Gender Differences in Obstructive Sleep Apnea

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A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

Faculty of Medicine, The University of Sydney

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Statement of originality

This is to certify that to the best of my knowledge, the content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

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Date: 17 May 2019

Publications arising from this work

First Author Publications

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(Appendix A)

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(CHAPTER 6)

Wimms A, Kelly J, Benjafield A, Calverley P, Craig S, McMillan A, O'Reilly J, Penz E, Stradling J, Turnbull C, Willes L, Morrell M. Does treating mild obstructive sleep apnea with CPAP improve quality of life? Rationale and design of the MERGE study
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Conference Presentations

- Wimms *et al.* Rationale and design of the MERGE study: the effect of continuous positive airway pressure on energy and vitality in patients with mild obstructive sleep apnoea. Sleep and Breathing Symposium, Madison Wisconsin 2017
- Wimms *et al*. Impact of a female specific APAP device on quality of life in female patients. P183. Australasian Sleep Association, Brisbane, Oct 2018
- Wimms *et al.* Screening questionnaires and symptoms in female obstructive sleep apnea patients. P161. Australasian Sleep Association, Brisbane, Oct 2018
- Wimms *et al*. Rationale and design of the MERGE study: the effect of continuous positive airway pressure on energy and vitality in patients with mild obstructive sleep apnoea. P182. Australasian Sleep Association, Brisbane, Oct 2018
- Wimms *et al*. The MERGE Study: The Effect of Continuous Positive Airway Pressure on Energy and Vitality in Patients with Mild Obstructive Sleep Apnea. Abstract ID: 15333. American Thoracic Society Conference, Dallas, May 2019
- Wimms *et al*. Improvements in quality of life in female OSA patients using a gender specific APAP device. Abstract ID: 0535. Associated Professional Sleep Societies SLEEP conference, San Antonia, June 2019

Associated Publications

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Isetta, V.Montserrat, J. M. Santano, R. **Wimms, A. J**. Ramanan, D. Woehrle, H. Navajas, D. Farre, R., Montserrat J.M., Santano R, et al. Novel Approach to Simulate Sleep Apnea Patients for Evaluating Positive Pressure Therapy Devices. PLoS One 2016;11:e0151530.
(Appendix E)

Authorship attribution statement

Thesis	Resulting publication	Appendix	My role	Role of others
Sections of Chapter 1	Wimms A, *et al*. Obstructive Sleep Apnea in Women: Specific Issues and Interventions. BioMed Research International 2016;2016:1-9.	A	I conducted the literature review and wrote the draft publication.	Review of the publication.
Sections of Chapter 1	Wimms A, Ketheeswaran S, Ramanan D, Armitstead J, Woehrle H. Gender Differences in Obstructive Sleep Apnea. In: Obstructive Sleep Apnea. ISBN: 978-1-944685-89-8: http://www.smgebooks.com/obstructive-sleep-apnea/index.php; 2016.	B	I conducted the literature review and wrote the draft publication.	Review of the publication.
Sections of Chapters 2 and 3	Wimms *et al.* Does treating mild obstructive sleep apnea with CPAP improve quality of life? Rationale and design of the MERGE study (Submitted to Contemporary Clinical Trials for consideration).	C	Along with the steering committee, I designed the trial and wrote the protocol. I wrote the manuscript of the study design. I ran the analysis of data contained in this thesis.	Design of the study was done in conjunction with the steering committee. The manuscript in Appendix C was reviewed by the steering committee. Statistical plan and analysis of the study (not contained in this thesis) was done by Willies Statistical Services.
Sections of Chapter 4	Wimms A, *et al*. Obstructive Sleep Apnea in Women: Specific Issues and Interventions. BioMed Research International 2016;2016:1-9. Wimms A, Ketheeswaran S, Ramanan D, Armitstead J, Woehrle H. Gender Differences in Obstructive Sleep Apnea. In: Obstructive Sleep Apnea. ISBN: 978-1-944685-89-8: http://www.smgebooks.com/obstructive-sleep-apnea/index.php; 2016. McArdle, Nigel; King, Stuart; Shepherd, Kelly; Baker, Vanessa; Ramanan, Dinesh; Ketheeswaran, Sahisha; Bateman, Peter; **Wimms, Alison**; Armitstead, Jeff; Richards, Glenn; Hillman, David; Eastwood, Peter. Study of a Novel APAP Algorithm for the Treatment of Obstructive Sleep Apnea	A, B, D	I conducted the literature reviews on female sleep apnea. I then advised and guided the engineering team who wrote and tested the algorithm	Writing and implementing the algorithm was done by a small team of software and biomedical engineers, most notably Dinesh Ramanan and Jeff Armitstead.

	in Women. Sleep. 38 [11] pp 1775-1781. 2015.			
Sections of Chapter 5	McArdle, Nigel; King, Stuart; Shepherd, Kelly; Baker, Vanessa; Ramanan, Dinesh; Ketheeswaran, Sahisha; Bateman, Peter; **Wimms, Alison**; Armitstead, Jeff; Richards, Glenn; Hillman, David; Eastwood, Peter. Study of a Novel APAP Algorithm for the Treatment of Obstructive Sleep Apnea in Women. Sleep. 38 [11] pp 1775-1781. 2015.	D	I wrote the protocol, including statistics, analysed the data included in this thesis and wrote the study report, sections of which are included in this thesis.	The study was run at an independent site, and the first author wrote the draft manuscript which I reviewed.
Sections of Chapter 5	Isetta, V.Montserrat, J. M. Santano, R. **Wimms, A. J.** Ramanan, D. Woehrle, H. Navajas, D. Farre, R., Montserrat JM, Santano R, et al. Novel Approach to Simulate Sleep Apnea Patients for Evaluating Positive Pressure Therapy Devices. PLoS One 2016;11:e0151530.	E	I worked in conjunction with the site to modify their bench testing to introduce a female model. I assisted with the protocol and wrote the study report.	The bench testing design and protocol were done by the first author. The first author wrote the study manuscript which I reviewed.
Chapter 6	Wimms A, *et al.* Improvements in quality of life in female OSA patients using a gender specific APAP device (Submitted for consideration to Sleep and Breathing).	[Chapter 6]	I designed the trial, wrote the protocol, interpreted the results and wrote the draft publication.	Statistical analysis plan and analysis was conducted by Willies Statistical Services. Co-authors conducted the study and reviewed the publication.

Editor

This thesis was reviewed by Ian Shoebridge, who acted as editor and provided advice about spelling, grammar, and structure in accordance with *The University of Sydney: THESIS AND EXAMINATION OF HIGHER DEGREES BY RESEARCH PROCEDURES 2015* document.

Student Declaration

In addition to the statements above, in cases where I am not the corresponding author of a published item, permission to include the published material has been granted by the corresponding author.

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List of Abbreviations

Abbreviation	Description
AASM	American Academy of Sleep Medicine
AE	Adverse Event
AHI	Apnea Hypopnea Index
BMI	Body Mass Index
BP	Blood Pressure
CI	Confidence Interval
CPAP	Continuous Positive Airway Pressure
CSFQ	Changes in Sexual Function Questionnaire
EDS	Excessive Daytime Sleepiness
EEG	Electroencephalogram
EMG	Electromyogram
EOG	Electrooculogram
EQ-5D	EuroQol 5 Dimensions Health Questionnaire
ESS	Epworth Sleepiness Scale
FOSQ	Functional Outcomes of Sleep Questionnaire
FSS	Fatigue Severity Scale
HADS	Hospital Anxiety and Depression Scale
ISI	Insomnia Severity Index
ITT	Intent-To-Treat Population
MAD	Mandibular Advancement Device
MSLT	Multiple Sleep Latency Test
ODI	Oxygen Desaturation Index
OR	Odds Ratio
OSA	Obstructive Sleep Apnea
PAP	Positive Airway Pressure
PG	Polygraphy
PHQ	Patient Health Questionnaire
PSG	Polysomnography
RCT	Randomised Controlled Trial
REM	Rapid Eye Movement
RERA	Respiratory Effort Related Arousal
SAHS	Sleep Apnea Hypopnea Syndrome
SD	Standard Deviation
SDB	Sleep Disordered Breathing
SF-36	Short Form 36
SAQLI	Sleep Apnea Quality of Life Index
TMD	Total Mood Disorder
UARS	Upper Airway Resistance Syndrome
VAS	Visual Analog Scale

Abstract

The overall aim of this thesis was to understand gender differences in obstructive sleep apnea (OSA) and use this information to develop a tailored therapy for female patients. Specific aims were to determine whether gender differences commonly reported in the literature are present in mild OSA and upper airway resistance syndrome (UARS) patient groups, and whether symptoms could be linked to respiratory parameters in these groups. The final aim was to develop, test and validate a new AutoSet treatment for female OSA patients.

CHAPTER 1 of this thesis provides a detailed review of gender differences in the prevalence, symptoms, clinical experience, and health outcomes of OSA and UARS patients, with a focus on the implications of different scoring rules.

CHAPTER 2 reviews of quality of life questionnaires from 259 untreated patients with mild OSA. Females reported statistically significantly higher levels of sleepiness, fatigue, insomnia, and anxiety/depression compared to males.

CHAPTER 3 of this thesis reviews polygraphy data from patients with mild OSA. Male patients were found to have significantly more breathing disturbances than females, however many of these difference disappeared when updated scoring criteria were used. Some weak correlations were found between respiratory parameters and symptoms; however, no clear conclusions could be drawn.

CHAPTER 4 outlines the development of a new AutoSet device designed for female-specific breathing patterns. The remaining chapters (CHAPTER 5, and CHAPTER 6) of this thesis describe the testing and validation activities undertaken on the AutoSet F, including a clinical trial to test efficacy; a bench test to compare performance against other commercially available devices; a controlled product launch to validate the features of the algorithm; and finally a clinical trial which demonstrated improvements in sleep efficacy and quality of life over a three-month usage period.

In summary, this thesis has shown that at the mild end of the OSA spectrum females are more symptomatic than males, even though respiratory differences in the genders are less pronounced than those described in moderate-to-severe patients. An AutoSet designed specifically for female OSA patients was successful in demonstrating efficacy and clinical effectiveness.

CHAPTER 1. INTRODUCTION – GENDER DIFFERENCES IN OBSTRUCTIVE SLEEP APNEA

1.1. General introduction to the thesis

The overall aim of this thesis was to understand gender differences in OSA and use this information to develop a tailored therapy for female patients. Specific aims were to determine whether gender differences commonly reported in the literature still exist in the mild OSA and UARS patient groups, and whether symptoms could be linked to breathing parameters in these groups. The final aim was to develop, test and validate a new AutoSet treatment for female OSA patients.

The sections of this chapter are intended to provide a detailed background to this thesis, beginning with an overview of the difficulties in defining severity in OSA. In the next sections, the gender differences of OSA will be discussed, including prevalence, symptoms, clinical presentation, short and long-term health consequences, and suspected mechanisms. Mild OSA and UARS are then reviewed to determine whether gender differences are present in these patient groups. Gender differences in polysomnography data are then explored, along with mechanisms to explain why females appear to have different features of OSA. The final sections of this chapter describe the current treatments for OSA and options for female OSA patients, including the limitations of current treatments for female patients.

1.2. How should we define severity in OSA?

Sleep disordered breathing (SDB) can be conceptualised as a continuum, ranging from simple snoring through to severe OSA (Figure 1).

Figure 1: Continuum of sleep disordered breathing

OSA is defined as repetitive closures of the upper airway during sleep. The airway closures can either be partial (hypopneas), or complete (apneas), and are associated with reduced airflow, oxygen desaturation, and arousal from sleep. The severity of OSA is determined from the number of breathing events occurring each hour (the apnea-hypopnea index [AHI)]. Patients are defined as having mild (AHI 5 to <15), moderate (AHI 15 to <30), or severe OSA (AHI >30). While the definition of obstructive apneas has remained relatively constant, the exact definition of what qualifies as a hypopnea has been one of considerable debate (1). Table 1 displays the recent history of hypopnea definitions according to the American Academy of Sleep Medicine (AASM).

Table 1: Definitions of hypopneas

	Recommended	Alternative
AASM 2012 (1)	A hypopnea is scored when there is: • A decrease in oronasal airflow by ≥ 30% from baseline AND • The event is ≥ 10 sec long AND • The event is associated with ≥ 3% SpO_2 desaturation OR arousal	*Note: The AASM 2007 recommended definition may be used if the diagnosis is required for U.S. Medicaid or Medicare reimbursement.*
AASM 2007 (2)	A hypopnea is scored when there is: • A decrease in oronasal airflow by ≥ 30% from baseline AND • The event is ≥ 10 sec long AND	A hypopnea is scored when there is: • A decrease in oronasal airflow by ≥ 50% from baseline AND • The event is ≥ 10 sec long AND

	• The event is associated with ≥ 4% SpO_2 desaturation	• Associated with ≥ 3% SpO_2 desaturation OR an arousal
AASM Chicago Rules (Classic criteria) 1999 (3)	Those with a > 50% decrease in a valid measure of airflow without a requirement for associated oxygen desaturation or arousal	Those with a lesser airflow reduction in association with oxygen desaturation of > 3% or an arousal

In 2007, the criteria of a ≥4% decrease in oxygen saturation during hypopneas was set due to the evidence at the time demonstrating the strongest links between oxygen saturation of ≥4% and adverse cardiovascular outcomes (1). Further studies then showed that the risk was very similar with oxygen desaturation of ≥3%, and therefore in 2012 the taskforce recommended adoption of the ≥3% oxygen desaturation criteria for hypopneas (1). Arousals were added to the definition of hypopneas because the AASM wished to recognise the detrimental effects of repetitive arousals from sleep, regardless of oxygen saturation (1).

1.2.1. Impact of changes in scoring rules

It is well known that different hypopnea definitions result in different AHI values. The clinical consequence is that some patients may be denied treatment based on one set of scoring rules and provided treatment when using another set. This issue was discussed at length when the scoring rules changed in 2007. Guilliminault *et al.* found that up to 40% of patients who had been diagnosed with OSA based on the 1999 criteria would not have been diagnosed with OSA if they were scored according to AASM 2007 (4). Bahamman *et al.* (5) found that up to 45% (when using an AHI cut-off of 5) and 52% (when using an AHI cut-off of 15) of patients would have not been diagnosed with OSA using AASM 2007 criteria, but were diagnosed when using AASM 2012 criteria. Table 2 displays the changes in number of patients diagnosed with OSA when using AASM 2007 and 2012 scoring techniques.

Table 2: Percentage of patients with positive sleep studies based on AASM scoring criteria of hypopneas

Author	n	AASM 2007 Recommended (%)		AASM 2007 Alternative (%)		AASM 2012 Recommended (%)	
		AHI ≥ 5	AHI ≥ 15	AHI ≥ 5	AHI ≥ 15	AHI ≥ 5	AHI ≥ 15
Ruehland *et al.* (6)	328	59	38	76	50	-	-
Bahammam *et al*. (5)	100	24	11	31	21	19	31
Ho *et al*. (7)	6,441	30.4	21.7	-	-	38.15	44.8

1.2.2. Where does Upper Airway Resistance Syndrome fit in?

Upper Airway Resistance Syndrome (UARS) was first described by Guilleminault *et al*. in 1993 (8), although the characteristics of the disease were first described in the late 1950s (9). Guilleminault *et al.* studied a group of 15 subjects who complained of daytime sleepiness and displayed breathing abnormalities during sleep, but did not have obstructive sleep apnea based on guidelines at the time. Guilleminault *et al*. described periods of flow limitation during which esophageal pressure continually increased until a short EEG arousal occurred. These events were termed Respiratory Effort Related Arousals (RERAs). In UARS patients RERAs occur multiple times during the night and significantly disrupt sleep. The key components of RERAs are: increase in respiratory effort with small decrease in flow (less than 30%) (10), cortical or autonomic arousal (10), and very little oxygen desaturation (11). The increase in respiratory effort can be measured directly by esophageal pressure, or indirectly from flow limitation via a nasal cannula (11). Although esophageal manometry is considered the gold standard for detecting respiratory effort, it can be poorly tolerated and is restricted to use within a clinical environment. The inspiratory flow shape seen when using nasal cannula is sufficient to identify flow limitation events and RERAs with similar accuracy than the detail provided by esophageal manometry (12, 13).

The AASM has defined diagnostic criteria for RERAs and UARS (Table 3).

Table 3: Diagnostic criteria for RERAs and UARS

Diagnostic Criteria	
RERA (AASM 2007) (2)	A sequence of breaths lasting at least 10 seconds characterized by i. increasing respiratory effort or ii. flattening of the inspiratory portion of the nasal pressure (diagnostic study) or PAP flow waveform iii. which leads to an arousal from sleep and does not meet the criteria for an apnea or a hypopnea.
UARS (AASM 2005) (14)	<u>Major criteria</u> • Excessive daytime sleepiness • AHI< 5 • RERA Index/ hr > 20 <u>Minor criteria</u> • Snoring • Increase in the intensity of snoring before EEG arousal • Clinical response to CPAP therapy

1.2.3. Differentiating between UARS and Mild OSA

The main breathing events which contribute to UARS are RERAs. However, with the update to the hypopnea definition in 2012, RERAs and hypopneas terminated by arousal become very similar. In both classifications, the rules require the event to last at least 10 seconds, and to be concluded by arousal from sleep. The only difference is that hypopneas require a peak signal drop of ≥ 30%, while RERAs do not quantify the amount of flattening in the AASM definition (1). In clinical practice accurately measuring the reduction in flow is not common, and indeed the AASM stated that majority of RERAs can be re-classified as hypopneas when using 2012 scoring rules (10). This means that a significant proportion of patients previously identified as UARS may now be reclassified as having mild OSA.

The differing definitions of hypopneas and associated changes in patient populations make it difficult to navigate the literature, particularly in the mild OSA/ UARS definitions where there may be considerable overlap in the patient groups and much less data is available.

1.3. Are there gender differences in OSA?

Historically, OSA has been primarily regarded as a male disorder (15). The short and long-term health consequences of OSA are heavily documented and well understood in a population which has largely consisted of male patients. More recently, studies have specifically looked at the consequences of moderate-to-severe OSA in female patients and found gender differences in prevalence, symptoms, clinical experience and health consequences of the disease.

1.3.1. Prevalence of OSA by gender and severity

The population prevalence of moderate-to-severe OSA, was estimated to be around 9% of males, and 4% of females in 1993 (16). The impact of rising global obesity along with stronger global recognition of OSA gave more recent estimates of 13.5% of males and 6% of females (17). When updated diagnostic criteria is used, as many as 49.7% of males and 23.4% of females may have moderate-to-severe OSA, and 34% of males and 38% of females may have mild OSA (18) (Table 4).

Table 4: Prevalence data for OSA in the general population

Study	Mild OSA (AHI ≥5/h)		Moderate to severe OSA (AHI ≥15/h)	
	Males	Females	Males	Females
Young *et al.* (1993) (16)	24%	9%	9%	4%
Redline *et al*.(1994) (19)*	-	-	26%	13%
Bixler *et al*.(1998, 2001) (20, 21)	17%	-	7%	%2
Duran *et al*.(2001) (22)	26.2%	28%	14%	7%
Peppard *et al*.(2013) (17)	-	-	13.5%	6%
Franklin *et al*.(2013) (15)^#	-	50%	-	26%
Heinzer *et al*.(2015) (18)#	34%	38%	49.7%	23.4%

*Respiratory Disturbance Index (RDI) rather than AHI given.
^Women aged 20-70 years.
#Updated scoring criteria (AASM 2012) used.

1.3.2. Symptoms of OSA in moderate-to-severe patients

The typical symptoms that males with sleep apnea present with are snoring, witnessed apneas and excessive daytime sleepiness. The most common symptoms that females

complain of are insomnia, fatigue, lack of energy, headaches, muscle pain, depression, and anxiety (23-27). Indeed, a population-based sample found that up to 40% of females with an AHI ≥15/h did not report any of the classic OSA symptoms (snoring, witnessed apneas, and daytime sleepiness) (28).

1.3.2.1. Quality of life in women with OSA

Comparisons of women and men with untreated OSA have found that women experience more mood disturbances such as anxiety and depression, impaired daytime mood, reduced sleep quality, and worsened neurobehavioral symptoms (29, 30). Ye *et al.* compared women and men with untreated OSA using the Functional Outcomes of Sleep Questionnaire (FOSQ). They found that women had significantly lower scores in daily activity level, general productivity and overall daytime functioning. They also found that women had significantly higher total mood disturbances, and performed significantly worse on the psychomotor vigilance task compared with men (29).

1.3.2.2. Do women with OSA experience sleepiness?

Excessive daytime sleepiness (EDS) is a common identifying symptom of male OSA. The Epworth Sleepiness Scale (ESS) is a short questionnaire, developed in 1991 by Dr Murray Johns, which aims to assess levels of daytime sleepiness (31). Patients rate their likelihood to fall asleep in 8 different scenarios. The ESS has shown to be a reliable measure of sleepiness, with strong correlation to OSA severity and objective sleepiness, as well as good sensitivity to post-treatment changes (32-34).

In women, sleepiness may not be a common OSA symptom. Women typically have lower scores than men on the ESS (28), and despite its widespread use, the ESS has never been properly validated as a tool to measure sleepiness in female OSA patients (31). The Wisconsin Sleep Cohort, a large population-based exploration of the prevalence and health outcomes of sleep disordered breathing (35), found that OSA was not strongly associated with subjective or objective sleepiness in women (36). Similar results were reported from another large population-based study, the Sleep Heart Health Study. This study found that women had similar levels of self-reported daytime sleepiness as men, but were less likely to report falling asleep in public. The authors concluded that the ESS was not a sensitive measure of subjective sleepiness in women (31). A more recent population-based study including 400 women aged 20-70 years found that daytime sleepiness was not related to obstructive sleep apnea in females (37).

It remains unclear whether women have a higher threshold for sleepiness, feel sleepy but are less likely to fall asleep in public situations, or are simply less inclined to report excessive sleepiness. It is also possible that women feel fatigued rather than sleepy, or interpret feelings of sleepiness as fatigue. There may also be some confusion around the meanings of the terms sleepy, fatigued and similar adjectives (Table 5).

Table 5: Terms and definitions related to sleepiness

Term	Merriam-Webster's Dictionary Definition
Sleepy	• Ready to fall asleep • Sluggish, as if from sleep • Sleep-inducing
Lethargic	• Characterized by laziness or lack of energy
Tired	• Drained of strength and energy • Fatigued often to the point of exhaustion
Fatigue (d)	• Weariness or exhaustion from labour, exertion, or stress • Drained of strength and energy
Sluggish	• Averse to activity or exertion • Indolent • Torpid • Slow to respond (as to stimulation or treatment) • Markedly slow in movement, flow, or growth.
Weary	• Feeling or showing extreme tiredness, especially as a result of excessive exertion

In the ESS sleepiness is defined as "the likelihood of falling asleep in certain situations". This is fairly easy to quantify; however, it doesn't capture other feelings of daytime tiredness. Another short screening questionnaire which is similar to the ESS in length and ease of completion is the Fatigue Severity Scale (FSS). The FSS is designed to measure how feelings of fatigue impact an individual's daily life in terms of motivation, exercise, daily activity, work, family and social life. The FSS requires patients to report how fatigued they felt at various times, but it does not define what is meant by fatigued. The FSS was developed by Dr Laurent Krupp in 1989 as a tool to facilitate research in medical conditions where fatigue is a prominent syndrome (38). The FSS has been utilised successfully for a number of health conditions, including sleep apnea (39-41). While it has not been validated in OSA patients specifically, it has been shown to have excellent internal consistencies and re-test stability in multiple health conditions, including chronic fatigue and multiple sclerosis (38, 42-44).

The literature states that women report fatigue rather than sleepiness as a common symptom of OSA (28). In order to better understand symptoms and post-treatment improvements in female patients, the FSS, along with the ESS, was included as part of clinical routine in two UK-based sleep clinics. Consecutive female patients were asked to complete the FSS, along with the ESS at their first clinic visit. When reviewing the outcomes of the screening questionnaires, 50% of symptomatic patients reported normal levels of sleepiness on the ESS, but high levels of fatigue on the FSS (45). This finding is consistent with the literature which states that females are more likely to report fatigue than sleepiness, and also highlights the importance of not relying solely on sleepiness when screening for OSA.

1.3.3. Clinical experience of women with OSA

OSA has been estimated to have a male to female ratio of between 3:1 and 5:1 in the general population and a much greater ratio of between 8:1 and 10:1 in some clinical populations (16, 23, 46). It is thought that the large discrepancy between the population prevalence of OSA and the clinical populations is due to females being frequently misdiagnosed (23, 47).

Men often attend clinical appointments with their partner, whereas women are more likely to attend on their own (23, 46). This may mean that snoring and apneas in women are less frequently observed (46), or that male partners tend to be less concerned about the events (48). Women may also not know if they snore (37), or could be reluctant to complain about their own snoring as they consider it unladylike or embarrassing (23, 26).

Less-frequent reporting of classic OSA symptoms (snoring, witnessed apneas and daytime sleepiness) plus a higher prevalence of atypical symptoms (insomnia, headache, anxiety and depression), means that physicians may not associate the complaint with OSA. Women with OSA are often misdiagnosed with depression or other illnesses (23, 24, 47). The result is lower referral rates to sleep clinics and an under-evaluation of OSA in women (47, 49), (23, 26, 49). It has been stated that recognizing the different features of SDB in women is central to effectively detecting and treating the condition (50).

Young and colleagues found that even when women reported the classic symptoms of OSA (snoring, witnessed apneas and daytime sleepiness), they were still less likely to be referred to sleep clinics than men. This raised concerns that physicians tend to disregard these symptoms in women (47). Young *et al*. published this data in 1996, and therefore it is

plausible that this situation has improved due to increased awareness among primary care physicians and potential patients. However, data presented by Lindberg *et al.* during the 2015 European Respiratory Society Congress showed that women who reported classic symptoms of OSA were significantly less likely to have a diagnosis or treatment for OSA than males with the same risk score (51).

1.3.4. Health consequences of OSA in women

The clinical impact of moderate-to-severe OSA (AHI ≥ 15) has been well documented in a male-dominated population. It is known to cause excessive daytime sleepiness, impaired cognitive function, and reduced quality of life (52, 53). Moderate-to-severe OSA is also associated with poor health consequences such as hypertension, diabetes, stroke, and cardiovascular morbidity and mortality (52, 54-57). Effective treatment with continuous positive airway pressure (CPAP) has been shown to improve symptoms and health outcomes in patients with moderate-to-severe OSA (53, 54, 57-61).

Data comparing females with and without OSA has shown that those with OSA are at greater risk of reduced quality of life and impaired cognitive function. Yaffe *et al*. studied a group of women with OSA and found that they were more likely to develop cognitive impairment and dementia than women without OSA. Cognitive issues were more likely to develop in patients with increased oxygen desaturation and higher periods of time spent in apnea or hypopnea (62). Another study showed that female OSA patients experienced more brain white matter injury than their male counterparts (30). It is hypothesised that this change in white matter structure may be responsible for the long-term cognitive impairment found in some women with OSA (30). Further research in this area identified lateral and sex-specific volume differences in the hippocampus, demonstrating that females with OSA experience more volume decreases and injury in the brain compared to males with OSA (63).

The correlation between OSA and sexual dysfunction in males has been explored in a number of studies (64, 65), with one meta-analysis estimating a pooled relative risk for male sexual dysfunction of 1.82 (95% CI: 1.12-2.97) (65). Female sexual health may also be impacted by OSA, although research in this area is scarce and no randomised controlled trials have been conducted. Small studies have reported that females with OSA have significantly more sexual distress and sexual dysfunction compared to females without OSA (66) (67). One meta-analysis of four small studies estimates the pooled relative risk of female sexual dysfunction in OSA patients as being 2.00 (95% CI: 1.29-3.08) (65).

Greenberg-Dotan *et al*. found that, compared to female controls, women with OSA were more likely to have a comorbid diagnosis of cardiovascular disease (OR 1.4) (68). Campos-Rodriguez *et al.* followed 1116 females diagnosed with OSA between 1998 and 2007 in two Spanish sleep units. Patients with an AHI ≥ 10 were considered the OSA group while those with an AHI < 10 served as the control group. The study endpoint was cardiovascular death (including deaths from stroke, heart failure, arrhythmia, or myocardial infarction). The authors found that in women, untreated severe OSA is associated with cardiovascular death (adjust hazard ratio of 3.50, CI 1.23-9.98) (69).

When reviewing the impact of OSA in females compared with males, studies have found that women with OSA are at increased risk of developing several health conditions. One study found that women with OSA have a higher odds ratio (OR) than men with OSA of developing hyperlipidemia (OR 1.5), hypothyroidism (OR 1.6), arthropathy (OR 1.6), diabetes (OR 1.6), asthma (OR 2.1), and reflux/gastritis (OR 2.5) (68). These women also experienced lower perceived health status, overuse of psychoactive drugs, and increased healthcare costs of 1.3 times compared with men with OSA (68).

Data from a cohort of 1,704,905 patients with matched controls taken from a collection of U.S. health insurance data found that overall comorbidities were more common in OSA patients than non-OSA patients (70). Compared with male OSA patients, hypertension was more prevalent in female OSA patients (70). It is possible that women with moderate-to-severe sleep apnea are more susceptible to the adverse cardiovascular consequences of OSA than men. Females with OSA have more marked endothelial dysfunction (71), and respond less effectively to autonomic challenges than males, which may reduce the effectiveness of BP regulation (72).

In summary, the limited data available suggest that although the prevalence and severity of OSA is lower in women than in men, the consequences of the disease in moderate-to-severe females are at least the same, and potentially even worse in some quality of life and cardiovascular outcomes (29).

1.3.4.1. Pregnancy and OSA

Pregnancy is one area which highlights the importance of OSA recognition in women. Women are at increased risk of OSA during pregnancy due to a number of factors. The growing uterus elevates the diaphragm which changes pulmonary mechanics (73). During pregnancy neck circumference increases (74, 75), nasal patency is reduced (76), and

pharyngeal edema occurs (77). Substantial increases in snoring, snorting/gasping and witnessed apneas have been documented in pregnant women (75). Snoring during pregnancy appears to be a risk factor for both pregnancy-induced hypertension and intrauterine growth retardation (78). An observational study of 1.5 million pregnant women found significant associations between OSA and gestational diabetes (adjusted OR 1.51, 1.34-1.72); pre-eclampsia (adjusted OR, 2.22, CI 1.94-2.54); and eclampsia (adjusted OR 2.95, CI 1.08-8.02) (79). Similarly, a large observational cohort of nearly 3 million women found that OSA during pregnancy increased risk of preterm birth by 1.5 (O.R 1.2–1.8, P<.001, 15.5%) (80).

A recently published prospective cohort study reviewed the prevalence and outcomes of OSA during pregnancy in 3705 women (81). Preliminary data from this group showed that OSA affects 8.1% of pregnant women by the second trimester, and that there was an association between OSA and hypertension and diabetes in this group (82). The final data set confirmed the findings that there is an independent association between OSA during mid-pregnancy and hypertension (OR 1.73, CI 1.19-2.52), pre-eclampsia (OR 1.95, CI 1.18-3.23), and gestational diabetes (OR 2.79, CI 1.63-4.77) (83).

1.4. Do the same gender differences exist in mild OSA and UARS?

It is difficult to navigate the literature regarding gender differences in the milder patient groups for two reasons. The first is due to the changing definitions and overlap in patient groups described in Section 1.2. Secondly, there is a lack of research exploring these groups, with minimal data available on the gender differences.

The literature available for moderate-to-severe patients implies that there are clear-cut symptomology differences between males and females with OSA. A conflicting hypothesis is that women do not suffer from different symptoms, but instead more women have mild OSA, and mild OSA itself, rather than gender, is responsible for the different symptoms reported by women. It is possible that characteristic symptoms such as snoring, witnessed apneas and excessive daytime sleepiness may be more prominent at higher AHIs, and perhaps patients with mild OSA dominated by flow limitation and constant arousals have different symptoms.

This hypothesis is supported by data from patients enrolled in the Wisconsin Sleep Cohort. Young *et al*. reported that snoring was the strongest and most sensitive predictor of OSA in both genders (47). Daytime sleepiness and pauses in breathing during sleep were reported equally by both genders with mild OSA. Reports of morning headache, depression and anxiety were reported equally by both genders across all severities of sleep apnea (47). Young *et al*. did, however, find that more females had mild OSA than males, and that females with an AHI of 2-5 had similar symptoms to females with an AHI of ≥ 15, while the same didn't hold true for males (47). Similar analysis from the Wisconsin University Sleep Laboratory showed that lower rates of recognition of OSA in women compared with men only occurred in the subset of patients with an AHI of 5-20/h (84), again supporting the notion that symptoms may be based on severity rather than gender.

1.4.1. Prevalence of OSA and UARS

The prevalence of female OSA is consistently lower than male OSA, and as a group women have lower AHIs than men. Therefore, it is understandable if symptoms of mild OSA are attributed to females rather than the characteristics of the mild condition. When the updated (AASM 2012) hypopnea definition is used, which includes 3% oxygen desaturation and/or arousal from sleep, the prevalence of OSA in female patients becomes much higher. This is consistent with studies of UARS patients, where females represent close to 50% of the study population (85-87).

The exact prevalence of UARS is not known. From the limited clinical trial data available, prevalence has been reported as 6% (88), 8% (89) 15% (90) 19% (87), and 32% (86) of patients reporting to sleep clinics with suspected OSA. However, as described in Section 1.2 it seems that many of these patients may now be reclassified as OSA patients.

1.4.2. Symptoms of mild OSA and UARS

Common symptoms of mild OSA and UARS are reported as being similar to those of moderate-to-severe OSA: daytime sleepiness, snoring, nocturia, nocturnal awakenings, poor sleep efficiency and reduced cognitive function (11, 90). However, in the literature for these patient groups there are more complaints of sleep onset insomnia, sleep maintenance insomnia, and generally disrupted sleep (11, 85). Other symptoms which have been reported in the UARS group are irritable bowel syndrome and headaches (85).

Although snoring is commonly listed as a symptom of UARS, it does not occur in every instance. Guilleminault *et al*. reported snoring in only 67% (8) of patients during the original description of UARS. The same authors found in a later study that only 71% of men and 11% of women with UARS reported snoring (91). A similar study reviewing the prevalence of OSA in military personnel found that 8.4% had UARS despite no reported snoring from the participants, and no significant snoring measured on the PSG (89). This indicates that snoring is not a reliable symptom of UARS, particularly in female patients.

1.4.2.1. Quality of life in mild OSA

The Sleep Heart Health Study found that quality of life in mild OSA subjects was significantly worse than in controls. This study also reported that patients with snoring, but an AHI < 5, reported significantly more sleepiness and quality of life issues than the control group (92). They found that females were more likely to report insomnia than males, and that mild OSA was associated with reduced vitality in both genders (92).

A recent study of interest is the Apnea Positive Pressure Long Term Efficacy Study (APPLES) (93). A review of the mild patients in this study showed that, when compared with the participants with no OSA, the mild group did not have worse quality of life, as measured using the SAQLI questionnaire (no OSA vs Mild OSA: 4.5 ± 0.8 vs. 4.7 ± 0.7, p=0.39) (94).

1.4.2.2. Quality of life in UARS

An in-depth comparison of personality characteristics in UARS patients and OSA patients was recently conducted in a Korean population (87). Researchers compared 88 UARS patients to 365 OSA patients. They found that UARS patients reported very poor sleep quality, and were more likely to complain of insomnia and excessive daytime sleepiness, despite PSG studies showing that, objectively, their sleep efficiency and total sleep time was superior to that of OSA patients. They also found that UARS patients tended to rate significantly worse on a range of psychiatric scales, including: somatization, obsessive-compulsiveness, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism, global severity index, positive symptoms distress index, and total positive symptoms. They concluded that UARS patients had a higher degree of neurotic and sensitive tendencies than their OSA counterparts (87).

1.4.2.3. Do mild OSA and UARS patients experience sleepiness?

There is no consensus as to whether mild OSA is associated with EDS. A review by the American Thoracic Society (ATS) of suitable studies comparing mild OSA to no OSA found that 20 studies reported no significant difference between sleepiness in mild OSA compared to no OSA (95). Conversely, 9 studies did show a significant relationship between mild OSA and sleepiness measured using the ESS tool (95).

Daytime sleepiness is reported as a significant indicator of UARS (8). However, an investigation of military personnel with UARS found that only one third had a mean sleep latency significantly less than normal (86). This may indicate that the majority of UARS patients are not objectively sleepy. Insomnia is reported by approximately 20% of UARS patients (11), which may be a reflection of constant arousals and disturbed sleep throughout the night (11, 31).

1.4.3. Clinical experience of mild and UARS patients

1.4.3.1. Clinical experience of mild OSA patients

There is no universal agreement on the appropriate treatment for mild OSA patients, or indeed if treatment at this stage of the disease is warranted. The definition of mild OSA was revised in 2012 by the AASM in an attempt to recognize the potentially detrimental effects of repetitive breathing-related arousals from sleep (1). An unintended outcome of the updated classification is that some healthcare providers, most notably the U.S. Centres of Medicaid Services (CMS), have taken the decision not to offer CPAP treatment based on AASM 2012 guidelines, citing a lack of evidence that treatment of these is beneficial (1, 96). In many European countries, including France, Czech Republic, Belgium, and the Netherlands, treatment for mild OSA is not reimbursed by healthcare systems. The consequence of this to a patient with mild OSA is that they may not be offered treatment, depending on which scoring criteria is used, and where they are physically located. The MERGE clinical trial aims to provide evidence on the benefits of treatment mild OSA patients with CPAP, with a focus on AASM 2012 scoring (clinicaltrials.gov ID: NCT02699463; Appendix C). Results for this study are expected at the end of 2019.

1.4.3.2. Clinical experience of UARS patients

Clinical diagnosis of UARS is rare, partly due to the lack of use of the diagnosis in sleep clinics, and partly due to inconsistent definitions used. In their description of the syndrome, Guilleminault *et al.* listed complaints of daytime fatigue and/or sleepiness, increased upper

airway resistance during sleep, frequent arousals from the increased upper airway resistance, and no significant hypoxia (97). Pepin *et al.* placed more emphasis on the sleepiness of the patient, and described UARS as being present when a complaint of excessive sleepiness does not have any other causes (e.g. insomnia, periodic leg movements or obstructive sleep apnea) and when a sleep study shows that >50% of arousals during sleep are due to RERAs (11).

Köktürk *et al.* (88) highlighted the importance of oxygen saturation during sleep, and defined UARS as being likely when AHI<5, RERA index >20 and excessive sleepiness was present without nocturnal oxygen desaturation.

Bao *et al.* (98) reported that UARS patients are more likely to seek treatment for somatic functional syndrome than daytime sleepiness. As a result, they are often referred to psychiatrists, and consequently remain untreated.

1.4.4. The importance of flow limitation

One glaring omission from the AHI based definition of OSA is flow limitation. Currently, the percentage of flow limitation a patient experiences during the night does not influence their AHI. Flow limitation increases work of breathing, causes arousals and disrupted sleep, and impacts on daytime cognitive function (13). Upper airway resistance alone, without obstructive apneas, has been shown to produce clinical symptoms such as daytime fatigue and depression (99), both of which are symptoms reported by women with OSA. Women with partial upper airway obstruction have been shown to have similar symptoms, including sleepiness, to women with OSA, resulting in a call for partial upper airway obstruction to be clinically recognized in the same way as OSA in women (100).

It is not clear at what level flow limitation, without OSA, becomes harmful. Flow limitation frequently occurs in normal patients to some degree, particularly during sleep onset (101). A population-based study of over 1000 individuals in Sao Paulo found that 95% of individuals with >30% flow limitation had symptoms of excessive daytime sleepiness and chronic fatigue similar to those with mild OSA (102). This was consistent with findings from a pathophysiological investigation, which found that >30% flow limitation was associated with nasal and palatal abnormalities (102). The authors concluded that >30% of flow limitation during the night may be a good measure of SDB in subjects with an AHI < 5 (102).

Hosselet *et al.* paired complaints of EDS with different measures of abnormal breathing patterns and found that an index which included inspiratory flow limitation provided better sensitivity and specificity for identifying subjects with SDB than AHI (103).

1.4.5. Health consequences of mild and UARS patients

There is some evidence to suggest that even minor sleep-related breathing disturbances have a negative impact on hypertension (104, 105), cognitive function (106, 107), quality of life (95, 108), and the risk of motor vehicle accidents (109). However, the evidence is mixed, with a recent review by the American Thoracic Society (ATS) stating that the impact of mild OSA on cognitive function, mood, vehicle accidents, cardiovascular events, stroke and arrhythmias is inconsistent (95).

UARS appears to be associated with adverse cardiovascular consequences, in particular the development of hypertension, however the evidence is scarce. One study reported that 35% of UARS patients had drug resistant hypertension (110), and a similar investigation showed that 36% of UARS patients had systemic hypertension (111).

1.4.5.1. What are the mechanisms for adverse cardiovascular outcomes in mild and UARS patients?

The association between moderate-to-severe OSA and cardiovascular morbidity and mortality has been well documented, and repetitive hypoxia during sleep appears to play the most important role in this association (11). The potential mechanisms for how mild OSA and UARS could be associated with poor cardiovascular consequences are not clear, as these patients do not have significant oxygen desaturation (11, 111). It appears that flow-limited breaths and repetitive arousals from sleep are both harmful. In 1996 Guilleminault *et al.* demonstrated through continuous 24-hour blood pressure (BP) monitoring that flow-limited breaths without significant hypoxia were associated with increases in systolic and diastolic blood pressure (97). These findings were supported by a larger investigation of 448 subjects. Stradling *et al*. found that the level of respiratory effort was an independent predictor for the overnight change in systolic BP. The authors concluded that increased respiratory effort during sleep prohibits the normal nocturnal fall in BP, and this may be one mechanism for the development of hypertension in patients with nocturnal flow limitation (112). It has also been shown in a small group of patients that prolonged flow limitation increases CO_2 (113). It has previously been established that any increase in CO_2 stimulates the sympathetic nervous system (11).

The repetitive arousals seen in UARS and many mild OSA patients may also be responsible for increased BP. Arousals from sleep are shown to coincide with autonomic and cardiovascular activations during the night (11, 114). Guilleminault *et al.* showed that EEG arousal is significantly associated with an increase in heart rate, and that an increase then decrease in parasympathetic activity can be seen immediately after an arousal (115). The investigators demonstrated a relationship between RERA events and increases in systemic BP. They also found that the magnitude of the increase in BP was directly related to the severity of the arousal (116). Asker *et al*. demonstrated an association between arousals and uncontrolled hypertension in a small study of 14 patients (110). In their study they were able to establish a strong association between the patient's arousal index and systolic BP (110). A study of healthy volunteers also provides evidence of the harmful effects of sleep disruption. In these healthy subjects, two nights of sleep fragmentation lead to a 20% decrease in insulin sensitivity and a significant reduction in glucose effectiveness (117). It was hypothesized that increases in sympathetic nervous system activation and adrenocortical activity were responsible for these metabolic consequences (117).

Therefore, it appears that flow limitation during sleep combined with repetitive arousals lead to chronic increases in sympathetic activity, which may be responsible for hypertension, cardiovascular consequences, and potentially adverse metabolic outcomes (11).

Another potential mechanism of cardiovascular damage may be through snoring, although the evidence for this hypothesis is mixed. Lee *et al*. found that snoring was an independent factor for the development of atherosclerosis (118). The researchers proposed that the vibrations generated during heavy snoring may be transmitted to the carotid artery wall. These vibrations may then cause endothelial damage which eventually leads to carotid atherosclerosis (118). However, a large population study of 380 participants over a 17-year period was unable to find any independent correlation between snoring and cardiovascular morbidity and mortality (119).

