THE EFFECT OF ACUPUNCTURE ON UPPER AIRWAY FUNCTION AND
PHYSIOLOGY IN OBSTRUCTIVE SLEEP APNOEA

By
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Doctor of Philosophy
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Abstract

Obstructive sleep apnoea (OSA) involves repetitive obstruction of the upper airway during sleep. Continuous positive airway pressure (CPAP) is the most common treatment, however, many patients cannot tolerate CPAP and adherence rates are low. Recent research has suggested that acupuncture can reduce the severity of OSA. The past research, while promising did not conform to normal Chinese medicine (CM) practice as the researchers failed to diagnose CM syndromes in their patient sample nor design their treatment based on CM syndrome analysis. It was also not possible to rule out potential confounding effects of the sham treatment, as the method employed was not guaranteed to be biologically inert. The aim of the present study was to address these limitations and determine whether acupuncture is an effective alternative treatment for OSA, and to identify underlying physiological changes as a result of acupuncture treatment. Initially, 39 patients admitted for investigative PSG to diagnose OSA underwent standard CM diagnostic procedures to identify common CM syndromes in the OSA population. Four CM phenotypes of OSA were identified and the most common phenotype (occurring in >44% of the sampled population) was then incorporated into the inclusion criteria for the clinical trial of acupuncture treatment. The acupuncture treatment employed was also designed to target the CM phenotype pathology. Further, the sham method employed in the present study, was also guaranteed to be biologically inert. Twenty OSA patients were randomly assigned to receive either 12 weeks of active needle acupuncture (n=10 (3 F); mean age=56.3 years) or sham laser acupuncture (n=10 (3 F); mean age=45.3 years) treatments. Prior to and following the treatment period subjects underwent detailed polysomnography, including measurement of epiglottic pressure, calibrated airflow and genioglossus muscle activity. In addition, subjective health and wellbeing, sleepiness and mood were assessed. AHI, waking nasopharyngeal resistance, ventilation, arousal threshold and genioglossus muscle activity were analysed while blinded to treatment type and study time. One participant was excluded due to an insufficient amount of sleep
for analysis. There was no significant effect of treatment type on pre- and post-treatment measurement of NREM AHI (mean pre-treatment: active=38.10, sham=26.44; mean post-treatment: active=38.83; sham=37.06 events/hour) or NREM AI (mean pre-treatment: active=57.71, sham=49.03; mean post-treatment: active=58.98, sham=58.60 events/hour). There were no significant differences within the active or sham groups, nor between groups across time for the subjective questionnaires. All upper airway physiology measurements made during NREM sleep were also unchanged following both sham and active acupuncture treatment. The data indicates that there are no differences between active- versus sham-acupuncture on subjective health and wellbeing, sleepiness, or mood, nor their AHI or upper airway function and physiology in a clinical OSA population. Once theoretical and methodological limitations of past research were controlled for our data suggest that acupuncture is not an effective treatment for OSA.
Declaration

I, Therese Thornton, declare that this thesis comprises only my own original work towards the Doctor of Philosophy, except where I have appropriately cited the original source. No part of this thesis has previously been submitted for assessment or publication. This document is fewer than the maximum word limit in length, exclusive of tables, figures, references and appendices.

Therese Thornton

December, 17th 2017
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This research has taken many years of hard work, and this manuscript has been through many iterations. It could not have been completed without the guidance and support of many wonderful people in my life.

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# Table of Contents

THE EFFECT OF ACUPUNCTURE ON UPPER AIRWAY FUNCTION AND PHYSIOLOGY IN OBSTRUCTIVE SLEEP APNOEA ................................................................. I

ABSTRACT .......................................................................................................................... II

DECLARATION ...................................................................................................................... IV

ACKNOWLEDGEMENTS ...................................................................................................... V

LIST OF FIGURES ............................................................................................................... XI

GLOSSARY OF ABBREVIATIONS ....................................................................................... XIII

CHAPTER 1 OBSTRUCTIVE SLEEP APNOEA ........................................................................ 1

1.1 Definition of OSA ........................................................................................................ 1

1.2 Diagnosis of OSA ......................................................................................................... 3

1.3 Prevalence of OSA ....................................................................................................... 5

1.3.1 Gender differences .................................................................................................. 10

1.4 Signs and Symptoms of OSA ..................................................................................... 11

1.4.1 Snoring ....................................................................................................................... 11

1.4.2 Hypersomnolence ..................................................................................................... 11

1.4.3 Daytime functioning and quality of life .................................................................. 14

1.5 Psychosocial and Neurocognitive Consequences of OSA ........................................ 18

1.5.1 Depression and mood disturbance .......................................................................... 19

1.5.2 Neurocognitive performance ................................................................................... 23

1.6 Risks of OSA ............................................................................................................... 25

1.6.1 Hypertension and cardiovascular disease ............................................................... 25

1.6.2 Obesity, metabolic syndrome, and diabetes ............................................................ 27

CHAPTER 2 PATHOPHYSIOLOGY, DISEASE PROGRESSION AND TREATMENT OF OSA34

2.1 Pathophysiology of OSA ............................................................................................ 34

2.1.2 Narrowed upper airway anatomy and increased upper airway resistance .......... 35

2.1.3 Increased upper airway collapsibility ....................................................................... 37

2.1.4 Poor upper airway muscle responsiveness ............................................................... 41

2.1.5 Lung volume ............................................................................................................. 46

2.1.6 Ventilatory control instability .................................................................................. 48

2.1.7 Respiratory arousal threshold ................................................................................... 50

2.1.7 Surface tension of upper airway liquid lining ......................................................... 53

2.1.8 OSA phenotypes ..................................................................................................... 55
CHAPTER 3  CHINESE MEDICINE AND OBSTRUCTIVE SLEEP APNOEA ................................................. 73

3.1  THE BASICS OF CHINESE MEDICINE ...................................................................................... 74

3.1.1  Yin and Yang.................................................................................................................................... 75

3.1.2  The vital substances......................................................................................................................... 78

3.1.3  The internal organs........................................................................................................................... 82

3.1.4  The meridians and collaterals........................................................................................................... 93

3.2  THE BASICS OF SLEEP ACCORDING TO CHINESE MEDICINE ..................................................... 96

3.2.1  The Mind............................................................................................................................................ 97

3.2.2  Sleep stages....................................................................................................................................... 98

3.3  SYNDROMES/CLINICAL PATTERNS AND DISEASES ....................................................................... 99

3.3.1  The eight principles of syndrome differentiation............................................................................... 99

3.3.2  Causes of disease............................................................................................................................ 100

3.4  THE DIAGNOSIS PROCESS ............................................................................................................... 103

3.5  TREATMENT OF DISEASE IN CHINESE MEDICINE .................................................................. 105

3.6  OSA ACCORDING TO CHINESE MEDICINE ................................................................................ 106

3.6.1  Treatment of OSA with Chinese medicine..................................................................................... 108

3.6.2  Limitations of Chinese medicine research on OSA treatment....................................................... 109

CHAPTER 4  CHINESE MEDICINE SYNDROME CLASSIFICATION OF THE SYMPTOMS OF
OBSTRUCTIVE SLEEP APNOEA: A REPORT ON 34 CASES................................................................. 111

4.1  METHODS ........................................................................................................................................... 113

4.1.1  Participants..................................................................................................................................... 113

4.1.2  Design............................................................................................................................................... 114

4.1.3  Materials & apparatus...................................................................................................................... 114

4.1.4  Procedure....................................................................................................................................... 114

4.1.5  Data analysis................................................................................................................................... 115

4.2  RESULTS ............................................................................................................................................ 116

4.2.1  Participant descriptive and demographic data............................................................................... 116

4.2.2  CM syndrome diagnosis.................................................................................................................. 116
4.2.3 OSA severity between CM phenotypes.................................................................117
4.2.4 Association between CM phenotype and comorbid conditions........................118
4.3 DISCUSSION........................................................................................................119

CHAPTER 5 CLINICAL TRIAL OF ACUPUNCTURE FOR THE TREATMENT OF
OBSTRUCTIVE SLEEP APNOEA.................................................................128

5.1 HYPOTHESES.................................................................................................132
5.2 DESIGN........................................................................................................133
5.3 PARTICIPANTS..............................................................................................133
  5.3.1 Inclusion criteria.........................................................................................133
  5.3.2 Exclusion criteria.......................................................................................135
5.4 BLINDING AND RANDOMIZATION.......................................................135
5.5 PROCEDURES.............................................................................................137
  5.5.1 Recruitment procedures........................................................................137
  5.5.2 Screening procedure...............................................................................137
  5.5.3 Overnight investigative sleep study procedure......................................138
  5.5.4 Treatment procedures............................................................................142
5.6 DATA ANALYSIS.........................................................................................148
  5.6.1 OSA severity measures..........................................................................148
  5.6.2 Sleep measures......................................................................................149
  5.6.3 Body habitus measures..........................................................................149
  5.6.4 Blood pressure measures......................................................................149
  5.6.5 Subjective symptomatology, wellbeing, and mood measures...............149
  5.6.6 Physiological measures.........................................................................151
5.7 STATISTICAL ANALYSIS........................................................................154

CHAPTER 6 - CLINICAL TRIAL RESULTS..............................................155

6.1 PATIENT DEMOGRAPHICS.........................................................................155
  6.1.1 Lateral vs. supine sleep comparisons....................................................155
  6.1.2 REM vs. NREM sleep comparisons.....................................................157
6.2 OSA SEVERITY MEASURES.......................................................................157
  6.2.1 Apnoea hypopnoea index......................................................................157
  6.2.2 Arousal index.........................................................................................157
  6.2.3 Oxygen desaturation index....................................................................159
  6.2.4 Mean oxygen saturation......................................................................160
6.3 SLEEP MEASURES......................................................................................160
  6.3.1 Sleep onset latency................................................................................160
6.3.2 Sleep efficiency................................................................. 161
6.3.3 Sleep architecture.......................................................... 162
6.4 BODY HABITUS MEASURES .............................................. 164
6.4.1 Body mass index .............................................................. 164
6.4.2 Neck circumference .......................................................... 164
6.4.3 Waist circumference ......................................................... 164
6.4.4 Blood pressure ................................................................. 166
6.5 SUBJECTIVE MEASURES OF HEALTH, WELLBEING, SLEEPINESS AND SYMPTOMS .................. 167
6.5.1 Sleepiness ................................................................. 167
6.5.2 Functional outcomes of sleep ............................................. 167
6.5.3 Medical outcomes survey – the short form-36. .................. 168
6.5.4 Profile of mood states – short-37 ....................................... 168
6.6 PHYSIOLOGICAL DATA ......................................................... 172
6.6.1 Wake recordings .............................................................. 172
6.6.2 Measures during sleep ....................................................... 173
6.7 SHAM CROSS-OVER .......................................................... 178
6.7.1 OSA severity measures ...................................................... 178
6.7.2 Sleep measures ................................................................. 180
6.7.3 Physiological Data ............................................................ 181

CHAPTER 7 - GENERAL DISCUSSION .............................................. 187
7.1 OSA SEVERITY ................................................................. 188
7.2 SUBJECTIVE FINDINGS...................................................... 192
7.3 PHYSIOLOGICAL FINDINGS ............................................... 195
7.4 CROSS-OVER PATIENTS ................................................... 197
7.5 LIMITATIONS ........................................................................ 197
7.6 CONCLUSIONS ...................................................................... 200

REFERENCES ............................................................. 202

APPENDIX A ........................................................................ 234
MEDICAL HISTORY QUESTIONNAIRE ............................................. 235
SHORT CM SYMPTOM QUESTIONNAIRE ........................................... 236
LONG CM SYMPTOM QUESTIONNAIRE ........................................... 239
TONGUE AND PULSE QUESTIONNAIRE ........................................... 248

APPENDIX B ........................................................................ 250
## List of Figures

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figure 1</td>
<td>Divisions of the upper airway</td>
<td>38</td>
</tr>
<tr>
<td>Figure 2</td>
<td>The Yin and Yang cycle</td>
<td>77</td>
</tr>
<tr>
<td>Figure 3</td>
<td>The 12 meridians in Chinese medicine</td>
<td>95</td>
</tr>
<tr>
<td>Figure 4</td>
<td>Chinese pulse diagnosis positions on the wrist</td>
<td>104</td>
</tr>
<tr>
<td>Figure 5</td>
<td>Average AHI, BMI, ESS and Age distribution across Chinese medicine OSA phenotypes</td>
<td>118</td>
</tr>
<tr>
<td>Figure 6</td>
<td>The percentage of patients with diabetes, depression, hypertension and asthma or rhinitis across Chinese medicine OSA phenotypes</td>
<td>119</td>
</tr>
<tr>
<td>Figure 7</td>
<td>Flow diagram of the recruitment, treatment and data collection timeline for the clinical trial</td>
<td>134</td>
</tr>
<tr>
<td>Figure 8</td>
<td>An example submental ultrasound and anatomical structures identified</td>
<td>141</td>
</tr>
<tr>
<td>Figure 9</td>
<td>An illustration of the apparatus used to measure physiological changes</td>
<td>142</td>
</tr>
<tr>
<td>Figure 10</td>
<td>Acupuncture point locations used in phase I, II and III of treatment</td>
<td>145</td>
</tr>
<tr>
<td>Figure 11</td>
<td>Flow diagram of recruitment process</td>
<td>156</td>
</tr>
<tr>
<td>Figure 12</td>
<td>Change in NREM AHI across study nights for each individual</td>
<td>158</td>
</tr>
<tr>
<td>Figure 13</td>
<td>Change in NREM AHI and AI across study nights for the active and sham groups</td>
<td>159</td>
</tr>
<tr>
<td>Figure 14</td>
<td>Change in REM AHI and AI across study nights for the active and sham groups</td>
<td>159</td>
</tr>
<tr>
<td>Figure 15</td>
<td>Change in ODI3% and mean oxygen saturation across study nights for the active and sham groups</td>
<td>160</td>
</tr>
<tr>
<td>Figure 16</td>
<td>Change in SOL across study nights for the active and sham groups</td>
<td>161</td>
</tr>
<tr>
<td>Figure 17</td>
<td>Change in SE across study nights for the active and sham groups</td>
<td>161</td>
</tr>
<tr>
<td>Figure 18</td>
<td>Change in BMI, Neck and Waist circumference across study nights for the active and sham groups</td>
<td>165</td>
</tr>
<tr>
<td>Figure 19</td>
<td>Change in blood pressure across study nights for the active and sham groups</td>
<td>166</td>
</tr>
<tr>
<td>Figure 20</td>
<td>Change in wakefulness measures across study nights for the active and sham groups</td>
<td>173</td>
</tr>
<tr>
<td>Figure 21</td>
<td>Change in respiratory measures during sleep across study nights for the active and sham groups</td>
<td>174</td>
</tr>
<tr>
<td>Figure 22</td>
<td>Change in AT across study nights for the active and sham groups</td>
<td>175</td>
</tr>
</tbody>
</table>
Figure 23  Change in muscle activation in response to flow limitation across study nights for the active and sham group  177
Figure 24  Change in AHI across study nights for cross-over patients  178
Figure 25  Change in average NREM AHI and AI across study nights for cross-over patients  179
Figure 26  Change in ODI3% and mean oxygen desaturation across study nights for cross-over patients  179
Figure 27  Change in SOL across study nights for cross-over patients  180
Figure 28  Change in SE across study nights for cross-over patients  180
Figure 29  Change in sleep architecture across study nights for cross-over patients  181
Figure 30  Change in wakefulness measures across study nights in cross-over patients  182
Figure 31  Change in respiratory measures during sleep across study nights in cross-over patients  183
Figure 32  Change in AT across study nights in cross-over patients  184
Figure 33  Change in peak muscle activity in response to flow limitation across study nights in cross-over patients  185
Figure 34  Change in tonic muscle activity in response to flow limitation across study nights in cross-over patients  186
**Glossary of Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDB</td>
<td>Sleep Disordered Breathing</td>
</tr>
<tr>
<td>OSA</td>
<td>Obstructive Sleep Apnoea</td>
</tr>
<tr>
<td>REM</td>
<td>Rapid Eye Movement</td>
</tr>
<tr>
<td>CSA</td>
<td>Central Sleep Apnoea</td>
</tr>
<tr>
<td>UARS</td>
<td>Upper Airway Resistance Syndrome</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalogram</td>
</tr>
<tr>
<td>ASDA</td>
<td>American Sleep Disorders Association</td>
</tr>
<tr>
<td>AHI</td>
<td>Apnoea/Hypopnoea Index (events/hour)</td>
</tr>
<tr>
<td>PSG</td>
<td>Polysomnography</td>
</tr>
<tr>
<td>RDI</td>
<td>Respiratory Disturbance Index (events/hour)</td>
</tr>
<tr>
<td>ODI</td>
<td>Oxygen Desaturation Index (events/hour)</td>
</tr>
<tr>
<td>OSAHS</td>
<td>Obstructive Sleep Apnoea/Hypopnoea Syndrome</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index (kg/m$^2$)</td>
</tr>
<tr>
<td>HRT</td>
<td>Hormone Replacement Therapy</td>
</tr>
<tr>
<td>EDS</td>
<td>Excessive Daytime Sleepiness</td>
</tr>
<tr>
<td>ESS</td>
<td>Epworth Sleepiness Scale</td>
</tr>
<tr>
<td>SHHC</td>
<td>Sleep Heart Health Cohort</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of Life</td>
</tr>
<tr>
<td>NHP</td>
<td>Nottingham Health Profile</td>
</tr>
<tr>
<td>SF-36</td>
<td>Medical Outcomes Survey Short-Form 36</td>
</tr>
<tr>
<td>nCPAP</td>
<td>nasal Continuous Positive Airway Pressure</td>
</tr>
<tr>
<td>FOSQ</td>
<td>Functional Outcomes of Sleep Questionnaire</td>
</tr>
<tr>
<td>MDD</td>
<td>Major Depressive Disorder</td>
</tr>
<tr>
<td>ABS</td>
<td>Australian Bureau of Statistics</td>
</tr>
<tr>
<td>DSM-IV</td>
<td>Diagnostic and Statistical Manual 4th Edition</td>
</tr>
<tr>
<td>BDI</td>
<td>Beck Depression Inventory</td>
</tr>
<tr>
<td>HADS</td>
<td>Hospital Anxiety and Depression Scale</td>
</tr>
<tr>
<td>MINI</td>
<td>Mini-International Neuropsychiatric Interview</td>
</tr>
<tr>
<td>POMS</td>
<td>Profile of Mood States</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>HAM-D</td>
<td>Hamilton Depression Inventory</td>
</tr>
<tr>
<td>PLMS</td>
<td>Periodic Limb Movement Syndrome</td>
</tr>
<tr>
<td>BP</td>
<td>Blood Pressure</td>
</tr>
<tr>
<td>HR</td>
<td>Heart Rate</td>
</tr>
<tr>
<td>CPAP</td>
<td>Continuous Positive Airway Pressure</td>
</tr>
<tr>
<td>IL-6</td>
<td>Interleukin-6</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>UA</td>
<td>Upper Airway</td>
</tr>
<tr>
<td>HDL</td>
<td>High Density Lipoprotein</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>RUA</td>
<td>Upper Airway Resistance</td>
</tr>
<tr>
<td>Pcrit</td>
<td>Critical Closing Pressure</td>
</tr>
<tr>
<td>O₂</td>
<td>Oxygen</td>
</tr>
<tr>
<td>CO₂</td>
<td>Carbon Dioxide</td>
</tr>
<tr>
<td>TP</td>
<td>Tensor Palatini</td>
</tr>
<tr>
<td>GG</td>
<td>Genioglossus</td>
</tr>
<tr>
<td>EMG</td>
<td>Electromyography</td>
</tr>
<tr>
<td>NREM</td>
<td>non-Rapid Eye Movement</td>
</tr>
<tr>
<td>EELV</td>
<td>End Expiratory Lung Volume</td>
</tr>
<tr>
<td>Pepi</td>
<td>Epiglottic Pressure</td>
</tr>
<tr>
<td>SWS</td>
<td>Slow Wave Sleep</td>
</tr>
<tr>
<td>APPLES</td>
<td>Apnea Positive Pressure Long-term Efficacy Study</td>
</tr>
<tr>
<td>UPPP</td>
<td>Uvulopalatopharyngoplasty</td>
</tr>
<tr>
<td>LAUP</td>
<td>Laser-assisted Uvuloplasty</td>
</tr>
<tr>
<td>MMA</td>
<td>Maxillomandibular Advancement</td>
</tr>
<tr>
<td>OA</td>
<td>Oral Appliance</td>
</tr>
<tr>
<td>MAS</td>
<td>Mandibular Advancement Splint</td>
</tr>
<tr>
<td>SASQ</td>
<td>Sleep Apnea Symptom Questionnaire</td>
</tr>
<tr>
<td>SSRIs</td>
<td>Selective Serotonin-reuptake Inhibitors</td>
</tr>
<tr>
<td>CM</td>
<td>Chinese Medicine</td>
</tr>
<tr>
<td>VMT</td>
<td>Visceral Manifestation Theory</td>
</tr>
</tbody>
</table>
PLMS  Periodic Leg Movement Syndrome
WHO  World Health Organisation
AI  Arousal Index (arousals/hour)
ANOVA  Analysis of Variance
SD  Standard Deviation
TENS  Transcutaneous Electrical Nerve Stimulation
SaO₂  Oxygen Saturation (%)
SOL  Sleep Onset Latency (mins)
EOG  Electrooculogram
EMG  Electromyogram
ECG  Electrocardiogram
MH  Mylohyoid
GH  Geniohyoid
AASM  American Association of Sleep Medicine
SE  Sleep Efficiency (%)
TMD  Total Mood Disturbance
RUA  Upper Airway Resistance (cmH₂O/l/s)
V₁  Inspired Minute Ventilation (l/min)
Vₜ  Tidal Volume (l)
Vₜ/T₁  Mean Inspiratory Flow (l/min)
PIF  Peak Inspiratory Flow (l/min)
T₁/TₜTOT  Duty Cycle
AT  Arousal Threshold (cmH₂O)
PSLOPE  Slope of Peak GG muscle activity
PINT  Intercept of Peak GG muscle activity
PCOR  Correlation coefficient of the relationship between GG muscle activity and epiglottic pressure
TSLOPE  Slope of Tonic GG muscle activity
TINT  Intercept of Tonic GG muscle activity
TCOR  Correlation coefficient of the relationship between GG muscle activity and epiglottic pressure
Chapter 1 Obstructive Sleep Apnoea

1.1 Definition of OSA

Sleep disordered breathing (SDB) is an umbrella term used to refer to a spectrum of disorders that involve abnormal respiratory patterns during sleep that first began drawing considerable interest in the 1960s (Gastaut, Tassinari, & Duron, 1966). Over the subsequent decades several conditions have been identified that involve abnormal respiration during sleep. As such, SDB now refers to conditions such as obstructive sleep apnoea (OSA), central sleep apnoea, and upper airway resistance syndrome. While collectively these conditions are similar, there are distinct differences in the signs, symptoms, and pathological mechanisms between them.

Obstructive sleep apnoea is a disorder characterised by repetitive partial or complete obstruction of the upper airway during sleep. During a hypopnoea or apnoea, collectively referred to as respiratory events, the airway partially or completely collapses, resulting in reduced or absent ventilation, respectively. Some of the major consequences of respiratory events are blood gas disturbances such as hypoxemia and hypercapnia. In obstructive sleep apnoea, chemoreceptor activity is thought to trigger an increase in neural ventilatory drive in order to compensate for the gas disturbances (Berry & Gleeson, 1997). Increased ventilatory drive stimulates the activity of compensatory mechanisms, including activation of the diaphragm and muscles of the upper airway, which attempt to re-establish airflow. In most OSA patients, however, the airway remains occluded until a brief arousal occurs, at which time the airway re-opens and normal breathing is restored (Guilleminault, Tilkian, & Dement, 1976). The collapse of the upper airway will recur on return to sleep leading to a cyclical pattern of airway occlusion, arousal, resumption of respiration and return to sleep.

The result of frequent obstructions and arousals is highly fragmented sleep. In part due to repetitive arousals, the architecture of sleep in OSA patients is altered. These patients have been shown to spend significantly more time in
lighter stages of sleep (Stages I and II) and less time in the restorative slow-wave sleep, causing them to have poor quality sleep in comparison to normal healthy individuals (Chokroverty & Sharp, 1981; Flemons et al., 1999; Stradling & Davies, 2004). It has been shown that some apnoeic patients also show reductions or a lack of rapid eye movement (REM) sleep, while other patients show normal REM sleep (Guilleminault et al., 1976). In some patients REM sleep is associated with longer respiratory events and greater levels of blood oxygen desaturation, yet the duration and severity of respiratory events during REM sleep is unchanged in other patients, or there may even be fewer events (Guilleminault et al., 1976).

The most common symptoms of OSA include excessive daytime sleepiness, snoring and witnessed breathing events (Epstein et al., 2009). The difficulty in identifying these latter two symptoms lies in the fact that they occur while the patient is asleep. Typically, apnoeic individuals present to clinics at the urging of their bed partners, who have witnessed respiratory events or complain of their partner’s snoring (Schlosshan & Elliot, 2004). While OSA patients are often unaware that they experience these disturbances during sleep they often experience considerable daytime sleepiness, and various neurocognitive impairments that are proposed to result from the sleep fragmentation and blood gas disturbances (Beebe & Gozal, 2002; Engleman & Douglas, 2004).

Central sleep apnoea (CSA) is distinguished from OSA based on the absence of airway obstruction or continued respiratory effort after cessation of breathing during sleep. Due to the cessation of breathing during central events, there is still the accompanying hypoxemia and hypercapnia, however, the time course of blood gas disturbance is altered (Guilleminault et al., 1976). It may seem intuitive to assume that different pathological mechanisms underlie obstructive and central events. Many OSA patients, however, exhibit both types of events as well as mixed events, which are defined by an initial lack of respiratory effort followed by a late increase in respiratory effort with concurrent airway obstruction prior to termination of the respiratory event (Flemons et al., 1999).
Upper airway resistance syndrome (UARS) refers to a condition in which patients present with the hallmark symptoms of OSA, however, polysomnographic investigation shows repeated arousals but does not show obstructive apnoeas or hypopnoeas (Flemons et al., 1999). The syndrome was described by Guilleminault and colleagues in 1993. They found that on polysomnographic investigation, these patients typically show periodic increases in respiratory effort without marked changes in airflow. Increasing negative oesophageal pressures during inspiration indicates, however, that there is an increase in respiratory effort. Just prior to arousal there is a brief period of slight flow limitation that is terminated by an electroencephalographic (EEG) arousal, typically within three breaths. Unlike a hypopnoea or an apnoea, there is no evident oxygen desaturation as the arousal from sleep interrupts the respiratory event before significant blood-gas disturbance have the opportunity to develop. These patients typically show similar changes in sleep architecture as OSA patients, such as significant reductions in slow wave and REM sleep (Guilleminault, Stoohs, Clerk, Cetel, & Maistros, 1993). The changes in sleep architecture and sleep fragmentation due to repeated arousals most likely account for the similar presentation of symptoms seen in these patients and patients diagnosed with OSA.

1.2 Diagnosis of OSA

High variability in reported symptoms among the OSA population has made OSA a difficult condition to diagnose. Self-reported sleepiness is a poor indicator of OSA, therefore it is standard practice to diagnose OSA through physiological measurement of sleep and respiratory changes. In 1999 The American Sleep Disorders Association (ASDA) published recommendations for the definition and measurement of OSA. These include recommendations based on both subjective ratings of sleepiness, as well as objective measurement of the number of respiratory events per hour of sleep (shown in table 1). The objective measurement is a frequency index, known as the apnoea/hypopnoea index (AHI), which reflects the number of respiratory events experienced during each
hour of sleep (Dingli et al., 2002; NHMRC, 2001), and is the factor that
determines a diagnosis of OSA. Although EDS is not strongly correlated with
AHI, it is still included in the diagnostic criteria of OSA as the subjective
experience of excessive sleepiness plays an important role in the determination of
appropriate treatment.

Patients suspected of having OSA are routinely recommended for an
overnight polysomnography (PSG) in order to obtain their AHI. A PSG involves
taking electroencephalographic, electrooculographic, electrocardiographic as
well as, chin and leg electromyographic measurements during sleep. Patients are
usually referred for such a study if they show the primary symptoms of daytime
sleepiness, snoring, witnessed respiratory events, and obesity. Following the
overnight study, patients are diagnosed based on their AHI.

Table 1. Severity Criteria for the Diagnosis of OSA According to the ASDA (1999)

<table>
<thead>
<tr>
<th>Subjective Measure</th>
<th>Objective Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>AHI &gt;5 ≤15 events/hr</td>
</tr>
<tr>
<td>Moderate</td>
<td>AHI &gt;15 ≤30 events/hr</td>
</tr>
<tr>
<td>Severe</td>
<td>AHI &gt;30 events/hr</td>
</tr>
</tbody>
</table>

The current standard by which OSA is diagnosed and AHI threshold values,
which define severity, are somewhat arbitrary. In addition, the criteria for
defining respiratory events have changed considerably over the past half-century.
Ruehland and associates (2009) performed an analysis of a large number of
studies and determined the prevalence of OSA according to the various criteria of the AHI published by the American Academy of Sleep Medicine over the years. The analysis showed that AHI varied considerably depending on which criteria were used (Ruehland et al., 2009). Thus, a comparison of research studies can be somewhat confounded by the specific criteria used. In addition to changing diagnostic criteria, there are other indices of OSA severity commonly reported in the literature. The respiratory disturbance index (RDI) is commonly reported instead of the AHI. This metric differs from the AHI in that in addition to hypopnoeas and apnoeas, this index includes the number of respiratory-effort related arousals experienced per hour of recording time (Zou, Grote, Peker, Lindblad, & Hedner, 2006). The oxygen desaturation index (ODI) is also sometimes reported as a measure of OSA severity. This metric is focused not on defined hypopnoeas, apnoeas or arousals, but is rather a measure of the number of episodes of oxygen desaturation of more than 4% of baseline, per hour of sleep (Zou et al., 2006). ODI may lead to an underestimation of OSA severity, and in particular an underestimation of the level of sleep fragmentation. While the ODI is a much easier and cheaper way to measure OSA severity, the AHI obtained from an in-laboratory sleep study is considered the most accurate index of OSA severity.

1.3 Prevalence of OSA

Obstructive sleep apnoea is becoming increasingly recognised as a pervasive health problem among the general population. Many large-scale cohort studies have been conducted in the last four decades across the world in an attempt to assess the prevalence and potential economic and health burden posed by SDB. Data from the Wisconsin cohort, a seminal population study, estimated that 4% of men and 2% of women aged between 30 and 60 have OSAHS, with men being 2-3.7 times more likely than women to have SDB (Young et al., 1993). In the absence of symptoms and with severity levels sufficient to warrant a clinical diagnosis the prevalence estimate jumped to 24% in men and 9% in women.
Later studies have found considerable variation in prevalence rates. Kripke and colleagues (1997) found, in their population study of men and women in San Diego, that 20.3% of men and 7.6% of women, aged between 40-65 years, had a 4% oxygen desaturation index (ODI) greater than 15. Results from the Pennsylvania cohort found similar prevalence rates to Young and colleagues (1993), when the sample age range was broadened to include any individual over 20 and up to 60 years of age finding prevalence rates of 3.9% in men and 1.2% in women (Bixler et al., 2001). The effects of age on OSA were also investigated and results showed a quadratic age-specific prevalence in men and increasing prevalence rates with age in women (Bixler et al., 2001; Bixler, Vgontzas, Have, Tyson, & Kales, 1998). For men the prevalence rates were greatest amongst middle-aged men, while elderly men were only slightly more likely than men younger than 45 to have OSA. Severity of OSA as defined by the number of hourly events and minimum oxyhaemoglobin levels appeared to decrease with age (Bixler et al., 1998). In women the rates were highest amongst those aged between 60-69 years of age. In addition, it was found that the prevalence rates in post-menopausal women without hormone replacement therapy was close to that seen in men (3.9%), however, after controlling for age and BMI the levels still showed significantly lower prevalence rates in women than in men.

More recent data suggests that approximately 1 in every 20 adults in the United States will have symptomatic OSA, with reports of daytime somnolence, and it is estimated that 1 in every 5 American adults has asymptomatic OSA (Young, Peppard, & Gottlieb, 2002a). This is similar to the estimated prevalence rates of roughly 25% of individuals being at high risk of OSA suggested by Hiestand and colleagues in 2006, based on data from the National Sleep Foundation’s Sleep in America Poll. These estimates are significantly higher than the early prevalence estimates derived almost a decade before from data collected from the Wisconsin Sleep cohort study. The increase may reflect an aging population that is becoming more obese, or changing diagnostic criteria and sensitivity.
Community-based studies from Europe show similar prevalence rates to American community-based studies. A study of Spanish men and women, based on the presence of nocturnal oxygen desaturation as well as snoring and daytime hypersomnolence, led to estimated prevalence rates of severe OSA in 2.2% of men and 0.8% of women (Marin, Gascon, Carrizo, & Gispert, 1997). These values jumped to 15% of men and 6% of women when nocturnal oxygen desaturations were used as the sole diagnostic measure. Most importantly they also found that male gender was the most significant predictor of snoring and OSA with overall similar male to female ratios of OSA prevalence (3.6:1) to the Wisconsin Sleep study (2.25:1). A second community-based study in Spain that used polysomnographic investigation found that 14.2% of men and 7.0% of women showed moderate to severe OSA (Duran, Esnaola, Rubio, & Iztueta, 2001). The male/female odds ratio, when adjusted for age and BMI was 1.2:1 when minimal diagnostic criteria were used, however, this value jumped to 3:1 for severe OSA (AHI ≥30). A study of 349 Italian men, between the ages of 40-65 years, found that 8.9% had a greater than 4% ODI (Ferini-Strambi et al., 1994). A more recent study of 2168 individuals from the general population in Switzerland revealed even greater prevalence rates with 49.7% of men and 23.4% of women showing evidence of moderate to severe OSA (Heinzer et al., 2015). These values were even higher, 83.8% of men and 60.8% of women, when individuals with mild OSA were included. The considerable jump in prevalence rates recorded in this particular study in comparison to past population studies is most likely due to the fact that each individual in this study underwent a full polysomnography, providing a more accurate assessment of sleep disordered breathing. A link between SDB and obesity, and in particular neck circumference was also reported in the Spanish, Italian and Swiss population studies (Ferini-Strambi et al., 1994; Heinzer et al., 2015; Marin et al., 1997), although on average the BMI within the Italian population was significantly lower than the average BMI seen in American samples.

A study of Australian men in Busselton, a rural town, showed that 12.2% had minimal, symptomatic sleep apnoea (Bearpark et al., 1995). Again this value
jumped considerably to 25.9% for asymptomatic minimal sleep apnoea. The BMI was the strongest correlate, showing significant associations with all sleep disordered breathing variables, including RDI, mean oxygen saturation and snoring. A South-Eastern Australian study of both men and women, conducted around the same time, estimated that the prevalence rate of individuals with an RDI ≥15 was between 3 to 18%, with an increase in prevalence with age (Olson, King, & Hensley, 1995). The estimates of SDB prevalence rates in Australia are similar to the more recent studies conducted in the United States.

Studies from Asia suggest slightly lower prevalence rates in the general population. A study of Malay, Indian and Chinese individuals in Singapore indicated prevalence rates of 0.43% overall (Ng, Seow, & Tan, 1998). Consistent with worldwide studies, prevalence was higher in men (0.61%) than women (0.22%). When ethnicity was investigated, it was shown that SDB was more prevalent amongst Malays (0.99%), than Indians (0.84%), than Chinese (0.29%). These estimates are considerably lower than estimated prevalence rates in the United States, Australia or Europe. The authors suggest that this is an underestimation due to the reliance on symptom report in their sample and the cultural stigma associated with symptoms of snoring and daytime hypersomnolence. In more recent community-samples of men and women in Hong Kong prevalence rates of symptomatic OSA were reported to be 4.1% in men and 2.1% in women. Prevalence rates of asymptomatic OSA, however, were considerably higher (8.8% in men and 3.7% in women) (Ip et al., 2001; Ip et al., 2004). Age was again found to be significant correlate of OSA in this Asian population, with prevalence rates increasing across age groups. Other anthropomorphic characteristics that showed to be significant correlates included body mass index (BMI), measures of body habitus, blood pressure, habitual snoring and shorter sleep onset latencies. Although the overall prevalence of SDB may be lower in Asian populations than in American and European populations, the same correlates appear to be of importance.

Many factors are likely to contribute to the variable reports of prevalence rates, including ethnicity, sampling bias, diagnostic techniques and definitions.
It has been argued that several studies under-represent the ethnic diversity within a given population, for example Kripke and colleagues (1997) argued that their sample had a more representative proportion of African-American, Hispanic and Asian individuals than the Wisconsin cohort. Early prevalence estimates are also complicated by oversampling of at-risk and clinical populations (Young, Peppard, & Gottlieb, 2002a). Other studies may have biased samples due to the use of government employed or housed populations (Ip et al., 2004; Ip et al., 2001; Ng et al., 1998; Young et al., 1993), however, employment status, income or education have not been found to correlate with OSA severity (Kripke et al., 1997). As previously mentioned, the diagnostic criteria for OSA is arbitrarily determined and has changed considerably over time, thus comparing prevalence rates between early studies and more recent studies can become difficult. Finally, many large community-based studies rely on interview, and subjective report of symptoms for diagnosis, while other studies have employed oximetry or full polysomnography. Different diagnostic techniques often produce conflicting results. Duran and colleagues (2001) found that 45.1% of men and 65.4% of women diagnosed as having OSA from symptomology and oximetry did not have OSA when given a full polysomnography. In contrast, 5.8% of men and 11.2% of women who were not diagnosed as having OSA based on symptomology and oximetry did in fact meet diagnostic criteria following a polysomnography.

In general, the consistent findings of high prevalence rates of asymptomatic OSA suggest that there are significant levels of undiagnosed individuals within the general population, as experience of symptoms is more likely to drive help-seeking behaviour (Young et al., 1993). In fact, Lindberg and Gislason (2000) estimate that approximately 0.3-5% of the population may have undiagnosed OSA. Despite the variation in reported prevalence estimates, however, it is clear that the high rates of diagnosed and undiagnosed individuals with OSA in the general population and the considerable associated comorbidity poses a significant health and economic burden.
1.3.1 Gender differences.

As previously described, being of male gender seems to be one of the most powerful predictors of snoring and OSA (Redline, Kump, Tishler, Browner, & Ferrette, 1994; Young, Shahar, Nieto, Redline, et al., 2002b). The prevalence of OSA is also found to be greater in post-menopausal women without hormone replacement therapy (HRT) than post-menopausal with HRT, 5.5% versus 0.6% (Bixler et al., 2001). Initially, identification of male predominance in prevalence data as well as post-menopausal women not receiving hormone replacement led to the suggestion that female hormones may be in some way protective against OSA and may be used as a treatment (Bixler et al., 2001; Block, Boysen, Wynne, & Hunt, 1979). Increases in ventilatory drive have been demonstrated during the luteal phase of the menstrual cycle when progesterone is at its highest levels (Cistulli, Barnes, Grunstein, & Sullivan, 1994). Supporting the suggested protective effects of progesterone, studies of exogenously administered medroxyprogesterone have shown reductions in the frequency of respiratory events (Block et al., 1981; Collop, 1994). The administration of medroxyprogesterone, however, did not show any significant effects on sleep disordered breathing in another study (Cook, Benich, & Wooten, 1989). The studies that did show an effect of medroxyprogesterone on OSA severity did so primarily through reductions in central apnoeas rather than obstructive apnoeas. The conclusion was that OSA may be more prevalent in men, not because of the protective effects of progesterones but rather due to risks resulting from high levels of testosterone. Indeed case studies have shown worsening of OSA with increases in testosterone levels in both men and women (Dexter & Dovre, 1998; Sandblom et al., 1983). Additionally, a four-fold increase in upper-airway resistance has been noted after administration of testosterone in one case (Johnson, Anch, & Remmers, 1984). Overall, the use of sex hormones as a treatment for OSA is not ideal due to the considerable side effects associated with fluctuations in these hormones and the relatively small alterations in OSA severity.
1.4 Signs and Symptoms of OSA

Physical examination of most patients with OSA generally shows no obvious physical abnormalities, however, there are many symptoms commonly reported by OSA patients or their bed-partners. The key symptoms that are typically reported when OSA patients initially present to sleep clinics include snoring, excessive daytime sleepiness and witnessed breathing pauses (Schlosshan & Elliot, 2004). Other commonly reported symptoms include insomnia, unrefreshing sleep, repeated awakenings from sleep, poor concentration and morning headache (Flemons et al., 1999; Guilleminault et al., 1976; Ingbar & Gee, 1985; Kales, Cadieux, Bixler, et al., 1985a). In a study observing the clinical characteristics of OSA patients it was found that commonly reported night-time symptoms amongst OSA patients include restlessness, profuse sweating, nocturnal enuresis, dry throat, sleep maintenance insomnia and sleep paralysis or hypnagogic hallucinations (Kales, Cadieux, Bixler, et al., 1985a). Other commonly reported symptoms upon waking in the morning include headaches, unrefreshed feeling, impaired alertness and incoordination.

1.4.1 Snoring.

Research has shown that 70-95% of OSA patients are habitual snorers and that this symptom can often precede the onset of OSA by more than a decade (Kales, Cadieux, Bixler, et al., 1985a). Epidemiological data from American and Australian populations, however, indicated that habitual snoring is also prevalent in 35-50% of the general population, indicating that the specificity of this symptom as a unique indicator of OSA is quite low (Bearpark et al., 1995; Duran et al., 2001; Young et al., 1993).

1.4.2 Hypersomnolence.

Hypersomnolence, or excessive daytime sleepiness (EDS), can be assessed using either subjective or objective measures, however, it is most commonly assessed subjectively. While early studies identified EDS through anecdotal report or through questions targeting sleepiness (Guilleminault et al., 1976; Ingbar & Gee, 1985; Kales, Cadieux, Bixler, et al., 1985a; Young et al., 1993), the
development of sleepiness questionnaires enabled more consistent measurement of hypersomnolence amongst the OSA community. The Epworth Sleepiness Scale (ESS), which contains items about experienced levels of sleepiness during specific situations, such as during meetings, or while driving is a well-validated and commonly used sleepiness scale within the body of OSA research (Johns, 1991). Population studies have shown significant levels of sleepiness reported via the ESS by OSA patients. A large sample of community-dwelling adults taking part in the Sleep Heart Health Study, a longitudinal study of the cardiovascular consequences of SDB, also completed the ESS. When all patients with RDI > 5 < 30 were considered, 28% reported EDS which was not drastically different, albeit significantly increased, from the 21% of patients with RDI < 5 who had EDS. When severe (RDI > 30) SDB patients were considered, however, the percentage of individuals reporting EDS jumped significantly to 35% (Gottlieb et al., 1999). A large-scale, multi-centre study in the United States also failed to find an association between EDS, as measured using the ESS, and mild OSA (Quan, et al., 2014). A population study in Switzerland found EDS was prevalent in 12% of the population, however, there was no association found between severity of sleep disordered breathing and degree of EDS (Heinzer et al., 2015).

Studies of clinical samples quite often show much higher rates of EDS, as it is one of the most common symptoms that lead individuals with OSA to seek medical help. Hypersomnolence, defined by the ESS was found in 53% of a sample of severe OSA patients in Japan (Akashiba et al., 2002). In an Australian clinical sample of mild to moderate OSA patients, 65% were found to have ESS scores ≥11 (Barnes, Houston, Worsnop, Neill, Myktyn, et al., 2002a). Despite evidence showing that daytime hypersomnolence is clearly a prevalent symptom, the majority of patients do not report this symptom (Duran et al., 2001; Kapur, Baldwin, Resnick, Gottlieb, & Nieto, 2005; Young et al., 1993; Young, Hutton, Finn, Badr, & Palta, 1996).

Many patients with OSA often deny that they experience excessive sleepiness (Ingbar & Gee, 1985). This denial may be due to the definitions and
perceptions that individuals apply to the term “sleepiness”. Chervin (2000) found that people reported fatigue, tiredness and lack of energy more often than sleepiness per se. In a study using multiple descriptors and questionnaires pertaining to daytime hypersomnolence, Kapur and colleagues (2005) found a relationship between moderate to severe SDB and sleepiness. When the definition of sleepiness was expanded to include feelings of being tired or worn out, the prevalence of EDS amongst patients with moderate to severe SDB was increased from 45.7% to 53.9%. Inclusion of mild OSA patients in prevalence rates of reports of hypersomnolence may skew the association of this symptom with OSA (Kapur et al., 2005). Self-reported sleepiness may underestimate the severity of sleepiness and objective measurement with a multiple sleep latency test is a more valid, albeit more expensive measure of EDS (Thorpy, Snyder, Aloe, Ledereich, & Starz, 1992). Indeed, there has been little association found between self-reported sleepiness and objective measurement of sleepiness using multiple sleep latency tests (Barbé et al., 2001). In particular, self-reported sleepiness may be a poor measure of sleepiness severity in cases of chronic hypersomnolence due to the slow and insidious progression of the condition.

