	y	3	H	n							
815	68	23.7	38.1	3	tab	5.8	2	0	y	y	2	H	n							
816	55	38	44.45	14	tab	8.6	4	2	y	y	3	H	n		7.8	93.9	75	11		
817	47	23.7	41.91	3	tab	6.3	2	2	y	y	3	H	n		0.5	95.7	89	9		
818	52	30.6	43.18	0.5	tab	10.1	4	0	y	y	2	H	n		9.7	94.8	76	11		
819	63	27.7	40.64		diet	5.7	5	1	n		2	H	n							
820	65	33.7	44.45	16	ins tab	7.4	3	2			2	H	n							
821	69	26	44.45	3	tab	7.1	0	0	n		0	L	n							
822	58	38.8	45.72	10	diet	6.7							yes	CPAP						
823	65	27.6	45.72	12	tab	8.9	5	2	y	y	3	H	n							
824	53	24.7	39.37	8	tab	8.5	0	0	n		0	L	n							
825	52	34.5	45.72	8	ins tab	9.4	5	0	n		2	H	n		4.1	95.8	88	13		
826	59	35.8	46.99	1	tab	9.7	7	2	y	y	3	H	n							
827	69	36.6	45.72	19	ins	9.2	4	2	y	y	3	H	n							
828	65	32.7	44.45		ins	9.7	0	2	y	y	2	H	n							
829	63	29.7	41.91	2	tab	5.4	0	0	y	y	1	L	n							
830	69	27.8	40.64	16	ins	7.4	5	0	n		1	L	n							
831	43	23.4	40.64	4	ins	7.1	0	0	n		0	L	n							
832	49	24.6	38.1	2	tab	8.1	1	0	n		0	L	n		1.4	96.7	87	2		
833	72	22.2	40.64	8	tab	6.7	0	0	y	y	1	L	n		2.3	96.3	64	9		
834	41	29.5	44.45	11	ins	7.6	5	0	y	y	2	H	n		1.3	96.6	87	5		
835	41		46.99	5	tab	12.9	6	0	n		1	L	n							
836	60	44.4	48.26	22	tab	7.7							yes	CPAP						
837	73	30.1	44.45	18	ins tab	10.6	0	2	n		2	H	n		3.9	94	87	10		
838	74	30.4	39.37	10	ins	8.4	0	0	y	y	1	L	n							
839	63	27.8	43.18	8	ins tab	8.5	6	2	n		2	H	n							
840	67	23.4	41.91	2	diet	7.1	1	0	y	y	1	L	n							
841	65	28.1	38.1	22	ins	8.7	0	2	y	y	2	H	n							
842	73	25.5	39.37	36	ins		5	0	n		1	L	n							
843	72	31	41.91	1	tab	7.5	3	0	n		2	H	n							
844	73	26.8	41.91	14	ins	9.8	0	0	n		0	L	n							
845	58	31.5	43.18		tab	13.5	4	1	y	y	3	H	n							
846	48	25.5	44.45	3	tab	8.2	6	2	y	y	3	H	n							

No	Age yrs	BMI kg/m2	Collar cm	DM yrs	Treatment	HbA1c	section 1	2	Known BP	BP treatment	Risk score	RISK	Known OSA	Treatment	Oxim 4%dip/hr	Mean SaO2	Min SaO2	ESS	Embletta AHI	Outcome
847	73	29.3	40.64	3	ins	7.6	4	2	n		2	H	n		6.3	94.6	76	19		
848	54	26.1	41.91	7	ins tab	7.9	1	0	n		0	L	n		11.8	95.8	85	8	2.9	No CPAP
849	60	38.2	45.72	11	ins	9.9	4	0	y	y	2	H	n							
850	67	26.7	40.64	8	ins tab	6.6	1	0	y	y	1	L	n							
851	72		38.1	20	tab	7.1	2	0	y	y	2	H	n							
852	71	36.9	46.99	10	ins	7.1	2	0	n		2	H	n		4.2	88.6	76	11		
853	76	30.6	45.72	24	ins tab	9.5	1	1	y	y	2	H	n							
854	68	25	41.91	20	ins tab	10.1	3	0	n		1	L	n							
855	75	29	43.18		diet	6.7	0	0	n		0	L	n							
856	75	30.6	45.72	9	tab	8.2	2	1	y	y	3	H	n							
857	52		40.64	7	ins	10.6	4	2	y	y	3	H	n							
858	48	39.3	48.26	3	tab	9.2							yes	CPAP						
859	63	26.7	44.45	15	ins tab	7.9	4	2	y	y	3	H	n							
860	64	27.4	38.735	28	ins	8.5	1	0	n		0	L	n		5.3	94.1	85	8		
861	58	40.1	46.99	23	ins	10.5	7	2	y	y	3	H	n							
862	60	26.7	40.64	8	tab	7.7	3	0	y	y	2	H	n							
863	63	31.2	43.815	8	ins	5.9	3	2	y	y	3	H	n							
864	53	28.2	44.45	18	diet	5.7	1	0	n		0	L	n							
865	64	25	40.64	13	ins	7.8	3	0	y	y	2	H	n							
866	56	23	38.1	9	ins tab	8.9	5	1	y	y	3	H	n							
867	72	32.5	45.72	8	ins	7.8	5	0	y	y	2	H	n							
868	54	35.4	45.72	9	ins tab	9.2	6	2	y	y	3	H	n							
869	72	31.2	43.18	19	ins tab	8.4	1	0	y	y	1	L	n		5.8	92.2	51	6		
870	49	27.2	43.18	10	ins tab	7	2	0	y	y	2	H	n							
871	58	27.1	40.64	11	ins	7.9	5	0	y	y	2	H	n							
872	58	34.2	45.72	9	tab	7.2	5	0	y	y	2	H	n							
873	69	25	40.64	26	ins	10	0	0	y	y	1	L	n							
874	68	27.5	39.37	10	ins	8.1			n				no							
875	71	30.5	45.72	15	tab	7.6	0	2	y	y	3	H	n							
876	59	33.8	44.45	9	tab	8.2							yes	CPAP						
877	57	31.3	44.45	3	diet	6.7							yes	CPAP						
878	70	27.9	43.18	3	tab	5.9	0	0	y	y	1	L	n							
879	54	29	40.64	8	ins	10.4	2	2	y	y	3	H	n							
880	53	32.1	40.64	13	ins tab	9.2	6	0	y		2	H	n							
881	70	21	36.83	5	tab	10	1	0	y	y	1	L	n							
882	72	31.1	41.91	8	tab	7.2	4	1	y	y	3	H	n							
883	53		44.45	1		6.8	4	2	n		2	H	n							
884	69	31.2	40.64	3	ins tab	8.2	3	0	y	y	2	H	n							
885	75	28.7	44.45	8	tab	8.6	5	2	n		2	H	n		4.6	95.7	85	10		
886	52	35.2	50.8	10	ins tab	12.2	5	2	y	y	3	H	n							
887	71	32.3	45.72	9	ins	6.5	7	2	y	y	3	H	n							
888	62	25.5	40.64	2	tab	7.3	6	2	y	y	3	H	n							
889	74	29.6	40.64	3	tab	6.9	1	0	y	y	1	L	n		0.4	94.2	91	7		
890	72		0	6	tab	8.7	5	2	y	y	3	H	n							
891	40	42.1	46.99	15	tab	10.2	2	0	y	y	2	H	n							
892	59		41.91		ins	11.8	5	1	n	y	2	H	n							
893	51	32.1	41.91	14	ins	8.8	0	0	y	y	1	L	n							

Table 1: Questionnaire and sleep study data from hospital and primary care databases combined

No	Age yrs	BMI kg/m2	Collar cm	DM yrs	Treatment	HbA1c	section 1	2	Known BP	BP treatment	Risk score	RISC	Known OSA	Treatment	Oxim 4%dip/hr	Mean SaO2	Min SaO2	ESS	Embletta AHI	Outcome
894	68	32.1	45.72	13	ins tab	6.2	1	0	y	y	1	L	n							
895	53	28.1	43.18	11	tab	8.2	4	2	y	y	3	H	n		12.6	95.7	75	14	0	CPAP
896	50	30	43.18	24	ins	10.8	1	0	y	y	1	L	n							
897	73	27.4	44.45	11	ins	7.6	1	0	y	y	1	L	n		1	96.2	89	7		
898	58	24.1	38.1	10	ins	8.4	0	0	n		0	L	n							
899	63	36.8	46.99	5	tab	14.2	1	0	y		1	L	n							
900	53	32	44.45	10	ins	10.9	2	0	y	y	2	H	n							
901	52	34.2	45.72	8	diet	7.9	4	0	n		2	H	n							
902	66	26	39.37	11	ins	9	0	1	y	y	2	H	n							
903	60	26	41.91	12	tab	10.1	1	1	y	y	2	H	n		7.2	95.6	81	15		
904	44	28.4	34.29	4	tab	10.2	0	0	n	n	0	L	n		5.1	95.8	86	7		
905	59	22.8	38.1	42	ins	9.4	0	0	y	y	1	L	n							
906	61	26.3	44.45	14	diet	5.3	0	1	y	y	2	H	n							
907	74	21.3	39.37	14	tab	6.8	1	2	n		1	L	n		0.6	96.8	91	16		
908	68	31.1	40.64	2	tab	6.9	1	0	y	y	1	L	n							
909	43	30.4	43.18	6	tab	7.6	5	2	n		3	H	n		0	93.3	91	3		
910	68	29.6	44.45	11	tab	7							yes	CPAP						
911	66	30.9	44.45	32	ins	10.1	7	2	y	y	3	H	n							
912	48	50.2	46.99	2	tab	6.6	5	1	y	y	3	H	n							
913	53	33.1	45.72	10	ins	12.6	4	2	y	y	3	H	n		5.1	92.9	81	12	4.3	no CPAP
914	66	26	39.37	7	diet		0	0	n		0	L	n							
915	75	26.4	41.91	2	tab	9.1	0	2	y	y	2	H	n							
916	36	31.6	43.18	4	tab	9.7	5	2	n		3	H	n							
917	65	26.9	41.91	3	tab	7.9	1	0	y	y	1	L	n							
918	54	32	43.18	7	ins tab	7.1	0	0	y	y	1	L	n							
919	65	27.3	41.91	18	ins	8.8	0	0	n		0	L	n							
920	63	26.9	39.37	3	tab	6.5	0	0	y	y	1	L	n							
921	54	34.1	46.99	4	tab	8.3	1	0	y	y	1	L	n							
922	72	23.7	39.37	2	tab	7	3	1	n		3	H	n							
923	65	34	43.18	6	tab	6.6	3	2	y	n	3	H	n							
924	51	23.8	40.64	29	ins		0	0	y	y	1	L	n							
925	57	32.8	45.72	7	tab	9.1	4	2	n		3	H	n							
926	64	40.8	43.18	9	ins tab	8.5	6	2	y	y	3	H	n							
927	51		45.72	8	ins tab	9.6	5	2	y	y	3	H	n		3.5	94.6	83			
928	59		0			6.5							n							
929	68	26.4	39.37	18	tab	9.1	2	2	n		2	H	n							
930	74	22.8	43.18		tab	5.3	0	1	y	n	2	H	n		3	88.7	83	0		
931	66	31.6	44.45	13	ins tab	8.8	0	0	y	y	1	L	n							
932	47	33.5	45.72	11	ins	8	5	1	n		3	H	n							
933	61	23.8	39.37	24	tab	12.6	7	2	n		2	H	n							
934	65	28	44.45	5	tab	9.2	7	1	y	n	3	H	n							
935	52	28.1	44.45	9	ins	9.8	6	2	y	y	3	H	n							
936	55	27	41.91	2	tab	9.8	0	1	n		1	L	n							
937	58	26.8	41.91	6	tab	9.5	0	1	n		1	L	n		1.1	95.4	90	2		
938	33	27.8	41.91	2	tab	10.4	5	1	n		2	H	n							
939	48	29.7	45.72	5	ins	11.2	3	0	y	y	2	H	n							

Table 2. Results from the overnight oximetry recorders, Minolta Pulsox 3I and RM50 in 28 subjects with varying severity of OSA (from severe to none)

No	Minolta				RM50			
	4% SaO_2 dips/hr	Total 4% dips	Mean SaO_2	Min SaO_2	4% SaO_2 dips/hr	Total 4% dips	Mean SaO_2	Min SaO_2
1	81	665	57	25	69	520	60	62
2	64	416	87	36	46	269	98	60
3	60	179	92	58	43	177	92	61
4	60	447	92	72	45	337	93	77
5	39	285	94	83	27	150	95	88
6	38	279	94	58	41	238	91	54
7	33	271	92	56	28	196	92	60
8	31	180	92	73	23	131	93	73
9	21	100	92	76	21	144	93	79
10	20	156	92	74	18	125	92	76
11	19	126	91	70	15	94	92	80
12	19	78	90	62	19	110	94	69
13	19	148	94	77	16	119	94	94
14	18	35	93	72	22	35	97	77
15	15	110	93	86	21	138	94	80
16	12	82	92	83	9	63	94	87
17	11	66	95	88	12	99	96	85
18	9	56	93	82	14	91	93	81
19	8	62	95	88	15	113	96	80
20	8	73	93	66	7	53	94	80
21	7	46	94	73	14	43	94	80
22	5	36	94	85	3	20	95	87
23	5	37	94	87	3	21	93	88
24	5	33	94	71	7	41	96	89
25	3	25	94	85	3	17	94	64
26	3	18	97	89	4	25	98	80
27	1	13	95	85	1	4	98	73
28	0	0	98	97	0	0	97	89

Table 3. Data from randomised controlled trial of CPAP in men with type 2 diabetes

Patient no	Treatment Group 0=placebo	Age	Ethnic group	DM duration years	Diet 0, tab1, ins 2, tab&ins3	PMHx	Smoker	ETOH/wk (units)	4%SaO2 dips/hr	AHI	VISIT 1 Weight kg	Height cm	Neck cm	Waist cm	Hip cm	waist:hip
1	0	24	Cauc	0.5	1	Nil	No	4	78.5		141	173	50.8	141	132	1.0681818
2	1	39	Cauc	3	1	Berger's dis, hrt block	Ex	0	22.12		119.5	174	48.26	124.5	116	1.0732759
3	0	53	Cauc	2	1	BP	Ex	2	19.5		114	178	48.26	119	118	1.0084746
4	1	58	Cauc	16	3	BP, Charcot joint	Ex	0		35.1	175.8	189	49.53	166	159	1.0440252
5	1	29	Cauc	0.5	1	Nil	No	0	62.62		124.25	171.5	45.09	132	128	1.0352941
6	0	53	Cauc	13	3	BP	y	48	77	77	110	181	44.45	120	122	0.9836066
7	1	54	Cauc	22	3	BP CVA, neurop, retinop, feet	Ex	0		27.2	121.5	188	46.23	118	121	0.9752066
8	0	59	Cauc	14	1	foot	Ex	20		40.4	151.5	191	52.07	147	134	1.0970149
9	0	52	Cauc	11	3	BP, CABG, neurop,?nephrop	Ex	0	21.75		109.3	175	45.72	123	112	1.0982143
10	1	64	Cauc	5	1	BP	Ex	0		43.5	127.5	185.4	48.26	137	132	1.0378788
11	1	57	Cauc	17	2	BP, periph neurop	Ex	0	11		110.7	187	49.53	118	111	1.0630631
12	0	53	Cauc	12	1	BP, angina	No	16	49.7		98.4	174.8	48.26	119	110	1.0818182
13	0	66	Cauc	8	1	BP, proteinuria, RA	No	3	40.12		114.8	180	46.99	130	106	1.2264151
14	0	57	Cauc	5	3	BP, gout	Ex	10	13.9	9.9	97.1	169.5	43.18	109	108	1.0092593
15	1	57	Cauc	11	1	memory probs	y	0		19.9	102	175.5	43.18	126	120	1.0543933
16	1	63	Cauc	?	1	BP, gout	No	2	57.6	70	112.7	171	46.99	126	123	1.0243902
17	0	50	Cauc	5	2	BP, circulation probs R foot	Ex	36	35.8	19.6	96.6	173	46.99	115	109	1.0550459
18	1	48	Cauc	5	1	BP	y 10/d	0	87.9	81.9	112.9	178	46.99	122	111	1.0990991
19	0	65	Cauc	8	3	Neuropathy feet	No	0	45		124.3	182	44.45	132	116	1.137931
20	1	71	Cauc	7	1	BP, AF, arthritis	ex	70	44		110.2	175	46.99	129	114	1.1315789
21	0	60	Cauc	8	3	BP	ex	1		41.2	127	180	46.99	128	128	1
22	1	59	Cauc	7	1	BP, Ca prostate	Ex	6	23	23	102.5	184	42.55	122	112	1.0892857
23	1	70	Cauc	3	1	MI, BP	Ex	49		15.2	102.5	173	45.09	122.5	127	0.9645669
24	1	59	Cauc	2	0	BP	Ex	0	20		110	182	46.99	113	110	1.0272727
25	0	42	Cauc	22	2	BP, foot dis	No	24	10.75		130	188	48.26	125	121	1.0330579
26	0	46	Cauc	1	3	MI BP	Ex	0	17.7		122.5	188	44.45	120	117	1.025641
27	0	49	Cauc	1	0	nil	y 10/d	24	62.77		99.3	184	45.72	108	106	1.0188679
28	0	50	Cauc	1	1	proteinuria, cardiomegaly	y 1 oz/wk	0	44.4		117.5	171	48.26	131	124	1.0564516
29	0	57	Cauc	1	1	BP, dilated heart	20/d	1		82.2	123.8	181	46.99	133	121	1.0991736
30	0	62	Cauc	1	1	BP	ex	7		35.2	113.9	172	48.26	137	129	1.0620155
31	1	74	Cauc	15	1	nil	ex	0	12.3		116.6	181	46.99	126	124	1.016129
32	0	62	Cauc	0.5	1	PE	ex	60		37.4	120.2	178	50.8	124	122	1.0163934
33	1	59	Asian	6	1	Charcot Marie Tooth, BP	ex	0	14.4		77.6	172	41.91	102	102	1.0049261
34	0	61	Cauc	2	0	IHD, BP, ca prostate	ex	28	11.25		118.4	190	44.45	105	115	0.9130435
35	1	59	W Ind	23	2	PVD, BP, Retinop, TIA, Pagets	ex	0	39.5		141.9	182	46.99	130	137	0.9489051
36	0	63	Cauc	3	1	IHD, BP, perip neurop	Ex	6	23.3	39.8	90.5	176	41.91	108	103	1.0485437
37	0	52	Cauc	1	0	nil	Ex	12	77		132	184	45.72	133	124	1.0725806
38	1	58	Cauc	5	1	nil	y 3/d	0	20.2		128.4	188	45.72	126	119	1.0588235
39	1	66	Cauc	1	1	OA	5/d	0		33	111.3	173	48.26	126	127	0.992126
40	0	62	Cauc	28	3	proteinuria, retinopathy, neuropathy	ex	4	23		124.7	176	49.53	128	117	1.0940171
41	1	59	Cauc	1	0	RA	Ex	22	27.6		101	169.5	43.18	113	110	1.0272727
42	1	52	Cauc	4	3	IHD, BP, proteinuria	20-30	28	17.8		114	169	18.5	135	113	1.1946903