1.4.6. Are mild OSA and UARS different from moderate and severe OSA?

There is not universal agreement on whether UARS is simply a very mild form of OSA, or whether it should be considered a completely different condition. Gold *et al.* proposed that if UARS is an extension of OSA then there should be an increasing progression in somnolence from minor in UARS patients to extreme sleepiness in severe OSA patients (120). A small comparison of 12 symptomatic OSA subjects, 12 UARS subjects, and 12 normal subjects found that the UARS subjects reported significantly worse tiredness and

daytime sleepiness than the normal subjects, although they were not significantly different from OSA patients (121). A larger study of 2783 patients with OSA, UARS, or snoring, found that patents with UARS described the highest degree of daytime impairment (90). UARS patients rated the quality of their daytime functioning as significantly worse than OSA patients. They also reported issues with daily functioning, such as difficulty concentrating and completing tasks, as well as depressed mood. They scored lower than OSA or snoring patients in their perception of sleep quality. The authors found that the female-to-male ratio was higher in the UARS group than those with OSA, although males still accounted for 60% of the group. The authors did not break down the study outcomes into gender differences (90).

Stoohs and colleagues compared the reaction time of UARS patients with OSA patients to determine if UARS patients had the same high risk of motor vehicle crashes as OSA patients (122). They found that UARS patients had significantly worse results than the OSA patients on the majority of psychomotor performance tasks, including reaction time, vigilance and attention tests. They concluded that UARS patients may be at an increased risk of motor vehicle crashes compared with the already elevated risk of OSA patients (122).

Taken together, the limited information available suggests that UARS patients experience much more excessive daytime sleepiness and reduced daytime functioning than expected if UARS was a very mild form of OSA. They also report high levels of insomnia not seen in severe OSA patients (120). This supports the hypothesis that patients with sleep disordered breathing characterised by flow limitation and frequent arousals from sleep have different symptoms than sleep disordered breathing characterised by obstructive apneas and severe oxygen desaturation.

1.5. Are there polysomnography (PSG) differences between the genders?

1.5.1. Gender differences in PSG data

There are a number of gender differences in both the severity of OSA and its distribution across the sleep cycle. One of the largest reviews of PSG data, including 830 patients, found that women had a significantly lower overall AHI compared with men (20.2/h vs 31.8/h; $p<0.001$). AHI during non-REM sleep was also significantly lower in women vs men (14.6/h vs 29.6/h; $p<0.001$), but there was no difference between females and males with respect to

AHI during REM sleep (42.7/h vs 39.9/h, respectively), indicating a greater clustering of apneic events during REM sleep in women (123). This study also found that OSA in the supine position occurred almost exclusively in men, indicating that positional OSA is not an issue for women (123).

PSG data from patients referred for suspected sleep disorders also showed that a difference between males and females in AHI was evident during stage 2 sleep, but not during REM sleep, further providing evidence that women often have mainly REM-based events (124). In addition, this data showed that women had shorter apnea events and less severe oxygen desaturations than men (both $p<0.001$) (124).

Gender differences have also been observed in sleep architecture. A study of 307 patients found that women took longer to fall asleep than men. Women also had fewer awakenings and more slow wave (deep) sleep, despite no differences between the sexes in age, respiratory disturbance index or oxygen saturation (125).

As a group, women with OSA have more episodes of upper airway resistance and flow limitation than men with OSA (126). This combined with the shorter apnea events and less severe oxygen desaturations (124) explains why more women are categorised as UARS and mild OSA than moderate-to-severe OSA.

1.5.2. Why do these PSG differences occur?

Overall females have less-severe OSA than males, which can be explained by several physiological differences. In women, the neck and upper airway are smaller in size than in men (23). Magnetic resonance imaging has shown that the airway length, tongue, soft palate, and total amount of soft tissue in the throat are all smaller in women (127). Intuitively, a smaller airway should occlude more easily than a larger one; however, this doesn't seem to be the case. Men have a longer, softer oropharynx, and a larger, fatter, more posterior tongue, increasing the susceptibility of the large airway to collapse (23). Upper airway collapsibility, determined by the pharyngeal critical closing pressure, has been shown to be less in women compared with men with the same OSA severity (128). Gender differences in airway collapsibility are most evident during non-REM sleep, suggesting that women may be more susceptible to pharyngeal collapse during sleep transition and REM sleep but not during established sleep when some muscle tone is preserved (129).

Obesity is a well-recognized risk factor for OSA, and higher body mass index (BMI) is associated with increased severity of OSA for both sexes (130). However, for the same AHI, women tend to be more obese than men (128, 131). One potential explanation for this is differences in fat distribution between the sexes (132). For the same BMI, men have higher mean body weight, more free fat mass, and larger neck circumference compared with women (133). MRI studies have confirmed more pharyngeal fat and increased soft tissue volume in the neck in obese men compared with obese women (127). Upper airway fat distribution, particularly in the posterior tongue, is important in the pathogenesis of OSA. The increased weight and fat in the upper airway leads to more severe occlusion when muscle tone is lost during sleep (23). Additionally, upper body and visceral adiposity are associated with reductions in lung function, including total lung capacity, forced vital capacity and forced expiratory volume (134). This reduction in lung function impacts the body's ability to achieve adequate ventilation, particularly during sleep when muscle tone is lost, and the positional load on the thorax is increased (135).

Fat distribution might have physiological as well as mechanical effects in patients with OSA. Obese women, particularly those with OSA, have increased hypercapnic and hypoxic responses, whereas this was not the case in obese men (136). This increased sensitivity to changing blood gases means a better maintenance of optimal minute ventilation when the chest wall load is increased.

Men and women have also been shown to respond differently to changing blood gases. Men experience respiratory instability from much lower levels of carbon dioxide in the blood, and as a result men are more susceptible to hypocapnic dysfunction during non-REM sleep than women (137), (138). There may also be gender differences in the arousal response to apneas. Jordan and colleagues found that during non-REM sleep men had a higher ventilatory response to apneas than women, but then they developed greater hypoventilation when they went back to sleep, especially in the supine position. This prolonged hypoventilation often leads to ventilatory instability upon returning to sleep. The study authors hypothesized that this may play a role in explaining why sleep apnea syndromes are more severe in men (139).

A further explanation for these PSG differences may be related to hormones. Post-menopause, the incidence of OSA markedly increases in female patients (21, 140, 141). Younger females (<30 years) are less likely to snore, have less severe OSA, and have a trend towards more upper airway resistance and flow limitation (50). Therefore, it has been

suggested that female sex hormones have some sort of protective effect on upper airway patency and/or ventilatory drive (24). The hormone progesterone is a known respiratory stimulant which increases chemoreceptor responses to hypercapnia and hypoxia, and has been shown to increase upper airway muscle tone (142). Progesterone levels increase during pregnancy and may play a protective role in maintaining ventilation against increasing weight of the developing fetus. Progesterone levels decrease after menopause. However, studies that have given males progesterone in an attempt to improve OSA have not yielded strong results (143).

Hormones also play a role in the distribution of body fat. Post-menopausal women have a higher fat mass than prior to menopause, and fat distribution is more likely to be in the upper body and trunk area compared with the lower body (144, 145).

In summary, women have less severe OSA. This is likely due to differences in body fat distribution, differing responses to blood gases, and the protective role of female sex hormones.

1.5.3. Why do some patients have UARS or mild OSA and others have moderate-to-severe OSA?

Individuals are susceptible to developing OSA due to a number of factors. In particular: upper airway anatomy; chemoreceptor responses to changes in blood oxygen and carbon dioxide levels; and the individual's reaction to negative intra-oesophageal pressures and upper airway dilator muscle stimulus.

UARS patients are commonly described as being younger with a lower BMI than OSA patients (87, 90, 110). Many UARS patients display defining craniofacial characteristics, including a long face with a short and narrow chin (11). In this patient group the mandible is retracted and the palate is narrow and high with reduced mouth opening (11, 146).

Patients with UARS and mild OSA arouse from sleep very quickly in response to upper airway resistance. It is likely that the mechanoreceptors in the upper airway, coupled with increased sympathetic function, increase efferent activity in the central respiratory receptors which leads to arousal from sleep (114). This sleep disruption impacts daytime mood, function and quality of life. Conversely, patients with more severe OSA have longer obstructive events and more severe oxygen desaturation, but have less sleep arousals and fragmentation.

High levels of resistance in the upper airway, resulting in excessive amounts of flow limitation, are found in UARS patients (11, 147). UARS patients have a higher mean resistance at peak pressure in the upper airway during wake compared with OSA and normal subjects (147). The required forces to collapse the airway can be measured using the PCrit (critical closing pressure). PCrit is a continuum from normal, to UARS, to OSA (148-150). The amount of collapse that occurs in the upper airway is due to a combination of factors, including bony structures, retropalatal mechanical load, soft tissues and upper airway narrowing (146). In OSA patients, the blend of a collapsible airway with the loss of tonic input to the upper airway dilator muscle motor neurons during sleep leads to airway occlusion (151). UARS patients are able to maintain higher levels of upper airway resistance without collapse (147), despite employing the same amount of respiratory effort as severe OSA patients (152). It appears that UARS patients have preserved protective reflexes in the pharynx, which lead to increasing muscle activity to counteract the upper airway resistance and prevent further upper airway collapse (11). This idea is supported by research showing that upper airway sensitivity in UARS is not impaired, while it is severely impaired in OSA patients (153).

Patients with UARS have much higher parasympathetic activation during sleep than OSA patients (115), which enables them to arouse quickly in response to small increases in respiratory effort (91). This appears to be because UARS patients respond efficiently to upper airway changes, while more severe OSA patients have dampened respiratory responses, which permits apneas to occur (98). While females as a group have less severe OSA and are more prone to flow limitation and respiratory-related arousals from sleep, it is not clear whether there are additional gender differences in the UARS and mild OSA groups.

1.6. Continuous Positive Airway Pressure (CPAP)

Continuous positive airway pressure (CPAP), first described by Sullivan *et al.* in 1981 (154), is considered the gold standard treatment for OSA. CPAP applies continuous positive pressure to the patient's airway via tubing and a mask. The pressure provides a pneumatic splint to the upper airway which prevents the airway from collapsing (154).

Effective CPAP treatment in compliant moderate-to-severe OSA patients has been shown to decrease elevated blood pressure, improve cardiovascular disease outcomes, and reduce the risk of cardiovascular fatal and non-fatal events (53, 155-157). CPAP treatment also eliminates excessive daytime sleepiness, improves quality of life, and restores cognitive

function to normal levels (53, 54, 57-61, 158). The majority of clinical trials of CPAP have included mainly male participants (159).

1.6.1. The impact of CPAP on quality of life in women

Studies that have split the results into genders found that CPAP improved symptoms and quality of life in both genders. A study by Ye *et al*. (160) compared a group of male and female patients presenting to sleep clinics. They found that despite similar age, BMI and AHI, women reported significantly worse scores in daily functioning measured by the functional outcomes of sleep questionnaire (FOSQ) (males 15 ± 2.9 vs females 12.8 ± 3.7, p = 0.002). Women also reported higher levels of sleepiness through the ESS (males 14.5 ± 4.8 vs females 16.8 ± 4.1, p = 0.032), and more mood disturbance, measured using the total mood disorder (TMD) scale (males 11.9 ± 25.9 vs females 21.0 ± 17.6, p = 0.007). CPAP treatment significantly improved daily functioning, sleepiness and mood equally in both genders (160).

A similar study which evaluated depression in OSA patients before and after treatment included 183 women with an average age of 52 ± 15 years and BMI of 32.1 ± 7.1 (161). Patients completed the PHQ-9, a questionnaire-based depression scale containing 9 items, asking about participants' feelings of sadness, tiredness, sleepiness, lack of interest in activities, perceived personal successes, ability to concentrate, self-confidence, slow/fast speech patterns, and suicidal thoughts. Participants rate each item on a scale of 0-3, with 0 indicating no symptoms and 3 indicating highly symptomatic. A total score of 27 is possible. Scores ≤ 4 are indicative of no depression; 5-9 is mild depression; 10-14 equals moderate depression; 15-19 is moderately severe depression; and ≥ 20 equals severe depression (162). In this study, the PHQ-9 in female patients at baseline was 10.4 ± 5.9, and after 3 months of CPAP therapy this had decreased to 3.4 ± 2.8 ($p < 0.001$) (161).

Campos-Rodriguez *et al*. published the first study to review quality of life in a female-only patient group. The authors studied 307 women diagnosed with moderate-to-severe OSA presenting concurrently to 19 sleep units throughout Spain. The average age was 57.1 + 10.1 years with an average BMI of 33.7 (range 20.0 – 38.5). Women were randomized to receive CPAP therapy or conservative treatment for three months. The primary outcome was quality of life using the Quebec Sleep Questionnaire (QSQ). After three months CPAP usage all quality of life domains of the QSQ were significantly improved in the CPAP group

compared with the control group, including sleepiness ($p<0.001$), mood ($p=0.012$), anxiety ($p=0.014$) and depression ($p=0.016$) (163).

1.6.2. The impact of CPAP on cardiovascular health in women

Recently, Campos-Rodriguez *et al.* found that CPAP use for 3 months resulted in a significant decrease in diastolic blood pressure in female subjects (164). A prospective study by the same group evaluated the long-term outcomes of OSA in treated and non-treated female patients. They found that severe OSA was associated with increased cardiovascular mortality risk (adjusted hazard ratio 3.50, 95% CI 1.23-9.98), and that CPAP treatment may reduce this risk (25).

1.6.3. CPAP in Pregnancy

There are limited data on the treatment outcomes of OSA during pregnancy, and no adequately powered randomized controlled trials have been conducted in this area. Small studies have shown that CPAP treatment reduces blood pressure during pregnancy even when OSA is mild (165), and may improve pregnancy outcomes compared with untreated OSA (166, 167); however, more research is required in this area.

1.6.4. CPAP compliance in women

Gender differences in the use and response to CPAP devices have not been extensively studied to date. A review of a database of 4281 patients found that average daily CPAP usage in male patients was slightly higher than in female patients. Average nightly usage in both genders was high (6.3 ± 1.6 vs. 6.2 ± 1.6) (168). One study followed a group of 708 women for a median of 6.2 (4.2-7.7) years. Long term compliance to treatment was good in these patients, with a median daily usage of 6 hours per day (IQR 4-7). 82.8% were still using CPAP after 5 years, and 79.9% were still using CPAP at 10 years (169).

1.6.5. Non-CPAP treatments for women

Non-CPAP treatments have rarely been studied for gender-specific effects. Weight loss is a common recommendation for mild patients; however, this may be more beneficial to males than females due to the increased fat distribution in the upper airway of males (170).

Mandibular Advancement Devices (MADs) are a treatment option for those with mild and moderate OSA or those who have rejected CPAP. One large study found female gender was a predictor of treatment success, particularly in the mild group (171).

1.6.6. Treatment of Mild OSA with CPAP

Effective treatment with CPAP has been shown to improve symptoms and reduce health risks in moderate-to-severe OSA patients (58). However, there is very little evidence regarding treatment of mild OSA, and the degree of severity at which symptoms are improved by treatment is not clear. Indeed, the few randomised controlled trials (RCT) in this area have yielded mixed results, potentially due to small sample sizes and methodology issues (58). Small studies in mild OSA subjects have generally shown that CPAP reduced AHI but did not improve objective sleepiness or blood pressure (BP) (58). Conflicting results were found for subjective sleepiness, neurobehavioral performance, mood and quality of life (58).

One early trial from 2000 which aimed to evaluate the effectiveness of CPAP in mild OSA evaluated 142 consecutive patients in Spain. Patients with an AHI between 10-30 were entered into the trial and were randomised to receive either conservative care (sleep hygiene and weight loss) or conservative care in addition to CPAP treatment (172). Quality of life was assessed at 3 months and 6 months using the Sleep Apnea Hypopnea Syndrome (SAHS) questionnaire. The questionnaire measures how frequently the patient experiences symptoms including snoring, breathing pauses, nocturia, choking, morning headaches, non-restorative sleep, morning drowsiness, and difficulty concentrating (173). The ESS, multiple sleep latency test (MSLT), FOSQ and Nottingham Health Profile (NHP) were also used to measure quality of life. The authors found improved quality of life in the CPAP group using the SAHS assessment ($p < 0.001$). There were also improvements in quality of life measured by the FOSQ, although these did not reach significance ($p = 0.06$). No significant improvements were seen in any of the other quality of life assessments. When reviewing the gender differences in this study no clear conclusions can be made, as 91% of the control group and 81% of the CPAP group were male.

A review of the trials using CPAP for mild OSA in 2006 by Gay *et al*., found that there was insufficient evidence regarding the effectiveness of treatment in the mild OSA group to draw conclusions (58). Following that review there have been two adequately powered studies in mild OSA populations.

The CPAP Apnea Trial North American Program (CATNAP) was conducted by Weaver *et al*. and published in 2012 (174). The rationale for the CATNAP trial was to understand the effect of CPAP on daily functioning in patients with daytime sleepiness (ESS >10) and mild to moderate OSA (AHI 5-30) (174). Patients were randomised to receive either CPAP treatment or sham-CPAP for a period of 8 weeks. The primary outcome was the FOSQ. 223 patients completed the trial. The investigators found a significant improvement in daily functioning in the active CPAP group compared with the sham-CPAP group (174). The results of this study have not been broken down into gender.

It remains unclear from the CATNAP study whether mild OSA patients without excessive daytime sleepiness would also benefit from CPAP treatment (174). The Multicenter Obstructive Sleep Apnea Interventional Cardiovascular (MOSAIC) clinical trial aimed to answer this question in an RCT of 391 patients who were diagnosed with OSA (ODI >7.5/h), but at a level not severe enough to warrant treatment (175). Patients were randomised to receive either CPAP therapy or standard care. The investigators found that CPAP improved daytime sleepiness (based on ESS scores), objective sleepiness and self-assessed health status, but not vascular health risk (175). A sub-group of the participants underwent endothelial function measurements. The study found a large improvement in brachial artery flow-mediated dilation in the CPAP group, particularly in those using CPAP for >4 hours per night. There was no effect on arterial stiffness. The authors concluded that minimally symptomatic OSA may be a cardiovascular risk factor (176). The improvement on ESS from CPAP was independent of gender, as was the 5-year vascular risk. In this study men accounted for 78% of the sample.

The CATNAP and MOSAIC clinical trials used the AASM 2007 scoring criteria. No studies in the mild population have used the AASM 2012 scoring criteria, although the MERGE clinical trial is currently examining this population group (Appendix C). By definition, the AASM 2012 scoring leads to inclusion of milder patients, so may yield different results.

It is difficult to draw conclusions due to various definitions of mild OSA being used in studies as well as the predominance of males and lack of gender-specific results. Currently there is no global consensus on how mild OSA should be scored and whether mild OSA should be treated (177, 178), so it is not surprising that gender differences in mild OSA have not yet been properly explored.

1.6.7. UARS Treatment

Very little data exists on the treatment of UARS with CPAP. Guilleminault *et al*. showed that CPAP was able to normalize breathing, significantly reduce nocturnal arousals, and eliminate daytime sleepiness in UARS (8). Non-randomised trials have examined the use of CPAP in UARS in subjects with an AHI <10 with positive results (114). Similarly, small studies have shown that CPAP can normalize breathing and assist in the control of BP in these patients (97, 110).

Oral devices may be an alternative to CPAP in UARS patients. One investigation of 32 patients found that treatment with a mandibular advancement device was able to significantly reduce daytime sleepiness, arousal index, and minimum oxygen saturation (179).

1.7. Auto-adjusting CPAP devices and gender

Auto-adjusting CPAP devices, commonly called AutoSet devices, monitor the patient's breathing on a breath-by-breath basis and make calculations about the appropriate pressure response. If the patient's breathing shows signs of obstruction, either through snoring, flow limitation or lack of breathing (apnea), the AutoSet algorithm is programmed to increase the pressure delivered to the patient until the obstruction is overcome and breathing is regular. Once breathing has been stable for a period of time, AutoSet devices then slowly decrease the delivered pressure to improve patient comfort. AutoSet devices have an advantage over fixed CPAP devices as they are able to overcome obstruction during changing circumstances, such as the intake of alcohol, supine sleeping, or weight gain. They can differentiate central apneas from obstructive apneas and only increase the pressure when obstruction is present. Theoretically, they are more comfortable and tolerable for patients because they keep the mean pressure lower.

The first AutoSet devices were developed in the late 1990s. At this time OSA was viewed primarily as a male disease (15). Indeed, the patient population described in studies during the development and validation of AutoSet algorithms is typically 100% male (180-182).

Personalised medicine, the practice of tailoring medical decisions and interventions to individual characteristics, has not yet penetrated OSA treatments. However, due to the different gender structures and pathologies of the disease, personalised diagnostic methods

and treatments may be a way to improve patient treatment and long term acceptance (183, 184).

1.8. Summary of the main themes and overall aims of the thesis

Gender differences in the symptoms of OSA are frequently reported. Females do not present with the classic OSA symptoms, such as snoring, obesity and daytime sleepiness. Instead, females may complain of depression, anxiety, mood disturbance, reduced quality of life, insomnia and fatigue (29, 185-187). However, a detailed review of the research shows that these 'female' symptoms appear to be commonly reported in both genders in the mild OSA and UARS patient groups. However, there is limited data available on these patient groups and it often is not analysed by gender.

What remains unclear is whether the gender differences described in moderate-to-severe OSA are present in the UARS and mild OSA patient groups.

The first aim of this thesis is:

1) **Determine whether gender-related differences exist in symptoms of mild OSA patients (CHAPTER 2)**

The severity of OSA appears to differ between genders, with PSG examinations finding that females have less-severe OSA with overall lower AHI, shorter apneas, and a higher likelihood to have REM-only events (123). Younger women, in particular, often have more episodes of flow limitation and RERAs (50, 123). However, UARS and mild OSA are comprised largely of flow limitation and RERAs/hypopneas terminated by arousal. Therefore, it is not clear whether the reported gender-specific respiratory characteristics are present in the mild patient groups. Additionally, some mild OSA patients are reported as being symptomatic, despite having low AHI's. It is hypothesised that the symptoms could be an outcome of flow limitation and arousals during the night rather than gender.

The next aims of this thesis are:

2) **Determine whether gender-related respiratory differences exist in respiratory data of mild OSA patients (CHAPTER 3).**

3) **Determine whether a relationship exists between respiratory data and patient symptoms in mild OSA patients (CHAPTER 3).**

Effective CPAP treatment in adherent patients has been shown to improve sleepiness and quality of life, and reduce the cardiovascular health risk in patients (54, 57-60). However, the majority of clinical trials of CPAP have included mainly male participants (159), and indeed the development of AutoSet devices has been conducted on primarily male participants.

As the final part of this thesis, the development of a new AutoSet device tailored specifically for females is outlined.

The final aim of this thesis is:

4) **Develop and validate new AutoSet for the treatment of female-specific breathing characteristics (CHAPTER 4, CHAPTER 5, and CHAPTER 6).**

CHAPTER 2. SYMPTOM COMPARISON IN MILD OSA PATIENTS

2.1. Introduction

As described in Section 1.3, the literature implies clear differences in symptoms between males and females with OSA. The typical symptoms that males with sleep apnea present with are snoring, witnessed apneas and excessive daytime sleepiness. The most common symptoms that females complain of are insomnia, fatigue, lack of energy, headaches, muscle pain, depression, and anxiety (23-27). However, detailed examination of patients with UARS and mild OSA indicates that symptoms attributed to females are common in both genders. To explore this further, this chapter examines a group of mild OSA patients to determine whether gender differences are present.

The aim of this review was to determine whether gender-related differences exist in symptoms of mild OSA patients. The hypothesis is that clear gender differences will still exist even in these patients at the very mild end of the OSA spectrum.

2.2. Methods

Baseline questionnaire data from the MERGE clinical trial was used in this analysis.

The full methodology for the MERGE study is contained in Appendix D. In summary, the MERGE study is a multi-centre, randomised, controlled study taking place in 11 centres in the UK Respiratory Sleep Research Network (clinicatrials.gov ID: NCT02699463). The MERGE study has been approved by South Central – Hampshire A Research Ethics Committee (approval reference 16/SC/0387).

Polygraphy data from patients with mild OSA (AHI 5-15) is scored using both AASM 2007 and AASM 2012 definitions. Patients are randomised to receive either CPAP treatment or standard care (sleep hygiene counselling) for three months.

Primary Endpoint (AASM 2012 scoring):

- Energy and Vitality Dimension of the SF-36 questionnaire

Secondary Endpoints (AASM 2007 & AASM 2012 scoring):

- Short Form 36 (SF 36)
- Epworth Sleepiness Scale (ESS)
- Fatigue Severity Scale (FSS)
- Functional Outcomes of Sleep Questionnaire (FOSQ)
- Hospital Anxiety and Depression Scale (HADS)
- Insomnia Severity index (ISI)

Patients who have either no OSA or mild OSA when scored with AASM 2007 scoring are entered into the trial. Those with no OSA are expedited for rescoring to see if they may have OSA when scored as per AASM 2012 scoring criteria (Figure 2).

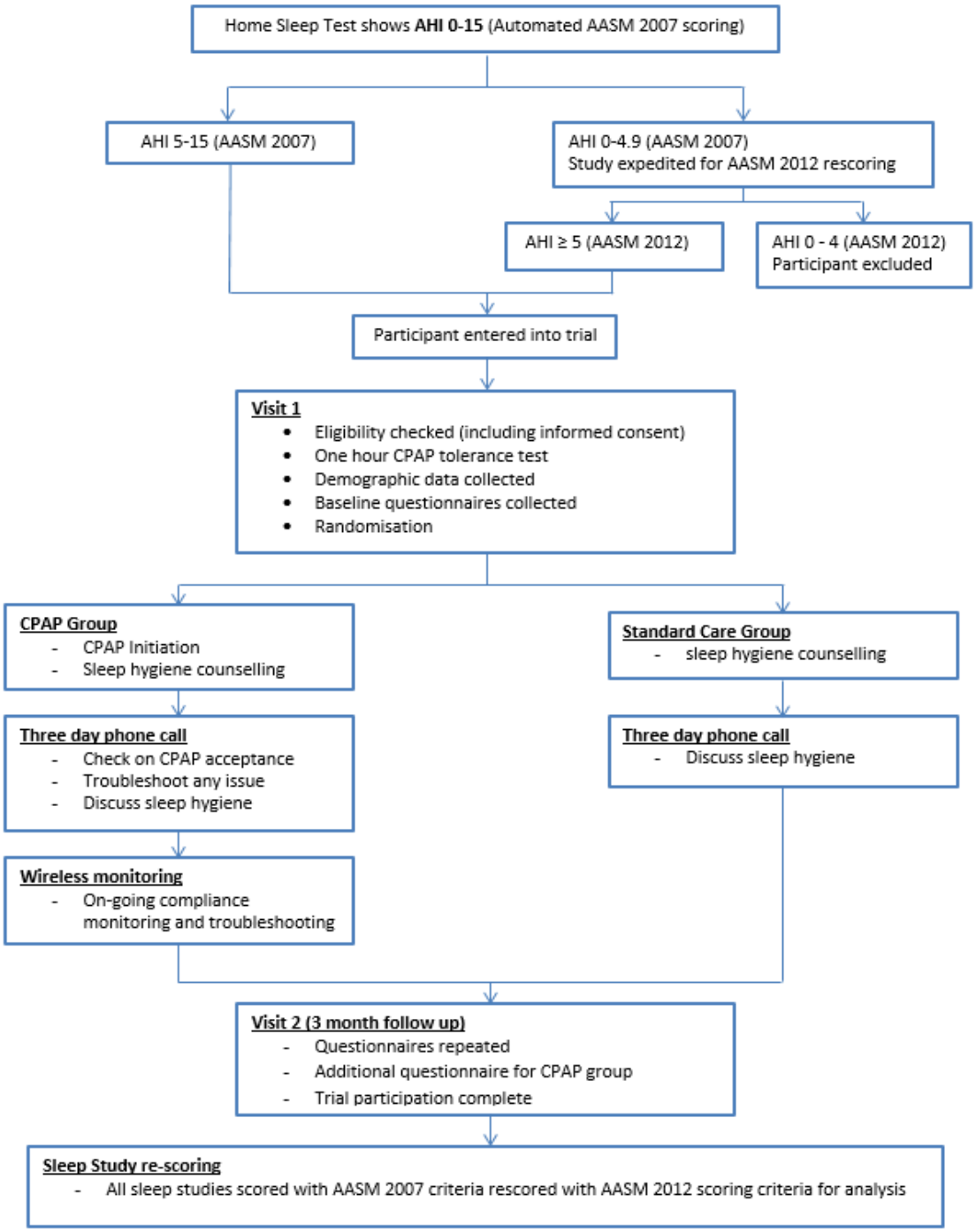

Figure 2: MERGE study methodology

In this chapter, baseline questionnaire data from the ESS, FSS, ISI, and HADS questionnaires were reviewed for gender differences.

Statistical analysis of the data was performed using MiniTab statistical software (Version 7.1.0). Data was split into genders in order to compare baseline questionnaires for females compared with males. Group means were first checked for normality, and then compared using the 2 sample T-test. A value of $P < 0.05$ was considered statistically significant.

A post hoc analysis of the data was undertaken to determine the power of the results. The minimally clinical important difference (MCID) of a questionnaire is the smallest change that would be expected to have clinical benefits. The MCID for the ESS is 2 points. A power calculation using a sample size of 4.34 (found in this data review) shows that a sample size of 74 is needed to show a 2-point increase in the ESS with 80% power. Using this sample size of 259 participants, power is 99.9%. A similar calculation using the MCID of the FSS (0.74) and standard deviation found in this data set (12.9) shows that the power of the FSS result is 99%.

2.3. Results

Baseline ESS, FSS, ISI and HADS questionnaire data from the first 259 participants in the MERGE study were examined for differences based on gender. Data from 186 males and 73 females was included in the analysis.

On average, the females were significantly older with a higher BMI than the males (Table 6). Comparison of AHIs from these patients is presented in Section 3.3.

Table 6: Demographics of the mild patient group

	males	**females**	**p-value**
Age (years)			
Mean ± SD	50.4 ± 12.1	54.9 + 9.8	
Min - Max	23 - 80	30 - 76	
			0.002
BMI (units)			
Mean ± SD	29.5 ± 3.6	31.8 ± 5.2	
Min - Max	21 - 39	19.7 - 39	
			< 0.000

ESS scores are contained in Table 7. There were significant differences between the genders in ESS scores. The female patients in this study were sleepier as a group than the males. When using the ESS, scores of 10 or higher indicate problematic sleepiness. In this mild group of patients, 87/186 (47%) of males and 46/73 (63%) of females reported being excessively sleepy with a score ≥ 10. As can been seen Figure 3, the ESS data spread is fairly similar; however, females have a spike of scores at 11 and 14.

Table 7: ESS Scores in mild patients

	n	min	Mean ± SD	Max	p-value
Males	186	0	9.13 ± 4.34	21	
Females	72	0	10.63 ± 4.34	20	
					0.014

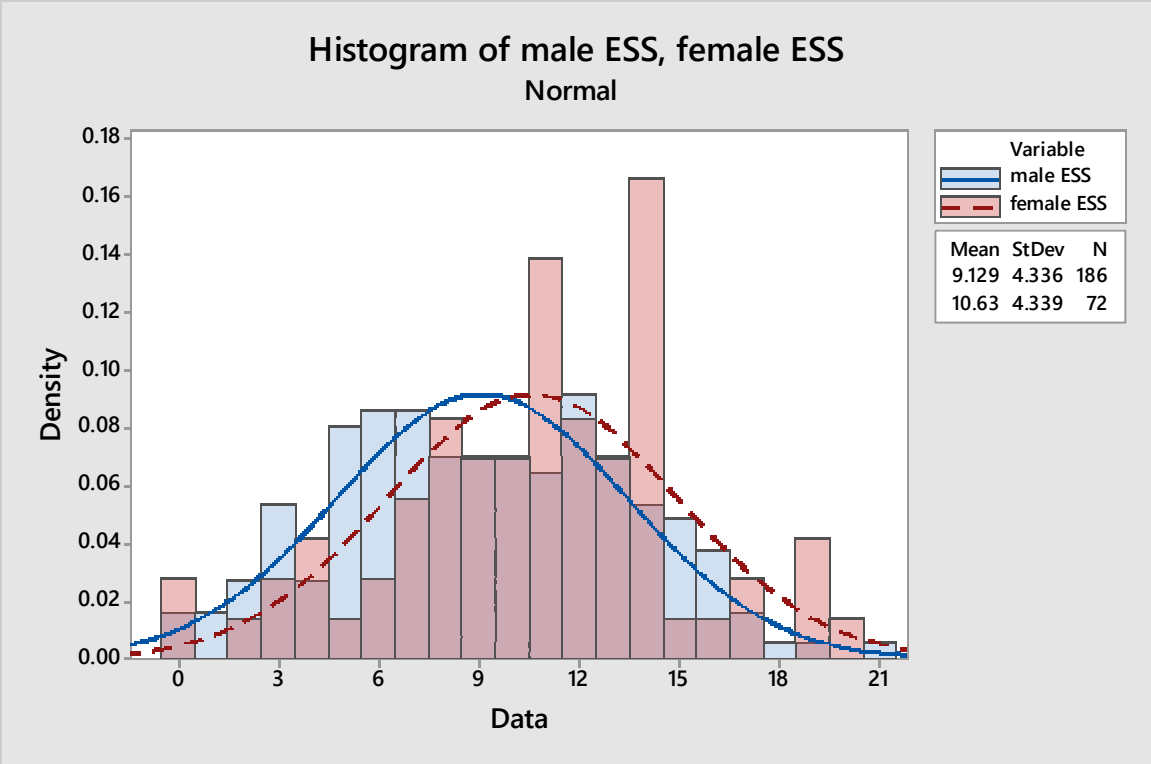

Figure 3: Histogram of ESS scores

FSS scores are displayed in Table 8. There were significant gender differences. An FSS score of 36 or greater indicates high levels of fatigue. In this patient group 82/186 (44%) of males and 56/73 (77%) of females were excessively fatigued. Figure 4 shows the spread of data, and demonstrates that the female scores were clustered around 50-60.

Table 8: FSS scores in mild patients

	n	min	Mean ± SD	Max	p-value
Males	186	9	33.69 ± 13.94	63	
Females	73	9	43.10 ± 12.94	63	
					0.000

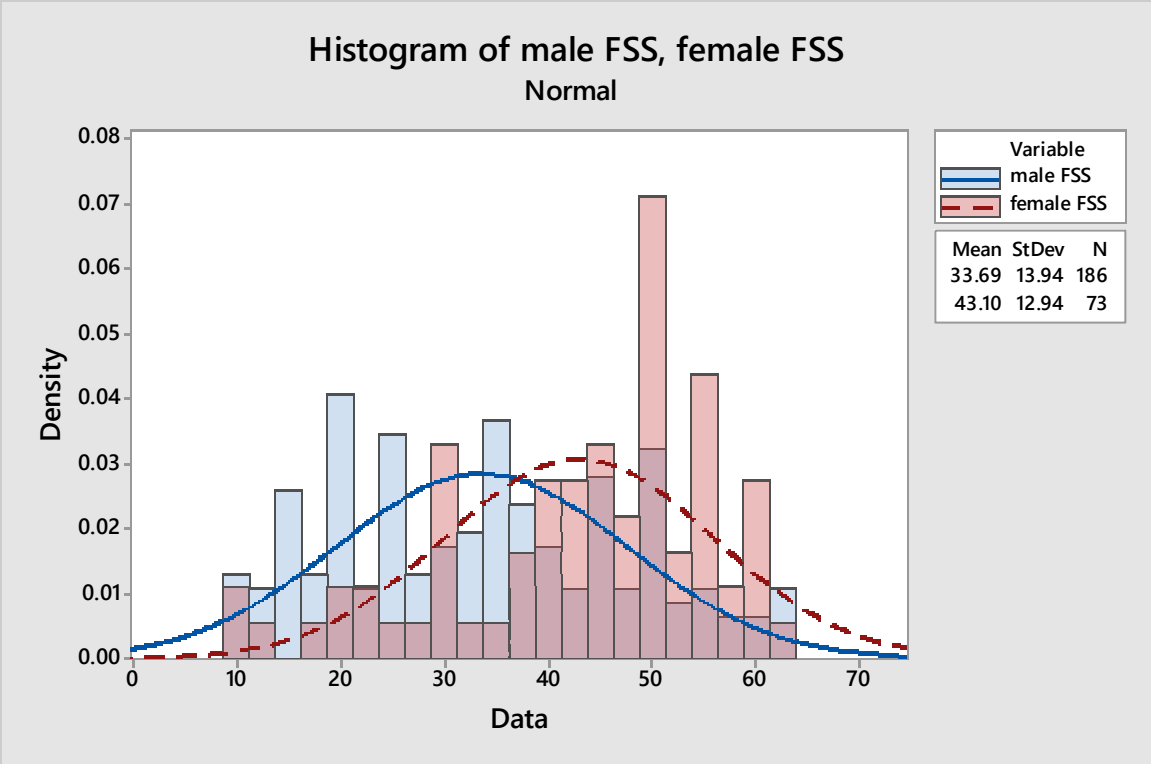

Figure 4: Histogram of FSS Scores

The ISI scores are displayed in Table 9. There were significant gender differences in the ISI scores.

Table 9: ISI Scores of mild patients

	n	min	Mean ± SD	Max	p-value
Males	186	0	11.90 ± 5.48	24	
Females	73	1	14.62 ± 5.67	28	
					0.001

Regarding the ISI questionnaire, scores of 0–7 indicate no clinically significant insomnia, scores 8-14 are indicative of subthreshold insomnia, and scores of 15 and over indicate clinical insomnia, with those above 21 being severe. Table 10 shows the breakdown of insomnia severity. 58% of females in this group had clinically significant insomnia, compared with only 31% of males. Figure 5 shows the spread of data and the higher scores from female participants.

Table 10: Insomnia severity in mild patients

Category	% of males	% of females
No insomnia	23	10
Subthreshold insomnia	46	33
Clinical insomnia	28	44
Severe insomnia	3	14

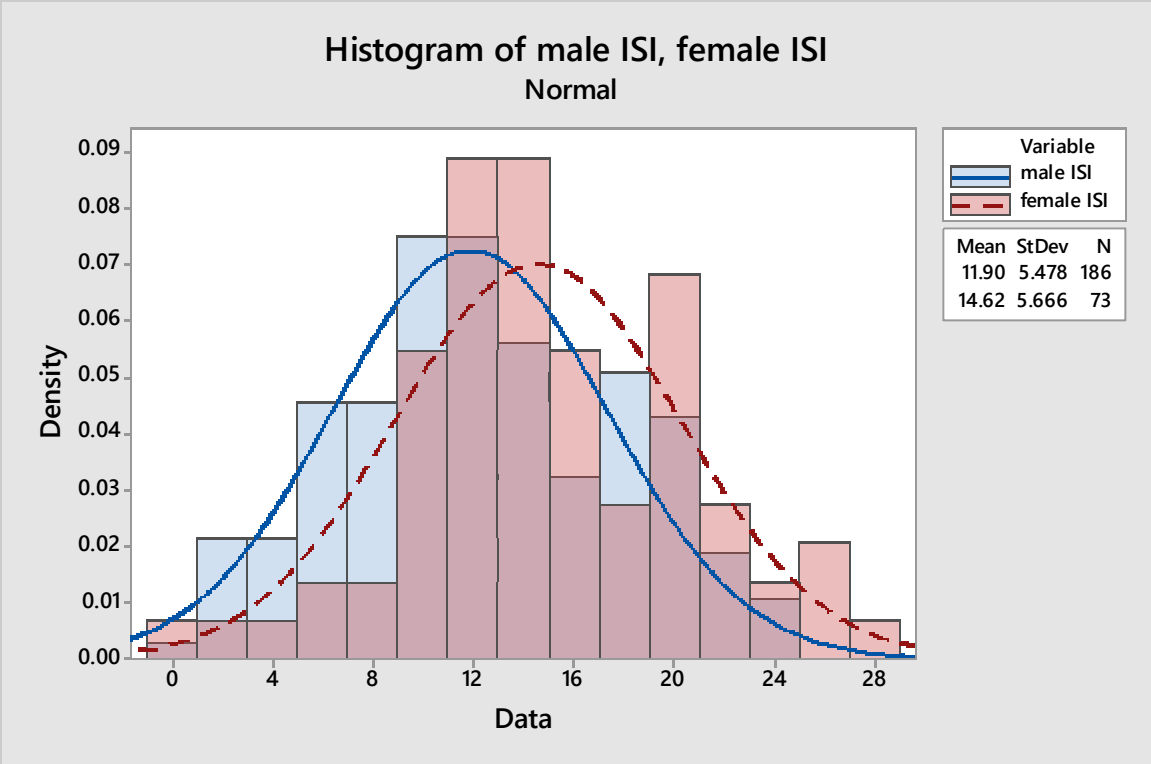

Figure 5: Histogram of ISI scores

The HADS scores from the data are displayed in Table 11. There were significant differences between males and females. Scores ≥ 11 indicate abnormally high levels of anxiety and depression. In this data set, 89/186 (48%) of males and 48/73 (66%) of females had high scores. As displayed in Figure 6, females had a pattern of higher scores than males.

Table 11: HADS scores from mild patients

	n	min	Mean ± SD	Max	p-value
Males	186	0	11.03 ± 6.94	33	
Females	73	0	14.81 ± 7.57	37	
					0.000

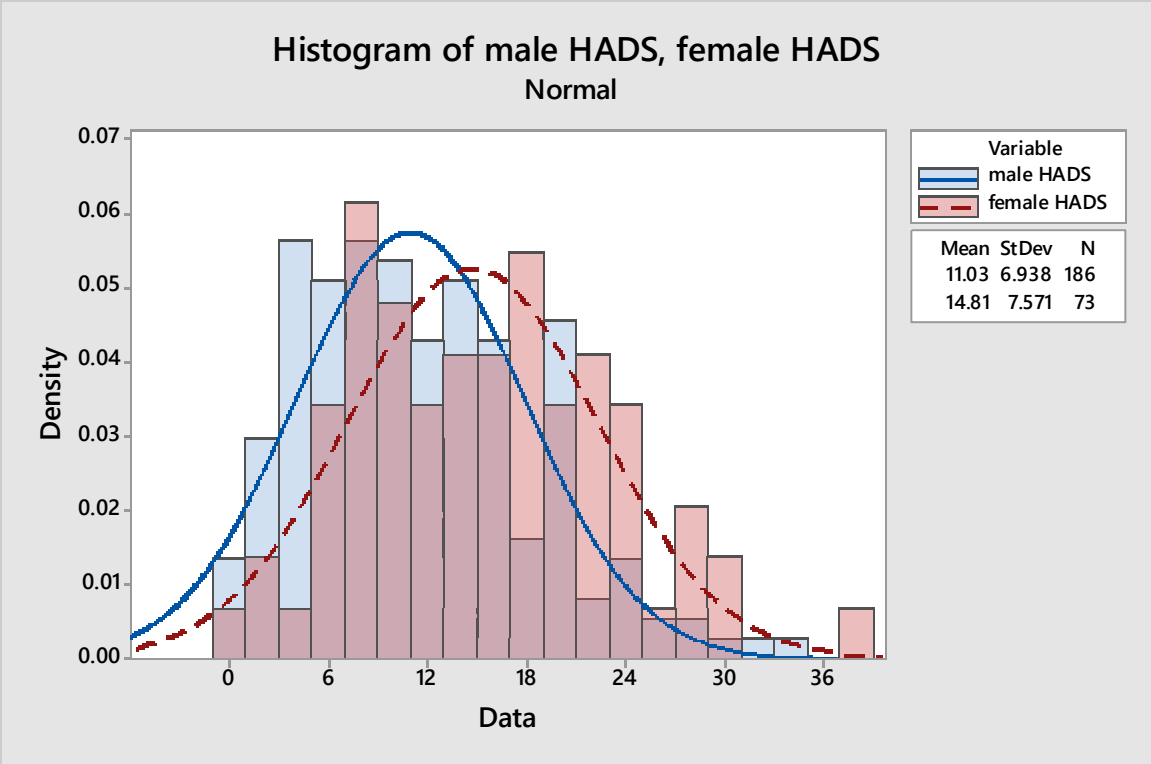

Figure 6: Boxplot of HADS Scores

2.4. Discussion

Patients in the MERGE study were scored using AASM 2012 scoring criteria, which allows the inclusion of hypopneas with arousals. As per Section 1.2.3, if these hypopneas were rescored as RERAs (using AASM 2007 criteria), it is likely that many patients in the MERGE study may meet a diagnosis of UARS. However, no formal UARS diagnosis was made for these patients in this analysis.