Despite evidence associating OSA severity and EDS, the strongest predictor of sleepiness in the Sleep Heart Health Cohort (SHHC), however, was self-reported estimates of sleep duration. Bixler and colleagues (2005) also found that there was a relationship between the subjective perception of insufficient sleep and daytime hypersomnolence, in the absence of objectively measures sleep deprivation. In their study, however, they also failed to show a relationship between SDB and daytime hypersomnolence. Several other studies have also failed to show a relationship between AHI and sleepiness (Aloia et al., 2005; Quan, et al., 2014). Aloia and colleagues (2005) failed to show a significant correlation between RDI and sleepiness ratings on the ESS in a sample of relatively severe OSA patients. A mild OSA patient subset from the Apnea Positive Pressure Long-term Efficacy Study (APPLES) demonstrated no significant differences in sleepiness (as measured by the ESS and Stanford Sleepiness Scale) when compared to non-OSA individuals (Quan, et al., 2014).
Daytime hypersomnolence was initially thought to be the result of sleep fragmentation experienced due to respiratory events in patients with SDB (Guilleminault et al., 1976). Indeed it has been shown that reductions in slow wave and REM sleep and increases in stage one sleep were associated with sleepiness (Punjabi et al., 1999). Conversely, Gottlieb and colleagues (1999) failed to find an association between arousal frequency and levels of EDS. Other studies, however, have shown correlations between lower levels of oxygen saturation and sleepiness rather than the number of arousals, or sleep stage distribution. Akashiba and colleagues (2002) found in their study that higher levels of sleepiness were associated with lower mean oxygen saturations as well as decreased percentages of REM sleep, suggesting that daytime sleepiness results from sleep disturbance and decreased oxygen levels experienced by these patients during sleep.

It has also been found that in general, a large proportion of non-OSA patients (as high as 35%) report daytime hypersomnolence suggesting that this symptom is not specific and may also be a poor indicator of OSA (Duran et al., 2001; Gottlieb et al., 1999; Kapur et al., 2005; Young et al., 1993). Other independent risk factors associated with excessive daytime sleepiness may confound the perceived relationship between SDB and sleepiness.

1.4.3 Daytime functioning and quality of life.

Sleepiness questionnaires measure an individual’s state of sleepiness, but do not measure how their sleepiness affects their general health, wellbeing and perceived quality of life (QoL). General health status and functioning are commonly reported as impaired amongst the OSA population. It is difficult, however, to determine the extent of impairment due to the wide variety of instruments and sample variation between studies. In a sample of OSA patients, ranging from mild to severe, it was found that general health status was significantly impaired in comparison to healthy, non-snoring individuals (Fornas, Ballester, Arteta, Ricou, & Diaz, 1995). The Nottingham Health Profile (NHP) was used to assess perceptions across six dimensions of health (energy, pain, emotional reactions, sleep, social isolation and physical mobility). While there
was no significant difference across any domain between mild, moderate and severe sleep apnoea patients, the OSA patients reported significantly poorer health on all dimensions, except emotional reactions, than the healthy control participants.

Studies have demonstrated that general quality of life is significantly impaired in severe OSA patients, as assessed using the Medical Outcomes Short-Form 36 (SF-36) Health Survey (Akashiba et al., 2002; Baldwin et al., 2001; D'Ambrosio, Bowman, & Mohsenin, 1999; Finn, Young, Palta, & Fryback, 1998). The SF-36 assesses limitations in functioning across several health constructs including: physical functioning, mental health, role in physical activities, role in emotional activities, bodily pain, vitality and perceptions of general health (Ware, Kosinski, & Keller, 1994). Studies have consistently shown that severe OSA patients show significant impairment across the majority of domains assessed by the SF-36 (Baldwin et al., 2001; D'Ambrosio et al., 1999). Not only do patients show impaired general health status, but when compared with population norms, the impairment is similar to that seen in other chronic illnesses such as hypertension, angina, arthritis, chronic back problems and diabetes (Baldwin et al., 2001; Finn et al., 1998).

While studies have consistently demonstrated impairment in general health status amongst the OSA population, the correlation between OSA severity and the degree of reported impairment is less clear. The Wisconsin Sleep Cohort Study did show a dose-response relationship between decreasing health status, on all but the bodily pain and role emotional domains, and increasing SDB severity (Finn et al., 1998). As is commonly found in clinical practice, some mild patients reported greater impairment than severe patients and vice versa (Kales, Cadieux, Bixler, et al., 1985b). The Sleep Heart Health Study found that only the Vitality domain of the SF-36 showed significantly poorer scores in patients with mild-moderate SDB in comparison to population norms (Baldwin et al., 2001). When degree of SDB, and symptoms such as pathological sleepiness and difficulty initiating or maintaining sleep were considered together, however, there was a more consistent relationship between increasing severity and
reduced quality of life across all domains of the SF-36, except role emotional and mental health perceptions.

Much of the research on QoL in the OSA population is limited by many uncontrolled confounding factors. Most studies have considerable variability in sample selection and composition, the way in which sleep apnoea is diagnosed, and comorbidity. There is also wide variability in the age, gender, BMI and smoking status of patients (Wright, Johns, Watt, Melville, & Sheldon, 1997). Few studies have attempted to statistically control for such confounds. Yang and colleagues (2000) compared a sample of primary care patients who either did or did not have sleep apnoea following a polysomnography. When controlling for age, gender, BMI and comorbidity sleep apnoea patients, regardless of severity, showed significantly worse physical health according to lower scores on the physical functioning, and role physical subscales of the SF-36. When the mental health and health perceptions subscales were broken down and analysed by their unidimensional components, they also found that moderate to severe patients showed significantly worse scores on positive affect and perceptions of health than patients who did not have sleep apnoea. The major limitation of this study was the comparison of asymptomatic patients and symptomatic patients who were screened for sleep apnoea. Ideally it would be best to compare asymptomatic patients with and without sleep apnoea.

Although there is considerable variability in the observed reductions in QoL amongst these studies of sleep apnoea patients, there is wide agreement that, in general, sleep apnoea does lead to reduced QoL. It is unclear, however, whether the observed reductions in QoL are due to hypoxemia or sleep fragmentation. Bennett, Barbour, Langford, Stradling and Davies (1999) conducted a study of 51 patients referred for PSG. The scores on the SF-36 showed that there was indeed impairment within the sample, which encompassed a wide range of OSA severity. All patients received four weeks of therapeutic nCPAP and regardless of OSA severity, improvement in health status was observed. At baseline, objective measures of sleep fragmentation, including ASDA arousals, respiratory arousals, and AHI showed poor
associations with scores on the SF-36. The dimensions of energy, vitality and to a lesser extent physical functioning, however, all showed improvement with nCPAP treatment, and the improvement on these dimensions weakly correlated with these objective measures of sleep fragmentation. This led the author’s to infer that the lower energy, vitality and physical component scores on the SF-36 seen in sleep apnoea patients is at least in some part due to sleep fragmentation.

Akashiba and colleagues (2002) demonstrated impairment in six of the eight subdomains of the SF-36 in severe OSA patients. Regression analysis, however, showed that while depression accounted for approximately 50% of the variance in overall SF-36 scores, the addition of lowest nocturnal oxygen saturation and degree of sleepiness accounted for 62% of the variance in the total SF-36 score. This suggests that various other factors, including depression, oxygen saturation and sleepiness may account for a large part of the decrease in quality of life observed in OSA patients. Moore, Bardwell, Ancoli-Israel andDimsdale (2001) investigated the relationship between polysomnographic measures including OSA severity (as measured by RDI) and sleep fragmentation (as measured by number of arousals) and QoL measures of mental and physical functioning as assessed by the long-form Medical Outcomes Survey. Neither OSA severity nor sleep fragmentation showed significant associations with reduced mental, physical or emotional functioning until age and gender were controlled for. The study, however, did show a relationship between pain and OSA severity. Interestingly pain was not a typical symptom associated with OSA and the sample was controlled for comorbid chronic and acute pain conditions.

Assessment of general health status using questionnaires, that are not disease- or treatment-specific, does provide a useful overview of how individuals with OSA perceive the overall impact of their disease. Similar to the shortcomings of generic sleepiness measures, however, generic measures of general health and wellbeing, such as the SF-36, also fail to specifically assess how fatigue or sleepiness affect daily functioning. While the SF-36 Vitality domain does address some common issues related to sleepiness, in general, the SF-36 and other generic wellbeing scales take a more developmental and neurocognitive
approach to functionality (Weaver et al., 1997). That is, the typical OSA patient may experience difficulty with daily functioning due to reduced alertness in response to environmental stimulation as opposed to difficulty due to diminished neurocognitive or physical development or disability. It is therefore, important to assess how sleepiness, per se, affects daily functioning using disease-specific tools.

Several disease-specific questionnaires have been developed to assess the degree or functional ability of adults who experience hypersomnolence. The Functional Outcomes of Sleep (FOSQ) is one such questionnaire that is commonly used to assess OSA patient’s daily functional ability. The FOSQ measures functional limitations across five dimensions of productivity: social outcomes, activity levels, vigilance and intimate relationships and sexual activity. One of the major strengths of this particular disease-specific questionnaire is that it addresses intimacy and sexual activity, which is often omitted from generic questionnaires. Another strength of this questionnaire is that for each item, respondents have the option to indicate that they do not engage in that activity for reasons other than sleepiness. This prevents individuals from skipping items because they do not engage in a particular activity for reasons other than disorders of excessive sleepiness, thereby preventing score bias (Weaver, et al., 1997). There is currently no large-scale epidemiological data on the observed deficits in daily functioning, as measured by the FOSQ, across mild to severe OSA patients. Weaver and colleagues (1997), however, showed that all subscales, as well as the FOSQ global score was significantly lower in moderate to severe OSA patients when compared to normal controls. In particular the OSA patients showed greater functional deficits in Activity levels, Vigilance and Social Outcomes.

1.5 Psycho-Emotional And Neurocognitive Consequences Of OSA

Personality changes, such as depression and anxiety, neurocognitive changes, and reduced quality of life (QoL) are commonly reported and present potential confounding factors when attempting to establish the relationship
between SDB and symptoms such as sleepiness. Neurocognitive ramifications of untreated OSA have also been widely reported with mixed findings. Understanding the impact of OSA on psycho-emotional and neurocognitive domains is complicated by the wide variety of measurement instruments available. Studies aiming to profile the neurocognitive characteristics of OSA patients have focused on investigating impairment across cognitive domains of attention and vigilance, memory and executive functioning.

1.5.1 Depression and mood disturbance.

Depression is a commonly reported comorbid illness amongst the OSA population. The classification of depressive disorders according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5™: American Psychiatric Association, 2013) includes several affective disorders including major depressive disorder (MDD) and persistent depressive disorder (dysthymia) among several others. These disorders are characterised by the presence of sad, empty or irritable mood, accompanied by somatic and cognitive symptoms that significantly impact on the functional capacity of the individual. The main factors that distinguish between the various depressive disorders are timing, duration and suspected causal factors. The main diagnostic criteria for MDD and dysthymia include depressed mood, weight and appetite fluctuations, sleep disturbance including insomnia or hypersomnia, fatigue or loss of energy, feelings of worthlessness or helplessness, psychomotor agitation or retardation and/or diminished concentration of capacity to make decisions.

In the United States of America, twelve-month prevalence rates for MDD and dysthymia are approximately 7% and 0.5%, respectively. For MDD there is a 3-fold higher prevalence amongst individuals aged between 18 and 29 years than in older individuals, and 1.5 to 3-fold higher prevalence in women versus men (American Psychiatric Association, 2013). The National Survey of Mental Health and Wellbeing (ABS, 2008) showed that for Australians aged between 16 and 85 years, there was a twelve-month prevalence of 6.2% for affective disorders. The ABS defined affective disorders as any disorder that involved mood disturbance or change in affect, including depressive episode, dysthymia and bipolar
affective disorders. Similar to American statistics, depressive episodes were the most prevalent at 4.1%, while dysthymia was prevalent in 1.3% of Australians.

Previous studies that have investigated the association between OSA and depression have shown rates of anti-depressant use or clinical diagnosis of depression among OSA populations ranging from 17-38% (Douglas et al., 2013; Schwartz, Kohler, & Karatinos, 2005). Other studies that have used mood and depression questionnaires have found even higher prevalence rates of depression or depressive symptoms amongst the OSA population (Akashiba et al., 2002; BaHammam et al., 2015; Douglas et al., 2013; Kales, Caldwell, et al., 1985b).

A phone survey study conducted across the U.K., Germany, Italy, Portugal and Spain revealed that 0.8% of the general population have both OSA and depression (Ohayon, 2003). A large population study in Switzerland also showed an independent association between OSA and depression (Heinzer et al., 2015). Using the DSM-IV criteria for both breathing-related sleep disorders and major depressive episode, it was determined from this cross-sectional study that depressed individuals were five times more likely to have a breathing-related sleep disorder even after controlling for confounding factors including obesity and hypertension. Another large-scale population-based, longitudinal study showed an association between polysomnographically determined sleep related breathing disorders and increased odds of developing depression (Peppard, Szklo-Coxe, Hla, & Young, 2006). This study employed the Zung depression scale and the model was adjusted for anti-depressant use. Further adjustment for factors such as insomnia, daytime sleepiness, fatigue, use of hypnotic or benzodiazepine medications, and diabetes did not alter this association. Although the association was present, a potential mechanism that could mediate this relationship was not apparent, as EDS, fatigue, sleep efficiency, and percentage of time spent in slow-wave sleep did not show any meaningful alteration of the model. The authors, however, speculate that the increased odds of developing depression may be related to sleep fragmentation or intermittent hypoxia. This study builds upon the cross-sectional findings of Ohayon and
colleagues through longitudinal analysis, and polysomnographically diagnosed sleep-related breathing disorder.

A population-based study in Taiwan of 2,818 newly diagnosed OSA patients assessed OSA as a longitudinal predictor of depression (Y.-H. Chen, Keller, Kang, Hsieh, & Lin, 2013). In comparison to 14,090 matched individuals, without OSA, the OSA patients had a 2.18 times increased risk of subsequent depressive disorder over a twelve-month period. This study controlled for the possible confounds of metabolic syndrome and cardiovascular disease and selection criteria was restricted to only polysomnographically diagnosed OSA and clinically diagnosed depressive disorder. Individuals younger than 40 years of age were at a greater risk of subsequent depressive disorder in comparison to individuals between 40 and 64 years, as were women in comparison to men. Again, however, the biological mechanism potentially linking OSA and depressive disorder was unable to be determined from this study.

Whether the association between OSA and depression identified by population-based studies is generalizable to clinical patients is unclear. Findings from cross-sectional studies of clinical populations are mixed. In 50 severe patients recommended for tracheostomy, 56% were depressed according to scores on the Minnesota Multiphasic Personality Inventory (MMPI) (Kales, Caldwell, et al., 1985c). In 60 male, severe OSA patients 48% were depressed according to scores on the Zung self-rated depression scale (Akashiba et al., 2002). A small study (N=45) of snoring and OSA patients revealed that according to results on the Beck Depression Inventory (BDI) approximately 20% also had moderate or severe depression (Jackson et al., 2010). A larger study (N=142) found prevalence rates of depression, that was either doctor diagnosed or diagnosed through the Hospital Anxiety and Depression Scale (HADS) or the Mini-International Neuropsychiatric Interview (MINI), of approximately 50% in patients with snoring or OSA (Douglas et al., 2013). Whilst the research shows a strong association between OSA and depression, it is unclear whether there is a causal relationship between these two conditions.
Several studies have failed to show a correlation between OSA severity and depression. A study of mild OSA patients revealed no significant evidence of higher levels of mood disturbance or depression (using the profile of mood states questionnaire: POMS, and the Hamilton depression inventory: HAM-D) in comparison to normal healthy individuals (Quan et al., 2014). Kjelsberg, Ruud and Stavem (2005) also found no association between OSA severity and depression, as measured by the HADS, however, patients who met the threshold for a diagnosis of depression had significantly higher levels of daytime sleepiness.

Some studies have shown increasing rates of depression with increasing severity of OSA. Aloia and colleagues (2005) showed a significant relationship between OSA severity and endorsement of depressive symptoms on the BDI, but also a significant relationship between OSA severity and obesity. Their research showed that gender moderated the relationship between OSA, obesity and depression. Men only demonstrated a significant relationship between OSA severity and depressive symptoms that were somatic in nature independently of BMI, while women only showed a significant relationship between BMI and depressive symptoms that were cognitive in nature independently of OSA severity. Their findings suggest that a large proportion of the association between OSA severity and depression may come from a subset of depressive symptoms that are somatic in nature such as lack of energy, tiredness, fatigue and irritability (Aloia et al., 2005). The relationship between obesity and depression is largely due to depressive symptoms that are cognitive in nature such as feelings of guilt, past failure and self-criticalness. Importantly, it appears that men and women with OSA manifest these two depressive dimensions differently.

The symptomology of depression and OSA overlap considerably and it is not clear from past research whether these two conditions commonly occur concurrently or whether there is a more causal relationship between them. Hypersomnia as a result of sleep fragmentation may lead to the presentation of many of the hallmark symptoms of depression, such as fatigue, tiredness, lack
of energy and irritability are commonly reported symptoms of OSA. This overlap in symptomology may lead to elevated depression scores in OSA patients and may be more reflective of depression as an epiphenomenon of OSA rather than a specific psychological disorder. Depressive disorder is also commonly associated with a variety of chronic medical illnesses. OSA may lead to lowering of quality of life in general, leading to the presentation of depressive symptoms. Alternatively, a shared signalling pathway involving proinflammatory markers, neurotransmitters or other neurochemical factors may be responsible for the development of both OSA and depression (Y.-H. Chen et al., 2013). OSA has been shown to be associated with increased levels of interleukin-6 and Tumor necrosis factor alpha (Vgontzas et al., 2000), whereas depressive disorder has been shown to be associated with increased interleukin-1 and -6 as well as increased interferon levels (Irwin & Miller, 2007). It is also possible that the relationship between OSA and depression is mediated by another common correlate of OSA, such as obesity, cardiovascular disease or metabolic syndrome.

It should also be noted that OSA and snoring are not the only sleep disorders commonly associated with depression. There is a high prevalence rate of depressive symptoms amongst patients with a variety of sleep disorders such as periodic limb movement syndrome (PLMS), narcolepsy, insomnia, and delayed sleep phase disorder, to name a few (Vandeputte & de Weerd, 2003). Insomnia, PLMS, and patients with inadequate sleep- and wake-hygeine and sleep state misperception had higher levels of depressive symptoms measured by the BDI than OSA patients. This particular study is likely to have overestimated the prevalence rates and severity of depressive symptoms, however, as the participants in this study had presented at the sleep laboratory due to severe sleep disorder.

1.5.2 Neurocognitive performance.

Neurocognitive performance has also been highlighted as an area in which deficits are noted amongst OSA patients. Kales and colleagues (1985b) reported impairments related to thinking, perception and memory in a sample of 50
severe sleep apnoea patients. Sleep apnoea patients were also found to perform worse than non-apnoeic hypersomnolent patients and healthy controls on measures of attention, and motor skills as well as global measures of neuropsychological function (Greenberg, Watson, & Deptula, 1987). A study of patients with only mild sleep disordered breathing showed similar results, with poorer performance on a task of sustained attention reflecting poor working memory, but no other attentional deficits in comparison to controls (Redline et al., 1997). There were also greater performance deficits in some tests of executive functioning, while no deficits in performance were found on tests of short or long-term memory or general information processing for the mild SDB patients in comparison to healthy controls. The sleep apnoea patients in this study did not show either pathological levels of sleepiness or hypoxemia, thus it could not be determined which of these variables mediate greater neurocognitive deficits in patients with mild SDB.

A subsequent study with more extensive neurocognitive testing showed that the areas that appear most affected in OSA patients relate specifically to cognitive control and learning and corresponded to deficits functionally related to the frontal lobe (Naëgelé et al., 1995). Moderate to severe sleep apnoea patients showed no attentional deficits except on a STROOP task, which involves not only focal attention and shifting processes, but additionally requires inhibition of automatic processes. A task of planning and sequential thinking showed significant impairment in apnoeic patients in comparison to controls. On a subsequent and more difficult extension of the task, however, there were no longer differences between the sleep apnoea patients and controls. It appeared that once the strategy used to solve the puzzle was established by the patients it was easily recalled and applied to the harder task. Several of the other cognitive measures were not significantly affected in the sleep apnoea patients, including measures of other mental processes functionally related to the frontal lobe. It was suggested that the deficits are limited predominantly to initiation of new mental processes and inhibition of automatic mental processes. Furthermore, the degree of impairment was sensitive to the severity of nocturnal hypoxemia, but
not to the degree of daytime hypersomnolence (Naëgelé et al., 1995). Similarly, the cross-sectional baseline data from the APPLES study showed that there were only mild associations between OSA and neurocognitive impairment in the domains of processing speed and mental flexibility, spatial perception and problem solving, and attention. Other areas that showed no deficits included general intelligence and psychomotor functioning. Severity of oxygen desaturation as opposed to AHI, sleep quality or sleep duration explained virtually all of the observed deficits in neurocognitive performance (Quan et al., 2011).

In general, the impact of untreated OSA on psycho-emotional and neurocognitive function is yet to be fully elucidated. The research to date, however, does show evidence of associations between depressed mood and OSA. Fewer studies have investigated the neurocognitive associations with OSA, and have produced inconsistent findings. The most commonly reported deficits relate to areas of executive function and mental flexibility. More research is required to provide a clear picture of the causal ramification of OSA on various neurocognitive domains.

1.6 Risks Of OSA

In addition to various signs and symptoms, which the patient may or may not be aware of, there are several risk factors associated with OSA. In general, being of male gender, hypertensive and obese are the major risk factors as well as having diabetes (Bearpark et al., 1995; Heinzer et al., 2015; IP et al., 2004; Ip et al., 2001; Young, Peppard, & Gottlieb, 2002a; Young et al., 1997).

1.6.1 Hypertension and cardiovascular disease.

Epidemiological data show that there is a higher prevalence of hypertension among OSA patients than the non-OSA general population (Duran et al., 2001; Young, Peppard, & Gottlieb, 2002a). The prevalence rates of hypertension within the clinical OSA population ranges from 35-70% (Drager, Pereira, & Barreto-Filho, 2006; Kales, Cadieux, Soldatos, et al., 1985b). In normal
healthy individuals, both blood pressure (BP) and heart rate (HR) decrease at sleep onset and decrease progressively through to stage 4 sleep (Somers, Dyken, Mark, & Abboud, 1993). During REM sleep, however, BP returns to wakefulness levels, while HR increases to a level between stable NREM sleep and wakefulness levels (Trinder et al., 2001). In the majority of healthy individuals this leads to an overall average drop in night time versus daytime blood pressure. It has been found that the normal drop in BP and HR that typically occurs rapidly during the period from sleep onset through to stable stage 2 sleep, is retarded by repetitive arousal from sleep (Carrington et al., 2005). Arousal stimuli during non-REM (NREM) sleep also lead to transient increases in BP and HR, (Carrington et al., 2005). Thus, it is believed that sleep fragmentation associated with OSA is a contributing factor to the above average BP levels observed overnight in these individuals (Noda, Okada, Hayashi, Yasuma, & Yokota, 1993; O’Brien, Sheridan, & OMalley, 1988; Somers, Dyken, Clary, & Abboud, 1995). In addition to BP increases due to repetitive arousals in OSA patients, it has been demonstrated that during sleep there is an increase in sympathetic nervous activity and blood pressure during respiratory events (Somers et al., 1995). OSA patients in general are at an increased risk of adverse cerebrovascular events and negative cardiovascular consequences, presumably as a result of strain on the cardiovascular system due to fluctuations in blood pressure during respiratory events and due to repetitive arousals from sleep (O’Brien et al., 1988; Palatini et al., 1992).

Drager, Pererira and Barreto-Filha (2006) found that the best predictors of hypertension among the OSA population were older age, female gender, higher BMI, diabetes and family history of hypertension. Age, however, is also a strong independent risk factor for hypertension. Therefore, determining whether older individuals were more likely to have hypertension as a product of having chronic OSA is difficult. A review of 6 clinical trials showed that treatment of OSA with continuous positive airway pressure (CPAP) produces beneficial reductions in blood pressures, albeit improvement in severe OSA patients was minimal (Robinson, Stradling, & Davies, 2004). Sleep-related or nocturnal
sweating is noted in some OSA patients. It was found in one study that OSA patients who experienced nocturnal sweating had higher BP and less REM sleep than patients who did not experience nocturnal sweating. It was also found that the use of CPAP reduced sweating in these patients (Arnardottir, Thorleifsdottir, Svanborg, Olafsson, & Gislason, 2009). Several studies have found a dose-response trend, with more severe hypertension associated with more severe OSA (Lavie, Herer, & Hoffstein, 2000; Peppard, Young, Palta, & Skatrud, 2000a; Young et al., 1997), while other studies have not found this to be the case (Duran et al., 2001). Data from the Wisconsin cohort suggests that blood pressure appears to plateau at very severe levels of OSA (Young, Peppard, & Gottlieb, 2002a).

During sleep, apnoeas and hypopneas can cause transient elevations in mean arterial blood pressure by 30mmHg or more. It is possible that repeated, nightly swings of blood pressure as a result of respiratory events may lead to a sustained elevation of blood pressure in OSA patients (Fletcher et al., 1995). The sustained elevation could be the result of mechanisms such as chronic elevations in sympathetic tonic activity, altered baroreceptor function, or cardiovascular remodelling.

1.6.2 Obesity, metabolic syndrome, and diabetes.

Obesity is a common risk factor for OSA. Approximately 50% of OSA patients present clinically with obesity (Bearpark et al., 1995; Mortimore, Marshall, Wraith, Sellar, & Douglas, 1998; Young et al., 1993). Young and colleagues (1993) found a three-fold increase in the likelihood of OSA (AHI >5) with an increase of only 1 standard deviation in any measure of body habitus in the Wisconsin cohort study. In their cross-sectional study, Bearpark and colleagues (1995) found obesity to be the most important risk factor for OSA, however, only in those individuals with BMI >30, suggesting a threshold effect. An early study of a clinical population with severe OSA found that 82% were obese and 24% had diabetes (Kales, Cadieux, Bixler, et al., 1985a). As a large proportion of the sleep apnoea patients reported onset of obesity secondary to onset of their hypersomnolence, Kales and associates proposed that this was evidence that, at least in some patients, obesity may be merely a manifestation of
a greater pattern of physiological abnormality underlying OSA, and therefore may not be the direct precipitator of hypersomnolence in these patients but may only be secondarily contributing to it.

Within clinical samples, the association between obesity and OSA is also commonly reported. In a study of morbidly obese patients being considered for bariatric surgery, 93.6% were found to have some degree of OSA (Daltro et al., 2007). There are slight differences in the association between obesity and OSA depending on gender and age. In men with OSA, there is a strong, consistent association found between increasing body mass index (BMI) and OSA severity (Schäfer, Pauleit, & Sudhop, 2002). When BMI is controlled for, however, there appears to be a negative association between OSA severity and age (Bixler et al., 1998). Obesity was found to be a significant risk factor for OSA exclusively in pre-menopausal, and post-menopausal women on hormone replacement therapy (Bixler et al., 2001). Of post-menopausal women not taking hormone replacement therapy, approximately 50% were obese (Bixler et al., 2001). Oestrogen administered to post-menopausal women is associated with reductions in plasma interleukin-6 (IL-6), a cytokine known to be elevated in obesity and individuals with insulin-resistance (Bastard et al., 2000; Vgontzas et al., 2000; 1997). This suggests that there may be a protective effect of oestrogen against OSA through its influence on factors linked to obesity.

Several studies have investigated measures of body habitus and obesity in order to assess whether there are specific patterns of weight gain that are associated with increased risk of OSA. Epidemiological data from the Wisconsin cohort suggested that neck circumference was the strongest predictor of OSA (Young et al., 1993). Schafer and colleagues (2002) performed a cross-sectional study of a clinical population and also reported that percentage body fat, sum of fat skin folds as well as BMI were good predictors of increased AHI. In contrast to the Wisconsin cohort, however, the amount of intra-abdominal fat appeared to be the strongest body habitus correlate with OSA. Li and colleagues (2012) also failed to show a significant difference in neck circumference between overweight OSA patients and non-OSA controls, despite significantly greater volumes of
retropalatal and retroglossal fat deposition. Other studies have also shown that increased pharyngeal fat may not necessarily be reflected in neck circumference. Mortimore and colleagues (1998) used magnetic resonance imaging to show that obese and non-obese OSA patients have significantly greater volumes of fat, especially located anterolateral to the upper airway, than non-obese controls. In a comparison between obese OSA and obese non-OSA controls, Horner and colleagues (1989) also demonstrated using magnetic resonance imaging (MRI) that there was significantly larger fat deposition in the soft palate, tongue and submental regions in the OSA patients (Horner, Mohiaddin, Lowell, Shea, Burman, et al., 1989a). In general the data currently available supports the suggestion that central obesity, rather than more global fat distribution may be the key link between obesity and OSA.

Studies from Asia have found correlations between obesity and sleep disordered breathing at significantly lower average BMI scores than equivalent studies with primarily Caucasian populations (Ip et al., 2004; Ip et al., 2001; Ng et al., 1998). The results suggest that even slightly increased adiposity among Asian individuals may carry a greater risk than in those of Caucasian ethnicity. Li and colleagues (2012) found, using MRI evaluation, that the volume of fat in the soft palate and pharyngeal fat pad in the retropalatal and retroglossal regions were significant predictors of OSA amongst Chinese individuals even at BMI values less than 30. It has been suggested that central obesity increases the collapsibility of the upper airway due to compression and narrowing of the upper airway. Some studies have shown that increased fat deposition in and around the upper airway (UA) does reduce the UA volume (Horner, Mohiaddin, Lowell, Shea, Burman, et al., 1989a; Mortimore et al., 1998), while other studies have not supported this finding (Schäfer et al., 2002). It is most likely, therefore, that differences in airway collapsibility between individuals with OSA and BMI-matched controls cannot be explained by increased retropalatal and retroglossal fat deposition alone. Li and colleagues (2012) also found that in their study of Chinese individuals, those with individuals with positive closing pressures of the upper airway had greater overall volumes of the tongue as well as pharyngeal fat.
pads, suggesting that abnormalities in other upper airway structures also contribute to collapsibility of the retroglossal airway in addition to the pharyngeal fat pad volumes. Interestingly, this increased fat deposition that appears to be associated with OSA was not reflected in significantly larger neck circumferences than in non-OSA individuals. Despite findings that OSA is associated with lower BMI values amongst Asian populations in comparison to white populations, the odds ratio for OSA with an increase of one standard deviation of BMI was greater amongst white individuals compared with Asian individuals (Ip et al., 2004).

Evidence from clinical and community based data consistently shows significant increases in AHI with weight gain and conversely, significant decreases in AHI following weight loss (Peppard, Young, Palta, Dempsey, & Skatrud, 2000b; Young, Peppard, & Gottlieb, 2002a). While the causal relationship between obesity and OSA is well accepted, the exact mechanism by which obesity contributes to the pathogenesis of OSA is less clear. It has been shown that respiratory resistance is significantly increased in obese individuals compared to non-obese individuals in both the non-supine and supine positions (Watson & Pride, 2005; Yap, Watson, Gilbey, & Pride, 1995). Presumably, the increased resistive load in obese individuals predisposes them to airway collapse and development of OSA. It was initially presumed that increased fat deposition in and around the pharyngeal region, including pharyngeal fat pads, tongue and soft palate, places increased pressure on the airway when the patient is supine, thereby narrowing the airway making it more susceptible to collapse. However, other factors may also play a role such as lung volume. Research has shown that functional residual capacity and expiratory reserve volume are reduced, even with only moderate increases in body weight (Jones & Nzekwu, 2006). Zerah and colleagues (1993) importantly showed that although there was an overall increase in respiratory resistance, there was no change in nasal or pharyngeal resistance and no change in chest wall compliance with increasing obesity. They suggested that the biggest factor contributing to the increased respiratory resistance in obesity is therefore, most likely the result of a higher resting
diaphragm position, leading to lower functional residual capacity. Supporting this suggestion, Stadler and colleagues (2009) found that experimental abdominal compression in obese OSA patients led to increased collapsibility of the upper airway, but no change in upper airway resistance.

The association between OSA and obesity is complex. Evidence from epidemiological and clinical samples has clearly highlighted obesity as potentially the most important risk factor for OSA. Recent research suggests that obesity may not only contribute to OSA, but that OSA also contributes to weight gain and may in fact lead to worsening of obesity. Hormonal changes have been associated with OSA as outlined below. In recent years, greater recognition has been given to the relationship between SDB and impaired glucose metabolism. In a large-scale study of community-dwelling adults it was found that sleep disordered breathing is associated with glucose intolerance and insulin resistance independent of age, gender, BMI, smoking status and self-reported sleep duration (Punjabi, 2004). Typically insulin acts to suppress the appetite, thus insulin resistance can lead to weight gain. Studies have shown that successful treatment with CPAP can improve insulin sensitivity in non-diabetic men (Lam, Lam, Yao, & Lai, 2010). It has been suggested that elevated sympathetic activity, or intermittent hypoxia may be responsible for the development of insulin resistance in OSA patients, however, the exact mechanism by which OSA leads to insulin resistance is still unclear.

Leptin is a hormone produced primarily by adipose tissues that is important for signalling satiety and thus a reduction in appetite and weight loss. There is evidence of abnormal leptin and ghrelin regulation in OSA patients (Harsch, Konturek, & Koebnick, 2003). Leptin levels are high in obese patients, despite the weight loss promoting effects, and it has therefore been suggested that obesity involves an abnormal resistance to the metabolic effects of leptin (Caro, Sinha, Kolaczynski, Zhang, & Considine, 1996). In their study, Phillips and colleagues (2000) found that plasma leptin levels are higher in OSA patients than similarly obese individuals without OSA. Eight weeks of CPAP use led to a decrease in plasma leptin to normal levels, without any concurrent change in
BMI in a sample of OSA patients (Harsch et al., 2003). It appears that OSA is associated with leptin resistance independently of abnormal leptin resistance seen in obesity alone; however, the mechanism by which this occurs is still unclear. Ghrelin is another, more recently identified, hormone involved in metabolic regulation; acting to stimulate the appetite. Research has shown ghrelin levels to be elevated in OSA patients. Elevated ghrelin levels in OSA patients have shown to decrease significantly following only 2 days of CPAP use (Harsch et al., 2003). Ultimately, the leptin resistance, elevated ghrelin levels and low physical activity due to fatigue and daytime sleepiness likely predisposes OSA patients to weight gain.

Metabolic syndrome refers to a cluster of at least three of the following five medical conditions: abdominal (central) obesity, elevated blood pressure, elevated fasting plasma glucose, high serum triglycerides, low high-density lipoprotein (HDL) levels. It has been identified as a risk factor for the development of cardiovascular disease and type II diabetes, and has several overlapping aspects with insulin resistance. While the cause of metabolic syndrome is still unclear, it is believed to be a disorder of energy utilisation and storage.

Epidemiological data shows an association between sleep disordered breathing and type II diabetes. Data from the Wisconsin cohort demonstrated an independent relationship between diabetes and SDB even after controlling for age, gender and body habitus (Reichmuth, Austin, Skatrud, & Young, 2005). Cross-sectional analysis showed that approximately 15% of OSA patients had diabetes and prevalence rates increased with increasing levels of OSA severity, with diabetes being three to four times more prevalent in individuals with more than fifteen events per hour in comparison to individuals with less than five events per hour of sleep (Reichmuth et al., 2005). In an Australian population, individuals with moderate to severe OSA were 2.13 times more likely to have diabetes than individuals without OSA after controlling for age, gender and waist circumference (Marshall et al., 2009). Data from the Sleep Heart Health Study, however, suggested that diabetic individuals at risk of cardiovascular
disease were not more likely to have sleep disordered breathing than non-diabetic individuals after controlling for obesity and other risk factors (Resnick et al., 2003). Although diabetes is often preceded by insulin resistance and glucose intolerance the subsequent development of diabetes is not guaranteed. A longitudinal study in Sweden showed that obese, male habitual snorers were 1.4 times more likely to develop diabetes during a 10-year period than obese non-snorers (Elmasry et al., 2000). The specificity of snoring as a symptom indicative of OSA is low, and in fact, longitudinal data from the Wisconsin cohort, assessed, at both 4 and 8 years, did not suggest that OSA plays a causal role in the development of diabetes (Reichmuth et al., 2005). While it does appear from various research studies that OSA can lead to abnormal insulin resistance and glucose tolerance, there may be another independent factor, such as a genetic predisposition, that is necessary for insulin secretion to falter completely and for diabetes to develop.
Chapter 2  Pathophysiology, Disease Progression and Treatment of OSA

2.1  Pathophysiology of OSA

Early studies endeavoured to identify the exact site of airway collapse during an apnoeic episode using a variety of different measurement techniques. An early study using fiberoptic imaging of the airway in 17 OSA patients demonstrated that invagination of the posterolateral walls of the oropharynx appeared to initiate a hypopnoeic event. Complete apnoeic obstruction would occur when there was also caudal movement of the tongue (Guilleminault, Hill, Simmons, & Dement, 1978). Another fiberoptic imaging study, showed consistent findings in 10 OSA patients. Video-fluoroscopy in this study showed that the invagination of the posterolateral walls of the pharynx consistently made contact at the level of the velopharyngeal sphincter, involving the superior constrictor, the palatopharyngeus, levator palatini, and muscularis uvulae, thus obstructing the nasal airway. Simultaneous upward and posterior movement of the tongue led to closure of the oral airway, and complete obstruction of respiration (Borowiecki, Pollak, & Weitzman, 1978). Suratt, Dee, Atkinson, Armstrong and Willhoit (1983) later demonstrated consistent findings regarding the site of collapse via fluoroscopy. Their results showed collapse of the airway specifically during inspiratory effort leading to the suggestion that obstruction occurs due to subatmospheric pressure in the already narrowed airway of OSA patients. Later studies used pressure measurements at different points along the airway (between the nose and lower portion of the oesophagus) to assess the site of airway collapse. The results showed that the site of collapse in approximately 50% of OSA patients is at the level of the soft palate, but for the remaining 50% of patients collapse occurs more caudally toward the epiglottis, behind the tongue (Chaban, Cole, & Hoffstein, 1988; Hudgel, 1986). Computed tomography (CT) and cine (ultrafast) CT imaging also showed that the site of airway collapse was at the level of the soft palate and uvula in approximately 50% of patients, but in the other half of patients the site of collapse extended lower to the hypopharynx (Horner, Shea, McIvor, & Guz, 1989b; Stein et al., 1987). From these early imaging studies it was generally accepted that the site of upper airway collapse
in OSA patients occurs in the oropharynx, either at the level of the soft palate, or at the base of the tongue. It was argued that knowing the location of airway collapse would help to identify the factors that influence the integrity of structures in this anatomical region. Research into the pathogenesis of OSA could then be more targeted, however, the exact mechanisms remain unclear.

Amongst the OSA population, there is a wide spectrum of severity and symptoms. Younes and colleagues (2001) explain that at the mild end of the spectrum, patients experience habitual snoring with infrequent respiratory events, causing sporadic interruptions in breathing and sleep with fairly mild oxygen desaturations. At the severe end of the spectrum, patients experience extremely frequent and disruptive respiratory events with large fluctuations in oxygen levels and considerable sleep fragmentation. Yet other patients experience respiratory events only when in a specific position, or stage of sleep. There are now several mechanisms known to play a role in the development of OSA, and the wide variation in severity and symptom presentation amongst OSA patients is suspected to be due to the relative contribution of each affected mechanism in a given patient.

2.1.2 Narrowed upper airway anatomy and increased upper airway resistance.

All humans have a potentially collapsible upper airway as there is no bony support in contrast to other animals. However, the key to understanding the pathogenesis of OSA lies in understanding why the oropharyngeal airway of OSA patients has a higher propensity to collapse during sleep than in normal healthy individuals. Computed tomography (CT) and cine CT imaging has shown that in general the cross-sectional area of the upper airway is narrower in OSA patients, and in particular there is a significantly smaller cross-sectional area at the level of the soft palate (Bohlman et al., 1983; Horner, Shea, McIvor, & Guz, 1989b; Stein et al., 1987). Isono and associates (1997) found that patients with sleep disordered breathing had significantly lower pharyngeal cross-sectional areas for any given luminal pressure than healthy controls under anaesthetic. Due to many OSA patients being overweight or obese, it is
suggested that increased pharyngeal fat pads can compress and narrow the upper airway (Koenig & Thach, 1988). Interestingly, CT imaging in one study of severe OSA patients showed that obese non-OSA controls did not have the same degree of airway narrowing as obese OSA patients, but failed to show significant differences in fat deposition around the airway (Bohlman et al., 1983). The same study did show, however, that in obese OSA patients several structures of the upper airway were abnormally enlarged, including the tongue, adenoids, mucous membranes and lymphoid tissues in comparison to obese non-OSA individuals. There are several anatomical conditions that are also thought to contribute to a narrow airway and could predispose some patients to develop OSA. These include micrognathia, tonsillar enlargement, acromegaly or muscular swelling/fat infiltration of the tongue, and enlargement of the uvula (Wheatley & Amis, 1998). Physical abnormalities in the nose may also contribute, such as a deviated septum, nasal polyps, or inflammation of the nasal mucosa seen with allergies, and rhinitis (Ingbar & Gee, 1985). Regardless of the cause, the general consensus is that OSA patients have a significantly narrower upper airway than healthy individuals (Akpinar, Çelikoyar, & Altundag, 2011; Chen et al., 2002; Hudgel, 1986; Rowley & Sanders, 2002).

One of the consequences of UA narrowing is an increased resistance to airflow. Resistance across the length of the airway is affected by the size of the lumen. A 50% decrease in lumen diameter will cause a 16 fold increase in resistance, however, doubling the length of the airway will only double the resistance (West, 2012). During wakefulness, OSA patients show a significantly higher baseline UA resistance (RUA) than normal healthy individuals (Choi, Goldman, Koyal, & Clark, 2000). It is normal for there to be an increase in RUA at the transition from wake to sleep in healthy individuals and a progressive increase across NREM sleep (Kay, Trinder, & Kim, 1995; Tangel, Mezzanotte, & White, 1991). While resistance measurements are difficult during airway obstruction (impossible during apnoea) and therefore during sleep in OSA patients, some studies have shown that there is a significantly greater increase in RUA during sleep in OSA patients than in normal healthy controls (Choi et al.,
It is known that increased upper airway resistance predisposes the airway to collapse in OSA patients (Kuna, 1991; Suratt, McTier, & Wilhoit, 1985).

In addition to anatomical narrowing of the airway due to increased fat deposition or increased size of pharyngeal structures, head and jaw position can affect the size of the upper airway lumen and thereby affect upper airway resistance. Choi and colleagues (2000) found that with flexion or extension of the neck, upper airway resistance was significantly increased in both healthy controls and OSA patients, whereas jaw protrusion significantly decreased upper airway resistance. Age also appears to influence the upper airway resistance. Eikermann and Jordan (2007) found that in elderly healthy non-OSA individuals, there was a greater increase in RUA at sleep onset than in young healthy non-OSA individuals. White, Lombard, Cadieux and Zwillich (1985) had previously identified that pharyngeal resistance correlated with age in men, but not in women.

2.1.3 Increased upper airway collapsibility.

The key characteristic that defines OSA is the repetitive pattern of partial or complete collapse of the upper airway during sleep. The UA extends from the posterior end of the nasal septum to the epiglottis (White, 2005). Figure 1 shows the three major divisions: the nasopharynx, the oropharynx and the hypopharynx. When assessing the factors that contribute to the collapsibility of the upper airway in OSA patients, the model of a collapsible tube contained with a sealed container is typically used. This model has been outlined by Gold and Schwartz (1996). It proposes that the upper airway acts as a collapsible tube that is open at one end (via the nose and mouth) and is contained within a sealed container (the bones, fat and tissues surrounding the upper airway within the neck). If the pressure surrounding the UA is greater than the pressure within the UA, it will collapse. Changes in pressure at one end of the tube lead to a change in pressure gradients across the tube. Thus, the pressure of the air within the lumen of the UA is variable, whereas the pressure within the sealed container surrounding the UA is constant, and reliant on the density and other characteristics of the bony, muscular and fatty structures in the neck. If the
intraluminal pressure is lower than the pressure outside the UA the airway will begin to flutter and close. For the airway to remain patent the intraluminal pressure must be greater than the pressure of the tissues in the neck.

*Figure 1.* The upper airway is divided into three major sections: the nasopharynx, the oropharynx and the hypopharynx.

The level at which the pressure outside the tube exceeds the pressure inside the tube and the tube snaps shut, is known as the critical closing pressure (Pcrit). During inspiration the external intercostal muscles pull the rib cage up and out while the diaphragm muscles pull downwards, thereby increasing the volume in the pleural cavity. Increasing the volume of the pleural cavity causes a sharp decrease in the intraluminal pressure of the airway. This leads to a sudden drop in pressure at the internal end (the region of the airway below the epiglottis) of the upper airway. Thus, the airway will collapse (Pcrit is reached) when the inspiratory pressure falls below the extraluminal pressure exerted by the tissues in and around the upper airway. Because Pcrit is equal to the pressure required
to collapse the airway it is therefore an index of airway collapsibility, with higher values indicating a more collapsible airway.

Upper airway collapsibility varies along a continuum from low (normal healthy breathing patterns) to high (disordered breathing patterns). As Pcrit values increase there is a progressive limitation to the amount of airflow through the upper airway during sleep. OSA patients have been shown to have significantly higher closing pressures than normal healthy controls (Jordan et al., 2007). It has also been demonstrated in several studies that Pcrit values are significantly higher in snorers with OSA than in non-snorers (Gleadhill et al., 1991; Issa & Sullivan, 1984a; 1984b). Thus, OSA treatment focuses on reducing airway collapsibility via reductions in Pcrit.

Kirkness and colleagues (2011) assessed both within-night and between-night variability in Pcrit in a sample of severe OSA patients. The data showed that there were no significant within- or between-night differences in Pcrit, indicating that Pcrit appears to remain stable within the individual. Nevertheless, it appears that for any given degree of BMI, men appear to have a higher Pcrit than women (Jordan et al., 2005). Despite well-noted decreases in event frequency during SWS compared with stage 2 sleep, there is no evidence to suggest that this is due to sleep-state-related changes in Pcrit (Ratnavadivel et al., 2010).