Table 3. Data from randomised controlled trial of CPAP in men with type 2 diabetes

BMI	Ideal body	Impedance	ESS	Osler	SBP	DBP	mean BP	day	day	mean	night	night	mean	HbA1c	Glucose	Insulin -10	-5	0	Av ins 1	%S	Insulin
kg/m2	weight			mins	mmHg			SBP	DBP	day BP	SBP	DBP	night BP	%	mmol/l	pmol/l					125
47.1	68.7	423	14	16.51	145	84	104.33333	141	80	100.3333	154	91	112	9.9	15.2	99.2	36	30.9	55.36667	67.8	
39.5	69.6	425	16	23.48	.	.	.	.	.	.	.	.	.	11.6	13.2	81.8	50.5	28.7	53.66667	78.4	
35.9	73.2	410	13	40	134	76	95.333333	139	82	101	120	65	83.333333	7.1	7	109.5	96.7	113.8	106.6667	47	
49.2	83.1	355	18	14.42	159	64	95.666667	167	67	100.3333	137	58	84.333333	11.7	16.3	109	98.7	98.4	102.0333	34.1	
41.9	67.7	386	11	24.21	.	.	.	116	75	89.33333	.	.	.	6.8	7.5	227.4	221	200.3	216.2333	23.5	
33.6	75.9	377	11	40	.	.	.	139	84	102.3333	.	.	.	9.4	18.2	47.2	47.2	45.7	46.7	60	
34.4	65.9	382	13	13.54	132	73	92.666667	133	73	93	132	70	90.666667	8.2	9.4		98.7	104.9	67.86667	68.7	
41.5	65.9	416	10	40	.	.	.	154	89	110.6667	.	.	.	8	7.4	246.2			246.2	20.9	
35.7	81.3	419	21	40	158	71	100	159	73	101.6667	157	68	97.666667	10.9	13.4	279.3	300.6	289.5	289.8	15.3	
37.3	73.2	444	12	5.39	121	65	83.666667	124	66	85.33333	112	63	79.333333	7.3	6.9	142.3	138.7	120.7	133.9	37.8	816.5
31.7	75	385	13	40	148	69	95.333333	150	69	96	143	71	95	6.7	10	120.6	118.7	112.5	117.2667	39.8	1293.2
32.1	61.4	449	14	20.18	133	71	91.666667	140	70	93.33333	120	72	88	7.5	11.8	86.3	86.3	117.6	96.73333	46.1	1451.4
35.4	68.7	363	12	40	141	74	96.333333	145	75	98.33333	118	67	84	7.7	9.3	113.5	121.6	123.8	119.6333	39.6	1340
33.6	61.4	385	13	40	144	83	103.33333	150	83	105.3333	131	83	99	7.8	9.2	51.1	54.4	49.9	51.8	90	1147.3
32.9	68.7	448	12	40	126	65	85.333333	129	67	87.66667	118	61	80	8.3	9.7	52	65.6	79.3	65.63333	70.6	
40.1	73.2	488	10	40	149	69	95.666667	150	70	96.66667	143	61	88.333333	7.3	8.6	96.9	106.2	145.3	116.1333	41.4	1611.5
32.3	75.9	339	13	40	.	.	.	127	72	90.33333	.	.	.	6	6.5	120.7	141.6	190.5	150.9333	34.1	1482.2
35.6	69.6	402	16	15.27	120	74	89.333333	122	78	92.66667	116	66	82.666667	9.2	11.7	146.2	141.8	179.2	155.7333	29.1	1074
38.2	75	406	15	38.03	130	75	93.333333	138	79	98.66667	109	64	79	11.5	15.7	215.8	295.2	221.5	244.1667	15.5	2097.1
36.3	78.6	364	10	40	.	.	.	146	65	92	.	.	.	7.8	6.1	33	25.9	66.4	41.76667	121.4	1182.4
39.2	64.1	416	17	29.33	133	70	91	139	71	93.66667	122	67	85.333333	6.9	3.3	58.8	52.6	55.4	55.6	108.7	1608.1
30.3	75.9	505	20	12.45	150	74	99.333333	156	76	102.6667	131	68	89	10.5	14.2	57.4	56.8	67.7	60.63333	66.2	1404.8
35.9	80.4	439	21	8	.	.	.	158	91	113.3333	.	.	.	7.8	8.4	114.1	182.8	191.3	162.7333	30.1	1142.7
33.2	82.2	468	17	10.54	107	69	81.666667	109	73	85	104	62	76	6.6	6.8	84.1	81.7	70.2	78.66667	63.6	1411.5
36.8	78.6	423	10	24.18	114	68	83.333333	124	71	88.66667	103	66	78.333333	7.6	11.7	70.1	72.5	69.9	70.83333	62.7	950.2
34.7	66.8	385	10	22.06	111	69	83	115	71	85.66667	105	66	79	8.1	5.5	147.6	144.4	151.6	147.8667	36.2	1727.2
29.3	75.9	443	10	40	147	82	103.66667	152	84	106.6667	140	81	100.66667	8.1	8	56.6	65.6	56.3	59.5	80.8	1157.2
40.2	67.7	388	20	40	119	75	89.666667	126	78	94	108	72	84	8.3	6.2	144.9	138.4	158.6	147.3	35.3	1577.4
45.5	73.2	431	14	8.33	134	83	100	132	82	98.66667	138	85	102.66667	13.6	16.5	61.2	64.5	59.5	61.73333	54.7	1242.5
38.5	74.1	455	11	40	138	81	100	147	83	104.3333	110	73	85.333333	7	6.4	104	124.7	102.9	110.5333	46.3	2167.9
35.6	81.3	427	12	40	133	68	89.666667	137	68	91	128	67	87.333333	7.6	9.6	46.8	53.5	57	52.43333	88.2	1192.4
37.9	81.3	410	12	14.36	.	.	.	128	60	82.66667	.	.	.	7	6.8	85.3	87.4	82	84.9	59	1333.2
26.2	76.8	740	20	34.03	118	78	91.333333	121	81	94.33333	114	73	86.666667	10	10.7	59.8	62.1	57.8	59.9	75.6	1356.4
32.8	70.5	388	18	34.42	143	77	99	146	80	102	136	69	91.333333	6.4	5.8	96.2	119.7	108.4	108.1	48.4	1729.7
42.8	77.7	319	17	11.42	124	70	88	128	71	90	118	66	83.333333	12.1	19.4	53.8	49.6	55.2	52.86667	45.2	1418
29.2	82.2	494	9	40	123	75	91	127	80	95.66667	115	66	82.333333	8	9.8	123.7	127.9	121.5	124.3667	37.7	1905.5
39	61.4	370	18	17.18	137	76	96.333333	141	79	99.66667	130	72	91.333333	6.8	7.3	196.4	186.8	190	191.0667	26.6	
36.3	70.5	367	13	27.45	118	74	88.666667	118	75	89.33333	119	67	84.333333	7.1	5.8	117.1	110.6	115.5	114.4	45.8	1518.8
37.2	65.9	427	12	11.45	148	72	97.333333	146	74	98	151	68	95.666667	7.6	7.7	122.3	165.2	144.4	143.9667	34.3	1569.8
40.3	64.1	318	12	40	.	.	.	157	79	105	.	.	.	11.1	18.7	27.2	29	34.2	30.13333	86.9	1768.1
34.9		459	13	19.45	115	71	85.666667	119	75	89.66667	108	62	77.333333	6.5	7.4	196.6	190.5	201.3	196.1333	25.2	1705.4
39.9		298	18	7.51	154	80	104.66667	160	82	108	132	73	92.666667	8.9	12.8					.	

Table 3. Data from randomised controlled trial of CPAP in men with type 2 diabetes

Insulin					Av insulin	Insulin	Bld gluc	SD	Bld gluc	SD	IV gluc	IV gluc	Use	Mean gluc	M	M/I	M/I
130	135	140	145	150	picamol	micromol	t-40 to t-20		t-20 to now		t-40 to t-20	t-20 to now		infusion ml/hr		l/min/kg	mg/min/pmol
789.3	863.6	958	949	605	830.23333	0.0008302	5.4	0.2	4.7	0.1	0	17.8	t-20	17.8	329.6296296	10644.3	0.071465853
1960.6	1921.2	1894	1888	1296	1708.9167	0.0017089	5.8	0.1	5.4	0.2	105.9	134.8	t-20	134.8	2496.296296	46080.37	0.262934608
1409	1352.5	1411	1286	1298	1368	0.001368	6.8	0.3	6.3	0.4	156.8	103.2	t-20	103.2	1911.111111	43520.59	0.251461988
1342	1361.6	1415	1270	1397	1354.1167	0.0013541	6.5	0.3	6.7	0.3	153.4	78.8	t-20	78.8	1459.259259	30442	0.193976393
1076	1226.8	1258	1120	1163	1165.1833	0.0011652	6.2	0.4	5.9	0.1	228.1	223.2	t-40	225.7	4179.62963	106758.9	0.645678076
1572.8	1519.2	1458	1533	1865	1589.62	0.0015896	5.9	0.5	6.4	0.7	154	124.8	t-20	124.8	2311.111111	44190.77	0.261697764
1630.7	1391.6	1585	1564	1527	1551.55	0.0015516	6.2	0.1	6	0.2	96.5	93.8	t-40	95.2	1762.962963	28335.64	0.204526656
1452.1	1525.6	1608	1576	1623	1544.3333	0.0015443	5.9	0.1	5.8	0.3	100	101.8	t-40	100.9	1868.518519	37458.8	0.217785452
1403.1	1192.2	1292	1430	1256	1274.5	0.0012745	5.6	0.4	5.6	0.3	80.4	106	t-20	106	1962.962963	43263.56	0.277232902
1940.9	1336.8	1507	1935	1426	1706.9667	0.001707	6.8	0.3	6	0.4	0	9.6	t-40	4.8	88.88888889	1363.198	0.009373352
1296.1	1209.4	1082	1199	1069	1172.8833	0.0011729	5.9	0.4	5.2	0.1	132.1	152.9	t-40	142.5	2638.888889	61981.15	0.404984866
1621.7	1660.6	1692	1622	1602	1634.3667	0.0016344	5.3	0.6	6.3	0.2	332	371.6	t-20	371.6	6881.481481	107410.4	0.757887867
1304	1290	1278	1325	1503	1350.7333	0.0013507	6.1	0.3	6.1	0.6	160.6	154.8	t-20	154.8	2866.666667	70043.03	0.382014708
1719.7	1244.5	1242	1213	1168	1288.4	0.0012884	5.9	0.2	5.7	0.2	165.8	181.9	t-20	181.9	3368.518519	72827.23	0.470609542
1451.5	1580.2	1638	1570	1597	1541.4333	0.0015414	5.6	0.4	5.9	0.6	181.5	194.9	t-20	194.9	3609.259259	70526.97	0.421469195
		938.3		488.1	713.2	0.0007132	6	0.4	6.1	0.3	121.3	116.2	t-20	116.2	2151.851852	81988.55	0.543092167
1548	1863.8	1755	1727	1593	1702.3167	0.0017023	6.2	0.2	6	0.4	287.9	287.8	t-20	287.8	5329.62963	90225.07	0.563545756
1191.2	1103.9	1172	1153	1259	1172.7667	0.0011728	6.3	0.5	6.3	0.8	247.1	229.2	t-40	238.2	4411.111111	128371.5	0.677031521
1704.4	1646.4	1651	1794	1722	1682.5	0.0016825	4.9	0.5	5.4	0.8	157.8	272.4	t-20	272.4	5044.444444	74581.69	0.539673105
1233.6	1191.7	1194	1265	1245	1228.5	0.0012285	6.7	0.6	6.2	0.6	0	0	t-40	0	0	0	0
2101.4	2256.1	2278	2228	2124	2192.4167	0.0021924	5.6	0.6	6.5	0.5	212.4	200.5	t-20	200.5	3712.962963	43988.26	0.304838648
1238	1242.3	1197	1214	1179	1210.4833	0.0012105	5.6	0.4	6.1	0.6	231.9	288	t-20	288	5333.333333	123762.7	0.793071638
1306.6	1278.1	1348	1384	1301	1325.0167	0.001325	7.2	0.7	6.1	0.6	119.2	92.9	t-20	92.9	1720.37037	34257.95	0.233707752
1356.4	1512.1	1544	1500	1449	1452.9	0.0014529	6.5	0.2	5.8	0.7	104.5	68.7	t-20	68.7	1272.222222	33421.5	0.157615803
1900.4	1704.4	1688	1285	918.7	1537.55	0.0015376	6	0.4	5.6	0.5	114.8	150.9	t-40	132.9	2461.111111	48800.93	0.288120712
1618.5	1707.1	1880	1791	1473	1647.9667	0.001648	6.1	1.2	6.7	0.3	188.2	100.7	t-20	100.7	1864.814815	26438.91	0.20368535
1811.5	1811.5	1949	1886	1804	1861.3	0.0018613	6.1	0.3	5.2	0.6	39.7	61.5	t-20	61.5	1138.888889	20954.73	0.110138076
1073.4	1603.1	1676	1625	1576	1258.95	0.001259	5.3	0.5	5.7	0.6	124.3	167.6	t-20	167.6	3103.703704	63213.11	0.44375604
1616	1561.4	1628	1666	1311	1550.0667	0.0015501	5.5	0.5	6.5	0.7	263.8	283	t-20	283	5240.740741	93139.88	0.608575975
1432.3	1502.2	1614	1558	1509	1530.95	0.001531	5.3	0.6	6.2	0.7	148.2	202.4	t-20	202.4	3748.148148	65813.17	0.440684978
1568.9	1738.6	1717	1682	1325	1633.1667	0.0016332	5.4	0.4	4.9	1	140.2	215.2	t-20	215.2	3985.185185	60549.83	0.439228493
1639.6	1590.2	1743	1752	1745	1695.9833	0.001696	5.9	0.3	6.1	0.1	106.3	95.5	t-20	95.5	1768.518519	29878.76	0.187698385

Table 3. Data from randomised controlled trial of CPAP in men with type 2 diabetes