Of the first 259 patients enrolled in the study, only 73 were female. The literature suggests that in the mild OSA/UARS patient groups the gender split is almost 50/50. It would be reasonable to expect that females would make up close to 50% of the patient population in this study. The lower presentation of female patients supports the notion that females are underdiagnosed and present less often to sleep clinics (23, 47).

Despite being considered a mild patient group, these patients experienced high levels of symptoms. Defining these patients as mild is misleading, and using AHI as the measure of severity categorisation may be inappropriate for this reason. Mild patients are often denied reimbursement for treatment. In many European countries a diagnosis of moderate-to-severe OSA is required before CPAP treatment is provided to patients (1, 96).

There were significant gender differences in each of the baseline questionnaire scores, with females as a group being more symptomatic than males. Patients in this study had relative high ESS scores, especially for female patients and those with mild OSA. This contradicts the general consensus in the literature that females report less sleepiness than males (28). It is possible that females in the MERGE study are more symptomatic than those in other studies, as they have been referred from primary care to a sleep clinic due to suspected sleep apnea, and may have previously been investigated for other sleepiness causes.

In this data set the groups were not completely matched. The females were older and slightly more obese. It is possible that this has driven the increased symptoms seen in these female patients. These relationships have been explored further in Section 3.3; however, future studies should match (or control for) participants on age and BMI.

While this data set has clearly shown that mild OSA female patients are more symptomatic than male patients, it does not answer the question of why. It is not clear whether females perceive symptoms differently, or whether they describe them differently. Future studies could investigate the psychology behind symptom perception and reporting in mild OSA patients in order to better understand why these differences occur.

2.5. Conclusion

In this data set, females were found to suffer significantly higher levels of sleepiness, fatigue, insomnia, and anxiety and depression than males with the same severity of OSA.

The literature regarding symptoms of OSA in females states that females with OSA do not often report daytime sleepiness (Section 1.3.2.2). However, in this patient group, 63% of female patients, compared to 47% of male patients had a score of ≥ 10 on the ESS, indicating excessive sleepiness. More female patients than male patients complained of high levels of daytime fatigue in this patient group, with 77% of females and 44% of males scoring highly on the FSS questionnaire. This is consistent with the literature cited in Section 1.3.2, which states that in females with OSA fatigue is commonly listed as a key symptom. Severe insomnia was present in 14% of females and only 3% of males. The literature also documents insomnia as a key symptom of female OSA. Insomnia is also frequently mentioned as a symptom of UARS. In this mild patient group clinically important levels of insomnia were present in 60% of females, and 31% of males, showing that insomnia impacts more females than males in the mild group. Anxiety and depression, scored using the HADS questionnaire, was high in both groups. Females reported more symptoms than males, and

clinically significant levels of anxiety and depression were found in 66% of females and 48% of males.

This data set has shown that these patients experienced high levels of symptoms, despite being considered mild when using AHI as the measure of severity. There are significant symptom differences in the genders. A higher percentage of female patients were considered symptomatic in sleepiness, fatigue, insomnia and anxiety/depression. In this group a higher proportion of females than males experienced excessive daytime sleepiness, which is inconsistent with the literature.

CHAPTER 3. DETAILED ANALYSIS OF GENDER DIFFERENCES IN RESPIRATORY EVENTS

3.1. Introduction

Women with OSA are characterised as having more flow limitation, lower AHIs, and shorter apneas (Section 1.5.1). However, as described in Section 1.5.3, the literature on UARS indicates that that both genders may have similar amounts of airway obstruction. Therefore, the following chapter will explore whether mild OSA and UARS patients have clear gender differences in their respiratory data.

As shown in CHAPTER 2, gender differences in symptoms still exist even amongst patients with mild OSA. What remains unclear is whether those symptoms are a result of gender, or whether they are related to different types of sleep disordered breathing events. This chapter will explore associations between the symptoms discussed in CHAPTER 2, and sleep study data taken from the PG studies of mild patients.

The aim of this review was to determine whether there are gender differences in respiratory data from mild OSA patients, and whether respiratory data can be correlated with symptoms.

The hypothesis is that gender differences will still exist in this respiratory data, and that worsening respiratory parameters will correlate with worsening symptoms.

3.2. Methods

The full methodology of the MERGE study is contained in Appendix D, and summarised in Section 2.2.

PG data used in this review was collected using the Apnealink Air home sleep test (ResMed). Data including AHI, ODI, hypopnea index, flow limitation, and snore were analysed using both the AASM 2007 and AASM 2012 scoring criteria (see Section 1.2 for details on the different scoring criteria).

The AASM 2007 analysis of the Apnealink Air was undertaken using AirView software (ResMed). Automated analysis of sleep studies using AASM 2007 criteria has been extensively validated and is closely correlated with manual PSG scoring (188-197).

The AASM 2012 analysis was done using a recently developed algorithm which estimates arousals from sleep. Although PSG is the most precise measure of arousals, surrogate measures such as pulse wave amplitude drops, respiratory changes, and movement have shown to accurately estimate arousals(198-200). The AASM 2012 scoring algorithm used in the MERGE study uses surrogate measures of arousal and machine learning to estimate arousals from sleep following hypopneas. This algorithm has been shown to have high sensitivity and specificity (92% and 80%) to rule in OSA at AHI ≥ 5, when compared with manual polysomnography scoring (201).Statistical analysis of the data was performed using MiniTab statistical software (Version 7.1.0). PG data was split into genders and compared using the Two-Sample T test. PG data was then analysed against baseline symptoms (as described in CHAPTER 2) using the Pearson's Correlation Test to determine correlations. These relationships were further explored using the coefficient of determination (R^2) in order to better understand the interactions between age, BMI, gender and symptoms.

3.3. Results

3.3.1. Gender comparison of PG data

The first 259 consecutively enrolled participants in the MERGE study with full data sets were analysed. Of these 259 patients, 73 (28%) were female. Demographics for these participants can be found in Section 2.3.

When PG studies were scored according to the AASM 2007 criteria, the males had more severe SDB in all respiratory categories (AHI, ODI at 4%, and number of hypopneas). However, when re-scoring with AASM 2012, the differences were much less obvious.

When scored using AASM 2007 criteria, the males were found to have a higher AHI, ODI, and hypopnea index than the females (Table 12).

Table 12: Mild patients scored with AASM 2007 criteria

	males	**females**	**p-value**
2007 AHI	7.17 ± 3.4	5.97 ± 2.71	0.004
4% ODI	8.65 ± 2.3	7.06 ± 3.8	0.008
Hypopnea index	5.31 ± 3.71	4.26 ± 2.71	0.015

When scored using AASM 2012 criteria, the gender differences disappeared. The females did have slightly more hypopneas terminated by arousals; however, this was not statistically significant (Table 13).

Table 13: Mild patients scored with AASM 2012 criteria

	males	females	p-value
2012 AHI	12.52 ± 5.01	11.65 ± 4.69	0.197
3% ODI	17.02 ± 4.96	15.6 ± 5.25	0.111
Hypopneas terminated by arousal	3.2 ± 3.58	3.65 ± 3.58	0.370
Hypopnea index	9.54 ± 3.97	9.03 ± 3.46	0.410

Males had significantly more snore than females. The percentage of overall flow-limited breaths was similar between the genders; however, the females had significantly less flow-limited breaths with snore (Table 14).

Table 14: Flow limitation and snore in mild OSA patients

	males	females	p-value
% flow-limited breaths	39.8 ± 13.8	38.4 ± 15.6	0.598
% flow-limited breaths without snore	33.2 ± 13.3	35.3 ± 14.3	0.348
% flow-limited breaths with snore	6.55 ± 8.14	3.09 ± 4.69	0.001
No. of snore breaths	1147 ± 1139	843 ± 845	0.022

Patients who were classified as having no OSA at baseline (AHI < 5 by AASM 2007 scoring) were re-scored using AASM 2012 guidelines. Following the rescoring, 26/73 (36%) of females and 52/184 (28%) of males had an increased AHI sufficient to lead to diagnosis of OSA (AHI ≥ 5).

The average AHI of this female group when scored with AASM 2007 was 5.97; it increased to an average of 11.65 when rescored according to AASM 2012 rules. The average AHI of the male group was 7.17, and it increased to 12.52 when rescored. The two groups were not significantly different regarding AHI changes between AASM 2007 and 2012 scoring.

3.3.2. Relationships between PG data and symptoms

There were correlations between AHI (scored with both AASM 2007 and AASM 2012) and daytime symptoms (Table 15). However, all the relationships were inverse: the higher the symptom, the lower the AHI. Flow limitation was only correlated with the ISI score, with an inverse relationship, with higher scores of insomnia being linked to lower percentages of flow limitation scores. Hypopneas terminated by arousals had no relationship with symptoms.

Table 15: Correlations between symptoms and respiratory parameters

	2007 AHI	2012 AHI	Percent of flow limited breaths	Hypopneas terminated by arousal
ESS				
r	-0.169	-0.158	0.047	0.025
p-value	**0.007**	**0.012**	0.537	0.692
FSS				
r	-0.152	-0.179	-0.10.2	-0.031
p-value	**0.016**	**0.004**	0.182	0.622
HADS				
r	-0.166	-0.144	-0.093	0.081
p-value	**0.008**	**0.022**	0.228	0.202
ISI				
r	-0.139	-0.156	-0.159	-0.029
p-value	**0.027**	**0.014**	**0.037**	0.646

When analysing the data by gender, there were far fewer correlations between SDB measures in the males than the females (Table 16). In the males, correlations were only found between AASM 2012 AHI, and FSS. In the female patients, correlations were found between AASM 2007 AHI and ESS, HADS, and ISI. In the female data scored with AASM 2012 rules, correlations were found between AHI, and HADS, and ISI (Figure 11). There were no correlations between flow limitation and symptoms in the male group. In the female group correlations were found between percent of flow limited breaths and FSS, and ISI. Again these correlations were inverted, with higher symptoms being associated with lower percentage of flow limitation.

Table 16: Correlations between symptoms and respiratory parameters analysed by gender

	2007 AHI	2012 AHI	% flow limited breaths	Hypopneas terminated by arousal
Males				
ESS				
r	-0.093	-0.130	0.043	-0.042
p-value	0.213	0.083	0.633	0.571
FSS				
r	-0.074	-0.153	-0.006	-0.105
p-value	0.321	**0.040**	0.943	0.160
HADS				
r	-0.043	-0.026	-0.048	0.035
p-value	0.563	0.735	0.598	0.637
ISI				
r	-0.054	-0.103	-0.033	-0.085
p-value	0.468	0.171	0.712	0.253
Females				
ESS				
r	-0.317	-0.197	0.070	0.164
p-value	**0.007**	0.099	0.639	0.171
FSS				
r	-0.218	-0.192	-0.300	0.100
p-value	0.068	0.109	**0.040**	0.408
HADS				
r	-0.372	-0.381	-0.178	0.146
p-value	**0.001**	**0.001**	0.231	0.224
ISI				
r	-0.242	-0.240	-0.416	0.055
p-value	**0.042**	**0.044**	**0.004**	0.648

In male patients, the strongest relationship was seen between AASM 2012 AHI and FSS (Figure 7).

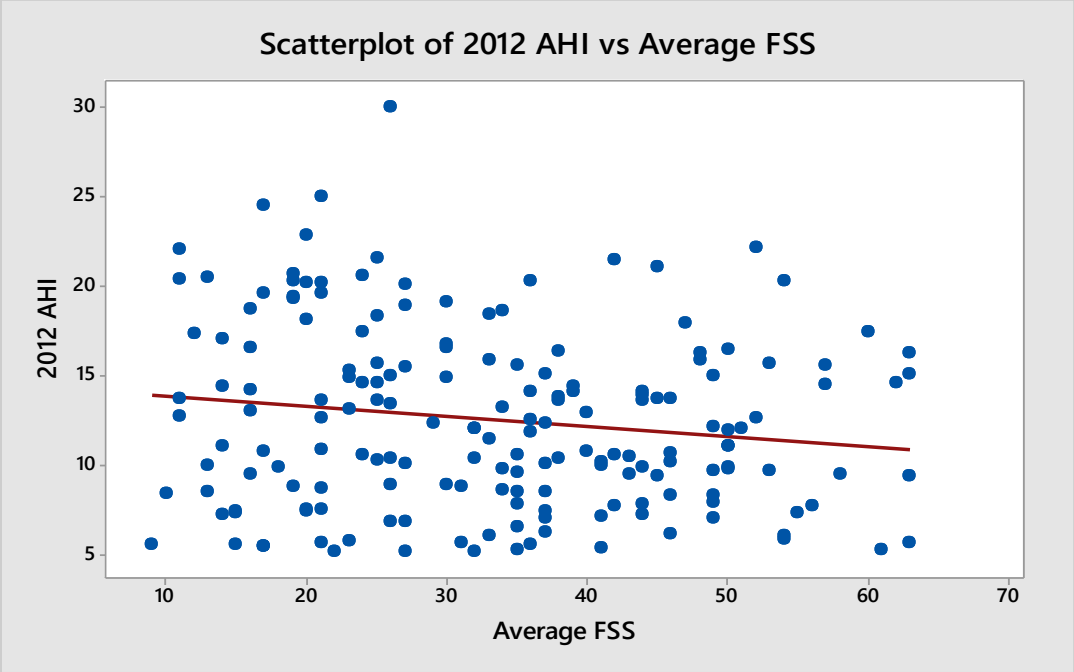

Figure 7: Relationship between AASM 2012 AHI and average FSS in male patients

In the female patients the strongest relationships were seen between flow-limited breathing and ISI (Figure 8); AASM 2007 AHI and ESS (Figure 9); AASM 2007 AHI and HADS (Figure 10); and AASM 2012 AHI and HADS (Figure 11).

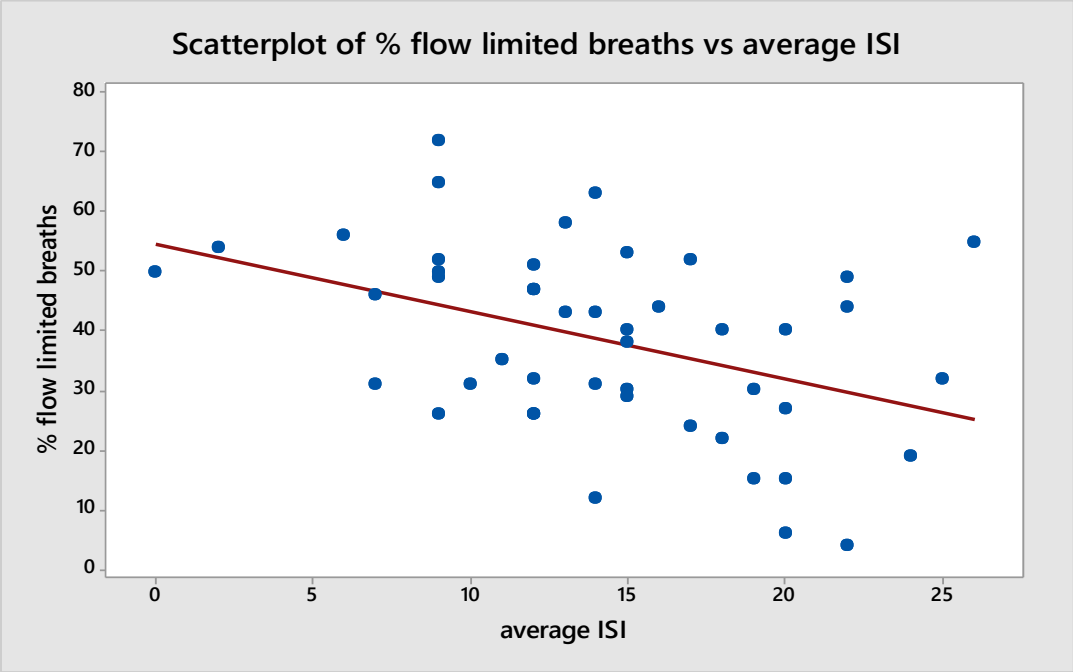

Figure 8. Relationship between flow limited breaths and average ISI score in female patients

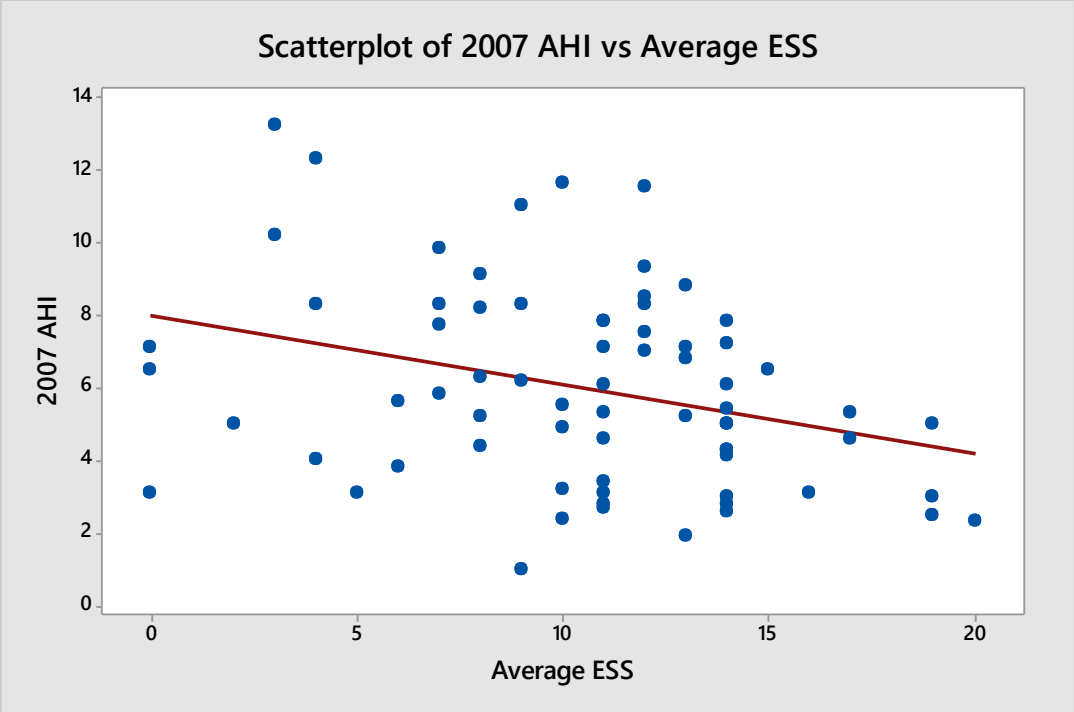

Figure 9: Relationship between AASM 2007 AHI and average ESS in female patients

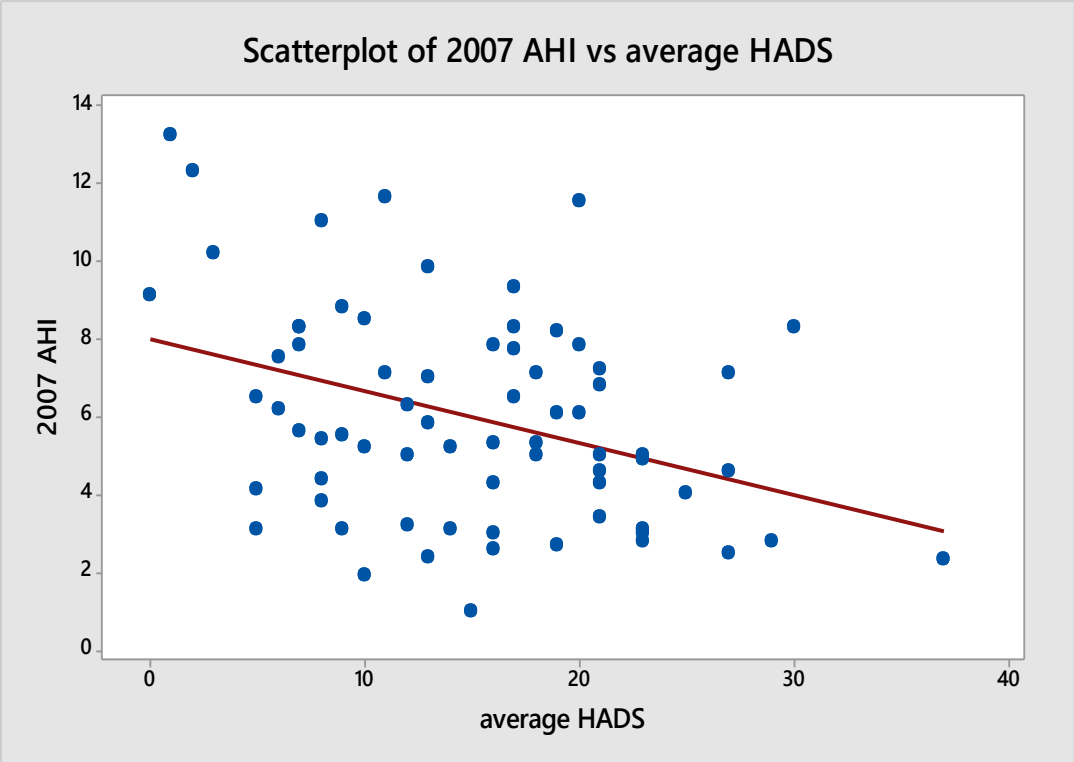

Figure 10: Relationship between AASM 2007 AHI and average HADS score in female patients

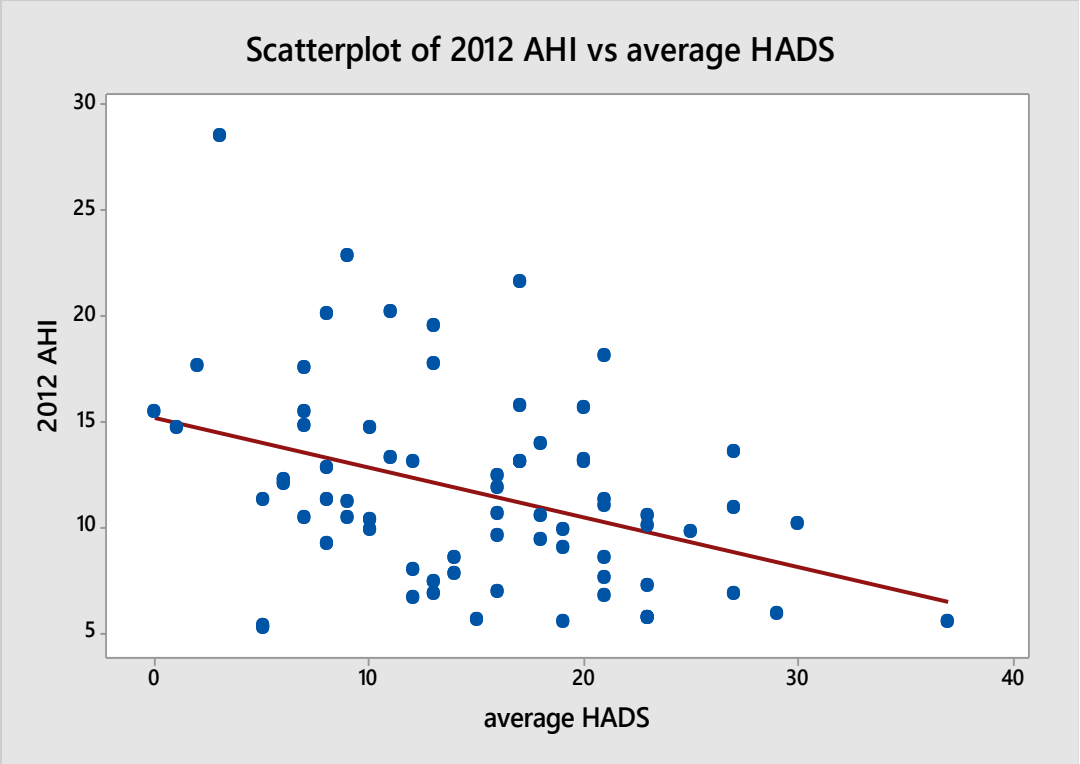

Figure 11: Relationship between AASM 2012 AHI and average HADS score in female patients

3.3.3. Correlations between PG data, symptoms, gender, age and BMI

When reviewing the data by the adjusted R^2, accounting for BMI and AHI, the FSS values of females are 33 points higher than that of males. They increase by 1.1 per unit of BMI increase and drop by 0.5 points for every one-unit increase in AHI. The increase of FSS per unit rise in BMI is 0.8 points lower in women than in men (Table 17, Figure 12).

Table 17: Correlations between FSS and Gender, AHI, and BMI

Dependent Variable: FSS			
Variable	Estimated change per unit	95%-C.I.	p-value
Female gender	33	[8.5 ; 57.5]	0.008
BMI	1.1	[0.6 ; 1.6]	<0.001
2012AHI	-0.5	[-0.8 ; -0.2]	0.004
Female gender and BMI	-0.8	[-1.6 ; -0.1]	0.037

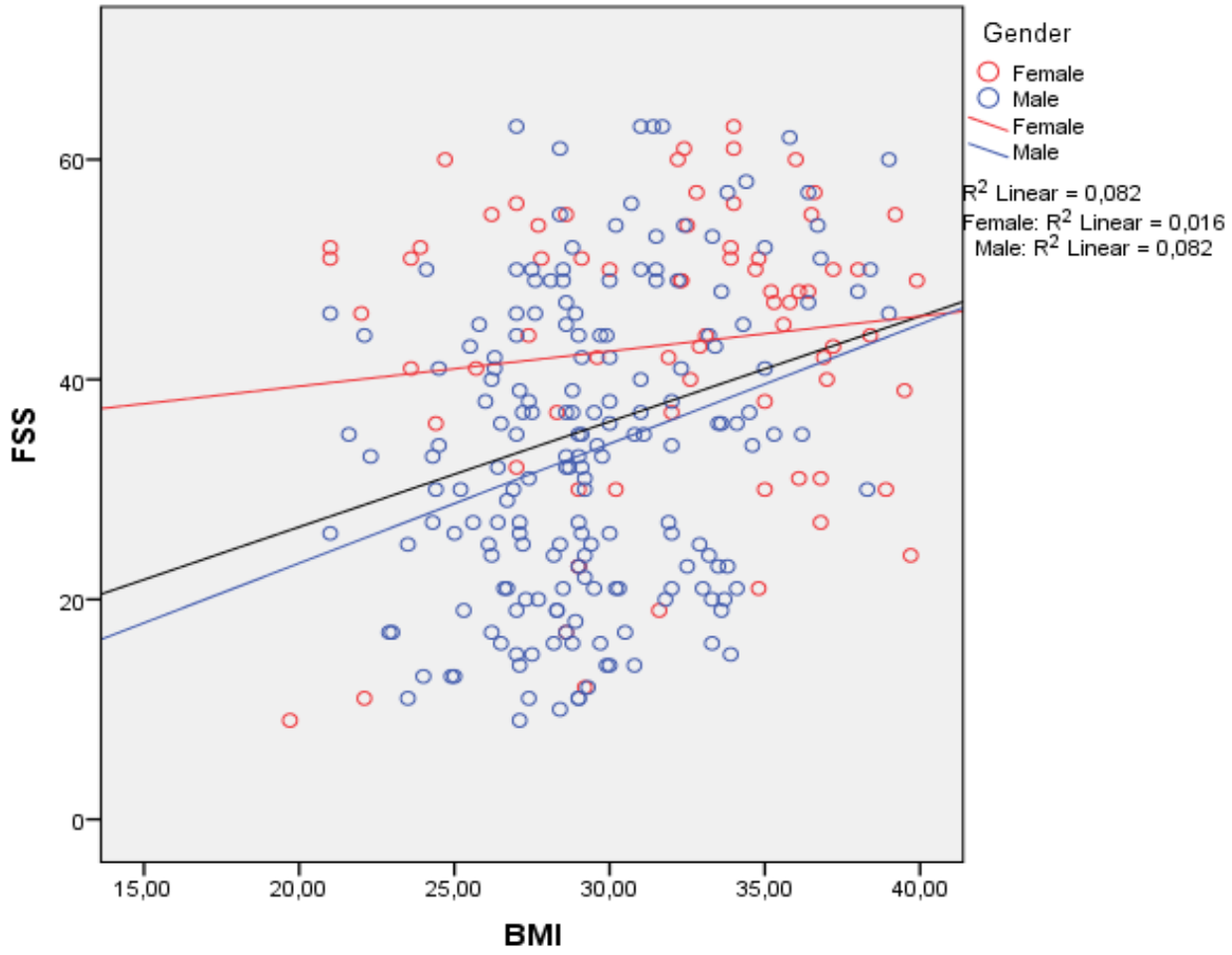

Figure 12: Correlations between FSS, gender and BMI

The HADS values of females are 11.1 points higher than that of males. In contrast to males, the values of females decrease with rising AHI by 0.6 per unit of AHI. There is a slight but significant decrease of 0.1 points per year of age (Table 18, Figure 13).

Table 18: Correlation of HADS, gender, age and AHI

Dependent Variable: HADS			
Variable	Estimated change per unit	95%-C.I.	p-value
Female gender	11.1	[6 ; 16.1]	<0.001
Age	-0.1	[-0.2 ; 0]	0.048
2012 AHI	0	[-0.2 ; 0.2]	0.992
Female gender and 2012 AHI	-0.6	[-1 ; -0.2]	0.005

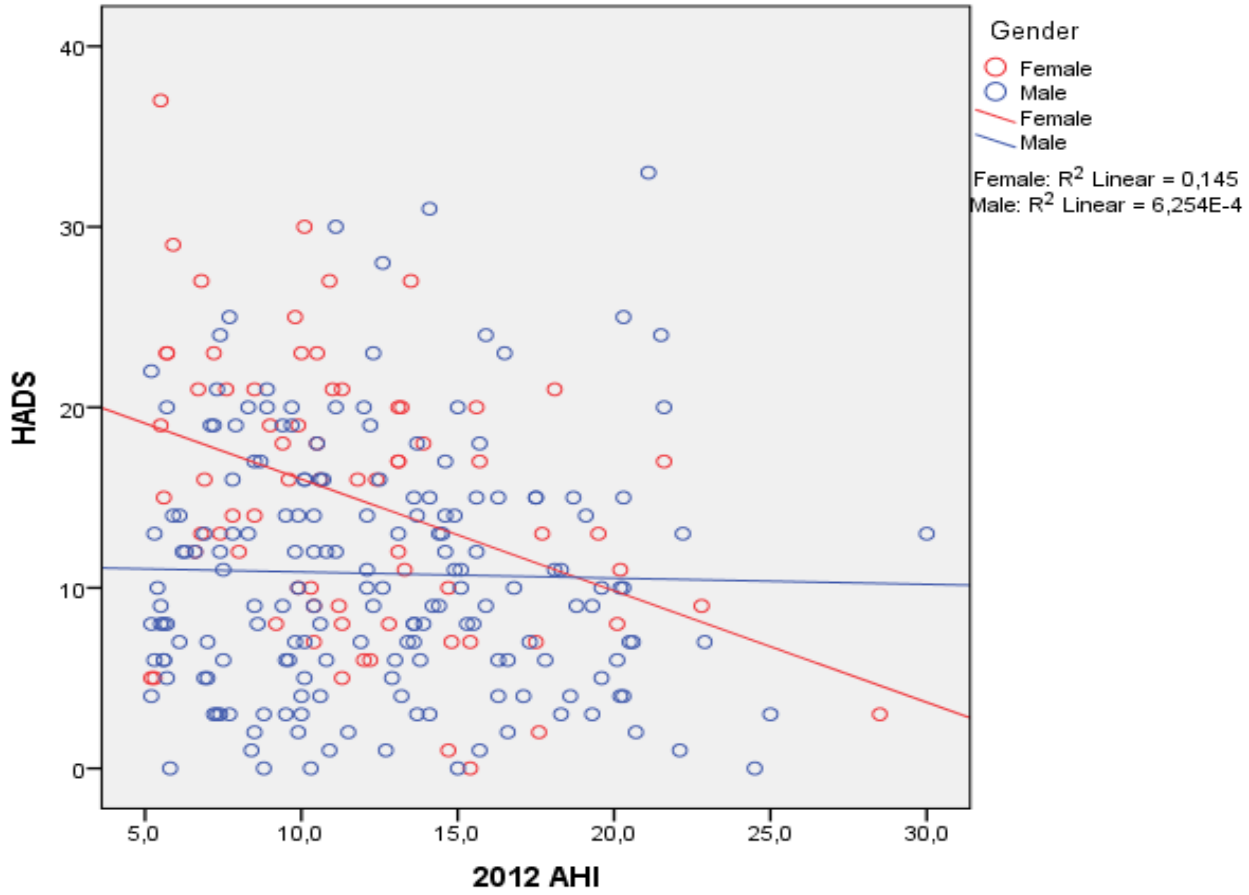

Figure 13: Correlations between HADS, AHI and gender

Regarding sleepiness, in this group the risk of having an ESS of ≥11 is 90% higher in women than in men, and it decreases in both genders by 3 % per year of age (Table 19, Figure 14).

Table 19: Correlations between ESS, gender and age

Dependent Variable: ESS			
Variable	Estimated change per unit	95%-C.I.	p-value
Gender=Female	0.9	[0.3 ; 1.5]	0.002
Age	-0.03	[-0.06 ; -0.01]	0.005

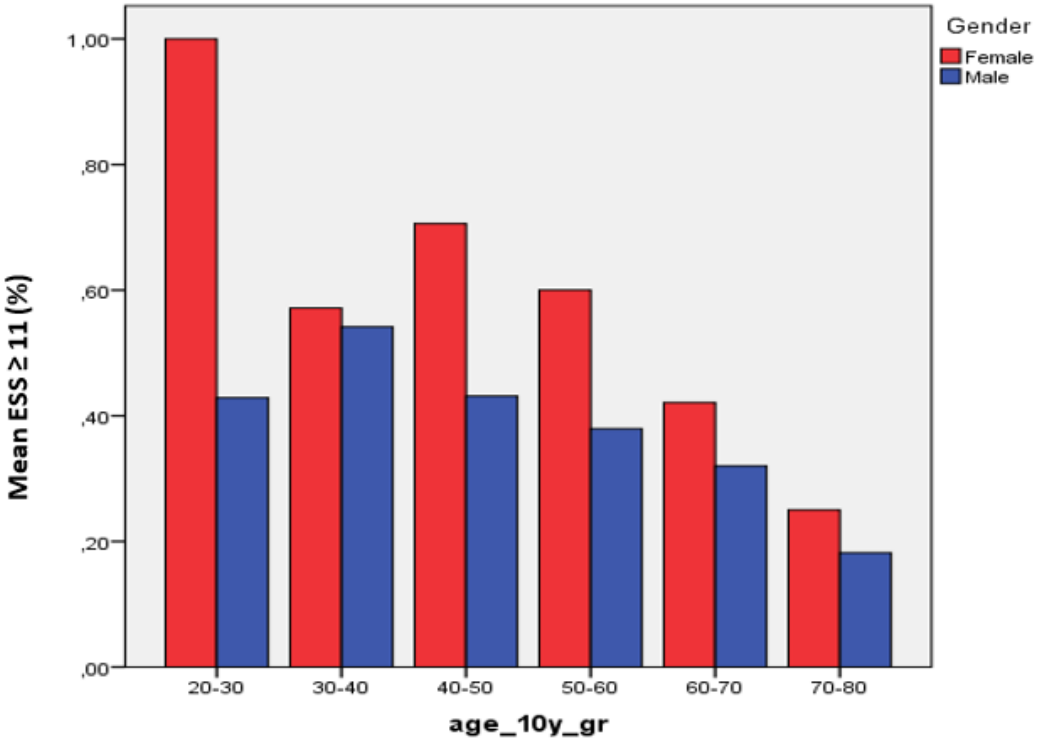

Figure 14: Relationship between ESS, age and gender

The ISI values of females are 12.8 points higher than that of males. In contrast to females, the values of males increase with rising BMI values by 0.3 per unit. In both genders there is a small but significant decrease with increasing AHI values (Table 20, Figure 15, Figure 16).

Table 20: Correlations between ISI, gender, BMI and AHI

Dependent Variable: ISI			
Variable	Estimated change per unit	95%-C.I.	p-value
Female gender	12.8	[2.8 ; 22.9]	0.012
BMI	0.3	[0.1 ; 0.6]	0.001
2012AHI	-0.2	[-0.3 ; 0]	0.014
Female gender and BMI	-0.3	[-0.7 ; 0]	0.042

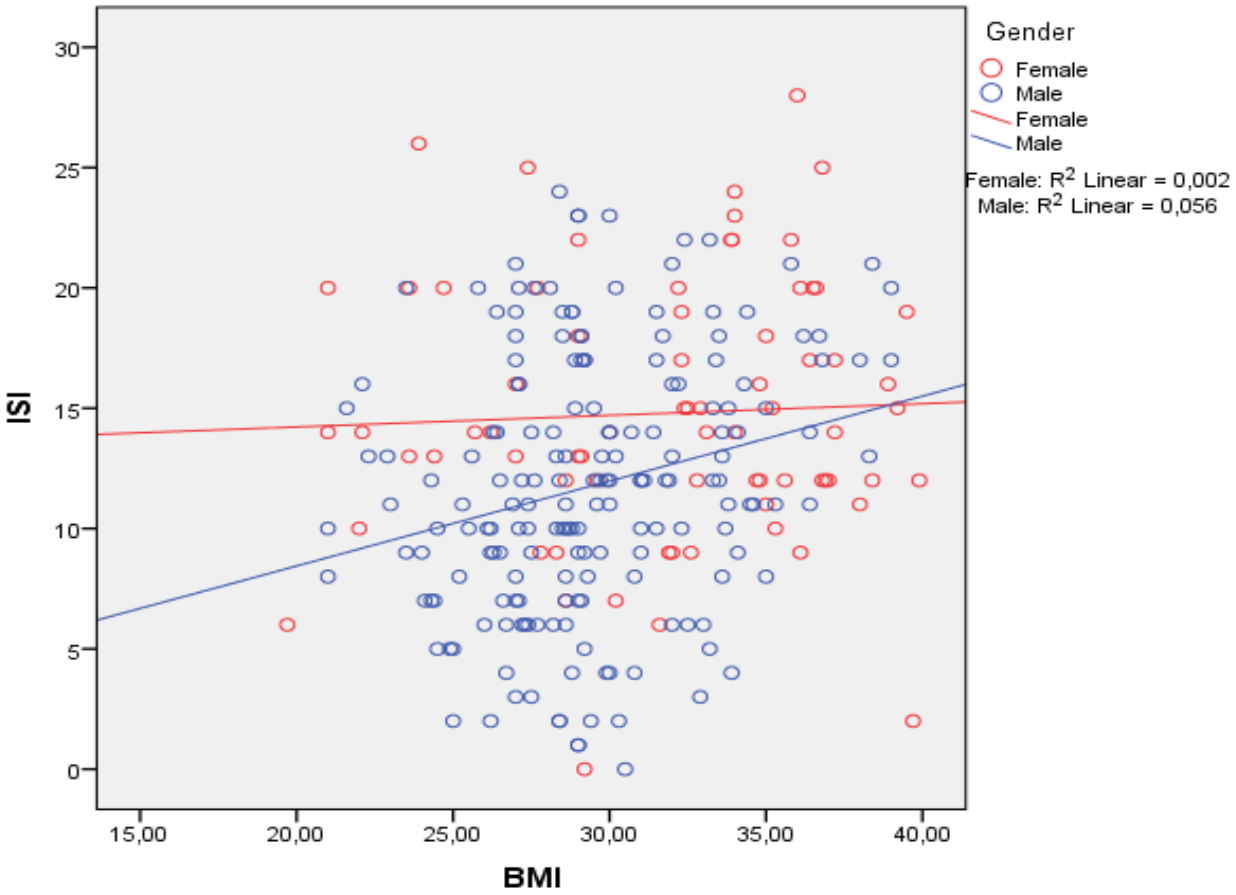

Figure 15: Correlations between ISI, BMI and gender

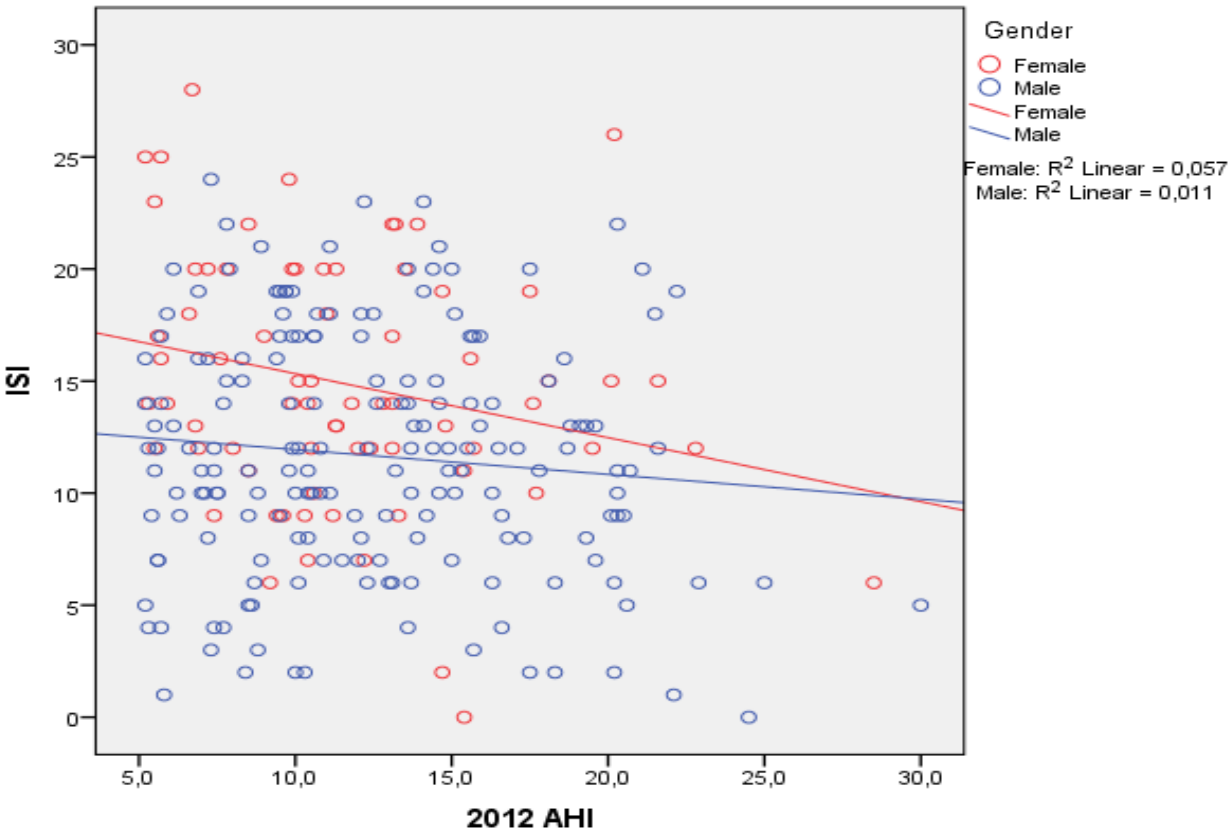

Figure 16: Correlations between ISI, AHI and gender

3.4. Discussion

Many more male patients were enrolled in the MERGE study than female patients (72% vs. 28%). Therefore, it appears true that more males are presenting to the clinics, even in this very mild group. Snoring was significantly more common in the male patients than females. It is possible that one reason female patients had worse symptoms is that their motivation for attending the sleep clinic was due to symptoms, whereas more males may have been referred due to snoring. The reasons for referral to sleep clinics were collected as part of the MERGE study (Appendix C). This will allow future analysis of the MERGE study data to describe any relationship between snoring as a reason for referral, and gender.