The collapsibility of the UA is primarily affected by two major collapsing forces: intraluminal negative pressure and extraluminal positive pressure. Lung volume and mediastinal traction contribute to UA collapsibility. It has been demonstrated in various animal studies that during inspiration, the trachea moves caudally. This caudal tracheal traction increases the tension longitudinally across the upper airway causing it to stiffen and help maintain airway patency as well as decrease the critical closing pressure of the airway (Thut et al., 1993; Van de Graaff, 1991). The lungs and upper airway are therefore linked mechanically, and alterations in lung volume affect the collapsibility of the upper airway.
Koenig and Thach (1988) found that in anaesthetised rabbits, mass loading of the neck, designed to mimic increased cervical fat deposition seen in obesity, led to increases in $P_{crit}$. Importantly, their findings showed that even small increases in upper airway loading could influence the critical closing pressure. In obese OSA patients it is possible that increased neck or abdominal fat deposition is a major contributing factor to increased extraluminal pressure and upper airway collapsibility. Stadler and colleagues (2009) showed that in a sample of obese, moderate to severe OSA patients, abdominal compression significantly increased $P_{crit}$ and upper airway collapsibility. Other studies have shown that using an iron lung to increase extrathoracic pressure and thereby reduce lung volume led to increases in $P_{crit}$ (Heinzer et al., 2005; Stanchina, Malhotra, Fogel, & Trinder, 2003). Thus, abdominal compression may increase airway collapsibility via changes in $P_{crit}$ resulting from changes in lung volume. It was not possible to determine from the experimental methods used in these studies whether abdominal compression led to increased $P_{crit}$ via mechanical (reduced lung volume lowering mediastinal traction) or hemodynamic effects or increased oedema around the UA.

In non-obese patients there can also be an increase in extraluminal pressure due to crowding of pharyngeal structures, such as enlarged tonsils or adenoids. There are other factors that affect the UA pressure, including vascular perfusion, airway secretions, posture and tissue microstructure (White, 2005). Of these, the factor of greatest importance is postural change. When moving from an upright to supine posture the tongue and other palatal structures move posteriorly as a result of gravitational force leading to increased positive pressure on the upper airway. Increasing age has also been linked to increasing $P_{crit}$ (Eikermann et al., 2007). Eikermann and colleagues (2007) speculate that diminished negative-pressure reflex and muscular response in the elderly may predispose the airway to collapse due to failure of the dilating forces that typically oppose collapsing forces exerted on the upper airway. In support of this suggestion Pierce and colleagues (2007) found a direct correlation between $P_{crit}$ and both awake and asleep levels of muscle activity of the major airway dilator muscles.
The collapsing pressures exerted on the upper airway are counteracted by several factors. The major opposing force is that of the UA dilator muscles (Fogel, Malhotra, & White, 2004; Pierce et al., 2007). Several dilator muscles respond reflexively to fluctuations in upper airway resistance, and changes in blood gas concentrations of oxygen (O\textsubscript{2}) and carbon dioxide (CO\textsubscript{2}) to maintain airway patency. Changes in the magnitude or timing of these reflex responses can contribute to UA collapsibility.

2.1.4 Poor upper airway muscle responsiveness.

Research targeting oropharyngeal muscles in the pathogenesis of OSA has focused on both tonic muscles and phasic muscles. Tonic muscles show a consistent basal level of activity that is not modulated by changes in respiration. The most widely researched tonic muscle is the tensor palatini (TP), which stiffens the palate such that other muscles including the levator palatini can move the palate as a single unit away from the posterior pharyngeal wall. Alternatively, phasic muscles show activation that is coordinated with phases of the respiratory cycle and include the genioglossus, palatoglossus, palatopharyngeus. The most widely researched phasic muscle is the genioglossus (GG) muscle, which is the major extrinsic muscle of the tongue, and when activated causes anterior movement (protrusion) of the tongue. The GG muscle is considered to be an inspiratory phasic muscle, meaning that peak GG activation is seen during inspiration. More recent research has shown that the TP and GG actually contain motor units with a variety of discharge patterns; including some that only fire at certain parts of the respiratory cycle as well as others that fire continuously and either modulate their speed with the respiratory cycle or not: tonic, inspiratory phasic, expiratory phasic, inspiratory tonic and expiratory tonic (Nicholas et al., 2012; Saboisky et al., 2006). Although each of these muscles contains all of the different types of motor units, the TP has a high proportion of tonic motor units and is considered to be representative of a tonic muscle, while the GG has a high proportion of phasic motor units and is considered to be representative of a respiratory phasic muscle.
Early electromyographic (EMG) studies showed that, during obstructed sleep in OSA patients, there were significant decreases in the activity of the UA dilating muscles including the palatoglossus, palatopharyngeus, genioglossus compared with normal healthy individuals (Guilleminault et al., 1978). In normal, healthy individuals, it was noted that increases in retropalatal airway resistance were associated with decreases in TP activity across non-rapid eye movement (NREM) sleep stages. This observation led to the suggestion that the TP potentially played a pivotal role in the maintenance of upper airway patency (Tangel, Mezzanotte, & White, 1991). In support of this theory, it has been demonstrated that TP activity decreases at sleep onset in normal healthy individuals (Mezzanotte, Tangel, & White, 1996; Tangel, Mezzanotte, & White, 1991; Worsnop, Kay, Pierce, Kim, & Trinder, 1998). Later studies, however, have demonstrated that the TP EMG activity decreases progressively across the first twenty breaths after sleep onset until plateauing at approximately 60% of the baseline activity seen during wakefulness (Worsnop et al., 1998). Furthermore, when resistive loading has been applied to the upper airway, low correlations have been demonstrated between changes in TP EMG activity and changes in nasopharyngeal resistance across the sleep-wake cycle. Despite greater activation of the TP during wakefulness and a greater decrease in TP activity at sleep onset in OSA patients than in normal healthy subjects (Mezzanotte et al., 1996), the lack of TP augmentation in response to local stimulation suggests that the TP alone is not responsible for the maintenance of airway patency (Malhotra et al., 2000).

Sleep-related changes in GG EMG activity have been extensively researched. In normal healthy individuals when awake and supine, the GG typically has tonic activation, as well as inspiratory phasic activation (Sauerland & Harper, 1976). At sleep onset, however, there is a dramatic drop in activation, with even greater reductions during REM sleep (Horner, 2000; Mezzanotte et al., 1996). At sleep onset and during non-REM sleep the tonic activity is reduced with minimal subsequent change until a return to a state of wake (Worsnop et al., 1998). At the transition from wake to sleep there is also a drop in phasic GG activity. Within
five breaths, however, the level of activity returns to that seen during quiet wakefulness indicating that the muscle has undergone recruitment. This is presumably a response designed to maintain airway patency in the face of increasing resistance and rising levels of CO₂ in the blood (Worsnop et al., 1998). Studies have also shown that the GG in particular maintains the ability to adapt to changes in respiratory loading during sleep (Tangel, Mezzanotte, Sandberg, & White, 1992). Based on these, and similar findings, it is now generally accepted that the main muscle capable of increasing activity to maintain airway patency during sleep is the GG, rather than the TP.

Patients with OSA have greater activation of the GG during wakefulness than healthy individuals (Mezzanotte, Tangel, & White, 1992). Inspiratory activation of the GG has been shown to depress the tongue and move it anteriorly, which produces enlargement of the pharyngeal space (Tortora & Grabowski, 2000). Greater activation during wakefulness, therefore, is presumably a compensatory mechanism that maintains patency in the already narrowed airway as the application of CPAP can reduce the level of activation to a level observed in non-OSA patients (Mezzanotte et al., 1996). At sleep onset, however, the reductions in GG EMG activity in OSA patients are even greater than the reductions seen in healthy individuals (Fogel et al., 2004; Remmers, DeGroot, Sauerland, & Anch, 1978; Saboisky et al., 2007). As a result, the baseline level of activity and effectiveness of GG muscle activation to counteract the collapsing forces on the UA during sleep are significantly reduced in OSA patients.

Understanding the role that the GG muscle plays in the pathophysiology of obstructive sleep apnoea requires an understanding of the various stimuli that modulate GG activity. There are three major neural input pathways of relevance to OSA that influence the activity of the GG. These include state-dependent neural processes, respiratory-related influences and reflex activation. The “wakefulness stimulus” refers to the activity of serotonergic or noradrenergic neurons that cause tonic excitation of hypoglossal motoneurons (Fogel et al., 2003; Jelev, Sood, Liu, Nolan, & Horner, 2001; Orem & Trotter, 1992). Output
from the hypoglossal motoneurons leads to increased activation of the GG muscle (Fenik & Veasey, 2003; Kubin, Tojima, Davies, & Pack, 1992). The respiratory pattern generator comprises neurons located in the medulla, which send excitatory signals to the hypoglossal motoneurons during inspiration, thus leading to increased GG activation that is influenced by the pattern of respiration (Horner, 2000). The negative pressure reflex also modulates GG activity. Negative pressure generated during inspiration causes activation of mechanoreceptors in the larynx. This reflex activation leads to increased activity of the afferent superior laryngeal nerve, which in turn leads to an increase in hypoglossal output to the GG muscle (Horner, Innes, Murphy, & Guz, 1991; Mathew, Abu-Osba, & Thach, 1982a; 1982b).

Change in negative pressures within the upper airway is believed to be the critical stimulus for the respiratory modulation of the GG muscle (Malhotra et al., 2000). A study of tracheostomized OSA patients demonstrated increased GG activity during nasal breathing awake, in comparison to breathing through a tracheal stoma, albeit not a statistically significant difference. By observing GG modulation during nasal breathing versus tracheal stomatic breathing, it is possible to isolate negative pressures detected by upper airway receptors specifically (Malhotra et al., 2000). In OSA patients, it is believed that the activation of the upper airway dilator muscles during sleep is insufficient to oppose the negative pressure generated during inspiration against a narrowed airway (Remmers et al., 1978). Past research has shown that in healthy individuals there is a marked decrease in the degree of negative pressure reflex activation as well as increased latency of response during NREM sleep in both the TP and GG muscles (Horner, Innes, Morrell, Shea, & Guz, 1994; Mezzanotte et al., 1996; Wheatley, Tangel, Mezzanotte, & White, 1993). Thus, it was believed that attenuation of the negative pressure reflex during sleep, and corresponding reduced respiratory modulation of GG activity, may be partly responsible for increased upper airway collapsibility.

A recent study by Eckert and colleagues (2007), suggests that the observed latency of reflex activation in past research may be due to methodological
techniques that smooth the EMG recording for analysis. This EMG smoothing technique tends to distort short latency reflex components (Eckert, McEvoy, George, Thomson, & Catcheside, 2007). Eckert and colleagues performed analysis without employing these smoothing techniques and observed no difference in the latency of the GG negative pressure reflex between untreated OSA patients and healthy controls during wake (Eckert et al., 2011b). Their findings demonstrated evidence of shorter latencies to GG fatigue in OSA patients than healthy controls. This observation led them to suggest that in untreated OSA patients GG muscle fatigue coupled with vulnerable upper airway anatomy may contribute to UA collapsibility.

In their study utilising respiratory-related evoked potentials, Eckert, Lo, Saboisky and colleagues (2011b) attempted to clarify the role of respiratory-related neural and reflex processing in the pathogenesis of OSA. The study showed that in awake, untreated OSA patients the reflex activation of the GG muscle in response to negative pressure pulses remained intact. The component of the evoked potential representing sensory processing, however, was slightly delayed in OSA patients compared with healthy controls. The authors suggest that this delay could be interpreted to mean that there is cognitive impairment resulting from hypoxia or sleep fragmentation/deprivation in OSA patients. They further speculate that, should the delay continue to be present during sleep, that this delay might lead to altered neural responses to respiratory stimuli. Delays in reflexive neural processing in OSA is therefore a possible factor in OSA pathogenesis.

An alternative cause of decreased UA muscle activation may be due to poor contractile strength, atonia or myopathy of the upper airway muscles suggesting an organic or mechanical problem with the upper airway muscles themselves. The study by Eckert and colleagues (2011b) showed that short-term peak GG activation in awake OSA patients actually exceeded that seen in normal healthy individuals, they also showed shorter latencies to muscle fatigue. Despite these findings, it has been found that submental transcutaneous stimulation of the muscle does not effectively relieve OSA (Edmonds, Daniels, Stanson, Sheedy, &
It was suggested that submental, transcutaneous stimulation of the GG causes such widespread activation, that both protruders and retractors may be simultaneously activated or may not be synchronized with the respiratory phase (Horner, 1996). Several clinical trials of implanted targeted hypoglossal nerve stimulators have shown improvement in OSA severity (Eastwood et al., 2011; Mwenge, Rombaux, Dury, Lengelé, & Rodenstein, 2013; Strollo et al., 2014; Van de Heyning et al., 2012). At six-months post implantation in one study, the AHI had reduced by approximately 50% (Eastwood et al., 2011). A study that investigated the effects in moderate to severe (AHI ≤50), non-obese OSA patients, without complete concentric airway collapse showed a reduction in AHI of 74.3% at six-months post implantation (Van de Heyning et al., 2012). At twelve-months post implantation in another study, the mean AHI had decreased by 53% in moderate to severe, non-obese OSA patients (Mwenge et al., 2013). In a much larger study of 126 moderate to severe OSA patients, median AHI score had decreased by 68% at twelve months post implantation (Strollo et al., 2014). The hypoglossal nerve stimulation, however, did not cure the OSA in all of these patients. The evidence suggests that for a large proportion of OSA patients, the upper airway muscles and their control systems remain relatively intact, therefore, it is unlikely that poor muscle activation is the major pathological mechanism responsible for the development of OSA. It may be, rather, that other factors cause the airway to be vulnerable in OSA patients and the UA muscles are simply unable to compensate sufficiently to counteract collapsing airway forces or re-open the airway following collapse.

2.1.5 Lung volume.

In adults lung volume is decreased when in a supine position compared to lung volume in an upright position (Hudgel & Devadatta, 1984). Upon the transition from wake to sleep, functional residual capacity has also been shown to decrease (Ballard et al., 1990; Owens, Malhotra, Eckert, White, & Jordan, 2010). Decreases in lung volume below end-expiratory lung volume (EELV) have been
shown to decrease the size of the pharyngeal lumen (Hoffstein, Zamel, & Phillipson, 1984), and to increase pharyngeal resistance (Series, Cormier, & Desmeules, 1990). Decreases in lung volume have also been shown to increase Pcrit (Owens et al., 2010; Stanchina et al., 2003). Importantly, these changes in lung volume have a greater impact on the airway size of OSA patients than non-OSA patients (Hoffstein et al., 1984). The decreased lung volume seen following the transition from wake to sleep is, therefore, a likely factor contributing to airway collapse during sleep in OSA patients.

Obese individuals demonstrate significantly reduced lung volumes with increasing BMI (Zerah et al., 1993). In a study of obese male OSA patients, abdominal compression significantly decreased lung volumes and increased Pcrit (Stadler et al., 2009). It is likely that due to a more rostral resting placement of the diaphragm, there is reduced tracheal traction during lung inflation, thereby contributing to the collapsibility of the upper airway during sleep. Whether the decrease in lung volume in obese patients is significantly greater than the decreases in lung volume seen in healthy individuals is unclear. A study in which lung volume was experimentally increased using an iron lung, however, showed that increases in lung volumes were more effective at reducing OSA severity in more obese OSA patients (Heinzer et al., 2006).

Not only does reduced lung volume contribute to collapsibility of the upper airway due to the direct mechanical link between the upper airway and the lungs, but reduced airflow and hypoxemia that occurs with lower lung volumes may also contribute to OSA. At higher lung volumes, the stores of O$_2$ are greater, which may provide a buffer against blood gas disturbance, thereby stabilising the ventilatory control system and protecting against cyclical breathing (Younes, Ostrowski, Thompson, Leslie, & Shewchuk, 2001). Increases in EELV using an iron lung resulted in a decrease in ODI in obese OSA patients. The improved oxygenation may in this situation may reduce the effects of oxygen saturation fluctuations and stabilise respiratory control (Heinzer et al., 2006).

Lung volume clearly has a role in the pathogenesis of OSA, and in particular in obese OSA patients. Owens and colleagues (2010) found that Pcrit
was decreased by approximately 3cmH2O when lung volume was increased by only 500mL. Heinzer and colleagues (2006) also showed that the AHI could be reduced with increases in lung volume due to applied negative pressure in an iron lung, however, the improvement in AHI was not significantly greater than the improvements seen with continuous positive airway pressure alone. Despite studies showing improved oxygen saturation, improved airway stability and reduced OSA severity with increased lung volumes, there is not a significantly greater therapeutic benefit of increasing lung volumes than the improvement seen with CPAP.

2.1.6 Ventilatory control instability.

Control of ventilation during quiet wakefulness and NREM sleep is predominantly involuntary. The regulation of ventilation is designed to maintain oxygen and carbon dioxide levels within fairly narrow limits and is largely driven by chemical and metabolic stimuli in negative feedback loops (Ingbar & Gee, 1985; Weiner, Mitra, & Salamone, 1982). Thus, the primary stimuli are the partial pressure of oxygen and carbon dioxide detected by peripheral chemoreceptors in the carotid and aortic bodies. Another major stimulus for ventilation is the pH of extracellular fluid and partial pressures of carbon dioxide, which are detected at the ventrolateral surface of the medulla. When changes are detected in these blood gas concentrations, respiratory drive is altered in order to restore imbalances to a homeostatic set point which differs depending on the state of wakefulness or sleep (Richardson & Bailey, 2010). Hypercapnia has been shown to double ventilatory output and increase GG muscle activation in awake, healthy individuals (Richardson & Bailey, 2010). During sleep, however, the CO2 set point rises and the ventilatory control mechanisms are driven mainly by CO2 centrally, while peripheral CO2 response is attenuated (Douglas, White, Pickett, Weil, & Zwillich, 1982a; Douglas, White, Weil et al., 1982b). As a result, at sleep onset there is a reduction in ventilation (Trinder, Whitworth, Kay, & Wilkin, 1992) as well as reductions in the ability to respond to fluctuations in CO2 levels with changes in respiratory effort during sleep.
The ventilatory control mechanism, like any feedback system can lose stability. The engineering concept of loop gain is commonly used to describe the fluctuations in the ventilatory control system output. High loop gain is seen when there is a large and rapid response, while low loop gain yields a much slower and weaker response to a given perturbations in blood gas levels. Thus, high loop gain indicates a highly unstable neural circuit, while low loop gain indicates a highly stable neural circuit (Younes et al., 2001). The loop gain of the ventilatory control system has two primary influences: controller gain (chemoresponsiveness) and the plant gain (the effectiveness of a unit of change in ventilation). Instability in the system can occur when there is a delay between the sensory arm of the system (chemoreceptors) and the effector portion of the system (the lungs) or when the response becomes excessive (high loop gain) (White, 2005). This means that in individuals with high loop gain, there is a large increase in respiratory drive following the termination of respiratory event that may lead to an overshoot and hyperventilation after arousal from sleep. This may lead to excessive reductions in CO₂ levels predisposing to further respiratory events and thus causing repetitive cyclical apnoeas.

Recent studies have identified high loop gain in OSA patients (Hudgel, Gordon, Thanakitcharu, & Bruce, 1998; Younes et al., 2001). In particular, Younes and colleagues (2001) found that high loop gain was associated with more severe OSA. Although high loop gain was identified in OSA patients, in these, and later studies, it was found that high loop gain alone did not produce periodic breathing. Wellman and colleagues (2004) showed that there was only an association between high loop gain and AHI in patients whose Pcrit was at or near atmospheric pressure. Thus for ventilatory control instability to lead to airway obstruction there needs to be an underlying predisposition to airway collapse. Therefore, the contribution of ventilatory control instability to the pathogenesis of OSA in a given individual is likely related to the degree of collapsibility and anatomic properties of their upper airway.
2.1.7 Respiratory arousal threshold.

Despite upper airway muscle augmentation in response to chemical and mechanical stimuli during sleep this neuromuscular compensation is usually incomplete or insufficient to re-establish normal respiration during a respiratory event in OSA patients. Therefore, as a final compensatory mechanism, respiratory events are often terminated by an arousal or a micro-arousal from sleep. These arousals were historically thought to be life-saving events as they allow the airway to re-open and for blood-gas disturbances to be corrected. It was unclear what mechanism occurring during a respiratory event led to arousal. It was initially believed that during a respiratory event chemoreceptors would detect the decreasing levels of oxygen, and increasing levels of carbon dioxide in the blood that would initiate an arousal response once a critical threshold was reached. Further research in dogs, however, showed hypoxia to be a relatively poor arousal stimulant. Hypercapnia appeared to be a more potent stimulus for arousal than hypoxia, however, the addition of resistive loading greatly increased the likelihood of an arousal response (Berry & Gleeson, 1997). It was found that, in healthy individuals, arousal occurred more consistently at a given level of intrathoracic negative pressure during attempted inspiration as opposed to given levels of other respiratory stimuli (Gleeson, Zwillich, & White, 1990). Thus, the stimuli eliciting arousal is thought to be respiratory effort and the index of arousal threshold is described as the maximal respiratory effort, typically measured as the maximal negative epiglottic (or eosophageal) pressure (Pepi), on the final breath prior to the termination of a respiratory event by arousal from sleep.

Several factors in addition to homeostatic chemical and mechanical stimuli can affect the frequency of arousals and the arousal threshold. The sleep fragmentation or deprivation associated with OSA has been suggested to increase the arousal threshold (Berry, Kouchi, Der, Dickel, & Light, 1996). OSA severity is associated with arousal threshold in that the arousal threshold has been found to be higher as AHI increases (Eckert & Younes, 2014). It is likely that the increased sleep pressure due to sleep fragmentation in the severe OSA
patients leads to greater respiratory effort required to initiate arousal from sleep. In support of this postulation is the common finding that CPAP therapy reduces arousal threshold (Berry et al., 1996; Haba-Rubio, Sforza, Weiss, Schröder, & Krieger, 2005; Loewen, Ostrowski, Laprairie, Gnietecki, & Younes, 2009). The frequency of arousals in healthy men in response to applied resistive loads has been shown to vary depending on sleep stage (Gugger, Bogershausen, & Schaffler, 1993). Gugger and colleagues (1993) demonstrated a significant increase in arousal frequency to such loads during REM in comparison to NREM sleep and decreasing frequency of arousal responses across the stages of NREM sleep. Studies that have measured the arousal threshold show consistent findings with a progressive increase in arousal threshold across stage 2 to SWS (Ratnavadivel et al., 2009). Arousal threshold was also found to be considerably lower in REM and stage 1 sleep than in stage 2 and SWS (Eckert, Jordan, & Malhotra, White & Wellman, 2011a). Despite several homeostatic, circadian and sleep-state dependent influences on arousal threshold across the night (R. Berry & Gleeson, 1997; Sforza & Krieger, 1999) the majority of untreated OSA patients have a higher arousal threshold than normal healthy individuals (Berry & Gleeson, 1997; Jordan et al., 2007).

It has recently been suggested that arousals that commonly occur at the termination of respiratory events may actually play a role in perpetuating obstructive sleep apnoea, at least in some OSA patients. Younes (2004) found that in some instances, OSA patients were able to re-open the airway prior to arousal, and that arousal did not always occur at the termination of a respiratory event. The suggestion was made that in response to the build-up of blood-gas imbalances during a respiratory event the patient will hyperventilate at arousal. On return to sleep the drive to the genioglossus muscle will be lower than normal due to hypocapnia following the event, thereby predisposing the airway to collapse on return to sleep (Younes, 2004). This large stimulus to the ventilatory control system could thus perpetuate the occurrence of respiratory events in some patients. However, a study that induced arousals in normal healthy individuals found that although hyperventilation does in fact occur at
arousal the GG muscle activity at return to sleep is either above or at the same level noted prior to the arousal (Cori et al., 2012; Jordan et al., 2015). Further research investigating this theory in OSA patients with naturally occurring arousals in response to flow limitation or airway occlusion also failed to find evidence of reduced GG activation following an arousal at the termination of an event (Cori et al., 2017). Thus, while arousals may destabilise the respiratory system, they do not likely result in an increased predisposition to collapse based on reduced GG activity.

Investigation of differences in ventilatory and respiratory factors across sleep stages was conducted to try to determine why there is typically a significant drop in the number of respiratory events during SWS compared with stage 2 sleep. Ratnavadivel and colleagues (2010) found that in a sample of OSA patients who typically achieve stable SWS, there was a significant delay in time to arousal and a reduced probability of arousal following induced occlusions in SWS compared with stage 2 sleep. Although they noted a simultaneous post-occlusive increase in ventilatory drive during SWS compared with stage 2 sleep, however, this augmentation did not lead to improved ventilation or airflow prior to arousal. The results of this study suggest that during SWS, OSA patients appear to tolerate reductions in ventilation for longer periods without arousing (Ratnavadivel et al., 2010). It is not clear whether this is an adaptive or maladaptive effect as it may lead to reduced frequency of respiratory events, however, this occurs at the cost of longer periods of hypoventilation.

It has been suggested that there are different arousal types amongst the OSA population (Eckert & Younes, 2014; Younes, 2004). Type 1 patients are believed to have the capacity to re-establish airway patency without arousal. They argue that in 10-25% of patients, respiratory events resolve without an arousal. Type 2 patients appear to experience coincidental arousals that begin at the time of, or shortly after airway reopening. Eckert and Younes suggest that the arousals may occur coincidentally rather than as a result of the respiratory event because the stimuli that lead to reflexive recruitment of upper airway dilator muscles, which are naturally increasing across the course of the
respiratory event, also promote wakefulness. Alternatively, it may be an audible snort that occurs when the airway reopens that wakes the patient. Finally, in type 3 patients, they postulate that the arousal threshold is too low, causing the patient to wake before the GG muscle has had adequate time to increase activity to a sufficient level to re-establish airway patency. Further research is required to support this theory and investigate the different approaches to treatment that should be applied to different arousal types.

2.1.7 Surface tension of upper airway liquid lining.

As has already been described, the collapsibility of the upper airway is dependent on the relationship between collapsing and dilating forces. Wheatley and colleagues (1993) demonstrated that after the airway in normal individuals was artificially collapsed via the application of negative pressure, the airway remained occluded even after the removal of that pressure. It appeared that the force required to open the airway was considerably greater than the force required to close it. The authors suggested that this hysteresis in closing and opening pressures indicated that intraluminal surface forces could play a role in the maintenance of airway patency. Van der Touw and colleagues (1997) later showed that in supine, healthy individuals, when surfactant was topically applied to the pharyngeal airway during wake, the upper airway was more resistant to collapse when negative intraluminal pressure was applied. They also showed that in comparison to saline solution, surfactant significantly reduced the force required to reopen an occluded airway. This suggested that properties of the mucosal lining of the pharyngeal airway, such as surface tension of the liquid lining, or adhesive forces, may play a role in the pathogenesis of OSA. In a small sample of mild to moderate OSA patients, Jokic and colleagues (1998) found that the application of a topical lubricant significantly reduced OSA severity as measured by the AHI. Although the application of surfactant was shown to assist with maintaining airway patency and reducing OSA severity, the mechanism of action is unclear from these studies.

It was later shown that the application of surfactant specifically reduced the surface tension of the lining of the upper airway, and decreased Pcrit (Kirkness,
These were the first studies to quantitatively show the specific effects of topically applied surfactant on surface tension of the liquid lining, and collapsibility of the upper airway. Furthermore, the authors investigated these effects in OSA patients during sleep and found that not only did the surfactant significantly reduce the RDI, but that the reduction in RDI was correlated with the reduction in surface tension (Kirkness, Madronio, Stavrinou, Wheatley, & Amis, 2003b). Consistent with the suggestion that surfactant makes the airway less collapsible, it has also been demonstrated that application of surfactant also reduces the pharyngeal resistance and the pressure required to re-open an occluded airway (Kirkness, Eastwood, Szollosi, Platt, Wheatley, Amis, et al., 2003a; Morrell et al., 2002). Thus, reducing the surface tension of the upper airway lining liquid through the application of a topical surfactant appears to be somewhat protective against airway collapse and may lead to reductions in OSA severity.

There is natural variability in the surface tension of the upper airway lining liquid between individuals. It has been speculated that salivary flow rate, breathing route, or even trauma to the pharyngeal mucosa as a result of snoring are all possible mechanisms that contribute to such variability (Schwartz, Schneider, & Smith, 2003). It is also possible that decreases in salivary flow rate may occur during sleep, leading to reduced lubrication of the pharyngeal airway and increased susceptibility to collapse. Kirkness and colleagues (2005) in a later study, however, showed that salivary flow rate did not change significantly between the evening and morning (although measured during wake in both cases), nor was flow rate significantly different between normal healthy individuals and OSA patients. When OSA patients were compared to healthy controls, however, they did find that the surface tension of the pharyngeal mucosal lining was slightly higher. Interestingly, they found that in both healthy individuals and OSA patients, those that showed a reduction in surface tension of the pharyngeal mucosal lining across the course of the night spent more than 50% of their time asleep breathing through their nose as opposed to oro-nasal
breathing. Oro-nasal breathing presumably causes the mucosal lining to be exposed to colder and drier air that allows greater evaporation and moisture loss from the pharyngeal mucosa, thereby altering the surface tension (Cole & Haight, 1984). Kirkness and colleagues (2005) also postulated that because OSA patients are known to have smaller pharyngeal dimensions and increased mucosal folding (Morrell et al., 2002), even small changes in the surface tension of the pharyngeal lining liquid would be amplified in terms of its effect on airway collapsibility.

The clinical implications of the role that increased surface tension of the pharyngeal lining liquid plays in OSA pathogenesis is unclear. Reductions in RDI for OSA patients when surfactant was applied was primarily due to a decrease in the number of hypopnoeas, suggesting that surfactant may be able to reduce surface tension sufficiently to resist mild airway narrowing, but may be insufficient to prevent complete collapse (Kirkness, Madronio, Stavrinou, Wheatley, & Amis, 2003b). The drop in Pcrit observed with surfactant application was equal to approximately 2-3cmH₂O (Kirkness, Madronio, Stavrinou, Wheatley, & Amis, 2003b). Similar drops in Pcrit are observed with positional changes (Neill, Angus, Sjkov, & McEvoy, 1997). The therapeutic benefit of reducing surface tension of the upper airway liquid lining is still unclear. With only modest decreases in OSA severity and reductions in airway collapsibility, the application of surfactant may only be useful as an adjunct to CPAP or other therapy for OSA.

2.1.8 OSA phenotypes.

It has been suggested that there are multiple pathophysiological pathways leading to the development of OSA, suggesting that different phenotypes exist within the OSA population (Eastwood et al., 2010; Eckert et al., 2011a). The central premise of OSA phenotypes is that the pathophysiology underlying OSA is multifactorial including anatomical and physiological mechanisms. The mechanisms known to contribute to OSA play variable roles, in relation to each other, depending on the individual. In particular, 69% of OSA patients were shown in a large physiological study to have one or more of the proposed
pathophysiologic traits (Eckert, White, Jordan, Malhotra, & Wellman, 2013). This study identified four major pathophysiological traits that the authors suggest should be considered when phenotyping OSA patients. These traits relate to the closing pressure of the airway, the arousal threshold, the loop gain of the ventilatory control system and upper airway muscle responsiveness. For example, one individual may have adequate upper airway responsiveness to changes in oxygen and carbon dioxide levels, however, their arousal threshold is too low, thereby causing the individual to arouse before their muscles can be recruited and their airway returned to normal. On the other hand, another individual may have a sufficiently high arousal threshold that would allow adequate time for upper airway muscles to be recruited to reopen the airway following an occlusion, however, that regardless of having sufficient time, they may have insufficient muscle responsiveness to restore the airway.

The presence of OSA phenotypes may help to explain the low specificity of various signs, symptoms and risk factors when unselected OSA samples are studied. Although it is not possible to identify the specific abnormalities present in individual OSA patients using the current diagnostic criteria and standard diagnostic polysomnographic techniques, treatment tailored to address the main pathological factors on an individual basis is becoming an idealized goal.

2.2 Treatment Efficacy in Obstructive Sleep Apnoea

Treatment options for OSA patients range from relatively non-invasive techniques to surgical interventions. The spectrum of treatment options range from least invasive techniques such as lifestyle modifications including weight loss and positional devices, through mandibular advancement devices and continuous positive airway pressure, to more invasive methods such as surgical removal of palatal soft tissues or maxillofacial surgery. Different treatment techniques show varying degrees of efficacy within the OSA population. The most widely prescribed and effective treatment is continuous positive airway pressure, however, due to poor adherence and acceptance, sleep researchers are
now considering more tailored treatments that address the specific mechanisms that appear to contribute to the pathogenesis of OSA in individual patients.

2.2.1 Continuous positive airway pressure.

Currently, the recommended treatment involves the use of continuous positive airway pressure (CPAP). This form of treatment involves wearing a nasal or nose and mouth mask that is connected to a device that provides pressurised air to the upper airway during sleep (positive airway pressure). The increased pressure of air applied at the nares/mouth physically prevents collapse of the airway by splinting it open during the night.

Many studies have demonstrated improvements in objective measurements of OSA severity with CPAP use. A study of severe patients showed a reduction in AHI from 77± 9 to 4± 6 after 8 weeks of optimal nasal CPAP treatment (D’Ambrosio et al., 1999). The average length of time CPAP was used each night was 6± 1.6 hours per night in this particular study. This study also found a reduction in arousal indices from 67± 7 to 13± 3 (D’Ambrosio et al., 1999). Another study of 114 mild and moderate OSA patients similarly found that CPAP treatment was highly effective in reducing AHI (21.3± 1.3 to 4.8± 0.5) and arousal indices (22.0± 1.2 to 18.3± .09) after three months of treatment (Barnes et al., 2004). Measures of hypoxemia (ODI 12.4± 1.5 to 1.6± 0.2) were also improved following CPAP treatment in these patients. Together, the findings across mild to severe patients strongly support the claim of CPAP as an effective OSA treatment.

Various sleep parameters that are negatively affected by OSA are also improved with the use of CPAP. CPAP has been found to significantly reduce sleep onset latency on a multiple sleep latency test (MSLT) in comparison to a placebo pill (Engleman, Martin, & Douglas, 1994). This reduction in sleep onset latency was significant despite an average of only 3.7 hours of CPAP runtime per night. Although it is recommended that CPAP be used throughout the night, studies have identified that 4 hours is the minimum acceptable runtime to result in identifiable treatment benefits (Kribbs et al., 1993).
Subjective symptoms can also be improved with the use of CPAP. A placebo-controlled 4-week trial of CPAP led to significant improvements in subjectively reported daytime and night-time symptoms. Additionally cognitive functions, including vigilance, mental flexibility, and coding speed, were all significantly improved, as was mood, in comparison to the placebo treatment (Engleman et al., 1994). Another placebo-controlled trial of 8 weeks of CPAP treatment for mild-moderate OSA patients, however, showed that there were less clear differences in improvement on various measures of cognitive function, mood and sleepiness between CPAP and placebo treatment. CPAP and a placebo pill both led to significant decreases in the ESS scores with no significant differences between the improvements seen with CPAP versus placebo (Barnes et al., 2002). Sleepiness ratings (measured using the Epworth Sleepiness Scale) and symptoms (assessed via the sleep apnea symptoms questionnaire) have shown to be improved following a three month treatment trial of CPAP, however, this improvement was not reflected in objective measures of sleepiness (Barnes et al., 2004). In severe OSA patients, both objectively and subjectively measured sleepiness have been shown to be improved following two and six months of CPAP treatment (Kushida et al., 2012).

Overall quality of life has been shown to improve following CPAP treatment. An assessment of eight weeks of CPAP use in 29 severe patients demonstrated improvement in the vitality, social functioning and mental health domains of the SF-36 health questionnaire (D'Ambrosio et al., 1999). Interestingly, none of the variables, including OSA severity, arousal indices, BMI, age, or mean hours of CPAP use, were predictive of improvement in these SF-36 measures. Only the degree of impairment prior to treatment was predictive of improved outcomes, in that patients with more severe impairment, as measured by the SF-36, prior to treatment showed greater improvement following the eight weeks of CPAP treatment. Mild and moderate OSA patients also show improvement in quality of life measures following CPAP treatment. General wellbeing and the total SF-36 score as well as the total FOSQ score and the score on the activity domain were improved following three months of CPAP in a
study of mild to moderate OSA patients (Barnes et al., 2004). Barbe and colleagues (2001), however, found that for non-sleepy, severe OSA patients, there was no significant improvement in quality of life or daily functioning, measured using the SF-36 and the FOSQ, following 6-weeks of CPAP treatment. The improvements in quality of life and daily functioning seen following CPAP treatment, therefore, may be limited to those individuals experiencing EDS and more severe deficits in these measures prior to treatment.

Mood changes following CPAP treatment have also been investigated. CPAP was found to significantly improve the depression and fatigue subscales as well as the total mood disturbance score of the POMS, in seven severe sleep apnoea patients following two months of nasal CPAP. Furthermore, analysis of respiratory and sleep characteristics suggested that the improvement in mood may at least be partially related to improvements in nocturnal oxyhaemoglobin levels (Derderian, Bridenbaugh, & Rajagopal, 1988). More recent studies have also shown improvement in total mood disturbance, as assessed by the POMS (Barnes et al., 2004). This study showed, however, that improvement on the Beck depression inventory was only equal to observed placebo effects. In mild to moderate OSA patients the profile of mood states showed improvements in depression-dejection and confusion-bewilderment for both CPAP and placebo groups, but improvements in vigor-activity and fatigue-inertia were only significant following CPAP treatment (Barnes et al., 2002). Both CPAP and placebo improved all subscales of the FOSQ except intimate relationships/sexual activity, and there was no significant difference in improvement between the CPAP and placebo treatments.

Changes in neurocognitive functioning have also been assessed following CPAP treatment. Typically three major neurocognitive domains are assessed, including attention and vigilance, learning and memory and executive control and functioning. CPAP treatment led to improvements in vigilance (psychomotor vigilance lapses) and executive functioning (digit symbol substitution and paced auditory serial addition tasks) in mild to moderate OSA patients (Barnes et al., 2004). In mild-moderate OSA patients CPAP did improve
scores on a verbal fluency task, however, improvements in psychomotor vigilance, short term memory and digit symbol substitution tasks were similar between CPAP and placebo groups (Barnes et al., 2002). Similar results were found with mood and wellbeing. A large-scale randomized, double-blind, placebo-controlled study of 1,098 OSA patients in the United States (APPLES) showed that CPAP was effective at improving performance on tests of executive and frontal lobe function in severe OSA patients (AHI >30) only (Kushida et al., 2012). Mild and moderate OSA patients showed no significant difference in performance at either the two month or six month assessments. Patients who reported greater sleepiness at baseline showed a significant improvement in executive function variables at the 6-month assessment, which correlated with improvements in objective sleepiness at the 2-month assessment. It was suggested, therefore, that this particular neurocognitive domain might be associated with sleepiness. Similarly, Barbe and colleagues (2001) found no improvement in any neurocognitive measure in non-sleepy OSA patients following 6 weeks of CPAP treatment.

A study by Kingshott et al. (2000) aimed to identify what factor predicted improvements in daytime functioning with CPAP therapy in 67 moderate to severe OSA patients. They found that CPAP use itself, as well as degree of OSA severity and degree of sleep fragmentation were not significantly related to improvements in most measures of cognitive functioning. The baseline oxygenation level, however, did significantly associate with improvements in objective sleepiness, self-reported symptoms, quality of life, reaction time, attention and visuomotor speed. Despite this connection observed between hypoxemia improvement and daytime functioning improvement, this did not account for more than 22% of the observed variance. In addition, this study was not placebo controlled, therefore, neither learning nor placebo effects can be ruled out. Other studies that have employed placebo controls, however, have found correlations between CPAP use and improved subjective ratings of sleepiness, symptoms and QoL (Engleman et al., 1994; 1999).
Treatment with CPAP has also been shown to reduce cardiovascular risks associated with OSA. A meta-analysis of randomized, controlled trials conducted by Bazzano and colleagues (2007) showed small but significant reductions in blood pressure following CPAP treatment. Not all studies show reductions in blood pressure with CPAP treatment. For example, changes in 24-hour ambulatory blood pressure measurement following three months of CPAP treatment were non-significant in a study of mild to moderate OSA patients (Barnes et al., 2004). Non-sleepy OSA patients also failed to show significant changes in blood pressure measurements following 6 weeks of CPAP (Barbé et al., 2001). Several other studies, however, have shown reductions in blood pressure with CPAP treatment (Barnes et al., 2002; Coughlin, Mawdsley, Mugarza, Calverley, & Wilding, 2004; Monasterio et al., 2001). There is considerable variability in findings, however, the majority of studies have investigated only small samples of predominantly male OSA patients and included many patients who did not have hypertension. A larger study that included men and women with both un-treated hypertension and un-treated OSA found a significant reduction in both systolic and diastolic blood pressure at 6 and 12 weeks after commencing CPAP treatment. The reductions in blood pressure were not found following sham CPAP use (Durán-Cantolla et al., 2010). Overall, the research suggests that CPAP treatment has the potential to reduce the cardiovascular risks that OSA poses and may help prevent hypertension.

Despite the wide acceptance of CPAP as the most effective treatment for OSA, there are still limitations to its use. In general, studies have found that the average reported length of CPAP use per night is low, and many patients refuse to use CPAP due to discomfort. Over time many patients cease to use their device with long-term adherence rates between 30-60% (Kribbs et al., 1993; Sawyer, Deatrick, & Weaver, 2010). There is a 10% increased risk of all-cause mortality in non-adherent CPAP users vs. adherent users (Campos-Rodriguez et al., 2005). In an effort to try and develop programs that may improve adherence rates, many studies have investigated the factors that influence CPAP use.
Ethnicity and patient demographics, disease severity, symptom severity, advances and improvements in the comfort and effectiveness of the equipment and psychological factors can all influence CPAP adherence (Weaver & Sawyer, 2010). The most investigated factors include disease and symptom severity. In a review of disease severity as defined by AHI, it was reported that the majority of studies show that greater disease severity is predictive of CPAP adherence (Gay et al., 2006). The degree of objective and subjective sleepiness has also shown to predict greater CPAP adherence (Gay et al., 2006; McArdle et al., 1999; Waldhorn et al., 2006; Rolfe, Olson, & Saunders, 1991). However, compliance rates have not been consistently found to correlate with baseline, or change in quality of life or health status (Bennett, Barbour, Langford, Stradling, & Davies, 1999). The duration and frequency of CPAP use in the first few months is also predictive of ongoing use (Kribbs et al., 1993; McArdle et al., 1999). Together, these findings imply that there are many factors that vary considerably between individuals that contribute to CPAP adherence. The lack of consistency with the findings across various studies is likely due to the way in which adherence has been defined, and highlights the importance of the outcomes that are used to define successful treatment and normalcy. Importantly, the research shows that patients who experience the greatest benefit from CPAP treatment are not necessarily those who use it the most. Despite low adherence rates and the high financial and physical costs of CPAP treatment, its undeniable efficacy means that it remains the benchmark against which to compare any other form of treatment.

2.2.2 Surgery.

An alternative treatment that is used in some OSA patients is surgical intervention. The type of surgery employed depends on the site of airway collapse and identified abnormalities in various anatomical and craniofacial structures. While anatomical obstructions such as nasal polyps, deviated septum, enlarged tonsils and enlarged adenoids can play a role in narrowing of the upper airway, it is rare that such abnormalities are the sole cause of OSA. Surgical removal of these particular structures, therefore, are not typically considered
surgical treatment for OSA per se (Powers, Allan, Hayes, & Michaelson, 2010). There are two main types of surgical intervention that are specifically considered as potential treatments for OSA. Surgery targeting soft tissue in the upper airway, such as Uvulopalatopharyngoplasty (UPPP), and laser-assisted uvuloplasty (LAUP), are the most common surgical interventions, however, success rates are low (Powers et al., 2010). Maxillomandibular advancement (MMA), involves expanding the skeletal framework to which the soft tissues of the upper airway attach, thereby enlarging the pharyngeal space (Holty & Guilleminault, 2010). MMA is less commonly prescribed, however, it is a more successful treatment than UPPP (Sundaram, Bridgman, Lim, & Lasserson, 2005).

The goal of UPPP and LAUP is to shorten the soft palate and enlarge the posterior airway space. The palatal muscle is excised and mucosa from the lateral walls of the nasopharynx is pulled forward. The uvula and palatine tonsils are also removed to enlarge this space. Scarring from the excision causes the tissue to stiffen, thereby decreasing the vibratory flow of air across the palatal soft tissue and reducing the flutter associated with snoring and airway obstruction (Powers et al., 2010). Despite findings that UPPP can successfully treat snoring (Fujita et al., 1985; Simmons, Guilleminault, & Miles, 1984), OSA is only successfully reduced following LAUP or UPPP surgery in approximately 40-50% of patients (Riley, Guilleminault, Powell, & Simmons, 1985; Sher, Schechtman, & Piccirillo, 1996). The high failure rate can be explained by the observations that a single site of collapse in OSA patients is rare (Rojewski, Schuller, Clark, Schmidt, & Potts, 1984) and the site of upper airway collapse is at the level of the hypopharynx, close to the base of the tongue, in approximately 50% of OSA patients (Borowiecki et al., 1978; Guilleminault et al., 1978; Hudgel, 1986; Stein et al., 1987). The long-term success rates decrease even further, as the short-term benefits resulting from scarring and stiffening of the palate fade with time (Powers et al., 2010).