												VISIT 2						
HDL	Chol	Tg	Adiponectin	HS-CRP	FFA	FBC	Plasma	ACTIWATCH				Drug chg	Weight	Neck	Waist	Hip	waist:hip	BMI
mmol/l			ug/ml	mg/l	mmol/l	plets	platelet	Av activity	RMS	L5	M10		kg	cm	cm	cm		kg/m2
1.42	8.1	8.5	1.4	4.3		130	.	155	256.5	2718	14300	y stopped metform	137	48.26	137	134	1.0223881	46.3
0.94	4.7	2.6	1.7	3.3		188	.	143.3	245.29	1693	15094	n	120	46.99	126.5	119	1.0630252	37.5
1.07	4.3	2	2.1	2.1	616.1	168	.	239.8	365.2	2429	21038	n	104.5	45.72	117	116	1.0086207	33
1.14	3.9	1.5	4.9	9.6	734.5	354	359	55.2	145.72	710	5200	y ins up by 2u	178.5	49.53	165	157	1.0509554	49.2
0.79	3.6	1.2	0.5	9.5	292.5	267	.	110.6	199.34	1093	10604	n	126	44.45	131	131	1	42.6
1.1	5.4	3.4	2.9	0.5	585.2	185	405	147.6	279.49	1446	16001	n	110	45.72	122	115	1.0608696	33.6
0.78	3.1	1	3.1	2.1	231.6	256	495	169.2	317.21	819	15579	N	126	44.45	121	125	0.968	35.6
1.14	4	1.4	2.5	2.9	332.4	154	240	160.4	262.01	612	14536	n	148	52.07	147	138	1.0652174	40.6
0.68	3.1	3.4	2.8	10.7	428.4	175	208	159.9	314.53	976	16664	insulin incr by 4u	110	46.99	123	111	1.1081081	35.9
0.9	3	1	4.7	3.9	552.2	105	142	87.3	181.68	1105	9154	n	128.4	48.26	140	126	1.1111111	37.5
0.96	4.2	2.2	2.0	2.3	420.7	171	212	.	.	.	.	ins decr by 16 u/d	112.5	49.53	116	109	1.0642202	32.2
0.74	2.5	0.7	4.3	2.9	468.2	214	443	191.8	331.12	926	18791	n	97.75	48.26	118	104	1.1346154	31.9
0.82	4	1.6	4.1	20.2	536.3	221	313	120.8	215.19	2189	11645	n	113.9	48.26	128	108	1.1851852	35.2
1.18	5.9	3.2	4.9	1.3	514.0	186	358	283.3	439.21	823	27399	ins dose up	99.3	44.45	114	111	1.027027	34.4
0.98	6.5	3.8	3.8	3.6	391.4	288	541	269.3	446.53	1234	25542	n	104.3	43.18	125	121	1.0330579	33.7
1.61	4.4	1	16.5	1.2	477.4	121	195	121.8	247.65	906	11440	n	115	45.085	131.5	132	0.9962121	39.3
0.87	3.3	3.3	2.8	4.4	360.7	207	445	225.4	391.54	1270	21676	n	100	46.99	112	113	0.9911504	33.4
0.76	4	1.5	1.8	6.2	458.1	180	281	200.1	331.78	1207	18344	n	112.9	48.26	120	113	1.0619469	35.6
1.04	4.3	.	3.9	3.4	666.7	244	484	113.2	227.52	3472	7983	n	123.8	45.72	133	118	1.1271186	37.4
1.81	3.7	0.9	11.3	3.0	767.2	275	470	102.5	219.97	41	13873	stopped gliclazide	107.5	45.72	124	111	1.1171171	35.1
0.96	3.8	1.5	2.2	3.3	73.5	214	385	166.1	269.56	1785	14203	n	132	48.26	133	134	0.9925373	40.7
1.03	4.5	2.2	7.7	0.8	552.1	146	242	.	.	.	.	n	100.2	44.45	118	113	1.0442478	29.6
1.45	5.7	2.1	3.6	2.2	753.9	194	340	183.3	335.15	2203	17998	n	101.6	45.72	119	124	0.9596774	33.9
1.16	4.9	1.1	4.2	2.1	693.3	214	370	254.6	490.6	715	29990	n	105.7	46.99	109	113	0.9646018	31.9
1.46	3.8	0.9	3.8	1.7	1276.4	242	417	270	437.17	2972	24258	n	122.5	45.72	122	121	1.0082645	34.7
1.05	3.2	2.6	3.9	2.2	273.6	183	82	180.3	304.23	7254	11517	ins decr	128	44.45	122	121	1.0082645	36.2
.	.	.	1.5	1.0	729.0	211	377	337	547.23	1593	33564	n	98.4	43.18	112	102	1.0980392	29.1
0.88	3.5	2.1	1.4	4.2	260.2	285	.	142.6	280.36	1460	13661	n	114	46.99	129	121	1.0661157	39
0.95	5.5	5.9	1.9	1.9	465.5	247	499	92.1	178.31	1271	12298	withdrawn	.	.	.	.	.	.
0.87	3.9	1.5	6.3	1.3	613.5	162	371	152.4	253.98	1045	13486	n	112	48.26	132	123	1.0731707	37.9
1.03	3.9	1.2	11.6	2.0	644.8	247	404	210.6	393.45	789	23495	n	116	46.99	127	123	1.0325203	35.4
0.95	3.1	1.1	4.6	5.6	607.7	217	399	197.2	320.58	2174	22111	n	121.6	50.8	127	123	1.0325203	38.4
0.96	3.3	2.1	4.7	0.2	529.2	228	336	.	.	.	.	n	78.9	43.18	104	102	1.0196078	26.7
1.02	5.1	5.3	3.3	0.6	273.9	186	259	177.3	310.38	1276	17001	B blocker decr	119.3	44.45	114	116	0.9827586	33
0.83	3	1.4	3.4	1.3	434.9	245	281	147.3	301.74	3260	13438	ins inc	139.8	48.26	134	137	0.9781022	42.2
0.85	3.7	1.4	1.9	0.6	304.7	205	443	151	297.8	654	15349	n	90.3	41.91	107	104	1.0288462	29.2
1	3.5	1	2.1	9.3	436.2	200	315	140.5	273.77	569	13154	n	134.4	46.99	137	125	1.096	39.7
1.09	4.1	1.6	4.6	2.7	578.5	236	419	289.5	442.94	1845	29651	n	131.75	44.45	131	121	1.0826446	37.3
0.73	3.6	4.9	2.9	1.7	904.6	189	389	116.2	233.57	694	13417	n	111.1	49.53	124	127	0.976378	37.2
0.97	3.5	0.8	2.5	2.2	625.2	206	371	136.9	244.12	676	13522	n	123	50.8	129	121	1.0661157	39.7
0.97	6.2	3.2	1.8	3.7		175	268	119.9	251.44	1014	12065	started metformin	102.3	44.45	117	111	1.0540541	35.4
0.81	3.7	1.2	2.9	4.6		249	414	.	.	.	.	withdrawn	.	.	.	.	.	.

Table 3. Data from randomised controlled trial of CPAP in men with type 2 diabetes

Impedance	ESS	Osler	SBP	DBP	Mean	day	day	mean	night	night	mean	HbA1c	Glucose	Insulin -10	-5	0 Av ins	%S	Insulin		
		mins	mmHg		BP	SBP	DBP	day BP	SBP	DBP	night BP	%	mmol/l	pmol/l				125	130	135
470	1	40	141	88	105.67	145	89	107.6667	135	87	103	10.8	16.9		199	217.3	208.15	16.2			
419	11	14.48	138	90	106	.	.	.	.	.	.	7.2	8.9	81.2	99	81.4	87.2	54.4			
445	12	40	129	68	88.333	134	71	92	115	61	79	7	6.8	98.4	96.9	92.7	96	52.4			
360	18	14.03	142	62	88.667	145	66	92.33333	135	54	81	11.3	15.3	178.3	109.1	174.2	153.866667	24.9			
408	3	30.52	119	69	85.667	129	74	92.33333	106	63	77.3333333	7.3	8.1	227.5	244.9	227.5	233.3	21.5			
437	9	40	.	.	.	122	80	94	.	.	.	10.8	19.5	88.9	88.9	87	88.2666667	26.9			
.	13	16.39	139	73	95	145	75	98.33333	126	69	88	8.3	7	315.8	300.2	327.9	314.633333	16.8			
408	9	40	133	73	93	131	78	95.66667	135	67	89.6666667	8	8.8	197	177.2	195.6	189.933333	25.7			
471	7	19.51	150	75	100	155	80	105	141	64	89.6666667	10.8	12.4	321	327.3	348.4	332.233333	14			
470	9	40	116	60	78.667	117	60	79	111	60	77	7	7.9	461.7	432.4	432.4	442.166667	13.2	1340.1	1290	1378
377	0	40	163	75	104.33	166	77	106.6667	159	72	101	8.5	12.4	118.7	108.5	101.4	109.533333	40.1	1814.9	1776	1839
503	14	14.57	136	74	94.667	141	75	97	126	73	90.6666667	7.6	10.1	42.6	40.8	46.6	43.3333333	105.4	1111.4	1043	1108
365	11	32.45	163	77	105.67	166	78	107.3333	132	71	91.3333333	7.9	9.2	102.6	111.7	102.7	105.666667	44.8	1167.8	1177	1202
375	4	40	142	82	102	145	83	103.6667	134	80	98	8.3	9.1	38.6	44.2	73.2	52	89.9	931.7	868.8	842.5
433	7	40	118	62	80.667	125	66	85.66667	108	57	74	8.7	11.8	56.3	59.2	78.2	64.5666667	68.4	1390.2	1333	1275
425	1	40	144	64	90.667	152	66	94.66667	122	57	78.6666667	7.2	7.8	139.2	134.6	145.6	139.8	35.3	1613.8	1531	1603
366	12	21.54	.	.	.	124	77	92.66667	.	.	.	6.2	9.1	255.2	270.9	277.6	267.9	18.5	1925.7	1975	1926
412	6	40	118	75	89.333	122	78	92.66667	112	69	83.3333333	9.3	14.3	338.3	338.1	329.2	335.2	12.8	1696.9	1725	1536
409	8	26.45	123	72	89	126	76	92.66667	119	65	83	10	11.4	228	247.6	275.3	250.3	18.7	1755.2	1818	1856
350	9	.	.	.	.	130	71	90.66667	.	.	.	6.4	6.8	47.2	47.9	44.8	46.6333333	106.4	1202.4	1161	1093
409	18	6.21	141	72	95	149	78	101.6667	124	59	80.6666667	7.4	5.9	127.5	129	123.6	126.7	41.3	2029.5	2163	2090
504	14	40	142	84	103.33	148	86	106.6667	127	79	95	10.2	13.7	74.2	75.8	70.9	73.6333333	56.2	1285.1	1353	1355
466	15	8.54	150	81	104	159	86	110.3333	134	72	92.6666667	8.3	9.2	88.3	89.2	90.7	89.4	52.7	1146.8	1197	1138
456	3	40	113	70	84.333	120	74	89.33333	96	60	72	6.5	7	108.8	116.8	96.2	107.266667	46.7	1359.7	1409	1368
448	7	6.18	120	74	89.333	129	76	93.66667	106	70	82	8	6.1	154.8	159	163	158.933333	33	1369.4	1376	1214
384	11	31.33	111	68	82.333	115	74	87.66667	100	57	71.3333333	7	5.6	195.5	191.9	185.1	190.833333	28.3	1656.2	1556	1441
426	11	40	134	85	101.33	141	90	107	117	73	87.6666667	9.2	10.3	58	58.9	62.2	59.7	76.5	1084.7	943.5	1168
342	23	25.27	109	68	81.667	114	68	83.33333	102	67	78.6666667	7.2	5.7	94.3	100.5	95	96.6	54.2	1591.3	1524	1414
.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
408	15	24.12	.	.	.	132	91	104.6667	.	.	.	7.2	6.4	74.9	73.7	77.6	75.4	67.2	1757.7	1665	1675
403	5	.	132	63	86	132	60	84	132	67	88.6666667	7.6	8.8	67.2	59.6	61	62.6	75.4	1056.7	1059	1175
389	12	.	123	70	87.667	125	70	88.33333	121	70	87	7.2	6.2	96.3	108.6	113.9	106.266667	48.4	1483	1496	1410
679	5	40	122	76	91.333	132	81	98	112	72	85.3333333	9.8	10.9	71.7	62.9	51.7	62.1	72.6	1493.6	1346	1462
392	13	40	131	80	97	135	82	99.66667	125	77	93	6.6	7	191.5	166.3	158.2	172	29.6	1904.9	1937	1883
374	7	40	124	68	86.667	123	71	88.33333	124	61	82	15.7	25.5	66.3	70.8	67.5	68.2	1.5	2392	2325	2318
480	8	40	128	79	95.333	133	83	99.66667	119	72	87.6666667	7.7	7.2	53.5	49.4	57.4	53.4333333	91.9	1645.2	1706	1775
390	19	18.33	139	78	98.333	147	81	103	126	72	90	6.9	7.4	315.8	310.4	302.8	309.666667	16.9	1824.8	1869	1844
362	6	40	124	71	88.667	132	74	93.33333	106	63	77.3333333	6.7	5.8	138	141.8	145.2	141.666667	37.2	1587.1	1614	1624
427	9	7.15	.	.	.	146	81	102.6667	.	.	.	7.7	7.9	115.5	125.3	127.3	122.7	40	1348.4	1417	1326
355	4	40	151	71	97.667	153	74	100.3333	146	64	91.3333333	11.7	18.8	23.9	25.6	26.5	25.3333333	101.9	1678.7	1582	1424
454	10	40	134	68	90	139	70	93	126	65	85.3333333	6.7	6.6	150.7	180.7	147.8	159.733333	32.2	1782.7	1817	1925
.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

Table 3. Data from randomised controlled trial of CPAP in men with type 2 diabetes

Insulin			Av insulin	Insulin	Bld glucose	SD	Gluc	SD	IV gluc	IV gluc	Use	Mean gluc	M	M/I	M/I	HDL	Chol
140	145	150	picamol	micromol	t-40 to t-20		t-20 to now		t-40 to t-20	t-20 to now		infusion ml/hr		l/min/kg	mg/min/pmol	mmol/l	
																1.77	10.3
																1.1	6.3
																0.89	2.8
																1.13	4.4
																0.71	3.9
																1.33	6
																0.84	4.1
																0.93	3.7
																0.74	2.7
1367	1369.2	1279.8	1337.31667	0.00133732	4.9	0.2	5.2	0.3	152.6	217.8	t-20	217.8	4033.333333	45766.15676	0.542878152	0.89	3.6
1645	1730.1	1779.4	1764	0.001764	5.8	0.4	6.8	0.2	127	82.8	t-20	82.8	1533.333333	10691.71689	0.156462585	0.92	4.3
995.5	1091.7	969.8	1053.18333	0.00105318	5.4	0.2	6.1	0.7	98	159.6	t-20	159.6	2955.555556	38337.52466	0.505135225	0.91	3.1
1141	1167.8	1173.5	1171.6	0.0011716	6.4	0.3	5.9	0.3	129	132.1	t-20	132.1	2446.296296	27839.94875	0.375839308	0.9	4
878.7	852.4	734.2	851.383333	0.00085138	5.9	0.1	5.9	0.2	151.6	163.2	t-40	157.4	2914.814815	55759.31796	0.616251982	0.87	2.3
1232	1266.4	1270.7	1294.5	0.0012945	6.2	0.7	6.6	0.4	251.4	167.2	t-20	167.2	3096.296296	34816.38863	0.430539462	0.93	5.8
1591	1485.2	1518.4	1557.11667	0.00155712	5.9	0.2	5.8	0.2	91.9	110.6	t-40	101.3	1875.925926	19621.22695	0.2168538	1.32	3.5
1958	1829.6	1823.2	1906.15	0.00190615	6	0.4	5.9	0.3	87.7	88.3	t-40	88	1629.62963	12444.43266	0.153887854	0.8	2.7
1673	1781.3	1743.2	1692.53333	0.00169253	5.4	0.2	5.2	0.4	44.7	60.2	t-20	60.2	1114.814815	8998.17468	0.11855995	0.72	4
1916	1791.4	1723	1809.9	0.0018099	6.9	0.3	6.1	0.2	79.8	84.3	t-40	82.1	1520.37037	11067.58947	0.151205407	0.99	4.1
1021	1248.3	1165.2	1148.41667	0.00114842	5.9	0.3	5.2	0.2	178.6	203.4	t-40	191	3537.037037	44251.79391	0.554386474	2.32	4.2
1159	1393.6	1937.4	1795.55	0.00179555	6.2	0.5	6.3	0.3	218.6	207.9	t-20	207.9	3850	28589.19737	0.385954164	0.91	3.7
1393	1293.1	1295.1	1329.01667	0.00132902	6	0.3	5.8	0.4	190	226.9	t-20	226.9	4201.851852	40224.23217	0.569092437	0.92	3.7
793.2	1264	959.5	1083.05	0.00108305	6	0.9	5.6	0.2	78.3	121	t-20	121	2240.740741	32276.3989	0.372405091	1.52	6.2
1458	1357.7	1502.7	1409.06667	0.00140907	6.1	0.9	6.5	0.9	273.1	131.4	t-20	131.4	2433.333333	22752.45627	0.310844058	1.1	4.4
1388	1324.6	1345.8	1336.35	0.00133635	6.1	1.1	6	0.7	249.3	155.2	t-20	155.2	2874.074074	26749.8709	0.387124132	1.46	3.7
1535	1696.1	1618.7	1583.65	0.00158365	4.7	0.3	5.6	0.5	200.6	262.9	t-20	262.9	4868.518519	37399.50065	0.553363012	0.96	3.5
1095	1138	1082.6	1085.33333	0.00108533	5.9	0.7	6.3	0.8	204.8	209.6	t-40	207.2	3837.037037	44979.05261	0.636363636	1.17	6.8
1612	1691.7	1460.8	1549.01667	0.00154902	5.5	0.6	4.6	0.4	87.4	100.2	t-20	100.2	1855.555556	17932.5235	0.215620663	0.85	3.1
											t-40						
1646	1665	1584.1	1665.36667	0.00166537	5.8	0.4	5.9	0.7	120.4	162.9	t-20	162.9	3016.666667	26756.46827	0.326054322	0.93	3.9
1206	1155.2	1072	1120.51667	0.00112052	5.5	0.3	6.4	0.3	215.2	246.1	t-20	246.1	4557.407407	55563.35384	0.73210275	0.9	4
1614	1688.9	1555.9	1541.16667	0.00154117	6.6	0.2	6.2	0.5	95.4	110.2	t-20	110.2	2040.740741	17869.81348	0.238347572	0.97	3
1334	1264.6	1180.9	1346.98333	0.00134698	5.7	0.4	5.7	0.4	83.2	125.7	t-20	125.7	2327.777778	21256.35283	0.311065467	0.84	3.2
1888	1758	1966.2	1889.43333	0.00188943	5.9	0.2	5.7	0.5	106.1	112.7	t-40	109.4	2025.925926	13188.68342	0.193003193	0.88	4.4
2380	2500.1	2284	2366.41667	0.00236642	9.7	1.2	8.4	1.6	0	21.1	t-20	21.1	390.7407407	2149.989109	0.029721449	0.9	4.2
1654	1813.6	1507.4	1683.41667	0.00168342	6.5	0.6	6.2	0.4	141.7	51.1	t-20	51.1	946.2962963	7973.452305	0.10118311	0.88	3.6
1869	1783.3	1810.2	1833.38333	0.00183338	6.4	0.5	5.4	0.6	97.4	84.3	t-20	84.3	1561.111111	10958.71209	0.153268547	1.08	3.6
1648	1645.8	1586.9	1617.63333	0.00161763	5.7	0.3	6	0.3	160.1	212.6	t-20	212.6	3937.037037	29608.58108	0.438088566	1.24	4.3
1408	1245.9	1314.2	1343.06667	0.00134307	5.6	0.6	5.8	0.7	171.9	174.1	t-20	174.1	3224.074074	39096.60707	0.432095701	1	5
1549	1454.2	1589	1546.11667	0.00154612	8.4	0.7	6.6	0.5	0	16.5	t-20	16.5	305.5555556	2803.230473	0.035572995	1.06	3.4
1997	1925.3	1807.2	1875.7	0.0018757	5.5	0.4	6	0.3	82.2	114.6	t-20	114.6	2122.222222	17168.88394	0.203657301	0.92	5