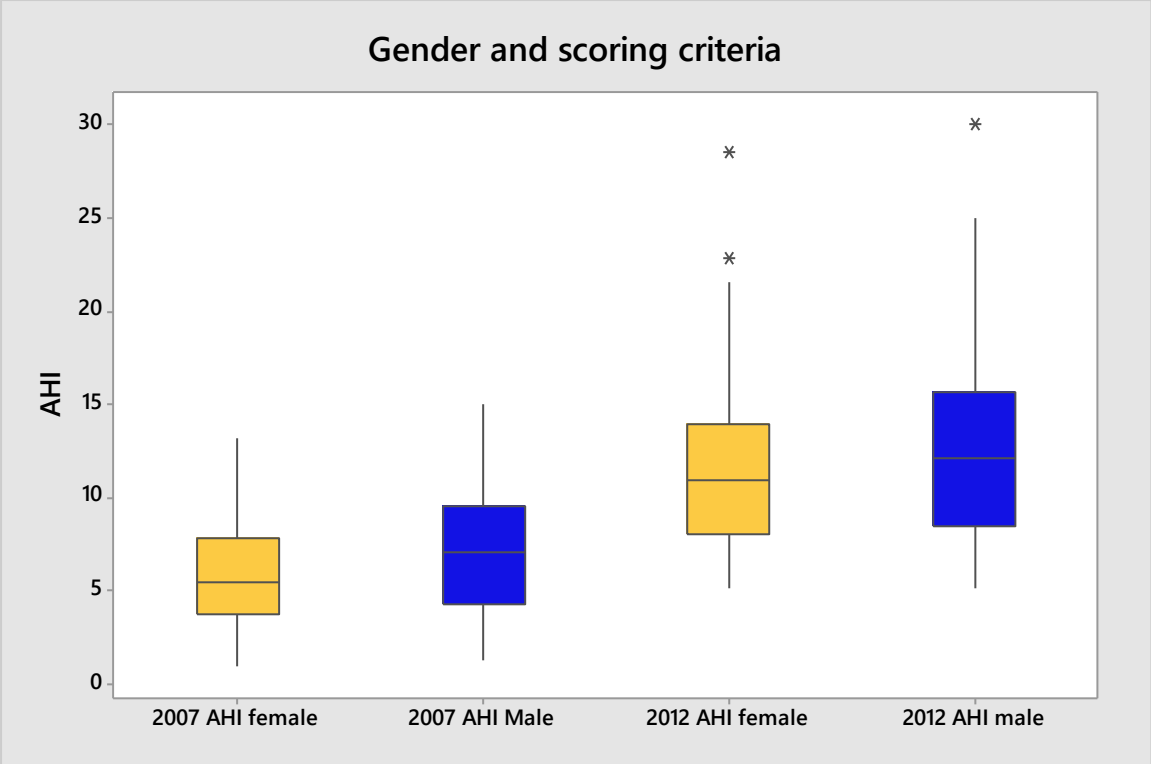

Figure 17: Gender and AASM scoring criteria

This data found that males do have more severe OSA (more events with 4% desaturation) than females, however the differences were much less clear when using AASM 2007 scoring (Figure 17). Changing the scoring criteria to AASM 2012 is more inclusive for females with OSA, as this allows for scoring of events with 3% desaturation, and also hypopneas terminated by arousals. The females did not have more of these types of hypopneas than the males; rather, they had a higher proportion of hypopneas terminated by arousal making up their AHI.

Interestingly, this data did not show that females have more flow limitation than males. This was a surprising finding as this is commonly stated in the literature (section 1.5.1). It is possible this finding is due to how flow limitation is measured in different studies. It is difficult to get a consensus on what qualifies as flow limitation from manual scoring and different algorithms. The quality of the signal obtained, along with recognition of flow shapes, can lead to inconsistency. This is a known issue in sleep medicine, and in response the American Thoracic Society (ATS) workshop "Non-Invasive Identification of Inspiratory Flow Limitation in Sleep Studies" aims to standardise the methodology of visually identifying flow limitation (202).

It is difficult to interpret the results correlating the patient symptoms and measures of SDB. Though some correlations were found, there was a wide scatter of data and no clear

conclusions can be drawn. The females, who were more symptomatic as a group, had more correlations, but the correlations were inverse. The higher the SDB measures, the less symptomatic the female patients were. In female patients, ESS was strongly correlated with age, with younger females much more likely to have high levels of daytime sleepiness. Female FSS scores were more strongly associated with BMI than AHI, whereas, in male patients increasing BMI was associated with worsening insomnia. Obesity, even without comorbid OSA, is associated with anxiety, depression and sleepiness (203). The underlying obesity in some of these participants may have a stronger impact on daytime symptoms than their OSA. The female patients, as a group, were more obese than the males, and were more symptomatic. In order to understand the different roles of obesity and OSA on daytime symptoms, treating the OSA in these patients and measuring any change in their BMI levels is important. The MERGE study (Appendix C) aims to do this, with results expected late 2019.

The literature comparing UARS to moderate and severe OSA patients has found that UARS patients are more symptomatic despite lower AHIs (section 1.4.6). In this data it was found that even within a mild patient population the less severe OSA patients had more symptoms. It was originally hypothesised in the introduction to this chapter that these symptoms may be correlated with other measures of SDB such as flow limitation, or hypopneas terminated by arousals, which appear more often in women. However, although some correlations did exist between measures of SDB and symptoms, the relationships were inverse. In this data there were no clear relationships between symptoms and sleep. Confounding factors such as age and BMI appear to have a large influence on symptoms. Additionally, there may be changes to symptoms over time, with patients becoming habituated to poor quality of life. Individual differences, including sensitivities to disrupted sleep and coping mechanisms, potentially play a large role and are difficult to quantify. It is also possible there are other SDB measures not collected during this study which correlate more strongly with symptoms.

One limitation of this patient data is that it was gathered using PG rather than PSG. PG studies are less accurate than PSG studies, as they cannot definitively measure states of sleep and wake. This means that PG studies tend to underestimate AHI. This is a well-known limitation of PG (204). As PGs are unable record to EEG waves, they cannot measure arousals from sleep, and therefore currently cannot identify hypopneas terminated by arousals. In the MERGE study a new PG algorithm was employed, which estimates arousals from surrogate measures such as pulse wave amplitude drops, respiratory changes and movement. The new algorithm has been shown to have high sensitivity and specificity

(92% and 80%) to rule in OSA at AHI ≥ 5, when compared with manual PSG scoring (201)(clinicaltrials.gov ID: NCT03470493). The benefits of PG studies are that they are simpler and more cost effective to use on large volumes of patients. Overall, studies suggest that home sleep testing is suitable for home diagnosis of OSA (204-206), and for the most part national sleep societies have recommended the use of PG studies for symptomatic patients at risk of moderate-to-severe OSA without other pathologies (207-209) (204, 210). However, the use of PG in mild patients has not been widely studied, and it is quite possible that AHI was underestimated in this study. Conversely, night-to-night variability in AHI is another known issue, which may have led to over-estimation of AHI in some of these patients (211). A single night study was used to facilitate a pragmatic trial design which is in line with majority of clinical pathways used in the diagnosis of OSA.

3.5. Conclusion

The gender differences in respiratory data described in the literature do still exist in this mild patient group; however, they are much less pronounced. When AASM 2012 scoring criteria is used, the gender differences in AHI are even less obvious. This indicates that women have less-severe oxygen desaturations, more flow limitation without snore, and more hypopneas terminated by arousals than men. There were some correlations between AHI, and flow limitation, and symptoms. These correlations primarily occurred in the female patient group and were inverse (higher SDB was correlated with lower symptom profile). Confounding factors including age, and BMI were also correlated with symptoms. High sleepiness was strongly correlated with age in younger patients. BMI was associated with increased FSS in female patients and increased ISI in male patients. No clear conclusions regarding symptoms and sleep measures could be drawn from this data. Future studies which investigate the changes in symptomology after application of OSA treatment will provide important insights into what level of symptoms can be attributed to OSA.

CHAPTER 4. DEVELOPMENT OF A FEMALE SPECIFIC AUTOSET DEVICE

4.1. Introduction

As described in Section 1.7, AutoSet devices have been developed for and validated with exclusively male patients. The aim of this chapter was to develop an AutoSet algorithm specifically for female patients.

The differences in PSG data between males and females with OSA is described in Section 1.5.1. In summary, females with OSA:

- Have more episodes of upper airway resistance (flow limitation), and RERAs (126)
- Have a higher occurrence of apneas during REM sleep (123)
- Require lower CPAP pressures (212)
- Have less severe OSA with lower apnea/ hypopnea index (AHI) (123)
- Have shorter apneas/ hypopneas (124)
- Take longer to fall asleep (125)

The new AutoSet (described in this document as AutoSet F, and commercially released as AutoSet for Her [ResMed, Sydney]), was designed to appropriately treat these characteristics of female OSA.

The AutoSet F algorithm was designed at ResMed. The first step in development was a thorough literature review to understand the differences in female and male OSA patients. As part of this review, detailed analysis of existing AutoSet algorithms was done to understand how they currently respond to female-specific breathing patterns. The next part of the algorithm development involved reviewing de-identified PSG files kept at ResMed from previous clinical trials to determine if the breathing patterns described in the literature could be quantified in PSGs from female patients compared with PSGs from male patients. Finally, in-house computer simulations were run to test various new algorithm learning and parameters in order to make final decisions about the behaviour of the algorithms. The following Sections describe the features of the algorithm and how they correspond to female-specific breathing patterns. Clinical trials validating the algorithm and involving patients are described in CHAPTER 5.

4.2. Development of a new female-specific algorithm

4.2.1. Modified Flow Limitation Response

Females have more upper airway resistance, flow limitation, and hypopneas terminated by arousal (126). Therefore, the AutoSet F has a more sensitive flow limitation response. The algorithm will calculate and respond to a single breath of flow limitation (as opposed to the 3 breath average used in the standard AutoSet algorithm). The purpose is to make it more responsive to flow limitation. This faster response allows the female patient's flow limitation to be treated more efficiently, hopefully leading to a reduction in associated arousals from sleep.

The algorithms' response to flow limitation, although faster, has a gentler and lower pressure increase overall (Figure 18). This is to ensure the pressure changes remain comfortable for female patients and the pressure doesn't increase too much or too quickly.

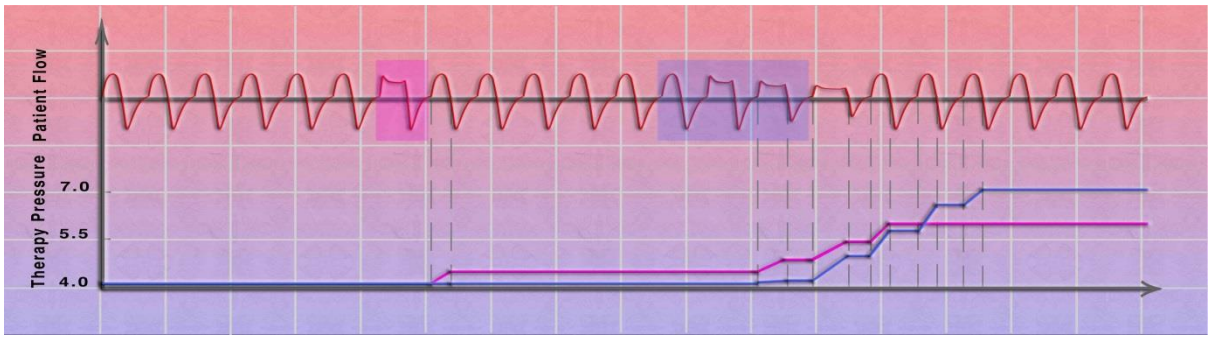

Figure 18: The AutoSet F response to flow limitation (pink), compared to the standard AutoSet response to flow limitation (blue).

4.2.2. Floor Pressure to protect against REM OSA

As it is common for females with OSA to exhibit clusters of events during REM sleep (123), the AutoSet F contains a floor pressure. The floor pressure works by calculating a minimum pressure at which obstructive apneas no longer occur. If the algorithm detects two obstructive apneas occurring within one minute, then the pressure reached in response to the second apnea will become the new floor pressure. For example, when the algorithm senses a run of apneas and the patient requires a pressure of 8cm H_2O to overcome the run of events, then for the remainder of the night the pressure will not drop below 8cm H_2O.The floor pressure is capped so it will never increase higher than 10cm H_2O. It is reset every time the device is stopped.

Figure 19 shows an example of a female patient with all her obstructive apneas occurring during REM sleep. If a standard AutoSet algorithm were used in this situation, the pressure would decay down to 4cm H20 during non-REM sleep when ventilation was stable. When the female patient requires higher pressure during REM sleep, the AutoSet may take some time to increase the pressure. During this pressure increase the patient may continue to have obstructive apneas. Once pressure is stable, REM sleep could be over, and the pressure would decay again before the next period of REM. In this case, the residual AHI could remain quite high.

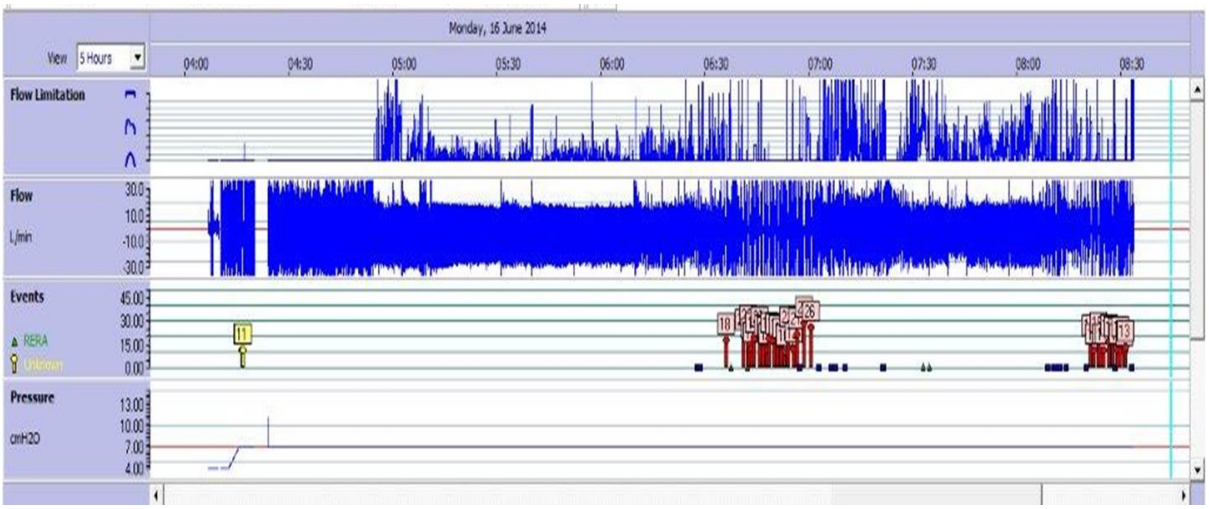

Figure 19: Female with obstructive events clustered during REM sleep

4.2.3. Lower Mean CPAP Pressures

Clinical trial data suggest that men require higher pressures during CPAP therapy than females, after adjusting for baseline OSA severity or BMI (168, 212, 213). To accommodate this, the AutoSet F algorithm has been designed to keep the CPAP pressure lower (and therefore more comfortable) while still adequately treating the majority of females. The maximum pressure that can be attained due to an obstructive apnea is 12cm H_2O. In the standard AutoSet, the pressure increases from closed airway apneas were permitted up to 20cm H_2O. The AutoSet F therapy pressure can still rise above 12cm H_2O for obstructions other than apneas (e.g. if the device detects flow limitation or snore). However, the algorithm includes logic to reduce the likelihood of reaching high pressures over short periods.

The majority of research on women with CPAP has demonstrated the requirement for pressures at an average of around 10cm H_2O (29, 212-214). The AutoSet F targets a pressure range of 8-12cm H_2O and actively slows pressure increases as delivered pressure gets higher than 12cm H_2O.

4.2.4. RERA Detection

Respiratory Effort-Related Arousals (RERAs), have been described in Section 1.2.1. When scoring with AASM 2012 criteria, the majority of RERAs are likely to be reclassified as hypopneas terminated by arousals (1).

Women tend to have short apneas and increased levels of flow limitation, and, as shown in CHAPTER 3, are more likely to arouse from sleep during a hypopnea rather than have continued lowering of their oxygen saturation. Therefore, the count of RERAs/hypopneas terminated by arousals is higher in female patients. An example of this event is shown in Figure 20.

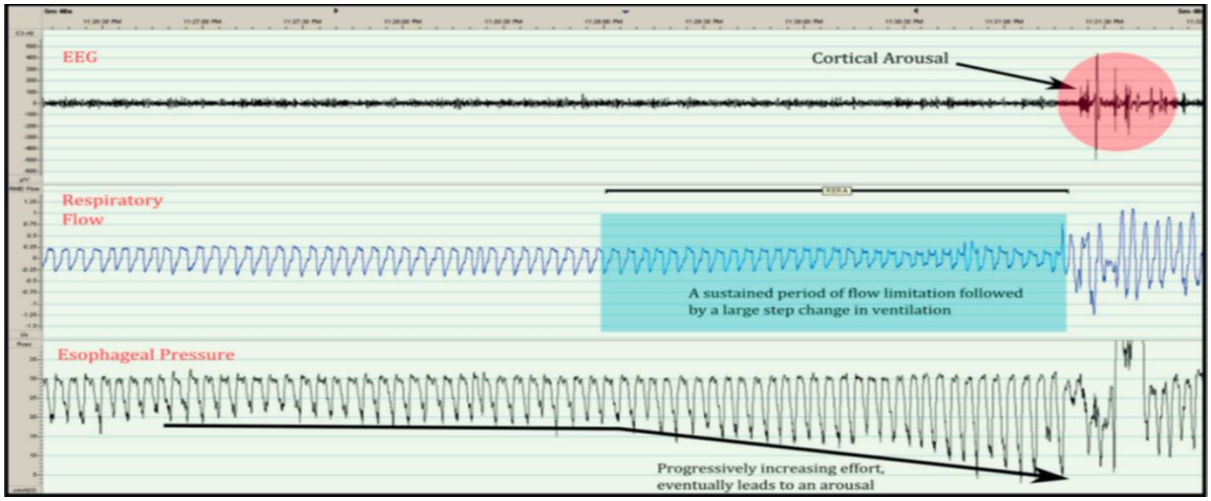

Figure 20: Example of a RERA (AASM 2007 scoring), or hypopnea with arousal (AASM 2012 scoring).

Device-scored AHIs are typically correlated with AASM 2007 scoring, and therefore do not include hypopneas terminated by arousals. To ensure that these events are still recognised, the algorithm detects and reports RERAs. RERA reporting is based on the following rules:

- A minimum of two flow-limited breaths (flat/m-shape) AND
- A reduction in the magnitude of these breaths.

The RERA algorithm calculates three quantities:

1. Flow limitation present in the three most recent breaths
2. Flattening and length of event does not meet the criteria for a hypopnea
3. Ventilation step change of at least 50%

If at least two breaths are flow-limited and a step change in ventilation of 50% from one breath to the next is identified, then a RERA is scored.

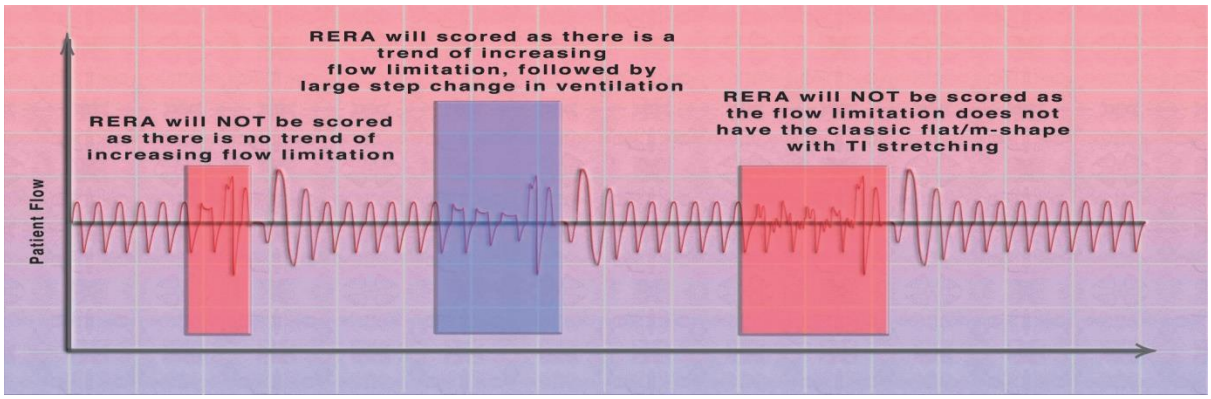

Figure 21: Example of how the RERA detection algorithm identifies RERAs and avoids false positives.

The purpose of the RERA index is to help physicians to review their patient's treatment and ensure they are not having residual events. Figure 22 shows an example of a RERA occurring (scored as per AASM 2007 rules). In this case, the patient may require a higher minimum CPAP pressure to prevent partial airway closure.

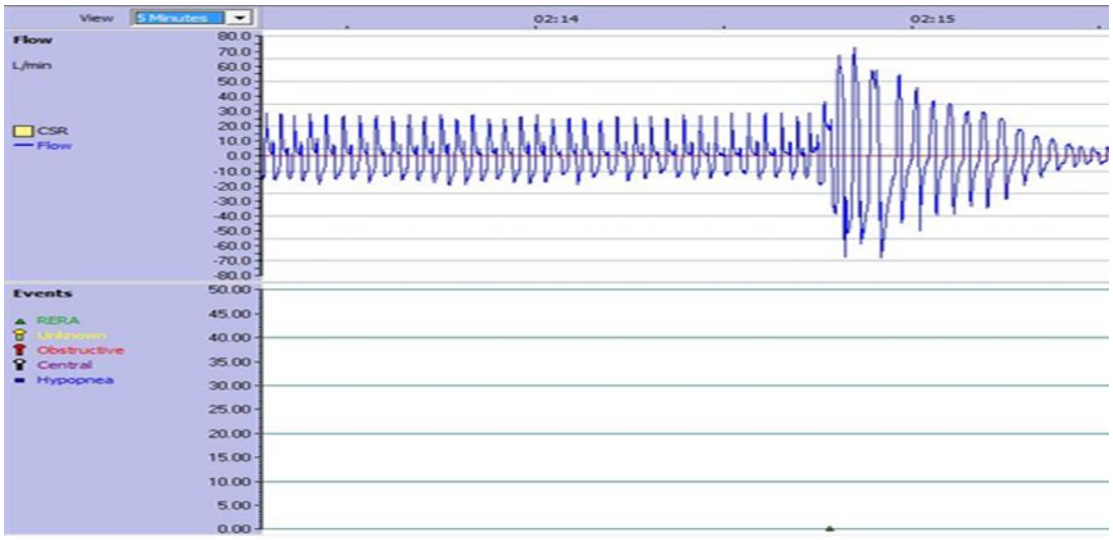

Figure 22: Example of a RERA from a CPAP download

4.2.5. Automatic Ramp

As women take longer, on average, to fall asleep than men (125), an automatic ramp has been introduced to the AutoSet F. Traditional ramp options work by starting at a minimum pressure and slowly increasing the pressure over a user-defined period of time until a suitable treatment pressure is reached. For example, a patient who uses a CPAP set to 10cm H_2O may find it difficult to fall asleep starting at 10cm H_2O. Therefore, they may set a ramp period starting at 4cm H_2O to increase to 10cm H_2O over a period of 30 minutes.

The automatic ramp (AutoRamp, ResMed) measures the patient's breathing and waits until sleep is established before increasing the pressure. Sleep onset is inferred via one of the following events:

- Presence of 3 obstructive apnea or hypopnea events within 2 minutes
- Presence of 5 consecutive snore breaths
- Detection of stable metronomic (consistent) breathing indicative of sleep (30 consecutive breaths which have similar breath durations, tidal volumes and peak flows). An example of this is available in Figure 23.

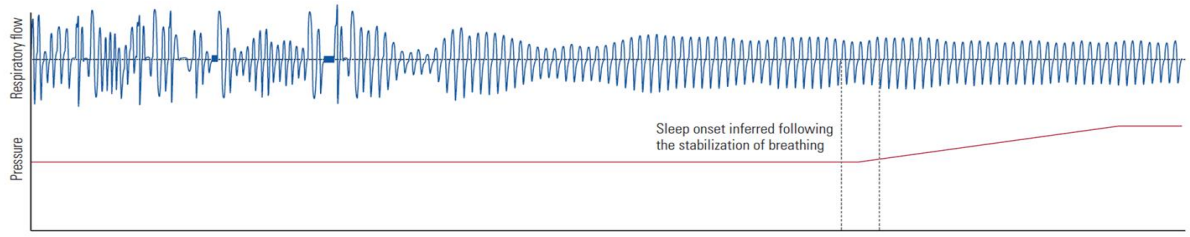

Figure 23: Automatic ramp activated after 30 consecutive breaths inferring sleep onset.

4.2.6. Gentle Pressure Adjustments

There are anecdotal reports that some women may be disturbed by the changes in pressure when using standard AutoSet. The AutoSet F contains several modifications which effectively result in a slower (and lower) pressure rise and decay when compared to the standard AutoSet algorithm. An example is provided in Figure 24.

The main changes from the standard AutoSet to the AutoSet F are:

- The level of pressure increase has been dropped by 0.5 for every pressure rise, and the maximum increment per breath has been capped at 0.5 cm H_2O.
- The flow limitation response has been de-weighted linearly from 1 at 10 cm H_2O to 0 at 20 cm H_2O. The higher the CPAP pressure goes, the less the AutoSet will increase in response to flow limitation.
- The decay period has been increased 60 minutes (from 20 minutes in the standard AutoSet). When stable breathing is detected the algorithm will slowly decrease the pressure to the minimum over 60 minutes.

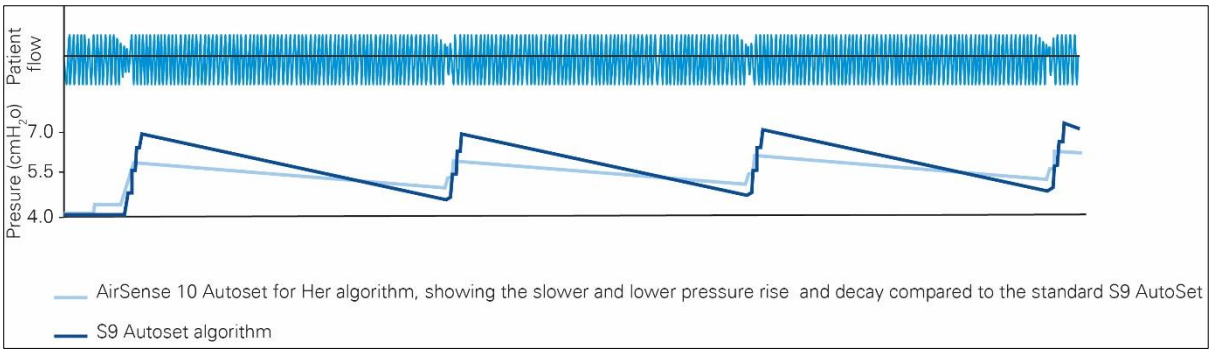

Figure 24: Example of the slower and more gentle female specific algorithm

4.3. Summary of new algorithm features

As demonstrated above, female-specific respiratory breathing patterns found in the literature have been used to for the development of a new AutoSet algorithm designed specfically for female patients.

Table 21: Summary of AutoSet F algorithm features

Parameter	New female-specific algorithm	Benefit to female patients
Females have lower AHIs with shorter apneas and less severe hypopneas	The algorithm reports a flow-based RERA measure	The RERA detector is a measure of events (RERAs and hypopneas terminated by arousals) which disturb the patient's breathing during their sleep. This allows the clinician to understand residual breathing issues and modify treatment.
Females have more upper airway resistance and flow limitation	A single-breath index is used to calculate and respond to the patients flow limitation (as opposed to the 3-breath average used in the standard AutoSet algorithm). Additional changes have also been made to the algorithm to make it more sensitive to flow limitation.	This change makes the AutoSet more responsive to flow limitation. The flow limitation is identified and the device responds quickly, avoiding long period of flow limitation or development into RERA or hypopnea.

Females have more REM-based events	The algorithm includes the addition of a closed airway apnea floor pressure.	The floor pressure protects females against a string of REM-based events by setting a minimum pressure based on the patients breathing each night.
Females take longer to fall asleep	A smart ramp has been introduced. The therapy pressure will remain low until sleep onset occurs.	The female patient can set a long ramp time (45 minutes) which will allow lower (more comfortable) pressure to be delivered while she falls asleep. The smart ramp means that if the female patient does fall asleep during this time the algorithm will identify and respond to obstructive events.
Females require lower CPAP pressures	The algorithm will increase the pressure to a maximum of 12cm H_2O when an obstructive apnea occurs. NOTE: The therapy pressure can still go above 12 cmH2O as a response to snore or flow limitation. However, the algorithm includes logic to reduce the likelihood of reaching high pressures over short periods.	As females require lower CPAP pressures than males, the new algorithm has been designed to keep the CPAP pressure lower (and therefore more comfortable) while avoiding large pressure increases.
Some females may be disturbed by the standard AutoSet changes in pressure	The pressure changes which occur in response to respiratory patterns have been programmed to be slower than those of a standard AutoSet.	The AutoSet F increases and decreases pressure at a slower rate than a standard AutoSet, aiming to increase comfort and decrease therapy-related disturbances during the night.

4.4. Use of the AutoSet F in male patients

When development was commenced on the AutoSet F, it was under the assumption that the literature pertaining to gender differences in OSA was accurate. That is to say that females with OSA have more flow limitation, more RERAs, more hypopneas terminated by arousals, lower AHIs, shorter events, less severe oxygen desaturations and require lower CPAP pressures. Further investigations in the areas of mild OSA and UARS indicated that the differences may not be as clearly defined as the literature first indicated. Findings from CHAPTER 2 support the notion that females are overall less severe, but shows that the differences are much less pronounced in the mild groups, with no gender differences found in the amount of flow limitation or hypopneas terminated by arousal.

Despite these findings, the development of the AutoSet F focused solely on female OSA patients. An important driver for this was the clinical experience of female patients described in Section 1.3.3. Females are less likely to be referred to sleep clinics, and may feel embarrassed to be diagnosed with what was historically considered a male disease. CHAPTER 3 shows that, even in very mild patients, females with OSA have significantly worse symptoms than males with OSA. It is hoped that, by developing and commercialising a device for female with OSA, awareness is increased and the stigma that some female patients may feel is reduced.

The AutoSet F is likely a suitable treatment for any patients with mild OSA dominated by flow limitation and RERAs, however exploring that area was outside the scope and purpose of the development of the AutoSet F.

CHAPTER 5. TESTING AND VALIDATION OF THE AUTOSET F

5.1. Introduction

As described in Section 1.5.1, female OSA patients have different breathing patterns from male patients. A new AutoSet algorithm was developed in order to optimally treat these differences to improve treatment for female patients. This chapter describes the methods for testing and validating that the AutoSet F was working as designed. The first validation activity was a clinical trial which evaluated efficacy, based on AHI and ODI, of the AutoSet F on 20 female patients. The second validation involved a bench test which was used to simulate the breathing of a standard female patient. The AutoSet F was evaluated on the bench test in order to review its performance on a standardised, repeatable test, compared with other AutoSet devices. Finally, the AutoSet F was commercially released in a controlled product launch where data was collected to ensure correct functioning and appropriate treatment of female OSA in uncontrolled conditions.

5.2. Clinical trial to evaluate the efficacy of the AutoSet F

5.2.1. Introduction

Following on from development of the new algorithm designed for female patients, a clinical trial was conducted to evaluate treatment efficacy of the AutoSet F in female patients.

5.2.2. Methods

The full methodology of this clinical trial is described in Appendix E.

This was a single-blind, randomised, crossover, non-inferiority study comparing the efficacy of the new AutoSet F algorithm to the standard AutoSet algorithm undertaken at two West Australian sleep disorders research institutes.

The study was approved by The University of Western Australia HREC (Approval No.: RA/4/1/5919) and by Sir Charles Gairdner HREC (Approval No.: 2013-042). All participants provided informed consent.

Female participants established on AutoSet treatment underwent consecutive polysomnography (PSG) studies in a randomised order where they received either the AutoSet F algorithm or the standard algorithm. At visit 1, baseline information was collected, including demographics and data from their diagnostic PSG. Following each treatment night, participants completed a questionnaire about the comfort of the device.

PSG data was scored by an expert independent scorer from six lead EEGs.

Primary Objective:

1) To evaluate the efficacy of the new algorithm (AutoSet F)
    - Comparison of AHI and ODI of new algorithm compared with a standard algorithm to demonstrate non-inferiority

Secondary Objectives:

1) To evaluate whether sleep parameters are improved using the new algorithm (AutoSet F) compared with the standard algorithm
2) To evaluate the patient's subjective feedback of the modified algorithm (AutoSet F) compared with the standard algorithm

5.2.3. Results

5.2.3.1. 5.2.3.1. Participant demographics

Twenty participants took part in the study. Table 22 displays participant demographics.

Table 22: Participant demographics

Participant Demographics and baseline characteristics	
Age *(n=20)*	44.85±5.02 years
Ethnicity *(n=20)*	Caucasian: 90% Aboriginal: 10%
Height *(n=20)*	164.51±6.04 cm
Weight *(n=20)*	104.02±20.45 kg

Diagnostic AHI *(n=20)*	19.08±8.69 events/hr
Mask Type *(n=20)*	Nasal Pillows: 35% Nasal: 55% Full Face: 15%
Chin Strap *(n=20)*	Yes: 15% No: 85%
Duration of PAP Therapy *(n=19)**	23.3±34.5 months; range 1-144 months

5.2.3.2. Comparison of treatment efficacy

No significant differences were found between participant AHI and ODI values when treated with the new algorithm compared to the standard AutoSet algorithm as shown by paired t-test (Table 23 and Table 24).

Table 23: AHI comparison

Efficacy Results – AHI (events/hr)					
	Valid N	**Mean**	**Std. Dev.**	**Min**	**Max**
Standard AutoSet	20	0.96	1.40	0.00	4.34
AutoSet F	20	0.91	0.90	0.00	2.84
	Valid N	**Difference in means**	**95% CI for mean diff**		**p-value**
Paired t-test analysis	20	0.05	(-0.562, 0.658)		0.870

Table 24: ODI comparison

Efficacy Results – ODI (desaturations≥3%/hr)					
	Valid N	**Mean**	**Std. Dev.**	**Min**	**Max**
Standard AutoSet	20	1.92	1.82	0.13	6.57
AutoSet F	20	2.19	2.15	0.12	6.70
	Valid N	**Difference in means***	**95% CI for mean diff**		**p-value**
Paired t-test analysis	20	-0.28	(-1.072, 0.521)		0.477

Further comparison analysis with patients' diagnostic AHI values shows a statistically and clinically significant reduction in AHI with treatment of either the standard AutoSet [diagnostic

vs. standard AutoSet (19.07 vs. 0.95; p=0.000)] or AutoSet F algorithms [diagnostic vs. AutoSet F (19.07 vs. 0.91; p=0.000)] (Table 25 and Figure 25).

Table 25: Comparison of untreated AHI vs. AutoSet F AHI

AHI Comparison Analysis (Untreated vs. Standard AutoSet vs. AutoSet F)					
	Valid N	**Mean**	**Std. Dev.**	**Min**	**Max**
Untreated	20	19.07	8.69	7.00	33.00
Standard AutoSet	20	0.96	1.40	0.00	4.34
AutoSet F	20	0.91	0.90	0.00	2.84
Paired t-test analysis	**Valid N**	**Difference in means**	**95% CI for mean diff**		**p-value**
Untreated vs. Standard AutoSet	20	18.12	(14.01, 22.24)		0.000
Untreated vs. AutoSet F	20	18.17	(14.19, 22.14)		0.000

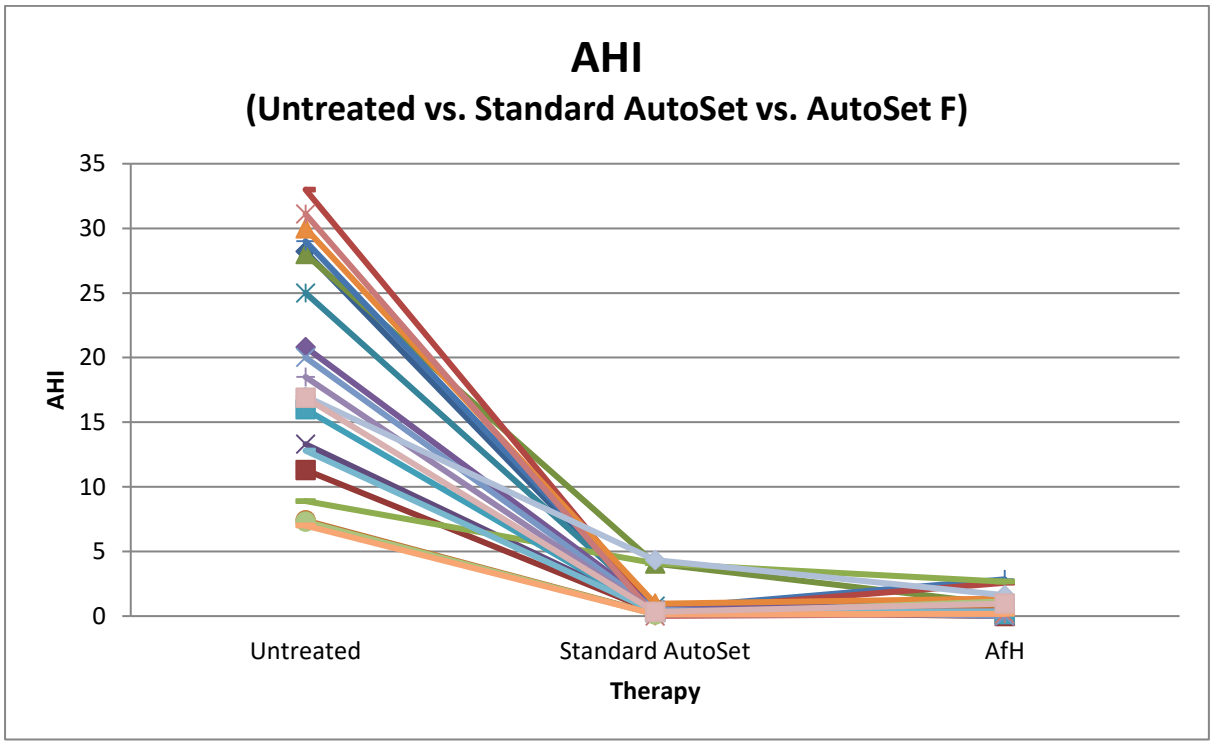

Figure 25: Individual patient AHI comparison (Diagnostic vs. standard AutoSet vs. AfH (AutoSet F algorithm)).

5.2.3.3. Comparison of sleep parameters

When comparing the sleep parameters, the data shows that flow limitation (% of breaths) was significantly lower when participants were treated with the new algorithm compared with the standard AutoSet algorithm (0.14% vs. 0.20%; p=0.003) as shown by paired t-test (Table 26). No other significant differences were found between sleep parameters.

Table 26. Comparison of sleep parameters

Sleep Parameter Results						
	Therapy	**Valid N**	**Mean**	**Std. Dev.**	**95% CI for mean diff**	**p-value**
Sleep Efficacy (%)	**Standard AutoSet**	20	85.99	8.55	(-2.92, 6.62)	0.427
	AutoSet F	20	84.14	9.62		
Wake after Sleep Onset (mins)	**Standard AutoSet**	20	47.52	34.57	(-29.72, 9.92)	0.309
	AutoSet F	20	57.42	43.31		
Sleep Latency (mins)	**Standard AutoSet**	20	16.52	19.58	(-8.84, 9.39)	0.950
	AutoSet F	20	16.25	12.70		
# of Spontaneous Arousals	**Standard AutoSet**	20	85.55	40.88	(-12.30, 20.60)	0.604
	AutoSet F	20	81.40	33.91		
# of RERAs	**Standard AutoSet**	20	2.60	3.32	(-0.249, 2.849)	0.095
	AutoSet F	20	1.30	1.84		
Flow Limitation (% of breaths)	**Standard AutoSet**	20	0.20	0.13	(0.0217, 0.0937)	**0.003**
	AutoSet F	20	0.14	0.09		
# of Hypopneas	**Standard AutoSet**	20	1.45	2.33	(-2.455, 1.355)	0.553
	AutoSet F	20	2.00	3.42		
# of Obstructive Apneas	**Standard AutoSet**	20	1.30	4.44	(-1.030, 2.030)	0.502
	AutoSet F	20	0.80	1.36		
# of Central Apneas	**Standard AutoSet**	20	3.55	7.45	(-1.94, 3.04)	0.649
	AutoSet F	20	3.00	3.78		
	Standard AutoSet	20	96.56	0.78	(-0.064, 0.551)	0.114

Mean SpO_2 (%)	**AutoSet F**	20	96.31	0.81		
Time in S1 Sleep (%)	**Standard AutoSet**	20	6.05	4.63	(-2.40, 2.11)	0.894
	AutoSet F	20	6.20	3.33		
Time in S2 Sleep (%)	**Standard AutoSet**	20	51.28	12.91	(-4.12, 7.81)	0.525
	AutoSet F	20	49.44	12.01		
Time in S3 Sleep (%)	**Standard AutoSet**	20	24.83	11.58	(-3.32, 3.76)	0.898
	AutoSet F	20	24.60	10.77		
Time in REM Sleep (%)	**Standard AutoSet**	20	17.93	11.05	(-7.07, 3.38)	0.469
	AutoSet F	20	19.77	7.54		

5.2.3.4. Comparison of device data

The mean, median and 95th percentile pressures required to treat OSA in this female population was less with the AutoSet F algorithm compared with the standard AutoSet algorithm, although this did not reach statistical significance (Table 27 and Figure 26).