By expanding the pharyngeal space, MMA decreases pharyngeal collapsibility (Holty & Guilleminault, 2010). Maxillomandibular advancement is the most effective craniofacial surgical treatment for OSA, with the exception of
complete tracheostomy (Powers et al., 2010). In their systematic review of 22 MMA studies, involving 627 adult OSA patients, Holty and Guilleminault (2010) described four major findings. Firstly, the success rate for MMA was 86% compared with 50% who underwent UPPP. Furthermore, they found that complete cure (AHI <5) occurred in approximately 43% of patients. Unlike the return to a pre-operative state often seen in long-term follow-up studies of UPPP patients, at 44 months post MMA, successful alleviation of OSA was maintained. In addition to significant reductions in AHI, the review showed that in general there is a significant drop in reported daytime sleepiness. The second finding was that the main predictors for surgical success were younger age, lower pre-operative AHI, lower pre-operative BMI and greater degree of maxillary advancement. Although lower pre-operative AHI and BMI were predictors of greater success, MMA is generally a successful treatment even in severe and obese patients. Thirdly, the review showed MMA to be a relatively safe procedure with major and minor complications reported in only 1% and 3.1% of patients, respectively. The final major finding was that in general patients reported satisfaction with the surgery. While Holty and Guilleminault suggest that MMA is a safe alternative to CPAP treatment, other authors caution that it should be recommended as a first line alternative to CPAP only in patients with age <45 years, pre-operative BMI <25 and AHI <45 as well as specific craniofacial characteristics and pre-surgical orthodontic preparation (Booth, Djavadkhani, & Marshall, 2014; Vigneron, Tamisier, Orset, Pepin, & Bettega, 2017).

2.2.3 Oral appliances.

Many patients with mild to moderate OSA have had limited success with oral appliances (OA). The mandibular advancement splint (MAS) is currently the most commonly prescribed OA and is custom made for each individual patient. This device is designed to pull the mandible forward during sleep. While the exact mode of action is unclear, it is presumed to act in a similar fashion to surgical interventions that increase pharyngeal space and improve upper airway calibre thereby, reducing pharyngeal collapsibility (Barnes et al., 2004). Choi and colleagues (2000) showed that jaw protrusion significantly
decreased RUA during wakefulness in both normal healthy individuals and individuals with OSA. These devices, however, are not successful in many patients.

Several studies investigated the effects of MAS in comparison to placebo controls. In a study comparing MAS with a placebo oral plate found that the MAS was able to significantly lower the AHI and arousal index and improve mean oxygen saturation (Mehta, Qian, Petocz, Darendeliler, & Cistulli, 2001). A similar study comparing MAS to a tablet placebo it was found that MAS, but not the placebo pill led to reductions in RDI, arousal index, lowest mean oxygen saturation and subjectively and objectively measured sleepiness (Gotsopoulos, Chen, Qian, & Cistulli, 2002).

Although studies show that there can be considerable improvement in OSA symptoms with the use of MAS, the improvements may not be as significant as those seen with CPAP use. Several studies assessing the effectiveness of MAS in comparison to CPAP in OSA patients, have shown that while MAS can significantly decrease OSA severity the reductions in severity following CPAP were significantly greater (Barnes et al., 2004; Clark, Blumenfeld, Yoffe, Peled, & Lavie, 1996; Ferguson, Ono, Lowe, Keenan, & Fleetham, 1996). These findings were confirmed by a systematic review conducted by Li, Xiao and Hu in 2013. This review of 14 comparative studies between oral appliances and CPAP therapy showed that CPAP was significantly more effective for improving OSA severity, reduce arousal index and minimum oxygen desaturation (Li, Xiao, & Hu, 2013).

Changes in subjective quality of life and general health status following treatment with the MAS have been conducted to assess effectiveness. Significant improvement has been shown via the total mean FOSQ, and social functioning domain and SF-36 overall health scores following MAS use (Barnes et al., 2004). This improvement was comparable to the improvement achieved with the use of CPAP. Additionally, MAS was able to produce a reduction in subjectively rated sleepiness (ESS), and OSA symptoms, measured using the sleep apnea symptoms questionnaire (SASQ), in this study to roughly the same extent as CPAP therapy.
Neurocognitive functioning has also shown some improvement in specific domains with the use of MAS. In particular, tests of executive control (paced auditory serial addition task) show improvement following MAS treatment (Barnes et al., 2004). The systematic review by Li and colleagues (2013) showed that the differences in improvement in sleepiness, quality of life, cognitive performance and blood pressure, however, were negligible between OA and CPAP.

One of the benefits of MAS is that it is commonly reported to be a more tolerable treatment than CPAP (Barnes et al., 2004; Clark et al., 1996; Ferguson et al., 1996; Mehta et al., 2001). The treatment, however, is only effective for approximately one third of OSA patients although patients tend to overestimate their improvement (Mehta et al., 2001). Due to the relative superiority of CPAP treatment with regards to the improvement seen in polysomnographically recorded outcomes of OSA, MAS is typically recommended for snoring and mild-moderate OSA or for patients who are unable to tolerate CPAP.

2.2.4 Pharmacotherapy.

Several pharmacotherapy studies have focused on manipulating ventilatory drive, for example using Acetazolamide, a carbonic anhydrase inhibitor that leads to metabolic acidosis and results in increased respiratory drive (Smith & Quinnell, 2004). A trial in OSA patients demonstrated a reduction in apnoea frequency by up to 25% (Tojima et al., 1988). Another randomized controlled trial with OSA patients showed reductions in AHI, but number of arousals and subjective symptoms were unchanged (Whyte, Allen, Jeffrey, Gould, & Douglas, 1989).

Nicotine is known to increase respiratory drive and affect hypoglossal nerve output (Shao & Feldman, 2002). One study of OSA patients chewing nicotine gum showed reductions in the number of apnoeas in the first two hours of sleep, however, sleep architecture was not changed (Gothe, Strohl, Levin, & Cherniack, 2006). Another study found a reduction in snoring but no change in AHI. There were, however, side effects of poorer sleep quality as well as gastrointestinal adverse effects (Davila, Hurt, Offord, Harris, & Shepard, 1994). Due to
the side effects and the highly addictive nature of nicotine, this is an impractical option for treating OSA.

Targeting drive to upper airway dilator muscles has also been investigated. Motor activation of the genioglossus, via the hypoglossal nerve, decreases from sleep onset through NREM sleep, finally reaching lowest levels of activation during REM sleep (Jacobs & Azmitia, 1992). The reductions in GG activity across the early stages of sleep through to REM have been suggested to result from decreases in tonic serotonergic input to the hypoglossal motor neurons from the raphe nuclei in the medulla. Serotonergic activation of the hypoglossal nerve (Fenik & Veasey, 2003; Kubin et al., 1992) has led some researchers to suggest tricyclic antidepressants as a potential pharmaceutical intervention for treating OSA. Antidepressant medications are also suggested because serotonin cannot pass the blood-brain barrier, the approach of the research in this area has been to use anti-depressant medications. Several studies using tricyclic antidepressants in comparison to a placebo did not show any effect on OSA severity, however, significant adverse effects of the medication including impotence, and visual disturbances were reported (Brownell, West, Sweatman, Acres, & Kryger, 1982; Whyte, Gould, Airlie, Shapiro, & Douglas, 1988). This class of drug has a strong effect not only on the re-uptake of serotonin but they also have a strong effect on other vital neurotransmitters (Smith & Quinnell, 2004).

Selective serotonin-reuptake inhibitors (SSRIs) have been investigated in the hope that the more selective nature of this class of drugs would produce more targeted results. A study of paroxetine in OSA patients did show a reduction in AHI with a 35% drop in events during NREM sleep. There was, however, no change during REM sleep (Kraiczi, Hedner, Dahlof, Ejnell, & Carlson, 1999). In a comparison of fluoxetine and protryptiline, fluoxetine was found to reduce AHI more effectively than protryptiline, however, there was again no effect on AHI during REM sleep (Hanzel, Proia, & Hudgel, 1991). The lack of effect during REM sleep as well as the relatively small reductions in AHI and predisposition to weight gain seen with the use of SSRIs has not led to its use as a treatment option for OSA.
In some OSA patients, it has been suggested that a low arousal threshold may be a significant causative factor in their pathophysiology. For patients whose arousal threshold is too low, arousal from sleep might occur during periods of airflow limitation before the upper airway dilator muscles can be adequately recruited to compensate for increases in carbon dioxide in the blood (Dempsey, Veasey, Morgan, & O'Donnell, 2010). Choosing an appropriate sedative is challenging as several common sedatives may be able to delay arousal, however, they can also attenuate UA dilator muscle activity or even abolish the negative pressure reflex (Eikermann et al., 2008). Eikermann and colleagues (2010) investigated the effects of pentobarbital, which was found in previous animal studies to increase phasic genioglossus muscle activity (Berry, Kouchi, Bower, Prosise, & Light, 1995; Younes et al., 2007). Their study showed that although arousal was delayed and genioglossus muscle activation was greater with pentobarbital administration compared with a placebo, there was also a drop in ventilation, and an increase in carbon dioxide and upper airway resistance (Eikermann et al., 2010). Heinzer and colleagues (2008) demonstrated in OSA patients that Trazadone, a non-myorelaxant sedative, increased the arousal threshold under artificially induced hypercapnic conditions, thereby delaying arousal. A more recent study showed that Trazadone successfully increased arousal threshold without affecting UA muscle activity or Pcrit. Despite the increase in arousal threshold, however, the study found no improvement in OSA severity (Eckert & Younes, 2014). A recent review by Jordan and colleagues (in-press) reported that the majority of studies investigating the use of sedatives as a treatment for OSA have shown that sedatives do increase arousal threshold, however, whether this increase in arousal threshold translates to improvements in OSA is less clear. They point out that the general inconsistencies in results from various sedative studies may be due to considerable between-subject variability in the underlying pathogenic factors. Sedatives are unlikely to have any effect when airway closure is primarily driven by anatomical factors that cause the airway to be severely collapsible, or when the patient already has a high arousal threshold.
Additionally, delaying arousal will only be beneficial when respiratory drive, and the increase in respiratory muscle activation are adequate to reopen the upper airway. Jordan and colleagues therefore argue that sedatives may be an effective treatment in a subset of OSA patients with mild to moderate airway collapsibility, adequate muscle function and responsiveness, and low arousal threshold from sleep. After assessing the findings from studies that specifically identified participants with low arousal threshold they found that less than one third of OSA patients are likely to benefit from treatment with sedatives alone. They caution, however, that the use of sedatives in patients with a severely collapsible airway, or insufficient upper airway muscle response to re-establish airway patency would lead to prolonged periods of hypercapnia and hypoxaemia. More research is needed to clearly identify which phenotypic traits are best suited for sedative treatment and also to understand the inherent benefits and risks of this treatment approach.

2.2.5 Weight loss.

There are several conservative treatment approaches or treatment adjuncts when tackling OSA. Weight loss is often the first suggestion made by a sleep physician following a diagnosis of OSA, especially in overweight and obese individuals. Weight loss is typically achieved either through dietary and behavioural alteration, or through surgical interventions such as gastric banding. Regardless of the method of weight loss, several studies have shown significant improvement in OSA severity with weight loss in many patients (Browman et al., 1984; Foster, Borradale, & Sanders, 2009; Schwartz et al., 1991; Smith, Gold, Meyers, Haponik, & Bleecker, 1985; Suratt, Findley, Pohl, & Wilhoit, 1987).

Suratt and colleagues (1987) found that moderate weight loss following a calorie-restricted diet in 8 morbidly obese, male OSA patients led to improved oxygenation as well as decreased nasopharyngeal collapsibility. Only 6 of the 8 patients, however, showed an improvement in the number of respiratory events. Another study employing a calorie-restricted diet intervention in mild to moderately obese patients showed that only a 9% reduction in weight was associated with reduced respiratory events, increased oxygenation (Smith et al.,
During REM sleep, however, the frequency of respiratory events was unchanged and patients continued to experience episodes of desaturation throughout all stages of sleep. A study comparing intensive lifestyle modifications and diabetes education in a large sample of OSA patients with type II diabetes showed that intensive lifestyle modification was significantly more effective at producing reductions in both weight and OSA severity (Kuna et al., 2013). They also reported that the beneficial effects persisted at 4 years follow-up despite regaining weight of up to 50%.

Studies that have investigated the effect of weight loss on OSA severity via surgical intervention have found similar results to dietary interventions. A study of obese individuals who underwent either dietary restriction or gastroplasty showed that in surgery led to greater weight loss, but regardless of the method of weight loss, those with greater amounts of weight loss showed greater reductions in OSA severity (Rajala et al., 1991). In 25 morbidly obese, severe OSA patients who underwent laproscopic gastric banding, there was a significant decrease in OSA severity at approximately one and a half years post-surgery (Dixon, Schachter, & O'Brien, 2005). These patients also experienced improvement in sleepiness, sleep architecture and quality of life, as assessed via the SF-36. A study by Pillar and colleagues (1994) showed that in morbidly obese patients who underwent gastric bypass surgery the AHI was significantly decreased four and half months following surgery. Interestingly, in a seven-year follow-up assessment, the BMI for these patients had increased only slightly, however, the number of respiratory events had significantly increased.

The exact mechanism through which weight loss leads to improvements in OSA severity are unclear. Weight loss should reduce the pressure on the airway due to fat deposition, thereby decreasing airway collapsibility. Schwartz and colleagues (1991) found that the patients who showed improvement in their OSA following weight loss began with lower Pcrit values than those individuals who do not show improvement. Foster and colleagues (2009) found that lower pre-intervention AHI, male gender and amount of weight lost were significant predictors of improved OSA.
While weight loss does appear to be effective for improving OSA severity in overweight or obese patients it rarely cures the condition completely. Foster and colleagues (2009) found that in a sample of moderate OSA patients with type II diabetes, a behavioural weight loss program led to significant weight loss at 1 year with each kilogram of weight lost correlated with a 0.6 events per hour improvement in AHI. In general, however, there is no consistent correlation found between the amount of weight loss and degree of improvement in OSA (Barvaux, Aubert, & Rodenstein, 2000). The fact that some patients appear cured of their OSA following weight loss, while the same amount of weight loss in another individual leads to little or no change in their OSA severity underscores the point that weight is only one of several potential causes of OSA. Additionally, the process of weight loss can be difficult and long-term maintenance of that weight loss is also difficult, therefore, weight loss, although commonly recommended as a treatment for OSA, is not necessarily guaranteed to be successful and regular long-term follow-up is vital as weight is easily regained.

2.2.6 Complementary and alternative medicine.

A recent pilot study in Brazil (Freire et al., 2007) included three randomized groups: acupuncture, sham acupuncture and non-treatment control. Following ten weekly acupuncture treatments, patients treated with acupuncture showed significant reductions in their apnoea/hypopnoea index (AHI) values, and sleep onset latency, as well as increased oxygen saturation compared with baseline measures. All three groups showed a significant improvement in sleep efficiency when compared with baseline, however, the difference between the three groups was not significant. Additionally, measures on the Epworth sleepiness scale (ESS), and measures of physical, general health, vitality and mental health dimensions on the SF-36, were shown to be significantly improved as a result of acupuncture, but not the sham acupuncture or in the non-treatment control group. When the three groups were compared on these measures, however, there was no significant difference identified between the groups on any measure of the SF-36 except for significant improvement in the mental health dimension.
in the acupuncture group compared with the sham and control groups. The results of this study are promising, however, they are subject to both theoretical and methodological limitations, and generalizations should be viewed cautiously until further evidence in larger samples can be provided.
Chapter 3 Chinese Medicine and Obstructive Sleep Apnoea

Since the 1970s, Chinese medicine (CM) has grown in popularity and is now regularly sought as a method of treatment for various health conditions, especially those conditions for which Western medical treatments have limited effective therapeutic options to offer. The therapeutic principles and practices involved in CM have been developed over more than 2,500 years and continue to evolve with modern advances in technology. Despite a long history of anecdotal evidence of benefit there is a relative paucity of high-level, clinical evidence to support routine clinical application and related therapeutic claims. One of the major hurdles for conducting valid scientific research utilising CM treatment methods is the difficulty involved with the explanation of the underlying theoretical framework of CM, which guides treatment principles and techniques in a normal CM clinical situation.

Recognition of the deficiency of scientific research has in recent years prompted an increase in clinical research involving CM modalities, including both acupuncture and herbal medicines. Researching the treatment techniques, however, is only one facet of the larger dilemma. A western medical treatment is, mostly, determined based on the underlying pathological changes. For example, when blood pressure is high, one treatment approach is to lower it by using a diuretic. Diuretics signal the body to eliminate sodium. Water binds to the sodium and is lost during the process of sodium elimination via urination. The result is lower blood volume and decreased rate of blood flow and hence a decrease in blood pressure. This example illustrates how important it is to understand the underlying pathophysiology not only of the disease, but also the underlying mechanism of action of the medication in order to produce the desired effect. CM applies the same principles of syndrome differentiation, pathology pattern identification, and targeted treatment. The difference, however, is that CM is built upon a theoretical framework that describes anatomy, physiology and pathology in ways that are not easily understood or explained using western scientific terms or knowledge. Often, research
involving CM techniques fails to adequately investigate quantifiable changes in physiological mechanisms from a western medical standpoint. For the purposes of this thesis, the most basic and necessary parts of CM theory will be explained to provide an understanding of the CM explanation of the phenomenon of sleep and the pathophysiology involved in obstructive sleep apnoea.

Although the terminology used in CM is often identical to modern western medical terms, the use of these terms in CM encompasses meaning beyond that which is defined by western medicine. The concepts of the substances, and the organs in CM, therefore, go beyond the anatomical and functional conceptions of their western medical counterparts. It is important to note that when the terms are being used to denote the CM conception of that organ or substance, the word will be capitalised.

3.1 The Basics of Chinese Medicine

At a glance, the Chinese medicine theoretical system takes a holistic and integrated approach to the human mind and body. Within this system there are twelve major organs, each of which controls the state and performance of not only various anatomical structures, but also various physiological functions as well as maintaining a certain aspect of the psyche. The organ systems in the body are interconnected through different relationships based on principles of Yin and Yang, the vital substances (Qi, Blood and Body Fluids) and the theory of the Five-Elements (Metal, Water, Wood, Fire and Earth). Illnesses or diseases are viewed as the result of an imbalance within individual organs systems and imbalances in the relationships between the organ systems. Secondary and comorbid disorders are often the result of an imbalance in one organ system interacting with related organ systems thereby transferring the imbalance. These imbalances disrupt the functioning of the various anatomical structures, physiology and emotions associated with the affected organs.

Chinese medicine theory has its roots in ancient Taoist philosophy, which itself takes its origins from the I-Ching (The book of Changes, ~700BC). As such, many of the theoretical descriptions and explanations of physical health and
medicines strongly emphasise the relationship between nature and the human body. All phenomena in the universe are considered to be microcosmic reflections of the entire universe, akin to the concept of fractals. At the most basic level changes in the human body, as with changes in nature, are explained through the principles of Yin and Yang.

3.1.1 Yin and Yang.

According to Taoist philosophy, the primary state of the Universe was in the form of Qi (pronounced “chee”). All things within the universe were thought to be the result of the movement of Qi. These movements are known as Yin and Yang. All phenomena in the Universe are the result of the interplay between these two opposing forces. All of the natural world exists, develops and is constantly manipulated by the interaction of Yin and Yang (Zuo, 2002). The character for Yin is made up of radicals that are interpreted as shade or darkness, while the radicals that make up the character for Yang mean sunshine or sunbeams. Thus, Yin and Yang represent the concept that all things naturally exist in opposition but are interdependent to something else. Yin and Yang not only oppose each other, but also mutually complement each other and represent two phases of a cyclical movement; thus they mutually complement each other.

In the context of medicine, Yin and Yang are applied to both anatomical and physiological functions. The cyclical movement of Yin and Yang emphasise that all opposing pairs exist upon a spectrum that gradually moves from one extreme to another. For example, night-time is Yin in nature and daytime is Yang in nature. Yin is thought to contain the properties of being cold, solid, and still. Yang is thought to contain the properties of being warm, immaterial and active. The state of sleep is Yin in nature corresponding to restfulness, and does not exist without an opposing state of wakefulness and activity, which is Yang in nature. Men exist in opposition to women, night to day, light to dark, etc. Each item in every opposing pair is, therefore, classified as Yin or Yang. Although all phenomena can be categorized as either Yin or Yang, these aspects are relative, not absolute. This categorization must consider that 1) the Yin and Yang properties can vary with time and circumstance; 2) any aspect of Yin and Yang
can be further, and infinitely divided – Yin within Yang, Yang within Yin. That is not to say that a woman is able to change into a man, but rather, that a woman (Yin in nature) has the capacity to perform Yang activities and contains masculine traits.

The Yin and Yang aspects of all phenomena are in a constant interaction with each other. There are four major interactions. Firstly, Yin and Yang, being opposites, mutually repel and attract or restrain each other like poles of a magnet. Through this action these two aspects always maintain a balanced equilibrium. Secondly, Yin and Yang are interdependent, meaning that one cannot exist without the other. The third interaction is that of mutual consumption. Yin and Yang are in a constant balance with each other through a dynamic waxing and waning. There is a continuous adjustment of the relative levels of Yin and Yang. As one is waning, the other is waxing. When the balance between Yin and Yang is lost the other will change in proportion to achieve a new balance. After waning has reached a certain level, there will be a change to waxing and vice versa, thereby preventing excessive wax or wane. This alternating relation creates a dynamic balance. The final interaction is that of mutual transformation between Yin and Yang. At the point of maximal wax or wane of Yin or Yang, they will transform into the other. An example illustrating the interactions of Yin and Yang is the movement from day to night and back to day. The 24-hour day can be seen as a direct analogy to the process by which Yin transforms into Yang and vice versa (see figure 2 for a depiction of the waxing and waning of Yin and Yang). At midday, the sun is at its highest point, which corresponds to the maximal state of Yang. As the afternoon passes, the sun begins to descend. During this phase of the circadian oscillator the Yang is declining. At dusk the sun sets and the moon begins to rise. This is the point of transformation from Yang to Yin. The Yin continues to grow until it reaches a maximal state of Yin at midnight. After midnight the Yin will start to decline. At the transition of dawn when the moon sets and the sun rises Yin transforms to Yang which grows until reaching maximum at midday, thereby completing a cycle.
Figure 2. At 12pm the Yang is at maximal wax. As the time approaches mid-afternoon at 3pm there is a higher proportion of Yang energy to Yin energy indicating the waning of Yang and waxing of Yin. At 12am the Yin reaches maximal wax. As dawn approaches at 6am the waxing and waning of Yin and Yang energy are roughly equal. Notice that the graphical representation of the growth and decline of Yin and Yang over a 24-hour period closely resembles the sinusoidal movement of the circadian oscillator that occurs within the body.

Within the medical context, the Taoist principles of Qi and the interactions of Yin and Yang are applied to both anatomy and physiology. The body, the organs, meridians, and tissues are thus created through the movement, transformation and accumulation of Qi, and the human anatomy can therefore be classified as Yin or Yang in nature.

The internal organs, their functions and the vital substances require more explanation. There are four main substances in the body that are considered vital to life’s activities: Qi, Blood, Body fluids and Essence. The former three substances have specific roles in the physiological functioning of the body, while the latter is more of a building block for the other substances similar to DNA in a western medical framework. For the purposes of this thesis, the discussion of these substances will be restricted to Qi, Blood and Body Fluids. These three
substances are interdependent and must be continuously produced and circulated throughout the body in order to maintain life.

3.1.2 The vital substances.

Qi.

Qi can be conceptualised as an energy force that has both a congenitally acquired component and a postnatally acquired component during the life span of an individual, similar to the concepts of nature (genetics) and nurture (environment and lifestyle) in Western medicine. At the point of conception, new life comes about through the production of Innate Qi from maternal and paternal Qi. Whilst within the womb this new life is supported by the Qi of the mother. After birth, the individual must support itself by continually transforming ingested nutrients with inhaled clear Qi, from the air, to produce Acquired Qi. The acquired Qi supplements the Innate Qi, and the Innate Qi is essential to support the process of producing Acquired Qi, thus they are mutually dependent. The Acquired and Innate Qi work together to engender proper growth and development and to maintain healthy bodily function. All other forms of Qi, Blood and Body Fluids in the body arise from the combination of Innate and Acquired Qi.

Qi has several functions. The specific functions performed by Qi are determined by the type of Qi and the location of the Qi. In general, theses functions can be considered to have: a propelling, warming, protective, stabilising, fixing or transforming function. The propelling function refers to the process of stimulating and maintaining the physiological functions performed by the various organs and tissues of the body. When it is said that Qi has a warming function, this refers to the fact that Qi is considered to be the source of heat energy in the body. By this it is meant that Qi plays an important role in the thermoregulatory process. The protective nature of Qi refers to the ability to resist pathogenic invasion and prevent disease. It also refers to the ability of the body to fight against a pathogen and promote healing; in essence, our immunity and immune response. The stabilising function relates to the control of fluids in
the body. This is most closely interpreted as the control of constriction and
dilation of the blood vessels and lymphatic systems. In addition this refers to the
control of the excretion of all fluids such as the movement of digestive fluid
through the digestive tract and defecation, the controlled excretion of urine, and
semen. Finally, fixing also refers to the general tonicity in the body that keeps
organs and muscles from prolapsing. The final function is transformation. Qi
transformation refers to the ability to form a new substance or tissue from
circulating Qi, and ingested or inhaled Qi. This can be likened to the production
and recycling of hormones, minerals and neurotransmitters.

Qi is constantly moving throughout the body, however, there is the
tendency for specific types of Qi to move in certain directions. The four types of
movement are ascending, descending, inwards and outwards. These are viewed
as opposing movements along two dimensions. These movements occur
through the coordinated actions of the organs and meridians. The Qi of each
organ has a propensity to move in a specific direction and will coordinate its
movement with an organ whose movement is in the opposing direction thereby
regulating the overall movement of Qi. Likewise the meridians are paired so that
movement of Qi in one meridian is opposed to the direction of Qi flow in its
paired meridian thereby ensuring Qi flow and distribution is balanced.

Qi can be classified into different types. Innate Qi is determined at
conception. Although the quality and quantity of Innate Qi is prenatally
determined it must be continually nourished and supplemented by Acquired Qi.
Acquired Qi is produced by the transformation of nutrients extracted from food.
The Innate Qi and Acquired Qi are combined in the Kidney and distributed
throughout the body in a form known as Genuine Qi. The Genuine Qi that is
distributed to each specific organ is the substance that maintains the functions
performed by each organ.

Ancestral Qi, is another classification of Qi. It is accumulated in the chest
and is then divided into Nutrient Qi and Defence Qi. Ancestral Qi is produced
by the combination of Qi from inhaled air and nutrients absorbed and
transformed from food. As it is produced, Ancestral Qi, accumulates in the chest.
From here it infuses into the Heart and cardiovascular system and also nourishes the respiratory tract. The two main functions of the Ancestral Qi, therefore, are to ensure the smooth function of the circulatory and respiratory processes.

Nutrient Qi and Defence Qi are borne from the Ancestral Qi. The Nutrient and Defence Qi can be considered Yin and Yang in nature, respectively. The most nourishing portion of Qi extracted from food is used to produce Nutrient Qi, while the more active portion is used to produce Defence Qi. The Nutrient Qi, because it is more nourishing, flows inside the blood vessels, while the Defence Qi flows outside the vessels. Therefore, the Nutrient Qi is distributed to the organs, while the Defence Qi is distributed to the body surface. Functionally, the Nutrient Qi is transformed into Blood and nourishes the body. The Defence Qi warms and nourishes the muscles and regulates sweating thereby protecting the body from pathogenic factors and is linked to the respiratory process and function of the Lung.

**Blood.**

The second vital substance essential for life is Blood. Similar to the western medical concept of blood, it is characterised as a sticky fluid of red colour that flows within the blood vessels. It is composed of Nutrient Qi and Body Fluid. In addition to Nutrient Qi and Body Fluid, an important component of Blood is Essence. This can be viewed as the combination of cells from bone marrow and dietary nutrients such as iron, which are essential for Blood production. The main function of Blood is to nourish and moisten the entire body. The secondary function is to transport waste Qi to the Lung and Kidney for excretion from the body. This is akin to the process of eliminating built up carbon-dioxide and trace toxins, minerals and chemicals from the blood that these organs perform in western medicine. In addition to the circulatory system defined by western medicine, Blood is thought to circulate around the body via the meridians and collaterals. The movement of Blood is influenced initially by the Heart, which propels the Blood through the vessels. The Lung is also considered to play a vital role through its production of Ancestral Qi, the necessary precursor for the production of Blood, but also through its function of assisting the Heart to propel
the Blood through the circulatory system. The Spleen ensures the integrity of the Vessels, thereby preventing leaking of Blood. The Liver dredges the Vessels thus ensuring smooth and unhindered flow of Blood throughout the system. The Liver also regulates the volume of circulating Blood: increasing the volume during periods of activity, and reducing the volume during rest periods. The Qi of each of these organs is vital for the flow of Blood to be maintained. Circulation can also be affected by other factors such as Heat, Cold, Phlegm, Dampness, swelling and nodules.

**Body Fluid.**

Body Fluid is a vital substance composed largely of water, but also contains many nutritive substances. A portion of the Body Fluid enters the blood vessels and is one of the components that is transformed to produce Blood. The remaining Body Fluid flows outside the vessels, through the interstitial spaces, the muscles and organs, similar to lymph and extracellular fluid within the western medical framework. The Body Fluids are classified as either Fluid or Humor, depending on whether they flow inside or outside the vessels, respectively. The function of the Body Fluids is determined by the type of fluid. Fluids flow and circulate quickly around the body, moistening the skin and external orifices. Humor, however, moves slowly and mainly functions to lubricate the organs, the brain, nervous system, and the joints.

Body fluid is produced from fluid that is absorbed by the Stomach, Small and Large intestine from the liquid part of the diet. In addition to the moistening function and transformation into Blood, Body Fluid also transports the waste materials out of the body. This is accomplished through the excretion of urine and sweat.

The movement of Body Fluid throughout the body relies on the coordinated efforts of several organs. After its production by the Spleen and Stomach, it is transported to the Lung and Heart. In the Heart it is partly absorbed into the blood vessels to complete the production of Blood and is therefore transported around the body via the circulatory system and meridians. From the Lung, the Body Fluid is transported all around the body and down toward the Kidney.
The Kidney receives the fluids, separates the clear from the waste and sends the clear fluid back upwards to re-enter circulation while the waste fluid is transformed into urine. Excretion of Body Fluid from the body is achieved through sweating, urination, defecation and respiration, albeit predominantly through the two former methods. The Liver and Triple Energizer also play an important role in the distribution of Body Fluid by ensuring that the passageways for the movement of fluid are clear and unhindered.

The Body Fluids that are specifically excreted from the mouth, nose and eyes are also related to specific organs. The snivel, or fluid that moistens the nasal mucosa is controlled by, and can reflect the state of the Lung. The tears reveal the state of the Liver and the spittle and saliva reflect the state of the Kidney and Spleen, respectively. Sweating is controlled by the Heart and Lung. The Lung ensures that the body Fluids are distributed to the superficial layers of the body and the Heart Yang Qi controls the opening and closing of the pores.

The functional importance of these vital substances and their movement throughout the body is complex. Each of the internal organs has its own specific form of Qi, Blood and Body Fluids, which provide the energy and substances necessary for maintaining the function of those organs. Complex relationships exist between the organs both in relation to the production of these substances, and maintaining the functional balance within the body.

3.1.3 The internal organs.

The complex system of understanding anatomy and physiology that is present in western medicine is not exactly translatable to the understanding of the different organs and their functions according to Chinese medicine. In CM the Visceral Manifestation Theory (VMT) is the system by which organs and their functions are explained. The earliest mention of this theory can be traced to the Inner Classic of the Yellow Emperor; the seminal treatise on Chinese medicine, dated to have originated between the Warring states period (475-221BCE) and the Han dynasty (206BCE – 220CE). VMT explains the internal organs and the external manifestations of their physiological and pathological states. The theory can be divided into three components: the physiological functions and
pathological changes of the internal organs; the relationships between the organs 
and the body as a holistic organism; and the relationships between the five 
Viscera (the five Yin organs) of the body and the six Bowels (the six Yang organs) 
of the body.

According to the Simple Questions (Su Wen) of the Yellow Emperor’s 
Canon of Internal Medicine, there are five Viscera and six Bowels (Wu & Wu, 
1997). These are defined by their structure and functionality. The Viscera are 
thought to be solid organs that produce and store the nutritive substances used 
by the body. The Bowels are hollow and are said to transport, transform and 
discharge. That means they receive and digest food and drink, absorb the 
nutrients that are then used by the viscera to produce and store the vital 
substances, and eliminate waste products and toxins.

Visceral manifestation theory states that the vital substances – Qi, Blood, 
Body Fluids, and Essence – are responsible for maintaining the physiological 
functions of the organs. Pathology or illness is the result, therefore, of deficiency 
or disturbance of the normal production, movement and function of these 
substances. According to VMT each organ has a relationship with one of the 
tissues of the body, and the state of each organ can be determined by observing 
that tissue. Functionally, each organ is also related to one of the sense organs, 
and changes in the acuity or ability of those senses can provide information 
about the associated organ. Each organ is also associated with an emotion or 
aspect of the psyche, and mental health changes can be indicative of disease or 
imbalance in an associated organ. The following provides a brief overview of the 
main functions, tissues, senses and emotions associated with each of the organs.

The five viscera.

The Heart.

The major physiological roles that the Heart performs are related to the 
Blood and the circulation. As it has been stated above, the Heart completes the 
process of Blood production, akin to the process of oxygenation following 
pulmonary circulation, then acts as the pump that ensures circulation of the
Blood throughout the body. Through Heart Qi and Blood, the Heart also maintains the blood vessels. The sense organ associated with the Heart is the tongue. The state of the Heart, therefore, can be observed through changes in the physical appearance of the tongue, the ability to taste or difficulties with speech (Maciocia, 1989). The Heart is also said to house the mind. This refers to the clarity of the mind as well as the contentedness or experience of joy and happiness. Any noticeable change in mental clarity or levels of happiness or depression will reflect the health of the Heart organ (Maciocia, 1989).

The Lung.

The Lung is sometimes referred to as “the delicate organ” (Zuo, 2002). The Lung serves major functions related to the Qi. Respiratory movements are controlled by the Lung. It is said that the normal movement of the Lung Qi is to descend and disperse. The descending function allows the inhalation of air deep into the Lung. The Qi of the whole body is controlled by the Lung, primarily through the initial production and residence of ancestral Qi in the Lung. The general descending and dispersing movement of Lung Qi also influences the movement of all Qi in the body via respiratory movement. Additionally the Lung plays a major role in the process of fluid metabolism in the body. Many organs contribute to the fluid metabolism process, however, the Lung plays a vital role. The dispersing function of the Lung Qi allows for the movement of fluid around the body, both outwardly and inferiorly. The tissue associated with the Lung is the skin and therefore, the Lung plays a vital role in sweating and thermoregulation as well as immunity. The Lung disperses the Defence qi and Body Fluid to the skin surface. Naturally as part of the respiratory system the Lung is connected to the sense of olfaction via the nose. Disruptions to smell, or any difficulty breathing through the nose would be indicative of Lung disorder (Maciocia, 1989).

The Lung also contributes to the circulation of Blood. Sadness and grief are emotions that can affect the state of the Lung function. Similarly, a weakness of the Lung Qi can lead to a propensity to these emotions.
The Liver

The major function performed by the Liver in CM is to maintain the emotional states and ensure the unhindered movement of Qi throughout the body. The Liver performs the function of dredging and fumigating the pathways by which Qi, Blood and Body Fluids move through the body. This function has widespread influence for several body systems. From a purely physiological perspective the Liver secretes bile into the Gallbladder, which stores the bile for release when necessary into the Stomach during the digestive process. If the release of bile is not well regulated, the digestive process will be disrupted. The process of digestion itself, performed by the Spleen and Stomach also relies heavily on unhindered movement of Qi as it is a continual process. Disruption in the flow of Qi can lead to poor extraction of nutrients, poor production of, or poor quality Qi, Blood and Body Fluids. Any blockage or stagnation in the movement of Qi and Body Fluids can also affect respiration and the metabolism of fluid within the body leading to dyspnoea and oedema. The Liver is connected to the eyes and, thus the sense of sight. The eyes rely on nourishment from the Liver for acuity and moisture. Decrements in visual acuity or abnormal lacrimation and ocular pain typically reflect diseases of the Liver (Zuo, 2002).

The tissues associated with the Liver are the sinews and tendons. The Liver Blood nourishes and moistens the sinews and tendons, and maintains their flexibility and suppleness. Deficiency of the Liver Qi or Liver Blood will often manifest as stiffness in the tendons and ligaments and muscular twitching. The Liver contributes to the emotional state again via the function of promoting free flow of Qi, Blood and Body Fluids. When the Qi, in particular, is not able to flow freely the emotions cannot be properly regulated and the result is a tendency towards irritability, frustration and outbursts of anger.

The Liver contributes to the circulatory process through its function of storing the Blood. The Liver is therefore in charge of ensuring that there is sufficient Blood in circulation and is responsible for storing excess Blood. When activity levels increase it is the responsibility of the Liver to release excess stores of Blood into circulation in order to meet increasing metabolic demands and
remove that Blood and return it to storage when it is no longer needed. Disruption to the Liver function of dredging the pathways can lead to problems with blood pressure. Storage of Blood also plays a role in the regulation of menstruation in women.

*The Spleen.*

The major function of the Spleen is to transform ingested food and drink and absorb necessary nutrients for the production of Qi, Blood and Body Fluids. The Spleen contributes to the circulatory system by controlling the blood vessels. This function ensures that the vessels do not leak and Blood is not lost. For example, the Spleen would be failing in the function of controlling the vessels if an individual bruises or bleeds easily and profusely (Zuo, 2002). The movement of the body is achieved through coordinated effort of the Liver Blood, which nourishes the tendons and ligaments, while the Spleen Qi nourishes the muscles and provides strength to the limbs. The natural movement of Spleen Qi is ascending. This ascending movement helps to prevent prolapse or leaking, and provides basic muscle tone. It also helps the Spleen to move fluids and Qi upwards to the Lung where it contributes to the water metabolism process.

The Spleen is connected to the mouth. Dryness of the mouth, swelling of the cheeks and changes in the moistness or colour of the lips are typically indicative of Spleen disorders. Emotionally the Spleen controls thought. If a person is prone to anxiety or excessive thinking, this can deplete the Spleen Qi. Conversely, if the Spleen Qi becomes weak, the result may be an inability to stop thinking and ruminating (Zuo, 2002).

*The Kidney.*

The Kidney is arguably the most important organ in the body. All Innate Essence is inherent to, or produced and stored in the Kidney. The Innate Yin and Yang that is formed at conception are thought to reside in the Kidney. This Innate Yin, Yang and Essence can be analogized to the blueprint for the body. Innate Yin is the body’s potential, while Innate Yang is the body’s functional capability. The Kidney also contains the Life Gate Fire. According to the Simple
Questions from the Yellow Emperor’s Classic of Internal Medicine, the Life Gate Fire is the basis for the Yang of the whole body that is ignited at conception. The Kidney is the organ of the Water element (according to the theory of Five Elements) and as such, needs the heat from the Life Gate Fire to produce the Innate Qi, akin to a vapor or steam, for the production of the vital substances in the body (Wu & Wu, 1997).

The Kidney plays a role in the process of fluid metabolism in the body. The Lung is often referred to as the upper source of water and the Kidney the lower source of water (Maciocia, 1989). With the help of the Life Gate Fire, the Kidney is able to transform the fluid that it receives from the other physiological processes in the body including respiration, blood circulation and fluid circulation to extract any remaining fluid that can be recycled and returned to the productive processes, similar to the filtration role that the kidneys plays in western medicine. Any impure fluid that is not to be recycled is transformed into urine and excreted via the Urinary Bladder, while the clear or recyclable portion is returned to circulation. The Kidney also contributes to the respiratory process by controlling the reception of Qi. This process refers to the ability to grasp the inhaled Qi and bring it deep within the Lung. When there is difficulty inhaling deeply this is indicative of failure of the Kidney to properly receive Qi (Zuo, 2002). The Kidney is connected to the ears and, therefore, nourishes the ear leading to clear audition. As the Kidney Qi becomes weak hearing acuity will decrease. The Kidney is vitally important to growth, development, aging and reproduction because it stores the Essence. As an extension of the Essence, the Kidney produces Marrow, which fills the bones and brain. The strength of the bones is therefore reliant on the functional state of the Kidney. The Marrow that is produced by the Kidney to fill the brain also manifests in the ability to concentrate and remember. Memory and concentration difficulties are often manifestations observed as the Kidney Qi becomes weak (Zuo, 2002). The emotions that are influenced by the Kidney are fear and worry. The combination of the Kidneys control of urination and controlling fear is why young children or even adults who are sufficiently afraid may become incontinent.
The Pericardium.

In certain texts a sixth Visceral organ is defined as the Pericardium, while other texts do not separate the Pericardium from the Heart and consider them to be one single organ. Regardless of whether the Pericardium is considered as separate to the Heart or not, the main function of the Pericardium is to protect the Heart. From a western medical perspective this is performed physically as the pericardium forms a physical cavity around the heart and lungs. In CM, however, the protective function of the Pericardium is more than simply a physical barrier but is an energetic barrier as well. Functionally, the Pericardium is more or less identical to the Heart with regards to Blood production and circulation as well as housing the Mind. Any pathological factor that affects the Heart will necessarily affect the Pericardium. Similarly, any treatment of the Heart should also include treatment of the Pericardium (Maciocia, 1989; Zuo, 2002).

The six bowels.

The Stomach.

The main function of the Stomach is to receive ingested food and drink and initiate digestion. The natural movement of Stomach Qi is to descend.

The Gallbladder.

Storage and release of bile for digestion as required is the major function of the Gallbladder. The Bowels only receive, transform and excrete, however, the Gallbladder stores bile like the Viscera, and is therefore, considered one of the Extraordinary Organs (see below). The Gallbladder controls the ability to make decisions. When the Gallbladder has become excessive the result may be rash decisions, while a deficiency may lead to indecisiveness.

The Small Intestine.

The major function of the Small Intestine is a process of discrimination. As it receives the chyme from the Stomach, it separates the clear from the turbid, which refers to extraction of nutrients for use within the body. Transformation
of the nutrients is performed with the assistance of the Spleen. The fluid that is extracted from the chyme that is not easily transformed by the Spleen for use to produce Qi and Blood is descended to the Kidney for a final transformation process.

*The Large Intestine.*

Similar to the Small Intestine, the Large Intestine performs a discriminatory process in the last stages of the digestive process. More fluids that can be absorbed and re-circulated are extracted by the Large Intestine while the remaining waste is churned to produce stool for excretion from the body.

*The Bladder.*

The role of the Bladder is to receive, and excrete urine. Although the Bladder is the last organ involved in the process of eliminating fluid waste from the body, the control of the urethra to release the urine is controlled by the Kidney Yang.

*The Triple Energizer.*

The Triple Energizer is an intangible organ that exists and functions energetically and has no individual western medicine counterpart. Instead, the functions considered to be under the control of the Triple Energizer from a CM perspective are controlled by various hormonal and neural processes within the western medical framework. The Triple Energizer separates the organs in the torso into three major sections. The Lung and Heart are contained within the Upper Energizer. Within the Middle Energizer are the Stomach, Spleen, Liver and Gallbladder. The Lower Energizer contains the Small and Large Intestines, the Kidney and Bladder. The major function of the Triple Energizer is to allow movement of fluid from one Energizer to another. Using the analogy of dams and floodgates, it must be possible to open and close the gates appropriately to allow the movement of fluids (water) throughout the body. This opening and closing of the body’s water cavities is controlled by the Triple Energizer, thus the Triple Energizer is said to control the water in the body.
The extraordinary organs.

There are several organs that are considered to be Extraordinary Organs. These organs are considered extraordinary because they have a hollow structure, like the six Bowels, however, they store clear and vital substances and perform functions in a similar way to five Viscera. These organs include the Brain, the Marrow, the Bones, the Blood Vessels, the Gallbladder and the Uterus. For the clinical purposes of this study an understanding of these organs and their functions is unnecessary and will not be discussed.

The relationships among the organs.

The organs are related to each other both structurally and functionally as is clear from the explanations of Visceral Manifestation Theory (VMT), however, they are also connected via the meridian network and theoretically via the Five Elements. Through these connections they coordinate in order to maintain and regulate bodily functions. Pathological states, however, can also be transmitted through these connections.

The Heart and Lung are connected through the Qi and Blood. The Lung plays an important role in assisting the Heart to propel the Blood around the body. The Heart Blood also plays a vital role in nourishing the Lung and maintaining respiration. When there is disorder of the Lung, the circulation will become abnormal. Conversely when there is insufficient Heart Qi to propel the Blood, the respiration will become abnormal (Zuo, 2002). The Heart is also connected to the Spleen via the Blood. The Spleen maintains the integrity of the Blood Vessels. Through the coordinated efforts of the Heart and Spleen, circulation of Blood will be smooth and consistent. In addition to the connection through blood circulation, these two organs are connected through the process of Blood production. Through the Blood once again, the Heart is related to the Liver. The Liver stores the Blood and regulates the quantity of blood in circulation. Abnormalities in the ability of the Liver to regulate the quantity of circulating blood can affect blood pressure, thereby affecting the Heart. These two organs are also connected through psycho-emotional factors. When the dredging and dispersing function of the Liver becomes impaired the supply of Qi
and Blood to the whole body becomes irregular. When this occurs, the Heart’s ability to regulate the emotions and thoughts will become intermittent and can lead to dysphoria, insomnia, irritability and susceptibility to rage (Zuo, 2002). Finally, the mutually transformative nature of Blood and Essence connect the Heart and the Kidney. The Kidney stores the Essence and releases it as needed during the process of Blood production. A weakness or deficiency of either Heart Blood or Kidney Essence will necessarily cause deficiency in the other.