Table 3. Data from randomised controlled trial of CPAP in men with type 2 diabetes

Tg	Adiponectin	HS-CRP	FFA	FBC	Plasma	ACTIWATCH				CPAP			Hrs used on
	ug/ml	mg/l	mmol/l	plets	platelet	Av activity	RMS	L5	M10	use last month(hrs)	%days used	AHI	nights used
15.2	1.1	2.5	1653.7	135	143	141	261.41	1167	11965				0
2.5	1.7	1.2	130.1	190	347	119.2	227.7	1864	12611	5.09	16.66666667	1.9	0.848333333
1.3	2.0	1.5	638.0	204	302	237.7	377.12	2853	20164	5.08	36.66666667	13.9	1.862666667
2.7	4.6	9.5	690.8	337	304	50.8	136.68	200	4778	8.35	100	11.2	8.35
1.1	0.4	5.3	320.8	267	357	110.9	204.3	995	10266	3.5	70	4	2.45
3.7	3.2	3.0	824.3	176	359	178.5	322.43	2483	17693	5.18	43.33333333	66.9	2.244666667
1.7	3.2	2.0	230.2	267	469	116	236.4	0	13311				0
1.8	2.0	8.8	385.3	172	241	81.3	179.65	867	7227	8.3	90	1	7.47
5	2.9	13.2	426.1	175	227	242.9	414.35	1089	26197	7.3	100	0	7.3
1.2	5.2	3.9	319.9	228	365	76.6	164.29	1484	6946	4.35	63.33333333	3.7	2.755
2.9	1.6	1.6	565.2	236	386	59.7	127.31	986	5511				0
0.8	4.8	3.1	1052.3	233	421	206.1	386.25	1151	19940	9.08	100	8.2	9.08
1.4	3.7	48.8	559.4	255	363	122.1	243.71	1150	12918	1.54	60	7.6	0.924
0.8	2.1	2.1	452.0	177	330	253.1	402.81	394	24780	3.28	36.66666667	3.4	1.202666667
2.6	3.5	5.8	497.0	286	468	219	379.53	2301	20766	3.35	50	3.2	1.675
1	12.2	1.3	781.3	116	154	121.1	248.2	1061	13077	7.37	100	5.7	7.37
3.4	2.6	7.1	592.3	166	289	193.2	358.66	1265	19530				0
2.3	1.5	11.4	402.2	193	396	249.2	425.26	928	25075	4.4	96.66666667	6.6	4.253333333
2	3.6	4.1	199.7	259	507	110.3	240.78	1126	12097	6.49	93.33333333	16.4	6.057333333
0.7	11.8	1.9	1237.8	280	374	252.3	396.62	4	282203	6.53	97.5	10.3	6.36675
1.7	2.0	3.4	322.0	211	307	181.1	321.94	2034	17693	2.43	63.33333333	2.9	1.539
1.3	5.0	0.8	664.0	149	184					2.43	63.33333333	2.9	1.539
1.8	3.1	6.1	1005.6	198	319								0
0.8	3.5	1.2	522.5	235	436	229.3	374.3	674	24984	6.09	93.33333333	6.3	5.684
.	4.0	1.5	396.5	256	480	258.2	414.8	4315	26057	5.05	33.33333333	0	1.683333333
3.4	2.7	3.2	324.2	220	291	173.2	292.03	1303	16172	8.09	56.66666667	0	4.584333333
9.5	1.5	1.0	760.0	191	333	180.3	346.13	2017	27788	3.46	36.66666667	3.9	1.268666667
1.4	1.3	2.6	700.9	281	426	310.2	512.86	3034	28366	9.07	63.33333333	0	5.744333333
.	.	.	816.7	.	.	.	.	.	.	.	.	.	0
2.1	4.8	1.4	827.5	173	321	167.8	292.14	653	16794	5.55	100	17	5.55
1.2	10.6	2.3	955.2	246	371	133	234.89	838	14637	7.18	96.66666667	9.4	6.940666667
0.9	4.0	2.7	559.4	209	420	187.5	295.57	69	20734	3.32	73.33333333	11.9	2.434666667
1.7	4.8	0.2	493.3	222	317					6.04	100	15.1	6.04
3.9	2.1	0.8	531.2	193	315	179.6	309.41	2240	17441	8.48	100	10.9	8.48
2.7	4.5	7.6	671.6	248	325	129.6	259.94	1080	12917	6.14	90	7.4	5.526
1.6	1.6	0.6	464.9	180	151	122.9	242.81	675	12184	4.1	96.66666667	3.9	3.963333333
1.3	1.9	19.7	495.7	194	337					0.18	10	16.3	0.018
2	5.0	2.4	683.0	246	375	131.4	270.63	1536	16412	6.02	96.66666667	5.9	5.819333333
4.2	3.7	2.8	658.2	198	432	75.6	163.73	771	8159	2.05	6.666666667	6.6	0.136666667
1.2	2.6	7.0	506.9	201	245	212.7	323.38	995	20453	4.34	50	0	2.17
2	1.9	5.4		283	283	88.3	207.2	964	11116	4.33	56.7	14.1	2.453666667
.	.	.	.	.	.	.	.	.	.	.	.	.	.

Table 4. Short Form-36 data from randomised controlled trial of CPAP in men with type 2 diabetes

Patient no	Treatment Group	SF36 VISIT 1																									
		1.00	2.00	3A	3B	3C	3D	3E	3F	3G	3H	3I	3J	4A	4B	4C	4D	5A	5B	5C	6.00	7.00	8.00	9A	9B	9C	9D
1	0	2.00	3.00	2.00	3.00	3.00	2.00	3.00	3.00	2.00	3.00	3.00	3.00	1.00	0.00	1.00	0.00	1.00	1.00	1.00	4.00	6.00	5.00	3.00	6.00	6.00	3.00
2	1	2.00	2.00	1.00	2.00	2.00	2.00	3.00	3.00	1.00	1.00	2.00	3.00	0.00	0.00	1.00	1.00	1.00	1.00	1.00	4.00	6.00	5.00	3.00	6.00	5.00	5.00
3	0	3.40	3.00	2.00	3.00	3.00	2.00	3.00	2.00	3.00	3.00	3.00	3.00	1.00	1.00	1.00	1.00	1.00	1.00	0.00	5.00	5.00	5.00	4.00	6.00	6.00	5.00
4	1	4.40	3.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	2.00	1.00	1.00	0.00	1.00	1.00	1.00	1.00	5.00	1.00	4.00	4.00	6.00	5.00	6.00
5	1	4.40	3.00	2.00	3.00	3.00	2.00	3.00	2.00	3.00	3.00	3.00	3.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	2.00	4.00	4.00	2.00	2.00	3.00	2.00
6	0	2.00	2.00	1.00	2.00	2.00	1.00	2.00	1.00	2.00	2.00	2.00	2.00	1.00	1.00	0.00	0.00	0.00	1.00	1.00	4.00	2.00	2.00	2.00	6.00	4.00	2.00
7	1	2.00	3.00	1.00	1.00	2.00	1.00	2.00	1.00	1.00	1.00	2.00	2.00	0.00	0.00	0.00	0.00	1.00	0.00	1.00	4.00	3.00	2.00	1.00	6.00	3.00	6.00
8	0	2.00	3.00	3.00	3.00	3.00	2.00	2.00	2.00	3.00	3.00	3.00	3.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	5.00	3.00	5.00	3.00	3.00	6.00	5.00
9	0	2.00	3.00	1.00	3.00	2.00	3.00	3.00	1.00	1.00	2.00	2.00	3.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	4.00	3.00	3.00	3.00	6.00	6.00	5.00
10	1	3.40	2.00	1.00	1.00	2.00	1.00	2.00	2.00	1.00	1.00	2.00	2.00	0.00	0.00	0.00	0.00	1.00	1.00	1.00	5.00	2.00	2.00	3.00	6.00	6.00	4.00
11	1	2.00	2.00	1.00	1.00	2.00	1.00	2.00	1.00	1.00	1.00	2.00	2.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00	2.00	1.00	2.00	2.00	6.00	6.00	2.00
12	0	3.40	3.00	2.00	2.00	3.00	3.00	3.00	2.00	3.00	3.00	3.00	3.00	1.00	0.00	1.00	0.00	0.00	0.00	0.00	4.00	3.00	4.00	3.00	5.00	5.00	4.00
13	0	1.00	2.00	1.00	1.00	2.00	1.00	2.00	1.00	1.00	1.00	2.00	1.00	0.00	0.00	0.00	0.00	1.00	1.00	1.00	2.00	2.00	2.00	3.00	6.00	6.00	3.00
14	0	4.40	3.00	2.00	3.00	3.00	3.00	3.00	2.00	3.00	3.00	3.00	3.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	5.00	3.00	4.00	4.00	6.00	6.00	5.00
15	1	2.00	3.00	1.00	3.00	2.00	3.00	3.00	3.00	2.00	2.00	2.00	3.00	1.00	0.00	0.00	0.00	1.00	1.00	1.00	4.00	3.00	3.00	2.00	6.00	5.00	2.00
16	1	4.40	3.00	1.00	2.00	3.00	2.00	3.00	1.00	1.00	2.00	2.00	3.00	1.00	1.00	0.00	0.00	1.00	1.00	1.00	4.00	4.00	4.00	5.00	6.00	6.00	5.00
17	0	3.40	5.00	2.00	2.00	3.00	3.00	3.00	2.00	2.00	2.00	2.00	3.00	1.00	1.00	0.00	0.00	1.00	1.00	1.00	5.00	3.00	3.00	4.00	5.00	5.00	4.00
18	1	3.40	3.00	3.00	3.00	3.00	2.00	3.00	2.00	3.00	3.00	3.00	3.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	5.00	6.00	5.00	5.00	6.00	6.00	5.00
19	0	2.00	2.00	1.00	2.00	2.00	1.00	2.00	1.00	1.00	3.00	3.00	2.00	1.00	0.00	1.00	1.00	1.00	0.00	0.00	1.00	3.00	4.00	1.00	6.00	4.00	4.00
20	1	3.40	2.00	1.00	2.00	2.00	2.00	3.00	2.00	1.00	2.00	3.00	3.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	4.00	3.00	4.00	3.00	5.00	5.00	5.00
21	0	3.40	3.00	2.00	3.00	3.00	2.00	3.00	3.00	2.00	3.00	3.00	3.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	5.00	6.00	5.00	5.00	6.00	6.00	4.00
22	1	3.40	2.00	2.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	5.00	6.00	5.00	3.00	6.00	6.00	5.00
23	1	2.00	3.00	1.00	1.00	1.00	1.00	2.00	2.00	1.00	2.00	2.00	2.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	5.00	3.00	2.00	4.00	4.00	4.00	5.00
24	1	2.00	2.00	3.00	3.00	3.00	3.00	3.00	2.00	3.00	3.00	3.00	3.00	1.00	0.00	1.00	0.00	0.00	0.00	0.00	4.00	4.00	5.00	2.00	6.00	4.00	3.00
25	0	2.00	3.00	2.00	3.00	3.00	2.00	3.00	3.00	3.00	3.00	3.00	3.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	3.00	4.00	4.00	2.00	5.00	4.00	2.00
26	0	2.00	3.00	1.00	3.00	2.00	2.00	3.00	2.00	3.00	3.00	3.00	3.00	1.00	0.00	0.00	0.00	1.00	1.00	0.00	3.00	6.00	5.00	2.00	4.00	4.00	4.00
27	0	3.40	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	5.00	6.00	5.00	3.00	6.00	6.00	1.00
28	0	2.00	3.00	1.00	2.00	1.00	1.00	2.00	2.00	1.00	2.00	2.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.00	2.00	2.00	3.00	6.00	4.00	3.00
30	0	3.40	2.00	2.00	3.00	3.00	1.00	2.00	2.00	1.00	1.00	2.00	2.00	1.00	0.00	0.00	0.00	1.00	1.00	1.00	5.00	2.00	2.00	4.00	6.00	6.00	3.00
31	1	4.40	3.00	2.00	2.00	3.00	2.00	2.00	2.00	1.00	2.00	2.00	3.00	0.00	0.00	0.00	0.00	1.00	1.00	1.00	5.00	5.00	5.00	4.00	6.00	6.00	5.00
32	0	3.40	2.00	1.00	2.00	2.00	1.00	2.00	1.00	2.00	2.00	3.00	3.00	1.00	0.00	0.00	0.00	1.00	1.00	1.00	5.00	3.00	3.00	3.00	6.00	4.00	3.00
33	1	4.40	3.00	1.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	5.00	6.00	5.00	6.00	6.00	6.00	6.00
34	0	3.40	4.00	1.00	1.00	2.00	2.00	3.00	2.00	3.00	3.00	3.00	2.00	1.00	0.00	0.00	0.00	1.00	1.00	1.00	3.00	3.00	3.00	3.00	5.00	6.00	5.00
35	1	2.00	2.00	2.00	2.00	1.00	1.00	3.00	2.00	2.00	2.00	3.00	2.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.00	3.00	2.00	1.00	6.00	1.00	4.00
36	0	3.40	3.00	1.00	3.00	3.00	3.00	3.00	2.00	3.00	3.00	3.00	3.00	1.00	0.00	1.00	1.00	1.00	0.00	1.00	4.00	4.00	4.00	4.00	5.00	6.00	5.00
37	0	4.40	1.00	1.00	2.00	2.00	2.00	3.00	1.00	2.00	3.00	3.00	2.00	1.00	1.00	1.00	0.00	1.00	1.00	1.00	4.00	6.00	5.00	4.00	6.00	6.00	3.00
38	1	5.00	3.00	1.00	3.00	3.00	3.00	3.00	1.00	2.00		3.00	3.00	1.00	0.00	1.00	1.00	1.00	1.00	1.00	4.00	2.00	3.00	5.00	6.00	4.00	5.00
39	1	2.00	3.00	1.00	2.00	2.00	1.00	3.00	2.00	1.00	2.00	3.00	3.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	5.00	6.00	5.00	5.00	6.00	6.00	5.00
40	0	2.00	4.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	2.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.00	3.00	2.00	1.00	4.00	1.00	1.00
41	1	2.00	4.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	2.00	2.00	2.00	0.00	0.00	0.00	0.00	1.00	0.00	1.00	2.00	2.00	2.00	3.00	4.00	4.00	2.00