Table 27: Comparison of device pressure

Pressure Comparison (Standard AutoSet vs. AutoSet F)						
	Valid N	**Mean**	**Median**	**95th %ile**	**IQR**	**Kurtosis**
Standard AutoSet	20	8.34	8.31	11.63	2.48	4.38
AutoSet F	20	7.89	7.94	10.56	2.35	4.99
	Valid N	**Difference in means**	**95% CI for mean diff**		**p-value**	**Kurtosis p-value**
Paired t-test analysis	20	0.45	(-0.977, 0.077)		0.089	0.68

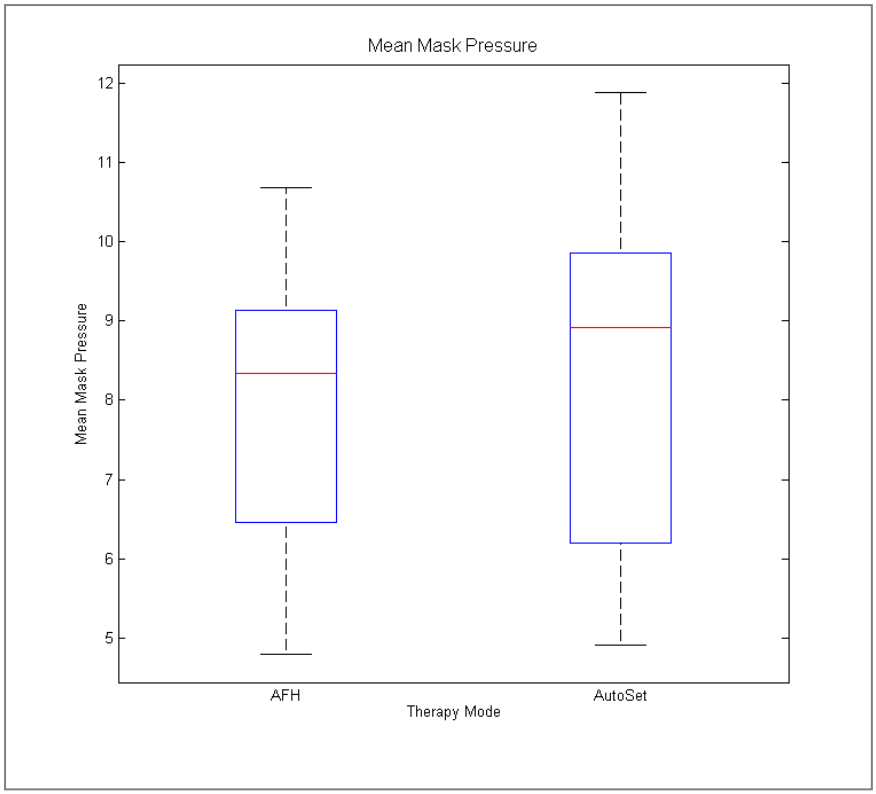

Figure 26: Mean mask pressure of AutoSet F (AutoSet F) and standard AutoSet

Participants were asked to rate breathing comfort, ease of falling asleep, sleep disturbance caused by CPAP, and feeling of being refreshed, after using the standard AutoSet device and after using the AutoSet F using an 11 point Likert scale. One participant did not complete the questionnaires. No significant differences were found between the subjective ratings for both devices as shown by Mann-Whitney statistical analysis (Table 28).

Table 28: Comparison of patients subjective ratings

Patient Subjective Ratings							
	Valid N	**Mean**	**Std. Dev.**	**Min**	**Max**	**Median**	**p-value**
Standard AutoSet comfort of breathing	19	8.21	1.32	6.0	10.0	8.0	0.9405
AutoSet F comfort of breathing	19	8.05	1.78	4.0	10.0	8.0	
Standard AutoSet ease of falling asleep	19	7.84	1.77	4.0	10.0	8.0	0.5117
AutoSet F ease of falling asleep	19	7.26	2.05	2.0	10.0	8.0	
Standard AutoSet sleep disturbance	19	8.26	1.70	4.0	10.0	9.0	0.1171
AutoSet F sleep disturbance	19	7.47	1.71	4.0	10.0	8.0	

Standard AutoSet feeling of being refreshed	19	7.63	1.61	5.0	10.0	8.0	0.0582
AutoSet F feeling of being refreshed	19	6.32	2.24	2.0	10.0	7.0	

5.2.3.5. Technical functioning of the AutoSet F algorithm

The technical aspects of the new algorithm, including RERA-detection, slower and softer increasing and decreasing pressures, increased sensitivity and responsiveness to flow limitation, floor pressure and automatic ramp, were all monitored during the clinical study and found to be working as expected.

RERAs scored by the AutoSet F algorithm were compared with RERAs scored by a blinded PSG scorer. This data was compared using the Wilcoxon Signed Rank non-parametric test. Analysis, comparing human (0.21 ± 0.3) and algorithm (0.22 ± 0.27) scoring showed no significant difference in the outcome, based upon the scoring method used (p = 0.87). The results gave a P-value of 0.87, which indicates that the RERAs scored by human and those scored by the AutoSet F are not statistically different.

Table 29: Validation of RERA Index

Parameter	Score
P-Val (2-tail)	0.87
W-Score	-7
Z-Score	-0.163314

Figure 27 shows the algorithm-scored RERA index plotted against the human-scored RERA index.

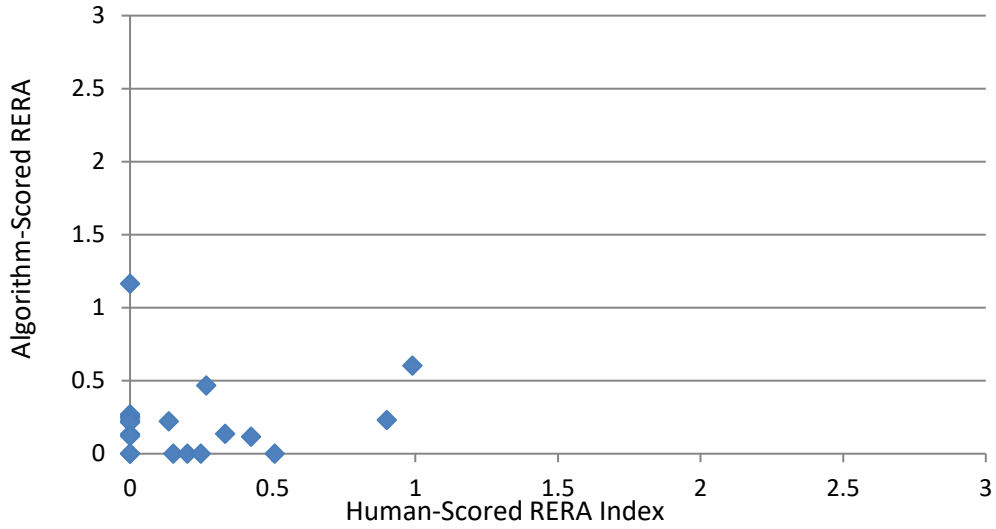

Figure 27: RERA algorithm plotted against manually scored RERA data.

5.2.4. Discussion

This clinical trial has shown that there are no significant differences in AHI or ODI when female patients are treated with the AutoSet F algorithm, compared with the standard AutoSet algorithm, demonstrating that the two algorithms are equivalently efficacious in the treatment of OSA.

The clinical benefit of this data is that the AutoSet F algorithm, like the standard AutoSet algorithm, effectively treats OSA in female patients, with a residual mean AHI <5/hr shown for both algorithms. Further comparison analysis with patients' diagnostic AHI values shows a statistically and clinically significant reduction in AHI with treatment of either the AutoSet F or Standard AutoSet.

Analysis of sleep parameters also showed a significant decrease in flow limitation (percentage of breaths) with the AutoSet F algorithm compared with the standard AutoSet algorithm. As females with OSA tend to exhibit greater amounts of flow limitation and upper airway resistance (159), the AutoSet F algorithm was designed to be more responsive to flow limitation than the standard AutoSet algorithm. A significant reduction in flow-limited breaths when patients were treated with the AutoSet F algorithm, compared with the standard AutoSet algorithm, suggests that female OSA patients are being treated more effectively with the AutoSet F algorithm.

Whilst no other statistically significant beneficial differences were seen in sleep parameters between the AutoSet F and standard AutoSet algorithms, non-statistical improvements were noted in the number of RERAs that occurred (1.30 vs. 2.60; p= 0.095) and the percentage of REM sleep (19.77 vs. 17.93; p=0.469) with the AutoSet F algorithm. Due to female OSA patients frequently exhibiting more REM-based apnoeic events(123), the standard AutoSet algorithm may decay below the critical airway pressure during REM sleep. To counter this, the AutoSet F algorithm contains a floor pressure (i.e. a set minimum the pressure decays toward during periods absent of respiratory events). This reduces the likelihood of obstructive events occurring due to insufficient pressure, which has the potential to increase periods of consolidated sleep (in particular during REM sleep). As such, the observed reduction in respiratory arousals and increased REM sleep is suggestive of more efficacious treatment of OSA in females with the AutoSet F algorithm, compared with the standard AutoSet algorithm.

Whilst not statistically significant, the mean, median and 95th percentile pressure required to effectively treat OSA in this population was less with the AutoSet F algorithm compared with the standard AutoSet algorithm. This suggests that while both algorithms effectively treat OSA in female patients, the AutoSet F algorithm does so whilst utilising lower pressures, which may be attributed to the AutoSet F algorithm's design of limiting pressure increases with a slower and more gentle response to obstruction. As research demonstrates that female OSA patients require less pressure than males (215), the AutoSet F algorithm may provide the benefit of increasing comfort of therapy by using a lower but still efficacious pressure response.

Participant subjective feedback revealed no significant differences in regards to self-reported comfort of breathing, ease of falling asleep, sleep disturbance, and feeling of being refreshed between the AutoSet F and standard AutoSet algorithms. Median subjective ratings for all outcomes for both algorithms ranged from 7.0 to 9.0 on an 11-point Likert scale (10=good; 5=OK; 0=poor) indicating that both algorithms were rated above average for all subjective outcomes.

5.2.5. Conclusion

This trial showed that the AutoSet F algorithm was non-inferior to the standard AutoSet algorithm, with both algorithms effectively reducing AHI and ODI in female patients. The AutoSet F algorithm reached a lower mean pressure than the standard AutoSet algorithm. Investigation of respiratory parameters showed that flow limitation was significantly decreased with the AutoSet F algorithm compared to the standard AutoSet algorithm. There were trends towards improvements in REM sleep percentage and RERAs. Taken together,

this data shows that the AutoSet F is able to effectively treat OSA in women, and may be a more suitable treatment option than a standard AutoSet.

5.3. Bench Testing of the AutoSet F

5.3.1. Introduction

The clinical trial outlined above demonstrated the efficacy of the AutoSet F in female patients. The next assessment of the AutoSet F was how it reacted on a controlled, repeatable model compared to other commercially available AutoSet devices.

Professor Ramon Farré and colleagues at Barcelona University have developed a simulation patient bench model to test various AutoSet devices for their capability at treating OSA (216, 217). Professor Farré was approached and asked to collaborate on the development of a new bench test designed to replicate a female OSA patient. The new model was then used for testing of the AutoSet F along with other AutoSet devices.

5.3.2. Methods

The original bench test model created by Farré and colleagues is described in detail in Rigau *et al.* (216), and Appendix F. The model (Figure 28) consists of one generator of breathing (flow generator) controlled by a computer. The flow generator can reproduce either pre-designed flows, or it can reproduce the respiratory flow of a patient recorded during PSG. The model contains an obstruction valve, which introduce central or obstructive events. There are two additional valves, which allow for the simulation of mask leaks and mouth breathing. A loudspeaker provides vibrations to simulate snoring. The computer is able to control each of these elements. Standard tubing links a commercial CPAP device to the bench test. The response from the AutoSet algorithm is picked up by two sensors in the model, one pressure sensor and one flow sensor. The response from the CPAP is fed back into the computer which is then able to adjust the output accordingly.

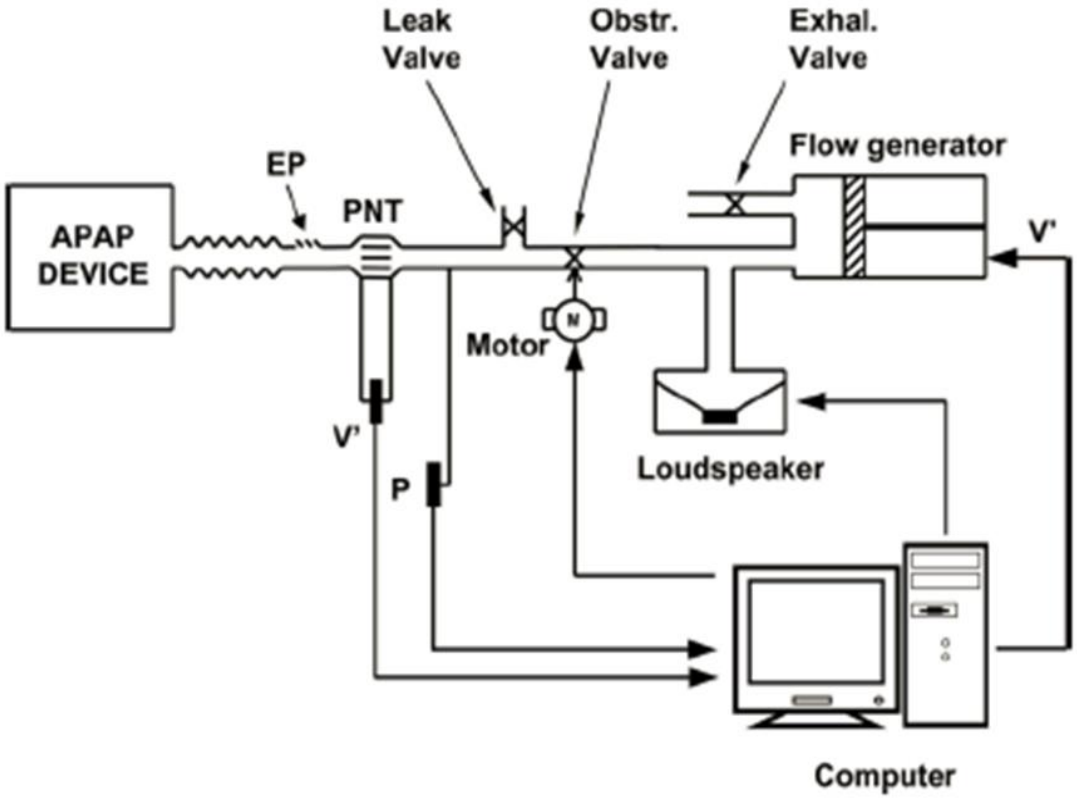

Figure 28: Diagram of the bench test model
PNT = pneumotachograph; EP = exhalation port; Obstr. = obstructive; Exhal. = exhalation V = flow; m = motor; p = pressure. Image reproduced from Rigau *et al*., 2006 (216) with permission.

The original patient model used to create breathing flow in these bench tests was developed from typical male OSA patients. The simulated bench model is programmed to have obstructive apneas when the AutoSet pressure is between 0-5cm H_2O. As the AutoSet algorithm increases the pressure to 5-7cm H_2O, the obstructive apneas on the bench model develop into hypopneas. As the pressure is increased towards 10 cm H_2O, the hypopneas are overcome and prolonged flow limitation remains. The AutoSet needs to reach a pressure of at least 12 cm H_2O for normal breathing to resume (Figure 29).

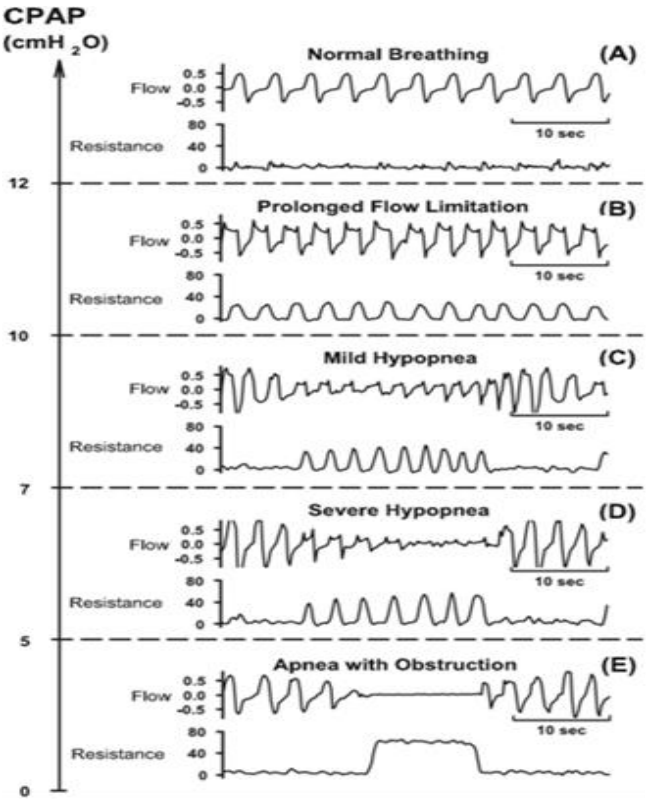

Figure 29: Typical Male patient model and the required CPAP pressure needed to overcome obstructive breathing
Image reproduced with permission from Rigau *et al*., 2006 with permission (216)(216)(215)(201).

Professor Farre and colleagues developed an updated patient model based on characteristics of female OSA patients described in Section 1.5.1. Compared with the male patient model, the new female patient model had:

- **Lower AHI**: less frequent events for each pressure range
- **More episodes of flow limitation**: the pressure range in which prolonged flow limitation is reproduced was extended
- **Longer sleep onset**: 30 minutes of normal breathing before sleep onset
- **Lower CPAP pressures required**: pressure ranges were rescaled and normal breathing was achieved with pressures of 10cm H_2O.

The flow and obstructive breathing events used in the bench testing were extracted from several PSG recordings of typical female OSA patients. Period of sleep and wake, sleep onset, body position, and REM were added to the bench model to create a realistic night of sleep (Figure 30).

Stage	Duration	AHI	Features
Sleep onset	45 min	-	
			16 breaths/min
			V_T 500 mL
			Random insertion of changes in breathing rate and V_T, and swallowing
Non-REM cycle 1	60 min	15/h	
			Body position: side
			Apneas (0–5 cmH_2O): event length 12 sec
			Hypopneas (5–7 cmH_2O): event length 16 sec
			Flow limitation (7–9 cmH_2O)
			Normal breathing (>9 cmH_2O)
REM cycle 1	15 min	30/h	
			Apneas (0–8 cmH_2O): event length 18 sec
			Hypopneas (8–10 cmH_2O): event length 16 sec
			Flow limitation (10–12 cmH_2O)
			Normal breathing (>12 cmH_2O)
Non-REM cycle 2	45 min	15/h	
			Body position: side
			Apneas (0–5 cmH_2O): event length 12 sec
			Hypopneas (5–7 cmH_2O): event length 16 sec
			Flow limitation (7–10 cmH_2O)
			Normal breathing (>10 cmH_2O)
REM cycle 2	25 min	30/h	
			Apneas (0–7 cmH_2O): event length 18 sec
			Hypopneas (7–9 cmH_2O): event length 16 sec
			Flow limitation (9–11 cmH_2O)
			Normal breathing (>11 cmH_2O)
Non-REM cycle 3	30 min	15/h	
			Apneas (0–5 cmH_2O): event length 18 sec
			Hypopneas (5–7 cmH_2O): event length 16 sec
			Flow limitation (7–10 cmH_2O)
			Normal breathing (>10 cmH_2O)
REM cycle 3	30 min	30/h	
			Body position: supine
			Apneas (0–9 cmH_2O): event length 18 sec
			Hypopneas (9–11 cmH_2O): event length 16 sec
			Flow limitation (11–13 cmH_2O)
			Normal breathing (>13 cmH_2O)
Awake	5 min	-	Normal breathing

AHI: apnea-hypopnea index; REM: rapid eye movement; V_T: tidal volume.

Figure 30: Description of the patient simulation implemented in the bench test model
Image reproduced from Isetta *et al*., 2016 (218) with permission.

The simulator would create breathing events at each pressure until the AutoSet device increased the pressure to overcome the events. The bench test patient model was tested using ten different AutoSet devices. Devices were all set to default AutoSet mode (minimum pressure 4cm H_2O, maximum pressure 20cm H_2O), and all devices were set to a starting pressure of 4cm H_2O. In order to standardise the testing, optional comfort features such as expiratory pressure relief (EPR), humidification, ramp, and any additional optional settings were turned off. Each device was tested twice, with the tests running for 4 hours and 15 minutes each. The average of the two tests was taken as the result.

5.3.3. Results

The results of the bench testing are shown in Figure 31. The AutoSet F is Device B. Only devices A, B and D were able to overcome obstructive events and overcome flow limitation, although the residual flow limitation in device D was 12% of sleep time compared with 2% of sleep time for the AutoSet F.

Device	P_{max}, cmH_2O	P_{mean}, cmH_2O	Residual AHI, /h	Overcome obstructive events?	Overcome flow limitation?	Residual flow limitation, min (% sleep time)
A	18.65	13.25	0.7	Yes	Yes	4 (2%)
B	15.4	11.8	0.7	Yes	Yes	4 (2%)
C	11.4	6.75	16.5	No	No	24 (12%)
D	15.3	11.3	0.6	Yes	Yes	24.5 (12%)
E	11.35	7.7	11.9	No	No	81 (40%)
F	12.6	9.5	2.4	Yes	No	167 (81%)
G	12.1	10.05	1.6	Yes	No	122 (60%)
H	12.45	7.75	10	No	No	76 (37%)
I	10.6	8.3	6.5	Yes	No	142 (69%)
J	10.1	8.2	8.5	No	No	132.5 (65%)

AHI: apnea-hypopnea index; P_{max}: maximum positive airway pressure applied; P_{mean}: mean positive airway pressure; A: AirSense 10 by ResMed; B: AirSense 10 AutoSet for Her by ResMed; C: Dreamstar by Sefam; D: Icon by Fisher & Paykel; E: Resmart by BMC; F: Somnobalance by Weinmann; G: Prisma 20A by Weinmann; H: System One by Respironics; I: iCH by Apex; J: XT-Auto by Apex.

Figure 31: Responses of AutoSet devices to the female OSA patient bench model.
Image reproduced from Isetta *et al*., 2016 (218) with permission.

5.3.4. Discussion

AutoSet devices are often considered a ‘black box’, with their inner workings and decision-making quite difficult to interpret (219). Comparing AutoSet devices is difficult as there is always night-to-night variability in patient breathing. A small number of studies have examined the technical functioning of AutoSet devices and found clinically important differences in each algorithm’s ability to treat OSA, and in patient compliance (220-222). The benefits of bench-testing compared to patient studies is that they allow review of algorithm functioning under a controlled environment. Individual patient differences are

removed, so the pure functioning of the algorithm can be examined. This allows comparison of different devices under the same conditions to better understand differences in how algorithms treat the same breathing patterns.

In this bench test, we found significant differences in the way the AutoSet algorithms responded to the female breathing patterns. There was a high residual AHI (AHI > 5) at the end of the test from four of the devices. It is concerning that four commercially available devices were not able to reduce the residual AHI. A patient using these devices may only be partially treated and still experience daytime symptoms and longer-term health consequences.

Only three of the devices were able to achieve full breathing normalisation, with prolonged flow limitation being an issue for seven devices. Considering the frequency with which flow limitation occurs in female patients, and the concern that it leads to RERAs, arousals and disruption from sleep, the ability of the AutoSet to treat flow limitation is something that clinicians should examine closely when reviewing the effectiveness of their patient's treatment.

Meurice *et al.* conducted an experiment in which two groups of patients diagnosed with OSA were treated with different CPAP pressures. Group 1 was treated with CPAP pressures targeted to eliminate flow limitation, while Group 2 was titrated with pressures to overcome apneas, hypopneas and snoring. Group 1 pressures were higher on average. This group had an increase in sleep time and more consistent improvement in maintenance of wakefulness. These results suggest that normalizing flow limitation, although frequently overlooked, may be a key part of effectively treating SDB (223).

5.3.5. Conclusion

The new bench test model provided a controlled, repeatable method of comparing different AutoSet devices and their treatment responses to female breathing patterns.

The bench testing shows that the AutoSet F was able to overcome all obstructive events and flow limitation while keeping the pressure low, and that some commercially available devices may not provide optimal treatment for female patients.

5.4. Controlled product launch

5.4.1. Introduction

During the development of the AutoSet F, a clinical trial and bench testing (described above) were used to validate that the algorithm was functioning as intended and able to efficiently treat OSA. At the time of releasing the AutoSet F for commercial use, ResMed conducted a controlled product launch (CPL). During a CPL the devices are heavily controlled and monitored. The AutoSet F was provided to a selected number of clinics, and data was collected nightly to ensure correct functioning.

5.4.2. Methods

Devices were dispensed by multiple sleep clinics in Germany and France to patients diagnosed with OSA who qualified for CPAP treatment. Data was collected from devices used on female patients participating in the CPL. The device records de-identified information each time it is used, including usage, mask leak, AHI, and pressure. This information is stored on SD cards within the device, which were returned to ResMed on a regular basis during the CPL.

The technical features of the algorithm were monitored to ensure they were working as intended. The data was also reviewed to check whether assumptions made during algorithm development were appropriate for treating female patients.

5.4.3. Results

De-identified device functioning information was collected from 163 devices, over 2272 nights of use. Average daily usage was 5.9 hours per night. Residual AHI was 2.61 events per hour. The average 95th percentile pressure was 8.76cm H_2O.

The average number of RERAs for those patients prone to RERAs was 0.63 events/ hour (Table 30, Figure 32).

Table 30: Activation of RERA index in female patients

Parameter	RERA Average	SD
All AutoSet F patients	0.30	0.63

AutoSet F patients with at least one RERA during the night	0.63	0.79

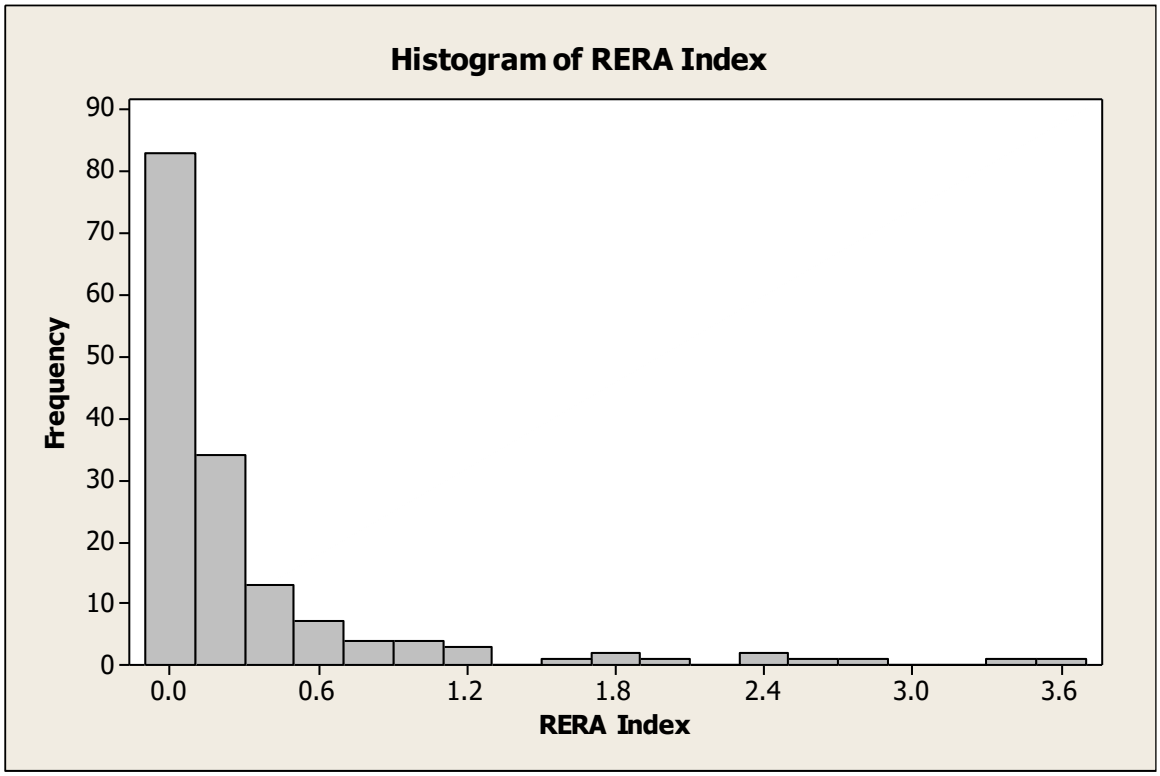

Figure 32: Histogram of RERA Indexes occurring in female patients

In this CPL data, the floor pressure had been activated in 50/401 (13%) sessions monitored (Table 31). Each session where the floor pressure had been activated was examined in more detail for further strings of apneas. No additional strings of apneas were found.

Table 31: Review of floor pressure use in female patients

Total sessions	Number of sessions when floor pressure was triggered	Average floor pressure (cmH_2O)	Median floor pressure (cmH_2O)
401	50	9.6576	10

In the 2272 data sessions available from the CPL, the pressure cap was activated in only four cases.

All devices were found to be functioning as intended during the CPL, with no software bugs, unexplained algorithm behaviour, or missing data reported.

5.4.4. Discussion

Average daily usage was high, at 5.9 hours per night. Residual AHI was 2.61 events per hour, well below what is considered efficacious (<5). This efficacy was achieved with a group average 95th percentile pressure of 8.76cm H_2O.

The RERA index was used to alert the clinician of disrupted breathing during treatment. Almost half (45%) of AutoSet F sessions had at least one RERA during the night This shows that respiratory events with flow limitation leading to disruption from sleep are common in female patients. The residual RERA index remained low, at 0.63 events/ hour, demonstrating that the algorithm was effectively able to treat the flow limitation and avoid large RERA indexes.

The floor pressure in the AutoSet F was designed to protect patients against strings of REM-related events. The floor pressure was activated in 13% of cases. After each initial activation, no more strings of obstructive events occurred during the session, demonstrating that the floor pressure was working as intended to prevent untreated OSA during subsequent REM phases.

The pressure cap was designed to keep the average pressures lower and more comfortable for female patients. Clinical trial data shows that women rarely require pressures above 12cm H_2O (168). The pressure cap was only activated in 4 of the 2272 data sessions recorded. An examination of those cases confirmed that obstructive apneas were still occurring above 12cm H_2O. This confirms that majority of female patients do not need high CPAP pressures, although a very small proportion of female patients will continue to have obstructive apneas at or above 12cm H_2O. The AutoSet F was designed to provide lower and more gentle pressures by removing any response to obstructive apneas above 12cm H_2O. The algorithm still responds to flow limitation and snore at these pressures, however the response is much more gentle with less pressure increases. For the patients who did require pressures above 12cm H_2O, the algorithm increased the pressure and overcame obstructive events; however, this was done in response to flow limitation and snore, which resulted in a slower and more gentle pressure increase.

The limitations of a CPL are that almost no demographic data is available on participants. This is the reality of a CPL compared with a clinical study. The benefits of a CPL compared with bench testing and clinical studies is that a CPL allows testing of the device in uncontrolled conditions. In a clinical trial, participants are carefully selected based on

inclusion and exclusion criteria. The participants' medical history and comorbidities are known, and further investigations can be done if a device does not respond as expected. During a CPL, no information is available on users of the device. This allows the device to be challenged in a range of situations. The CPL also allows for assumptions made during the development of the algorithm to be tested in real-world conditions.

5.4.1. Conclusion

Data collected during the CPL showed that all technical aspects of the device were working as intended, and that the design of the algorithm was appropriate for treatment of female OSA patients. This data show that, in uncontrolled, real-world conditions, the AutoSet F is effective for treating female OSA.

CHAPTER 6. EVALUATION OF QUALITY OF LIFE IN FEMALE PATIENTS USING THE AUTOSET F

Note: This thesis chapter is a direct copy of the manuscript sent for consideration to Sleep and Breathing Journal in April 2019

Improvements in quality of life in female OSA patients using a gender specific APAP device

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Abstract

Purpose Females with obstructive sleep apnea (OSA) have more flow limitation, lower apnea-hypopnea index (AHI), shorter apneas, and less severe oxygen desaturations than males. A female-specific auto-adjusting continuous positive airway pressure (fAPAP) algorithm has been developed to target these characteristics. This study investigated the effects of fAPAP therapy on quality of life (QoL) in women with OSA.

Methods Female patients with AHI ≥15/h were eligible. Participants underwent polygraphy or polysomnography. The primary endpoint was change from baseline in Functional Outcomes of Sleep Questionnaire (FOSQ) score after 3 months' fAPAP (AutoSet for Her, ResMed). Secondary endpoints included other sleep-related and QoL questionnaires.

Results A total of 122 patients were enrolled in the study (age 53.7±9.5 years, body mass index 32.8±6.2 kg/m^2, apnea-hypopnea index [AHI] 39.0±18.2/h); 111/122 completed the study. There was a significant improvement ($p<0.0001$) in FOSQ score from baseline (15.0±3.3) to 3 months (16.9±3.2). Significant improvements were also seen in the Patient Health Questionnaire-9 score (12.3±6.0 vs. 7.2±5.4), Epworth Sleepiness Scale score (10.8±4.9 vs. 7.3±4.7), EuroQol (EQ)-5D Index score (0.636±0.248 vs. 0.763±0.210), EQ-5D visual analogue scale score (54.4±21.7 vs. 64.5±21.5) (all $p<0.0001$), and Changes in Sexual Functioning Questionnaire score (38.7±9.5 vs. 42.4±8.5; $p=0.001$). In patients with PSG data, fAPAP improved other respiratory parameters (AHI, oxygen desaturation index, oxygen saturation; all $p<0.0001$), and increased time spent in rapid eye movement (REM) sleep (39.7±24.0 vs 48.1±24.5 min; $p=0.022$). Average daily fAPAP usage was 4.8±2.0 h/night.

Conclusion Usage of fAPAP significantly improved QoL and increased REM sleep, with good treatment compliance.

Introduction

Obstructive sleep apnea (OSA) is a common disorder characterized by upper airway closure during sleep, resulting in disrupted breathing and arousals. Moderate to severe OSA (apnea-hypopnea index [AHI] ≥15/h) is present in 4–23% of the female population (17, 224), and may impact as many as 26% of females aged between 20-70 years (17, 37, 224).

There are well known gender differences in OSA. This includes both clinical manifestations and impact on quality of life (QoL). Females often do not present with classic OSA symptoms, such as snoring, obesity and difficulty staying awake during the day. Instead females with OSA may complain of depression, anxiety, mood disturbance, reduced QoL, insomnia and fatigue (29, 185-187). The presence of OSA in women appears to increase the risk of developing diabetes, dementia and cardiovascular diseases (62, 68, 69). Female sexual health may also be impacted by OSA, although this has not yet been fully explored. A recent study found that females with OSA had significantly more sexual distress and sexual dysfunction compared to those without OSA (67).

The severity of OSA also often differs between genders, with polysomnography (PSG) data showing that females have less severe OSA with overall lower AHI, shorter apneas, and a higher likelihood of REM-only events (123). Younger women in particular often have more episodes of upper airway resistance rather than obstructive apneas (123).

Continuous positive airway pressure (CPAP) is considered the gold standard treatment for OSA. CPAP applies a fixed pressure that acts as a pneumatic splint to the upper airway, preventing collapse. Auto-adjusting CPAP (APAP) devices monitor breathing on a breath-by-breath basis and respond by delivering the appropriate pressure throughout the night. Effective CPAP treatment in adherent patients has been shown to improve

sleepiness and QoL and reduce cardiovascular risk (58-60). However, the majority of clinical trials of CPAP have included predominantly male participants. Indeed, patient populations in studies during the development and validation of early APAP devices were typically 100% male (180-182). Only one study to date has examined QoL changes in an entirely female population of OSA patients treated with CPAP (163).

A female-specific APAP (fAPAP) treatment algorithm has been developed with the goal of optimally treating the characteristics of OSA in women, including more sensitive treatment of flow limitation, and systems for overcoming REM-based events and lowering overall pressure. fAPAP has been shown to effectively control AHI while reducing residual flow limitation and lowering 95th percentile pressure in female OSA patients during a two-night study (225), but longer term improvements in symptoms have not been determined.

This study investigated changes in symptoms and sleep parameters in female OSA patients during 3 months' treatment with fAPAP.

Methods

Study design

This prospective, observational, open-label, single cohort study was conducted at one sleep clinic in Spain and two sleep clinics in Germany. The study was approved by local ethics committees and all participants provided informed consent.

Patients

Female patients who presented to the sleep clinic with suspected OSA were screened for OSA as per the usual clinical routine (home polygraphy (PG) in Spain or in-lab polysomnography (PSG) in Germany). Eligible patients were those aged ≥18 years who had an AHI of ≥15/h on diagnostic testing. Participants were excluded from the study if they were

unable to complete a one-hour CPAP run in. Additional exclusion criteria included: current use or experience with CPAP; use of supplemental oxygen; pregnancy or planned pregnancy in the next 3 months; pre-existing lung disease or condition predisposing to pneumothorax.

Procedures and assessments

At the first study visit, tolerance of CPAP was assessed with a one-hour run in on therapy.

Baseline data, including height, weight, age, blood pressure and comorbidities, were collected from patients continuing in the study. Participants were then asked to complete the following questionnaires, with assistance from the nurse/clinician if required: Functional Outcomes of Sleep Questionnaire (FOSQ); Patient Health Questionnaire (PHQ-9); Epworth Sleepiness Scale (ESS); Changes in Sexual Function Questionnaire (CSFQ); and EuroQol 5D (EQ-5D). Patients also provided information on subjective sleep quality based on a Likert scale from 0 (worst) to 10 (best).

Participants were then initiated on fAPAP therapy (AutoSet for Her; ResMed), with humidification and an appropriately fitting mask, and instructed to use fAPAP every night while sleeping for the next 3 months. All participants were phoned during the first weeks of therapy to troubleshoot any issues. If necessary, the participant was invited back to the clinic for a face-to-face visit. All participants returned to the clinic after one month for a visit. During this visit study staff reviewed device usage and attempted to resolve any problems that the participant was experiencing.

Three months after initiation of CPAP, participants returned to the clinic for a final visit. Patient data were downloaded from the device for analysis, including usage, AHI, mask leak, and pressures. At this time participants completed all questionnaires again. In addition, patients in Germany underwent an on-treatment PSG.

Endpoints

The primary endpoint was change in QoL during fAPAP based on the FOSQ. Secondary endpoints included change in QoL and sexual function based on other questionnaires, change in sleep quality at 3 months versus baseline based on PSG data, and change in other respiratory parameters at 3 months versus baseline.

Sample size

Sample size was determined based on the results of the CATNAP-trial (174), which showed an unadjusted mean change in FOSQ total score from baseline to week 8 in the modified intention-to-treat population of 0.98±2.89. To achieve power of 80% at α=0.05 it was calculated that a total of 71 patients would be required to detect an increase in FOSQ total score in this study. Assuming a drop-out rate of approximately 10%, the target minimum sample size was set at 80 participants.

Statistical analysis

Differences in baseline characteristics and study endpoints between Germany and Spain were assessed using the t-test or Wilcoxon-Mann-Whitney test for continuous parameters, and Fisher's exact test for categorical parameters. All study results were presented combined because pool-ability was confirmed (i.e. it was determined that there was no significant difference between the countries with respect to the primary study endpoint [change in FOSQ]). Primary and secondary endpoints are displayed separately when significant differences were detected.

Demographic data, baseline characteristics, medical history, medications, baseline PG/PSG data, CPAP data, device usage and QoL endpoints for combined data were summarized descriptively. Number evaluated, mean, standard deviation (SD), median, minimum and maximum were generated for continuous variables. Number evaluated,

proportion of patients and 95% confidence intervals (CI) were calculated for categorical variables.

Changes in quality of life scores from baseline to 3 months were analyzed for combined data using a paired t-test, testing the null hypothesis that there is no change in QoL scores. Wilcoxon paired signed rank tests were also generated when a non-parametric test was warranted. For comparison of EQ-5D dimensions between baseline and 3 months, a Mantel-Haenszel test was performed with modified ridit scores. All statistical analyses were performed using SAS version 9.4.

Results

Study population

A total of 122 patients (25 from Spain and 97 from Germany) were enrolled in the study (age 53.7±9.5, body mass index [BMI] 32.8±6.2, 56% with hypertension) (Table 1). The majority of patients (74%) used an AirFit P10 for Her mask as the device interface (Table 1). Of the 122 enrolled patients, 111 completed the study.

Participants from Spain and Germany were similar for most baseline characteristics, but those from Spain versus Germany had a significantly higher BMI (36.0±7.8 vs. 31.9±5.5 kg/m^2; p=0.02), and were significantly more likely to have comorbid insomnia (36% vs. 9%; p=0.002), anxiety (44% vs. 3%; p<0.0001) or depression (36% vs. 7%; p=0.001).

Questionnaire results

The change in FOSQ total score for participants in Spain versus Germany was not significantly different (2.6±3.7 vs. 1.8±3.2; p=0.31), thus primary and secondary endpoints are presented as pooled results. FOSQ total score (primary endpoint) improved significantly

from baseline to 3 months (Table 2). Significant improvements from baseline were also seen in total scores for the PHQ-9, ESS, CSFQ, indexed EQ-5D (based on country-specific reference values), and EQ-5D health status visual analog scale (Table 2). When individual EQ-5D dimensions were assessed, patients reported a significant improvement in their ability to perform usual activities, significantly fewer participants reported extreme pain or discomfort at 3 months compared with baseline, and patients also reported significant improvements in the Anxiety and Depression dimension after 3 months' fAPAP therapy (Table 3).

Improvements in the majority of secondary outcome questionnaires were similar in the Spanish and German subgroups. The exception was the ESS score, which improved to a significantly greater extent in Spain versus Germany (mean ± SD change from baseline to 3 months of –6.9±5.7 (median –4) vs. –2.7±4.4 (median –3); p=0.002).

None of the mean questionnaire scores reached normal population values after 3 months of fAPAP, but changes from baseline were greater than the minimal clinically important difference (MCID) (Table 4).

Respiratory and sleep parameters

Patients from the Spanish center had OSA diagnosed using PG. Baseline PG data and device data after 3 months of fAPAP in these patients are shown in Table 5. OSA and related respiratory events were largely eliminated in all patients. Participants enrolled in Germany underwent full PSG at baseline and after 3 months of fAPAP. There were no significant changes in total sleep time, sleep efficiency or time in slow wave sleep from baseline to 3 months, but the time spent in stage 1 sleep decreased significantly and time in REM sleep was significantly increased (Table 6). Combined 3-month device data from all participants showed that OSA was effectively treated (AHI 1.3±1.7/h, respiratory event-

related arousals 0.2±0.5/h) with low mean mask leak (2.4±4.1 L/min, range 0–23). The 95th percentile pressure was 10.2±1.8 cmH_2O.

Device usage

For the 111 patients who completed the study, average device usage was 4.8±2.0 h/night (median usage 5.1 h/night), and 75% of patients used their device for at least 4 h/day (Table 7). For those calculations, zero hours usage was assumed for the duration of the study in patients who stopped using the device prior to the 3-month visit, providing a conservative estimate of device usage. In analyses that included only days where the device was used, average device usage was 5.2±1.9 h/night (median 5.5 h/night) and 83% of patients used their device for at least 4 h/day. There was a trend towards greater use of the fAPAP device in Spain versus Germany (calculated average usage 5.5±1.4 vs. 4.6±2.2 h/day); findings were similar for the proportion of days with usage >4 hours (78.2±21.4 vs. 63.1±31.6%).

Subjective sleep quality

Subjective sleep quality improved from baseline after fAPAP therapy, as did the number of hours patients reported that they slept each night (Table 8).