The relationship between the Lung and the Liver relates to the regulation of Qi. Lung Qi naturally has a descending motion while the natural movement of Liver Qi is ascending. When coordinated, the Lung and Liver promote the smooth and cyclical movement of Qi in the body and respiratory tract. If the Liver Qi becomes stagnant, the Lung Qi will not descend and can cause coughing and pain in the chest or dyspnoea (Zuo, 2002). The Lung and the Spleen are connected in two ways: through production of Ancestral Qi; and through fluid metabolism. The Lung is responsible for distributing fluids throughout the body and the Spleen is responsible for absorbing and transporting water from the digestive process. Disruption to one of these organs or the balance between these organs will manifest as problems with water metabolism, such as Phlegm production or oedema. If there is a deficiency of Spleen or Lung Qi the production of Ancestral Qi will be affected and will lead to symptoms such as shortness of breath, oppression of the chest, poor appetite and loose stools. The Lung and Kidney are also related through the respiratory and water-metabolism processes. The coordinated efforts of the Lung and Kidney ensure normal distribution and excretion of water. Failures of the Kidney to receive Qi will cause coughing, tightness in the chest and short, difficult breathing. Disruption to either organs role in fluid metabolism will lead to oedema and dysuria.

The relationship between the Liver and Spleen involves the digestive and circulatory processes. The dredging and dispersing function of the Liver ensures the unhindered movement of Spleen and Stomach Qi during the digestive process. Failure of this Liver function will lead to interference with the digestive process with symptoms such as hypochondriac pain, distension of the abdomen,
loose stools and reduced appetite (Zuo, 2002). The Blood and Essence have the same source thereby linking the Liver and Kidney. Blood and Essence are transmutable substances, thus, deficiency of one will cause overconsumption of the other leading to a mutual deficiency.

Finally, the Kidney is related to the Spleen through the transformative function of Qi. The Spleen transforms food to support the Kidney and the Kidney provides the Yang energy to fuel the transformative function of the Spleen. When these organs fail to support each other the Spleen’s function will be diminished and the Kidney will be overtaxed.

The six Bowels are related through the digestive and excretory processes. The Stomach has a major transformative function, acting as the first step in the digestive process. The digested food is then transported to the Small Intestine as chyme and is digested further. Bile is excreted into the Small Intestine at this point, from the Gallbladder, promoting the digestion of fats. Nutrients extracted from ingested and digested food are absorbed and transported by the Stomach and Small Intestine to be used in the production of Qi, Blood and Body Fluids. The remaining waste is then separated into solid and liquid. The liquid is filtered and transformed by the Kidney. The clear fluid is re-absorbed, while the turbid fluids are excreted via the Bladder. Solid waste is passed from the Small to the Large Intestine where any remaining clear fluid is absorbed. The waste is then excreted from the body. The Triple Energizer plays a role in assisting the flow of fluid from the upper body to the lower body, thereby providing a framework for communication between the Lung, Spleen and Kidney. Because the six Bowels operate together in a progressive way to ingest, process and eliminate food and drink, any blockage in this pathway will affect the other Bowels.

Not only are there relationships between the Viscera and relationships between the Bowels, but there are also relationships between the Viscera and the Bowels. These are known as Internal-external relationships (Maciocia, 1989). The Viscera are Yin in nature, and are considered more internal. These organs are not typically connected directly to the exterior of the body (with the
The Bowels are Yang in nature and form a tract, which directly opens to the exterior at each end. There are five major internal-external relationships: Heart-Small Intestine, Spleen-Stomach, Lung-Large Intestine, Kidney-Bladder, and Liver-Gallbladder. The Triple Energizer is not related to a Yin organ in this way, but instead is a solitary organ that connects the exterior to interior within itself. The internal-external relationship is based on connections between the meridians, and coordinated physiological functions.

The organs are all related in various ways that allow the optimal functioning of the body through their coordinated efforts. Similar to the homeostatic processes according to western medicine, imbalances will disrupt these relationships and cause illness according to CM. Addressing the cause of the illness is therefore vital for effective treatment.

3.1.4 The meridians and collaterals.

The meridians and collaterals are lines that run along the length of the limbs, torso and head like lines of longitude on a map. There are twelve major meridians, each of which has smaller branches known as collaterals. The main function of the meridians and collaterals is to form a network of passageways to facilitate the movement of Qi, Blood and Body Fluids, and connect the Viscera and Bowels. Each meridian has many points along its path where Qi gathers. Clinically, these points are referred to as acupuncture points and needles can be inserted at these locations to affect the Qi that gathers there. The effect of the needle at that location can be transmitted through the meridian to distal or proximal locations depending on the function of the Qi gathering at those points. Each of the five Viscera and six Bowels has an associated meridian. In addition there is a twelfth major meridian associated with the Pericardium which is clinically used to assist in the treatment of Heart conditions and conditions of related organs. See figure 3 for a representation of the major meridians.

There are also eight extra meridians that are highly specialised in their function and location. The eight extra meridians act as reservoirs for the main meridian system, thereby maintaining an internal balance and allowing for the body to adapt to its surroundings. Together the eight extra meridians distribute
Essential Qi to the five Viscera and six Bowels, and serve to connect and integrate them into the entire body system. Through the ability to absorb excess Yang or Yin, and through the extensive connections to all meridians of the body the eight extra meridians function mainly to regulate the quantity of Qi in the meridians by transferring and redistributing Qi between different areas of the body as needed and circulate Defence Qi over the chest, abdomen and back (Deadman, Al-Khafaji, & Baker, 1998).
Figure 3. There are twelve major meridians that traverse the surface of the body and are linked to each of the twelve major organs. There are also eight extra meridians and each major and extra meridian has many branching collaterals and vessels (not shown here) that form a network throughout the body.
3.2 The Basics of Sleep According to Chinese Medicine

Understanding the natural movements and changes that occur over a twenty-four hour cycle and when moving from a state of wake to sleep and vice versa from a CM perspective is important to understanding the pathology underpinning OSA. According to Yin-Yang theory, the circadian rhythm can be divided into four phases that represents the balance between Yin and Yang. Yin within Yang, Yang within Yang, Yang within Yin and Yin within Yin – review figure 2.

The balance that must be maintained between Yin and Yang also applies to the process of wake and sleep. If the Yin and Yang of the body are in harmony, the circadian process will be smooth and regular. Sleepiness will not disturb the individual during the daytime, and wakefulness will not disturb the individual during the night-time. The interdependence between Yin and Yang will affect the depth and intensity of sleep that is achieved during the night-time. The length and depth of sleep is also synchronized by the eight extra meridians. Therefore, the extra meridians are vital to the control of the circadian rhythm. The extra meridians that are of greatest importance are the Yin and Yang Heel Vessels and the Yin and Yang Linking Vessels. These vessels are also connected to the five Viscera and six Bowels and it is through the action of the extra meridians that the internal body and organs are entrained to the external environment. In particular, the Yin Heel Vessel controls the length of sleep while the Yin Linking Vessel controls the depth of sleep during the night-time and the Yang Heel Vessel controls the length or stamina available for activity and the Yang Linking Vessel controls the strength available for activity during the daytime (Montakab, 2012).

The Spiritual Pivot from the Yellow Emperor’s Classic of Medicine states that during the night-time the Defence Qi, that has been circulating through the superficial layers of the body during wake, predominantly along the sinews and meridians providing muscle tone and flexibility, penetrates into the deeper layers of the body. The point of entry into the deep layers of the body is at the ankle and the individual enters sleep at that moment. In the morning the Defence Qi
moves to the surface again exiting the interior at the inner canthus of the eye thereby allowing the eyes to open. The inward movement of the Qi allows the muscles to relax during the first stages of sleep. Defence Qi is also known to be strongly involved in the maintenance of thermoregulation, thus as the Defence Qi moves inwardly at sleep onset, the core body temperature drops. Core body temperature then reaches its lowest point at the point of maximal Yin, when the Defence Qi is deepest within the body. Then the body temperature increases again as the Defence Qi moves back to the surface at wake.

The Blood is also transported to the interior of the body during the night, also contributing to the relaxation of the muscles and tendons. The movement of the Blood internally is partly motivated by the internal movement of the Defence Qi. If the Blood is not able to enter deeply into the body for storage in the Liver during the night there may be stirring Wind in the meridians, thus the muscles retain some activity and the individual may experience symptoms of periodic leg movement syndrome (PLMS) (Montakab, 2012). When the blood is able to enter deep within the body and rest, the muscles will rest and stable, deep sleep can be achieved akin to slow wave sleep.

3.2.1 The Mind.

The Mind is the collective term for the various emotional, mental and spiritual aspects of the human mind. The Mind is involved in processes of learning, intelligence, memory and the ability to differentiate emotions, coherent thoughts and associations, and alertness. When emotions disrupt the balance of the Mind, which is housed in the Heart, sleep disorders may manifest (Montakab, 2012). All mental activity is believed to be a combination of consciousness, Qi activity and function of the brain. Mental activity can refer to the reception of sensory input, information processing, memory consolidation, and the processing and comprehension of emotional stimuli. During sleep the Mind rests within the Heart Blood. Because the Heart Blood moves internally consciousness is lost and the Mind will not respond to external stimuli. If the Mind is unable to rest during the night due to a deficiency of Blood or excessive
emotional stimuli there may be difficulty in initiating sleep. This is often seen in patients with insomnia (Montakab, 2012).

3.2.2 Sleep stages.

From the view of Yin-Yang theory, the sleep stages represent the waxing and waning of Yin and Yang and normal sleep is an outcome of the dynamic balance and effective control between the two. During quiet wakefulness as the Mind prepares for sleep the Yang is beginning to wane. From sleep onset through to slow wave sleep the Yang continues to wane as the Yin waxes leading the mind smoothly through to deep slow wave sleep where the Yin is at maximal waxing point. Then as the Yin once again begins to wane and Yang begins to wax, REM sleep will begin and continues until Yang has reached maximal wax and an arousal occurs, temporarily restoring consciousness before the cycle begins again. Because the Yin-Yang sleep cycle is occurring within the Yin-Yang circadian cycle, the proportion of Yin (deeper slow wave sleep) is greater earlier in the night. As the circadian oscillator begins to rise in the morning there is a predominance of Yang (lighter REM) sleep.

Montakab (2012) described the sleep stages in relation to Qi, Blood and the internal organs. Stage 1 sleep is largely controlled by the Liver and the Lung. The movement of Defence Qi inwards allows relaxation of muscles and the mind to enter unconsciousness. When the Liver or Lung are diseased there can be difficulty in initiating sleep. In stage 2, sleep is maintained by the activity of the Liver and Spleen. If there is disease of either of these two organs there can be difficulty in maintaining stable sleep during stage 2. The deep sleep attained during SWS is reliant on the functioning of the Liver and Kidney. Restless sleep will occur if the Liver and Kidney are imbalanced. The regenerative and rejuvenating aspect of stage 4 sleep is thought to involve the Liver, Heart and Pericardium. If these organs are balanced there will be pleasant dreams. During REM sleep the eyes move rapidly due to the increased flow of Liver blood leading to internal Liver wind.
3.3 Syndromes/Clinical Patterns and Diseases

The most basic premise when viewing health and disease in CM is that when the body is balanced there will be good health and optimal functioning. Illness and disease arise when there is an imbalance that disrupts the normal functional process of the body. Regardless of how a disease arises, it is possible for disease to be transmitted easily throughout the body. It does so through the relationships between the various organs and meridians.

3.3.1 The eight principles of syndrome differentiation.

The process of syndrome differentiation involves the application of eight diagnostic principles. Syndromes are differentiated based on aspects of Yin and Yang, Heat and Cold, Excess and Deficiency, and External and Internal causes. Yin and Yang are the most general differentiation. Syndromes that are externally caused, hot and excessive in nature are considered Yang syndromes. Those illnesses that are internally caused, cold and deficient in nature are considered Yin syndromes. When differentiating syndromes of the Viscera and Bowels, these can also be considered as either Yin or Yang syndromes based on which functional aspect of the organ is affected. For example, a disorder of the Kidney in which an insufficiency of Yin failed to nourish the ears leading to attenuated auditory acuity would be considered a Yin syndrome. Thus, although an oversimplification, illness and disease will arise when the balance between Yin and Yang in the body is lost. The imbalances that can arise can be highly complex, depending on the organ, substance and function involved. Generally, however, all pathology can be reduced to the principles of Yin and Yang. When the balance is disturbed, illness results. Balance between Yin and Yang can be lost in four ways.

When the Yin or Yang of the body becomes excessive it will disrupt the balance. This is known as a relative predominance of Yin or Yang (Zuo, 2002). When there is an excess of Yin energy the pathology is considered Yin in nature, while an excess of Yang energy will cause pathology that is Yang in nature. For example, when we are exposed to a pathogen that causes fever and sweating, red complexion and rapid pulse – an excessive-heat pathogen – the Yin fluids will be
overly consumed and damaged by the heat. The pathogenic heat causes the Yang of the body, which is warm and active by nature, to become hyperactive and is thus classified as a Yang Disorder.

The other alternative that will cause imbalance between Yin and Yang is when either component declines or is depleted below normal levels. This is referred to as a relative decline of Yin or Yang (Zuo, 2002). More specifically, this relates to the relative deficiency of either the Yin-fluids or Yang-Qi. When either of these becomes deficient the result is usually hypofunction of the organs. Because of the ways in which Yin and Yang mutually affect and transform, a deficiency or excess of one will necessarily lead to impairment or damage to the other if left untreated.

Disease pathogens can be external or internal in cause. An external pathogen is one that invades from the outside of the body and will enter via the pores, Lung or digestive tracts. These include, but are not limited to western medical pathogens such as bacteria, viruses and allergens. In CM, there are six external excesses that can cause disease: Wind, Cold, Heat, Summerheat, Dampness and Dryness. These pathogens, when left untreated, may progress with an inward movement and can eventually infect the internal organs once it has passed through the superficial layers of the skin and muscles, then into the vessels and meridians and stagnate the joints until finally lodging in the organs. Alternatively, an internal disease will begin within the organs due to imbalance or the seven emotions and will start to move outward to the most superficial regions of the body. The seven emotions are: joy, anger, anxiety, thought, sorrow, fear and fright. These emotions can cause disruption to organ function if they become excessive or repressed, thus causing disease.

3.3.2 Causes of disease.

In CM, diseases are caused by pathogenic factors that can be divided into 4 main categories: 1) External pathogenic factors, 2) Internal pathogenic factors, 3) Secondary pathogenic factors, and 4) Trauma.
**External pathogenic factors.**

When the climate changes suddenly and people do not adapt appropriately climatic factors may invade the body and cause disease. Typically when the cause is due to climatic factors this refers to disease that has come about due to the six external excesses. The climatic factors may invade singly or collectively. For example, if there is a sudden drop in temperature and people do not have adequate clothing, pathogenic Cold can enter through the superficial layers of the skin and muscles or through the Lung. When the pathogenic factor is mild, the Defence Qi of the body may be able to repel the external pathogenic factor, thereby preventing illness. If the Defence Qi is weak or the pathogenic factor is particularly strong, however, the person may not be able to fight off the invading pathogen and will fall ill. Although these pathogenic factors typically refer to climate changes and are therefore commonly linked with seasonal change, with modern artificial environments, these factors can cause disease at any time of year. Living or working in a damp or mouldy environment, for example can cause Dampness to invade the body even if there is not an excess of humid and rainy weather. Similarly, central heating can lead to invasion of Dryness and Heat even during the winter months. Pestilence, or acute infectious diseases are also considered to be external causes of disease.

**Internal pathogenic factors.**

Diseases that are caused by internal imbalances within and between the organs are typically due to emotional dysregulation, poor diet and eating habits or overworking. As explained above, each Viscus is associated and influenced by a particular emotion. Excessive or unregulated expression of any of these emotions has detrimental effects on the associated organ. Excessive joy, for example can cause the Heart Qi and Yang to become excessive leading to Heat in the Heart, which can manifest as manic type behaviour. Another example is when excessive anger and frustration cause Qi to ascend, while excessive fear causes Qi to descend. These movements are in opposition to the natural direction of Qi flow in the associated organs of the Liver and Kidney, respectively. Thus, these emotions cause the counter-flow of Qi when they
become excessive. Excessive worry and contemplation, or suppression of emotional expression has a stagnating effect on Qi, which interferes with the flow of Qi necessary to perform the normal bodily functions. In these ways, excessive and unregulated emotional response is viewed as an internal cause of disease.

Improper diet is also an internal cause of disease. Not only is the excessive consumption of fried, sugary, processed, and nutrient poor food problematic, but also irregularity of meal times, and over-eating can cause imbalance within the digestive system. Additionally, excessive intake of raw, cold or hot foods can damage the Spleen and Stomach. Finally, the tendency to overwork in modern society can deplete the Qi and Blood of the body leading to disease. In the Simple Questions of the Yellow Emperor’s Classic of Internal Medicine, it is described how tempering one’s lifestyle to accommodate changes in season, tempering emotions and diet and refraining from overwork promotes balance and health and increases longevity (Wu & Wu, 1997).

Secondary pathogenic factors.

When an imbalance arises in the body, whether initially due to an external or internal pathogenic factor, the result can be the development of secondary pathogenic factors that can be transmitted to other regions of the body. For example, any disease that leads to disruption any organ involved in the water metabolism processes will result in the secondary production of Phlegm and oedema. In CM Phlegm refers to both the substantial phlegm that can be understood from a western medical standpoint that collects in the respiratory tracts and can be expectorated, but it also refers to an insubstantial form that lodges within the meridians and organs inside the body. Phlegm is particularly stagnating and obstructive in nature. It interferes with the normal movement of Qi, Blood and Body Fluids, thereby affecting many processes within the body. Other secondary pathogenic factors include Blood stasis when a pathogen interferes with Blood circulation, Qi stagnation resulting from hindered flow of Qi, and various other complications from protracted or chronic imbalance within the body.
Trauma.

The final disease category involves traumatic injury. This includes any physical or chemical injury, animal or insect bites and stings. Typically, these causes of disease are treated using western medical techniques in the initial stages. Recovery, however, is often aided with the use of herbal or acupuncture treatment to prevent secondary pathogenic factors such as Qi stagnation and Blood stasis.

3.4 The Diagnosis Process

In CM it is important to understand the onset and progression of a disease or illness in order to treat the disease effectively, as it is in western medicine. In western medicine this is often determined by assessing blood or histological samples, taking other measurements, such as x-rays or MRI scans, but it will invariably begin by an observation of the patients signs and symptoms as well as taking a verbal account of the patient’s experience.

Chinese medical diagnosis and syndrome differentiation is performed using 4 diagnostic techniques. The first is inquiry of symptoms, and their progression since onset. Imbalance in one area of the body can affect related organs leading to the manifestation of co-morbid symptoms in other regions of the body. Therefore, in CM, typical clinical inquiry is extensive and can sometimes appear trivial or unrelated to the primary symptoms at hand. These avenues of inquiry, however, are often necessary to distinguish one syndrome from another and in order to determine causality, disease progression and prognosis.

The second diagnostic method involves observation. Many aspects relating to the health of the internal body can be ascertained by observing the different physical characteristics of the tongue, skin, hair and body. Due to the use of hair dyes, conditioning treatments, skin lotions, spray tan, and cosmetic surgery, the latter three physical characteristics are not given the same emphasis today as they were in ancient times. The tongue, however, is still a widely used indicator of internal physiological states in CM practice. The features of the tongue that are given attention are the physical shape (e.g., long, thin, swollen, etc.), specific
abnormalities or features (e.g., teeth marks, cracks or fissures, etc.), the colour of the tongue body (e.g., pale, red spots, etc.), and the tongue coating (e.g., thick or greasy tongue fur, etc.).

The third method of diagnosis is olfaction and auscultation. Auscultation, or listening, as a diagnostic method involves taking note of the quality of the patient’s voice (e.g., hoarse, soft, barking, etc.). Using olfaction is generally a passive tool that can provide diagnostic information if a strong odour is present (e.g., pungent smelling breath, etc.).

The last diagnostic method involves bilateral palpation of the radial pulse. The radial artery can be felt with the tips of the fingers at three adjacent locations just proximal to the palmar crease (see figure 4 for a representation of the pulse locations). There is considerable variety in the pulse qualities described by different CM texts (e.g., string-like, floating, slippery, rapid, etc.). Despite considerable variation in the description of pulse qualities across the ancient texts, the WHO created a recognized standard of pulse qualities in 2007. All registered practitioners in Australia now conform to these standards. Each different quality indicates a pathological condition in the body. When they are felt in different locations of the pulse or in combination with other qualities the condition of health of different regions or organs in the body can be ascertained.

*Figure 4.* An illustration of the three pulse locations along the radial aspect of the forearm.
3.5 Treatment of Disease in Chinese Medicine

Chinese medicine treatment includes acupuncture, moxibustion, herbal medicine, massage, and dietary therapy. For the purposes of the present study, only acupuncture treatment will be discussed. Acupuncture involves inserting fine needles to varying depths through the dermal layers of the skin, into the muscles. The majority of acupuncture points lie along the twelve primary meridians and the various branches of these meridians. Placing needles along the meridians at specific points will influence the associated organs, and the various physiological functions under the control of that organ.

Acupuncture is typically performed with filiform needles that are of varying length and diameter. In modern times, these needles are available in single-use, pre-sterilised packages and are inserted with the aid of a disposable guide tube to ensure accuracy with needle location. Needle insertion typically involves three stages: 1) insertion of the needle into the superficial dermal layer, 2) deep insertion of the needle to an appropriate depth to access the desired acupuncture point, and 3) elicitation of De Qi – a physiological sensation obtained when the Qi at the acupuncture point interacts with the needle (Ellis, Wiseman, & Boss, 1991). The depth and angle of needle insertion is dependent on the anatomy, physiology and intended treatment effect for each acupuncture point used. The age and constitution of the patient is also considered when choosing a needling depth.

Once the needle has been inserted into the appropriate location and depth and the De Qi sensation has been elicited, the desired treatment effect requires stimulation of the needle. The basic methods of stimulation involve manually lifting and thrusting, and twirling or rotating the needle (Ellis et al., 1991). As CM has advanced throughout the years, other methods such as electrical stimulation and laser have been used to stimulate acupuncture points. Manual stimulation, however, is still the most commonly used form of needle stimulation in clinical practice. Depending on the direction in which the needling is rotated, or the strength with which the needle is lifted or thrusted, different treatment effects can be achieved.
3.6 OSA According to Chinese Medicine

Sleep apnoea was not defined as a disease entity in Chinese medicine literature until recently due to the promotion of integration of Chinese and western medical practice. Many experts and researchers in China have used Chinese herbs to treat OSA both in individual case studies and as part of larger clinical trials over the past several decades. These studies have each sought to identify the disease mechanisms underlying OSA in order to inform the choice of treatment. Primarily there is a strong consensus that obstruction due to Phlegm is the most important pathological factor involved in OSA within the Chinese population. Several causes, including obesity, overwork, chronic illness, dietary irregularity and excessive intake of alcohol and smoking are thought to damage the functions of the Spleen and Stomach. When the Spleen fails to adequately transform and transport Body Fluids, the fluids accumulate and produce Dampness and Phlegm. The Phlegm lodges in the Lung and obstructs the smooth flow of Qi through the respiratory system leading to apnoeas and hypopnoeas (Cui, Zhang, & Luo, 1997; Cui, Zhu, & Liu, 2002; Liu, Wang, Xue, Chen, & Han, 2010; Shi & Shi, 1998; Su & Li, 2004; Su et al., 2008). Su and Li (2004) explain that the symptoms of daytime sleepiness, and poor memory are due to Phlegm obstruction of the head. The Phlegm obstructs and prevents the clear Yang from ascending to nourish the head leading to daytime hypersomnolence, and poor memory.

The classification of syndromes underlying the symptoms of OSA can be divided into deficiency and excess patterns. Deficiency types such as Spleen deficiency, Spleen and Kidney deficiency, Yang deficiency, and Lung and Kidney deficiency all produce the symptoms of OSA, essentially through the same disease mechanism, in that eventually these syndromes disrupt the fluid metabolism process leading to the production of Phlegm, which obstructs the airways (Liu et al., 2010). The Spleen Qi is vital for the transformation of food nutrients into usable energy, Qi and Blood, in the body. When the Spleen Qi becomes deficient, or the Spleen Yang is weak, this process becomes sluggish. As the fluid from the digestive substances cannot be transformed the fluid
accumulates creating an environment of dampness. Over time the stagnation of Dampness can thicken to produce Phlegm, which obstructs movement of Qi and Blood throughout the body. Chronic illness, chronic overwork, and anxiety, are common causes of Spleen Qi deficiency. The Spleen and Lung work in tandem during the process of fluid metabolism. The phlegm is easily transmitted from the Spleen to the Lung. Lung Yang is primarily made up of Defence Qi. When the Lung Yang or Lung Qi is deficient the individual will easily and repeatedly become ill from external pathogenic attacks, there will be rhinitis and spontaneous sweating due to an inability of the Defence Qi to close the pores. The Spleen and Lung Yang is typically depleted during chronic illness or when excessive consumption of cold and raw foods damage the internal Yang. This is also common in the elderly as the Life Gate Fire begins to diminish. The Life Gate Fire is the source of all Yang in the body and the failure of Kidney Yang to support the functions of the Spleen and Lung in fluid metabolism will ultimately lead to production of Dampness and Phlegm.

Excess types of OSA include Phlegm, and Qi and Blood stasis. Regardless of the underlying disease pattern, in each of these situations the mechanism of disease is congestion and obstruction of the chest and head causing respiratory disruption (Su et al., 2008). Pathogenic Heat is also a factor in some patients, either in the absence or presence of Phlegm. Smoking can also be a factor since tobacco is hot in nature and is constantly creating pathogenic Heat and Dryness in the Lung. Syndrome patterns such as Yin and Blood deficiency, Wind-Heat attacking the Lung, and Liver-Lung Fire lead to an upward movement of internal Heat, which mutually binds with Phlegm, or an external pathogenic factor, in the respiratory tract and the resulting struggle obstructs the airway (Liu et al., 2010; Su et al., 2008; Xiao, 1994). The Liver function of promoting the smooth flow of Qi influences the Lungs function of descending. If Liver Qi stagnates over a long period of time it can turn into Liver-Fire. Fire tends to ascend and therefore Liver-Fire flares upwards towards the chest and head. Here it prevents Lung Qi from descending resulting in breathlessness and asthma. The stagnation of Liver Qi causes a feeling of fullness and distension of the chest. This pattern can also
be caused by anger, which causes the formation of Liver-Fire, usually after a prolonged time of Liver Qi stagnation. It is also compounded by the excessive consumption of hot and greasy goods, which tend to create Heat (Maciocia, 1989). This pattern can also be precipitated or aggravated by an external Wind-Heat pathogen.

3.6.1 Treatment of OSA with Chinese medicine.

The therapeutic effectiveness of manual acupuncture treatment for OSA was investigated in a recent randomized, placebo-controlled trial (Freire et al., 2007). Following ten weekly acupuncture treatments, 10 patients treated with acupuncture showed significant improvements in their OSA severity, oxygenation and other polysomnographic measures compared with 7 placebo and 9 control patients. Additionally, subjective measures of sleepiness and measures of health and wellbeing, were shown to be significantly improved as a result of acupuncture, but not by placebo acupuncture or in the non-treatment control group. The results of this study by Freire and colleagues (2007) are promising, however, the study is subject to limitations, and generalizations should be viewed cautiously until further evidence to support their initial pilot study can be provided.

In 2010, Freire and colleagues conducted another study investigating the immediate effect of a single acupuncture treatment on AHI. The study compared the changes in AHI in four groups of ten moderate to severe OSA patients receiving either traditional manual stimulation, applying an electrical pulse to the needles at either low or high frequency or no treatment. The results showed an immediate reduction in night-time AHI for the patients receiving manual or high frequency electrical stimulation, but not for the low frequency electrical stimulation or non-treatment control groups. In addition to significant reductions in AHI the manual acupuncture group also showed a significant reduction in micro-arousal, not shown in the high frequency electro-acupuncture group. The acupuncture points selected for manual treatment were the same as their previous study, while the electro-acupuncture groups were only needled at a sub-set of those points.
Data from a recent systematic review of six randomized controlled trials of acupuncture for the treatment of OSA suggests that acupuncture in various forms can be an effective treatment of moderate OSA in which reduced AHI and improved oxygenation have been reported (Lv, Jiang, Huang, Zhang, & Chen, 2016). In addition, no adverse events or side effects were reported with acupuncture treatment. Only two of the six studies included in the review were conducted outside of China and reported in English.

3.6.2 Limitations of Chinese medicine research on OSA treatment.

The majority of research conducted on the treatment of OSA using CM has been conducted without stringent adherence to normal scientific methods. Many studies do not include a valid control or placebo comparison groups, while other studies have combined multiple treatment modalities, such as herbal and acupuncture treatment. The major limitation of the study by Freire and colleagues (2007) relates to a lack of appropriate diagnostic and pathophysiological explanations of OSA according to Chinese medicine. The acupuncture points used in treatment were selected based on their known effects of: strengthening Qi, treating somnolence, and treating throat and respiratory disorders (Freire et al., 2007). It has been demonstrated, however, that there are several CM phenotypes of OSA. While there is some overlap between the pathological underpinnings of some of these phenotypes, there are several distinct aetiological factors that, depending on the diagnosis, should be addressed by the treatment. For maximally effective treatment, the underlying aetiology must be addressed. Treating all OSA patients with the same acupuncture treatment is only appropriate if all patients have similar underlying CM disease patterns. CM emphasises that it is important to have a clear diagnosis in order to maximise effectiveness through individually tailored treatment. Failure to adequately address the causative factors associated with any condition will reduce the efficacy of the overall treatment in both the short- and long-term (Zuo, 2002). The study by Freire and colleagues (2007), failed to indicate whether a CM diagnosis had been performed on any of their
participants, or whether a specific disease pattern was used as a basis for selecting acupuncture points for treatment.

Successful CM treatment cannot simply consist of treating the patient with the same acupuncture or herbal prescription repeated indefinitely. As a treatment begins to take effect, the energetic state of the patient should begin to change. In normal clinical practice, the treatment prescription should be altered on a session-by-session basis to address the change in symptoms and energetic state (Lucas, 2009). For the purposes of scientific research, such alteration to treatment from week to week would lead to highly inconsistent treatments across the sample. The most appropriate way to combat this issue is to ensure the sample has similar diagnoses and provide an appropriate treatment that allows for change over time. While this is not ideal, it is likely the most appropriate approach to assessing the effectiveness of acupuncture within a scientific research framework.

A major limitation of the current literature on acupuncture as a treatment for OSA is the lack of identification of the physiological effects of acupuncture treatment. A decrease in AHI should be accompanied by changes in physiological factors known to play a role in OSA aetiology. Assessing the way in which acupuncture can reduce AHI may help to identify whether the treatment is applicable to all OSA patients or whether it suitable only for a subset of OSA phenotypes.
Obstructive sleep apnoea is a relatively new disease even within the western medical system, having only emerged as a defined disorder in the literature approximately 40 years ago (Guilleminault et al., 1976). It is, therefore, not surprising that CM classical texts do not refer specifically to OSA or its pathogenesis. A recent study investigated the effectiveness of acupuncture as a treatment for obstructive sleep apnoea (Freire et al., 2007). Their results were mixed, but promising. Despite finding improvements in daytime sleepiness and the apnoea/hypopnoea index (AHI), the conclusion that acupuncture is an effective treatment for OSA should be viewed with caution due to small sample size and several theoretical and methodological limitations. An important aspect of Chinese medicine treatment, including acupuncture, is to take an individually tailored approach that is based on disease syndrome. Recent research and case study reports have outlined several CM disease syndromes that can underlie the presentation of OSA. There is as yet no conclusive data showing the frequency of each of these syndromes within the OSA population.

In order to determine the efficacy of acupuncture as a treatment for OSA through randomised controlled clinical trials, the treatment needs to address a specific CM syndrome. In CM the human body is viewed as an interconnected entity, and as such two patients with similar signs and symptoms may have considerably different underlying pathology, and would therefore be diagnosed with different syndromes. For optimally effective treatment, the underlying syndrome causing the manifestation of certain signs and/or symptoms must be addressed. Treating all OSA patients with the same acupuncture treatment is only appropriate if all patients have similar underlying CM pathogenesis. CM emphasises that it is important to have a clear diagnosis in order to maximise therapeutic benefits through individually tailored treatment. Failure to adequately understand the causative factors associated with any condition will compromise the intended benefit of the overall treatment.
The major theoretical limitation of the study by Freire and colleagues (2007) relates to a lack of appropriate diagnostic and pathophysiological explanation of OSA according to CM. Acupuncture points used by Freire and colleagues (2007) were selected based on their known effects of: strengthening Qi, treating somnolence, and treating throat and respiratory disorders. Hence, this study failed to indicate whether a CM diagnosis had been performed on any of their participants or whether a specific syndrome was used as a basis for the selection of the acupuncture points used in their treatment.

As described in the previous Chapter, many case studies have sought to identify the disease mechanisms underlying OSA. There is a wide spectrum of CM syndromes that can cause OSA, however, the general consensus is that, regardless of whether the primary syndrome is the result of deficiency or excess, or a cold or heat syndrome, the secondary production of Phlegm appears to be the most important factor. Phlegm that lodges in the Lung leads to obstruction of Qi flow throughout the respiratory tract (Su & Li, 2004; Su et al., 2008). The presence of Phlegm also explains the common presentation of daytime somnolence as the Phlegm prevents the Yang from rising and nourishing the head.

Many of the pathological factors that contribute to the symptoms of OSA can also contribute to the development of comorbid conditions seen in the OSA population. Liver Qi stagnation and Liver Fire are fundamental syndromes involved in the presentation of Hypertension (Flaws & Sionneau, 2005; Zuo, 2002). Spleen deficiency, Dampness and Phlegm are common CM syndromes seen amongst obese, overweight and diabetic individuals (Flaws & Sionneau, 2005; Shi & Shi, 1998). Liver Fire and Lung deficiency play a vital role in the pathogenesis of asthma and rhinitis (Zuo, 2002). Finally, Heart and Spleen deficiency as well as Liver Qi stagnation, Phlegm and Heat are all common CM syndromes underlying depression (Maciocia, 2009). The wide variety of different CM syndromes that can present with secondary Phlegm obstruction of the respiratory system also help to explain the lack of specificity of various OSA symptoms and comorbidities.
The aim of this study was to identify the CM syndromes presenting in an Australian sample of OSA patients in order to better understand the contributing pathological mechanisms underlying the symptoms of OSA and guide development of an appropriate treatment. It is not possible to compare the distribution of syndromes identified in the present sample with past research, as past research has not provided an analysis of syndrome frequency. To our knowledge this is first diagnostic study looking to identify the CM syndromes underlying the symptoms of OSA and their frequency outside of China. A secondary aim was to determine whether different CM syndromes identified within the OSA population could be associated with obvious differences in OSA severity, sleepiness, age, and BMI or distribution of comorbid conditions including diabetes, depression, hypertension and asthma or rhinitis.

4.1 Methods

4.1.1 Participants.

Forty participants (15 female), ranging in age from 19 to 59 years (\(M = 44.18, SD = 11.73\)), who were individually and independently admitted to the Sleep Laboratory at the Department of Respiratory and Sleep Medicine for polysomnography to investigate possible OSA, were asked to first undergo a CM diagnosis. Individuals were excluded if they were: younger than 18 years or older than 60 years of age, were dependent on a carer or guardian, were pregnant, or were unable, by reason of cognitive impairment, to give informed written consent, or unable to communicate clearly (e.g., requiring a translator). Any patient who had undergone bypass or gastric banding surgery, had chronic obstructive pulmonary disease, emphysema, or stroke were also excluded. Participants were not excluded on the basis of any other co-morbid cardiovascular, respiratory or digestive conditions unless the co-morbid condition was a significant threat to life or the patient had undergone significant surgery to address these conditions.
4.1.2 Design.

The present study adopted a cross-sectional, semi-blind design. The CM diagnosis was performed prior to confirmation of OSA through polysomnographic exploration, thus decreasing the likelihood that the CM practitioner would be biased in their syndrome diagnosis. This study was granted ethical approval by the Austin Health Human Research Ethics Committee, project number 04344.

4.1.3 Materials & apparatus.

Information about the patient’s medical background and symptom patterns were collected via three questionnaires, including a medical history and basic demographics questionnaire and two symptom questionnaires (see Appendix A for copies of these questionnaires). The symptom questionnaires included 75 questions about general physical and mental health symptoms in order to form a full diagnostic picture. For each symptom, patients were to rate how much each symptom interfered with daily life on a scale from 0 – 3 (0 – do not experience/never or rarely; 1 – mild/once a month; 2 – moderate/once a week; 3 – severe/more than 3 times per week). A fourth questionnaire was completed by the Chinese medicine practitioner to record information from the patient’s pulse and observation of the patient’s complexion, and tongue as well as the food and drink consumed in the two hours prior to the diagnosis session. All questionnaires were designed using Adobe Acrobat Professional 9.0 and were completed on a laptop computer.

4.1.4 Procedure.

The hospital database was used to identify patients who had been referred for a polysomnographic study to investigate possible OSA. Each patient was contacted by phone two weeks prior to their scheduled PSG and informed of the CM diagnosis study. If patients met the inclusion and exclusion criteria, and were interested in taking part in the study, they were sent a plain language statement and consent form one week prior to their sleep study in order to
provide adequate time for them to understand what their participation in the study involved.

Upon arrival to the sleep clinic, participants were shown to a private, comfortable, well-lit room. The CM diagnostic procedures were explained to the participant and informed consent was obtained. The participant was first asked to complete the medical history questionnaire. This questionnaire was used to obtain data regarding age and medical background including experiences of hypertension, diabetes, depression and asthma and hay fever. Subsequently, the participant was asked to fill in the two symptom questionnaires. Once the questionnaires were completed, the investigator felt the pulse bilaterally at the radial pulse, and observed the tongue. This process took no longer than one hour. The data from the symptom questionnaires and tongue and pulse analysis was used to develop syndrome profiles for each patient. Trained technicians then prepared the participant for their polysomnographic study, which also included completing the Epworth Sleepiness Scale (ESS) and calculation of body mass index (BMI).

The polysomnographic results, including the apnoea/hypopnoea index (AHI), arousal index (AI) as well as the number of events with oxygen desaturation greater than 4% of baseline (ODI4%), were obtained from the sleep clinic database once the data had been scored and analysed by trained sleep technicians, and reported by an attending sleep physician.

4.1.5 Data analysis.

The collected information pertaining to medical background, symptoms, tongue and pulse characteristics were analysed using traditional techniques for each participant. These techniques involved applying theory based on the Eight Principles, Principles of Qi, Blood and Body Fluids and Visceral Manifestation Theory by the CM practitioner to form a diagnosis. A one-way ANOVA was used to determine if there were significant differences in AHI, BMI, ESS and age across the identified CM syndromes. Chi-square analysis, with equal distribution of comorbid conditions expected, across CM syndromes was used to assess the distribution of comorbid conditions between the identified syndromes.
4.2 Results

4.2.1 Participant descriptive and demographic data.

One of the 40 participants was excluded due to a medical condition that posed a significant threat to life that was not disclosed during screening. Of the remaining 39 participants, 5 did not meet the threshold for diagnosis of OSA and were excluded from further analysis. For the 34 identified OSA sufferers, the average BMI was 35.15 (SD=8.64) (ranging from 19 to 57.1) and average sleepiness ratings were 9.23 (SD=5.52) (ranging from 1 to 23, with scores ≥16 indicating severe sleepiness, Johns, 1991).

4.2.2 CM syndrome diagnosis.

The CM methods of syndrome differentiation, including observation, symptom report and tongue and pulse characteristics led to the identification of 10 CM syndromes in total. Of the 34 OSA patients, 14 patients (41.18%) exhibited Spleen Qi deficiency with Liver-Lung Fire and Phlegm. Seven patients (20.59%) exhibited Spleen Qi deficiency and Kidney Yin deficiency and Phlegm. Three patients (8.82%) had Spleen and Kidney Yang deficiency with Dampness encumbrance and Kidney Yin deficiency, 3 patients (8.82%) had Kidney Yin deficiency with Fire effulgence with Liver-Lung Fire and Phlegm. Two patients (5.88%) had Spleen and Lung Qi deficiency with Phlegm-Dampness. One patient (2.94%) had Spleen deficiency with Dampness encumbrance and Liver-Lung fire, 1 patient (2.94%) had Spleen and Kidney Yang deficiency with Dampness encumbrance, 1 patient (2.94%) had Kidney Yin deficiency and Phlegm, 1 patient (2.94%) had Liver-Lung Fire, and 1 patient (2.94%) had Heart and Spleen Qi deficiency.

Several of the identified syndromes share underlying pathophysiology, and can be treated using similar treatment formulas despite slight differences in their syndrome classification. Due to the similarity of the underlying pathological mechanisms, several CM syndromes were grouped together to produce a distinct CM phenotype that is distinguishable from other phenotypes based on different underlying pathophysiology. There were 4 CM phenotypes of OSA identified by
grouping together similar CM syndromes. Common to all phenotypes was the report of snoring, dry throat and daytime somnolence. Table 2 shows the grouping of similar CM syndromes into phenotypes and patient distribution as well as the five most frequently observed symptoms in each CM phenotype.

Table 2. CM Syndrome Classifications for OSA Patients: their CM Phenotype Membership and Symptom profile.

<table>
<thead>
<tr>
<th>Identified CM syndromes</th>
<th>CM Phenotype</th>
<th>Main symptom profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spleen Qi deficiency and Liver-Lung Fire and Phlegm N=14</td>
<td>1. Spleen deficiency and excess heat N = 15</td>
<td>Poor memory, Dizziness, Lassitude, Temple headaches, Outbursts of anger, Palpitations, Insomnia</td>
</tr>
<tr>
<td>Spleen deficiency with Dampness encumbrance and Liver-Lung fire N=1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spleen Qi deficiency and Kidney Yin deficiency and Phlegm N=7</td>
<td>2. Spleen deficiency and deficiency heat N = 10</td>
<td>Lassitude, Depression, Irritability, Evening heat sensations and night sweating, Loose stools</td>
</tr>
<tr>
<td>Spleen and Kidney Yang deficiency with Dampness encumbrance and Kidney Yin deficiency N=3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart and Spleen Qi deficiency N=1</td>
<td>3. Spleen deficiency N = 4</td>
<td>Lassitude, Poor memory, Oppression of the chest, Heaviness of the head, Cough with phlegm, Catch colds easily, Poor appetite</td>
</tr>
<tr>
<td>Spleen and Lung Qi deficiency with Phlegm-Dampness N=2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spleen and Kidney Yang deficiency with Dampness encumbrance N=1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney Yin deficiency with Fire effulgence and Phlegm N=3</td>
<td>4. Heat (excess or deficiency) N = 5</td>
<td>Tinnitus, Insomnia, Poor concentration, Dry Skin, Heat Sensations, Excessive appetite and thirst</td>
</tr>
<tr>
<td>Kidney Yin deficiency and Phlegm N=1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver-Lung Fire N=1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4.2.3 OSA severity between CM phenotypes.

The average AHI, BMI and ESS for each CM phenotype are shown in figure 5. A one-way ANOVA comparing AHI showed no significant differences across
the 4 CM phenotypes, $F_{(3,30)}=1.102$, $p=.364$, $\eta^2=.267$. There was a significant difference in BMI across the CM phenotypes, $F_{(3,30)}=3.606$, $p=.025$, $\eta^2=.737$. Pairwise comparisons showed that patients with phenotypes 1 and 2 had a significantly higher BMI than patients with phenotype 4, $p=.005$, and $p=.002$. There were no significant differences in ESS, $F_{(3,30)}=1.764$, $p=.175$, $\eta^2=.412$, or age, $F_{(3,30)}=1.860$, $p=.158$, $\eta^2=.433$, between the CM phenotypes.

**Figure 5.** The figure shows the mean a) AHI, b) BMI, c) ESS and d) Age for each CM Phenotype. Error bars represent standard error. Asterisks indicate significance at <.05.

### 4.2.4 Association between CM phenotype and comorbid conditions.

Figure 6 shows the percentage of patients with various common comorbid health conditions in each of the identified CM phenotypes. A Chi-square test of independence showed that the distribution of common comorbid conditions of
OSA were not significantly different between the CM phenotypes. The presence of diabetes, $\chi^2 (3, N=34)=0.627, p=.890$, depression, $\chi^2 (3, N=34)=4.068, p=.254$, hypertension, $\chi^2 (3, N=34)=1.580, p=.664$, and asthma or rhinitis were not significantly more prevalent amongst a particular CM phenotype, $\chi^2 (3, N=34)=4.543, p=.208$.

![Figure 6](image)

Figure 6. The figure shows the percentage of patients with a) diabetes, b) depression, c) Hypertension and d) Asthma or hay fever within each CM Phenotype

### 4.3 Discussion

This study aimed to determine the common CM syndromes identified within an Australian sample of OSA patients and assess the distribution of those syndromes. The results indicate that the most common CM syndrome seen in patients with obstructive sleep apnoea, was Spleen Qi deficiency accompanied by Liver-Lung Fire with Phlegm. Although ten different CM syndrome patterns were identified within the sample, syndromes with similar symptom profiles and disease mechanisms were grouped together to classify four CM phenotypes of
OSA. Each classified CM phenotype requires a different treatment approach. The most common CM phenotype consists of syndromes predominantly characterised by the presence of Spleen deficiency and Excessive Heat. This phenotype was attributed to more than 44% of the sample population. The second most common phenotype was comprised of syndromes characterised by Spleen deficiency and deficient Heat, and was present in approximately 29% of the population. Characteristics of simple Spleen deficiency without evident Phlegm or Heat defined the third phenotype, being present in approximately 12% of the sample. Finally, a simple Heat phenotype consisting of syndromes manifesting with either excess or deficient Heat but without evident Spleen deficiency or Dampness was present in approximately 15% of the population.

Each of the five non-OSA patients displayed symptoms consistent with at least one of the 4 proposed CM phenotypes. Two of the excluded patients had the Spleen deficiency and Excessive Heat phenotype and two had the simple Spleen deficiency phenotype. Night-to-night variability, or the presence of only mild disease may explain why these patients did not meet threshold diagnostic levels for OSA.