Table 4. Short Form-36 data from randomised controlled trial of CPAP in men with type 2 diabetes

										Physical functioning	Role Physical	Role Emotional	Social functioning	Mental Health	Energy/Vitality	Bodily pain
9E	9F	9G	9H	9I	9J	10A	10B	10C	10D	PF	RP	RE	SF	MH	EV	P
3.00	5.00	4.00	4.00	4.00	5.00	2.00	4.00	3.00	2.00	85.00	50.00	100.00	77.78	76.00	50.00	100.00
2.00	4.00	3.00	6.00	3.00	4.00	1.00	14.00	3.00	1.00	50.00	50.00	100.00	66.67	84.00	35.00	100.00
3.00	5.00	4.00	5.00	3.00	6.00	4.00	1.00	2.00	3.00	85.00	100.00	66.67	100.00	88.00	50.00	88.89
4.00	6.00	4.00	6.00	2.00	5.00	1.00	3.00	2.00	4.00	5.00	75.00	100.00	88.89	96.00	50.00	33.33
2.00	3.00	2.00	3.00	2.00	3.00	4.00	3.00	4.00	3.00	85.00	25.00	0.00	33.33	32.00	20.00	66.67
2.00	6.00	3.00	3.00	2.00	6.00	3.00	2.00	2.00	1.00	35.00	50.00	66.67	88.89	64.00	25.00	22.22
3.00	4.00	2.00	6.00	4.00	4.00	3.00	1.00	3.00	1.00	20.00	0.00	66.67	66.67	80.00	30.00	33.33
2.00	2.00	2.00	4.00	4.00	6.00	3.00	3.00	3.00	4.00	85.00	100.00	100.00	100.00	60.00	35.00	66.67
3.00	4.00	4.00	6.00	3.00	6.00	4.00	2.00	3.00	1.00	55.00	100.00	100.00	88.89	88.00	45.00	44.44
2.00	6.00	4.00	5.00	2.00	4.00	5.00	4.00	3.00	3.00	25.00	0.00	100.00	77.78	88.00	35.00	22.22
2.00	6.00	3.00	2.00	2.00	2.00	3.00	2.00	2.00	2.00	20.00	0.00	33.33	22.22	68.00	25.00	11.11
4.00	5.00	5.00	5.00	3.00	5.00	3.00	4.00	3.00	4.00	85.00	50.00	0.00	77.78	76.00	55.00	55.56
2.00	5.00	2.00	3.00	2.00	6.00	4.00	1.00	1.00	1.00	15.00	0.00	100.00	66.67	72.00	25.00	22.22
4.00	6.00	3.00	5.00	4.00	6.00	4.00	4.00	2.00	3.00	90.00	100.00	100.00	100.00	92.00	55.00	55.56
1.00	6.00	1.00	5.00	1.00	1.00	4.00	3.00	3.00	2.00	70.00	25.00	100.00	33.33	76.00	5.00	44.44
3.00	6.00	5.00	6.00	3.00	6.00	5.00	3.00	3.00	4.00	50.00	50.00	100.00	88.89	96.00	60.00	66.67
3.00	4.00	3.00	3.00	2.00	4.00	3.00	3.00	4.00	4.00	70.00	50.00	100.00	77.78	64.00	40.00	44.44
4.00	5.00	4.00	4.00	4.00	6.00	5.00	4.00	3.00	4.00	90.00	100.00	100.00	100.00	84.00	65.00	100.00
1.00	3.00	3.00	5.00	3.00	5.00	5.00	1.00	1.00	2.00	40.00	75.00	33.33	44.44	68.00	20.00	55.56
3.00	5.00	4.00	5.00	3.00	5.00	4.00	3.00	4.00	3.00	55.00	25.00	33.33	77.78	80.00	45.00	55.56
4.00	6.00	4.00	5.00	4.00	6.00	5.00	3.00	5.00	4.00	85.00	100.00	100.00	100.00	88.00	65.00	100.00
3.00	6.00	2.00	5.00	2.00	6.00	5.00	4.00	4.00	2.00	95.00	100.00	100.00	100.00	92.00	30.00	100.00
3.00	4.00	5.00	5.00	2.00	2.00	3.00	3.00	2.00	2.00	25.00	100.00	100.00	55.56	68.00	50.00	33.33
2.00	5.00	4.00	3.00	1.00	1.00	3.00	1.00	2.00	2.00	95.00	50.00	0.00	33.33	64.00	25.00	77.78
2.00	4.00	3.00	3.00	2.00	4.00	2.00	3.00	3.00	2.00	90.00	100.00	100.00	55.56	52.00	25.00	66.67
2.00	3.00	3.00	3.00	3.00	4.00	3.00	2.00	3.00	2.00	75.00	25.00	66.67	55.56	52.00	30.00	100.00
3.00	5.00	5.00	5.00	4.00	6.00	5.00	4.00	4.00	4.00	100.00	100.00	100.00	100.00	72.00	55.00	100.00
3.00	4.00	3.00	3.00	2.00	3.00	5.00	1.00	1.00	1.00	25.00	0.00	0.00	33.33	60.00	35.00	22.22
3.00	6.00	4.00	5.00	5.00	6.00	5.00	3.00	3.00	3.00	45.00	25.00	100.00	100.00	84.00	60.00	22.22
3.00	6.00	5.00	5.00	4.00	6.00	5.00	5.00	2.00	5.00	55.00	0.00	100.00	100.00	92.00	60.00	88.89
3.00	4.00	4.00	5.00	3.00	6.00	3.00	4.00	4.00	3.00	45.00	25.00	100.00	100.00	68.00	45.00	44.44
4.00	6.00	4.00	6.00	3.00	6.00	5.00	4.00	3.00	4.00	90.00	100.00	100.00	100.00	100.00	65.00	100.00
2.00	5.00	2.00	5.00	3.00	4.00	3.00	2.00	4.00	4.00	60.00	25.00	100.00	55.56	84.00	30.00	44.44
2.00	1.00	1.00	6.00	1.00	3.00	4.00	2.00	2.00	2.00	50.00	0.00	30.00	0.00	166.67	22.22	44.00
3.00	6.00	4.00	5.00	4.00	5.00	3.00	2.00	1.00	2.00	85.00	75.00	70.00	75.00	300.00	44.44	76.00
2.00	5.00	3.00	5.00	2.00	6.00	5.00	1.00	3.00	4.00	55.00	75.00	50.00	75.00	366.67	44.44	64.00
3.00	6.00	2.00	5.00	6.00	4.00	5.00	5.00	3.00	4.00	60.00	75.00	45.00	100.00	233.33	66.67	72.00
5.00	2.00	5.00	4.00	4.00	6.00	4.00	4.00	5.00	4.00	50.00	100.00	45.00	100.00	400.00	77.78	68.00
1.00	1.00	1.00	3.00	2.00	4.00	1.00	1.00	1.00	1.00	5.00	0.00	0.00	44.44	20.00	5.00	33.33
1.00	4.00	2.00	4.00	2.00	2.00	2.00	2.00	3.00	1.00	15.00	0.00	66.67	22.22	52.00	20.00	22.22

Table 4. Short Form-36 data from randomised controlled trial of CPAP in men with type 2 diabetes

Gen Health Percep	Change in health			SF36 VISIT 2																	
GHP	CH	PCS	MCS	1.00	2.00	3A	3B	3C	3D	3E	3F	3G	3H	3I	3J	4A	4B	4C	4D	5A	5B
40.00	50.00	70.31	72.10	3.40	4.00	2.00	3.00	3.00	2.00	3.00	3.00	2.00	3.00	3.00	3.00	1.00	1.00	1.00	1.00	1.00	1.00
80.00	25.00	67.25	73.06	1.00	3.00	1.00	2.00	2.00	2.00	3.00	3.00	1.00	2.00	3.00	3.00	0.00	0.00	0.00	0.00	1.00	1.00
42.00	50.00	79.99	74.75	3.40	3.00	2.00	3.00	3.00	2.00	3.00	3.00	3.00	3.00	3.00	3.00	0.00	0.00	0.00	0.00	1.00	1.00
47.00	50.00	49.82	76.30	2.00	2.00	1.00	1.00	1.00	1.00	1.00	2.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
67.00	50.00	51.22	29.40	4.40	4.00	2.00	3.00	3.00	3.00	3.00	2.00	3.00	3.00	3.00	3.00	1.00	1.00	1.00	1.00	0.00	0.00
25.00	25.00	41.30	53.92	2.00	2.00	1.00	3.00	3.00	2.00	3.00	1.00	2.00	2.00	3.00	3.00	1.00	0.00	0.00	0.00	1.00	0.00
25.00	50.00	29.47	51.88	2.00	3.00	1.00	2.00	2.00	1.00	2.00	1.00	1.00	1.00	2.00	2.00	0.00	0.00	0.00	0.00	1.00	0.00
50.00	50.00	75.63	72.03	3.40	3.00	2.00	3.00	3.00	2.00	2.00	2.00	2.00	3.00	3.00	3.00	0.00	0.00	0.00	0.00	0.00	0.00
35.00	50.00	63.63	75.16	3.40	4.00	1.00	3.00	2.00	2.00	3.00	1.00	1.00	1.00	2.00	3.00	1.00	1.00	0.00	1.00	1.00	1.00
67.00	25.00	37.84	66.86	3.40	4.00	1.00	2.00	2.00	2.00	2.00	2.00	1.00	1.00	1.00	3.00	1.00	0.00	1.00	0.00	1.00	1.00
30.00	25.00	18.72	33.85	3.40	5.00	1.00	3.00	3.00	3.00	3.00	2.00	2.00	3.00	3.00	2.00	0.00	0.00	1.00	0.00	1.00	1.00
62.00	50.00	63.08	53.42	2.00	4.00	2.00	2.00	3.00	3.00	3.00	2.00	3.00	3.00	3.00	3.00	1.00	1.00	0.00	0.00	1.00	0.00
15.00	25.00	24.99	54.05	2.00	2.00	1.00	2.00	2.00	2.00	2.00	1.00	1.00	1.00	2.00	1.00	1.00	0.00	0.00	0.00	1.00	1.00
62.00	50.00	79.17	83.56	3.40	3.00	2.00	3.00	3.00	2.00	3.00	2.00	3.00	3.00	3.00	3.00	1.00	0.00	1.00	1.00	1.00	1.00
45.00	50.00	43.25	52.40	4.40	3.00	1.00	1.00	1.00	1.00	2.00	1.00	1.00	1.00	2.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00
72.00	50.00	65.09	81.42	4.40	3.00	2.00	2.00	3.00	2.00	3.00	2.00	2.00	2.00	3.00	3.00	1.00	1.00	1.00	1.00	1.00	1.00
62.00	100.00	58.94	66.88	2.00	3.00	2.00	3.00	3.00	3.00	3.00	2.00	1.00	1.00	2.00	3.00	1.00	1.00	1.00	1.00	1.00	1.00
72.00	50.00	89.89	86.96	3.40	4.00	2.00	3.00	3.00	3.00	3.00	2.00	3.00	3.00	3.00	3.00	1.00	1.00	1.00	1.00	1.00	1.00
30.00	25.00	47.22	43.98	3.40	3.00	1.00	2.00	3.00	1.00	3.00	1.00	3.00	3.00	3.00	3.00	1.00	0.00	0.00	1.00	0.00	0.00
62.00	25.00	52.75	57.01	2.00	2.00	1.00	2.00	3.00	1.00	2.00	2.00	1.00	2.00	3.00	2.00	0.00	0.00	0.00	1.00	0.00	1.00
77.00	50.00	89.83	88.31	3.40	3.00	2.00	2.00	3.00	2.00	3.00	2.00	2.00	3.00	3.00	3.00	1.00	1.00	1.00	1.00	1.00	0.00
67.00	25.00	87.11	81.83	3.40	3.00	2.00	3.00	3.00	3.00	3.00	2.00	3.00	3.00	3.00	3.00	1.00	1.00	1.00	1.00	1.00	1.00
35.00	50.00	51.37	65.24	2.00	2.00	3.00	2.00	2.00	2.00	2.00	2.00	3.00	2.00	2.00	2.00	0.00	0.00	0.00	0.00	0.00	0.00
25.00	25.00	54.78	35.32	3.40	5.00	3.00	3.00	3.00	3.00	3.00	2.00	3.00	3.00	3.00	3.00	1.00	1.00	1.00	1.00	0.00	1.00
35.00	50.00	67.51	59.61	2.00	3.00	2.00	3.00	3.00	2.00	3.00	2.00	3.00	3.00	3.00	3.00	1.00	1.00	1.00	1.00	1.00	1.00
35.00	50.00	56.75	50.63	2.00	3.00	2.00	3.00	3.00	2.00	3.00	2.00	3.00	3.00	3.00	3.00	0.00	0.00	0.00	0.00	0.00	0.00
77.00	50.00	91.31	83.11	3.40	3.00	2.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	1.00	1.00	1.00	1.00	1.00	1.00
25.00	50.00	22.22	29.29	2.00	1.00	1.00	2.00	1.00	1.00	1.00	2.00	1.00	1.00	2.00	2.00	0.00	1.00	0.00	0.00	1.00	1.00
62.00	25.00	50.50	75.56	3.40	3.00	2.00	2.00	2.00	1.00	2.00	1.00	1.00	1.00	2.00	2.00	1.00	0.00	0.00	1.00	1.00	1.00
82.00	50.00	63.92	81.35	4.40	3.00	1.00	2.00	2.00	1.00	2.00	2.00	1.00	1.00	2.00	2.00	1.00	1.00	0.00	0.00	1.00	1.00
62.00	25.00	52.87	70.39	3.40	3.00	1.00	2.00	3.00	2.00	2.00	2.00	2.00	3.00	3.00	3.00	1.00	0.00	1.00	0.00	1.00	1.00
77.00	50.00	91.16	91.03	4.40	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	1.00	1.00	1.00	1.00	1.00	1.00
57.00	75.00	48.52	63.55	2.00	3.00	1.00	2.00	2.00	2.00	3.00	2.00	2.00	3.00	3.00	3.00	0.00	0.00	0.00	0.00	0.00	0.00
15.00	55.56	255.00	25.00	3.40	5.00	2.00	2.00	2.00	1.00	2.00	1.00	3.00	2.00	3.00	2.00	1.00	1.00	1.00	1.00	0.00	0.00
65.00	77.78	795.00	50.00	1.00	3.00	1.00	3.00	3.00	3.00	3.00	2.00	3.00	3.00	3.00	3.00	1.00	1.00	1.00	1.00	1.00	1.00
60.00	88.89	665.00	25.00	1.00	2.00	1.00	2.00	3.00	2.00	3.00	1.00	3.00	3.00	3.00	2.00	1.00	1.00	1.00	1.00	1.00	1.00
65.00	100.00	690.00	50.00	4.40	5.00	3.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	1.00	1.00	1.00	1.00	1.00
75.00	100.00	775.00	25.00	4.40	5.00	3.00	3.00	3.00	2.00	3.00	3.00	3.00	3.00	3.00	3.00	1.00	1.00	1.00	1.00	1.00	1.00
5.00	75.00	14.77	14.94	1.00	4.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.00	0.00
25.00	75.00	19.02	35.91	2.00	4.00	1.00	2.00	1.00	1.00	2.00	1.00	1.00	2.00	3.00	2.00	1.00	1.00	0.00	1.00	1.00	1.00

Table 4. Short Form-36 data from randomised controlled trial of CPAP in men with type 2 diabetes