Discussion

This is the first appropriately-powered study to examine the impact of a new female-specific APAP device on QoL in female OSA patients. The results showed that APAP therapy using a female-specific algorithm was associated with improvements in a range of QoL measures.

Our population was, on average, middle-aged and moderately obese with a moderate level of sleepiness at baseline and low levels of anxiety and depression. The primary endpoint, FOSQ score, improved significantly from baseline during the 3-month study in this group of women. Weaver *et al*. described a FOSQ score cut-off value of ≥17.9

as being normal (226). Based on this, the proportion of patients with normal FOSQ values at baseline in our study was 23%. After treatment, this had increased to 53%, but 47% of patients still had FOSQ scores below normal. These results are similar to another study of CPAP patients, where only 35% of patients had normal scores after treatment (227). The MCID for the FOSQ is 0.75. The average improvement in our patient group during fAPAP therapy was 1.9 points. Thus, although QoL was not normalized in all patients, improvements were of a magnitude that would result in a relevant improvement in clinical symptoms. Clinically relevant improvements (based on the MCID) were also seen in the ESS, PHQ-9 and EQ-5D index scores in our study, while the CSFQ score MCID has not yet been defined.

We used the CSFQ in this study to better explore the area of female sexual heath and function in OSA. In men, untreated OSA is associated with erectile dysfunction and low sexual hormone levels, which are improved by treatment with CPAP (228). However, there are comparatively few data on the implications of OSA for female sexual health. Two small questionnaire-based studies in female patients (n=22 and n=25) found that women with OSA score lower on sexual function questionnaires compared with controls (229, 230). One study found that women with untreated OSA (n=80), regardless of severity, were at higher risk of having sexual difficulties, and rated higher on the sexual dysfunction and sexual distress scales than a population-based sample of women without OSA (67). In the current study, we also showed that females with OSA rated lower than the population average on the CSFQ. During the conduct of our study, it was emphasized that completion of the CSFQ was optional. This was done to avoid any feelings of embarrassment for participants. The response rate to the CSFQ was significantly lower than the other questionnaires. Therefore, future studies will need to carefully consider the methodology used to collect female sexual function information. Our findings that the CFSQ score improved from outside the normal range to the lower end of what might be considered normal, suggest that fAPAP has the

potential to improve sexual function in female patients with OSA. Increases in the CFSQ score reached statistical significance versus baseline, and this beneficial effect of fAPAP warrants further investigation.

The questionnaires used in our study had been validated in both the German and Spanish languages. Therefore, it is reasonable to conclude that the improvements reported between countries were referring to the same symptoms. However, we did see some regional differences. At baseline, patients from Spain had a higher BMI and reported more sleepiness, anxiety and depression than those from Germany, although rates in Germany were particularly low compared with similar studies [4-7]. They also showed a significantly greater improvement in sleepiness (ESS score). It is possible that the higher BMI in the Spanish group was responsible for the higher levels of sleepiness, anxiety and depression, as obesity is associated with these symptoms even in the absence of OSA (203). Greater sleepiness at baseline may also have meant greater potential to improve. In addition, device usage was greater in the Spanish group (average 5.5±1.4 vs. 4.6±2.2 h/night; p=0.02), which may have been due to the higher levels of baseline sleepiness, and also may have contributed to the greater improvement in sleepiness seen in this group. It has been suggested previously that CPAP usage for ≥5 h/night is required to achieve significant improvements in daytime sleepiness (231), a finding supported by our results.

Only one previous clinical study focused on QoL in female-only CPAP users (163). Campos-Rodriguez *et al.* used the Quebec Sleep Questionnaire as a primary endpoint, plus the Hospital Anxiety and Depression scale (HADS), the abbreviated Profile of Mood Stages (POMS), and the Short Form Health Survey (SF-12), none of which were used in our study. Our questionnaires were selected, in part, due to the availability of validation in both the German and Spanish languages. Despite the different questionnaires used, the study by Campos-Rodriguez *et al.* reported significant improvements in all QoL measures in females using fixed CPAP compared with the control group, consistent with our findings. In addition,

both studies showed a similar improvement in ESS scores during CPAP therapy (by 3 points in the Campos-Rodriguez *et al.* study and 3.6 points on average in this study). The findings of these two trials strengthen the limited pool of data evaluating females during CPAP therapy.

Women in our study showed adequate compliance with fAPAP therapy, with mean daily usage of 4.8±2.0 hours. Generally, device usage of >4 h/night is considered acceptable. An analysis of female CPAP compliance published in 2013 found that females were generally compliant with CPAP, with 79.9% still using CPAP after 10 years and median usage of 6 h/day (232). In our study population, median usage of fAPAP was nearly as high, at 5.5 h/day in Spain and 4.6 h/day in Germany.

Use of fAPAP in our study resulted in patients spending significantly less time in stage one sleep and significantly more time in REM sleep compared with baseline, as measured by PSG in Germany. Time spent in slow wave sleep was also increased, but this did not reach statistical significance. REM sleep is thought to be important for consolidation of procedural memories, while slow wave sleep may help patients feel rested and benefit declarative memories (233).

The most important limitation of this study was its design (single cohort rather than randomized trial) and the resulting lack of a comparator group (e.g. APAP with a standard, rather than female-specific, algorithm). It is therefore not possible to categorically state that the improvements in QoL that occurred during fAPAP treatment were due to optimization of therapy based on the female-specific algorithm or whether standard APAP therapy would have had similar effects.

In conclusion, this study showed significant improvements in QoL in female OSA patients treated for 3 months with a female-specific APAP device. This included improvements in sexual function, which have been rarely studied in these patients. The

female-specific algorithm evaluated in this study represents one approach to targeting therapy for individual patients (personalized medicine). The majority of existing data relate to OSA populations with a predominance of males, particularly with respect to treatment. A growing body of evidence suggests that there are substantial differences between females and males in the symptoms, diagnosis and consequences of OSA. Better knowledge of gender differences in OSA will help to improve the awareness and diagnosis of OSA in women. In addition, the development and availability of therapeutic options that take into account differences in the physiology and presentation of OSA in women could have the potential to improve outcomes for these patients.

Compliance with Ethical Standards

Funding: This study was funded by ResMed Ltd

Conflict of interest: Authors Alison Wimms, Holger Woehrle, Dagmar Martens and Adam Benjafield are employees of ResMed Ltd. The study was funded by ResMed Ltd. Authors Volker Topfer, Aline Lips, Ingo Fietze, Leslee Willes and Francisco Campos-Rodriguez declare that he/ she has no conflict of interest.

Ethics approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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Table 1. Baseline characteristics of the study population.

Parameter	Spain (N = 25)	Germany (N = 97)	p-value
Age (years)			
n	25	97	0.37 [1]
Mean ± SD (Median)	52.1 ± 8.6 (54.0)	54.1 ± 9.8 (55.0)	
Min, Max	39, 68	25, 76	
BMI (kg/m^2)			
n	25	95	0.02 [1]
Mean ± SD (Median)	36.0 ± 7.8 (35.0)	31.9 ± 5.5 (32.0)	
Min, Max	22, 51	18, 49	
Systolic blood pressure (mmHg)			
n	25	91	0.08 [1]
Mean ± SD (Median)	137.6 ± 13.7 (140.0)	143.7 ± 19.5 (142.0)	
Min, Max	110, 165	100, 214	
Diastolic blood pressure (mmHg)			
n	25	91	0.07 [1]
Mean ± SD (Median)	87.0 ± 11.0 (90.0)	92.7 ± 14.4 (94.0)	
Min, Max	70, 114	11, 122	
Comorbidities n/N (%):			

Parameter	Spain (N = 25)	Germany (N = 97)	p-value
Heart Disease	2/25 (8.0%)	2/97 (2.1%)	0.19 [3]
Hypertension	12/25 (48.0%)	56/97 (57.7%)	0.38 [3]
Diabetes	2/25 (8.0%)	9/97 (9.3%)	1.00 [3]
Anxiety	11/25 (44.0%)	3/97 (3.1%)	< 0.0001 [3]
Depression	9/25 (36.0%)	7/97 (7.2%)	0.0007 [3]
Insomnia	9/25 (36.0%)	9/97 (9.3%)	0.002 [3]
Other	22/25 (88.0%)	33/97 (34.0%)	< 0.0001 [3]
Mask Type, n/N (%)			
AirFit N10 for Her	1/25 (4.0%)	0/97 (0.0%)	< 0.0001 [3]
AirFit N10	11/25 (44.0%)	1/97 (1.0%)	
Mirage FX For Her	0/25 (0.0%)	1/97 (1.0%)	
AirFit P10 for Her	13/25 (52.0%)	95/97 (97.9%)	

[1] Independent samples t-test [2] Wilcoxon-Mann-Whitney test [3] Fisher's exact test (or Chi-square where applicable)

Table 2. Change in questionnaire scores after 3 months' female-specific auto-titrating positive airway pressure therapy.

	Baseline	fAPAP (3 months)	Change from baseline	p-value
FOSQ total score	**(n=121)**	**(n=111)**	**(n=110)**	
Mean ± SD (range)	15.0±3.3 (6–20)	16.9±3.2 (6–20)	1.9±3.3 (–14, 13)	<0.0001
PHQ-9 total score	**(n=119)**	**(n=111)**	**(n=108)**	
Mean ± SD (range)	12.3±6.0 (1–27)	7.2±5.4 (0–24)	–5.0±4.9 (–16, 5)	<0.0001
ESS score	**(n=122)**	**(n=108)**	**(n=108)**	
Mean ± SD (range)	10.8±4.9 (1–24)	7.3±4.7 (0–20)	–3.6±5.0 (–20, 6)	<0.0001
CSFQ total score	**(n=87)**	**(n=70)**	**(n=63)**	
Mean ± SD (range)	38.7±9.5 (21–63)	42.4±8.5 (22–63)	2.4±5.9 (–12, 16)	0.001
EQ-5D index score	**(n=115)**	**(n=108)**	**(n=102)**	
Mean ± SD (range)	0.64±0.25 (0.1–1.0)	0.76±0.21 (0.1–1.0)	0.12±0.21 (–0.4, 0.6)	<0.0001
EQ-5D health status (VAS score)	**(n=108)**	**(n=110)**	**(n=98)**	
Mean ± SD (range)	54.4±21.7 (5–100)	64.5±21.5 (7–100)	9.7±21.5 (–45, 75)	<0.0001

CSFQ: Changes in Sexual Function Questionnaire; ESS, Epworth Sleepiness Scale; fAPAP: female-specific auto-titrating positive airway pressure; FOSQ: Functional Outcomes of Sleep Questionnaire; PHQ-9: Patient Health Questionnaire-9; SD: standard deviation; VAS: visual analog scale.

Table 3. Change in EuroQol 5D dimensions after 3 months' female-specific auto-titrating positive airway pressure therapy.

Dimension; n (%)	Baseline	fAPAP (3 months)	p-value*
Mobility	**(n=116)**	**(n=109)**	
No problems in walking about	91 (78.4)	89 (81.7)	
Some problems in walking about	25 (21.6)	20 (18.3)	0.55
Confined to bed	0	0	
Self-care	**(n=117)**	**(n=111)**	
No problems with self-care	108 (92.3)	106 (95.5)	
Some problems with washing or dressing	9 (7.7)	5 (4.5)	0.32
Unable to wash or dress myself	0	0	
Usual activities	**(n=117)**	**(n=111)**	
No problems performing usual activities	64 (54.7)	78 (70.3)	
Some problems performing usual activities	51 (43.6)	32 (28.8)	0.02
Unable to perform usual activities	2 (1.7)	1 (0.9)	
Pain/discomfort	**(n=115)**	**(n=110)**	
No pain or discomfort	22 (19.1)	32 (29.1)	
Moderate pain or discomfort	64 (55.7)	69 (62.7)	0.002
Extreme pain or discomfort	29 (25.2)	9 (8.2)	
Anxiety/depression	**(n=115)**	**(n=111)**	
Not anxious or depressed	40 (34.8)	57 (51.4)	
Moderately anxious or depressed	62 (53.9)	49 (44.1)	0.005
Extremely anxious or depressed	13 (11.3)	5 (4.5)	

fAPAP: female-specific auto-titrating positive airway pressure.

*p-values generated using Mantel-Haenszel test with modified ridit scores.

Table 4. Questionnaire scores in relation to healthy populations and minimal clinically important difference.

Questionnaire	Healthy population scores	Baseline score (mean ± SD)	fAPAP (3 months) (mean ± SD)	Change from baseline with fAPAP	MCID
FOSQ	≥17.9	15.0±3.3	16.9±3.2	1.9±3.3	0.75
ESS	≤9	10.8±4.9	7.3±4.7	–3.6±5.0	2–3
PHQ-9	≤4	12.3±6.0	7.2±5.4	–5.0±4.9	5
CSFQ	47.8±9	38.7±9.5	42.4±8.5	2.4±5.9	Unknown
EQ-5D Index	1	0.636±0.248	0.763±0.210	0.12±0.21	0.074

CSFQ: Changes in Sexual Function Questionnaire; ESS, Epworth Sleepiness Scale; fAPAP: female-specific auto-titrating positive airway pressure; FOSQ: Functional Outcomes of Sleep Questionnaire; MCID: minimal clinically important difference; PHQ-9: Patient Health Questionnaire-9; SD: standard deviation.

Table 5. Respiratory data at baseline (polygraphy) and 3 months (device) for patients from Spain.

	Baseline	**fAPAP (3 months)**
	(n=25)	**(n=23)**
AHI, /h	39.2±20.5 (17–76)	0.9±0.7 (0–3)
ODI, /h	39.8±21.5 (13–79)	-
RERA, /h	-	0.2±0.3 (0–1)
OAI, /h	8.2±10.6 (0–36)	0.3±0.3 (0–1)
CAI, /h	0.4±1.1 (0–5)	0.2±0.3 (0–1)
Mean SaO_2, %	97.1±1.6 (92–99)	-
Minimum SaO_2, %	77.3±8.3 (52–88)	-
Total sleep time, min	381.5±56.5 (273–486)	-
Mean leak, L/min	-	3.8±3.8 (0–16)
95^{th} percentile leak, L/min	-	18.7±8.2 (5–35)
Median pressure, cmH_2O	-	9.1±1.4 (7–11)
95^{th} percentile pressure, cmH_2O	-	11.0±1.1 (9–13)

Values are mean ± standard deviation (range).

AHI: apnea-hypopnea index; CAI: central apnea index; fAPAP: female-specific auto-titrating positive airway pressure; OAI: obstructive apnea index; ODI: oxygen desaturation index; RERA: respiratory event-related arousals; SaO_2: oxygen saturation.

Table 6. Polysomnography data at baseline and 3 months for patients from Germany.

	Baseline (n=97)	fAPAP (3 months) (n=87)	p-value
Respiratory parameters			
AHI, /h	39.0±17.7 (14-100)	3.3±6.0 (0-50)	<0.0001
ODI, /h	19.1±18.0 (1-86)	4.3±7.0 (0-56)	<0.0001
OAI, /h	27.2±34.4 (0-289)	0.9±2.4 (0-14)	<0.0001
CAI, /h	1.1±3.1 (0-27)	1.2±3.0 (0-25)	0.03
Basal SaO_2, %	93.5±2,2 (87-97)	94.6±2.2 (89-98)	<0.0001
Minimum SaO_2,%	79.9±8.3 (53-95)	86.7±4.8 (69-96)	<0.0001
Sleep parameters			
Total sleep time, min	321.0±63.9 (160–568)	326.5±72.2 (116–478)	0.80
Sleep efficiency, %	79.4±12.6 (34–99)	79.7±14.7 (25–99)	0.91
Time in S1 sleep, min	39.1±38.1 (5–260)	29.4 ± 25.2 (3–150)	0.02
Time in S2 sleep, min	197.2±57.9 (38–326)	193.4±49.0 (25–296)	0.50
Time in SWS, min	40.0±26.3 (0–132)	47.0±29.4 (0–113)	0.07
Time in REM sleep, min	39.7±24.0 (0–142)	48.1±24.5 (0–110)	0.02

Values are mean ± standard deviation (range).

AHI: apnea-hypopnea index; CAI: central apnea index; fAPAP: female-specific auto-titrating positive airway pressure; OAI: obstructive apnea index; ODI: oxygen desaturation index; REM: rapid eye movement; SaO_2: oxygen saturation; SD: standard deviation; SWS: slow-wave sleep.

Table 7. Device usage (completed cases)

	fAPAP (3 months) **(n=111)**
Average usage, h/day	4.8±2.0 (0.1–8.2)
Days with usage >4 h/day, %	66.2±30.4 (1.9–100.0)
Average usage ≥4 h/day, n (%)	75 (67.6)

Values are mean ± standard deviation (range) or number of patients (%).

fAPAP: female-specific auto-titrating positive airway pressure.

Table 8. Subjective sleep quality

	Baseline	fAPAP (3 months)	Change from baseline	p-value
How easy/difficult was it to fall asleep?	**(n=120)**	**(n=107)**	**(n=106)**	
Mean ± SD (range)*	5.2±2.9 (0–10)	6.3±2.5 (0–10)	1.1±2.7 (–5, 7)	<0.0001
How well did you feel like you slept most nights?	**(n=119)**	**(n=109)**	**(n=107)**	
Mean ± SD (range)*	3.5±2.4 (0–10)	6.1±2.3 (1–10)	2.6 ± 2.7 (–3, 8)	<0.0001
How refreshed did you feel in the mornings on waking?	**(n=120)**	**(n=108)**	**(n=107)**	
Mean ± SD (range)	2.4±2.0 (0–10)	6.3±2.4 (0–10)	3.8±3.0 (–5, 10)	<0.0001
On average, how many times did you wake up each night? n (%)	**(n=119)**	**(n=109)**		
None	7 (5.9)	19 (17.4)		
1-2	43 (36.1)	58 (53.2)		
3-4	56 (47.1)	31 (28.4)		<0.0001**
5-6	12 (10.1)	1 (0.9)		
More than 6	1 (0.8)	0		

*Score on a scale from 0 (worst) to 10 (best).

**Mantel-Haenszel test (modified ridit scores).

SD: standard deviation.

CHAPTER 7. GENERAL CONCLUSION TO THE THESIS

7.1. Summary of thesis aims

The overall aim of this thesis was to understand gender differences in OSA and use this information to develop a tailored therapy for female patients.

Specific aims of this thesis were to:

1) **Determine whether gender-related differences exist in symptoms of mild OSA patients (CHAPTER 2)**

2) **Determine whether gender-related differences exist in respiratory data of mild OSA patients (CHAPTER 3).**

3) **Determine whether correlations exists between respiratory parameters and patient symptoms in mild OSA patients (CHAPTER 3).**

4) **Develop, test and validate a new AutoSet for the treatment of female-specific breathing characteristics (CHAPTER 4, CHAPTER 5 and CHAPTER 6).**

7.2. Summary of the literature review

CHAPTER 1 of this thesis provides a detailed review of OSA and UARS, with a focus on gender differences. OSA is a common disorder characterised by repetitive nocturnal complete collapses (apneas) or partial collapses (hypopneas) of the upper airway during sleep. These events are associated with oxygen desaturation and/or arousal from sleep. The severity of OSA is measured by the number of occurrences of airway collapse per hour (the apnea-hypopnea index [AHI]). Measuring the severity of OSA is complicated due to changes in scoring rules introduced by the American Association of Sleep Medicine (AASM) in 2007 and 2012. In 2012 the definition of a hypopnea was modified, which increases the number of

patients achieving diagnostic criteria. In particular, many patients who may have previously been diagnosed with UARS are likely to qualify for an OSA diagnosis if later scoring criteria are used.

OSA is less prevalent in females than males. When AASM 2012 scoring criteria is used, as many as 49.7% of males and 23.4% of females may have moderate-to-severe OSA (18). Females present with different symptoms than males. While the typical OSA symptoms are snoring, witnessed apneas and daytime sleepiness, females are more likely to complain of fatigue, insomnia, depression and anxiety (23-26). Females with moderate-to-severe OSA have significantly worse quality of life and mood disturbances than males with OSA (29, 30). It is not clear whether women with OSA experience daytime sleepiness. Women consistently score lower on questionnaires assessing daytime sleepiness, and are more likely to complain of fatigue and tiredness than sleepiness (36, 37). Females with OSA are frequently misdiagnosed with depression and other illnesses, most likely due to the atypical symptoms they report (23, 24, 47). However, even when women do report the typical OSA symptoms they are still less likely to be referred to sleep clinics, indicating that OSA in female patients is often overlooked (47). Compared to males with OSA, females have a higher likelihood of developing a range of health conditions including diabetes (68) and hypertension (70). Women with OSA are more likely than those without OSA to be diagnosed with cardiovascular diseases (68), and severe untreated OSA in females has been associated with cardiovascular death (69).

As defined by the AHI, females have less-severe OSA compared to males (126). Females have lower AHIs, comprised of shorter events and less-severe oxygen desaturations, than males (124). Females are more likely to have clusters of obstructive events during REM sleep (123), and less likely to experience positional OSA (123). Less severe OSA in females appears to be due to a combination of anatomical, hormonal, and chemoreceptor differences (23, 137, 138, 142).

The gender differences in prevalence, symptoms, clinical experience, and health consequences of OSA patients appear to be clearly defined. However, a review of patients with mild OSA and UARS shows that the proportion of females reporting to sleep clinics is much closer to 50% (85-87). The symptoms that mild OSA and UARS patients report are similar to those attributed to female OSA patients, including insomnia, poor quality of life, and daytime tiredness (11, 85). Patients with mild OSA and UARS experience large amounts of flow limitation during sleep. Flow limitation alone, with obstructive apneas, has been

shown to produce clinical symptoms such as fatigue and depression (99). It is therefore possible that symptoms of OSA may be more closely related to severity of the disease than gender.

The most effective treatment for OSA is continuous positive airway pressure (CPAP). CPAP provides a pneumatic splint by applying pressurized air from a device to a patient's airway via a mask and tubing. Effective CPAP treatment in women has been shown to improve quality of life (160), sleepiness (163), anxiety (163) and depression (161). CPAP also appears to reduce the risk of cardiovascular mortality in adherent female patients (25).

AutoSet is a mode of CPAP therapy which automatically adjusts the pressure delivered to the patient based on a breath-by-breath assessment of ventilation. AutoSet devices assess the patient's breathing for flow limitation, snore, and reduction or lack of ventilation (hypopnea or apnea). The AutoSet devices then increase the pressure to overcome obstruction until ventilation is stable. AutoSet devices are also able to reduce pressure during periods of stable breathing to improve patient comfort. An advantage of AutoSet devices is their ability to provide efficacious treatment for patients during changing circumstances, for example after alcohol intake or weight gain. AutoSet devices have been developed and validated in patient groups consisting of 100% male patients (180-182). As female-specific characteristics have not been considered during the development of AutoSet devices, they may not be optimal for treatment of women with OSA.

7.3. Summary of the main findings of this thesis

CHAPTER 2 of this thesis aimed to determine whether the literature-reported female symptoms of OSA (fatigue, insomnia, anxiety and depression) are still a gender-specific phenomenon in UARS and mild OSA patients. Patient data from the MERGE clinical trial (Appendix C) was used for this analysis. Patients were entered into this clinical trial if they had mild OSA (AHI 5-15) according to either AASM 2007, or AASM 2012 criteria. At the first trial visit patients were asked to complete a range of quality of life questionnaires, including the Epworth Sleepiness Scale (ESS), Fatigue Severity Scale (FSS), Hospital Anxiety and Depression Scale (HADS), and Insomnia Severity Index (ISI). Baseline questionnaire scores of the males and females were compared to see if gender differences were present in this mild patient group.

Included in this analysis were 186 males and 73 females. On average, the females were significantly older (54.9 + 9.8 vs. 50.4 ± 12.1, p = 0.002), and had a higher BMI (31.8 ± 5.2

vs. 29.5 ± 3.6, p < 0.000). There were significant gender differences in each questionnaire response. The female patients reported significantly higher sleepiness according to the ESS (10.63 ± 4.34 vs. 9.13 ± 4.34, p = 0.014). Females also reported significantly higher levels of fatigue (FSS scores 43.10 ± 12.94 vs. 33.69 ± 13.94, p = 0.000), insomnia (ISI scores 14.62 ± 5.67 vs. 11.90 ± 5.48, p = 0.001), and anxiety/depression (HADS scores 14.81 ± 7.57 vs. 11.03 ± 6.94, p = 0.000). Overall, this data from 259 mild OSA patients shows that, even at the lower end of the OSA spectrum, the symptoms of females are still significantly worse than those of males.

CHAPTER 3 of this thesis aimed to determine whether the gender differences reported in respiratory parameters of moderate-to-severe patients also exist in mild OSA and UARS patients. Females are reported to have more flow limitation, shorter apneas, less-severe oxygen desaturation, and more RERAs/hypopneas terminated by arousal. UARS is characterised by excessive flow limitation and RERAs. It is not clear if females have less-severe sleep disordered breathing (SDB) within the mild OSA and UARS groups. Patients enrolled in the MERGE study (Appendix C) underwent polygraphy (PG) home sleep testing. PG data from the participants was analysed according to gender to assess for differences. PG data was then correlated with patient symptoms to determine whether there were relationships between SDB events and symptoms.

PG studies from 259 patients (73 females) were collected. Studies were scored both with AASM 2007 and AASM 2012 scoring criteria. When scored according to AASM 2007 criteria, the male patients had significantly higher AHI (7.17 ± 3.4 vs. 5.97 ± 2.71, p = 0.004). This difference disappeared when the studies were rescored with AASM 2012 criteria (male vs. female AHI 12.52 ± 5.01 vs. 11.65 ± 4.69, p = 0.197). There were no significant differences in the number of hypopneas terminated by arousals (male vs. female score 3.2 ± 3.58 vs. 3.65 ± 3.58, p = 0.370). There was also no significant difference in the percentage of flow limited breaths between the genders (males vs. female percentage 39.8 ± 13.8 vs. 38.4 ± 15.6, p = 0.598).

In the male patient group, correlations were only found between AASM 2012 AHI, and FSS (r = -0.153, p = 0.040). In the female patients, correlations were found between AASM 2007 AHI and ESS (r = -0.317, p = 0.007), AHI and HADS (r = -0.372, p = 0.001), and AHI and ISI (r = -0.242, p = 0.042). In the female data rescored with AASM 2012 rules, correlations were also found between AHI and HADS (r = -0.381, p = 0.001), and AHI and ISI (r = -0.240, p = 0.044). In all correlations found, the relationship was inverse, meaning that the symptoms

were higher for lower AHIs. There were no correlations between flow limitation and symptoms in the male group. In the female group correlations were found between percent of flow limited breaths and FSS (r = -0.300), and percent of flow limited breaths and ISI (-0.416, p = 0.004). Again, these correlations were inverted, with higher symptoms associated with lower percentages of flow limitation. In the female patients, ESS was strongly associated with age, with younger females more likely to report excessive sleepiness. BMI was associated with FSS increases in females, and ISI increases in males.

This data confirmed that, even in this mild patient group, females have less-severe SDB, with lower AHIs and a higher proportion of hypopneas terminated by arousals. There was no significant difference in the percentage of flow limitation between genders. It was not possible to draw clear conclusions from the associations between symptoms and measures of SDB.

CHAPTER 4 of this thesis outlined the development of a female-specific AutoSet device. Females are reported as having different breathing patterns to males, including more flow limitation, shorter and less-severe apneas, lower AHIs, less severe-oxygen desaturations, more events during REM sleep, and a longer sleep latency. Traditionally, AutoSet devices were developed and tested on male patient groups and therefore may not appropriately recognise and respond to female-specific breathing events and may not provide optimal treatment for female patients.

Development of the new AutoSet (AutoSet F) involved designing a new algorithm which would detect and respond to female-specific breathing patterns. The AutoSet F algorithm includes a sensitive flow limitation detection and response, a floor pressure to protect against strings of OSA in REM, lower overall mean pressures than a standard AutoSet, a new RERA detection algorithm, gentle and slow pressure increases and decreases, and an automatic ramp feature which keeps delivered pressure low until sleep onset is detected.

CHAPTER 5 of this thesis detailed the testing and verification activities undertaken on the AutoSet F. The first activity was a clinical trial conducted on 20 female OSA patients to test device efficacy. Female patients with a diagnostic AHI ≥ 15 were randomised to receive AutoSet F or standard AutoSet on consecutive nights while undergoing PSG. The primary objective was to compare the AHI and ODI of the AutoSet F to the standard AutoSet to demonstrate non-inferiority. Secondary outcomes were sleep parameters and patient satisfaction.

Female participants were primarily Caucasian with a mean age of 44.85 ± 5.02 years and diagnostic AHI of 19.08 ± 8.69. No significant differences were found between the standard AutoSet and AutoSet F in AHI (0.96 vs. 0.91, p = 0.870); or ODI (1.92 vs. 2.19, p = 0.477). When comparing the sleep parameters, the data shows that flow limitation (% of breaths) was significantly lower when participants were treated with the AutoSet F compared with the standard AutoSet (0.14% vs. 0.20%; p=0.003). This study shows that the AutoSet F is able to efficaciously treat OSA in female patients and may be a more suitable option than standard AutoSet.

The next activity for validating the AutoSet F was testing using a bench test designed to simulate a female OSA patient. The primary objective of this activity was to test the performance of the AutoSet F compared to other commercially available devices, on a test which is controlled and repeatable. The bench test in this study was developed Professor Farré and colleagues at Barcelona University.

In this bench test, the simulated patient was designed to replicate a typical female OSA patient with a lot of flow limitation, short apneas, mild hypopneas and a requirement for overall lower treatment pressures.

From the ten AutoSet devices tested, only the AutoSet F and two other AutoSet devices were able to completely overcome obstructive events and flow limitation. There was a high residual AHI (AHI > 5) at completion of the testing for four of the devices. This bench testing demonstrated that the AutoSet F was able to completely normalize breathing of a simulated female patient, while several other commercially available AutoSet devices were unable to normalize breathing.

The next validation test for the AutoSet F was a controlled product launch (CPL). During a CPL, product commercial release is carefully controlled and data from participants is collected and analysed for correct device functioning. De-identified device functioning information was collected from 163 devices, over a total of 2272 nights of use. Average daily usage was high, at 5.9 hours per night. Residual AHI was 2.61, well below what is considered efficacious (< 5). This efficacy was achieved with a group average 95th percentile pressure of 8.76 cm H_2O. During the CPL, the technical features of the AutoSet F were found to be working as intended, and the internal algorithm was able to treat female patients in real world, uncontrolled conditions.

CHAPTER 6 of this thesis reported a clinical trial evaluating quality of life in female patients before and after using the AutoSet F for three months. The literature, as well as data in this thesis, has shown that female OSA patients experience worse symptoms, including fatigue, quality of life, anxiety and depression, insomnia, than males with OSA. The purpose of this study was to evaluate whether ongoing use of the AutoSet F was able to improve these symptoms in female patients.

Participants underwent PG (Spain) or PSG (Germany) at study entry. Those with a diagnostic AHI of ≥ 15/h were eligible to participate. The primary endpoint was change in baseline in the Functional Outcomes of Sleep Questionnaire (FOSQ) score after 3 months' AutoSet F use. Secondary endpoints included other sleep-related and QoL questionnaires.

A total of 122 patients were enrolled in the study (age 53.7 ± 9.5 years, body mass index 32.8 ± 6.2 kg/m^2, apnea-hypopnea index [AHI] 39.0±18.2/h); 111/122 completed the study. There was a significant improvement ($p<0.0001$) in FOSQ score from baseline (15.0 ± 3.3) to 3 months (16.9 ± 3.2). Significant improvements were also seen in the Patient Health Questionnaire-9 score (12.3 ± 6.0 vs. 7.2±5.4), Epworth Sleepiness Scale score (10.8 ± 4.9 vs. 7.3 ± 4.7), EuroQol (EQ)-5D Index score (0.636 ± 0.248 vs. 0.763 ± 0.210), EQ-5D visual analogue scale score (54.4 ± 21.7 vs. 64.5 ± 21.5) (all $p<0.0001$), and Changes in Sexual Functioning Questionnaire score (38.7 ± 9.5 vs. 42.4 ± 8.5; $p=0.001$). In patients with PSG data, AutoSet F improved other respiratory parameters (AHI, oxygen desaturation index, oxygen saturation; all $p<0.0001$), and increased time spent in rapid eye movement (REM) sleep (39.7 ± 24.0 vs 48.1 ± 24.5 min; $p=0.022$). Average daily usage was 4.8 ± 2.0 h/night.

This study showed significant improvements in quality of life in female OSA patients treated for 3 months with the AutoSet F device. This included improvements in sexual function, which have been rarely studied in these patients. Significant improvements were seen in respiratory parameters as well as time in REM sleep. Taken together, this data shows that the AutoSet F can improve sleep and quality of life in female OSA patients.

7.4. Conclusion to this thesis and future direction

During this thesis I aimed to determine whether gender differences described in OSA patients still exist in those patients on the mild end of the spectrum. I found that significant gender differences do exist in mild OSA patients, with females suffering from significantly worse sleepiness, fatigue, insomnia, and anxiety/depression. It was clear that these patients were extremely symptomatic, and defining them as mild is misleading, as is only looking at

AHI as a measure of severity. The reasons that female patients express worse symptoms remain unclear, and future studies should investigate the psychology behind how females perceive and report symptoms of OSA compared with males.

Gender differences in the severity of OSA are also present in mild OSA patients, although they are far less pronounced than those in moderate-to-severe patients, with no significant differences found between the percentage of flow limitation or number of hypopneas terminated by arousal. I was unable to conclusively find relationships between measures of SDB and symptoms. Although correlations were found between some measures of SDB and symptoms in female patients, they were inverse, meaning that lower SDB scores were associated with higher symptoms. There were also strong confounding factors, including BMI and age, which were associated with symptoms for both genders. Future research should review symptom improvement following OSA treatment, as this will provide further insights as to which symptoms are caused by untreated OSA. The MERGE trial (Appendix C) aims to investigate this area further, with results expected late 2019.

The final aim of this thesis was to develop a new AutoSet treatment for female patients. Using respiratory parameters commonly found in female patients, I developed an appropriate AutoSet which I then tested for efficacy, effectiveness, and long-term use in female patients. The studies demonstrated that the AutoSet F is able to significantly improve OSA and improve symptoms of female patients, and may provide more optimal treatment than other commercially available AutoSet devices. This work has contributed to the field of sleep medicine by bringing awareness to the gender differences that exist in OSA, and introducing personalised medicine for female OSA patients. It is hoped that through this work it will be easier for female OSA patients to be identified and treated for obstructive sleep apnea, which will then improve their quality of life.

Further research in this area should compare the AutoSet F to standard AutoSet in a longer clinical trial to see if PAP acceptance and compliance can be improved with the use of the AutoSet F. Future research may also investigate the use of the AutoSet F on male patients with mild OSA and excessive amounts of flow limitation to see if similar improvements are seen in the male population.

Female patients may benefit from introducing new definitions of OSA which move away from traditional AHI measures. As shown in this thesis, the AASM 2012 definition of OSA appears to be more beneficial to female patients as it recognises more respiratory events, however prolonged flow limitation and some RERAs are still not included in this definition. Finally,

new therapies emerging to treat OSA, including mandibular advancement devices, phrenic nerve simulation, and combinations of new drugs, should all be separately analysed on female patients. These therapies could then be optimised for the female patients, who have been shown to be very different from the male patients.

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Appendices – Publications relating to this thesis

Appendix A - Wimms A, Woehrle H, Ketheeswaran S, Ramanan D, Armitstead J. Obstructive Sleep Apnea in Women: Specific Issues and Interventions. BioMed Research International 2016;1-9.

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Review Article

Obstructive Sleep Apnea in Women: Specific Issues and Interventions

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Abstract

Obstructive sleep apnea (OSA) has traditionally been seen as a male disease. However, the importance of OSA in women is increasingly being recognized, along with a number of significant gender-related differences in the symptoms, diagnosis, consequences, and treatment of OSA. Women tend to have less severe OSA than males, with a lower apnea-hypopnea index (AHI) and shorter apneas and hypopneas. Episodes of upper airway resistance that do not meet the criteria for apneas are more common in women. Prevalence rates are lower in women, and proportionally fewer women receive a correct diagnosis. Research has also documented sex differences in the upper airway, fat distribution, and respiratory stability in OSA. Hormones are implicated in some gender-related variations, with differences between men and women in the prevalence of OSA decreasing as age increases. The limited data available suggest that although the prevalence and severity of OSA may be lower in women than in men, the consequences of the disease are at least the same, if not worse for comparable degrees of severity. Few studies have investigated gender differences in the effects of OSA treatment. However, given the differences in physiology and presentation, it is possible that personalised therapy may provide more optimal care.

1. Introduction

Obstructive sleep apnea (OSA) is characterized by repetitive nocturnal complete collapses (apneas) or partial collapses (hypopneas) of the upper airway during sleep. These events are associated with oxygen desaturation and/or arousal from sleep. The severity of OSA is measured by the number of occurrences of airway collapse per hour (the apnea-hypopnea index [AHI]). OSA is the most common form of sleep disordered breathing (SDB) and its prevalence has been increasing steadily, in part due to the global rise in obesity and in part due to changes to the recommended OSA scoring ruleswhichwereupdatedin2012toallowabroaderdefinition of OSA [1]. Table 1 summarizes prevalence data for OSA in the general population.

OSA has been estimated to have a male-to-female ratio of between 3 : 1 and 5 : 1 in the general population and a much higher ratio of between 8 : 1 and 10 : 1 in some clinical groups [2–4]. Perhaps not surprisingly then, OSA has historically been regarded as a male disease [5]. Prevalence data do show that more men than women are affected by OSA; however, these differences are not reflected in clinical populations. This indicates that females are being diagnosed and treated for OSA less frequently than males.

2. OSA Classification, Diagnosis, and Symptoms

2.1. Sleepiness. It has been suggested that discrepancies between males and females in the prevalence of OSA could be a result of women frequently being misdiagnosed or underdiagnosed due to reporting different symptoms [4]. In the past, sleepiness has been seen as a key component of OSA. Obstructive sleep apnea syndrome (OSAS), which refers to OSA with accompanying symptoms, has been the main focus

Table 1: Estimated population prevalence of OSA.

Study	Mild OSA (AHI ≥ 5/h)		Moderate-to-severe OSA (AHI ≥ 15/h)	
	Males	Females	Males	Females
Young et al. [2]	24%	9%	9%	4%
Redline et al. [21]*	—	—	26%	13%
Bixler et al. [22, 23]	17%	—	7%	2%
Duran et al.´ [24]	26.2%	28%	14%	7%
Peppard et al. [25]	—	—	13.5%	6%
Franklin et al. [5]^#	—	50%	—	26%
Heinzer et al. [26]#	34%	38%	49.7%	23.4%

*Respiratory disturbance index (RDI) rather than AHI given.
^Women aged 20–70 years.
#Updated scoring criteria (AASM 2012) used.

of treatment in the past. Furthermore, because the majority of clinical trial participants with OSA have been sleepy, it is still not clear whether asymptomatic OSA should be treated.

The Epworth Sleepiness Scale (ESS) is a tool used to measure the likelihood of falling asleep in certain

situations and is commonly used to screen for OSA [5, 6]. Despite its widespread use, the ESS has not been validated for use in female OSA patients and has not been strongly associated with daytime sleepiness in female patients in population based studies [5, 6]. In fact, even women who report similar levels of daytime sleepiness to men are less likely to have an ESS score >10 [6]. It is not clear why these differences occur; however, it is possible that women have a different threshold for feeling sleepy and/or complain differently about sleepiness compared with men [4].

2.2. Other Symptoms. Making a differential diagnosis of OSA in women might be more difficult given that they tend to present with more generalized daytime symptoms than men [4]. Women with OSA complain of symptoms such as insomnia, restless legs, depression, nightmares, palpitations, and hallucinations whereas men are more likely to report snoring and apneic episodes [7]. Women may consider their own snoring "unladylike" and therefore be less likely to mention it [4]. In addition, women are more likely to attend clinical appointments on their own, whereas men often attend with their partner [3]. Therefore, information from a partner on snoring and witnessed apneas may not be as readily available for women versus men. Less frequent reporting of "typical" OSA symptoms such as sleepiness and snoring by women, plus a higher prevalence of atypical symptoms such as insomnia, headache, anxiety, and depression, could contribute to the under-evaluation of OSA in women, lower referral rates to sleep clinics, and underrepresentation in clinical studies [8, 9].

In a community-based sample, women with OSA reported the same symptoms as men across a range of severities, and snoring was the most significant predictor of OSA for both sexes [9]. However, a similar study of a population-based sample found that up to 40% of women with an AHI > 15/h did not report any of the classic OSA symptoms (snoring, witnessed apneas, and daytime sleepiness) [7].

2.3. Recognition and Diagnosis. It is clear that many women do report classic OSA symptoms, suggesting that factors other than symptoms also contribute to gender disparity in OSA populations [9]. These include failure of women to acknowledge OSA symptoms and seek medical help or failure of medical professionals to respond to OSA symptoms in women [4, 9]. Adding to the difficulty in correctly diagnosing female patients is the reporting of symptoms such as depression and anxiety, which are also more common in female than male patients without OSA [10].

Data from the Wisconsin University Sleep Laboratory showed that lower rates of recognition of OSA in women versus men only occurred in the subset of patients with an AHI of 5–20/h [11]. Their findings led the study authors to hypothesize that there may be greater gender-related differences in OSA

symptom expression at lower AHI values, particularly with respect to characteristic symptoms such as snoring, witnessed apneas, and excessive daytime sleepiness.

Another difficulty in correctly diagnosing and treating OSA is understanding where the disease becomes significant and at what point treatment should be initiated. Large studies have typically shown an association between moderate severe OSA and poor cardiovascular outcomes, whereas the same association has not been found in mild OSA [12]. Growing evidence suggests that mild OSA is associated with reduced quality of life, including general tiredness, fatigue, daytime impairment, difficulty concentrating and completing tasks, depressed mood, poor sleep quality and insomnia, and poor psychomotor performance [1, 13–17].

3. Gender Differences in the Upper Airway, Fat Distribution, and Respiratory Stability

Definitive explanations for differences between men and women in the symptoms, characteristics, and severity of OSA are not yet available, but various factors may contribute.

The focus of a number of studies has been on the upper airway. Magnetic resonance imaging has shown that airway length, the tongue, the soft palate, and the total amount of soft tissue in the throat are all smaller in women than in men [18]. Although, intuitively, a smaller airway might be expected to occlude more easily than a larger one, this does not seem to be the case. It appears that men have a longer, softer oropharynx and a larger, fatter, more posterior tongue, increasing the susceptibility of the large airway to collapse [4]. Upper airway collapsibility, determined by the pharyngeal critical closing pressure, has been shown to be less in women versus men when the severity of OSA is the same [19]. Sex differences in airway collapsibility were most evident during non-REM sleep, suggesting that men may be more susceptible to pharyngeal collapse than women during established sleep, but not during sleep transition [20].

Obesity is a well-recognized risk factor for OSA, and higher body mass index (BMI) is associated with greater severity of OSA for both sexes [18]. However, for the same AHI, women tend to be more obese than men [19, 27]. One potential explanation for this is differences in fat distribution between the sexes [28]. For the same BMI, men tend to have higher mean body weight, free fat mass, and neck circumference compared with women [29]. MRI studies have confirmed less pharyngeal fat and lower soft tissue volume in the neck for obese women versus obese men [30]. Upper airway fat distribution, particularly in the posterior tongue, appears to be important in the pathogenesis of OSA and is related to gender [4]. Upper body and visceral adiposity have

been associated with reductions in lung function, including total lung capacity, forced vital capacity, and forced expiratory volume [31]. In addition, the independent effects of body fat distribution on lung function were more pronounced in men than in women [32].