The first 2 phenotypes produce symptoms of OSA largely through the same disease mechanism; through the mutual obstruction of Phlegm and Heat. The third phenotype likely produces the symptoms of OSA through Phlegm obstruction alone, while the fourth phenotype likely produces symptoms through an obstruction of the Lung primarily due to upward flaring of internal pathogenic Heat. While the sample of patients showed many of the syndromes suggested in the Chinese literature, not many patients in the present sample were found to exhibit Blood stasis as had been suggested by past research (Cui et al., 2002; Y. Liu et al., 2010; Su & Li, 2004; Su et al., 2008). This may be due to the fact that patients were excluded from the present study if they had undergone coronary bypass surgery, had experienced a cerebrovascular event or who had serious cardiovascular conditions that posed a significant threat to life.

The results suggest that OSA severity (AHI) and severity of sleepiness (ESS) are not related to CM phenotype. The lack of difference in sleepiness severity
across the CM phenotypes is consistent with past findings. It should be noted that selection bias could have confounded this finding, as symptoms of hypersomnolence typically lead patients to seek help. There are a high proportion of undiagnosed OSA patients in the community and sleepiness severity may therefore differ in these individuals. Each of the classified CM phenotypes may present the symptom of sleepiness, albeit caused by different underlying factors. In phenotypes 1, 2 and 3 phlegm will typically lead to obstruction of Qi, Blood, and Yang to the head, which leads to undernourishment and sleepiness. Syndromes characterised by Heat typically cause difficulty with initiating sleep and maintaining sleep. Daytime somnolence in this case is not necessarily a pathological symptom of the syndrome itself, but rather, it is a by-product of later sleep onset times, fragmented sleep, or overall shorter sleep durations (Maciocia, 2004). In comparison to phenotypes 1 and 2, the sleepiness ratings by patients with phenotype 4 are generally less severe, however, this difference was not significant. A tendency to lower levels of sleepiness might be expected in this group due to the fact that the internal excessive Heat, or hyperactive Yang, overrides the effect of sleepiness during the day.

Spleen deficiency and dampness are more often seen in overweight and obese patients (Shi & Shi, 1998). This is consistent with the finding that the BMI was found to be significantly higher in the patients with phenotype 1 and 2 than in phenotype 4. The sample size for phenotype 4, however, was much smaller than that obtained for phenotype 1 or 2. The generalization of the differences in BMI should therefore be viewed with caution. Obesity is a common risk factor for OSA (Bearpark et al., 1995), thus it is not surprising that 27.5% of the present sample was overweight, 40% were obese, and 25% were morbidly obese. It is also not surprising then that the most common CM syndrome seen in these patients involved a deficiency of the Spleen Qi, Dampness encumbrance and Phlegm.

There is a well-established link between OSA and type II diabetes. Several large, population studies have shown significant associations between OSA and
insulin resistance and diabetes (Marshall et al., 2009; Punjabi, 2004; Reichmuth et al., 2005). In the present sample the prevalence of diabetes was approximately 17%, which is consistent with estimated prevalence rates of 20% in the OSA population (Meslier et al., 2003). The distribution of diabetics was not significantly different between the CM phenotypes. Chinese medicine typically describes the disease mechanism that leads to the symptoms of diabetes as the result of chronic Heat in the Stomach with a deficiency of Spleen Qi (Flaws & Sionneau, 2005). Chronic Heat damages the Yin fluids in the Stomach and the Lung, which can be transmitted to the Kidneys, causing Kidney Yin deficiency as well. The Heat leads to symptoms of excessive appetite and excessive thirst. Chronic Spleen Qi deficiency can eventually lead to Spleen Yang and eventually Kidney Yang deficiency as well. The deficiency in its initial stages leads to fatigue and weight gain, however, in the later stages of the disease the chronic deficiency can cause symptoms of poor appetite, emaciation and muscular atrophy. If the syndrome becomes a chronic deficiency of Kidney Yin and Yang, urinary and reproductive complications arise. The causes of Heat in the Stomach are usually due to excessive consumption of hot, spicy, greasy and rich foods or alcohol. There can, however, be chronic Heat transmitted to the Stomach from depression of the Liver due to damage from chronic emotional disturbance. Spleen deficiency can be caused by a myriad of factors, already discussed. CM classifies several syndromes that may present in patients with diabetes, including dual Stomach and Lung Heat accumulation and damage to fluids; excessive Stomach Heat; Kidney Yin deficiency; Spleen and Stomach Qi deficiency, Damp-Heat obstruction of the middle Energizer; and Spleen and Kidney Yang deficiency. Considerable overlap in the syndromes underlying the symptoms of diabetes and OSA is evident, explaining the common comorbid presentation seen in these populations.

Major depressive disorder, or self-reported depression, was observed in approximately 40% of the patients in this study. There was no significant difference, however, in the distribution of patients with depressive disorders amongst the different CM phenotypes. Previous studies that have investigated
the association between OSA and depression have shown rates of depression among OSA populations ranging from 17-38% (BaHammam et al., 2015; Ohayon, 2003; Schwartz et al., 2005). Studies have also shown increasing rates of depression with increasing severity of OSA (Millman, Fogel, McNamara, & Carlisle, 1989). The overall stability of the emotional state and regulation of emotion is controlled largely by the activity of the Liver according to CM. Emotional regulation involves the smooth flow of Liver Qi towards desired goals, and away from undesired goals (Flaws & Lake, 2001). The major cause of depression is emotional disturbance, which suppresses Liver function (Maciocia, 2009). Liver patterns of depression are typically precipitated by feelings of anger. Excessive expression of anger leads to hyperactivity of Liver Yang. Conversely, suppression of anger leads to Liver-Qi stagnation. Although depression will always involve dysfunction of the Liver, the Heart and Lung are also often involved. Chronic Qi deficiency, due to sadness or grief, leads to Qi stagnation primarily in the Heart and Lung. Excessive worrying can also bring on depression as it will lead to stagnation of Qi in the Spleen, and transmit easily on to the Heart, Lung and Liver. The Qi of the Heart and Kidney will also become stagnant if there are excessive feelings of guilt. Regardless of the precipitating emotional disturbance, the result is a stagnation and restraint of the flow of ideas, aims, goals and dreams leading to a lack of direction and motivation. Although emotional disturbance is the most commonly observed cause of depression, poor diet, poor physical constitution, aging and overexertion can also play a causative role (Flaws & Lake, 2001). Diets that are high in glucose, dairy and yeast promote the production of Phlegm. Phlegm clouds the mind causing mental confusion and difficulty concentrating. When there is already Qi stagnation, or Qi deficiency present, Phlegm is a significant aggravating factor. From a constitutional standpoint, those with a congenital deficiency of the Kidney will generally have greater difficulty exercising will power and are more susceptible to the development of depression. Congenital Heart deficiency is also a pre-disposing factor in the development of depression. Overexertion, and aging deplete the Kidney Yin, which is necessary to support and nourish Liver function.
An underlying deficiency of the Kidneys, therefore, provides a poor foundation for the stable and appropriate regulation of emotion, thereby creating a predisposition towards the development of depression. The comorbid presentation of depression and OSA is, therefore, not surprising from a CM perspective given that both conditions share similar underlying pathological mechanisms.

Hypertension was present in 23.53% of the present sample. Again, however, there was no significant difference in the distribution of patients with hypertension between the CM phenotypes. Past research has shown a concurrent presentation of hypertension in 48.6% of OSA patients and it is well established that OSA is an independent risk factor for hypertension (Chen et al., 2011; Young et al., 1997). It has been suggested that repeated transient alterations in blood pressure during the night in response to respiratory events may lead to sustained elevation of blood pressure during the daytime in OSA patients (Fletcher & Brown, 1985). Hypertension within the CM framework is primarily the result of either Liver Yin deficiency with hyperactive Liver Yang or Liver Qi stagnation transforming into ascendant Heat. In CM the Liver has a major function of regulating blood volume in response to altering levels of physical activity. Normally blood pressure should drop in the evening and excess blood in the circulatory system should return to the Liver to be stored during rest. Upon waking the Liver increases the amount of circulating blood to compensate for increased metabolic needs. With repetitive spikes in blood pressure due to arousals from sleep in OSA patients, the Liver is being forced to become active which will deplete Liver-Yin and Blood. There are typically three main causal factors seen in hypertensive patients. Firstly, dietary irregularities (diets high in simple carbohydrates, and fats), a lack of exercise or overexertion can damage the Spleen leading to poor fluid transformation. The resulting accumulation of Dampness and Phlegm interferes with the flow of Liver Qi leading to Qi stagnation. Secondly, when there is emotional dysregulation and excessive anger, in the same way that has been discussed previously in the mechanism that causes depression, the function of the Liver is damaged leading to Qi stagnation.
Finally, the precipitating factor may be due to a deficiency of Kidney Yin and Yang as a result of aging or chronic illness. Insufficient Kidney Yin will fail to nourish and moisten the Liver. Simultaneously, insufficient support from the Kidney Yang will fail to warm the Liver. Regardless of the initial cause, prolonged Qi stagnation will transform into Heat, leading to Liver Fire, and upward movement of hyperactive Liver Yang and consumption of Yin (Flaws & Sionneau, 2005; Zuo, 2002). It is likely that OSA will aggravate hypertension. The Qi stagnation and Heat, as well as the involvement of Phlegm in both hypertension and OSA disease mechanisms explains the common comorbid presentation of these two conditions.

Patients within the present sample also commonly reported having asthma and/or rhinitis; self-reported asthma and rhinitis was present in 24% of patients. As was found with the other comorbid conditions, however, the distribution of patients with asthma or rhinitis was not significantly different between the CM phenotypes. It is not clear whether rhinitis constitutes a significant independent risk factor for OSA or it is merely a common comorbid condition (Canova et al., 2004; Dogan, Abadoglu, & Cakmak, 2011; Kramer, La Chaux, Dreher, Pfrogner, & Rasp, 2001). The CM aetiology of rhinitis involves simultaneous internal and external factors (Liu & Liu, 2009). Internally, it is thought that there is an underlying deficiency of one or all of the Lung, Spleen and Kidneys. During an acute attack of rhinitis, external airborne pathogens (external wind pathogens) invade the Lung. The Defence Qi engages with, and struggles, to fight off the external pathogenic factor leading to obstruction of the Lung, hindering the movement of Lung Qi. The Qi in the Lung will become stagnant and begin to accumulate and rebel upwards. The upward movement of Lung Qi brings with it fluids that likewise could not be purified and sent downward through the normal water metabolism process, resulting in nasal discharge and nasal congestion. In a normal healthy individual an external attack by a Wind pathogen will not lead to symptoms because the Defence Qi of the body is adequate and does not allow the external pathogen to interfere with the Lung function. Therefore, patients who experience rhinitis are all thought to have an
underlying deficiency of Lung and Defence Qi. Defence Qi is produced by the Spleen and Lung. The Spleen transforms nutrients extracted from ingested food and drink, which is then combined with Qi from the Lung. When the Spleen Qi is deficient the quality of Defence Qi is poor and the amount is insufficient. Spleen Qi deficiency will also lead to production of Phlegm, which is transported to, and stored deep within the Lung. During an acute attack the Phlegm is brought upwards by the rebellion of stagnant Lung Qi leading to nasal congestion.

The disease mechanisms underlying asthma, according to CM, are essentially the same as the disease mechanisms underlying rhinitis. According to CM there are two major types of asthma referred to as either endogenous or exogenous asthma (Zuo, 2002). Endogenous asthma is thought to arise due to congenital deficiency of Kidney Qi, which will typically present in young children. Another important cause of endogenous asthma is Phlegm accumulation in the Lung. An acute attack of asthma can be induced by sudden changes in climate or temperature, aspiration of allergens, improper diet, emotional upset or overexertion. When asthma attacks occur for extended periods and occur frequently and repeatedly the Lung, Spleen and Kidney Qi are damaged and, thus, the Defence Qi fails to protect the body from diseases and external pathogens. Due to the lowered immune response the attacks are recurrent in response to external pathogens. Kidney deficiency typically results in a failure of the Kidney to receive Qi from the Lung leading to shortness of breath and difficulty inhaling deeply. Wheezing and panting occur when Wind and Cold invade the Lung, which become obstructed with Phlegm and Dampness thereby preventing Qi from descending (O'Connor & Bensky, 1981). Syndromes involving Phlegm, and simultaneous deficiencies of the Spleen, Lung and Kidneys are again implicated in the development of rhinitis, asthma and OSA symptoms, thereby explaining common co-presentation of these conditions.

The CM syndromes commonly identified in an Australian population of OSA patients were consistent with the CM syndromes described in past case studies of OSA patients in China. Although the CM phenotypes identified in this
study did not differ with respect to the severity of OSA or sleepiness, they did appear to be related to BMI. The samples size, however, was small and the results should be interpreted with caution. The disease mechanisms underlying the identified CM phenotypes were also consistent with the disease mechanisms underlying common comorbid conditions prevalent amongst the OSA population. The classification of CM syndrome is important for guiding the selection of appropriate treatments using herbal medicine or acupuncture. Additionally, clinical trials employing acupuncture or Chinese herbs should ensure that their sample population are classified with a consistent CM phenotype in order to justify applying the same treatment across all patients. The most common phenotype identified in the present study, Spleen deficiency with Excessive Heat, will be used to guide patient selection and treatment design in the following clinical trial of acupuncture for the treatment of OSA.
Chapter 5 Clinical Trial of Acupuncture for the Treatment of Obstructive Sleep Apnoea

In CM the emphasis is placed on treating not only the symptoms, but rather the root cause of disease in order to maximise effectiveness through individually tailored treatment. Failure to adequately address the causative factors associated with any condition will reduce the efficacy of the overall treatment. CPAP provides a patch that effectively eliminates the symptoms of OSA, however, if the use of CPAP is discontinued the symptoms return, as the underlying pathology has not been addressed. Discontinuing acupuncture treatment after relief from symptoms has been achieved, and the pathological imbalance has been restored, should not lead to an immediate recurrence of symptoms. This benefit, coupled with the fact that acupuncture treatment does not require the regular use of bulky apparatus during sleep would make this an attractive treatment option if it can be shown to be effective at reducing the severity of OSA and its psychological and physiological sequelae.

As discussed previously, recent research has demonstrated reduction in AHI following 12 weeks of acupuncture treatment (Freire et al., 2007). The lack of CM diagnosis and syndrome analysis in their study has been discussed. Their study, however, is subject to a methodological limitation as well. The major methodological limitation inherent in the study by Freire and colleagues (2007), and indeed clinical acupuncture research more generally, relates to the method of placebo control. According to Ernst and White (1997), a true placebo should realistically mimic the active treatment, while being physiologically inert. Randomised, placebo controlled trials are the most effective way to test for specific effects of a particular type of therapy. One of the most important challenges for randomized, placebo controlled clinical trials of acupuncture is the ability to find an adequate placebo control. There are two major types of placebo methods commonly employed in acupuncture research: non-needling and needling techniques (Tough, White, Richards, Lord, & Campbell, 2009). The most commonly used placebo method is the use of needles that are either placed
superficially in the subcutaneous layers of the skin, or inserted to appropriate depths at either non-acupuncture or irrelevant acupuncture points. It is difficult to ensure that these techniques are physiologically inert. Japanese acupuncture, for example, involves only superficial needling in normal practice. Non-needling techniques, such as inactive laser, or inactive transcutaneous electrical nerve stimulation (TENS) produce a physiologically inert treatment. Irnich and colleagues (2011) found that in a comparative study of active versus placebo laser acupuncture, participants were not able to distinguish between the placebo or active treatment methods. There was also no difference in the number of trials that reportedly elicited the De Qi sensation between the active or placebo laser treatment methods. For either of these techniques to be considered a true placebo, however, it would be best to compared them with active laser or active TENS treatment. Overall, because neither non-needling, nor needling placebo methods meet both criteria defining a true placebo, they are better referred to as sham controls (Tough et al., 2009). The study by Freire and colleagues (2007) used needling of non-acupuncture points as the sham treatment. Despite an absence of significant improvement in the sham acupuncture group for most measures the possibility that their sham treatment was physiologically active cannot be ruled out.

Another limitation of the study by Freire and colleagues (2007) is a small sample size. As identified by the authors, the sample size was insufficient to provide adequate statistical power, therefore, it is important to replicate their findings in a larger sample. Finally, the mechanisms of action produced by acupuncture treatment were not investigated in their study. For acupuncture to be considered as a potential treatment, it is vital that the biological mechanism of action through which acupuncture leads to reductions in AHI and experienced symptoms is made clear.

The current study aimed to build on the results of the study by Freire and colleagues (2007), by addressing the limitations of their study and incorporating a more physiological approach to the measurement of treatment outcomes. There has been no study to date that has investigated the physiological
mechanism of action produced by acupuncture treatment of obstructive sleep apnoea. It is possible that acupuncture may affect only one physiological factor known to play a role in OSA, such as arousal threshold or upper airway muscle activity. Alternatively, it is possible that acupuncture may affect several of the known pathophysiological factors of OSA simultaneously. The most common phenotype, Spleen deficiency with excess Heat, was targeted in the present clinical trial. In CM, syndromes involving deficiency of the Spleen typically manifest with symptoms of poor muscle tone, or prolapse. This is because one of the main functions of Spleen Qi is to ascend and provide support for the various internal organs and blood vessels. In the context of OSA, this may be reflected as poor upper airway muscle activation in response to flow limitation during sleep. It might be expected, therefore, that acupuncture treatment that aims to strengthen the Spleen Qi could improve muscle tone and reflexive activation. Spleen Qi deficiency that is complicated by accumulation of Dampness and Phlegm often manifests with oedema and swelling. In particular, because the Spleen is connected to the mouth and cheeks, within the context of OSA, Dampness and Phlegm may cause swelling and fluid retention in the mucosa lining the upper airway, nose and mouth. As such, acupuncture treatment aimed to drain Dampness and resolve Phlegm could lead to a reduction in upper airway resistance through reductions in swelling and increased upper airway dilation. Finally, Excess Heat affecting the Liver can cause difficulties in initiating sleep because the Heat agitates the Spirit and keeps the Mind active. This prevents the Yin from entering more deeply into the body and the smooth transition from wake to sleep. From the perspective of OSA, this may present as a low arousal threshold or high loop gain. Acupuncture treatment to clear Heat and subdue Liver Yang may, therefore, lead to an increase in arousal threshold or reduce loop gain.

Based on the pathophysiological mechanisms underlying the Spleen deficiency and excess Heat phenotype, the overall principles of treatment in the present study were to tonify the Spleen and Qi, drain Dampness and resolve Phlegm, and clear Heat and pacify the Liver. The points selected for treatment
have actions that are consistent with these treatment aims. As mild to moderate patients were the intended target patients the treatment period was designed to address these different pathological factors in three distinct phases. The initial phase was designed to clear excessive Heat; the second phase of treatment was designed to tonify the Spleen and Qi, drain Damp and resolve Phlegm; the third phase of treatment was designed to pacify the Liver and promote sleep. A list of the acupuncture points used in treatment and their specific actions are shown in Appendix B.

Through investigation of the specific physiological effects of acupuncture, it may be possible to identify whether acupuncture is an appropriate treatment, at least for certain OSA patients. In order to ensure that the standardized treatment given to all patients is appropriate, only OSA patients with the most common CM phenotype, Spleen deficiency and excess Heat, identified by the previous diagnostic study were included in the current clinical trial. The major objective of this research project was to show that, for patients with mild to moderate OSA and the target CM phenotype, active acupuncture was a more effective treatment for OSA than sham acupuncture. The sham treatment in the present investigation involved the use of laser acupuncture in which the diode within the laser probe was removed. Using inactive laser acupuncture as a sham treatment has been previously validated (Irnich, Salih, & Offenbächer, 2011). This method ensures that the sham acupuncture treatment is biologically inactive; therefore the needling effects of the active acupuncture could be evaluated. The secondary objective of this research project was to identify the physiological effects of acupuncture on upper airway function by observing changes in known pathophysiological factors for patients receiving active acupuncture treatment versus sham acupuncture treatment.

The effectiveness of acupuncture as a treatment for OSA was assessed objectively via the number of obstructive respiratory events per hour of sleep (AHI), the level of oxygen saturation in the blood (SaO2), Sleep Onset Latency (SOL), and sleep architecture (amount of total sleep time spent in each stage of sleep). Physiological changes were measured to determine the mechanism of
acupuncture treatment. Factors that were assessed include changes in nasopharyngeal resistance during wake, arousal threshold, ventilation, and genioglossus muscle activity in response to respiratory-related stimuli.

Subjective measures of symptoms including sleepiness, mood and quality of life were also taken to assess the effectiveness of acupuncture as a treatment for OSA. The Epworth Sleepiness Scale (ESS) was used to assess changes in sleepiness. The Functional Outcomes of Sleep Questionnaire (FOSQ) was used to assess daytime functioning and symptoms in relation to factors specifically affecting sleep. As a measure of general quality of life, the SF-36 Health Questionnaire (SF-36) was used. Overall mood was measured via the Profile of Mood States (POMS) questionnaire. Although previous research has shown that neurocognitive impairment in OSA can show improvement with CPAP treatment, these improvements are limited to the domain of executive functioning and for patients with severe OSA (Kushida et al., 2012). It was determined that neurocognitive assessments would not likely yield any noticeable results for the target population of mild to moderate OSA patients in the present study, and therefore, were not conducted.

5.1 Hypotheses

For the investigation of the effectiveness of acupuncture treatment, it was hypothesised that active needle acupuncture, but not sham laser acupuncture treatment in OSA patients with the Spleen deficiency and excess Heat phenotype would lead to significant reductions in the AHI, AI, ODI3% and sleepiness symptoms as measured by the ESS, and improve mean oxygen saturation across the night as well as improve symptoms of mood, and/or mental and physical wellbeing as measured by the POMS, FOSQ, and SF-36.

Finally, with respect to the investigation of physiological effects of acupuncture, it was hypothesised that active acupuncture treatment would lead to reduced waking nasopharyngeal resistance, increase arousal threshold,
and/or increase upper airway muscle responsiveness to respiratory flow limitation.

### 5.2 Design

This study was a randomized, sham-controlled, semi-blind clinical trial with a longitudinal, parallel groups design. This was a single-centre study conducted at Austin Health. This study was granted ethical approval by the Austin Health Human Research Ethics Committee, project number 04654; and was registered with the Australian New Zealand Clinical Trials Registry, trial ID ACTRN12612000992808.

Physiological measures of the upper airway of OSA patients, objective severity of OSA and subjective measures of sleepiness and quality of life were measured prior to, and at completion of the course of active or sham acupuncture treatment (week 15). In addition, subjective measures were also collected at week 8. Figure 7 shows a flow diagram of the recruitment, treatment and data collection timeline.

### 5.3 Participants

#### 5.3.1 Inclusion criteria.

The aim was to recruit mild to moderate OSA patients (AHI >5 ≤30), consisting of both newly diagnosed OSA patients as well as previously diagnosed patients who had been unsuccessfully treated by conventional means. Due to difficulties with recruitment this criterion was expanded to include patients with diagnostic AHI ≤40. The primary criterion was that the patient had not received any treatment for their OSA for at least 4 weeks, and agreed not use any other form of treatment (including CPAP) for their OSA during the study. It was deemed that delaying routine CPAP treatment in newly diagnosed patients was not likely to harm these individuals as most OSA patients have had their condition for months, if not years, prior to diagnosis. Patients also needed to have a CM syndrome diagnosis consistent with the Spleen Deficiency and Excess
Heat phenotype, described in the previous diagnostic study, in order to be included in the present clinical trial.

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<th>Screening</th>
<th>Week 1</th>
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<td>Consent and Screening Appointment</td>
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<tr>
<th>Data Collection</th>
<th>Week 2</th>
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<td>Overnight Investigative Sleep Study</td>
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<tr>
<th>Treatment - phase 1</th>
<th>Weeks 3,4</th>
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<td>two treatments per week for two weeks</td>
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<tr>
<th>Treatment - phase 2</th>
<th>Weeks 5,6,7,8,9,10</th>
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<tr>
<td>one treatment per week for six weeks - Subjective questionnaires completed again during week 8</td>
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<tr>
<th>Treatment - phase 3</th>
<th>Weeks 11, 12, 13, 14</th>
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<tr>
<td>one treatment per fortnight for two fortights</td>
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<th>Data Collection</th>
<th>Week 15</th>
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<td>Overnight Investigative Sleep Study</td>
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Figure 7. The figure demonstrates the study timeline for each participant and the various investigative or treatment measures conducted at each phase of the study.
5.3.2 Exclusion criteria.

Patients were excluded from participating if they were younger than 20 years of age, or pregnant women, as pathophysiological mechanisms underpinning childhood OSA and OSA in pregnancy are likely to differ from pathophysiological mechanisms observed in the normal OSA population. Individuals dependent on a carer or guardian, unable by reason of cognitive impairment or inadequate language skills to complete the questionnaires, or give informed consent were also excluded. Patients who experienced insomnia, periodic limb movement syndrome, central sleep apnoea, or parasomnias were excluded on the basis that the assessment of obstructive sleep apnoea and its sequelae could be confounded by symptoms or side-effects of these other conditions. Patients were also excluded if they regularly took medication to assist with attaining sleep, such as sedatives, because these medications would likely alter pathophysiological variables of interest. Patients with co-morbid health conditions that were a significant threat to mortality or significantly altered respiratory or cardiovascular anatomy or physiology (e.g., patients who have had an acute cardiac or cerebral event in the previous 3 months, or patients with cardiac disease and oxygen saturation less than 90% for more than 10 minutes as recorded on their diagnostic PSG) were also excluded. Finally, individuals for whom withholding treatment would lead to a significant risk to them or the general population were also excluded. This included: bus/taxi drivers or heavy machinery operators; individuals with severe daytime sleepiness (ESS ≥16); or those individuals in whom, in the opinion of their treating physician, it was unsafe to withhold definitive treatment for a period of 15 weeks.

5.4 Blinding and Randomization

It was not possible to blind the CM practitioner, however, patients were blind to the treatment group in which they were allocated.

Patients were randomly assigned to either an active needle acupuncture or sham laser acupuncture group. The randomization procedure involved
randomly allocating all participants to the two groups according to a computer-generated random number schedule (www.randomizer.org) in five blocks of six. An individual who was not a member of the research team performed the randomization. Allocation was concealed through use of sealed, consecutively numbered opaque envelopes. A master document with the randomization information for each participant number was kept in electronic format on a secure computer at the University of Melbourne.

All patients were told that some participants in the study would be randomly allocated to receive a sham treatment and that they would not know until the end of the trial whether they had received active or sham treatment. In reality, all members allocated to the needle acupuncture group received active acupuncture treatment while all members allocated to the laser acupuncture group received the sham treatment. None of the participants were made aware during the study whether they were receiving active or sham treatment. Patients were given a questionnaire at the completion of the final overnight study on which they were asked to state whether they believed that they were receiving active or sham treatment. Patients who received sham treatment were offered active treatment following completion of the trial.

All data analysis and scoring of sleep data was conducted on the blinded and de-identified files by the same trained technician, who had a minimum 75% concordance rate through the QSleep, quality assurance for PSG scoring test. An individual that was not a member of the research team de-identified the data and randomly arranged the studies so, that for any given data file, it was not possible for the scorer to identify the participant to whom it belonged, which treatment the participant had received nor whether the data file being analysed was collected pre- or post-treatment. At the completion of the trial, once all files had been analysed, the files were re-identified for statistical analysis.
5.5 Procedures

5.5.1 Recruitment procedures.

An introductory letter was sent to inform suitable patients that the study was taking place, and to provide them with lay details about the study. Suitable patients were identified from the Austin Health Sleep laboratory database. Patients were deemed suitable if they were newly diagnosed with OSA, or had recently been re-assessed and were given a continued diagnosis of OSA. The letter informed the potential participants that they would be contacted by telephone within a week at which point they had the opportunity to volunteer for the study. Eligible patients were also identified from the database of patients attending Austin Health to receive the results of their diagnostic PSG. During their consultation their attending physician informed them of the study and patients were able to indicate if they would like to be further contacted about the study. A research participation database was also used to identify patients who had previously volunteered for OSA research trials. When these patients were contacted by phone, only those who were not using any treatment for their OSA were considered for recruitment. The patients were briefed regarding the procedures and, if they were interested, were sent a participant information and consent form. Participants were also recruited through flyers placed in the Sleep and Respiratory Laboratory. Patients that were eligible and interested in participating were invited to attend a screening session at Austin Health.

5.5.2 Screening procedure.

Each participant was screened based on their medical history, OSA severity and sleepiness rating. Screening also involved a CM diagnosis to ensure that they had the target CM phenotype. These assessments were made during a screening interview. The entire screening interview lasted approximately one hour.

The participants received a copy of the patient information and consent form at least one week prior to their screening session, ensuring adequate time to read the document thoroughly. At the beginning of the screening session a
member of the research team explained in plain language what the study involved. The participant was able to ask questions if they were unsure of any of the information provided. When it was deemed that the participant understood clearly, and was happy to participate, they gave written consent to participate, and was witnessed by a second researcher.

After the patient was consented, the CM practitioner, performed a full CM diagnosis on each participant according to the method described for the diagnosis study. A general medical history was taken and the patient then completed the CM OSA differential diagnosis questionnaire. Following this, the patient’s tongue was observed and the pulse was palpated. Because food and drink can change the appearance of the tongue, the patient was also asked to report any food or drink they had consumed in the previous three hours.

If the patient’s CM diagnosis did not match the target CM phenotype, they were informed that they were ineligible to participate. Patients found to have the target CM phenotype then underwent a treatment tolerance test. Because the patient was not yet randomized to a treatment group, the treatment tolerance test involved testing the participant’s tolerance to both needle and laser acupuncture (sham). The test involved inserting one acupuncture needle into the arm, retained for one minute and then removed, and the sham laser was applied to the skin on the opposing arm for sixty seconds in order to determine whether the participant could tolerate the treatment sensations. If the participant could tolerate the needle and laser sensations they were booked for their overnight study, and the screening session concluded. Patients were asked to inform the researcher if they exhibited any reaction to the treatment tolerance test within 24-48 hours.

5.5.3 Overnight investigative sleep study procedure.

The purpose of the overnight study was to measure several physiological variables that may influences OSA severity and may change as a result of acupuncture treatment as well as to determine the OSA severity. Sleep studies were conducted at the Bowen Centre, at Austin Health. The overnight diagnostic sleep study was performed using continuous polysomnography based on a
computerised system (Spike2) in order to monitor sleep and breathing. This provided a comprehensive assessment of both respiratory and sleep state variables. Each overnight sleep study involved physiological measurements, in addition to the standard polysomnographic measurements. Studies were considered adequate provided they contain at least 180 minutes of sleep. The apparatus and procedures are outlined below. Two investigators were present throughout each study night.

Participants were asked to attend the Bowen Centre 3 hours prior to their normal bedtime. Upon arrival the participant was given approximately an hour to complete the various health and wellbeing questionnaires. Once the questionnaires were complete the participant was prepared for their overnight study. While in a standing position, the participant’s height, waist and neck circumference were measured and recorded. The participant was weighed on a digital scale. In a comfortable chair in a seated and upright position the participant had their blood pressure measured. Blood pressure was measured 3 times over a ten-minute period and the average was recorded. The participant was then asked to change into comfortable clothes to sleep in.

Once the participant was dressed for bed and had completed their pre-bedtime routines, the polysomnographic apparatus were applied. Anaesthetic gel (1-2g 4% Amethocaine) was applied percutaneously over the GG muscle. This was performed first as the anaesthetic achieves maximal effectiveness approximately 30 minutes after application. The electrodes to record electroencephalography (EEG), electrooculography (EOG), and electromyography (EMG) were applied to the face and scalp using Elefix® conductive paste, gauze and tape as per standard clinical protocol. In order to record EEG information, two scalp electrodes, positioned at O2 and C4 (from the 10-20 electrode placement system), were used with an opposing mastoid reference (M1). The EOG recordings were measured using bilateral electrode placement 1cm lateral, and 1cm inferior, to the outer canthus of the eye, coupled with a central reference electrode placed in the centre of the glabella. Electrodes were also applied bilaterally 1cm lateral and 1cm inferior to the corners of the
mouth to obtain chin EMG recordings. The electrodes to record
Electrocardiography (ECG) were applied to the chest as per standard clinical
protocol, with one electrode at the lateral border of the right clavicle and the
second electrode on the mid-axillary line on the lower left rib-cage between ribs
8-10. The magnetometer pads were placed on the chest, mid sternum; and on the
abdomen, 1cm above the umbilicus. Corresponding magnetometer pads were
placed at equal levels on the patient’s back.

In order to determine the exact depth to which the intramuscular electrodes
should be placed, an ultrasound was taken of the submental region. The
genioglossus muscle was located on the scan and the depth for insertion was
recorded (see figure 8 for an example of the anatomical structures identified on
the ultrasound to inform the depth of needling). Fine-wire, bipolar
intramuscular electrodes were inserted into the GG muscle, via a percutaneous
approach. The wires were inserted approximately 10mm posterior to the inferior
border of the mandible, 3mm on either side of the midline (See figure 9 for an
illustration of the insertion location). The depth of insertion was approximately
20-30mm from the dermal surface depending on the anatomical structures
identified in each patient’s submental ultrasound. The needle was immediately
removed after placement leaving the wires in place. The wires were taped in
place.

Topical anaesthetic nasal spray (<0.5ml Lignocaine 4%) was administered to
one nostril. A soft Millar® pressure catheter (2mm diameter) was inserted
through the anaesthetised nostril and passed through the nasal cavity to the level
of the epiglottis and secured in place with tape. A pulse oximeter was attached
to the patient’s index finger and gently taped in place as per standard clinical
practice. Finally a modified nasal mask (Respirronics®) with silicone sealant
applied to the exhalation port was fitted over the patient’s nose and secured with
a head strap. If necessary a small piece of micropore tape was applied over the
mouth to ensure nasal breathing during the night. If the patient could not
breathe comfortably through their nose a full-face mask was used for sleep
recordings. A pneumotachograph was attached to the mask in order to measure
airflow. Mask pressure and CO\textsubscript{2} levels were continuously measured. See figure 9 for a diagram of the additional apparatus used for the study.

Once all of the equipment was in place the patient was asked to perform certain activities in order to calibrate the equipment. This included, swallows, deep breaths and tongue protrusions against the top teeth. The patient was asked to relax, in a supine position, with their eyes open, and breathe normally through the nasal mask for five minutes in order to record waking baseline measurements.

Following five minutes of wakefulness recordings, the lights were turned off and the participant was allowed to sleep. The placement of leads and wires permitted normal positional changes during the night and both sleep and wake times were determined by the patient. Positional changes were observed through an infrared camera placed next to the bed and manually recorded. Upon waking in the morning the equipment was removed and the participant was free to go home.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{ultrasound_image.png}
\caption{The figure shows an example of the ultrasound image obtained for each patient showing a transverse view of the submental region. The ultrasound shows the various layers of tissue and muscles interspersed with fat tissue from the skin surface, through the mylohyoid (MH), the geniohyoid (GH), to the genioglossus (GG) muscle layers. Submental ultrasound enabled precise localisation of the GG muscle to inform depth of electrode wire insertion for each patient.}
\end{figure}
Figure 9. The diagram above shows a mid-sagittal view through the upper airway. The pressure catheter was advanced to the level of the epiglottis and the nose was fitted with a CPAP mask to which the pneumotachograph was attached. The diagram also shows the needle insertion of the fine wire electrodes into the GG muscle.

5.5.4 treatment procedures.

*Needle (active) acupuncture treatment.*

Participants were asked to attend Austin Health for their acupuncture sessions. Acupuncture treatment involved the use of single-use, sterilized, Sensei™ needles (with guide tubes) between 15mm to 50mm in length and
between 0.18mm to 0.25mm in diameter. Each treatment session lasted one hour from the time the patient entered the treatment room to the time they left.

During a typical treatment session patients attended Austin Health at their scheduled time and were shown to a consulting room. They were left for five minutes to remove their outer clothing and cover themselves with a blanket while the CM practitioner prepared according to standard hygiene practices set out by the Australian Health Practitioners Registry of Australia. Once the patient was comfortable and appropriately covered the CM practitioner returned to the room and cleaned each point location with an alcohol swab of 70% isopropyl alcohol.

Needles were inserted and manipulated until the De Qi sensation was reported. Needles were placed at appropriate locations and depths depending on the phase of treatment (see figure 10a, 10b and 10c for point locations used during phase I, II and III of treatment, respectively). The needles were retained for thirty minutes with manual stimulation applied to the needles at ten-minute intervals. The rotation method was used to apply reinforcing or reducing stimulation to the needle. Reinforcing method was applied by rotation of the needle slowly in a clockwise direction (each rotation not exceeding 180°). Reducing method was applied by rotation of the needle rapidly in a counter-clockwise direction (each rotation not exceeding 360°) (Zuo, 2002). Following the treatment the needles were removed and disposed of in a sharps container. The CM practitioner then left the room allowing the patient sufficient time to dress.

**Laser (sham) acupuncture treatment.**

Participants were asked to attend Austin Health for their laser acupuncture sessions. Laser acupuncture was performed using a Metron® Advanced Laser probe that had the diode removed. Throughout this session the laser was inactive. Each treatment session lasted one hour from the time the patient entered the treatment room to the time they left.

During a typical treatment session patients attended Austin Health at their scheduled time and were shown to a consulting room. The patient was left for five minutes to remove their outer clothing and cover themselves with a blanket
while the CM practitioner prepared according to standard hygiene practices set out by the Australian Health Practitioners Registry of Australia. Once the participant was comfortable and appropriately covered the CM practitioner returned to the room and covered their own as well as the patient’s eyes with protective eye wear, as is standard practice when applying laser acupuncture.

The laser probe was applied to the skin for 1-5 minutes at each point to be used in treatment (points varied depending on the phase of treatment – refer to figure 10). This process was repeated for approximately thirty minutes, or until the laser probe had been applied for an amount of time that would normally constitute an application of 5 joules. Following the treatment the CM practitioner then left the room allowing the patient sufficient time to dress.
Figure 10. The location for needle/laser acupuncture varied by treatment phase. The figure shows the locations of needle insertion or laser application during a) phase I, b) phase II, and c) phase III of the treatment schedule.
5.6 Data Analysis

5.6.1 OSA severity measures.

On each overnight sleep study, the severity of OSA was defined according to the apnoea/hypopnea index (AHI); measured as the number of respiratory events experienced per hour of sleep. Respiratory disturbances were identified as events lasting ≥10 seconds, with ≥30% decrease in peak-to-peak airflow (hypopnea), or ≥90% decrease in peak-to-peak airflow (apnoea), as measured through a pneumotachograph, that was associated with either a blood oxygen desaturation of ≥3% from baseline, or an arousal (Iber, Ancoli-Israel, Chesson, & Quan, 2007). Events were considered hypopnoeas or obstructive apnoeas if thoracic and or abdominal movements continued, and the epiglottic pressure trace continued to show respiratory effort during flow limitation. Events were classified as central apnoeas in the absence of respiratory effort as measured through the magnetometers and pressure catheter. Respiratory events that demonstrated an initial absence of respiratory effort that then returned prior to termination of the event were classified as mixed apnoeas.

The arousal index (the number of arousals experienced per hour of sleep, AI) was also measured. Arousal from sleep was scored according to the AASM 2013 criteria which requires an abrupt shift of EEG frequency including alpha, theta or frequencies ≥16Hz (not including spindles) lasting at least 3 seconds, with at least 10 seconds of stable sleep preceding the change. For an arousal to be scored during REM sleep there also needs to be a concurrent increase in submental EMG that lasts for at least 1 second.

The oxygen desaturation index (the number of oxygen desaturations events during which oxygen saturation decreased by >3% of baseline per hour of sleep, ODI3%) and mean oxygen saturation across the whole night were also measured. According to the AASM scoring criteria, the ODI is defined as the number of desaturations multiplied by 60 and divided by the total sleep time in minutes (Berry et al., 2017).
5.6.2 Sleep measures.

Other standard PSG measures were also taken, including sleep efficiency (the percentage of total sleep time spent asleep, SE), sleep onset latency (the time taken to achieve stable sleep, SOL), and analysis of sleep architecture (percentage of total sleep time spent in each stage of sleep).

5.6.3 Body habitus measures.

Body habitus was assessed through the body mass index (BMI) which is calculated as weight in kilograms divided by height in meters squared (kg/m$^2$). Neck and waist circumference were also measured in centimetres (cm).

5.6.4 Blood pressure measures.

Blood pressure was measured on both pre- and post-treatment sleep study nights. Three measurements were taken on each study night over a ten-minute period and an averaged blood pressure value was calculated. Measurements were taken using an Omron Healthcare Co., Ltd. Automatic blood pressure monitor, model HEM-7200, with the HEM-CR24 cuff.

5.6.5 Subjective symptomatology, wellbeing, and mood measures.

**Epworth sleepiness scale.**

Subjective measures of sleepiness were obtained through the Epworth Sleepiness Scale (ESS). This questionnaire consists of eight items describing various activities. Respondents are asked to rate how likely they are to doze during each activity on a Likert scale ranging from 0 – would never doze, to 3 – high chance of dozing, to obtain a possible score ranging from 0 to 24. Higher scores indicate more severe levels of sleepiness (Johns, 1991).

**Functional outcomes of sleep questionnaire.**

The Functional Outcomes of Sleep Questionnaire (FOSQ) consists of 30 items, which load onto 5 subscales that provide information about how sleepiness affects a broad range of activities relating to daytime and social functioning (Weaver et al., 1997). These subscales include: general productivity, social outcomes, general activity level, vigilance, and intimate relationships. The
questionnaire contains items relating to various activities and respondents are required to indicate the level of difficulty they experience conducting these activities due to sleepiness or tiredness. Responses ranged from 1 – Yes, extreme difficulty, to 4 – no difficulty. If the respondent does not participate in the activity regularly they can select 0 – I don’t do this activity for other reasons. For each subscale a mean-weighted item score is calculated that only includes activities in which the respondent indicates they regularly participate, thus preventing distortion of the score. The subscale scores are summed together to produce a global FOSQ score (range from 5 to 20). Lower scores indicate greater dysfunction due to sleepiness (Weaver et al., 1997).

**Medical outcomes survey short form – 36.**

The Short Form- 36 (SF-36) is a common functional status, health and wellbeing questionnaire that has previously been validated (Brazier et al., 1992; McHorney, Ware, & Raczek, 1993; Ware & Sherbourne, 1992). This questionnaire contains 36 items that load onto 8 subscales, assessing various aspects of general health and wellbeing. These aspects include: physical functioning, bodily pain, role limitations due to physical health problems (Role Physical), role limitations due to personal or emotional problems (Role Emotional), emotional wellbeing (Mental Health), social functioning, energy/fatigue (Vitality), and general health perceptions (General Health). Each item response is coded on a scale from 0 to 100. Items in each subscale are then averaged together to produce a score between 0 and 100. Total scores for each subscale are averaged together to produce a global SF-36 score ranging between 0 and 100. Lower scores indicate poorer health outcomes (Ware et al., 1994).

**Profile of mood states – short 37.**

The Profile of Mood States – short 37 (POMS-37) was used to assess mood. This shortened version of the POMS has been previously validated (Shacham, 2010). The POMS-37 consists of 37 items that describe emotional states. Respondents are asked to rate how strongly they felt each item described their mood over the specified time-frame on a five-point Likert scale ranging from 0 –
Not at all, to 4 – Extremely. The items load onto 6 subscales: Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Confusion-Bewilderment, and Fatigue-Inertia. A Total Mood Disturbance (TMD) score (possible score range from 0 – 20) was obtained by summing the mean scores for each subscale excluding the Vigor-Activity subscale. Lower scores indicate greater stability of mood. The POMS-37 was employed instead of the POMS full version in order to try and minimize the time-consuming nature of this study due to the high number of questionnaires being completed by each participant. It has been shown that internal consistency remains high when the POMS-37 is compared with the POMS (Curran, Andrykowski, & Studts, 1995).

5.6.6 Physiological measures.

*Measures during wakefulness.*

While the patient was awake, and resting quietly prior to sleep, normal nasal breathing was recorded for five minutes to establish wake baseline measures of the following variables:

*Upper airway resistance.*

Resistance of the upper airway (RUA) was measured as the change in airway pressure per unit airflow, and was calculated from measurements of nasal pressure, pharyngeal pressure and airflow. This measure provides, among other things, information about the anatomical size of the airway. Greater upper airway resistance with minimal changes in ventilation may indicate a narrower airway.

*Inspired minute ventilation.*

Inspired minute ventilation (Vi) provides a measure of the volume of air entering the lungs in litres per minute. The value for minute ventilation was calculated by electronically integrating the airflow signal as measured by the pneumotachograph. This measure provides information about waking ventilation requirements.
**Measures during sleep.**

GG muscle activity, respiratory measures, and epiglottic pressure, were recorded during natural flow limitation and respiratory events over the course of each study night. For each of the measures described below, values were averaged from a sample of 20 events across the night from each of stages 2, and SWS. For each participant the 20 events were selected based on the following procedure: the total number of events of each type (apnoeas and hypopnoeas) was determined and each total divided by 20 to achieve the number n. Each n\textsuperscript{th} event was then selected for analysis. In the instance where the event was unsuitable for analysis, either the event immediately preceding it or following it was selected instead. In the event that there were fewer than 20 apnoeas or hypopnoeas, all events were analysed. A minimum of 20 NREM events (either apnoeas or hypopnoeas) was necessary for inclusion in the analysis. If REM sleep was present another 20 events across REM sleep were sampled using the same method and averaged.

**Inspired minute ventilation.**

Calculated in the same way as \( V_1 \) during wake, the measure of \( V_1 \) during respiratory events was used to provide a measure indicating the severity of airflow limitation during respiratory events.

**Tidal volume.**

Tidal volume (\( V_T \)) provides a measure of the amount of gas, in litres, inspired during a breath. The value for \( V_T \) was calculated from individual breaths and averaged for each respiratory event. Analysing the average \( V_T \) across an event provides a measure of the severity of flow limitation during that event.