																		Physical functioning	Role Physical	Role Emotional	Social functioning
5C	6.00	7.00	8.00	9A	9B	9C	9D	9E	9F	9G	9H	9I	9J	10A	10B	10C	10D	PF	RP	RE	SF
1.00	5.00	6.00	5.00	5.00	6.00	6.00	5.00	4.00	6.00	5.00	5.00	5.00	6.00	5.00	3.00	5.00	2.00	85.00	100.00	100.00	100.00
1.00	4.00	5.00	5.00	2.00	6.00	6.00	5.00	2.00	6.00	4.00	5.00	4.00	5.00	1.00	1.00	1.00	1.00	60.00	0.00	100.00	77.78
1.00	5.00	3.00	3.00	5.00	4.00	6.00	5.00	4.00	4.00	6.00	5.00	5.00	4.00	4.00	4.00	2.00	3.00	90.00	0.00	100.00	77.78
1.00	5.00	1.00	3.00	3.00	6.00	5.00	5.00	3.00	5.00	3.00	5.00	3.00	4.00	3.00	4.00	1.00	4.00	5.00	100.00	100.00	77.78
0.00	4.00	5.00	4.00	4.00	5.00	4.00	2.00	4.00	4.00	5.00	2.00	4.00	5.00	5.00	1.00	2.00	4.00	90.00	100.00	0.00	77.78
1.00	5.00	3.00	3.00	2.00	6.00	5.00	4.00	3.00	2.00	2.00	4.00	2.00	6.00	3.00	2.00	2.00	1.00	65.00	25.00	66.67	100.00
1.00	2.00	2.00	2.00	3.00	6.00	5.00	5.00	2.00	5.00	3.00	6.00	4.00	2.00	3.00	3.00	3.00	3.00	25.00	0.00	66.67	22.22
0.00	1.00	1.00	1.00	6.00	1.00	4.00	4.00	2.00	4.00	4.00	5.00	3.00	6.00	5.00	4.00	3.00	4.00	75.00	0.00	0.00	55.56
1.00	5.00	3.00	4.00	4.00	6.00	6.00	5.00	5.00	6.00	6.00	5.00	5.00	6.00	4.00	2.00	3.00	2.00	45.00	75.00	100.00	100.00
1.00	4.00	3.00	2.00	3.00	5.00	6.00	4.00	2.00	5.00	4.00	5.00	3.00	3.00	5.00	4.00	3.00	2.00	35.00	50.00	100.00	55.56
1.00	4.00	3.00	3.00	3.00	6.00	6.00	4.00	4.00	6.00	4.00	4.00	5.00	6.00	3.00	2.00	3.00	2.00	75.00	25.00	100.00	88.89
0.00	4.00	2.00	2.00	4.00	5.00	4.00	3.00	4.00	4.00	5.00	5.00	3.00	6.00	3.00	4.00	3.00	3.00	85.00	50.00	33.33	88.89
1.00	4.00	2.00	4.00	3.00	6.00	5.00	3.00	1.00	4.00	4.00	3.00	4.00	6.00	4.00	1.00	1.00	1.00	25.00	25.00	100.00	88.89
1.00	5.00	4.00	4.00	4.00	6.00	6.00	5.00	4.00	6.00	5.00	5.00	3.00	6.00	2.00	4.00	2.00	4.00	85.00	75.00	100.00	100.00
0.00	2.00	3.00	2.00	2.00	4.00	3.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	4.00	2.00	1.00	1.00	10.00	0.00	0.00	11.11
1.00	5.00	6.00	5.00	5.00	6.00	6.00	5.00	3.00	6.00	5.00	6.00	5.00	6.00	5.00	4.00	3.00	4.00	70.00	100.00	100.00	100.00
0.00	4.00	5.00	4.00	3.00	4.00	5.00	3.00	4.00	4.00	3.00	5.00	3.00	3.00	4.00	3.00	2.00	4.00	65.00	100.00	66.67	55.56
1.00	5.00	5.00	5.00	4.00	6.00	6.00	4.00	4.00	6.00	6.00	4.00	5.00	6.00	4.00	4.00	3.00	3.00	90.00	100.00	100.00	100.00
1.00	3.00	5.00	5.00	2.00	6.00	6.00		3.00	5.00	4.00	5.00	5.00	1.00	2.00	2.00	2.00	2.00	65.00	50.00	33.33	22.22
1.00	4.00	4.00	4.00	3.00	5.00	6.00	3.00	3.00	6.00	4.00	5.00	4.00	4.00	2.00	2.00	4.00	2.00	45.00	25.00	66.67	66.67
1.00	4.00	4.00	3.00	4.00	6.00	6.00	5.00	5.00	5.00	5.00	5.00	4.00	5.00	5.00	4.00	3.00	3.00	75.00	100.00	66.67	77.78
1.00	5.00	3.00	4.00	5.00	6.00	6.00	5.00	3.00	6.00	4.00	5.00	3.00	6.00	5.00	4.00	5.00	4.00	90.00	100.00	100.00	100.00
0.00	2.00	3.00	3.00	3.00	4.00	2.00	4.00	2.00	3.00	2.00	6.00	4.00	1.00	1.00	3.00	3.00	1.00	60.00	0.00	0.00	11.11
1.00	5.00	4.00	4.00	2.00	6.00	4.00	2.00	1.00	4.00	5.00	2.00	5.00	5.00	3.00	3.00	2.00	3.00	95.00	100.00	66.67	88.89
1.00	4.00	5.00	4.00	2.00	5.00	5.00	2.00	2.00	5.00	3.00	5.00	3.00	4.00	2.00	2.00	3.00	2.00	85.00	100.00	100.00	66.67
0.00	4.00	5.00	4.00	3.00	5.00	5.00	3.00	2.00	3.00	3.00	3.00	3.00	4.00	3.00	3.00	3.00	3.00	85.00	0.00	0.00	66.67
1.00	5.00	5.00	5.00	5.00	6.00	6.00	5.00	5.00	6.00	5.00	5.00	4.00	6.00	5.00	5.00	4.00	4.00	95.00	100.00	100.00	100.00
1.00	3.00	2.00	3.00	1.00	6.00	3.00	3.00	2.00	4.00	3.00	3.00	2.00	3.00	3.00	2.00	1.00	2.00	20.00	25.00	100.00	44.44
1.00	5.00	2.00	3.00	3.00	6.00	6.00	3.00	3.00	6.00	5.00	6.00	6.00	6.00	5.00	3.00	3.00	2.00	30.00	50.00	100.00	100.00
1.00	4.00	5.00	4.00	5.00	6.00	6.00	5.00	4.00	6.00	5.00	5.00	5.00	6.00	5.00	4.00	6.00	4.00	30.00	50.00	100.00	88.89
1.00	5.00	3.00	4.00	3.00	6.00	6.00	3.00	2.00	6.00	5.00	5.00	4.00	6.00	3.00	4.00	4.00	2.00	65.00	50.00	100.00	100.00
1.00	5.00	6.00	5.00	6.00	6.00	6.00	6.00	5.00	6.00	6.00	6.00	4.00	6.00	5.00	5.00	5.00	5.00	100.00	100.00	100.00	100.00
0.00	2.00	3.00	3.00	3.00	4.00	4.00	2.00	1.00	4.00	3.00	3.00	2.00	2.00	3.00	2.00	4.00	3.00	65.00	0.00	0.00	22.22
1.00	2.00	2.00	2.00	3.00	1.00	5.00	4.00	1.00	2.00	4.00	5.00	4.00	6.00	5.00	1.00	5.00	1.00	50.00	100.00	33.33	66.67
1.00	5.00	4.00	5.00	4.00	6.00	6.00	5.00	4.00	5.00	5.00	5.00	5.00	6.00	4.00	1.00	1.00	1.00	85.00	100.00	100.00	100.00
1.00	5.00	3.00	3.00	1.00	6.00	5.00	3.00	2.00	3.00	3.00	5.00	1.00	6.00	5.00	2.00	3.00	2.00	65.00	100.00	100.00	100.00
1.00	5.00	2.00	3.00	5.00	6.00	4.00	6.00	3.00	5.00	5.00	6.00	6.00	2.00	3.00	4.00	3.00	4.00	55.00	100.00	100.00	55.56
1.00	5.00	6.00	5.00	5.00	6.00	6.00	6.00	5.00	6.00	6.00	6.00	3.00	6.00	5.00	5.00	4.00	4.00	95.00	100.00	100.00	100.00
0.00	3.00	3.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	2.00	1.00	1.00	1.00	1.00	1.00	1.00	0.00	100.00	0.00	22.22
1.00	4.00	3.00	3.00	2.00	4.00	4.00	2.00	1.00	4.00	4.00	3.00	5.00	3.00	3.00	2.00	3.00	1.00	30.00	75.00	100.00	55.56

Table 4. Short Form-36 data from randomised controlled trial of CPAP in men with type 2 diabetes

Mental Health	Energy/Vitality	Bodily pain	Gen Health Percep	Change in health			change in EV	change in PCS	change in MCS
MH	EV	P	GHP	CH	PCS	MCS			
92.00	75.00	100.00	67.00	75.00	89.31	89.98	25.00	19.00	17.88
92.00	40.00	88.89	0.00	50.00	47.47	65.46	5.00	-19.78	-7.60
76.00	80.00	44.44	57.00	50.00	56.86	73.37	30.00	-23.13	-1.38
84.00	40.00	22.22	45.00	25.00	49.31	70.82	-10.00	-0.51	-5.48
48.00	65.00	77.78	57.00	75.00	76.78	52.97	45.00	25.56	23.57
64.00	25.00	44.44	25.00	25.00	48.13	55.63	0.00	6.83	1.71
88.00	40.00	22.22	45.00	50.00	27.02	49.80	10.00	-2.45	-2.08
52.00	55.00	0.00	72.00	50.00	39.35	39.28	20.00	-36.28	-32.75
92.00	80.00	55.56	47.00	75.00	65.82	84.39	35.00	2.19	9.23
80.00	40.00	33.33	62.00	75.00	47.75	65.78	5.00	9.91	-1.08
84.00	60.00	44.44	42.00	100.00	56.03	73.15	35.00	37.31	39.30
64.00	60.00	22.22	50.00	75.00	57.20	57.07	5.00	-5.88	3.66
64.00	40.00	44.44	20.00	25.00	40.48	62.09	15.00	15.49	8.04
92.00	60.00	66.67	52.00	50.00	74.62	82.31	5.00	-4.55	-1.25
20.00	5.00	33.33	37.00	50.00	16.54	12.91	0.00	-26.71	-39.49
96.00	70.00	100.00	77.00	50.00	87.63	90.81	10.00	22.54	9.40
64.00	45.00	77.78	50.00	50.00	68.47	61.24	5.00	9.54	-5.64
84.00	75.00	88.89	62.00	75.00	87.13	87.17	10.00	-2.76	0.22
68.00	50.00	88.89	32.00	50.00	54.10	46.46	30.00	6.87	2.48
80.00	50.00	66.67	35.00	25.00	48.67	60.25	5.00	-4.08	3.25
88.00	70.00	55.56	67.00	50.00	74.64	75.58	5.00	-15.19	-12.73
92.00	55.00	55.56	82.00	50.00	82.29	85.67	25.00	-4.82	3.84
56.00	35.00	44.44	25.00	25.00	30.32	26.34	-15.00	-21.06	-38.90
52.00	45.00	66.67	47.00	100.00	75.50	63.54	20.00	20.72	28.22
68.00	30.00	77.78	30.00	50.00	70.24	65.88	5.00	2.72	6.27
56.00	35.00	77.78	45.00	50.00	51.61	39.58	5.00	-5.14	-11.05
92.00	75.00	88.89	82.00	50.00	91.46	91.12	20.00	0.14	8.01
56.00	20.00	33.33	25.00	0.00	30.51	49.24	-15.00	8.29	19.95
88.00	65.00	33.33	57.00	50.00	54.13	78.85	5.00	3.63	3.29
92.00	75.00	77.78	92.00	50.00	67.73	85.71	15.00	3.80	4.36
84.00	50.00	55.56	57.00	50.00	63.64	76.78	5.00	10.77	6.39
100.00	85.00	100.00	97.00	50.00	98.05	96.94	20.00	6.89	5.91
48.00	25.00	44.44	45.00	50.00	34.63	26.72	-5.00	-13.89	-36.84
48.00	40.00	22.22	52.00	100.00	54.84	49.22	17.78	-200.16	24.22
88.00	70.00	77.78	15.00	50.00	76.37	81.56	25.56	-718.63	31.56
68.00	15.00	44.44	40.00	25.00	64.37	67.68	-29.44	-600.63	42.68
88.00	75.00	33.33	67.00	100.00	65.07	78.02	8.33	-624.93	28.02
100.00	75.00	100.00	87.00	100.00	94.61	93.99	-2.78	-680.39	68.99
4.00	0.00	22.22	0.00	75.00	25.58	12.17	-5.00	10.82	-2.77
48.00	40.00	44.44	30.00	75.00	47.54	57.44	20.00	28.52	21.53

Table 5. Sleep Apnoea Quality of Life data from randomised controlled trial of CPAP in men with type 2 diabetes

Patient no	Treatment group	Pre CPAP SAQLI																
		A: Daily activities				B: Social interactions				C: Emotions			D: Symptoms					SAQLI score
		1	2	3	4	5	6	7	8	9	10	11	12	13	14			
1	0	3	4	3	3	2	6	6	6	5	5	5	3	3	3	4.071428571		
2	1	7	5	6	4	1	1	4	4	7	7	4	4	3	1	4.142857143		
3	0	3	4	3	4	4	5	5	3	6	3	5	5	4	2	4		
4	1	4	5	4	2	7	6	7	6	7	6	7	6	5	1	5.214285714		
5	1	3	2	2	5	6	5	5	3	3	4	4	3	3	2	3.571428571		
6	0	3	3	2	4	3	6	6	4	6	6	6	4	3	3	4.214285714		
7	1	4	2	4	7	1	1	4	7	4	4	7	4	4	1	3.857142857		
8	0	6	7	4	5	1	1	7	1	6	4	7	5	4	1	4.214285714		
9	0	4	5	7	4	2	4	3	6	7	6	7	6	5	3	4.928571429		
10	1	3	4	4	2	7	7	3	5	7	3	4	3	2	1	3.928571429		
11	1	4	3	4	3	2	4	5	5	4	5	4	3	3	3	3.714285714		
12	0	4	4	3	6	3	6	7	5	4	4	4	5	3	2	4.285714286		
13	0	4	6	4	3	4	5	7	6	3	6	2	3	3	4	4.285714286		
14	0	5	6	6	4	2	4	5	5	7	6	7	6	6	4	5.214285714		
15	1	1	3	1	2	7	7	7	6	7	6	4	3	1	1	4		
16	1	4	5	3	5	7	7	7	7	7	3	7	5	4	4	5.357142857		
17	0	5	4	4	4	2	4	5	2	6	4	5	6	6	3	4.285714286		
18	1	5	6	5	4	1	6	5	6	7	6	7	4	5	4	5.071428571		
19	0	4	3	2	3	4	7	4	3	5	5	4	2	6	1	3.785714286		
20	1	5	6	6	5	4	6	5	5	5	4	6	5	4	6	5.142857143		
21	0	4	3	3	3	2	3	4	4	6	3	5	4	2	2	3.428571429		
22	1	3	3	6	2	2	7	7	6	7	5	7	5	5	2	4.785714286		
23	1	2	4	2	2	5	2	3	2	2	2	2	3	2	2	2.5		
24	1	4	2	3	2	1	2	3	3	2	2	3	3	3	2	2.5		
25	0	3	4	2	4	3	4	6	3	3	3	3	3	3	1	3.214285714		
26	0	4	5	2	5	6	3	4	3	3	4	5	3	3	2	3.714285714		
27	0	5	7	5	3	4	7	6	6	6	6	6	6	6	4	5.5		
28	0	2	3	4	3	7	6	7	4	6	6	3	3	2	3	4.214285714		
30	0	4	6	6	4	7	7	7	6	7	7	7	6	6	6	6.142857143		
31	1	5	6	5	5	2	3	5	7	7	6	7	6	6	5	5.357142857		
32	0	5	4	5	4	3	4	4	3	3	4	5	5	5	4	4.142857143		
33	1	4	4	5	4	6	7	7	6	7	3	7	5	5	4	5.285714286		
34	0	3	2	2	2	2	4	3	3	6	6	3	2	2	2	3		
35	1	2	4	4	4	1	2	6	4	1	2	3	3	3	3	3		
36	0	6	6	6	7	6	6	7	6	7	4	6	6	6	6	6.071428571		
37	0	2	3	4	3	2	3	5	5	2	2	5	6	7	4	3.785714286		
38	1	4	3	1	2	7	7	2	6	6	4	6	2	6	7	4.5		
39	1	7	7	7	6	7	7	7	7	6	7	7	7	7	7	6.857142857		
40	0	6	1	1	6	7	7	5	4	2	1	5	2	3	3	3.785714286		
41	1	2	3	3	4	1	2	5	3	5	5	5	3	3	1	3.214285714		

Table 5. Sleep Apnoea Quality of Life data from randomised controlled trial of CPAP in men with type 2 diabetes