Fat distribution might have physiological as well as mechanical effects in patients with OSA. Obese women, especially those with OSA, have been shown to have significantly increased hypercapnic and hypoxic responses, whereas this was not the case in obese men [33]. This adaptation might maintain adequate minute ventilation when the chest wall load is increased. In addition, men and women have been shown to require different levels of carbon dioxide in the blood to cause respiratory instability, and men were more susceptible to hypocapnic dysfunction during non-REM sleep than women. It is possible that women preserve ventilation output during hypocapnia more efficiently than men [34]. Indeed, the ventilatory response to hypercapnia has been shown to be greater in men than in women [35]. Thus, reduced lung function and decreased chemoresponsiveness are additional reasons why men are more susceptible to OSA than women.

There may also be gender differences in the arousal response to apneas. Jordan and colleagues found that during non-REM sleep men had a higher ventilatory response to apneas than women, but then they developed greater hypoventilation when they went back to sleep, especially in the supine position. This prolonged hypoventilation often leads to ventilatory instability upon returning to sleep. The study authors hypothesized that this may play a role in explaining why sleep apnea syndromes are more severe in men [36].

4. Manifestations

There are a number of gender differences in the manifestations of OSA; both the severity of OSA and its distribution across the sleep cycle differ in males and females. In patients with existing OSA, women had a significantly lower overall

AHI compared with men (20.2/h versus 31.8/h; $p < 0.001$); AHI during non-REM sleep was also significantly lower in women versus men (14.6/h versus 29.6/h; $p < 0.001$) but there was no difference between females and males with respect to AHI during REM sleep (42.7/h versus 39.9/h, resp.), suggesting greater clustering of apneic events during REM sleep in women [37]. This study also showed that OSA in the supine position occurred almost exclusively in men, indicating that positional OSA is not really an issue for women [37].
Polysomnographic data from patients referred for suspected sleep disorders also showed that a difference between males and females in AHI was evident during stage 2 sleep, but not during REM sleep [38]. In addition, women had shorter apnea

events and less severe oxygen desaturations than men (both p = 0.001) [38].

An interesting finding is that women are symptomatic at lower AHI cut-off values compared with men with the same AHI [9]. Females with an AHI of 2–5/h had a similar level of symptoms to men with an AHI of ≥15/h. In contrast, males with an AHI of 2–5/h were indistinguishable from those with an AHI of 0–2/h with respect to symptoms. One possibility is that the long-term effects of REM sleep disruption contribute to greater symptomatology at lower AHI values in women compared with men [39].

Another theory is that women may be more symptomatic because they have more episodes of upper airway resistance during sleep. Obstructive events can be thought of as a continuum from partial to complete upper airway obstruction. Upper airway resistance occurs early in this spectrum and describes events where resistance to airflow in the upper airway increases during sleep, presenting as flow limitation during polysomnography [40]. This increase in upper airway resistance could increase work of breathing, cause arousals and disrupted sleep, and impact daytime cognitive function [40]. Upper airway resistance alone, without complete obstructive apnea or respiratory disturbance, has been shown to produce clinical symptoms such as daytime fatigue and depression [41], both of which are symptoms reported by women with OSA.

Sleep architecture is another aspect that has been shown to differ between males and females. A study of 307 patients found that women took longer to fall asleep than men and, once asleep, had fewer awakenings and more slow wave (deep) sleep, despite no differences between the sexes in age, respiratory disturbance index, or oxygen saturation [42].

The occurrence of multiple episodes of upper airway resistance without frank apneas means that an AHI value may not provide a physician with a true indication of the degree of sleep fragmentation being experienced by patients. As a result, episodes during sleep where flow is reduced, respiratory effort increases, and the episode is terminated by an arousal have been termed respiratory effort-related arousals (RERAs) [40] (Figure 1). The importance of measuring and reporting RERAs has been emphasized by a task force of the American Academy of Sleep Medicine (AASM) [43].

Women with partial upper airway obstruction have been shown to have similar symptoms, including sleepiness, to women with OSA, resulting in a call for partial upper airway obstruction to be clinically recognized in the same way as OSA in women [44]. It has also been suggested that recognizing and understanding the different features of SDB in women are central for effectively detecting and treating the condition [45]. An update to the AASM

scoring criteria in 2012 broadened the definition of OSA, and this may

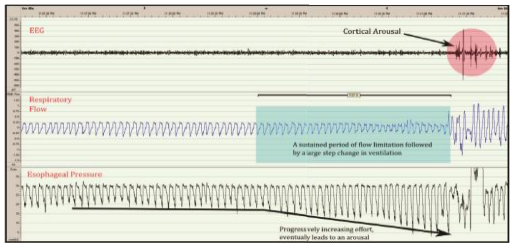

Figure 1: Respiratory effort-related arousals (RERAs). Trace shows a sustained period of flow limitation leading to increasing respiratory effort and arousal typical of RERAs. EEG: electroencephalography.

theoretically increase the number of patients with mild OSA. The AASM felt that there was sufficient evidence that hypopneas without associated oxygen desaturation, but rather hypopneas associated with arousal from sleep, were associated with significant daytime impairment and impacted quality of life to the point where treatment may be of benefit [1]. This is particularly relevant for female OSA patients because they are more likely to experience milder OSA with less severe oxygen desaturations. In addition, RERAs are now very rare with the new definition because most events of this nature can now be classified as hypopneas [1]. No prospective studies have investigated continuous positive airway pressure (CPAP) treatment in this newly defined group of patients with mild OSA; however, there is one randomized controlled trial underway which aims to do so (merge study, NCT02699463).

5. Menopause and Pregnancy

Differences between men and women in the prevalence of OSA decrease as age increases, largely as a result of a marked increase in the prevalence and severity of SDB in women after menopause [22, 46, 47]. Therefore, it has been suggested that female sex hormones have some sort of protective effect on upper airway patency and/or ventilatory drive [39]. The hormone progesterone is a known respiratory stimulant which increases chemoreceptor responses to hypercapnia and hypoxia and has been shown to increase upper airway muscle tone [48]. Progesterone levels decrease after menopause.

Hormones may also play a role in the distribution of body fat. Postmenopausal women have a higher fat mass compared to the period prior to menopause, and fat distribution is more likely to be in the upper body and trunk area compared with the lower body [49, 50]. In female volunteers, activity of the genioglossus muscle during wakefulness was lower in postmenopausal women compared with premenopausal women and significantly increased after 2 weeks of hormone replacement therapy [51].

Women may be at increased risk of OSA during pregnancy due to a number of factors. The growing uterus elevates the diaphragm, changing pulmonary mechanics [52]. In addition, during pregnancy, neck circumference increases [53, 54], nasal patency is reduced [55], and pharyngeal edema occurs [56]. Substantial increases in snoring, snorting/gasping, and witnessed apneas have been documented in

pregnant women [54]. Snoring during pregnancy appears to be a risk factor for both pregnancy-induced hypertension and intrauterine growth retardation [57]. An ongoing study in this area will enrol 3702 women to understand the prevalence and outcomes of OSA during pregnancy [58]. Preliminary data from this group found that OSA affects 8.1% of pregnant women by the second trimester and that there was an association between OSA and hypertension and diabetes in this group [59].

There are limited data on the treatment outcomes of OSA during pregnancy, and no randomized controlled trials have been conducted in this area. Small studies have shown that CPAP treatment reduces blood pressure during pregnancy even when OSA is mild [60] and may improve pregnancy outcomes compared with untreated OSA [61, 62]; however, more research is required in this area.

6. Quality of Life

Several comparisons of women and men with untreated OSA have found that women report impaired quality of life. Women complain of more mood disturbances such as anxiety and depression, report low quality of life scores on a range of questionnaires, and display increased daytime fatigue, reduced sleep quality, and worsened neurobehavioral symptoms [63–66]. One limitation of these studies is that females were generally compared to males with OSA, rather than matched controls, meaning that there are no data on how female OSA patients differ from those in the general female population, where mood disturbances such as anxiety and depression can be common.

7. Health Consequences of OSA and Effects of Treatment

OSAS has been associated with elevated cardiovascular risk and increased morbidity and mortality [67]. Observational studies have shown that adequate treatment of OSA with CPAP can reduce the incidence of cardiovascular events in patients with any severity of symptomatic OSA [68, 69]. The evidence for non-sleepy patients is mixed, with two short-term randomized studies showing no cardiovascular improvement in non-sleepy patients [70, 71]. However, a recent study by Barbe et al. included 725 non-sleepy patients´ with an AHI ≥20/h who were randomized to CPAP or a control group. There were fewer cases of new hypertension and cardiovascular events in the CPAP group, although this did not reach statistical significance (CPAP versus control group incidence density ratio (IDR) 0.81, confidence interval [CI] 0.61–1.06; □ = 0.13). However, an analysis of those using PAP for ≥4 hours/night compared with the control group had an IDR of 0.69 (CI 0.50–0.94; □ = 0.02) compared with an IDR of 1.12 (CI 0.77–1.64; □ = 0.55) for those using CPAP <4 hours/night [72]. Due to the associations between OSA and harmful cardiovascular

consequences, many researchers advocate for CPAP treatment of all patients, regardless of symptoms [73].

It has been postulated that non-sleepy patients will not be adherent to treatment; however, a recent large prospective trial has shown that long-term CPAP treatment is feasible in non-sleepy moderate-to-severe OSA patients [74].

7.1. Gender Differences in the Health Consequences of OSA. In the past, the belief that OSA was primarily a male disorder meant that clinical trial populations were comprised almost entirely of males [5]. Recently, studies have focused more specifically on the unique consequences of OSA in female patients.

Greenberg-Dotan et al. found that, compared to female controls, women with OSA were more likely to have a comorbid diagnosis including cardiovascular disease (odds ratio [OR] 1.4), hyperlipidemia (OR 1.5), diabetes (OR 1.6), asthma (OR 2.1), hypothyroidism (OR 1.6), arthropathy (OR 1.6), and reflux/gastritis (OR 2.5) [65].

Yaffe et al. studied a group of women with SDB and found that they were more likely to develop cognitive impairment or dementia than those without SDB. Cognitive issues were more likely to develop in patients with increased oxygen desaturation and higher periods of time spent in apnea or hypopnea [75]. Another study showed that female OSA patients experienced more brain white matter injury than their male counterparts [64]. It is hypothesized, though not yet known, that this change in white matter structure may be responsible for the worsened quality of life reported by women.

Sympathetically mediated responses to autonomic challenges in patients with OSA are blunted to a significantly greater extent in women versus men with OSA; this deficit is likely to reduce the effectiveness of BP regulation and brain perfusion [76]. In addition, it is possible that women with moderate sleep apnea are more susceptible to the adverse cardiovascular consequences of OSA than men, having been shown to have more marked endothelial dysfunction [77]. Certainly, untreated severe OSA has been independently and significantly associated with cardiovascular death in women [78, 79]. Conversely, the contribution of OSA to hypertension has been shown to be lower in women versus men [80].

The ability of CPAP treatment to improve outcomes in females has not been studied as extensively as in males. A prospective study by Campos-Rodriguez et al. evaluated the long-term outcomes of OSA in treated and non-treated female patients. They found that severe OSA was associated with increased cardiovascular mortality risk (adjusted hazard ratio 3.50, 95% CI 1.23–9.98) and that adequate CPAP treatment may reduce this risk [78].

In summary, the limited data available suggest that although the prevalence and severity of OSA may be lower in women than in men, the consequences of the disease are at least the same, if not worse [63].

8. OSA Treatment

In 2006, the American Academy of Sleep Medicine (AASM) reviewed all available evidence for CPAP and concluded that treatment was effective in improving quality of life in severe and moderate OSA, but there was insufficient evidence for the effectiveness of CPAP in mild OSA [81]. More recent data showed that CPAP treatment significantly improved quality of life compared with sham treatment in 223 mild-moderate patients (AHI 5–30/h) [82]. In addition, CPAP treatment was associated with significant improvements in quality of life in female OSA patients on a number of measures including daytime functioning, activity levels, daytime sleepiness, mood disturbances, and impact of sickness on daily life [63]. Campos-Rodriguez et al. recently published the first study to review the quality of life impact of CPAP treatment in women with moderate-to-severe OSA. Compared with the control group, the CPAP group had significantly greater improvements in all quality of life measures, including sleepiness

(< 0.001), mood (= 0.012), anxiety (= 0.014), and depression (= 0.016) [83].

Craig et al. randomized 391 non-sleepy mild OSA patients to CPAP therapy or standard care for 6 months and found that CPAP improved daytime sleepiness (based on ESS scores), objective sleepiness, and self-assessed health status (SF36), but not vascular health risk [84]. Interestingly, Craig et al. found no relationship between OSA severity and improved quality of life, indicating that the severity of OSA may not accurately predict CPAP effectiveness. In 2016, the American Thoracic Society again reviewed the evidence available for CPAP treatment of mild OSA. They concluded that patients with sleepiness may benefit from treatment and that CPAP may also improve quality of life. They found that there was still insufficient evidence to understand the impact of mild OSA treatment on cardiovascular events, stroke, and arrhythmias [17].

8.1. Gender Differences in OSA Treatment. Sex differences in the response to different OSA treatment strategies have not been extensively studied to date. The limited data available indicate that usage is similar between males and females. A review of a database of 4281 patients found that average daily CPAP usage in male patients was slightly higher than in female patients; however, average usage time in both genders was high (377±94 versus 370±96 min) [85]. A similar analysis followed up a group of 708 women for a median of 6.2 (4.2– 7.7) years. Overall long-term compliance with treatment was good in female patients, with median daily usage of 6 hours per day (interquartile range 4–7); 82.8% of patients were still using CPAP

after 5 years, and 79.9% were still on CPAP at 10 years [86].

Clinical trials have indicated that males require higher CPAP pressure than females, after adjusting for baseline OSA severity and BMI [87, 88]. However, there do not appear to be differences between men and women in the types of interfaces used for CPAP or overall satisfaction with mask treatment [89].

Given that there are marked differences between men and women in the physiology and presentation of OSA, it is possible that treatment options specifically targeting female presentations of OSA may result in better treatment outcomes for these patients [85, 87, 88]. One recent bench test has found that there are significant differences in the way commercially available CPAP devices respond to flow limitation common in female patients [90]. Personalized medicine has not made major inroads into OSA, despite the potentially different gender and potential symptom specific phenotypes [91]. One commercially available CPAP device contains an algorithm which aims to address female-specific OSA characteristics. This device was tested in a randomized, double-blind, crossover clinical trial and was found to be as effective as standard CPAP, with a significant reduction in residual flow limitation and lower mean pressures [92]. An ongoing clinical study is investigating the use of this device on quality of life in women, with outcome measures including daily functioning, sleepiness, depression, sexual function, and sleep quality (NCT02400073).

Non-CPAP treatments have rarely been studied for gender specific effects. Mild patients are often instructed to lose weight; however, this may be more beneficial for males than females based on the fat distribution in the upper airway of males [93].

Mandibular Advancement Devices (MADs) are a treatment option for those with mild-moderate OSA or those who have rejected CPAP. One large study found that female gender was a predictor of MAD treatment success, particularly when OSA was mild [94]. However, more research is needed in this area.

9. Conclusion

A growing body of evidence suggests that there are substantial differences between females and males in the symptoms, diagnosis, and consequences of OSA. The majority of existing data relate to populations with a predominance of males, particularly with respect to treatment. Better knowledge of gender differences in OSA will help to improve the awareness and diagnosis of OSA in women, and the development and availability of therapeutic options that take into account differences in the physiology and presentation of OSA in women could have the potential to improve outcomes for these patients.

Competing Interests

The authors are all employees of ResMed. ResMed is the manufacturer of products for the diagnosis and treatment of sleep-disordered breathing.

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Appendix B

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SMGroup

Gender Differences in Obstructive Sleep Apnea

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ABSTRACT

Historically OSA has been regarded as a male disease. Therefore, much of our knowledge comes from studies with largely male populations. Growing evidence suggests that there are significantly different gender aspects of OSA. The symptoms of OSA may manifest differently in female patients, and females tend to be diagnosed and treated less often, despite reporting worse quality of life outcomes. Comparisons of polysomnography data have shown that women appear to have less severe OSA overall with a higher incidence of flow limitation and REM related events. Severe OSA in women appears to be associated with cardiovascular morbidity and mortality, and effective treatment may reduce this risk. Researchers are beginning to understand more about gender differences in OSA, and the optimal treatment for these patients, although more research in this field is still needed.

PREVALENCE

Obstructive sleep apnea **(OSA)** is a condition during which the upper airway closes repetitively during sleep. Airway closures are identified as either apneas (full upper airway closure) or hypopnoea as (partial

upper airway closure), where the event is associated with oxygen desaturation and /or arousal from sleep. The count of events per hour; the apnea hypopnea index **(AHI)**, indicates the severity of the disorder.

The estimated prevalence of OSA changes depending on which scoring criteria are used. Table 1 displays the estimated population prevalence of OSA in males and females.

Table 1: Estimated population prevalence of OSA.

Study	Mild OSA (AHI ≥ 5)		Moderate to severe OSA (AHI ≥ 15)	
	Males	Females	Males	Females
Young *et al* (1993) [2]	24%	9%	9%	4%
Redline *et al* (1994) [5]*	-	-	26%	13%
Bixler*et al* (1998, 2001) [64,65]	17%	-	7%	2%
Duran *et al* (2001) [66]	26.2%	28%	14%	7%
Peppard *et al* (2013) [67]	-	-	13.5%	6%
Franklin *et al* (2013) [33]^#	-	50%	-	26%
Heinzer*et al* (2015)#	34%	38%	49.7%	23.4%

*Respiratory Disturbance Index **(RDI)** rather than AHI given.

^ Women aged 20-70 years.

#An updated scoring criteria (AASM 2012) was used.

The prevalence of OSA has been increasingly steadily, in part due to the global rise in obesity, and also due to an update to the recommended OSA scoring rules which were published in 2012 and allow a more liberal scoring of hypopnoeas [1].

CLINICAL FEATURES

While the prevalence of OSA in males is reported to be higher than that of females, there is a much higher discrepancy between the genders in the clinical population. OSA is estimated to have a male to female ratio of between 3:1 and 5:1 in the general population and between 8:1 and 10:1 in some clinical populations [2-5].

It has been hypothesised that the large discrepancy between the population prevalence of OSA, and the clinical populations is due to women being frequently misdiagnosed [4,6]. Women often present with different symptoms than what are considered the "typical" symptoms of sleep apnea [4,7]. The typical symptoms that men with sleep apnea present with are snoring, witnessed apneas and excessive daytime sleepiness. However approximately 40% of women with an AHI ≥ 15 do not report any of the classic OSA [8]. Instead women are likely to complain of insomnia, fatigue, daytime tiredness, headaches, muscle pain and depression [4,9,10]. As a result, women are frequently misdiagnosed with depression or another illness [4,9]. In addition, women typically have lower scores than men on the Epworth sleepiness scale **(ESS)**, a questionnaire designed to evaluate daytime sleepiness which is often used as a screening tool for

OSA [11,12]. The ESS has not been validated for use in female OSA patients, and indeed in population based studies OSA has not been strongly associated with daytime sleepiness in female patients [11,12]. It is hypothesized that women may use different words to describe sleepiness, and answer questions on sleepiness differently from men. Or they may have a higher threshold for sleepiness or simply be less inclined to complain about it [4].

Men often attend clinical appointments with their partner, whereas women are more likely to attend on their own [3,4]. This may mean that perhaps apneas in women are less frequently reported [3], or that male partners tend to be less concerned about the events [13]. It has also been hypothesized that women may be reluctant to complain about disturbed sleep and their own snoring, if they consider it unladylike or embarrassing [4].

Regardless of the symptoms which patients present with, Young and colleagues found that even when women did report the same classic symptoms of OSA, such as snoring, witnessed apneas and excessive daytime sleepiness, they were still less likely to be referred to sleep clinics than men. They raised the issue that physicians tend to disregard these typical symptoms in women [6]. Similar results were recently reported by Lindberg et al, who found that women were underrepresented at sleep clinics, and despite similar symptoms to males, less likely to be diagnosed or treated with OSA [14].

GENDER DIFFERENCES IN POLYSOMNOGRAPHY

Recent studies have shown that the polysomnography **(PSG)** features of female OSA are different from male OSA. Overall, women have less severe OSA with lower AHIs [15] and shorter apneas [16]. Although overall women have lower AHIs than males, research has shown that women are more symptomatic at lower AHI's than males with a similar diseases severity [6].

One reason women are more symptomatic may be because women have more episodes of upper airway resistance [17]. Obstructive events can be thought of as a continuum of partial to complete upper airway obstruction. Upper airway resistance occurs early in this spectrum, and refers to incidences where there are increases in resistance to airflow in the upper airway during sleep, presenting as flow limitation on a PSG [18].This upper airway narrowing has the potential to increase work of breathing, cause arousals and disrupted sleep, and effect daytime cognitive function [18]. Upper airway resistance alone, without complete obstructive apnea, has been shown to produce clinical symptoms such as daytime fatigue and depression [19].

As females may have multiple episodes of upper airway resistance without frank apneas, the AHI value may not give the physician a true indication of the degree of sleep fragmentation a patient is experiencing. As a result, episodes during sleep where the flow is reduced; respiratory effort increases; and the episode is terminated by an arousal have been coined Respiratory Effort Related Arousals **(RERAs)** [18]. The importance of measuring and reporting on RERAs has been emphasised by a task force of the American Academy of Sleep Medicine **(AASM)** in 2007[20]. Updates to the recommended scoring criteria by the AASM in 2012 meant that hypopnoeas could be defined by an arousal only, with no requirement for oxygen desaturation [1]. This broader definition means that less RERAs are scored and more female patients may now be diagnosed with OSA, who previously may not have met the requirements for hypopnoeas. This is likely reflected in the increase in the prevalence of female OSA seen in recent studies.

Women often have events mainly occurring during REM sleep [15]. Body position is far less important for the severity of OSA in women, while with men the severity is more based on position than sleep state [15]. In fact a study by O'Connor and colleagues found that in a group of 830 patients, positional OSA was almost exclusively a male presentation [15].

Sleep architecture is also different in healthy men and women with sleep apnea. A study of 307 patients by Valencia-Flores and colleagues found that women took longer to fall asleep than males. Once women were asleep, they then had fewer awakenings from sleep, and had slower wave (deep) sleep than males [21].

GENDER DIFFERENCES IN PATHOPHYSIOLOGY

In women, the neck and upper airway are smaller in size than in men [4]. MRI imaging has shown that the airway length, the tongue, the soft palate, and the total amount of soft tissue in the throat are all smaller in women than men [22]. Although common sense would dictate that a smaller airway size would collapse more easily than a larger one, this isn't the case. The pharyngeal critical closing pressure, or Pcrit, is lower in women with sleep apnea than men with the same severity of obstructive sleep apnea, meaning that the airway of males is more collapsible than that of females [4,23].

Obstructive sleep apnea has long been associated with obesity, and in both genders increased body mass index indicates a higher severity of the disease [24]. However women with OSA are typically more obese than men who have the same AHI [9]. One possible explanation for this is the differences in fat distributions between the genders. Men tend to put on weight in the upper body and trunk, including the upper airway soft tissue structures – the tongue, soft palate, and lateral pharyngeal walls; whereas when women put on weight it tends to be deposited in the lower body and extremities [4]. Newman and colleagues showed that small weight changes influence sleep disordered breathing in men more than in women as men may reduce fatty tissue in the upper airway more readily [25]. Fat distribution also affects the lungs in different ways between men and women. Women are better able to cope with an increased chest wall load, because with increased obesity women have improved chemosensitivity responses to hypoxia and hypercapnia [22].

Respiratory stability refers to efficacy of gas exchange, blood circulation and the functioning of central and peripheral chemoreceptors. There are distinctive differences between the efficacy of respiratory stability in men and women [4]. The response to low oxygen in the blood (hypoxia) declines in men during sleep compared with their awake values, whereas in women the hypoxia response is similar between sleep and wake [26]. Men have been shown to have a more significant ventilatory response to high levels of carbon dioxide in the blood (hypercapnia) [27]. Zhou and colleagues showed that men and women require different levels of carbon dioxide in the blood to cause respiratory instability, and that men are more susceptible to hypocapnic dysfunction during NREM sleep than women. This may be due to the notion that women preserve ventilation output during hypocapnia more efficiently than men [28]. Taken together, this may mean that women are better able to stabilise their breathing during sleep, leading to less severe apneas with minimal desaturation.

There may also be gender differences in the arousal response patients have to apneas. Jordan and colleagues found that during NREM men had a higher ventilatory response to apneas, but then they developed a greater hypoventilation when they went back to sleep, especially in the supine position. This

prolonged hypoventilation often leads to ventilatory instability upon returning to sleep. The result can be a cycle of respiratory instability leading to consecutive apneas during sleep. Jordan and colleagues hypothesised that this may play a role in explaining why sleep apnea is more severe in men [29]. However the same authors also found that loop gain was not different in males and females matched for AHI and BMI, and therefore respiratory control stability may be less significant than reduced upper airway collapsibility in female patients [30].

The prevalence of sleep apnea increases in post-menopausal women [9]. One reason for this increase may be that menstrual hormones play a role in the distribution of body fat. Post menopausal women have more body fat than menstruating women, and that body fat is distributed in similar areas to males, which is the upper body, specifically the trunk and neck [31]. A second reason that post menopausal women have increased incidence of sleep apnea may be due to the hormone progesterone. Progesterone is a known respiratory stimulant which increases chemoreceptor responses to hypercapnia and hypoxia and has also been shown to increase upper airway muscle tone [32].

HEALTH CONSEQUENCES OF OSA IN FEMALES

In the past, obstructive sleep apnoea **(OSA)** has been primarily considered a male disorder, and as a result clinical trial populations were comprised almost entirely of males [33]. Recently studies have focused more specifically on the unique consequences of OSA in female patients.

Several comparisons of women and men with untreated OSA have found that women experience a worsened quality of life. Women experience more mood disturbances such as anxiety and depression, report lower quality of life scores on a range of questionnaires, display increased daytime fatigue, reduced sleep quality and worsened neurobehavioral symptoms [34-37]. This worsened quality of life found in female patients may well be a reflection of the more severe flow limitation and sleep fragmentation seen in many women patients. Basically sleep physiology tells us that constant arousals during sleep in healthy subjects severely impacts daytime cognitive performance [38]. And indeed arousals from sleep without corresponding oxygen desaturation have been associated with a range of consequences including tiredness, fatigue and sleepiness [39]; significant daytime impairment, difficulty completing tasks, depressed mood and insomnia [40].

Women with OSA were also found to be more likely to develop hypothyroidism and arthropathy, as well as experience lower perceived health status, overuse psychoactive drugs, and experience increased healthcare costs of 1.3 times compared with men with OSA [36].

Yaffee al. studied a group of women with sleep disordered breathing **(SDB)** and found that they were more likely to develop cognitive impairment or dementia than those without the condition. They found that cognitive issues were more likely to develop in those with increased oxygen desaturation and higher periods of time spent in apnea or hypopnoea [41]. Further research undertaken by Macey and colleagues discovered that female OSA patients experienced more brain white matter injury than their male counterparts [35]. It is hypothesised, although not yet known, that this change in white matter structure may be responsible for the worsened quality of life reported by women.

Endothelial function, peak blood flow, systemic inflammation, and digital vascular function have been found to be more impaired in females than males with OSA [42-44]. These blunted responses may mean that women with OSA are more susceptible to the adverse cardiovascular consequences of OSA than males [44]. The association between OSA and hypertension in females is not conclusive, with some studies showing no association [45,46], and some studies finding an association in peri-menopausal and older females [47,48]. The largest dataset published to date included 1 704 905 patients with OSA and 1 704 417 matched controls. The authors reported that hypertension was more prevalent in women with OSA than males with OSA, with an overall odds ratio of developing hypertension of 2.14 in the OSA group compared with controls [49].

The same data set found that congestive heart failure was strongly associated with OSA in both sexes compare with controls ($p<0.000$) with no clear sex differences [49]. A prospective study by Campos-Rodriguez et al. evaluated the long term outcomes of OSA in a group of treated and nontreated female patients. They found that severe OSA was associated with increased cardiovascular mortality risk (adjusted HR 3.50, 95% CI 1.23-9.98), and that adequate CPAP treatment may reduce this risk [10].

THE ROLE OF PREGNANCY

Pregnancy may also increase the risk of developing OSA. During a typical pregnancy, elevation of the diaphragm leads to reduced functional residual capacity, the upper airway narrows, neck circumference enlarges, nasal patency is reduced, and there is substantial weight gain. All of these factors suggest pregnancy may induce or exacerbate OSA [4]. Conversely, pregnant women may be more protected from OSA, with increased levels of female sexual hormones stimulating respiration [50].

While the effect of OSA on pregnancy outcome is not completely understood, some studies have found that OSA is associated with higher rates of pre-eclampsia and intra-uterine growth retardation [51]. An ongoing study in this area will enrol 3702 women to understand the prevalence and outcomes of OSA during pregnancy [52]. Preliminary data from this group found that OSA affects 8.1% of pregnant women by the second trimester, and that there was an association between OSA and hypertension and diabetes in this group [53].

TREATMENT OF OSA IN FEMALES

The treatment of choice for OSA is continuous positive airway pressure **(CPAP)**. CPAP attaches to the user with a mask and tubing, and circulates air to increase pressure in the upper airway. The result is a pneumatic splint which holds the airway open and prevents collapse. Effective treatment with CPAP has been shown to improve symptoms and reduce health risks in OSA patients [54].

Personalized medicine has not yet made major inroads into OSA treatments. However due to the different structures and pathologies involved in the disease, personalized diagnostic methods and treatments should be introduced as a way to improve patient care [55]. Sex differences in the use and response to CPAP devices are one example of personalized treatment which has not been extensively studied to date. A review of a database of 4281 patients found that average daily CPAP usage in male patients was slightly higher than in female patients, however usage in both genders was high (377 ± 94 vs. 370 ± 96) [56]. A similar analysis followed a group of 708 women for a median of 6.2 (4.2-7.7) years. Overall

long term compliance to treatment was good in female patients, with a median daily usage of 6 (IQR 4-7) hours per day. 82.8% were still using CPAP after 5 years, and 79.9% were still on CPAP at 10 years [57].

The first study to investigate the role of CPAP therapy on quality of life in only female patients has recently been published. The authors studied 307 women with moderate to severe OSA and found that three months CPAP use improved quality of life, anxiety, depression, mood and daytime symptoms compared with controls [58].

Few studies have focused on the physiological differences in women when considering treatments. Clinical trial data suggest that men require higher pressures during CPAP therapy than females, after adjusting for baseline OSA severity or BMI [56,59,60]. One recent bench test has found that there are significant differences in the way commercially available CPAP devices respond to flow limitation common in female patients [61]. One CPAP device contains an algorithm which aims to address female specific OSA characteristics. This device was tested in a randomised, double-blind, cross-over clinical trial and was found to be as efficacious as a standard CPAP with a significant reduction in residual flow limitation and lower mean pressures [62]. An on-going clinical study is investigating the use of this device on quality of life in women, with outcome measures including daily functioning; sleepiness; depression; sexual function and sleep quality (clinicaltrials.gov registration: NCT02400073).

Non CPAP treatments have rarely been studied for gender specific effects. Weight loss is a common recommendation for mild patients; however this may be more beneficial to males than females based on the fat distribution in the upper airway of males [25]. Mandibular Advancement Devices **(MADs)** are a treatment option for those with mild-moderate OSA or those who have rejected CPAP. One large study found female gender was a predictor of treatment success, particularly in the mild group [63]. However more research is needed in this area.

CONCLUSION

Historically, our understandings of OSA and its treatments have been largely focused on male patients. There are clear gender differences in all aspects of OSA, including prevalence; symptoms; clinical recognition; anatomy (Including the upper airway, as well as obesity and fat distribution); physiology & pathophysiology (Including sleep architecture & respiratory stability) and the influence of hormones.

Knowledge is coming to light that there may also be differences in long term consequences and cardiovascular outcomes of female OSA. Additionally, there may be requirements for gender specific treatment options. More research is required to complete our understanding of the gender differences in OSA and the optimal treatment for patients.

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Appendix C

Wimms A, Kelly J, Benjafield A, Calverley P, Craig S, McMillan A, O'Reilly J, Penz E, Stradling J, Turnbull C, Willes L, Morrell M. Does treating mild obstructive sleep apnea with CPAP improve quality of life? Rationale and design of the MERGE study
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Does treating mild obstructive sleep apnea with CPAP improve quality of life?

Rationale and design of the MERGE study

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ABSTRACT

Evidence-based treatment of mild obstructive sleep apnea (OSA) is hindered by a lack of research, specifically whether continuous positive airway pressure (CPAP) treatment is beneficial in this group. In addition, definitions of respiratory events are not always consistent. The American Academy of Sleep Medicine (AASM) definition of hypopnea was revised in 2012, resulting in a significant increase in the number of patients meeting diagnostic criteria for mild OSA. The MERGE study is a multicenter, randomized, controlled clinical trial designed to investigate the efficacy of CPAP treatment in mild OSA, focusing on the AASM 2012 criteria to define disease severity. Patients with mild OSA, defined using both AASM 2007 and 2012 criteria, will be randomized to receive 3 months' treatment with either standard care (sleep hygiene counseling) alone or CPAP plus standard care. The primary outcome is change in the Energy and Vitality subscale of the Short Form-36 from baseline to three months in patients with mild OSA (apnea-hypopnea index 5–15/h) based on the AASM 2012 scoring criteria. The MERGE study will be the first randomized controlled trial to investigate the impact of CPAP treatment on symptoms and quality of life in patients with mild OSA according to the AASM 2012 criteria. It is hoped that the findings will provide evidence to inform physicians and policy makers about how to manage mild OSA in clinical practice.

Keywords: continuous positive airway pressure; obstructive sleep apnea; quality of life; study design; randomized controlled trial**;** treatment adherence

1. Introduction

The severity of obstructive sleep apnea (OSA) is conventionally defined using the number of disordered breathing events per hour of sleep (the apnea-hypopnea index [AHI]): mild when the AHI is 5–<15/h, moderate when AHI 15–<30/h, or severe when AHI is ≥30/h. However, the definition of AHI has evolved over time making development of clear guidelines difficult.

Moderate and severe OSA have been associated with increased risk of motor vehicle accidents, impaired cognitive function, reduced quality of life (QoL), and diseases such as hypertension, diabetes, stroke and cardiovascular morbidity (52, 54-57). In this setting, continuous positive airway pressure (CPAP) is an effective treatment, improving symptoms and reducing health risks (54, 57-61). Despite this, mild OSA has not been extensively studied. There is some evidence that low levels of sleep-disordered breathing have a negative impact on hypertension (104, 105), cognitive function (106, 107), QoL (95, 108), and the risk of motor vehicle accidents (109). However, there is no agreement on the best approach to treating mild OSA (95, 172). In terms of QoL, there is a lack of data on the effectiveness of CPAP in mild OSA (58), but it may be useful in this setting if QoL is impaired and other treatments have failed (234), or in the presence of sleepiness (95).

Interpretation of data from studies evaluating CPAP in patients with mild OSA is complicated by the fact that definitions of hypopneas have changed over time. The 2007 American Academy of Sleep Medicine (AASM) criteria defined hypopnea as a ≥30% decrease in oronasal airflow from baseline for ≥10 seconds with oxygen desaturation of ≥4% (1). In 2012, the AASM modified these criteria to allow scoring based on arousal only or with ≥3% oxygen desaturation (1) (Table 1). The rationale for updating the criteria was that some patients who experience frequent respiratory events and arousals (insufficient to cause significant hypoxia) were not captured using the 2007 criteria but may benefit from diagnosis and treatment (1). The change in scoring criteria markedly increases the number of patients achieving the diagnostic criteria for OSA, potentially by up to 40% (4, 5).

The 2012 change to hypopnea scoring criteria remains controversial, partly due to the lack of objective evidence that patients with mild OSA based on these criteria will benefit from treatment. To date, no adequately powered randomized controlled trials have studied the benefits of CPAP treatment in this expanded group of mild OSA patients. Therefore, the minimum degree of OSA likely to benefit from CPAP therapy has not yet been defined.

The majority of studies conducted in mild OSA have used sleepiness as the primary endpoint. However, the term “sleepiness” may not adequately capture the feelings of general tiredness, fatigue, poor sleep, insomnia, and lack of energy often reported by patients with mild OSA (11, 90, 95). Therefore, the MERGE study has been designed to evaluate the effects of CPAP treatment on QoL in patients with mild OSA, using outcomes such as energy and vitality that may reflect patient-relevant improvements.

2. Methods

2.1 Study overview

The MERGE study is a multicenter, randomized, controlled clinical trial (NCT02699463) designed to measure the response to CPAP using a patient-centered outcome, the Energy and Vitality subscale of the Short Form-36 (SF-36). A number of other QoL measures have also been included (e.g. fatigue, depression, anxiety and insomnia) in order to better understand the impact of treatment on OSA symptoms in patients diagnosed with mild disease. Patients will be provided with support to optimize adherence to CPAP, and a health economic analysis is included. The first patient was randomized in November 2016, and the study completed recruitment in February 2019.

2.2 Setting

Recruitment to the MERGE study is via the UK respiratory sleep network (Table 2), which has delivered other randomized controlled trials in the UK (61, 175, 235, 236). The MERGE study is a collaboration with industry, which has provided equipment, funding and ongoing study support. Eleven centers throughout the UK are recruiting to the study. Each site has completed standardized study training, and sites communicate regularly, both by phone and in-person meetings, to share experiences and best practice findings.

2.3 Eligibility criteria

Patients are screened for OSA by their local sleep service using a home sleep test (polygraphy; Apnealink Air, ResMed). Those with an AHI of 5-15/h based on automated analysis using AASM 2007 criteria or an AHI 0-4.9/h using AASM 2007 but ≥5/h using AASM 2012 scoring and

who meet all other selection criteria (Table 3) are eligible for inclusion (Figure 1). Patients who provide informed consent have their polygraphy data uploaded to a central study server.

2.4 Randomization

Randomization (1:1 ratio) to standard care (sleep hygiene counseling) alone, or standard care plus auto-adjusting CPAP (AirSense 10 AutoSet; or AirSense 10 AutoSet for Her, ResMed)) is performed centrally using a computer-generated schedule, with stratification by age, gender, and body mass index (BMI).

2.5 Blinding

Neither the patients nor the investigators can be blinded due to the nature of the study interventions. However, assessment of sleep studies is automated (unbiased and consistent), and research staff assessing outcomes are independent from the study and study sponsor.

3. Treatment intervention

3.1 Standard care

All patients are given sleep hygiene counseling, based on national guidelines and recommendations from the UK National Health Service. Patients receive standardized information on healthy sleep behaviors, such as spending adequate amounts of time in bed, and setting up a bedroom that is conducive to sleep. Patients are given a take-home sheet summarizing the main points of the consultation, and will receive a telephone call from a Central Support Laboratory three days later for a review of sleep hygiene behaviors.

3.2 Auto-adjusting CPAP

All patients use CPAP for a one-hour run-in at their local site as part of their eligibility testing. During this test, CPAP is slowly increased from 4 to 10cm H_2O. Patients are able to change the CPAP mask and test different comfort and humidification settings. Participants randomized to the CPAP group are given CPAP education by the local clinical team and then provided with an auto-adjusting CPAP device for home use (AirSense 10/AirSense 10 for Her; ResMed). CPAP patients also receive

a phone call from the central laboratory after 3 days, with a focus on CPAP usage and troubleshooting any issues identified by the patient. During study therapy, changes to CPAP settings will be made based on standard clinical practice by the Central Support Laboratory.

3.2.1 Supporting CPAP adherence

A Central Support Laboratory has been set up in order to assist CPAP patients. Throughout the study, patients in the CPAP group are monitored using a telemedicine solution (AirView patient management system, ResMed). The online system receives data wirelessly from registered devices each day after overnight use. These data are regularly monitored by the Central Support Laboratory (at least twice per week). The Central Support Laboratory intervenes when compliance is low (<4 h/night) for ≥3 consecutive nights, or when other issues are identified (e.g. high mask leak [>24 L/min] or suboptimal treatment [residual AHI ≥5/h]). If issues are identified, the Central Support Laboratory contacts the patient to discuss the issues and troubleshoot potential solutions. Contact is made via email, phone or video calls. Face-to-face visits are organized with the local sleep service if necessary. Patients are encouraged to contact the Central Support Laboratory at any time if they have any concerns. In addition to the ability to contact the Central Support Laboratory with any CPAP-related issues, patients are encouraged to use a web-based application (myAir, ResMed), which wirelessly collects data from the patient's device and provides automated feedback, education, resources and coaching tips direct to the patient.

4. Data collection and measures

At the first study visit, medical history and information on gender, age, ethnicity, height, weight, and neck circumference are collected, and patients are asked which symptoms prompted them to visit their health care provider. Patients also complete a range of QoL questionnaires: Short Form-36 (SF-36; 8 scales, and 2 domains [physical and mental composite]); Epworth Sleepiness Scale (ESS); Fatigue Severity Scale (FSS); Functional Outcomes of Sleep Questionnaire (FOSQ); Hospital Anxiety and Depression Scale (HADS); Insomnia Severity Index (ISI); and EuroQol five dimensions (EQ-5D). At the final study visit after 3 months' treatment with standard care or standard care + CPAP, patients return to their local sleep service for the final study

visit where they complete the same group of questionnaires as at baseline. Those in the treatment group will be asked if they wish to continue CPAP therapy.

All sleep studies are scored using automated scoring algorithms based on both AASM 2007 and AASM 2012 criteria. AASM 2007 scoring is done via AirView software (ResMed). This scoring algorithm has been shown to be consistent with manual polysomnography (PSG) scoring in several studies (189, 190, 237-241)_ENREF_11_ENREF_12_ENREF_15_ENREF_16. AASM 2012 scoring is done by an algorithm (ResMed) that is being concurrently validated in another clinical trial (clinicaltrials.gov ID: NCT03470493).

5. Outcomes

5.1 Primary outcomes

The primary endpoint is change from baseline to 3 months in the Energy and Vitality component of the SF-36 questionnaire in patients with mild OSA based on the AASM 2012 scoring criteria.

5.2 Secondary outcomes

Secondary endpoints are change from baseline to 3 months in patients with mild OSA based on either the AASM 2012 or AASM 2007 criteria in the following QoL measures: SF-36; ESS; FSS; FOSQ; HADS; ISI; and EQ-5D.

5.3 *Health economics analysis*

The main objective of the health economics analysis will be to determine the cost effectiveness of CPAP treatment versus standard care for the management of mild OSA over an individual's lifetime from the perspective of the publicly funded healthcare system. A Markov model will be developed, including health outcomes (health utility values, deaths) and costs over an individual's life time using data collected within the trial and from published literature. The base case model will include two health states: mild OSA (treated with CPAP or standard of care) and death, with cycle lengths of 1 year. Various scenarios will be modelled including a number of relevant health states (stroke, cardiovascular disease, motor vehicle collision). Secondary objectives of the health

economic analysis are: to compare different utility-based QoL questionnaires and scoring algorithms (SF-6D and SF-12 utility scores taken from the SF-36, EQ-5D, and SF-12 utility mapping to EQ-5D) using patient-level data collected within the clinical study; and to calculate incremental cost-effectiveness ratios for CPAP treatment versus standard care based on different utility-based QoL questionnaire and scoring algorithms.