**Mean and peak inspiratory flow.**

Mean inspiratory flow (\( V_T/T_i \)) is a measure of the average flow rate achieved during a normal breath. Peak inspiratory flow (PIF) is a measure of the maximal flow rate achieved during a normal breath. Both \( V_T/T_i \) and PIF were
calculated for each individual breath and averaged across an entire respiratory event. These measures provide information about severity of respiratory events.

**Duty cycle.**

The duty cycle \( (T_i/T_{TOT}) \), or fractional inspiratory time, is a ratio measure of the inspiratory time to total breath time. The duty cycle was calculated and averaged for each respiratory event. This measure provides information about the drive to breathe. During prolonged airflow obstruction the proportion of the breath spent inspirating increases as respiratory drive increases.

**Arousal threshold.**

The value for arousal threshold (AT) was taken as the greatest negative pressure (cmH\(_2\)O) recorded by the epiglottic catheter on the breath prior to the arousal that terminated a respiratory event. The AT provides a measure of the amount of respiratory effort required to cause an arousal from sleep.

**Genioglossus muscle activation.**

Bipolar, intramuscular recordings of GG activity during inspiration, in response to increasing negative pressures, were analysed across each respiratory event throughout the night. For each individual, muscle recordings were plotted against epiglottic pressure for each breath and a linear trend was applied. Separate plots were generated for peak and tonic GG activity. From the linear trend a mean value was established for the slope of peak GG muscle activation (PSLOPE) and tonic GG muscle activation (TSLOPE) in response to increasing negative pressure, during inspiratory efforts across respiratory events. The PSLOPE and TSLOPE values provide an indication of the strength of the peak and tonic GG muscle activation, respectively, in response to a unit of change in pressure during increased inspiratory effort (muscle responsiveness). The GG and epiglottic pressure recordings were also used to calculate the intercept of the slope of peak GG (PINT) and tonic GG (TINT) activation during respiratory events. The PINT and TINT values indicate the degree of peak, and tonic GG activation, respectively, at a theoretical epiglottic pressure of 0 cmH\(_2\)O. Finally, the correlation coefficient of the relationship between GG and epiglottic pressure
was calculated for peak (PCOR) and tonic (TCOR) GG activation across inspiratory efforts during respiratory events. The PCOR, and TCOR values indicate how consistent the degree of change in peak and tonic GG muscle activation is, respectively, per unit change in pressure.

5.7 Statistical Analysis

A 2 (pre- and post-treatment study night) x 2 (active- and sham-treatment groups) mixed-model ANOVA with repeated measures on the first factor were conducted for all severity and physiology measures. These measures included BMI, blood pressure, neck circumference, waist circumference, AHI, AI, ODI, mean SaO2, SOL, SE, and sleep architecture. A 2x2 repeated-measures ANOVA was also used to analyse RUA and V̇ during wake and to analyse V̇, VT, VT/TI, PIF, TI/TOT, PSLOPE, PINT, PCOR, TSLOPE, TINT and TCOR across selected respiratory events during NREM and REM sleep. A 2x2 repeated-measures ANOVA was also used to analyse AT for the final breath prior to arousal during selected respiratory events during NREM and REM sleep. Finally, for the participants who completed active treatment following the sham treatment a repeated-measures (pre-, post-sham, post-active study night) ANOVA was conducted for all of the above measures.

Subjective measures of sleepiness, wellbeing, and mood were analysed using a 3 (pre-, mid- and post-treatment assessment points) x 2 (active- and sham-treatment groups) mixed-model ANOVA with repeated measures on the first factor. Each of the questionnaires and their subscales were included in this analysis. Subjective measures were not analysed for the participants who completed active treatment following sham treatment as they were no longer blind to the type of treatment they were receiving.

The significance level was set at α=.05. All statistical analysis was performed using IMB SPSS Statistics software package, version 22.0. Where significant interactions were found individual t-tests were conducted.
Chapter 6 - Clinical Trial Results

6.1 Patient Demographics

Twenty-one adults ranging in age from 28 to 70 were recruited for this study and randomized into either the active or sham group. There were 10 (3 female) active patients with a mean age of 56.3 (SD=7.5) and 10 (3 female) sham patients with a mean age of 45.3 (SD=5.83). Patients ranged in OSA severity from mild to severe, had the target CM phenotype, and were not currently receiving treatment for their OSA.

A total of 318 patients were contacted and 48 attended the laboratory for screening. Figure 11 shows a flow diagram of the recruitment process. The most common reasons for declining to participate in the study were the invasive nature of the measurement apparatus, and inability to commit to 12 weeks of treatment. Several patients who met the initial inclusion criteria were later excluded for various reasons. Two patients failed to exhibit OSA on their baseline sleep study. One patient was unable to sleep on the baseline sleep night, while another was unable to achieve sufficient sleep on the post-treatment sleep night. A further patient was excluded after the baseline sleep night due to failure to attend treatments. The following analysis was performed on the data for the remaining 9 active, and 10 sham patients for whom there was sufficient data. The subjective questionnaire data for the active patient that failed to achieve sufficient sleep at the follow-up study night was complete, and therefore included in the analyses of subjective outcomes.

6.1.1 Lateral vs. supine sleep comparisons.

Eight patients slept exclusively in the supine position (6 active, 2 sham). Of the remaining 11 patients, only 2 active patients, and 8 sham patients had sufficient sleep in both the lateral and supine positions for analysis (>5 events per position). It was deemed, therefore, that the sample size was insufficient to proceed with analysis of events by sleeping position.
Figure 11. The figure shows the flow of the recruitment process and application of inclusion and exclusion criteria.
6.1.2 REM vs. NREM sleep comparisons.

Four patients (3 active, 1 sham) did not achieve sufficient REM sleep (> 6 minutes) on one or both sleep studies and were excluded from REM sleep analysis. For NREM analysis all patients who completed both sleep studies were included. Due to the large number of patients excluded from REM sleep analysis, separate analyses of the dependent variables were conducted for NREM and REM sleep. Figures 12a and 12b show the change in NREM AHI across the study nights for each individual. Average NREM apnoea/hypopnea index (AHI) and arousal index (AI) values for both the active and sham groups are shown in figure 13a and Figure 13b, respectively. Average REM AHI and AI values for both treatment groups are shown in figure 14a and 14b, respectively.

6.2 OSA Severity Measures

6.2.1 Apnoea hypopnoea index.

Analyses of each sleep stage showed no main effect of time, nor main effect of treatment group on NREM AHI, \( F(1,17)=2.517, p=.131, \eta^2=.322 \), and \( F(1,17)=0.121, p=.732, \eta^2=.062 \), respectively. There was no significant interaction effect between time and treatment group on NREM AHI, \( F(1,17)=2.608, p=.125, \eta^2=332 \). Similarly, there was no main effects of time or treatment group, nor interaction between time and treatment group on REM AHI, \( F(1,13)=0.915, p=.356, \eta^2=144, F(1,13)=0.002, p=.969, \eta^2=.050 \), and \( F(1,13)=0.341, p=.569, \eta^2=.084 \), respectively.

6.2.2 Arousal index.

The AI during NREM sleep showed a main effect of time where AI was significantly higher on the post-treatment study night for both groups but there was no significant difference in AI between treatment groups, and no interaction effect between time and treatment group on NREM AI \( F(1,13)=412.629, p=.028, \eta^2=.627, F(1,13)=0.017, p=.897, \eta^2=.052 \), and \( F(1,13)=2.861, p=.115, \eta^2=.347 \), respectively.
Figure 12. The figure shows the change in AHI for each individual across the two study nights for a) the active treatment group (N=9) and b) the sham group (N=10).
a) b)

Figure 13. The figure shows a) NREM AHI, b) NREM AI for the active (N=9) and sham (N=10) groups (±SEM) pre- and post-treatment.

a) b)

Figure 14. The figure shows a) REM AHI, b) REM AI for the active (N=6) and sham (N=9) groups (±SEM) pre- and post-treatment.

6.2.3 Oxygen desaturation index.

The ODI3% was analysed for all active and sham patients who completed both study nights. Figure 15a shows the average ODI3% for the active and sham groups by study night. There was no significant overall difference in ODI3% between study nights, nor was there an overall difference in ODI3% between the treatment groups, $F(1,17)=2.694, p=.119, \eta^2=.341$, and $F(1,17)=0.057, p=.815, \eta^2=.056$, respectively. There was also no evidence of a significant interaction effect of treatment group by study night on ODI3%, $F(1,17)=1.508, p=.236, \eta^2=.213$. 
6.2.4 Mean oxygen saturation.

Figure 15b shows the mean level of oxygen saturation during the entire night of sleep for the active and sham treatment groups for each study night. There was no significant difference in mean SaO$_2$ between study nights and no significant difference between the treatment groups, $F(1,17)=1.204$, $p=.288$, $\eta^2=.179$, and $F(1,17)=0.935$, $p=.347$, $\eta^2=.150$, respectively. There was no significant interaction between treatment group and study night on mean SaO$_2$, $F(1,17)=0.418$, $p=.527$, $\eta^2=.094$.

![Figure 15](image.png)

**Figure 15.** The figure shows a) mean ODI3% and b) mean oxygen saturation during sleep for the active ($N=9$) and sham ($N=10$) groups (±SD), pre- and post-treatment.

6.3 Sleep Measures

6.3.1 Sleep onset latency.

The average sleep onset latencies for both treatment groups at the pre- and post-treatment study nights are shown in figure 16. There was no significant effect of study night on SOL and no significant difference in SOL between groups, $F(1,17)=0.857$, $p=.367$, $\eta^2=.141$, and $F(1,17)=1.033$, $p=.324$, $\eta^2=.160$, respectively. Further, there was no significant interaction effect between treatment group and study night on SOL, $F(1,17)=0.000$, $p=.994$, $\eta^2=.050$. 
Figure 16. The figure shows the average SOL for the active (N=9) and sham (N=10) groups (±SD), pre- and post-treatment.

6.3.2 Sleep efficiency.

Figure 17 shows the average sleep efficiency for the active and sham treatment groups for each study night. There was no significant difference in SE between study nights and no difference in SE between groups, $F(1,17)=0.001$, $p=.970$, $\eta^2=.050$, and $F(1,17)=3.241$, $p=.090$, $\eta^2=.397$, respectively. There was no significant interaction between treatment group and study night on SE, $F(1,17)=0.583$, $p=.456$, $\eta^2=.111$.

Figure 17. The figure shows the average SE for the active (N=9) and sham (N=10) groups (±SD), pre- and post-treatment.
6.3.3 Sleep architecture.

The average percentage of total sleep time spent in each stage of sleep for each group on pre- and post-treatment study nights are shown in table 3. There was a significant increase in stage 1 sleep on the post-treatment night for both the active and sham treatment groups, $F(1,17)=9.872, p=.006, \eta^2=.841$, a significant overall difference between treatment groups in the amount of SWS, $F(1,17)=4.687, p=.045, \eta^2=.533$, and a significant reduction in REM sleep on the post-treatment night for both groups, $F(1,17)=24.756, p<.001, \eta^2=.997$. There were no other significant main effects of time, or treatment group or interaction effects between time and treatment for sleep architecture.
Table 3. Changes in Sleep Architecture

<table>
<thead>
<tr>
<th>Stage 1</th>
<th>Pre-Treatment (% Total Sleep Time)</th>
<th>Post-Treatment (% Total Sleep Time)</th>
<th>Significance (η²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time</td>
<td>Group</td>
<td>Interaction</td>
</tr>
<tr>
<td>Stage 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>20.18 (9.31)</td>
<td>25.93 (11.38)</td>
<td>.006** (.841)</td>
</tr>
<tr>
<td>Sham</td>
<td>20.98 (8.28)</td>
<td>26.08 (9.65)</td>
<td>.551 (.089)</td>
</tr>
<tr>
<td></td>
<td>.551 (.089)</td>
<td>.431 (.119)</td>
<td>.990 (.050)</td>
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<td>Stage 2</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Stage 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>45.19 (7.73)</td>
<td>47.97 (8.78)</td>
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</tr>
<tr>
<td>Sham</td>
<td>42.83 (6.45)</td>
<td>45.98 (6.80)</td>
<td>.990 (.050)</td>
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<td></td>
<td>.505 (.099)</td>
<td>.710 (.065)</td>
<td>.045* (.533)</td>
</tr>
<tr>
<td>SWS</td>
<td>24.03 (10.50)</td>
<td>19.95 (10.67)</td>
<td>.121 (.338)</td>
</tr>
<tr>
<td>Active</td>
<td>19.42 (8.78)</td>
<td>16.66 (7.91)</td>
<td>.045* (.533)</td>
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<tr>
<td>Sham</td>
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<td>22.91 (12.32)</td>
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<td>REM</td>
<td>10.02 (6.02)</td>
<td>6.15 (4.75)</td>
<td>&lt;.001** (.997)</td>
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<td>Active</td>
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<td>7.05 (5.99)</td>
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</tr>
<tr>
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<td>9.54 (4.52)</td>
<td>5.33 (3.40)</td>
<td>.810 (.056)</td>
</tr>
</tbody>
</table>

* significant at <.05  ** significant at <.001

^ The degrees of freedom for analysis of all main effects, between group and interaction effects (1,17)
6.4 Body Habitus Measures

6.4.1 Body mass index.

The mean BMI for each group pre- and post-treatment are shown in Figure 18a. There was no difference in BMI between study nights and no significant difference in BMI between treatment groups, $F(1, 17)=0.300, p=.591$, $\eta^2=.081$, and $F(1,17)=2.006, p=.175, \eta^2=.267$, respectively. Further, there was no interaction effect of study night and treatment group on BMI, $F(1,17)=0.126, p=.727, \eta^2=.063$.

6.4.2 Neck circumference.

The mean neck circumference for each group pre- and post-treatment are shown in Figure 18b. Again, there was no significant difference in neck circumference between study nights and no difference between treatment groups, and no interaction effect, $F(1,17)=3.923, p=.064, \eta^2=.464$, $F(1,17)=0.315, p=.582, \eta^2=.083$, and $F(1,17)=1.035, p=.323, \eta^2=.161$, respectively.

6.4.3 Waist circumference.

The mean waist circumference for each group pre- and post-treatment are shown in Figure 18c. There was no significant difference between study nights or between group on waist circumference, $F(1,17)=0.532, p=.476$, $\eta^2=.106$, and $F(1,17)=0.807, p=.381, \eta^2=.136$, respectively. There was no interaction effect of study night and treatment group on waist circumference, $F(1,17)=0.001, p=.978, \eta^2=.050$. 


Figure 18. The figure shows the a) mean BMI, b) mean neck circumference, and c) mean waist circumference, for the active \( (N=9) \) and sham \( (N=10) \) groups (±SD) pre- and post-treatment.
6.4.4 Blood pressure.

The mean systolic blood pressures for each group pre- and post-treatment are shown in Figure 19a. There was no significant difference in systolic blood pressure between study nights or between treatment groups, $F(1,17)=1.744, p=.204, \eta^2=.239$, and $F(1,17)=0.743, p=.401, \eta^2=.129$, respectively. There was no interaction effect of study night and treatment group on systolic blood pressure, $F(1,17)=0.049, p=.828, \eta^2=.055$.

The mean diastolic blood pressures for each group pre- and post-treatment are shown in Figure 19b. There was no significant difference in diastolic blood pressure between study nights or between treatment groups, $F(1,17)=1.007, p=.330, \eta^2=.157$, and $F(1,17)=0.457, p=.508, \eta^2=.098$, respectively. There was no interaction effect of study night and treatment group on diastolic blood pressure, $F(1,17)=0.015, p=.903, \eta^2=.052$.

Figure 19. The figure shows the a) mean systolic and b) mean diastolic blood pressures for the active ($N=9$) and sham ($N=10$) groups (±SD), pre- and post-treatment.
6.5 Subjective Measures of Health, Wellbeing, Sleepiness and Symptoms

The questionnaire data for all patients (10 active, 10 sham) who completed treatment were included in the following analysis. Each of the questionnaires was compared both within and between groups across the three time points, pre-, mid- and post-treatment.

6.5.1 Sleepiness.

There was no significant difference between assessment points or treatment groups in sleepiness ratings, and there was also no evidence of an interaction effect of treatment group across the treatment period. Table 4 shows the mean sleepiness ratings, and standard deviations, for the active and sham groups over the course of treatment.

Table 4. Mean Epworth Sleepiness Ratings Across Time

<table>
<thead>
<tr>
<th></th>
<th>Pre-treatment</th>
<th>Mid-treatment</th>
<th>Post-treatment</th>
<th>Significance (η²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time</td>
<td>Group</td>
<td>Interaction</td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8.70</td>
<td>8.20</td>
<td>7.40</td>
<td>.147 .285 .088</td>
</tr>
<tr>
<td></td>
<td>(4.398)</td>
<td>(3.190)</td>
<td>(3.273)</td>
<td>(.389) (.181) (.485)</td>
</tr>
<tr>
<td>Sham</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10.40</td>
<td>9.30</td>
<td>8.80</td>
<td></td>
</tr>
</tbody>
</table>
|        | (4.427)       | (5.272)       | (3.853)        | ^ The degrees of freedom for analysis of all within group and interaction effects (2,36), and between groups (1,18)

6.5.2 Functional outcomes of sleep.

None of the FOSQ subscales showed a significant change over time in either group, between treatment groups or an interaction effect between time and treatment group. Table 5 shows the mean scores and standard deviations on each subscale for the active and sham groups over the course of treatment.
6.5.3 Medical outcomes survey – the short form-36.

There was no significant main effect of time or treatment group and no interaction effect between treatment group and time on any of the subscales of the SF-36: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. Mauchly’s Test of Sphericity indicated that the assumption of sphericity had been violated for the physical functioning subscale, \( \chi^2(2) = 6.283, p = .043 \). For the physical functioning subscale data is reported using Greenhouse Geisser’s method of correction. Table 6 shows the average scores and standard deviation for the active and sham groups on each subscale across the treatment period.

6.5.4 Profile of mood states – short-37

There was no significant main effect of time or treatment group and no significant interaction effect between treatment group and time for any subscale nor for total mood disturbance. Mauchly’s Test of Sphericity indicated that the assumption of sphericity had been violated, \( \chi^2(2) = 12.455, p = .002 \), for the depression subscale. The data for the depression subscale is reported using Greenhouse Geisser’s method of correction. Table 7 shows the average scores and standard deviation for the active and sham groups on each subscale across the treatment period.
Table 5. *Mean FOSQ Scores Across Time*

<table>
<thead>
<tr>
<th></th>
<th>Pre-treatment</th>
<th>Mid-treatment</th>
<th>Post-treatment</th>
<th>Significance ($\eta^2$)</th>
<th>Time</th>
<th>Group</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General Productivity</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Active</td>
<td>3.13 (0.63)</td>
<td>3.32 (0.55)</td>
<td>3.34 (.072)</td>
<td>.152 (.384)</td>
<td>.847 (.054)</td>
<td>.795 (.083)</td>
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</tr>
<tr>
<td>Sham</td>
<td>3.15 (0.56)</td>
<td>3.24 (0.60)</td>
<td>3.26 (0.62)</td>
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<td></td>
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</tr>
<tr>
<td><strong>Social Outcome</strong></td>
<td></td>
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</tr>
<tr>
<td>Active</td>
<td>3.20 (0.75)</td>
<td>3.55 (0.45)</td>
<td>3.45 (0.69)</td>
<td>.438 (.183)</td>
<td>.922 (.051)</td>
<td>.657 (.113)</td>
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</tr>
<tr>
<td>Sham</td>
<td>3.39 (0.60)</td>
<td>3.44 (0.68)</td>
<td>3.44 (0.92)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Activity Level</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Active</td>
<td>3.04 (0.65)</td>
<td>3.14 (0.48)</td>
<td>3.03 (0.79)</td>
<td>.849 (.073)</td>
<td>.827 (.055)</td>
<td>.408 (.196)</td>
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</tr>
<tr>
<td>Sham</td>
<td>2.98 (0.59)</td>
<td>2.95 (0.73)</td>
<td>3.10 (0.72)</td>
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<tr>
<td><strong>Vigilance</strong></td>
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</tr>
<tr>
<td>Active</td>
<td>3.03 (0.60)</td>
<td>3.33 (0.37)</td>
<td>3.32 (0.66)</td>
<td>.068 (.531)</td>
<td>.284 (.182)</td>
<td>.925 (.061)</td>
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<tr>
<td>Sham</td>
<td>2.83 (0.48)</td>
<td>3.03 (0.76)</td>
<td>3.10 (0.56)</td>
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<tr>
<td><strong>Intimate Relationships</strong></td>
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<td>Active</td>
<td>3.48 (0.85)</td>
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<td>.586 (.133)</td>
<td>.335 (.155)</td>
<td>.886 (.067)</td>
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<tr>
<td>Sham</td>
<td>3.18 (1.00)</td>
<td>3.02 (1.17)</td>
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<tr>
<td><strong>Total FOSQ</strong></td>
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<tr>
<td>Active</td>
<td>15.08 (3.34)</td>
<td>15.93 (2.94)</td>
<td>15.87 (3.79)</td>
<td>.192 (.088)</td>
<td>.860 (.002)</td>
<td>.794 (.013)</td>
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<tr>
<td>Sham</td>
<td>14.99 (2.43)</td>
<td>15.34 (3.50)</td>
<td>15.86 (2.72)</td>
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<td></td>
<td></td>
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</tbody>
</table>

^ The degrees of freedom for analysis of all main effects and interaction effects (2,36), and between groups (1,18)
Table 6.  *Mean Scores on the SF-36 Across Time*

<table>
<thead>
<tr>
<th></th>
<th>Pre-treatment</th>
<th>Mid-treatment</th>
<th>Post-treatment</th>
<th>Significance (η²)</th>
<th>Time</th>
<th>Group</th>
<th>Interaction</th>
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<td><strong>Physical Functioning</strong></td>
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<tr>
<td>Active</td>
<td>75.00 (20.28)</td>
<td>69.50 (22.42)</td>
<td>74.00 (22.34)</td>
<td>.135 (.368)</td>
<td>.821 (.055)</td>
<td>.281 (.231)</td>
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<tr>
<td>Sham</td>
<td>73.00 (22.14)</td>
<td>73.50 (24.50)</td>
<td>78.50 (19.16)</td>
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<tr>
<td><strong>Role Physical</strong></td>
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<tr>
<td>Active</td>
<td>52.50 (39.88)</td>
<td>57.50 (44.18)</td>
<td>57.50 (42.57)</td>
<td>.899 (.065)</td>
<td>.368 (.141)</td>
<td>.343 (.228)</td>
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<tr>
<td>Sham</td>
<td>77.50 (38.10)</td>
<td>70.00 (43.78)</td>
<td>67.50 (35.45)</td>
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<td><strong>Bodily Pain</strong></td>
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<td>Active</td>
<td>57.6 (25.14)</td>
<td>59.40 (26.52)</td>
<td>59.40 (23.60)</td>
<td>.719 (.099)</td>
<td>.305 (.170)</td>
<td>.373 (.213)</td>
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<tr>
<td>Sham</td>
<td>73.10 (17.57)</td>
<td>66.40 (21.68)</td>
<td>66.50 (20.44)</td>
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<tr>
<td><strong>General Health</strong></td>
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<tr>
<td>Active</td>
<td>54.90 (19.76)</td>
<td>56.70 (20.87)</td>
<td>61.70 (21.76)</td>
<td>.417 (.192)</td>
<td>.890 (.052)</td>
<td>.779 (.086)</td>
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<tr>
<td>Sham</td>
<td>55.20 (20.26)</td>
<td>57.00 (21.53)</td>
<td>57.70 (16.42)</td>
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<tr>
<td><strong>Vitality</strong></td>
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<td>Active</td>
<td>47.00 (20.71)</td>
<td>45.50 (22.17)</td>
<td>49.50 (21.66)</td>
<td>.553 (.142)</td>
<td>.959 (.050)</td>
<td>.579 (.135)</td>
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<tr>
<td>Sham</td>
<td>45.00 (19.58)</td>
<td>49.50 (26.92)</td>
<td>49.00 (23.43)</td>
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<tr>
<td><strong>Social Functioning</strong></td>
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<tr>
<td>Active</td>
<td>63.75 (25.99)</td>
<td>68.75 (24.47)</td>
<td>76.25 (23.90)</td>
<td>.365 (.217)</td>
<td>.615 (.077)</td>
<td>.284 (.264)</td>
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<tr>
<td>Sham</td>
<td>76.25 (20.79)</td>
<td>72.25 (26.07)</td>
<td>75.00 (23.57)</td>
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<tr>
<td><strong>Role Emotional</strong></td>
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<tr>
<td>Active</td>
<td>59.99 (43.89)</td>
<td>53.33 (47.66)</td>
<td>60.00 (46.61)</td>
<td>.576 (.136)</td>
<td>.260 (.196)</td>
<td>.410 (.196)</td>
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<tr>
<td>Sham</td>
<td>83.33 (23.57)</td>
<td>80.00 (42.16)</td>
<td>66.67 (41.57)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mental Health</strong></td>
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<td></td>
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<tr>
<td>Active</td>
<td>65.60 (23.26)</td>
<td>67.60 (21.70)</td>
<td>64.80 (23.54)</td>
<td>.664 (.112)</td>
<td>.951 (.050)</td>
<td>.985 (.052)</td>
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<tr>
<td>Sham</td>
<td>66.40 (15.46)</td>
<td>67.60 (20.70)</td>
<td>65.60 (16.89)</td>
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</tbody>
</table>

^ The degrees of freedom for analysis of all main effects and interaction effects (2,36), and between groups (1,18)
Table 7. *Mean Scores on the Profile of Mood States – Short Form -37 Across Time*

<table>
<thead>
<tr>
<th></th>
<th>Pre-treatment</th>
<th>Mid-treatment</th>
<th>Post-treatment</th>
<th>Significance ($\eta^2$)</th>
<th>Time</th>
<th>Group</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tension</strong></td>
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</tr>
<tr>
<td>Active</td>
<td>1.32 (1.21)</td>
<td>1.10 (0.99)</td>
<td>1.17 (0.95)</td>
<td>.313 (.245)</td>
<td>.886 (.052)</td>
<td>.960 (.056)</td>
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</tr>
<tr>
<td>Sham</td>
<td>1.33 (0.86)</td>
<td>1.18 (0.76)</td>
<td>1.23 (0.59)</td>
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<td><strong>Depression</strong></td>
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</tr>
<tr>
<td>Active</td>
<td>0.90 (0.82)</td>
<td>0.73 (0.87)</td>
<td>0.80 (0.81)</td>
<td>.496 (.122)</td>
<td>.766 (.059)</td>
<td>.518 (.116)</td>
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<tr>
<td>Sham</td>
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<td>0.88 (0.80)</td>
<td>0.96 (0.60)</td>
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<td><strong>Anger</strong></td>
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<tr>
<td>Active</td>
<td>0.99 (0.75)</td>
<td>0.67 (0.51)</td>
<td>0.74 (0.54)</td>
<td>.182 (.349)</td>
<td>.415 (.124)</td>
<td>.406 (.197)</td>
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<tr>
<td>Sham</td>
<td>1.04 (0.66)</td>
<td>0.97 (0.71)</td>
<td>1.04 (0.66)</td>
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<tr>
<td><strong>Vigor</strong></td>
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<tr>
<td>Active</td>
<td>1.55 (0.84)</td>
<td>1.67 (0.85)</td>
<td>1.58 (0.89)</td>
<td>.350 (.224)</td>
<td>.895 (.052)</td>
<td>.764 (.090)</td>
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<td>Sham</td>
<td>1.57 (0.80)</td>
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<td><strong>Fatigue</strong></td>
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<tr>
<td>Active</td>
<td>1.70 (1.25)</td>
<td>1.60 (1.14)</td>
<td>1.68 (1.02)</td>
<td>.728 (.097)</td>
<td>.766 (.059)</td>
<td>.775 (.087)</td>
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<td>1.88 (0.88)</td>
<td>1.80 (1.07)</td>
<td>1.70 (0.89)</td>
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<tr>
<td><strong>Confusion</strong></td>
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</tr>
<tr>
<td>Active</td>
<td>1.32 (0.89)</td>
<td>1.20 (1.04)</td>
<td>1.20 (1.05)</td>
<td>.575 (.136)</td>
<td>.580 (.083)</td>
<td>.625 (.122)</td>
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</tr>
<tr>
<td>Sham</td>
<td>1.04 (0.83)</td>
<td>1.10 (0.67)</td>
<td>0.96 (0.55)</td>
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<td><strong>Total mood</strong></td>
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<td>disturbance</td>
<td>4.78 (0.82)</td>
<td>4.61 (0.75)</td>
<td>4.67 (0.79)</td>
<td>.181 (.350)</td>
<td>.885 (.050)</td>
<td>.803 (.082)</td>
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<td>4.77 (0.55)</td>
<td>4.68 (0.61)</td>
<td>4.73 (0.48)</td>
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</tr>
</tbody>
</table>

^ The degrees of freedom for analysis of all main effects and interaction effects (2,36), and between groups (1,18)
6.6 Physiological Data

6.6.1 Wake recordings.

One participant in the active group failed to achieve normal, stable respiration during resting wakefulness and was excluded from the averaged waking resistance and waking ventilation comparisons.

Upper airway resistance.

A total of 573 breaths were analysed in the active group ($M=71.63$, $SD=25.75$ breaths per patient) and 697 in the sham group ($M=69.70$, $SD=30.11$ breaths per patient) to form average RUA values pre-treatment. A total of 535 breaths were analysed in the active group ($M=66.88$, $SD=22.68$, breaths per patient) and 799 in the sham group ($M=79.90$, $SD=27.26$, breaths per patient) to form average RUA values post-treatment. Average values of RUA for both the active and sham groups are shown in figure 20a.

An ANOVA did not show a significant main effect of time or treatment group on RUA, $F(1,16)=0.959$, $p=.342$, $\eta^2=.152$, $F(1,16)=0.144$, $p=.710$, $\eta^2=.065$, respectively; nor was there a significant interaction effect between time and treatment group on RUA, $F(1,16)=0.213$, $p=.650$, $\eta^2=.072$.

Inspired minute ventilation.

Every breath during five minutes of quiet wakefulness was analysed. In total, 609 breaths in the active group ($M=76.13$, $SD=28.20$, breaths per patient) and 747 breaths in the sham group ($M=74.70$, $SD=32.38$, breaths per patient) were used to form average values of $V_i$ during quiet wakefulness on the pre-treatment study night. Average values of waking $V_i$ on the post-treatment study night were obtained from analysis of 570 breaths in the active group ($M=71.25$, $SD=28.98$, breaths per patient) and 747 breaths in the sham group ($M=83.90$, $SD=29.32$, breaths per patient). Average values of waking $V_i$ for both the active and sham groups are shown in figure 20b.

An ANOVA did not show a main effect of time or treatment group, and no significant interaction effect between time and treatment groups on $V_i$. 

172
F(1,16)=0.757, p=.397, \eta^2=.130, F(1,16)=0.095, p=.762, \eta^2=.060, and F(1,16)=0.550, p=.469, \eta^2=.107, respectively.

Figure 20. The figure shows mean waking values of a) RUA, and b) V̇_I for the active (N=8) and sham (N=10) groups (±SD), on the pre- and post-treatment study nights.

6.6.2 Measures during sleep.

For each of the following physiological variables comparison was made only for NREM sleep as not all patients experienced REM sleep and there was no significant difference between NREM and REM AHI for either group (see section 6.2.1 above).

Respiratory measures.

Every breath during each selected respiratory event was analysed during sleep. A total of 309 (M=34.33, SD=10.70 events per patient) events and 400 (M=40.00, SD=10.56 events per patient) events were used to generate pre-treatment average V̇_I, V̇_T, V̇_T/Ṫ_I, PIF and Ṫ_I/Ṫ_TOT values for the active and sham acupuncture groups, respectively. For post-treatment averages, 278 (M=30.89, SD=7.37, events per patient) events in the active group and 415 (M=41.50, SD=14.15, events per patient) events in the sham group were used. Figure 21 shows the average values for each respiratory variable for the active and sham groups both pre- and post-treatment. Analysis of variance showed no significant main effects of time, or group, nor interaction effects between time and treatment group for any of the respiratory measures.
Figure 21. The figure shows mean values for a) $V_I$, b) $V_T$, c) $V_T/T_I$, d) PIF, and e) $T_I/T_{TOT}$ (±SD), for both the active and sham groups on the pre- and post-treatment
study nights. The degrees of freedom for all mixed-model analyses of variance for respiratory measures were (1,17).

**Arousal threshold.**

Values for negative pressure on the breath prior to arousal were obtained for 295 events ($M=32.78$, $SD=10.52$, events per patient) in the active group and 349 events ($M=34.90$, $SD=8.92$, events per patient) in the sham group to form an overall average of pre-treatment AT. Post-treatment average AT was derived from a total of 263 ($M=29.22$, $SD=6.85$, events per patient) events from the active group and 361 ($M=36.1$, $SD=14.20$, events per patient) events from the sham group. Average values of AT for both the active and sham groups are shown in figure 22.

Analysis of variance revealed no significant main effect of time or treatment group on AT, $F(1,17)=0.176$, $p=.680$, $\eta^2=.068$, and $F(1,17)=0.630$, $p=.438$, $\eta^2=.116$, respectively. There was also no significant interaction effect between time and treatment group on AT, $F(1,17)=3.740$, $p=.070$, $\eta^2=.446$.

![Figure 22](image.png)

*Figure 22.* The figure shows the average AT values for the active ($N=9$) and sham ($N=10$) groups (±SD), on the pre-treatment and post-treatment study nights.

**Genioglossus muscle activation.**

Recording of muscle activity failed in one active patient, who was not included in the analysis. In total, 206 ($M=25.75$, $SD=12.31$ events per patient)
events were analysed from the active group and 365 ($M=36.50, SD=12.17$ events per patient) events were analysed from the sham group to produce average values for peak and tonic muscle activation pre-treatment. Average peak and tonic activation post-treatment was calculated using 233 ($M=29.13, SD=13.26$ events per patient) events from the active group and 335 ($M=33.5, SD=14.91$ events per patient) events from the sham group. Average values of slope, intercept and correlation coefficient for peak and tonic muscle activity-epiglottic pressure (PSLOPE, PINT, PCOR, and TSLOPE, TINT and TCOR, respectively) for both the active and sham groups with error bars showing standard deviation are shown in figure 23.

Analysis of variance showed no significant main effect of time or treatment group, however, there was a significant interaction effect between time and treatment group on PCOR, $F(1,16)=9.003, p=.008, \eta^2=.804$. Repeated-measures t-tests revealed that PCOR was significantly weaker on the post-treatment study night than the pre-treatment study night in the sham group, $t(9)=-3.452, p=.007, r=.755$. There was also a significantly greater correlation between the peak GG activation and epiglottic pressure in the active group than the sham group on the post-treatment study night, $t(7)=-3.007, p=.020, r=.751$. Although there was no significant main effect of time or interaction effect between time and treatment group, there was a significant main effect of treatment group on the correlation between tonic GG activation and epiglottic pressure across events, $F(1,16)=4.803, p=.044, \eta^2=.540$. Analysis of variance showed no significant main effect of time or treatment group, nor interaction effect between time and treatment group on any other measure of GG muscle activity.
Figure 23. The figure shows mean values for a) PSLOPE, b) PINT, c) PCOR, d) TSLOPE, e) TINT, and f) TCOR for the active (N=8) and sham (N=10) groups (±SD), on the pre-treatment and post-treatment study nights. The degrees of freedom for all mixed-model analyses of variance for GG muscle activity were (1,16).
6.7 Sham Cross-Over

Seven of the 10 patients who were randomized to receive the sham treatment chose to have the active treatment at the completion of the trial. For these 7 patients repeated-measures analysis of variance was conducted for all measures during NREM sleep across the three sleep studies. The assumption of homogeneity of variance was met for each of the following analyses, thus reported values assume sphericity.

6.7.1 OSA severity measures

*Apnoea hypopnoea index.*

The change in AHI for each individual across the three study nights is shown in figure 24. The average AHI at each of the study nights for the cross-over patients is shown in figure 25a. There was no significant change in AHI across time, $F(2,12)=1.807, p=.206, \eta^2=.304$.

*Arousal index.*

The average AI at each of the study nights for the cross-over patients is shown in figure 25b. There was no significant change in AI across time, $F(2,12)=1.364, p=.293, \eta^2=.238$.

Figure 24. The figure shows the AHI across the three study nights for cross-over patients ($N=7$).
Figure 25. The figure shows the mean (±SD) for a) AHI and b) AI across study nights for cross-over patients (N=7).

**Oxygen desaturation index.**

The average ODI3% at each of the study nights for the cross-over patients is shown in figure 26a. There was no significant change in ODI3% across time, $F(2,12)=2.799$, $p=.101$, $\eta^2=.447$.

**Mean oxygen saturation.**

The mean SaO$_2$ at each of the study nights for the cross-over patients is shown in figure 26b. There was no significant change in mean SaO$_2$ across time, $F(2,12)=1.060$, $p=.377$, $\eta^2=.193$.

Figure 26. The figure shows mean (±SD) for a) ODI3% and b) SaO$_2$ across study nights for cross-over patients (N=7).
6.7.2 Sleep measures.

**Sleep onset latency.**

The average SOL on each of the study nights for the cross-over patients is shown in figure 27. There was no significant change in SOL across time, $F(2,12)=0.985, p=.402, \eta^2=.182$.

![Figure 27](image_url)

*Figure 27.* The figure shows average sleep onset latency (±SD), across the study nights for cross-over patients ($N=7$).

**Sleep efficiency.**

The average SE on each of the study nights for the cross-over patients is shown in figure 28. There was no significant change in SE across time, $F(2,12)=1.172, p=.343, \eta^2=.210$.

![Figure 28](image_url)

*Figure 28.* The figure shows average sleep efficiency (±SD), across the study nights for cross-over patients ($N=7$).
Sleep architecture.

The average percentage of total sleep time spent in each stage of sleep on pre-treatment, post-sham and post-active study nights are shown in figure 29. There was a significant difference in the amount of stage 1 sleep across study nights, \( F(2,12)=5.829, p=.017, \eta^2=.770 \). However, pairwise comparisons did not show any significant difference between the pre-treatment study night and either the post-sham or post-active study nights, nor was there a significant difference in amount of stage 1 sleep between the post-sham and post-active study nights, \( p=.187, p>.999 \) and \( p=.054 \), respectively. There was, however, a significant quadratic trend, \( F(1,6)=8.260, p=.028, \eta^2=.670 \). There was no significant change across time in the amount of stage 2 sleep, \( F(2,12)=0.904, p=.431, \eta^2=.171 \). Likewise, there was no significant change across time in the amount of slow wave or REM sleep, \( F(2,12)=1.425, p=.278, \eta^2=.247 \), and \( F(2,12)=3.708, p=.056, \eta^2=.565 \), respectively.

Figure 29. The figure shows the average percentage of total sleep time spent in each stage of sleep (±SD), across the three study nights for cross-over patients (\( N=7 \)).

6.7.3 Physiological Data.

Measures during wakefulness.

Upper airway resistance.

A total of 607 breaths were analysed at baseline (\( M=86.71, SD=24.96 \), breaths per patient), 478 breaths were analysed post-sham treatment (\( M=68.29 \),
Average RUA values for both the active and sham groups are shown in figure 30a. Repeated-measures ANOVA did not show a significant change in RUA across time, $F(2,12)=0.266, p=.771, \eta^2=.083$.

**Inspired minute ventilation.**

Baseline average values of waking $V_1$ were derived from a total of 612 breaths ($M=87.43, SD=25.26$, breaths per patient). The average post-sham waking $V_1$ value was derived from a total 482 breaths ($M=68.86, SD=31.55$, breaths per patient), and the average post-active treatment waking $V_1$ value was derived from a total of 482 breaths ($M=68.86, SD=25.59$, breaths per patient). Average waking $V_1$ values for both the active and sham groups are shown in figure 30b. Repeated-measures ANOVA did not show a significant main effect of time on waking $V_1$, $F(2,12)=0.501, p=.618, \eta^2=.114$.

**Figure 30.** The figure shows mean values taken during wakefulness for a) RUA and b) $V_1$ (±SD), across study nights for cross-over patients ($N=7$).

**Measures during sleep.**

**Respiratory measures.**

A total of 294 events ($M=42.00, SD=10.65$ events per patient), 308 events ($M=44.00, SD=14.20$ events per patient), and 243 events ($M=34.71, SD=7.13$ events per patient) were used to generate baseline, post-sham and post-active
average \( V_l \), \( V_T \), \( V_T/T_l \), PIF and \( T_l/T_{TOT} \) values, respectively. Average values for these respiratory measures across study nights are shown in figure 31.

Repeated measure ANOVA showed no significant effect of time on \( V_l \), \( V_T \), \( V_T/T_l \), PIF or \( T_l/T_{TOT} \), \( F(2,12)=0.828, p=.460 \), \( \eta^2=.160 \), \( F(2,12)=0.969, p=.407 \), \( \eta^2=.180 \), \( F(2,12)=1.129, p=.355 \), \( \eta^2=.203 \), \( F(2,12)=0.806, p=.470 \), \( \eta^2=.156 \), and \( F(2,12)=1.417, p=.280 \), \( \eta^2=.246 \), respectively.

![Graphs](image)

**Figure 31.** The figure shows mean values for a) \( V_l \), b) \( V_T \), c) \( V_T/T_l \), d) PIF and e) \( T_l/T_{TOT} \) (±SD), across NREM events for each study night for cross-over patients (\( N=7 \)).
Arousal threshold.

A total of 242 breaths ($M=34.57$, $SD=9.52$ breaths per patient), 297 breaths ($M=42.43$, $SD=14.06$ breaths per patient), and 211 breaths ($M=30.14$, $SD=5.64$ breaths per patient) were used to generate baseline, post-sham and post-active average negative pressure values, respectively. Figure 32 shows the average AT values across study nights. A repeated-measures ANOVA revealed no significant effect of time on AT, $F(2,12)=1.523$, $p=.257$, $\eta^2=.262$.

![Arousal Threshold Graph](image)

Figure 32. The figure shows average AT values (±SD), across study nights for cross-over patients ($N=7$).

Genioglossus muscle activation.

In total, 260 events ($M=37.14$, $SD=13.97$ events per patient), 263 events ($M=37.57$, $SD=16.03$ events per patient), and 200 events ($M=28.57$, $SD=8.56$ events per patient) were used to generate average values for peak and tonic muscle activation at the baseline, post-sham and post-active treatment time points, respectively. Figure 33 shows the average values for PSLOPE, PINT and PCOR across study nights. Figure 34 shows the average values for TSLOPE, TINT and TCOR across study nights.

Repeated measures ANOVA revealed no significant effect of time on PSLOPE or TSLOPE across events, $F(2,12)=0.497$, $p=.620$, $\eta^2=.113$, and $F(2,12)=1.049$, $p=.380$, $\eta^2=.192$, respectively. There was no significant difference
between study nights on PINT or TINT, $F(2,12)=0.573$, $p=.578$, $\eta^2=.124$, and $F(2,12)=2.332$, $p=.174$, $\eta^2=.266$, respectively. There was a significant difference in PCOR across time, $F(2,12)=4.828$, $p=.029$, $\eta^2=.685$, however, pairwise comparisons did not show a significant difference between individual study nights. There was, however, a trend towards significance for a quadratic relationship for PCOR, $F(1,6)=5.660$, $p=.055$, $\eta^2=.514$. There was also a significant difference in TCOR across time, $F(2,12)=10.477$, $p=.002$, $\eta^2=.957$. Pairwise comparisons identified no significant difference between pre-treatment and post-sham study nights, but did show significant differences between the pre-treatment and post-active, as well as the post-sham and post-active study nights, $p>.999$, $p=.044$, and $p=.007$, respectively.

![Figure 33](image-url)

*Figure 33.* The figure shows the mean values for the a) PSLOPE, b) PINT, and c) PCOR (±SD), across the study nights for cross-over patients ($N=7$).
Figure 34. The figure shows the mean values for the a) TSLOPE, b) TINT, and c) TCOR (±SD), across the study nights for cross-over patients (N=7).
Chapter 7 - General Discussion

Acupuncture has previously been demonstrated to reduce the severity of OSA (Freire et al., 2007). However, the past research by Freire and colleagues did not determine a Chinese medicine diagnosis, and all patients received the same treatment without explanation of the treatment principles. Thus, their trial did not follow standard practice for Chinese Medicine. The aim of this thesis was firstly to determine the typical Chinese medicine syndromes present in OSA patients, and to then conduct a clinical trial of acupuncture in appropriately selected patients. In addition, I aimed to determine how acupuncture resulted in any change in AHI from a physiological point of view. Thus, the current clinical trial was conducted to investigate the efficacy of acupuncture for the treatment of obstructive sleep apnoea in patients with a specific phenotype of OSA. Patients underwent either active or sham acupuncture treatment for twelve weeks. Subjective and objective baseline and post-treatment measures of OSA severity were taken and compared. Measures included: standard polysomnographic measures, physiological measures and subjective accounts of health, wellbeing, mood and daily functional status. It was hypothesized that twelve weeks of active acupuncture, but not sham acupuncture, would result in significant reductions in AHI. This hypothesis was not supported. It was also hypothesized that active treatment, but not sham treatment, would lead to reductions in objective measurement of Al, ODI3%, and SE, and lead to increases in mean SaO2. It was similarly hypothesized that active, but not sham, treatment would lead to improvements in the ESS, POMS-37, FOSQ and SF-36 scores. For physiological measurements it was hypothesized that active, but not sham, treatment would lead to reductions in nasopharyngeal resistance, and increases in ventilation, arousal threshold and genioglossus muscle activity in response to flow limitation. The results of the clinical trial showed that the patients receiving active needle acupuncture had no change in any subjective or objective measure. The sham group also failed to show any change in OSA severity or any other measure. Thus, the results do not support any of the hypotheses.
7.1 OSA Severity

The active treatment in the present study did not affect OSA severity, nor did the sham treatment. The results of this study are inconsistent with the findings by Freire and colleagues (2007) who found a significant effect of acupuncture for lowering AHI in mild to moderate OSA patients. Freire and colleagues showed an average decrease in AHI by almost 10 events per hour following active treatment, but not following sham treatment, or in a non-treatment control group. The acupuncture points used in treatment were similar for both studies, as was the course of treatment. The treatment in the present study was designed to target mild to moderate OSA patients, similar to the sample population from the study by Freire and colleagues. However, in order to combat low recruitment numbers, severe OSA patients (8 patients began the trial with an AHI >30) were accepted into the present trial, thus the severity was considerably greater overall (mean AHI = 31.97) than in the study by Freire and colleagues (mean AHI = 19.01).