Post CPAP SAQLI														
A: Daily activities				B: Social interactions				C: Emotions			D: Symptoms			
1	2	3	4	5	6	7	8	9	10	11	12	13	14
7	7	6	7	6	7	6	6	7	6	7	7	7	7
5	5	6	6	1	1	6	5	7	1	3	3	2	4
6	7	5	6	6	7	6	6	7	6	6	6	6	6
4	4	3	3	7	6	7	6	6	6	6	5	5	2
6	6	4	6	7	5	7	6	4	4	6	6	6	5
4	5	3	4	3	6	5	7	6	5	4	4	3	2
4	4	4	6	1	4	5	6	4	1	4	5	4	4
6	4	5	6	1	1	6	1	1	1	1	5	4	1
7	7	7	6	6	7	7	6	7	7	7	6	7	6
4	5	3	4	7	7	6	4	7	6	4	3	3	6
6	6	5	6	6	6	7	6	7	6	6	6	6	7
5	4	4	5	2	3	7	5	6	5	7	6	4	4
6	6	7	6	7	6	7	7	4	6	4	6	6	7
6	4	5	5	1	5	5		6	4	6	5	5	6
1	1	1	2	7	4	2	7	2	7	2	1	1	1
7	7	7	7	7	7	7	7	7	4	7	6	6	7
6	4	5	5	1	5	5	7	6	4	6	5	5	6
6	5	7	6	7	6	6	7	7	5	7	6	6	7
4	7	4	5	7	2	7	6	7	3	5	3	5	4
6	6	4	7	7	6	6	5	6	6	6	5	5	6
3	3	3	2	2	3	3	4	4	3	3	2	2	2
6	6	4	5	3	2	7	7	7	6	6	6	6	5
3	4	2	2	7	5	6	3	2	2	4	3	3	5
6	6	4	7	2	5	4	2	2	4	5	5	5	6
4	4	3	4	3	5	4	4	4	3	4	3	4	1
3	2	1	4	3	5	5	3	3	3	3	3	3	3
6	7	6	5	5	7	6	6	7	6	6	6	6	6
3	2	3	2	7	4	5	4	4	4	3	2	2	3
7	6	7	7	7	7	7	7	7	7	7	7	7	7
2	6	6	7	7	7	7	7	7	7	7	7	7	7
4	4	4	4	5	5	6	4	7	5	7	5	5	5
7	7	7	7	7	7	7	7	7	6	7	7	7	7
2	2	1	1	5	4	2	2	3	4	3	1	1	1
6	3	4	7	7	7	7	4	1	6	4	4	4	7
5	6	6	6	7	7	6	6	6	6	6	6	6	4
2	3	2	3	1	5	6	6	3	4	5	2	2	3
6	7	3	7	7	7	7	7	7	7	7	7	6	6
7	7	7	6	7	7	7	7	7	7	7	7	6	7
3	3	2	7	6	7	7	5	3	1	4	3	2	7
4	4	4	6	7	7	6	6	6	6	6	6	6	6

Table 5. Sleep Apnoea Quality of Life data from randomised controlled trial of CPAP in men with type 2 diabetes

E: Treatment related side effects					Total 1	Total 2	Total 2	**Total SAQLI score**	**Effect of treatment**
15	16	17	18		Q1-Q14	Q15-17	xQ18		
					93	0	0	6.642857143	2.571428571
					55	0	0	3.928571429	-0.214285714
2	1	1	0.75		86	4	3	5.928571429	1.928571429
0	0	0			70	0	0	5	-0.214285714
3	2	1	0.5		78	6	3	5.357142857	1.785714286
2			0.75		61	2	1.5	4.25	0.035714286
6	6	6	1		56	18	18	2.714285714	-1.142857143
0	6	2	1		43	8	8	2.5	-1.714285714
1	1	1	0.5		93	3	1.5	6.535714286	1.607142857
0	0	0	0.25		69	0	0	4.928571429	1
2	1	1	0.5		86	4	2	6	2.285714286
1	1	1	0.25		67	3	0.75	4.732142857	0.446428571
5	3		1		85	8	8	5.5	1.214285714
3	0	2	0.5		63	5	2.5	4.321428571	-0.892857143
1	5	0	1		39	6	6	2.357142857	-1.642857143
1	2	4	0.25		93	7	1.75	6.517857143	1.160714286
3	0	2	0.5		70	5	2.5	4.821428571	0.535714286
4			0.5		88	4	2	6.142857143	1.071428571
5	4	4	0.75		69	13	9.75	4.232142857	0.446428571
4	1	1	0.75		81	6	4.5	5.464285714	0.321428571
5	6	5	1		39	16	16	1.642857143	-1.785714286
1	0	0	0.25		76	1	0.25	5.410714286	0.625
6			1		51	6	6	3.214285714	0.714285714
2	0		0.5		63	2	1	4.428571429	1.928571429
6	3	6	1		50	15	15	2.5	-0.714285714
4	1	1	0.5		44	6	3	2.928571429	-0.785714286
4			0.75		85	4	3	5.857142857	0.357142857
0	0		1		48	0	0	3.428571429	-0.785714286
0	0	0	1		97	0	0	6.928571429	0.785714286
1	1		0.25		91	2	0.5	6.464285714	1.107142857
2	2		0.5		70	4	2	4.857142857	0.714285714
2			0.25		97	2	0.5	6.892857143	1.607142857
3	4	2	1		32	9	9	1.642857143	-1.357142857
2	3	6	0.25		71	11	2.75	4.875	1.875
4	3		0.75		83	7	5.25	5.553571429	-0.517857143
5	5	5	1		47	15	15	2.285714286	-1.5
2	2	1	0.5		91	5	2.5	6.321428571	1.821428571
1	2		1		96	3	3	6.642857143	-0.214285714
4	5	5	0.5		60	14	7	3.785714286	0
4	3	6	1		80	13	13	4.785714286	1.571428571

Papers resulting from this research

SLEEP DISORDERED BREATHING

Prevalence of obstructive sleep apnoea in men with type 2 diabetes

S D West, D J Nicoll, J R Stradling

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See end of article for authors' affiliations

Correspondence to: Dr S D West, Sleep Unit, Oxford Centre for Respiratory Medicine, Churchill Hospital, Oxford OX3 7LJ, UK; sophie@west66.freeserve.co.uk

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Background: A study was undertaken to establish the prevalence of obstructive sleep apnoea (OSA) in men with type 2 diabetes.
Methods: Men with type 2 diabetes from local hospital and selected primary care practitioner databases received questionnaires about snoring, apnoeas, and daytime sleepiness based on the Berlin questionnaire. Selected respondents had overnight oximetry to establish whether they had OSA. Comparisons of oximetry were made with those from a previous general population study. HbA1c results were collected.
Results: 1682 men were sent questionnaires, 56% of whom replied. 57% scored as "high" and 39% as "low" risk for OSA; 4% were already known to have OSA. Oximetry was performed in 240 respondents from both risk groups: 31% of the "high" and 13% of the "low" risk group had significant OSA (more than 10 >4% SaO_2 dips/hour or SaO_2 tracing consistent with OSA). These results were verified by detailed sleep studies. Extrapolation of the oximetry data to the questionnaire respondent population suggests that 23% had OSA. Comparison of the oximetry results with men from a previous general population study (using only more than 10 >4% SaO_2 dips/hour to define OSA) showed the prevalence of OSA is significantly higher in this diabetes population (17% *v* 6%, $p<0.001$). Multiple linear regression revealed BMI and diabetes as significant independent predictors of OSA. Following correction for BMI (which explained 13% of the variance in OSA), diabetes explained a further 8% of the variance ($p<0.001$). There was a low correlation between OSA severity and HbA1c in the subgroup recruited from the hospital database ($r=0.2$, $p=0.006$) which remained significant after allowing for obesity ($p=0.03$).
Conclusions: OSA is highly prevalent in men with type 2 diabetes; most are undiagnosed. Diabetes itself may be a significant independent contributor to the risk of OSA.

Obstructive sleep apnoea (OSA) is common in the general population, with an estimated 1–5% of adult men and 1–2% of women being affected.[1 2] Upper airway resistance is increased during sleep, with resultant inspiratory flow limitation and obstruction causing snoring and apnoeas. In response to the obstruction, respiratory effort increases and arousals are usually necessary to terminate the apnoea. These are associated with increased sympathetic activity. If the arousals are frequent, sleep fragmentation occurs which can cause excessive daytime sleepiness. There is a causal relationship between central obesity and OSA, although OSA is also associated with craniofacial shape.[3 4] If significant OSA is diagnosed, successful treatment can be given, usually with continuous positive airway pressure (CPAP).[5]

Type 2 diabetes is a condition of impaired glucose tolerance and insulin resistance which also has a strong causal relationship with central obesity.[6] OSA is associated with insulin resistance, with higher levels of OSA associated with greater insulin resistance, independent of general obesity.[7 8] There is a high prevalence of impaired glucose tolerance and type 2 diabetes in patients with OSA.[9] The prevalence of OSA among patients with type 2 diabetes has not, however, been investigated.

We hypothesised that OSA would be highly prevalent in men with type 2 diabetes, more than in the general population. We also hypothesised that those with OSA were more likely to have higher glycosylated haemoglobin (HbA1c), reflecting poorer diabetic control. We therefore performed a study in men with known type 2 diabetes to establish the prevalence of OSA by a screening questionnaire and targeted sleep studies, and compared the prevalence rates of OSA with those in another community population.[10] We also established whether there was any correlation between OSA severity and diabetic control measured by HbA1c.

METHODS

Subjects

All men with type 2 diabetes aged 18–75 years on the databases of a tertiary specialist hospital centre (Oxford Centre for Diabetes, Endocrinology and Metabolism) and five local primary care centres (non-specialist, family doctor) were sent a questionnaire and explanatory letter about the study. A second questionnaire was sent to those who did not respond. Type 2 diabetes was a primary care practitioner diagnosis based on raised fasting blood glucose levels ≥7.0 mmol/l. The study was approved by the Oxford Radcliffe Hospitals ethics committee.

Questionnaire

The questionnaire requested information regarding age, the year diabetes developed, diabetes treatment, and about physical characteristics including neck circumference. A tape measure was provided with instructions on how to measure the neck, just below the larynx. Questions in three symptom categories were asked: snoring and apnoeas, daytime fatigue, hypertension and height and weight (to calculate body mass index (BMI)). The questions were those in the Berlin

Abbreviations: AHI, apnoea-hypopnoea index; BMI, body mass index; CPAP, continuous positive airway pressure; ESS, Epworth sleepiness score; HbA1c, glycosylated haemoglobin; OSA, obstructive sleep apnoea

questionnaire, designed to screen for likely OSA by determining whether people were "high" or "low" risk for OSA based on their responses.[11] This questionnaire has been used in a primary care population in Ohio, USA and the results validated with multichannel sleep studies. We omitted one question from the Berlin questionnaire, namely: "Have you ever nodded off or fallen asleep while driving a vehicle?" A change was noted in the answers given to questions regarding sleepiness when driving between two previous community studies performed by our department several years apart, thought to be due to increased population awareness of the dangers of sleepiness while driving which decreased the willingness to admit to this.[10 12] We therefore thought this question was unlikely to be answered accurately, could deter some respondents, and hence bias results. We also asked whether subjects had previously been diagnosed with OSA and whether they were receiving treatment for this.

Questionnaires were returned and scored according to the Berlin scoring criteria. Responses to the three symptom categories determined whether subjects were "high" or "low" risk for OSA. To be "high" risk, subjects had to qualify in at least two symptom categories.

Glycosylated haemoglobin (HbA1c)

The most recent HbA1c result was recorded for all questionnaire respondents. This was obtained by either accessing the hospital biochemistry database or by contacting the primary care practitioner. Patients who did not have an HbA1c result recorded within 3 months of completion of the questionnaire were asked if they would have this performed.

Screening sleep studies

A sample of "high" and "low" risk subjects were asked to participate in home overnight oximetry sleep studies. Subjects were selected on the basis of their postcodes; those within 20 miles of the base hospital were preferred, for ease of equipment delivery. If subjects agreed to participate, one of the investigators visited them to obtain written consent, deliver an oximeter, provide instructions on its use, and to complete an Epworth sleepiness score (ESS, an eight point questionnaire assessment of the tendency to fall asleep during various daytime situations).[13] The overnight oximetry studies were performed with a small portable battery operated wrist worn monitor and attached finger probe (Pulsox-3i, Konica Minolta, Japan). This measures the oxygen saturation of arterial blood (Sao_2) and the pulse rate and stores this data which can be downloaded via a computer and analysed (Download, Stowood Scientific Instruments, Oxford, UK). A normal overnight oximetry tracing has been found in a systematic literature review of home diagnosis of sleep apnoea to substantially reduce the probability of OSA in the majority of patients.[14] Measurements of Sao_2 correlate very well with apnoea-hypopnoea index (AHI).[15]

Subjects who had more than 10 dips in Sao_2 of >4% per hour on oximetry, consistent with a diagnosis of OSA, or those who had fewer than 10 dips in Sao_2 of >4% per hour but with an oxygen saturation tracing consistent with a diagnosis of OSA when viewed by an expert (JRS), were contacted to perform an unattended portable monitor home sleep study to verify the diagnosis of OSA. The equipment for this was delivered by one of the investigators who fitted it, explained how to use it, and provided full written instructions. The sleep study equipment measured body position, body movement, nasal pressure via nasal cannula, oximetry, pulse rate, and respiratory effort via thoracic and abdominal bands (Embletta PDS 3.0, Flaga Medical, Iceland). From these measurements a validated AHI per hour in bed and oxygen desaturation events per hour were automatically calculated, with manual review and editing.

All subjects found to have OSA on sleep studies were offered a clinic appointment to discuss the results and determine whether they were sufficiently symptomatic to require treatment.

Comparison of diabetes population with previous primary care population study

A previous study was performed by our department in which 275 men recruited randomly from a primary care population (diabetes was not an inclusion or exclusion criterion) underwent home overnight sleep studies with RM50 portable monitors (Parametric Recorders, London, UK); the results have been published elsewhere.[10] We wanted to compare the prevalence of OSA in this "normal" control population with the prevalence in our current study population of men with type 2 diabetes. We therefore needed to establish the equivalence or otherwise of the >4% Sao_2 dips per hour of the two oximeters which had been used in each study (RM50 and Pulsox-3i). Although the Sao_2 dip counting algorithm was identical, the actual oximeter devices came from different manufacturers. We performed overnight oximetry studies using both oximeters on the same night, mostly in patients with confirmed OSA of variable severity from the Oxford Sleep Clinic. The recordings were downloaded and scored automatically with manual review. This was exactly the same as the analysis performed in both the current and previous studies. The results of the two readings were then compared and correlated. Linear regression was performed to calculate a conversion factor to enable direct comparison of results from the two oximeters. The recordings from the diabetes population and the previous general practice population could thus be directly compared, to compare the prevalence of OSA in the two populations.

Analysis of data

The data were analysed using SPSS Version 12.0 and expressed as mean (SD, 0–100% range). Comparison of multiple groups was performed by one way analysis of variance (ANOVA), with Duncan's multiple ranging for post hoc analysis. Differences between the "high" and "low" risk groups and between the two different study populations were assessed using unpaired t tests and χ^2 tests when comparing proportions. A multiple linear regression analysis was performed using the two different study populations to determine predictors of >4% Sao_2 dips per hour. A p value of <0.05 was considered to be statistically significant.

RESULTS

A flow diagram of the study is shown in fig 1.

Questionnaire response rate

Questionnaires were sent to a total of 1433 men from the Oxford Centre for Diabetes, Endocrinology and Metabolism database and to 243 men from primary care databases. Sixty five men were on both databases but were only contacted via the hospital centre. The population of Oxfordshire is of mixed ethnicity, but is predominantly Caucasian. There were 793 replies (55%) in total from the hospital database and 145 (60%) from the primary care databases, representing a 56% overall response rate; 63% of the hospital database replies and 45% of the primary care database replies were received after the first mailing.

Questionnaire responses

Table 1 shows the physical characteristics of the respondents. The hospital and primary care database groups did not differ in their basic characteristics, other than the mean duration of

Figure 1 Flow diagram of study.

diabetes (12.1 *v* 7 years) and the treatment taken for this (hospital: 32% insulin, 22% insulin and oral hypoglycaemics, 41% oral hypoglycaemics, 5% diet; primary care: 4% insulin, 4% insulin and oral hypoglycaemics, 77% oral hypoglycaemics, 14% diet). The hospital database is likely to reflect those with more severe disease referred for specialist input. As the two groups did not differ otherwise in their characteristics, their results were analysed together.

Risk of OSA

From the 938 questionnaire responses, 528 men (56.2%) scored as being "high" risk of OSA, 362 (38.6%) scored as "low" risk, and 39 (4.1%) stated they had already been diagnosed with OSA, with 30 (3%) receiving treatment for this with CPAP. Nine questionnaires were incomplete and prevented assignment to a risk group. The characteristics of the groups are shown in table 2.

Sleep studies

Overnight oximetry studies were performed in 124 "high" risk and 116 "low" risk subjects. Ninety further men contacted refused to have oximetry performed. Comparison of the characteristics of those individuals selected for oximetry with their risk group as a whole showed no significant differences. In the "high" risk group, 38 (31%) had traces consistent with a diagnosis of OSA (29 with more than 10 >4% Sao_2 dips/hour and nine with fewer than 10 >4% Sao_2 dips/hour but oxygen saturation tracing consistent with a diagnosis of OSA), and 36 (29%) went on to have a portable monitor home sleep study. In the "low" risk group 15 (13%) had oximetry traces consistent with OSA (11 with more than 10 >4% Sao_2 dips/hour and four with fewer than 10 >4% Sao_2 dips/hour but oxygen saturation tracing consistent with a diagnosis of OSA) and 11 (9%) proceeded to have a portable monitor home sleep study. Those who did not have portable monitor sleep studies after completing overnight oximetry declined consent.

In the "high" risk group, automatic analysis and manual review of the portable monitor home sleep studies confirmed that 33 of the 36 people had OSA (27%). Two of these also had some central sleep apnoea and one had OSA and obesity hypoventilation. One of the 36 patients had only central sleep

Table 1 Physical characteristics of questionnaire respondents

	Mean	SD	Median	5–95% range	0–100% range
Age (years)	61.2	9.7	63.0	43.0–74.0	30.0–76.0
BMI (kg/m^2)	29.6	5.4	28.8	22.5–39.4	17.4–53.2
Neck size (cm)	42.9	3.1	43.2	38.1–48.3	33.0–55.9

Table 2 Characteristics of known OSA, "high" and "low" risk questionnaire respondents

	Known OSA (n=39)	"High" risk (n=528)	"Low" risk (n=362)	p value between groups
Age	61.1 (10.5, 30–75)[1]	60.5 (9.7, 30–76)[1]	62.3 (9.5, 31–76)[1]	0.03
BMI	34.9 (5.8, 24–50)[1]	30.8 (5.6, 17.4–53.2)[2]	27.5 (3.9, 18.1–42.6)[3]	<0.001
Neck size	45.5 (3.6, 35.6–53.3)[1]	43.4 (3.0, 35.6–55.9)[2]	41.7 (2.8, 33.0–50.8)[3]	<0.001
HbA1c%	8.1 (1.9, 5.8–14.7)	8.3 (1.5, 5.1–13.5)	8.3 (1.7, 5.2–14.2)	0.9

Results are shown as mean (SD, 0–100% range). Groups with different superscript numbers are significantly different from each other.

apnoea and he died soon after taking part in the study from a myocardial infarction and possibly left ventricular failure. One patient had low baseline oxygen saturations known to be due to concurrent chronic obstructive pulmonary disease with little evidence of OSA. One patient had difficulty performing the home sleep study and the recording was inadequate; this was not repeated. These three people who did not have confirmed OSA have been excluded from further analysis. In the "low" risk group the portable monitor home sleep study showed that all 11 had confirmed OSA (9%). These results are shown in table 3.

Of the 33 subjects found to have OSA on their portable monitor sleep studies in the "high" risk group, 16 (13%) were symptomatic with daytime sleepiness and were commenced on CPAP treatment following clinic review. In the "low" risk group, of the 11 people found to have OSA on their portable monitor sleep studies, one (1%) was symptomatic and commenced CPAP ($p<0.001$, χ^2 test).

Correlation of OSA indices with HbA1c

There was no significant difference in HbA1c levels between the "high" or "low" risk groups (table 2). There was also no significant correlation in the two groups combined between the number of >4% Sao_2 dips per hour from oximetry and HbA1c % ($n = 240$, $r = 0.11$, $p = 0.1$). If the hospital and primary care groups were analysed separately, however, there was a positive correlation in the hospital group ($r = 0.2$, $p = 0.006$) but not in the primary care group. A multiple linear regression model using HbA1c as the dependent variable showed that the strength of this correlation decreased when allowing for BMI, although it remained statistically significant ($p = 0.03$).

Comparison of results with previous primary care population study

Twenty nine individuals completed overnight oximetry studies with both the Pulsox-3i and RM50 recorders to investigate equivalence. There was a close positive correlation between the >4% Sao_2 dip rate from the Pulsox-3i recordings and the RM50 recordings ($r = 0.97$, $p = 0.01$). Both recorders use the same algorithm for calculating the number of >4% Sao_2 dips per hour, which presumably accounts for the strong correlation. A small conversion factor was calculated to allow direct comparison of the RM50 oximetry recordings in the previous primary care population and the current Minolta oximetry recordings (Minolta reading = 1.26×RM50 reading − 2.56). The results of the two study populations are shown in table 4.

The number of >4% Sao_2 dips per hour, unadjusted for any covariate, was significantly higher in the diabetes population ($p<0.001$), as was age, BMI, and neck size. In multiple linear regression models of the two populations, using >4% Sao_2 dips per hour as the dependent variable, significant predictors were BMI and diabetes status (having or not having diabetes). Once BMI was allowed for, neck size and age were not significant predictors. Diabetes status gave an additional small increase in the R^2 after correction for BMI ($R^2 = 0.13$ (13%) for BMI and 0.21 (21%) for diabetes status in addition). This shows that 13% of the variance in >4% SaO_2 dips per hour can be explained by BMI, but an additional 8% is explained by diabetes. The β coefficients of Sao_2 for BMI and diabetes were 0.6 and 5.2, respectively ($p<0.001$). Thus, for every 1 point increase in BMI, the >4% Sao_2 dips per hour rose by 0.6, and having type 2 diabetes increased the >4% Sao_2 dips per hour on average by 5, independent of BMI, neck size, and age (table 5). This confirms a significant independent effect of diabetes on >4% Sao_2 dips per hour.

DISCUSSION

This study shows that OSA is common in this population of men with type 2 diabetes. Based on answers to the Berlin questionnaire, 56% of men were considered to be at "high" risk of OSA and 4% stated they had known OSA. Of the subset of men studied, 22% had an overnight oximetry study compatible with a diagnosis of OSA. Diagnostic home monitor sleep studies largely confirmed these findings. If the results of the home monitor sleep studies are extrapolated proportionally to the whole questionnaire respondent population and added to those with known OSA, 213 of the 938 respondents (23%) would be likely to have OSA.

The number of men with type 2 diabetes scoring as "high" risk of OSA (57%) was higher than in the original Berlin questionnaire study in which 45% of 741 men scored as "high" risk.[11] The number of men with type 2 diabetes in our study confirmed as having OSA on oximetry was much

Table 3 Sleep study results according to questionnaire risk group

	"High" risk (n=124)	"Low" risk (n=116)	p value
ESS	9.8 (4.5, 0–21)	6.2 (3.7, 0–16)	<0.001
>4% SaO_2 dips per hour	9.1 (12.8, 0–70.7)	4.3 (4.7, 0–20.7)	<0.001
Mean SaO_2	93.9 (3.0, 76.5–97.5)	94.9 (1.6, 88.7–97.6)	0.002
Min SaO_2	79.9 (12.4, 25.0–93.0)	84.0 (8.3, 51.0–94.0)	0.003
No (%) with OSA on oximetry	38 (31%)	15 (13%)	<0.001
AHI per hour in bed (from portable monitor sleep study) in subset with confirmed OSA	32.2 (23.1, 1.7–77) (n=33)	26.2 (22.3, 1–67) (n=11)	0.5

ESS, Epworth sleepiness score; AHI, apnoea-hypopnoea index.
Results are shown as mean (SD, 0–100% range).

Table 4 Characteristics and overnight oximetry results from two study populations: men in primary care (Bicester, Oxfordshire, 1999)[10] and current diabetes study

	Bicester study RM50 (N=275)	Diabetes study Pulsox-3i (N=240)	p value
Age	51.2 (8.2, 33–72)	61.7 (9.9, 33–75)	<0.001
BMI	27.2 (3.7, 19.4–40.1)	28.8 (4.9,19.2–47.8)	<0.001
Neck size	39.7 (2.8, 31–47)	42.2 (3.0, 34.3–53.3)	0.002
ESS	6.7 (3.8, 0–17)	8.0 (4.5, 0–21)	<0.001
4% SaO_2 dips/hour	0.54 (6.1, 0–38)	6.8 (10.1, 0–70.7)	<0.001
Mean overnight SaO_2	96.0 (1.2, 91–98)	94.4 (2.5, 76.5–97.6)	<0.001
Min overnight SaO_2	89.2 (5.7, 55–96)	81.9 (10.8, 25–94)	<0.001
No with OSA (more than 10 >4% SaO_2 dips/hour)	16 (5.8%)	40 (17%)	<0.001

BMI, body mass index; ESS, Epworth sleepiness score; OSA, obstructive sleep apnoea.
Results are shown as mean (SD, 0–100% range).

higher than the number of men found to have OSA in a control primary care population in Bicester, Oxfordshire: 6% of 275 men in Bicester had overnight oximetry compatible with a diagnosis of OSA (based on more than 10 >4% Sao_2 dips/hour) compared with 17% of our diabetes population diagnosed on these criteria.[10] Although BMI was the best predictor of OSA, type 2 diabetes conferred a significant extra increase in the likelihood of having OSA after allowing for BMI, age, and neck size. On average, having type 2 diabetes increased the number of >4% Sao_2 dips per hour by 5. Although the comparison of the previous primary care and the diabetes populations was not ideal (different selection criteria, neck size and weight measured by nurse or individual, different oximeters requiring correction factor to be applied, studied at different times, and the possibility of some men in the Bicester sample having type 2 diabetes), we regard the results as valid. The population with type 2 diabetes studied here was predominantly hospital treated, which may add some bias to the sample. A high proportion (44%) were using insulin which causes weight gain, although this would have been taken into account by the multiple linear regression analysis.

OSA may therefore be a particular problem in men with type 2 diabetes. The reasons for this are not clear. There may be an aspect of central obesity in type 2 diabetes that contributes to the OSA which is not captured in BMI or neck size, despite the fact that neck size itself is a significant independent predictor of the rate of overnight hypoxic dipping in OSA.[12] It could be that OSA is a close correlate of the same central obesity distribution that also predisposes to insulin resistance. It is accepted that CT scanning is the gold standard method of quantifying abdominal fat; BMI, waist and waist to hip measurements are poorer correlates.[16 17] Using these indirect measurements to allow for this important central obesity distribution is probably not adequate.[18] Diabetic autonomic neuropathy may cause increased OSA, and this has been noted in other studies.[19 20] This study shows that, whatever the mechanism, OSA is extremely common in men with type 2 diabetes and may well be underdiagnosed. Women were not included in this study, and the sex differences in body fat distribution mean that further studies would be needed to gain an estimate of the prevalence of OSA in women with type 2 diabetes.

Clinicians who manage patients with type 2 diabetes must be aware of the increased likelihood of OSA, routinely asking about habitual snoring, witnessed apnoeas, nocturnal choking, and daytime sleepiness as part of their patient assessment, or using the ESS.[13] If OSA is considered likely, referral to the local sleep service for a diagnostic sleep study is appropriate. It may be difficult without a sleep study to differentiate sleepiness due to OSA from fatigue and tiredness associated with diabetes and co-morbid disease. As we have shown, screening questionnaires can predict risk but have poor sensitivities and specificities. Daytime sleepiness contributed to a "high risk" score on the questionnaire, and this is one of the main factors which determine whether someone is likely to receive and benefit from CPAP therapy. The Berlin questionnaire was useful in differentiating patients who were likely to require CPAP, evidenced by the fact that significantly more "high" risk than "low" risk patients found to have OSA received CPAP (13% *v* 1%; $p<0.001$). The benefits of CPAP to people with OSA are clear—namely, improvements in daytime sleepiness, cognitive function, driving ability, and blood pressure.[5 21–24] Improvements in blood pressure are likely to translate to improved cardiovascular risk, which is particularly important in a diabetes population.[25] It is not known whether CPAP improves glycaemic control in people with OSA and type 2 diabetes, as adequately controlled studies have not yet been performed.

We found no correlation between indices of sleep disordered breathing and HbA1c in the diabetes group as a whole, but the men with type 2 diabetes recruited from the hospital database did show a low but significant correlation when analysed separately. We postulated that the sleep fragmentation of OSA would lead to more disordered glucose

Table 5 Multiple linear regression results for >4% SaO_2 dips per hour of the two populations (primary care population and current diabetes study)

	Uncorrected (single regression)		Corrected	
Predictor variable	*r*	R^2	*r*	R^2
Age	0.2**	0.04	0.09	NS
BMI (kg/m^2)	0.35**	0.12	0.36**	0.13
Neck size	0.19**	0.04	0.04	NS
Diabetes status	0.36**	0.13	0.29**	0.09
Model			0.46**	0.22

Dependent variable = >4% SaO_2 dips per hour.
**$p<0.001$; NS, not significant.

metabolism, resulting in worse diabetic control. This was not the case overall, but may reflect the fact that the HbA1c level was closely controlled by physician intervention with extra hypoglycaemic treatment. This explanation is not, however, supported by examination of the proportions on diet versus oral hypoglycaemics versus insulin, there being no significant difference between "high" and "low" risk groups after allowing for obesity. The fact that there was a small correlation within the hospital population alone is interesting, and this remained significant after correction for BMI. It may be that the people with type 2 diabetes on the hospital database had more severe and perhaps less well controlled diabetes, allowing OSA to have an effect. This would be supported by the finding of a higher mean HbA1c level in the hospital group than in the primary care group (8.4 *v* 7.8, $p = 0.001$). There could, however, be other potential explanations.

Sleep disordered breathing has been found to be associated with insulin resistance independent of obesity, with higher levels of OSA associated with greater insulin resistance.[7 8] As insulin resistance is the precursor to type 2 diabetes, it is questioned whether OSA itself is an independent risk factor for developing diabetes. A cohort of 2668 men was asked about habitual snoring and diabetes by postal questionnaire on two occasions 10 years apart.[26] Habitual snorers had a significantly higher prevalence of diabetes on both occasions. The incidence of new diabetes after 10 years was higher among habitual snorers ($p<0.001$), and men who habitually snore had a more than twofold higher incidence of diabetes than non-habitual snorers in the same age group, with the risk largely attributable to obesity. A similar study sent two questionnaires asking about snoring and diabetes 10 years apart to 69 852 female nurses in the USA.[27] Following adjustment for age and BMI, snoring was independently associated with an increased risk of type 2 diabetes ($p<0.0001$). In both of these studies, however, central obesity was only allowed for by the surrogate of BMI. As mentioned before, this is a poor correlate of true intra-abdominal obesity and allowing for this might have removed any significance, given that OSA correlates better with upper body obesity (neck size) than BMI.[3 16]

We conclude that men with type 2 diabetes have a very high prevalence of OSA, much higher than that of men in the general population. Recognition and treatment of this is likely to be beneficial to them if they are symptomatic with excessive daytime sleepiness.

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Authors' affiliations

S D West, D J Nicoll, J R Stradling, Sleep Unit, Oxford Centre for Respiratory Medicine, Churchill Hospital, Oxford OX3 7LJ, UK

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The effect of CPAP on insulin resistance and HbA1c in men with obstructive sleep apnoea and type 2 diabetes

Sophie D West[1], Debby J Nicoll[1], Tara M Wallace[2], David R Matthews[2], John R Stradling[1]

[1]Sleep Unit, Oxford Centre for Respiratory Medicine, Churchill Hospital, Old Road, Headington, Oxford OX3 7LJ, UK
[2]Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Old Road, Headington, Oxford OX3 7LJ, UK

Corresponding author: Sophie D West, Sleep Unit, Oxford Centre for Respiratory Medicine, Churchill Hospital, Old Road, Oxford OX3 7LJ, UK
Email: sophie@west66.freeserve.co.uk,
Telephone 0044 1865 225227, Fax 0044 1865 225205

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Abstract

The effects of continuous positive airway pressure (CPAP) for obstructive sleep apnoea (OSA) on insulin resistance are not clear; trials have found conflicting results and no appropriate control groups have been used.

Methods: Forty two men with known type 2 diabetes and newly diagnosed OSA (>10, >4% SaO_2 dips/hour) were randomised to receive therapeutic (n=20) or placebo CPAP (n=22) for 3 months. Baseline tests were performed and repeated after 3 months. The study was double blind.

Results: Results are expressed as mean (SD). CPAP improved the Epworth sleepiness score significantly more in the therapeutic group than the placebo group (-6.6 (4.5) vs. -2.6 (4.9), p=0.01). The maintenance of wakefulness test improved significantly in the therapeutic group, but not in the placebo group (+10.6 (13.9) vs. -4.7 (11.8) mins, p=0.001). Glycaemic control and insulin resistance did not significantly change in either the therapeutic or placebo groups: HbA1c (-0.02 (1.5) vs. +0.1 (0.7), p=0.7, 95% CI -0.6% to +0.9%), euglycaemic clamp (M/I: +1.7 (14.1) vs. -5.7 (14.8), p=0.2, 95% CI -1.8 to +0.3 $l/kg/min^{1000}$), HOMA-%S (-1.5 (2.3) vs. -1.1 (1.7), p=0.4, 95%CI -0.3 to +0.08%) and adiponectin (-1.1 (1.2) vs. -1.1 (1.3), p=0.2, 95% CI -0.7 to +0.6 ug/ml). Body mass index, bioimpedance and anthropometric measurements were unchanged. Hours of CPAP use per night were: therapeutic 3.6 (2.8) vs. placebo 3.3 (3.0), p=0.8. There was no correlation between CPAP use and the measures of glycaemic control or insulin resistance.

Conclusion: Therapeutic CPAP does not significantly improve measures of glycaemic control or insulin resistance in men with type 2 diabetes and OSA.

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SD West, DJ Nicoll, JR Stradling.
Poster, 9th International Symposium on Sleep and Breathing, Rhode Island 2004

Prevalence of Obstructive Sleep Apnoea in men with type 2 diabetes
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