There was also no evidence from the present study that active needle acupuncture had any effect on other polysomnographic characteristics including arousal index, sleep efficiency, or mean oxygen saturation. The study by Freire and colleagues (2007) found improvement in all three of these measures within their sample following active needle acupuncture. Sleep efficiency, however, also improved in their sham acupuncture and non-treatment control groups. Thus the improvement in sleep efficiency may simply reflect adaptation effects. Many studies include an adaptation night to their study design due to abnormal sleep effects that can occur as a result of sleeping in an unusual environment. For the present study, it was assumed that the polysomnographic study conducted at the time of their diagnosis would have introduced them to the standard PSG apparatus, thereby providing an adequate substitution for an adaptation night. However, the location of the study and the equipment used to monitor sleep and physiological changes for the clinical trial were different from the initial diagnostic PSG. It is possible, therefore, that baseline parameters may have been confounded by first night effects. This is unlikely to affect the findings,
however, as typical first night effects include longer REM onset latency, more time spent in stages 1 and 2 NREM sleep and less time spent in REM sleep compared with subsequent nights (Agnew, Webb, & Williams, 1966). Interestingly, the patients in the present study appeared to have the opposite pattern to normal first night effects. There were significant increases in the percentage of stage 1 and 2 sleep, and significant decreases in the percentage of REM sleep on the post-treatment study night in the present study. It is unlikely, therefore, that first night effects can explain the lack of significant changes in any of the measured standard PSG sleep parameters. The baseline and post-treatment follow-up sleep studies for this trial also included more invasive apparatus than a standard PSG and may have added an additional challenge to their airway, thereby worsening the AHI and masking any changes.

The study by Freire and colleagues (2007), also found that active needle acupuncture, but not sham needle acupuncture was effective at significantly reducing sleep onset latency. First night effects cannot be ruled out as they did not include an adaptation night, and the reductions in SOL were observed across all three of their treatment groups, albeit only significantly in the active needle acupuncture group. We did not find that the active treatment in the present clinical trial effectively lowered sleep onset latency. In this present study, patients were asked to attend the laboratory for instrumentation three hours prior to their normal bed-time. This should have provided adequate time to complete the questionnaires and for the apparatus to be applied well before the participant’s normal bed-time. The actual arrival time and time taken to apply the apparatus varied considerably from study to study and many patients ended up going to bed considerably later than their normal bed-time. This variation was mostly due to work or family commitments for the patient, or equipment problems during instrumentation. Therefore, the measure of sleep onset latency in the present study is subject to confounding factors.

This study attempted to address limitations of past research by Freire and colleagues (2007) by targeting a specific subset of OSA patients with a specific CM phenotype of OSA. The data from the initial diagnostic study identified four
CM phenotypes of OSA. Each phenotype has a different underlying pathophysiological profile and requires a different treatment approach. The Spleen deficiency and Excess Heat phenotype was the most commonly observed and occurred in more than 44% of the patients sampled. Patients with this phenotype were recruited for the present clinical trial. The pathological mechanism in these patients relates to poor functioning of the Spleen leading to poor Qi production, retention of Dampness and the formation of Phlegm. Additionally, the stagnation of Liver Qi over time has transformed into Excess Heat or Fire, which flares upwards. The upward movement of the Heat combines with the Phlegm and obstructs the respiratory tract. Targeting a specific CM phenotype allowed for a more tailored treatment approach designed to address the underlying causal factors, which is more consistent with normal clinical acupuncture practice. The acupuncture point selection in the present trial included the points used previously by Freire and colleagues, as well as additional points to specifically address the underlying syndrome. Despite CM phenotypic targeting we were unable to replicate the findings from the past research.

Another limitation of the past research was the use of a sham method that was not guaranteed to be biologically inert. The present study employed a different sham method to that used by Freire and colleagues (2007). The use of laser acupuncture, in which the laser diode has been removed, has previously been validated, and has the advantage of being biologically inert (Irnich et al., 2011). In the morning, following the post-treatment sleep study, participants were asked to indicate if they thought they had been allocated to the active or sham group, if they had given thought to whether they had received the sham or active treatment during the trial and to provide an explanation as to why they felt they had received either type of treatment. The majority of sham patients (90%) believed that they were receiving active treatment. Those sham patients who gave a reason for why they believed they were in the active group reported that they were feeling better and sleeping better. Conversely, more of the active patients (20%) believed that they were receiving sham treatment. The active
patients who believed they were receiving sham treatment claimed that they did not feel as though they were improving, therefore, they assumed that they were receiving the sham treatment. Many patients claimed not to have given thought to whether or not they were receiving active or sham treatment. These reports suggest that the sham method was effective as patients were unable to determine with any accuracy if they were receiving active or sham treatment, and the reasons for believing one way or the other were unrelated to the method of treatment itself. Thus, once the theoretical and methodological limitations of the study by Freire and colleagues (2007) were addressed, the treatment effect previously observed was no longer found.

Sleeping position and breathing route were constrained as much as possible in this study as the primary objective was to investigate changes in normal sleep behaviour and patterns. Some patients were woken and asked to change to a supine decubitus position if they had spent the majority of the night on their side. Intervention of this kind was only done in order to obtain sufficient data for analysis. Sleeping in a prone decubitus position was not possible due to the apparatus worn over night. Many patients reported that it was normal practice at home for them to fall asleep either on their side or stomach and several patients did claim to have greater difficulty sleeping due to the supine/lateral restriction. Sleep apnoea is generally more severe in a supine decubitus position (Kavey, Blitzer, Gidro-Frank, & Korstanje, 1985; Oksenberg & Silverberg, 1998), and in some patients occurs exclusively when in a supine decubitus position (Joosten et al., 2015; Mador et al., 2005). A recent study, however, did find that sleeping position did not affect all individuals with OSA (Marques et al., 2017). Their findings suggested that in OSA patients who experience airway collapse at the level of the tongue are not affected by sleeping position, however, those patients with a locus of collapse at the epiglottis do benefit from a lateral decubitus position. The request for patients to sleep supine may have lead to inflated AHI values in at least some patients in the present study.

The protocol stipulated that patients would sleep with a fitted nasal mask and tape over their mouth to prevent mouth breathing. Some patients, however,
could not tolerate tape over their mouth. In some cases this was due to a normal tendency to breathe through the mouth, while in many cases it gave patients considerable anxiety to have tape over their mouth. Following wakefulness measurements using a nasal mask, these patients were fitted with a full-face mask prior to sleep. Resistance of the UA increases with oro-nasal breathing (Meurice et al., 1996). It is possible therefore, that resistance may have been increased in some patients leading to worsening of their OSA. It is unlikely that this would obscure the results as each participant was fitted with the same type of mask at both their baseline and follow-up study. Although the nasal and full-face masks may have increased the resistance during sleep and AHI, presumably the same degree of resistance increase would have been experienced on the follow-up night.

7.2 Subjective Findings

Previous studies have not consistently shown a relationship between sleepiness and sleep apnoea severity. Consistent with this, the current study sample did not demonstrate pathological sleepiness at baseline, as measured by the ESS (pathological sleepiness defined as ESS ≥11), and values were lower on average than mean values reported within mild to moderate clinical OSA populations (Barnes et al., 2004; Barnes, Goldsworthy, Cary, & Hill, 2009; Engleman, Martin, Deary, & Douglas, 1997; Engleman et al., 2002). However, it should be noted that patients were excluded from the present study if they had severe sleepiness (ESS >16) due to concerns over safety while the patient was not receiving CPAP treatment. Although excessive sleepiness is one of the hallmark symptoms of OSA the research shows an inconsistent pattern of association between somnolence and sleep disordered breathing. The Apnea Positive Pressure Long-Term Efficacy Study (APPLES), failed to show an association between EDS, measured by either the ESS or the SSS, and OSA severity in a mild population (Quan et al., 2014). Data from the Sleep Heart Health Study (SHHS), conversely, did show a small albeit significantly increased ESS mean score in mild OSA patients when compared to individuals with an AHI <5. More
consistent associations were found between OSA severity and sleepiness ratings
in moderate to severe samples (Akashiba et al., 2002; Barnes et al., 2002; Gottlieb
et al., 1999), however, there is still conflicting evidence. A population study in
Switzerland found no association between OSA and sleepiness regardless of
severity (Heinzer et al., 2015; Quan et al., 2014). While data from past research
shows mixed findings for an association between OSA severity and levels of
sleepiness, the past research does consistently find that this symptom is not
present in the majority of individuals with OSA (Duran et al., 2001; Kapur et al.,
2005; Young et al., 1993; 1996). The present study also showed that there was no
change in sleepiness levels after 12 weeks of active or sham acupuncture
treatment. The study by Freire et al. (2007) did show a significant reduction in
sleepiness levels as a result of 10 active acupuncture treatments, but not sham
acupuncture treatments. Their sample showed higher levels of sleepiness at
baseline in comparison to the present sample. The ESS levels for both the sample
from the Freire study and the present study were similar post-treatment,
however, the reduction was not significant in the present study.

The scores on the FOSQ did not show a significant change over the course
of treatment, for any subscale or the global FOSQ score. Baseline scores for both
the active and sham groups were higher (more normal) than scores seen
previously in other clinical samples of OSA patients, yet were still below
normative levels (Barnes et al., 2002; Doff et al., 2013; Weaver & Grunstein, 2008;
Weaver et al., 1997). Although the FOSQ is more sensitive to functional deficits
resulting from disorders of excessive sleepiness than generic measures of quality
of life, such as the SF-36, it may not be the most sensitive scale for detecting
change over a treatment period (Lacasse, 2004). It is possible that the degree of
daily dysfunction in this sample was less than that normally seen in OSA
populations, and that the FOSQ was not sensitive enough to detect change over
the treatment period. However, the lack of change is most likely due to the fact
that AHI was unchanged in the present study.

The American Academy of Sleep Medicine Task Force on Sleep-Related
Breathing Disorders in Adults reported that reduced quality of life is a
characteristic of OSA (1999). Findings by the task force from the SF-36 suggested that OSA patients consistently rated lower on the domains of Vitality, Role-emotional, Mental health and Social Functioning than population norms. Past research has suggested a correlation between poor quality of life and severe OSA (Akashiba et al., 2002). In particular, severe OSA patients typically show impairment across the majority of domains of the SF-36 (Baldwin et al., 2001; D'Ambrosio et al., 1999; Finn et al., 1998). Contrary to the suggestions from past research, the present sample did not show any evidence of impaired quality of life at baseline. Comparison of scores on the SF-36 in this sample with normative data from an Australian population failed to show significant differences for any subscale either at baseline or follow-up. The study by Freire and colleagues (2007) showed improvement in the Role physical, General Health, and Vitality domains of the SF-36 in their active acupuncture group, but not the sham or non-treatment control groups. All three of their groups showed significant improvement in the Mental Health domain of the SF-36. The baseline mean scores for their active acupuncture group for General Health, Vitality and Mental Health were lower than the mean baseline scores in the present study sample. The post-treatment mean scores obtained in the study by Freire and colleagues, however, were greater than post-treatment mean scores obtained in the present study. Given the lack of evident impairment in quality of life at baseline and lack of change in AHI with treatment in the present study it is not surprising that there was no detectable change in any of the domains of the SF-36.

No change in mood was found over the course of the treatment period for either group, nor any differences between the groups. A large multi-center study in the United States failed to find differences in mood disturbance, reported via the POMS and the Hamilton Depression Scale, in mild OSA patients (Quan et al., 2014). While depression has been found to be a prevalent comorbidity in OSA patients (Akashiba et al., 2002; BaHammam et al., 2015; Douglas et al., 2013), the POMS-37 does not specifically measure depression or depressive symptoms. It is more commonly used to identify changes in mood over a certain time period (Curran et al., 1995). Studies into the efficacy of CPAP for the treatment of OSA
have shown significant improvements in the total mood disturbance score of the POMS (Barnes et al., 2004; Derderian et al., 1988). The improvements seen as a result of CPAP treatment, however, seem to be most relevant for improvements in vigor-activity and fatigue-inertia domains (Barnes et al., 2002). The lack of change in the overall total mood disturbance score or any domain of the POMS-37 in the present study may be due to an overall lack of improvement in OSA severity as a result of active acupuncture treatment, however, it is also possible that mood was not significantly disturbed prior to treatment.

7.3 Physiological Findings

There were no significant changes in any measure of body habitus between or within the active and sham groups. Patient’s BMI, neck circumference and waist circumference were relatively constant across the sample. One patient did show an increase in BMI and waist circumference over the trial period, as well as a large increase in OSA severity. There was no change in blood pressure for either group. This was not surprising as the patients who presented with comorbid hypertension at baseline were being managed with antihypertensive medication. Although past research has shown that acupuncture may be effective at reducing blood pressure (Ren, 2000), the treatment in the present study was not designed to address hypertension specifically. Given that AHI was unchanged in the present study, the lack of change in blood pressure is not surprising.

Physiological measures of upper airway resistance and inspired minute ventilation taken during quiet wakefulness did not show a significant difference for either the treatment or sham group, from baseline to post-treatment follow-up. In general the RUA wake values found in the present sample were similar to values found in healthy individuals in previous research (Anch, Remmers, & Bunce, 1982; Meurice, Marc, Carrier, & Series, 1996; Stanchina et al., 2003; White, Lombard, Cadieux, & Zwillich, 1985; Wiegand, Zwillich, & White, 1989).

Neither active acupuncture nor sham acupuncture affected ventilation during respiratory events. There was no change in the inspired or expired
volumes, peak inspiratory flow rates or percentage of inspiratory time, nor was there a difference in the type or average event length of respiratory events between baseline and follow-up assessments. Past research has shown that healthy individuals are able to maintain ventilation during induced inspiratory airflow limitation by increasing duty cycle (Schneider et al., 2009). The mean values for duty cycle in the present study were similar to values seen amongst OSA patients in a previous study investigating the potential mechanisms involved in restoring airway patency following induced partial airway collapse (Jordan et al., 2007). Duty cycle was shown to increase across the duration of an event, however, there was no significant difference in the degree of increase between obese OSA patients and healthy non-snorers. Although the healthy non-snorers were more successful at restoring patency without arousing from sleep in general, the same degree of increase in both genioglossal muscle activation and changes in respiratory timing was seen for both OSA and non-OSA patients. Thus, while duty cycle and increased upper airway muscle activation do contribute, anatomical factors may be more important to re-establish breathing.

It has been suggested that a higher arousal threshold could allow enough time for muscular compensation to respond to hypercapnia during respiratory events (Eckert & Younes, 2014). However, arousal threshold did not show significant changes as a result of active or sham acupuncture treatment. The baseline and follow-up mean values for arousal threshold were slightly lower but still within normal values reported in the past for OSA patients (Eckert & Younes, 2014; Eikermann et al., 2007; Sforza & Krieger, 1999).

Physiological data showed no significant changes in genioglossus muscle responsiveness as a result of acupuncture or sham acupuncture treatment. Although the slope for both peak and tonic GG muscle activity showed no change, there was a trend to an increase in the intercept for both the peak and tonic GG activity in response to respiratory effort during an event as a result of acupuncture treatment, albeit not significantly. Despite mild (non-significant) improvements in the intercept of the relationship between muscle activity and
intraluminal pressure for patients, but not controls there was no observed improvement in waking upper airway resistance or reductions in AHI. The average values for the slope of the relationship between muscle activity and intraluminal pressure in the present study is similar to that seen in both controls and OSA patients in past research (Eckert et al., 2013).

7.4 Cross-Over Patients

Seven of the ten patients that were initially randomized to receive the sham treatment opted to receive the active treatment following completion of the study. The outcome for these patients was consistent with the findings from the main clinical trial. Five of these patients had slight improvement in their AHI following the active treatment, however, the change was not significant. There was a significant quadratic trend in the distribution of stage 1 sleep across the three nights, showing an initial increase in stage 1 sleep following the sham treatment with a return to baseline levels following active treatment. There was no significant change in the distribution of the other sleep stages across the three nights. These changes in stage 1 sleep most likely reflect simple night-to-night variability. No other measure of OSA severity or physiological variable showed a significant change across the three time points from baseline, to post-sham treatment and finally to post-active treatment. Subjective measures were not taken during the third treatment phase as the patients were no longer blind to the type of treatment they were receiving.

7.5 Limitations

There are several limitations that should be considered when reflecting on the results from the present study. Initially, this trial was designed for the treatment of mild to moderate OSA patients. However, due to low recruitment it was broadened to include more severe patients. It is possible that acupuncture treatment is less efficacious for severe patients (similar to several other secondary treatments) and that the inclusion of severe patients in the present study sample
therefore obscured any notable improvement. The treatment formula, and treatment period were also originally designed for a mild to moderate sample. The loosening of inclusion criteria to include more severe patients occurred after the trial had commenced and therefore amending the treatment protocol was not possible. The treatment period and protocol, therefore, may have been considered insufficient to produce noticeable change in more severe OSA patients after only one twelve week cycle of treatment. It is unlikely that either of these limitations explains the lack of improvements, however, as the mild OSA patients within the sample did not show greater improvement in comparison to severe OSA patients.

The mean scores for several of the subjective measures used in this study were atypical of OSA populations, and were instead within normative ranges. This suggests that there may be floor or ceiling effects present and, in addition to the unchanged AHI, may explain a lack of perceived improvement as a result of either active or sham treatment. Mean ESS scores suggest that the sample was not pathologically sleepy (defined as ESS ≥11: (Johns, 1991)), and therefore, we may not have seen improvement in this variable due to floor effects. The exclusion of participants that reported ESS ≥16 at baseline would also lead to a sampling bias towards a non-sleepy population, therefore, it cannot be confidently concluded that acupuncture does not improve daytime sleepiness. The mean scores on each of the SF-36 subscales suggest that the present sample experienced minimal impacts of their OSA on quality of life and functioning, and therefore ceiling effects cannot be ruled out as an explanation for no observable change in general health and quality of life as a result of acupuncture treatment. The global FOSQ scores in the present sample were not quite at levels seen in normal, healthy individuals, however, they were not as low as the global scores often seen in clinical OSA populations.

The sample size in the present study was small which jeopardizes the ability to detect any statistically significant changes. Most studies investigating physiological functions in OSA patients, however, have similar sample sizes. Power calculations are rarely reported, however, given that previous studies
have produced significant findings with similarly small sample sizes, it would suggest that it is not necessarily sample size that is preventing our results from reaching significance. It is more likely that there is no observable effect. Power analysis using G*Power (Faul, Erdfelder, Buchner, & Lang, 2009) indicated that at the relatively low levels of power obtained in this study, a sample size of more than 400 participants would be needed to achieve sufficient power. The only other study that has investigated acupuncture as a treatment for OSA did find that reductions in AHI of approximately 10 events per hour following active treatment were statistically significant (Freire et al., 2007). Both studies contain small samples and are underpowered. It is necessary to perform a larger scale study to establish whether the reductions in AHI, found by Freire and colleagues (2007) are replicable.

Although arousal threshold and muscle responsiveness were measured in the present study, neither loop gain of the ventilatory control system, nor the passive critical closing pressure of the airway were measured. These four pathophysiological traits have been highlighted as the major traits of importance for phenotyping OSA patients (Eckert et al., 2013). Although there was no significant improvement in OSA severity for the active or sham treatment groups, it is not possible to say that acupuncture has no physiological effect. The typical method of measuring Pcrit would have required the patient to undergo a second study night both at baseline and post-treatment follow-up during which pressure drops could be administered using a CPAP machine. Similarly, the measurement of loop gain requires intervention involving successive pressure dial-downs using a CPAP machine to quantify ventilatory overshoot (Wellman et al., 2013). It was determined that due to the high degree of instrumentation and complexity of the study design that only a single study could be performed at each assessment point in the present clinical trial, therefore, Pcrit and loop gain were not measured. It is possible that acupuncture may lead to decreases in Pcrit or improvements in loop gain that failed to reach a threshold effect due to the severity of OSA in the present sample, or insufficient treatment time. For example, from the CM perspective, obstruction of Phlegm and Heat that causes
difficulties in initiating sleep, which may affect loop gain rather than arousal threshold as was assumed in the present study.

It is possible that the CM phenotype targeted in this study do not suffer OSA as a result of something that can be improved with acupuncture. The CM phenotype, Spleen deficiency with Excess Heat, was targeted because it comprised the syndromes that were most prevalent amongst the local population. This phenotypic profile, however, may be most appropriately treated using Chinese herbal medicine or a combination of Chinese herbal medicine and acupuncture. This CM phenotype also presents with a complicated syndrome involving a strong underlying pathological imbalance that affects multiple organ systems. A single course of acupuncture treatment may therefore have been insufficient to produce a noticeable improvement in severe patients or patients with chronic disease, in particular because the treatment was designed to target mild to moderate patients. Different CM phenotypes, however, may respond more quickly to acupuncture treatment. For example, Phlegm as a pathological substrate is more difficult to treat than Heat.

7.6 Conclusions

The current clinical trial was conducted to investigate the efficacy of acupuncture for the treatment of obstructive sleep apnoea. Diagnostic and treatment protocols based on the initial diagnostic investigation were used to target ideal candidates in order to ensure maximal treatment efficacy. Thus, including only patients with the Spleen deficiency and Excess Heat CM phenotype of OSA, the use of the same treatment for all patients was justified and more closely represents normal acupuncture practice. A single course of active acupuncture treatment did not affect OSA severity, nor did the sham laser acupuncture treatment in our sample of moderate to severe OSA patients. Physiological measures taken during wakefulness as well as during respiratory events experienced during NREM sleep showed no significant changes for either the active or sham laser acupuncture groups. At this time it is unclear whether acupuncture is a suitable treatment for OSA patients, and if it is, whether it is
appropriate for all patients or just mild to moderate patients, like those studied by Freire and colleagues (2007). The mechanism by which acupuncture may improve OSA also remains unknown at this stage.

Future studies that include a larger sample and are adequately powered are required to show that outcome of the study by Freire and colleagues (2007) is replicable. In the event that these results can be replicated, it is important to establish, in an inclusive sample, the distribution of both CM and western phenotypes. Future study to investigate all of the physiological mechanisms known to play a role in the pathology of OSA may also help to identify which factor acupuncture alters. It would also be useful to perform a standard PSG midway through treatment or to incorporate the use of actigraphy or sleep diaries throughout the treatment period to ascertain whether or not the follow-up study was indicative of typical sleep at home.
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Appendix A

Questionnaires used in Chinese Medicine Diagnosis:
Medical History Questionnaire
Short CM Symptom Questionnaire
Long CM Symptom Questionnaire
Tongue and Pulse Questionnaire
Medical History Questionnaire

General and Medical History:

Thank you for agreeing to participate in the research project. Please complete this brief questionnaire as accurately as possible. All information you provide are for the purposes of research only and your answers will be kept confidential and any identifying information will be removed.

In what month and year were you born? /

What is your ethnicity? Caucasian

Please tick any condition below that you are currently suffering from:

☐ Cancer
☐ High Blood Pressure
☐ Low Blood Pressure
☐ Liver Disease
☐ Heart Disease
☐ Hyperthyroidism
☐ Hypothyroidism
☐ Asthma
☐ Hay fever
☐ Diabetes
☐ Chronic Fatigue
☐ Kidney Disease
☐ Epilepsy/Seizures
☐ Other (Please specify)

☐ Do you experience migraines?

☐ Do you suffer from mood or anxiety disorders? (e.g., depression, panic attacks, etc.)

Do you take any regular medication?

☐ No
☐ Yes

Please specify:

How many times a week do you exercise for more than 30 minutes? None

Do you have any of the following dietary complications?

☐ Coeliac Disease
☐ Crohn's Disease
☐ Lactose Intolerance
Short CM Symptom Questionnaire

Chinese Medicine Syndrome Differential Diagnosis for Obstructive Sleep Apnoea
(Research Team Use Only)

Severity Rating:
0 = None/never (do not have this symptom)
1 = Mild/sometimes (this symptom is present once in a while but does not affect daily life)
2 = Moderate/most of the time (this symptom can cause an inconvenience to daily life)
3 = Severe/all of the time (this symptom affects the performance of daily life)

In the last year have you experienced:

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<tr>
<th>Severity</th>
<th>0</th>
<th>1</th>
<th>2</th>
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<tr>
<td>1. Daytime sleepiness?</td>
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<td>2. Daytime sleepiness that is markedly worse after meals?</td>
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<td>3. A feeling of heaviness and muzziness of the head?</td>
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<td>4. Poor memory?</td>
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<td>5. Slight depression?</td>
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<td>6. Mental confusion?</td>
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<td>7. Dizziness?</td>
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<td>8. Dull aching headaches that are worse in the morning?</td>
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<td>9. Dull aching headaches that are worse in the afternoon?</td>
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<td>10. Dull aching headaches that feel like a tight head band?</td>
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<td>11. Sharp headaches behind the eyes and in the temples?</td>
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<td>12. A feeling of heaviness of the limbs?</td>
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<td>13. Weakness or aching, especially of the limbs?</td>
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<td>14. Weakness or aching, especially of the lower back and/or knees?</td>
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<td>15. Numbness or tingling of the limbs?</td>
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<td>16. Poor appetite?</td>
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<td>17. A feeling of mild and persistent nausea?</td>
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<td>18. A sticky taste in your mouth?</td>
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<td>19. A bitter taste in your mouth?</td>
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<td>20. Abdominal distension after meals?</td>
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<td>Question</td>
<td>Severity</td>
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<td>In the last year have you experienced:</td>
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<td>21. Epigastric fullness?</td>
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<td>22. Loose stools?</td>
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<td>23. Frequent urination?</td>
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<td>24. Night-time urination?</td>
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<td>25. Soft snoring?</td>
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<td>26. Loud snoring?</td>
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<td>27. High-pitched snoring?</td>
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<td>28. Physical tiredness?</td>
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<td>29. Waking in the night feeling like you are choking?</td>
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<td>30. Dry throat?</td>
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<td>31. No thirst?</td>
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<td>32. Thirst with no desire to drink?</td>
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<td>33. Barking cough with yellow/green sticky sputum</td>
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<td>34. Soft cough with clear or white sticky sputum?</td>
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<td>35. Dry cough with little or no sputum?</td>
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<td>36. Blocked nose without other cold or flu symptoms?</td>
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<td>37. Runny nose without other cold or flu symptoms?</td>
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<td>38. Tendency to catch colds easily?</td>
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<td>39. A feeling of something heavy pressing on your chest?</td>
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<td>40. Palpitations?</td>
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<td>41. Shortness of breath?</td>
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<td>42. Wheezing?</td>
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<td>43. Feeling of cold?</td>
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<td>44. Feeling of heat?</td>
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In the last year have you experienced:

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<tr>
<td>45. Intolerance of cold?</td>
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<td>46. Intolerance of heat?</td>
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<tr>
<td>47. Constant sweating?</td>
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<td>48. Night-time sweating?</td>
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<td>49. Sweat that is very oily and stains clothes yellow?</td>
<td>○</td>
<td>○</td>
<td>○</td>
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<tr>
<td>50. Sweat that is thin, clear and watery?</td>
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Please answer these questions to the best of your ability concentrating on whether or not you have experienced these symptoms in the previous six months.

Please rate each symptom according to how often you experience these symptoms and then tick one or more boxes that describe the symptom further.

0 Rarely/Don’t experience this symptom or experience it less than once every six months
1 Sometimes/At least once a month
2 Often/At least once a week
3 Regularly/At least three times a week

The following 16 questions relate to symptoms experienced in relation to the head, face, skin and hair:

1. Do you experience dizziness?  
   If yes:  
   □ Does this occur at random times  
   □ Does this occur when you stand up or sit up too quickly

2. Do you ever feel a heaviness or fuzziness of the head?  

3. Do you ever experience ringing in the ears?  
   If yes:  
   □ Is the sound more like static type background noise/ white noise  
   □ Is the sound high pitched  
   □ Is the sound low pitched  
   □ Is the sound accompanied by a feeling of pressure in the ears

4. Do you experience blurred vision or floaters?  

5. Do you have dry eyes?  

6. Do you have painful eyes?  

7. Do your eyes water?  

8. Do your eyes feel very tired?  

9. Does your vision become blurred at night?  
10. Do you experience headaches? 〇〇〇〇
   If yes:
   □ These are predominantly migraines
   □ Is the pain mostly sharp
   □ Is the pain mostly Dull/aching
   □ Do you feel it most on the sides of the head, near the temples
   □ Do you feel it most behind the eyes
   □ Does it feel as though the head is wrapped in cotton wool
   □ Is the pain in the forehead
   □ Does it feel as though a tight headband were encircling the head
   □ Do you feel it most in the top of the head
   □ Do you feel pain of the whole head
   □ Do you feel it as pain and stiffness in the base of the skull?
   □ Is the pain alleviated by rest
   □ Is the pain alleviated by activity

11. Do you experience earaches? 〇〇〇〇

12. Is your hair excessively greasy? 〇〇〇〇

13. Is your hair excessively dry? 〇〇〇〇


15. Is your skin excessively dry? 〇〇〇〇

16. Do you experience acne? 〇〇〇〇
   If yes:
   □ Do the pimples tend to be very red
   □ Do the pimples tend to be very purplish
   □ Do the pimples tend to be very pale
   □ Are they painful
   □ Do they make your skin feel hot
   □ Are they isolated to the face or do you also experience them on the chest or upper back
   □ Do the pimples tend to contain pus
   □ Do the pimples tend to appear as blackheads

The following 8 questions relate to symptoms experienced in relation to the nasal and air passageways and breathing:

17. Do you experience a blocked nose without concurrent cold or flu symptoms? 〇〇〇〇
   If yes:
   □ Is this related to seasonal changes
   □ Does your nose also feel dry
18. Do you experience a runny nose without concurrent cold or flu symptoms?  
   If yes:  
      ☐ Is the discharge yellow  
      ☐ Is the discharge clear  
      ☐ Is the discharge white  
      ☐ Is the discharge watery  
      ☐ Is the discharge thick  

19. Do you experience stickiness or phlegm in your throat?  
   If yes:  
      ☐ Do you feel the need to clear your throat often  
      ☐ Is there a rattling sound or does it feel as though there is a rattling in your throat when you breathe or speak  

20. Do you often experience a dry throat?  
   If yes:  
      ☐ Is your throat dry only after waking in the morning  

21. Do you have the feeling of an obstruction or a lump in your throat?  

22. Do you experience bouts of coughing?  
   If yes:  
      ☐ Is the cough strong and barking  
      ☐ Is the cough soft  
      ☐ Does the cough come on suddenly and go away quickly  
      ☐ Is the cough persistent and frequent  
      ☐ Is the cough dry  
      ☐ Do you often cough up sputum or phlegm  

23. Do you experience shortness of breath?  
   If yes:  
      ☐ Is it more difficult to breathe in  
      ☐ Is it more difficult to breathe out  
      ☐ Does this happen suddenly without reason  
      ☐ Does this happen on physical exertion  
      ☐ Does this happen on emotional stress  
      ☐ Is this often accompanied by palpitations  

24. Do you ever experience wheezing?  
   If yes:  
      ☐ Is the wheezing chronic and persistent  
      ☐ Is the wheezing brought on by certain activities or emotions
The following 10 questions relate to symptoms experienced in relation to the body and limbs:

25. Do you experience a sensation of heaviness pressing on your chest?  ○ ○ ○ ○ ○

26. Do you experience distension of the chest?  ○ ○ ○ ○ ○

27. Do you experience palpitations?  ○ ○ ○ ○ ○
   If yes:
   ○ Is the onset of the palpitations random
   ○ Are the palpitations usually brought on by a typical activity, situation, or emotion

28. Do you experience chills when you are not ill?  ○ ○ ○ ○ ○
   If yes:
   ○ Do you feel it most in the morning
   ○ Do you feel it most in the evening
   ○ Do you feel it most after sitting still for too long
   ○ Do you alternate between chills and fever

29. Do you feel feverish when you are not ill?  ○ ○ ○ ○ ○
   If yes:
   ○ Do you feel it most in the morning
   ○ I feel it most in the evening
   ○ I feel it most when I wake from sleep during the night

30. Do you experience general aches and/or pains in your body?  ○ ○ ○ ○ ○
   If yes:
   ○ I feel it most in the morning
   ○ I feel it most in the evening
   ○ I feel it most after sitting still for too long
   ○ I feel it most after strenuous activity
   ○ It feels better with warmth
   ○ It feels better with activity (e.g., stretching)
   ○ It feels better with rest
   ○ It feels worse with heat
   ○ It feels worse with activity
   ○ It feels worse with rest
   ○ I feel it most in my hands
   ○ I feel it most in my feet
   ○ I feel it most in my lower back
   ○ I feel it most in my neck
   ○ It is sharp
   ○ It is dull
31. Do you experience general stiffness and/or weakness in your body? 

If yes:
- [ ] I feel it most in the morning
- [ ] I feel it most in the evening
- [ ] I feel it most after sitting still for too long
- [ ] I feel it most after strenuous activity
- [ ] It feels better with warmth
- [ ] It feels better with activity (e.g., stretching)
- [ ] It feels better with rest
- [ ] It feels worse with heat
- [ ] It feels worse with activity
- [ ] It feels worse with rest
- [ ] I feel it most in the lower back
- [ ] I feel it most in the knees

32. Do you experience cold sensations in any or all parts of your body? 

If yes:
- [ ] I feel it most in the morning
- [ ] I feel it most in the evening
- [ ] I feel it most after sitting still for too long
- [ ] I feel it most in my hands
- [ ] I feel it most in my feet
- [ ] I feel it most in my lower back
- [ ] I feel it most in my neck

33. Do you experience hot sensations in any or all parts of your body? 

If yes:
- [ ] I feel it most in the morning
- [ ] I feel it most in the evening
- [ ] I feel it most in the palms of my hands
- [ ] I feel it most in the soles of my feet
- [ ] I feel it most in my lower back
- [ ] I feel it most in my neck

34. Do you experience itching of the skin? 

35. Do you ever experience numbness or tingling? 

If yes:
- [ ] I feel it most often in my arms and hands
- [ ] I feel it most often in my legs and feet
- [ ] I feel it most often in my torso
- [ ] I feel it most often in my neck

36. Do you experience tremors or tics?
The following 11 questions relate to symptoms experienced in relation to the appetite and thirst:

37. Do you feel that you have a normal appetite? ○ ○ ○ ○ ○
   If no:
   □ Is your appetite excessive
   □ Is your appetite insufficient

38. Do you feel hungry with little desire to eat? ○ ○ ○ ○ ○

39. Do you experience a taste in your mouth when not eating? ○ ○ ○ ○ ○

40. Do you have a strong preference for hot foods? ○ ○ ○ ○ ○

41. Do you have a strong preference for cold foods? ○ ○ ○ ○ ○

42. Do you feel that your thirst is excessive? ○ ○ ○ ○ ○

43. Do you have a strong preference for hot drinks? ○ ○ ○ ○ ○

44. Do you have a strong preference for cold drinks? ○ ○ ○ ○ ○

45. Do you feel thirsty but without a desire to drink? ○ ○ ○ ○ ○

46. Do you feel the desire to drink in small sips? ○ ○ ○ ○ ○

47. After eating do you feel epigastric or abdominal distension or fullness? ○ ○ ○ ○ ○

48. Do you experience indigestion or reflux? ○ ○ ○ ○ ○

49. Do you ever experience nausea when you are not ill? ○ ○ ○ ○ ○

The following 13 questions relate to symptoms experienced in relation to defecation and urination:

50. Do you have a tendency towards having diarrhoea and/or loose stools? ○ ○ ○ ○ ○
   If yes:
   □ Is this accompanied by a sense of urgency
   □ Is there undigested food in the stool
   □ Is this accompanied by abdominal pain or distension
   □ Is the stool especially foul in smell
   □ Is there mucus in the stool
51. Do you have a tendency towards having constipation?  ○ ○ ○ ○ ○
   If yes:
   □ Are you constipated because the stool is very dry
   □ Are you constipated because there is a lack of energy to push
   □ Is the constipation accompanied by pain, distension or fullness of the abdomen
   □ Do you feel exhausted after the bowel movement
   □ Is the stool small and pellet-like

52. Do you have a tendency to alternate between loose stools and constipation?  ○ ○ ○ ○ ○

53. Is there often blood in the stools?  ○ ○ ○ ○ ○
   If yes:
   □ Is the blood bright red
   □ Is the blood dark or black
   □ Is the bleeding profuse
   □ Is the bleeding minimal

54. Is your urine generally dark?  ○ ○ ○ ○ ○

55. Is your urine generally pale?  ○ ○ ○ ○ ○

56. Is your urine generally light yellow?  ○ ○ ○ ○ ○

57. Is your urine generally clear?  ○ ○ ○ ○ ○

58. Is your urine cloudy?  ○ ○ ○ ○ ○

59. Is urination difficult or painful?  ○ ○ ○ ○ ○

60. Do you feel the need to urinate very frequently?  ○ ○ ○ ○ ○
   If yes:
   □ Is this inappropriate for the amount of fluid you are drinking

61. Do you need to urinate during the night?  ○ ○ ○ ○ ○

62. Is there blood in your urine?  ○ ○ ○ ○ ○
The following 5 questions relate to symptoms experienced in relation to sweating:

63. Do you experience spontaneous sweating?  ○○○○○
   If yes:
   □ Is this worse with exercise
   □ Is there accompanying shortness of breath
   □ Is there accompanying sensation of heat
   □ Do you sweat throughout the day
   □ Is this accompanied by fever, or aversion to cold

64. Do you experience nighttime sweating?  ○○○○○

65. When you perspire, does your perspiration feel thick and oily?  ○○○○○
   If yes:
   □ Does the sweat form beads like thick sap that does not run
   □ Does the sweat run freely
   □ Is the sweat yellow that easily stains clothing
   □ Is the sweat yellow and more profuse on the upper back, hypochondrium
   □ and head, and worse after exertions

66. When you perspire, does your perspiration feel thin and watery?  ○○○○○
   If yes:
   □ Do you ever feel as though you are sweating excessively for the level of activity you are undertaking?

67. Do you feel that there is an absence of sweating for the amount of activity you do?  ○○○○○

The following 10 questions relate to symptoms experienced in relation to your emotions, sleep and mental state:

68. Do you often feel sad without reason?  ○○○○○

69. Do you easily become irritable or frustrated?  ○○○○○

70. Do you experience outbursts of anger with very little provocation?  ○○○○○

71. Are you easily startled or frightened?  ○○○○○

72. Do you experience moodiness (e.g., rapid changes in mood)?  ○○○○○

73. Do you experience a lack of motivation?  ○○○○○

74. Do you feel that you have poor memory or concentration?  ○○○○○
75. Do you feel refreshed upon waking in the morning?  ○ ○ ○ ○ ○

76. Do you experience insomnia?  ○ ○ ○ ○ ○
   If yes:
   ☐ Do you find it difficult to get to sleep
   ☐ Do you find it difficult to stay asleep (e.g., you wake easily during the night)
   ☐ After waking in the night do you find it difficult to fall back to sleep
   ☐ Do you often have dream-disturbed sleep
   ☐ Are you restless when trying to fall asleep

77. Do you experience excessive daytime sleepiness?  ○ ○ ○ ○ ○
   If yes:
   ☐ Is this worse after eating
   ☐ Is this worse during inactivity or monotonous activities
   ☐ Do you often feel slightly confused as well
Tongue and Pulse Questionnaire

Chinese Medicine Syndrome Differentiation for Obstructive Sleep Apnoea - Tongue and Pulse Diagnosis

Research Team Use Only

Complexion:
- Normal
- Pal
- Red
- Bright White
- Red around eyes
- Dark around eyes
- Yellow around eyes
- Yellow around mouth
- Blue lips

Hair:
- Normal
- Greasy
- Dry

Spirit:
- Present
- Strong
- Weak

Voice:
- Normal
- Soft
- Strong
- Hoarse
- Phlegm
- Nasal
- Cough
- Sighing

Tongue Shape:
- Normal
- Long
- Short
- Thin
- Flaccid
- Stiff
- Swollen
  - Partially Swollen
  - Liver (sides)
  - Chest (front sides)
  - Tip
  - Front third
- Toothmarked
- Quivering
- Moving
- Deviated
- Horizontal cracks
- Irregular cracks
- Transverse cracks
  - Spleen
  - Lungs
- Midline crack
  - Stomach
  - Heart
<table>
<thead>
<tr>
<th>Tongue Colour:</th>
<th>Normal</th>
<th>Pale</th>
<th>Red</th>
<th>Purple</th>
<th>Red Tip</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Red sides</td>
<td>Red Spots (sides)</td>
<td>Red Spots (tip)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tongue Coating:</th>
<th>Normal</th>
<th>Absent</th>
<th>Rootless</th>
<th>Peeled: all</th>
<th>middle</th>
<th>tip</th>
<th>root</th>
<th>sides</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>White: thick</td>
<td>thin</td>
<td>Yellow: thick</td>
<td>thin</td>
<td>Greasy: thick</td>
<td>thin</td>
<td></td>
<td></td>
</tr>
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</table>

| Wet | Dry |

<table>
<thead>
<tr>
<th>Pulse:</th>
<th>Right Hand</th>
<th>Left Hand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choppy</td>
<td>Cun</td>
<td>Guan</td>
</tr>
<tr>
<td>Deep</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Empty</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Firm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Floating</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full</td>
<td></td>
<td></td>
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<tr>
<td>Hidden</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hollow</td>
<td></td>
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<tr>
<td>Intermittent</td>
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<td>Irregular</td>
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<td>Rapid</td>
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<td>Slippery</td>
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<tr>
<td>Soft/Soggy</td>
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</tr>
<tr>
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<tr>
<td>Thready</td>
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<td></td>
</tr>
<tr>
<td>Weak</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wiry</td>
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Appendix B

List of Acupuncture points used in treatment and their actions
<table>
<thead>
<tr>
<th>Name</th>
<th>Action</th>
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</thead>
<tbody>
<tr>
<td>Lie Que (LU7)</td>
<td>Promotes the descending function of the Lung; Pacifies phlegm; Opens and regulates the Conception Vessel</td>
</tr>
<tr>
<td>He Gu (LI 4)</td>
<td>Regulates the Defence Qi; regulates the face, eyes, nose, mouth and ears</td>
</tr>
<tr>
<td>Qu Chi (LI11)</td>
<td>Clear Heat; drains Dampness; Regulates Qi and Blood</td>
</tr>
<tr>
<td>Ying Xiang (LI20)</td>
<td>Opens the nasal passages; clears Heat</td>
</tr>
<tr>
<td>Zu San Li (ST36)</td>
<td>Tonifies the Spleen and drains Dampness; tonifies Qi, Blood and Yin; clears Fire and calms the Spirit</td>
</tr>
<tr>
<td>Feng Long (ST40)</td>
<td>Resolves Phlegm; benefits the chest; clears Phlegm from the Lungs and Heart</td>
</tr>
<tr>
<td>Gong Sun (SP4)</td>
<td>Tonifies the Spleen; regulates Qi and drains Dampness; Benefits the Heart and chest</td>
</tr>
<tr>
<td>San Yin Jiao (SP6)</td>
<td>Tonifies the Spleen and Stomach; drains Dampness; harmonises the Liver and Kidneys</td>
</tr>
<tr>
<td>Yin Ling Quan (SP9)</td>
<td>Regulates the Spleen and drains Dampness; opens and harmonises the Liver and Kidneys</td>
</tr>
<tr>
<td>Tong Li (HT5)</td>
<td>Calms the Spirit; regulates the Heart; benefits the tongue</td>
</tr>
<tr>
<td>Zhao Hai (KI6)</td>
<td>Regulates the Yin Heel Vessel; nourishes the Kidney</td>
</tr>
<tr>
<td>Nei Guan (P6)</td>
<td>Unbinds the chest and regulates Qi; regulates the Heart and calms the Spirit; harmonises the Stomach; clears Heat; regulates the Yin Linking Vessel</td>
</tr>
<tr>
<td>Wai Guan (SJ5)</td>
<td>Regulates the Yang Linking Vessel; clears Heat</td>
</tr>
<tr>
<td>Xing Jian (LV2)</td>
<td>Clears Liver Fire; spreads Liver Qi; clears Heat</td>
</tr>
<tr>
<td>Tai Chong (LV3)</td>
<td>Spreads Liver Qi; subdued Liver Yang</td>
</tr>
<tr>
<td>Zhong Wan (CV12)</td>
<td>Harmonises the middle Energizer; tonifies the Stomach and Spleen</td>
</tr>
<tr>
<td>Shan Zhong (CV17)</td>
<td>Regulates Qi and unbinds the chest; descends rebellious Lung and Stomach Qi; tonifies the Ancestral Qi</td>
</tr>
<tr>
<td>Lian Quan (CV23)</td>
<td>Benefits the tongue; descends Qi and alleviates cough</td>
</tr>
<tr>
<td>Bai Hui (GV20)</td>
<td>Subdues Yang; benefits the head and sense organs; benefits the brain and calms the Spirit</td>
</tr>
<tr>
<td>An Mian (N-HN-54)</td>
<td>Calms the Spirit and pacifies the Liver; promotes sleep</td>
</tr>
</tbody>
</table>
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Author/s:
THORNTON, THERESE

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