5.4 Sample size

The sample size calculation was based on data from mild OSA patients in the Multicentre Obstructive Sleep Apnoea Interventional Cardiovascular (MOSAIC) study (175), 80% power and a two-sided significance level of 5%. It was calculated that a total of 224 patients (112 per group) would be required to detect a difference of 6.6 in mean score change (baseline to 3 months) on the Energy and Vitality subscale of the SF-36 questionnaire between the two treatment groups (CPAP mean 10.8±17.0; standard care mean 4.2±18.1). Assuming a 10% dropout rate and enrolment of patients who meet the mild OSA criteria based on AASM 2007 but not 2012 criteria, target recruitment is set at 300 participants.

5.5 Statistical analysis

All statistical analyses will be performed on an intention-to-treat (ITT) basis including all randomized patients, using a Type 1 error rate of 0.05, unless otherwise specified. The ITT population will be divided into two overlapping subgroups: all randomized patients with mild OSA based on the AASM 2012 criteria, and those with mild OSA based on the 2007 criteria. Comparison of the CPAP and standard care groups at baseline will be performed using a student's t-test or Wilcoxon signed rank test for continuous measures and Fisher's exact test for categorical or binary measures, as appropriate.

Homogeneity of the primary outcome across study sites will be assessed using a mixed-effects regression model. The effect of a treatment-by-site interaction will be tested at a significance level of 0.10. The primary endpoint will be analyzed using a mixed-effects repeated measures model to account for missing values. In the case that the primary endpoint is not homogeneous across study sites, a treatment-by-visit-by-site interaction will be included in the model. Results will be presented as

the mean between-group difference in the change in Energy and Vitality score from baseline to 3 months (adjusted for baseline score, as appropriate) with the associated 95% confidence interval (CI) and p-value. A sensitivity analysis of the primary outcome will be generated to include any baseline and demographic variables that were imbalanced between treatment groups using a mixed-effects repeated measures model to adjust the primary results for these factors.

All secondary outcome measures for all randomized patients who complete the 3-month study visit will be analyzed in the same way as the primary outcome. These secondary analyses will be considered exploratory and no formal adjustments for multiple significance testing will be made.

6. Protection of human subjects

This study protocol has been approved by the Institutional Review Boards at each of the study centers. The study steering committee meet regularly and review any adverse events. All patients provide written informed consent prior to enrolment in the study.

7. Discussion

There is a need for reliable data on the effectiveness of CPAP treatment in patients with mild OSA, particularly as defined by the AASM 2012 scoring criteria and with a focus on patient-centered outcomes (e.g. QoL). The MERGE study has been designed to help address this data gap. We hypothesize that some patients with mild OSA will experience improved QoL during CPAP therapy, including those with disease severity defined using only the AASM 2012 criteria. If this is the case, the MERGE study results will provide evidence to support the consideration of CPAP for all patients with OSA, including those with the mildest disease.

The SF-36 is a well validated and widely used generic QoL questionnaire (242). It has been used in previous studies to detect reduced QoL in OSA patients (243). One consideration when designing the MERGE study was whether SF-36 baseline values would actually be normal in patients with mild OSA, therefore excluding the possibility of any improvement with CPAP therapy. In a previous study of mild OSA patients, baseline FOSQ scores were within the normal range and did not improve significantly during CPAP therapy, although 62% of patients wanted to continue treatment at the end of the study (172). Those findings may also reflect the difficulty in measuring specific QoL

issues in patients with mild OSA, such as lack of energy and motivation rather than overt sleepiness. Therefore, we chose to use the Energy and Vitality dimension of the SF-36, as the primary endpoint in our study because this has consistently been shown to be the most sensitive dimension of the SF-36 for measuring QoL improvements in mild OSA patients (174, 175, 244-246). Normative scores for the Energy and Vitality dimension of the SF-36 are reported to be 60.9 for the United States general population (247). For example, in a population of 90 OSA subjects, the mean SF-36 Energy and Vitality score before and after CPAP treatment was 40.16±20.89 and 60.68±20.58, respectively, which gave a normalized effect size of 0.98 (243). For patients in the CPAP treatment group of the MOSAIC study, who were considered non-sleepy at baseline, the SF-36 Energy and Vitality score effect size was 0.3 compared with control (mean scores at baseline and 6 months of 49.8±22.4 and 60.6±20.9, respectively) (175)); these figures were used in the sample size calculation for the MERGE study. The CPAP Apnea Study North American Program (CATNAP) trial included a large proportion of sleepy mild OSA patients and found that the SF-36 Energy and Vitality subscale showed an adjusted mean change from baseline of 12.7 with CPAP versus 6.1 in the sham CPAP group (174).

Another consideration when designing the MERGE study was whether patients with mild OSA would tolerate, and therefore adhere to, CPAP therapy. A review of the evidence shows that CPAP can be used successfully by some asymptomatic patients. In a 12-month study of CPAP use in asymptomatic, non-sleepy patients with OSA, mean adherence was 4.7±2 h/night (248). At 4-year follow-up, those still using CPAP had median device usage of 5 h/night (interquartile range [IQR] 2.18–6.25) and 64% had usage of >4 h/night (249). In the MOSAIC trial 71% of patients wanted to continue CPAP despite reporting normal levels of sleepiness at the beginning of the study (175). Taken together, these data suggest that mild asymptomatic patients may benefit from treatment e.g.: improvement in snoring, emotional wellbeing, relationships, and functioning (driving, working, study).

Historically, clinical trials testing the efficacy of CPAP treatment have reported lower than desirable CPAP adherence (i.e. <4 h/night) (250-252). Factors that have shown to impact adherence include equipment (e.g. device, interface) (222), remote monitoring (253) and clinical support (254, 255). Given that regular and ongoing usage is required for the benefits of therapy to be realized (227, 231, 256-258), maximizing adherence to CPAP is a major focus of the MERGE study. Firstly, patients unable to tolerate a 1-hour CPAP trial are not included in the study. In addition, patients get regular

support from the Central Support Laboratory and telemonitoring solutions during the study, with the goal of maximizing device usage.

The use of automated versus manual scoring of the diagnostic sleep study (polygraphy) was considered carefully when the MERGE trial was designed. The decision to use automated scoring was based on the reliability and repeatability of this approach (259). Specifically, the automated algorithm for scoring using AASM 2007 criteria has been validated in multiple studies (192, 195-197). Scoring based on the AASM 2012 criteria in MERGE uses a new algorithm (ResMed) that is concurrently being validated against PSG (clinicaltrials.gov ID: NCT03470493). To score hypopneas with arousal (and ≥3% oxygen desaturation), the new algorithm uses surrogate arousal measures that utilize airflow shape information and machine learning techniques. Surrogate arousal measures have found to accurately estimate arousals from sleep (198, 199). All automated scoring using the AASM 2012 algorithm is reviewed by an expert to check for software errors in the scoring decisions. The choice was made not to use PSG in the MERGE study due to the pragmatic nature of home sleep testing and the desire to replicate common clinical practice in the UK National Health Service.

In this study we defined the mild patient group as those with an AHI of 5-15, rather than 5-<15. This was to ensure that those patients who are borderline mild (with an AHI between 15 and 16), who switch between mild-moderate categories on a regular basis (and therefore may not be offered treatment based on a one-night sleep study) were included in the analysis.

Conclusions

The definition of mild OSA, which was revised in 2012 in an attempt to recognize the potentially detrimental effects of repetitive breathing-related arousals from sleep, is complex. An unintended outcome of the updated classification is that some healthcare professionals and providers have taken the decision not to offer CPAP treatment for mild OSA diagnosed based on AASM 2012 criteria due to a lack of evidence that treatment of mild OSA could be beneficial. The MERGE study is a randomized controlled study that will assess, for the first time, whether CPAP treatment can improve quality of life in patients with mild OSA diagnosed using the AASM 2012 scoring criteria. The results of the study will indicate the clinical applicability of the updated scoring criteria and provide guidance for sleep professionals about disease classification and effective treatment options for

patients with mild OSA. If CPAP treatment is effective, the MERGE study will demonstrate the feasibility of a clinical model of assessment, treatment implementation, and ongoing CPAP therapy support in mild OSA patients.

Study Steering Committee

Mary J Morrell (chief investigator), John Stradling (chairperson), Alison Wimms, Julia Kelly, Peter Calverley (independent member), Sonya Craig, Alison McMillan, John O'Reilly, and Chris Turnbull.

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TABLES

Table 1. American Academy of Sleep Medicine (AASM) hypopnea scoring criteria

Recommended hypopnea definition	
AASM 2007 criteria	**AASM 2012 criteria**
≥30% decrease in oronasal airflow from baseline **AND**	≥30% decrease in oronasal airflow from baseline **AND**
Event duration ≥10 seconds **AND**	Event duration ≥10 seconds **AND**
Oxygen desaturation of ≥4%	Oxygen desaturation of ≥3% **OR** arousal

Table 2. MERGE sites participating in the UK Respiratory Sleep network

Site	**Principal Investigator(s)**
National Heart and Lung Institute, Imperial College London Royal Brompton and Harefield Hospitals, London	Prof Mary Morrell (MERGE CI) Dr Julia Kelly Dr Shirmila Withana
Aintree University Hospital, Liverpool	Dr John O'Reilly, Dr Sonya Craig
Oxford Centre for Respiratory Medicine, Oxford	Dr Annabel Nickol, Dr Chris Turnbull
Freeman Hospital, Newcastle	Dr Sophie West
Lister Hospital, Stevenage	Dr Alison McMillan
Guys & St Thomas Hospital, London	Dr Brian Kent
Derriford Hospital, Plymouth	Dr Neil Ward
Taunton and Somerset Hospital, Taunton	Dr Justin Pepperell
Blackpool Teaching Hospital, Blackpool	Dr Mohammad Paracha
Tayside Health Board, Ninewells Hospital, Dundee	Dr Will Anderson
Papworth Hospital, Cambridge	Dr Tim Quinnell

CI, chief investigator.

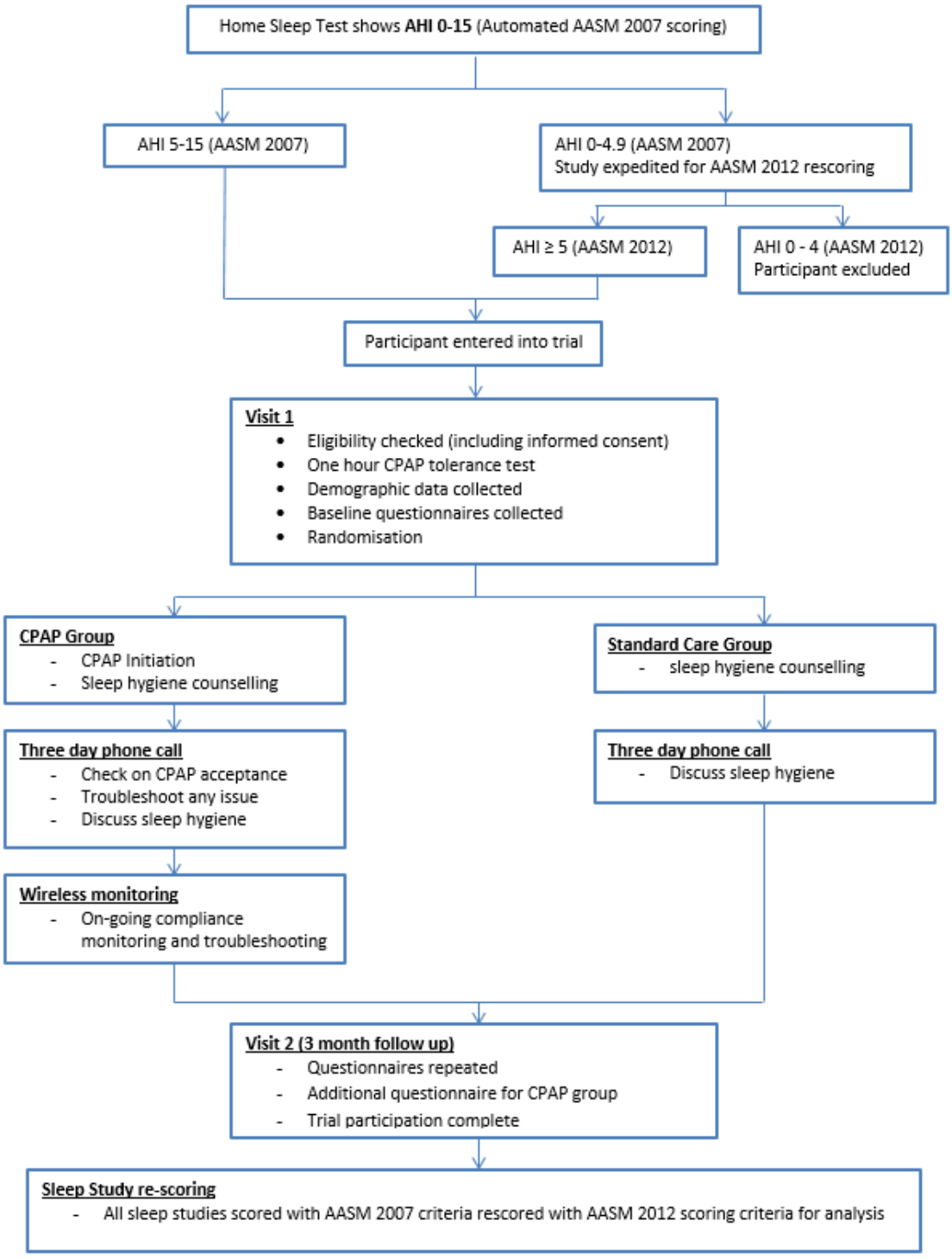
Table 3. Patient selection criteria for the MERGE study

Inclusion Criteria • Age ≥18 and ≤80 years • Ability and willingness to provide written informed consent • AHI 5-15/h as per AASM 2007 scoring criteria (or AHI ≥5/h based on AASM 2012 criteria if AHI was 0-4/h using AASM 2007 criteria) • Ability to tolerate a one-hour long CPAP run-in test
Exclusion Criteria • Unstable cardiac disease • Inability to give fully informed consent • Supplemental oxygen • Secondary sleep pathology (e.g. periodic limb movement syndrome, narcolepsy, circadian disorder, obesity hypoventilation syndrome) • Epworth Sleepiness Scale score ≥15, or concerns about sleepy driving from physician/ sleep lab staff • Body mass index ≥40 kg/m^2 • Previous CPAP usage

AASM, American Academy of Sleep Medicine; CPAP, continuous positive airway pressure.

FIGURES

Fig. 1. MERGE study flow chart. AASM, American Academy of Sleep Medicine; AHI, apnea-hypopnea index; CPAP, continuous positive airway pressure;



Appendix D

McArdle, Nigel; King, Stuart; Shepherd, Kelly; Baker, Vanessa; Ramanan, Dinesh; Ketheeswaran, Sahisha; Bateman, Peter; **Wimms, Alison**; Armitstead, Jeff; Richards, Glenn; Hillman, David; Eastwood, Peter. Study of a Novel APAP Algorithm for the Treatment of Obstructive Sleep Apnea in Women. Sleep. 38 [11] pp 1775-1781. 2015

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Study of a Novel APAP Algorithm for the Treatment of Obstructive Sleep Apnea in Women

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Study Objectives: To assess the efficacy of a novel female-specific autotitrating continuous positive airway pressure (CPAP) algorithm (AutoSet for her, AfH) in premenopausal women relative to a standard autotitrating algorithm (AutoSet, S9) (ResMed Ltd., Bella Vista, New South Wales, Australia).
Design: Prospective randomised crossover noninferiority trial.

Setting: Tertiary hospital sleep clinic and university research sleep laboratory.

Participants: 20 female patients with obstructive sleep apnea (OSA) established on long-term CPAP treatment.

Interventions: Treatment with 1 night each of AfH and AutoSet while monitored with overnight laboratory-based polysomnography (PSG); order randomly allocated.

Measurements and Results: The primary outcome variables were the apnea-hypopnea index (AHI) and 3% oxygen desaturation index (ODI 3%) determined from PSG. Treatment efficacy on the AfH night was noninferior to the AutoSet night as assessed by median (IQR) AHI (1.2 [0.60– 1.85]/h versus 1.15 [0.40–2.85]/h, respectively, P = 0.51) and 3% ODI (0.85 [0.25–1.5]/h versus 0.5 [0.25–2.55]/h, respectively, P = 0.83). Other PSG measures were similar, except for the percentage of the night spent in flow limitation, which was lower on the AfH (0.14%) than the AutoSet night (0.19%, P = 0.007). The device-downloaded 95th centile pressure on the AfH night was also lower than on the AutoSet night (10.6 ± 1.7 versus 11.6 ± 2.6 cmH_2O, respectively; mean difference [95% confidence interval]: −1.1 [−2.13 to −0.01] cm H_2O).

Conclusion: Among premenopausal women a novel female-specific autotitrating algorithm (AfH) is as effective as the standard AutoSet algorithm in controlling obstructive sleep apnea (OSA). The new algorithm may reduce flow limitation more than the standard algorithm and achieve control of OSA at a lower (95th centile) pressure.

Keywords: apnea-hypopnea index, automatic positive airway pressure algorithm, continuous positive airway pressure, obstructive sleep apnea, positive airway pressure titration, premenopausal women

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INTRODUCTION

Obstructive sleep apnea (OSA) is a common disorder characterized by repetitive collapse of the upper airway during sleep and associated nocturnal hypoxia and sleep fragmentation. It is a disorder that has widespread effects on health and is associated with reduced quality of life,[1] neurocognitive impairment (including increased risk of motor vehicle accidents[2]), and increased cardiovascular morbidity and mortality; from ischemic heart disease, congestive heart failure, and stroke.[3–5]

Early studies of OSA report a high male predominance, with male-to-female ratios ranging between 10:1 and 60:1 in clinic populations.[6] Hence, OSA is traditionally thought of as a predominantly male disorder and treatment options have often been developed and tested in male study populations. More recently, several studies have reported a male-to-female ratio closer to 3:1,[7,8] and indicate that women may present with different clinical features[8] and have different polysomnographic (PSG) patterns of obstructive sleep disordered breathing compared to men. In particular, PSG studies show a relative rapid eye movement (REM) predominance to obstructive events[9] and milder disease (i.e., lower apnea-hypopnea index; AHI) in women compared to men.[10,11] Women with obstructive sleep apnea are also less likely to manifest complete upper airway collapse (apneas)[12] and more likely to have flow limitation, which can manifest as an upper airway resistance syndrome (UARS).[11] These sex differences may affect therapeutic decisions and therapeutic effectiveness.

The gold-standard treatment for moderate and severe OSA is continuous positive airway pressure (CPAP),[13] which acts as a pneumatic splint to maintain patency of the upper airway. Long-term treatment may be delivered using a standard CPAP device at a set "fixed" pressure, or using automatic positive airway pressure (APAP) devices that vary the pressure throughout the night based on device-monitored physiological signals. The pressure response in these APAP devices is controlled by a computerized algorithm. ResMed Corporation has recently developed a female-specific 'AutoSet for Her' (AfH) algorithm; designed to optimize the pressure response to the specific patterns of obstructive sleep disordered breathing seen in women. The AfH algorithm is adapted from the S9 AutoSet algorithm (ResMed Ltd., Bella Vista, Sydney) with a number of modifications, including an increased sensitivity

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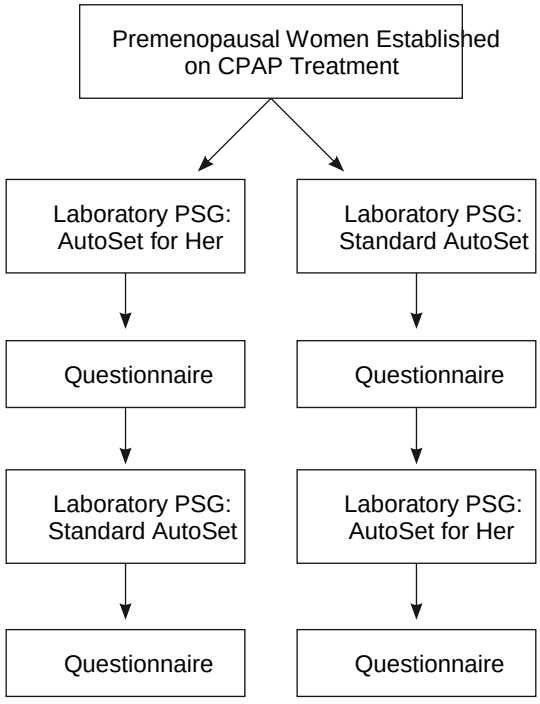

Figure 1—Study flow. Questionnaire asks about sleep quality And comfort using the device. PSG, polysomnography.

to flow limitation, an optimized internal gain (a slower, and lower, pressure rise and decay in response to flow limitation), a lower cap on the pressure response to obstructive apneas, and an adaptive minimum pressure.

We sought to assess the efficacy of this new algorithm in premenopausal women by comparing it to the standard ResMed S9 AutoSet algorithm. The primary aim of the study was to assess the efficacy of the AfH algorithm, based on a priori PSG outcome measures of the AHI and the 3% oxygen desaturation index (3% ODI). Secondary aims were to compare objective sleep quality measures and patient symptomatic responses between the 2 study nights. We hypothesized that the efficacy (AHI and 3% ODI) of the AfH algorithm would be noninferior to the standard AutoSet (ResMed) algorithm and speculated that its use would be associated with advantages in terms of patient comfort.

METHODS

Overview

A double-blind randomized crossover study design was used (Figure 1), which required participants to undergo 2 overnight laboratory-based PSGs, 1 night using an APAP device set in the AfH mode and the other night set in the standard AutoSet algorithm mode.

Study Participants

Inclusion criteria comprised premenopausal females aged 18 y or older; current positive airway pressure (CPAP or APAP) therapy use, where “current” was defined as on therapy for at least 1 mo prior to study entry; availability of a diagnostic PSG; diagnosis of mild-moderate OSA (5 < AHI ≤ 30); and willingness and ability to give written informed consent

Exclusion criteria comprised current use of bilevel positive airway pressure treatment; current use of supplemental oxygen; pregnancy; a preexisting lung disease or condition that would predispose the participant to pneumothorax (e.g., chronic obstructive pulmonary disease, lung cancer; pulmonary fibrosis; recent (< 2 y) pneumonia or lung infection; other lung injury); and any individual whom the researcher believes is unsuitable for inclusion because that person does not comprehend English or is unable to provide written

informed consent or physically unable to comply with the protocol.

Potential participants were identified from the Sleep Clinic database, contacted by phone and asked if they wished to take part in the study. The study was approved by the Institutional Review Boards of the University of Western Australia and Sir Charles Gairdner Hospital. Written informed consent was obtained prior to participation in the study. The trial was registered with ClinicalTrials.gov (Clinical Trials Registry number: NCT01826513).

Study Protocol

A double-blind randomized crossover study design was used (Figure 1). Participants spent 1 night using an APAP device set in the AfH mode and another night set in the standard AutoSet algorithm mode. An in-house questionnaire asking about sleep quality and comfort using the device was completed after each study night. The studies were done on consecutive nights, apart from one patient whose studies were separated by 2 nights. One member of the research team randomly determined the order of the nights, concealed the codes using opaque envelopes, and allocated device modes to each participant. Neither the patient nor the overnight research staff was able to ascertain the device mode because the device appeared identical irrespective of the algorithm used. Furthermore, all outcome analyses were performed by one sleep scientist, blinded to the study arm (i.e., scoring of respiratory events was performed without access to the pressure signal to ensure full blinding, i.e., using other respiratory signals, including mask flow signal). Self-reported menopause status, medical history, and concomitant medications were recorded. Comorbidities were identified based on reported history or treatment for the condition.

CPAP

During the study nights the device was set to a pressure range of 4–20 cm H_2O, and the ramp set at the patients' usual value (AutoSet night) or automatic with a maximum of 30 min (AfH night). All other settings (e.g., humidification) were set as per the patients' usual device and the patient used his or her own mask and chin strap (if required) on both study nights. The device was set by research staff in the evening prior to arrival of overnight staff to ensure the latter were blinded to the algorithm used.

PSG

In-laboratory PSG was performed using the Compumedics Grael HD-PSG (Compumedics Ltd., Abbotsford, Australia), which recorded the following signals: F3-M2, F4-M1, C3M2, C4-M1, O1-M2, O2-M1 electroencephalogram, bilateral electrooculograms, submental electromyogram, electrocardiogram, device analog outputs (i.e., mask pressure, unintentional leak and flow), oximetry (averaged over three beats, sampling 256 Hz), ribcage and abdominal movement (respiratory inductance plethysmography), body position, sound intensity (dB), and bilateral tibial electromyogram.

Questionnaire

Symptomatic responses to therapy, including questions about participant's perception of their sleep on the device and quality of sleep, were assessed in the morning after each study night using a Likert scale (see supplemental material).

Data Analyses

PSGs were manually scored at the study site by experienced sleep scientists according to standard criteria (AASM 2012).[14] Flow limitation was assessed by the site using the sponsor's

(ResMed Ltd.) flow limitation tool to perform automatic analyses of high-fidelity flow signals (25 Hz). The flow limitation tool utilizes the shape, tidal volume, and duty cycle (ratio of inspiratory time to total breath time) of each breath and automatically identifies whether each breath is flow limited or not.

Statistical Analyses

Statistical analyses were performed using SigmaStat version 3.5 (Systat, Richmond, CA, USA). Parametric data were described using means and standard deviations (SDs) and paired comparisons were performed using paired *t* tests and

95th percentile confidence intervals (95% CIs) were reported. Nonparametric variables were described using medians and interquartile ranges and paired comparisons made with the Wilcoxon signed-rank test. Statistical significance was considered to occur when $P < 0.05$.

Sample Size Calculation

We tested the hypothesis that the AfH algorithm was not worse (but not necessarily better) than the standard AutoSet algorithm. Hence, the null Hypothesis (H_0) was: AfH is inferior to standard AutoSet and the alternate Hypothesis (H_1) was: AfH is noninferior to standard AutoSet. The expected

AHI difference (mu) is 0 events/h and the NonInferiority Margin (delta) is 0.75 events/h (a difference of 1 event/h is seen as clinically significant: 0.75 events/h was chosen to ensure any relevant AHI change was observed). Unpublished data from a trial[15] supported by the sponsor showed that the SD of such a dataset is 1.06 events/h. Based on a power of

80% and two-sided alpha of 0.05 (one-sided alpha of 0.025 used in this noninferiority trial), the sample size (for paired Trial)[16] = $(Z(1 - a.2) + Z(1 - b))^2) * (SD / (mu - delta))^2$. Using our data, the sample size = $(1.96 + 0.85)^2 * (1.06 / (0 - 0.75))^2$ = 15.8. On this basis, and allowing for potential dropouts, we chose a sample size of 20 for the study.

RESULTS

Patient Characteristics

Twenty women participated in the study and all completed the protocol. Participants were

premenopausal, obese (body mass index; BMI = 38.5 ± 7.5 kg/m^2), predominantly Caucasian

Table 1—Baseline characteristics of study participants.

Baseline Characteristics	Premenopausal Women, n = 20
Age, y	44.6 ± 5.1
BMI, kg/m^2	38.5 ± 7.5
Self-reported ethnicity (Caucasian: Australian aboriginal)	9:1
History of hypertension	6 (30%)
History of hyperlipidemia	4 (20%)
History of diabetes	3 (15%)
History of hypothyroidism	5 (25%)
Diagnostic AHI, events/h	19.1 ± 8.7
Average duration of positive airway therapy, mo[a]	23.3 ± 34.5
CPAP, cm H_2O [b]	11.0 ± 2.0

Data presented as mean ± standard deviation, ratio or number (percentage). [a]Data missing in one. [b]Data for 18 participants receiving long-term fixed pressure CPAP (two participants were receiving automatic positive airway pressure as long-term therapy). AHI, apneahypopnea index; CPAP, continuous positive airway pressure.

females aged 44.6 ± 5.1 y, most of whom received a diagnosis of moderately severe OSA (AHI = 19.1 ± 8.7 events/h) (Table 1). Three participants were recruited with severe OSA after a decision was made by the study investigators to modify the protocol to assist with recruitment. This protocol variation was considered to be safe and was approved by the local ethics review board. Participants had a higher prevalence of cardiovascular risk factors (Table 1) than are typical for similar aged women in the community but similar to that expected in an OSA sleep clinic population. None had severe cardiac or pulmonary comorbidities. Participants had been using CPAP treatment for an average of 23 mo with a mean fixed CPAP pressure of 11.0 ± 2.0 cm H_2O, apart from two patients who had been using an APAP device (Table 1). The majority of patients were using a nasal mask (55%), with the remainder using nasal pillows (35%) or a full face mask (15%).

Outcomes

Treatment efficacy on the AfH night was noninferior to the AutoSet night as assessed by AHI (1.2 [0.60–1.85]/h versus 1.15 [0.40–2.85]/h, P = 0.51) and 3% ODI (0.5 [0.25–2.55]/h versus 0.85 [0.25– 1.5]/h, P = 0.83) (Figure 2 and Table 2). In comparison with the patients' diagnostic AHI there was a statistically and clinically significant reduction in AHI with treatment using the AfH (diagnostic versus AfH: 19.07 versus 1.2/h, P < 0.001) and AutoSet algorithms (diagnostic versus AutoSet: 19.07 versus 1.15/h, P < 0.001). Percentage of breaths with flow limitation during sleep was significantly less using the AfH algorithm (0.14%) than the AutoSet (0.20%, P = 0.02) (Table 2). Other PSG measures of sleep quality were similar between study nights (Table 2, all P > 0.05). The downloaded 95th centile pressure from the device on the AfH study night was lower than on the AutoSet night (10.56 ± 1.7 versus 11.63 ± 2.6 cmH_2O; mean difference (95% CI): −1.1 (−2.13 to −0.01) cm H_2O). The downloaded median pressure delivered by the AfH device was similar to that delivered by the AutoSet (P > 0.05). The downloaded median

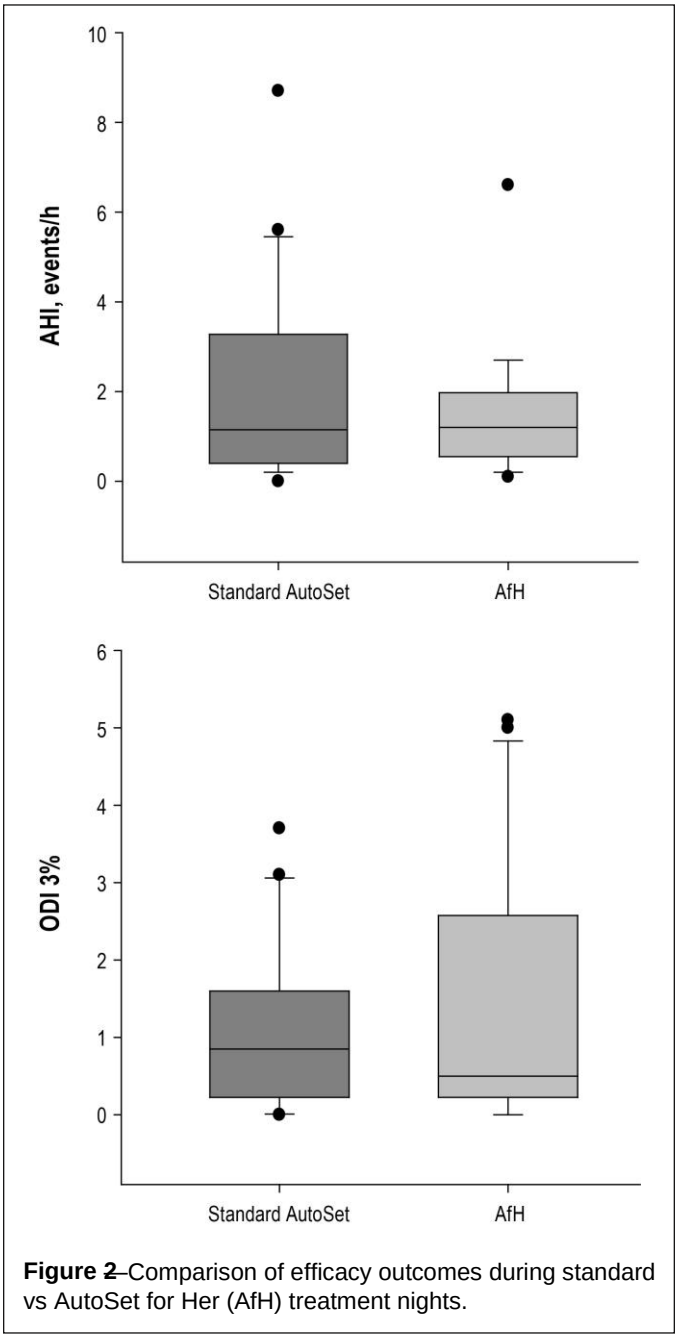

Figure 2–Comparison of efficacy outcomes during standard vs AutoSet for Her (AfH) treatment nights.

leak from the device was similar on the AfH and AutoSet nights ($P > 0.05$), as was the 95th centile leak (AfH: 9.0 ± 9.6 l/min, AutoSet: 12.6 ± 15.6 l/min, $P > 0.05$). Symptom response to the treatment nights and device tolerance were similar following a night using the AfH compared to AutoSet (all $P > 0.05$) (Table 3).

DISCUSSION

This study among premenopausal women shows the AfH algorithm to be as efficacious as the standard AutoSet algorithm, according to overnight full PSG evaluation. Compared to a diagnostic study night (i.e., without treatment) both algorithms reduced the AHI to 'well controlled' ($P < 0.001$), confirming that these are suitable algorithms for CPAP treatment of OSA. In addition, sleep efficiency was high on the AfH and AutoSet nights and other PSG measures of sleep quality were similar on both nights and similar to the quoted normal ranges for middle-aged females.[17,18] Notably, there was a statistically significant reduction in flow limitation (% of breaths), achieved at a lower (95th centile) pressure, on the AfH night compared to the AutoSet night.

Many of the early studies showing a high prevalence of OSA among males, compared to females, used clinic-based samples.[6,8] By contrast, community studies[7,19,20] have consistently shown male-to- female ratios to range from 2:1 to 4:1, suggesting clinical underrecognition of OSA in females, perhaps because females report less classic OSA symptoms such as snoring[19,21] and witnessed apneas[22] and for other sociocultural reasons.[22] The historically high male prevalence in clinical samples has resulted in most treatment options being developed and tested in predominantly male study samples. Moreover, several recent studies have reported sex-specific differences in the patterns of sleep and sleep disordered breathing, particularly among premenopausal

women.[9,10,23] These differences raise the possibility that tailoring OSA treatment according to sex-specific patterns of obstructive sleep disordered breathing may improve the efficacy of APAP treatment. The current device was, therefore, designed and developed to provide a female-specific APAP algorithm (AfH) with the aim of targeting the breathing abnormalities characteristic of female patients.

The primary aim of the current study was to test the hypothesis that the efficacy of the new AfH algorithm is noninferior to the standard AutoSet algorithm. The AHI and ODI were chosen as the primary outcome measures. AHI is the standard accepted metric used to determine severity of OSA and the ODI may have particular usefulness as a predictor of OSA-related vascular and metabolic consequences.[24] On both measures the new AfH algorithm performed similarly to the standard AutoSet algorithm, as assessed by the gold standard of laboratory-based PSG. This finding supports the use of the AfH algorithm as a new efficacious treatment option for mild moderate OSA among premenopausal patients.

The AfH algorithm has been designed to be more sensitive to flow limitation by responding to the first identified flow-limited breath rather than requiring three consecutive flow-limited breaths, as occurs with the standard AutoSet algorithm. The basis for this change is the increasing evidence that inspiratory flow limitation is more prevalent in women compared to men. For example, a recent study among consecutive sleep clinic patients referred for evaluation of sleep disordered breathing found women to have more UARS than OSA, whereas among men the prevalence of OSA was greater than UARS.[11] Similarly, women attending a sleep clinic appear to have fewer episodes of complete upper airway collapse (lower ratio of apneas to hypopneas) compared to men.[12] The precise mechanisms underlying these findings have yet to be resolved, but are most likely related to complex sex-related differences in the structure and function of the upper airway. For example, comparisons between men and women, matched for BMI, found the critical airway closing pressure (Pcrit) was lower in women compared to men without differences in respiratory control stability.[25] Overall, these studies indicate that women have a less collapsible upper airway, making obstructive apneas less likely and predisposing to partial airway collapse (hypopnoeas) and flow limited breathing abnormalities during sleep.

Table 2—Polysomnographic sleep characteristics during standard Autoset and AutoSet for her (AfH) treatment nights.

Polysomnographic Characteristic	Standard AutoSET, n = 20	AfH, n = 20	95% CI for Mean Difference	P
Total sleep time	383.8 ± 48.5	388.4 ± 56.0	−32.5 to 23.3	0.74
Sleep efficiency, %	84.1 ± 7.1	84.2 ± 9.2	−5.2 to 5.0	0.96
Sleep latency, min	16.2 ± 17.2	19.1 ± 15.6	−10.2 to 4.5	0.43
Wake after sleep onset, min	52.9 ± 31.8	52.8 ± 39.6	−22.9 to 23.0	0.99
Time N1, %	10.2 (8.7–15.5)	11.0 (9.3–14.2)		0.78
Time N2, %	51.4 (47.6–53.1)	51.4 (39.8–54.6)		0.73
Time N3, %	21.5 ± 8.2	22.4 ± 11.7	−3.7 to 1.8	0.49
Time REM, %	15.4 ± 7.1	16.6 ± 7.0	−4.9 to 2.5	0.52
Arousal number index, events/h	12.3 ± 6.4	11.7 ± 4.2	−1.16 to 2.47	0.46
AHI, events/h slept	1.15 (0.40–2.85)	1.20 (0.60–1.85)		0.51
Obstructive apnea index, events/h	0 (0–0)	0 (0–0)		0.81
Central apnea index, events/h	0.50 ± 0.68	0.38 ± 0.48	−0.15 to 0.37	0.39
Central apnea number	1 (0–5.5)	1 (0–4.5)		0.24
Hypopnea index, events/h	0.50 (0.20–1.7)	0.80 (0.25–1.35)		0.65
RERAS, number/h	0.75 (0.4–1.45)	0.80 (0.45–1.60)		0.50
Flow limitation, % of breaths	0.202 ± 0.151	0.145 ± 0.093	0.010 to 0.102	0.02
Mean SpO_2, %	97 (96–97)	96 (96–97)		0.16
Lowest SpO_2,%	91.65 ± 2.23	91.10 ± 0.56	−0.68 to 1.78	0.36
ODI 3%, events/h slept	0.85 (0.25–1.5)	0.5 (0.5–2.55)		0.83
ODI 4%, events/h slept	0.25 (0–0.55)	0.2 (0–0.55)		0.97

AHI, apnea-hypopnea index; CI, confidence interval; N1, stage N1 sleep; N2, stage N2 sleep; N3, stage N3 sleep; ODI 3%, oxygen desaturation index of 3% or more; ODI 4%, oxygen desaturation index of 4% or more; REM, rapid eye movement sleep; RERAS, respiratory event-related arousals; SpO_2, oxygen saturation.

Table 3—Subjective feedback from participants after standard Autoset and Autoset for her (AfH) treatment nights.

Questionnaire Response	Standard AutoSet, n = 20	AfH, n = 20	Mean Difference and 95% CI for Mean Difference	P
Comfort of breathing	8.0 (7.125–9.4)	8.0 (7.0–9.25)		0.67
Ease of falling asleep	7.9 ± 1.8	7.0 ± 2.3	0.58 (−0.78 to 1.94)	0.38
Sleep disturbance	9 (7.25–9.4)	8 (6.5–9.0)		0.12
Feeling of being refreshed	7.6 ± 1.6	6.4 ± 2.2	1.3 (−0.1 to 2.7)	0.07

An in-house questionnaire asked for responses using an 11-point Likert rating scale (questionnaire provided in supplemental material). Data presented as mean ± standard deviation, or median (Interquartile range). CI, confidence interval.

Despite the percentage residual flow limitation being low with both algorithms, the current study showed improved control of flow limitation on the AfH night (Table 2). It is unknown whether a reduction from 0.20 to 0.14% flow-limited breaths using AfH, compared to standard AutoSet, is of clinical significance. However, the participants were compliant users, established on CPAP treatment, who had excellent control of their OSA using APAP, producing 'floor effects' that limit the possibility of showing large improvements in disease control with the new algorithm. Studies on consecutive CPAP naïve patients in the standard clinical setting are needed to assess the potential magnitude of improvement in flow limitation obtainable from the AfH algorithm.

Another novel feature of the AfH algorithm is a moving minimum AutoSet pressure (i.e., a minimum pressure is set to which pressure decreases during sleep periods devoid of respiratory events). If apneas occur within a short time period the minimum AfH pressure will automatically increase and the pressure will not decline below this level for the remainder of the night's therapy. The purpose of this is to minimize inappropriate pressure decreases during REM sleep that could occur with the standard AutoSet algorithm. It is possible, for example, that the standard AutoSet algorithm pressure could decay below the critical closing airway pressure during REM sleep, which can result in several apneas at the beginning of REM sleep until the device responds with appropriate pressure increases. This could be particularly important in women, who have been shown to have a predominance of REM-related OSA compared to men.[9] During REM sleep CPAP pressures may need to be higher to maintain patency of the upper airway secondary to a REM-related reduction in the tone of upper airway muscles. It is also possible that this algorithm feature could reduce pressure variability, contribute to longer REM sleep, and reduce REM-related respiratory events. However, the current study did not find any statistically significant differences on these measures, although it was not designed or statistically powered to detect these differences and larger studies would be needed in order to demonstrate any such changes.

In order to prevent an excessive pressure rise, the AfH algorithm does not increase pressure above 12 cm H_2O in response to detected apneas (but pressure can increase above 12 cm H_2O if other respiratory events are present). Furthermore, the AfH algorithm increases pressure in response to flow limitation at a slower rate and to a lesser extent than the standard AutoSet algorithm (similarly the decay in the gain is lower). These features are in response to previous studies that have shown that women tend to have less severe OSA, for a given BMI, compared to men,[9–11] and that women appear to require lower CPAP pressures than men as determined by manual attended laboratory PSG titration.[26] The current study supports the use of this AfH pressure algorithm strategy among premenopausal female patients with OSA because equivalent control of apneas and hypopneas and improved control of flow limitation was achieved at a lower 95th centile pressure than the standard AutoSet algorithm. The 95th centile pressure is an important index of pressure requirements as it is the value commonly used when setting a fixed pressure from an AutoSet titration.

CPAP devices often incorporate a ramp to increase pressure gradually when the device is first turned on; this aims to keep pressure low and more comfortable when falling asleep. The AfH algorithm incorporates a novel automatic ramp that keeps the pressure at a minimum until there are changes in the breathing pattern indicative of either sleep onset (based on regularity of the breaths); or three obstructive apneas or hypopneas occurring within 2 min; or five consecutive snore breaths. The algorithm will then ramp up to minimum therapy pressure within 1 min of the event occurring at a rate of

1 cm H_2O/ min. Women with OSA have longer sleep latencies than men with OSA despite no difference in age, respiratory disturbance index, or oxygen saturation.[27] Hence, the rationale of the AfH automatic ramp is to allow sufficient time for sleep onset by minimizing disturbance from increasing ramp pressure, while still responding to changes consistent with sleep or obstructive events as necessary. The participants' sleep latency in the current study was not significantly different using the AfH and the standard AutoSet algorithm and similar to values reported in normal middle-aged women.[18]

In practice, overall treatment effectiveness is determined not only by efficacy but also by compliance with therapy in the home environment. An in-house questionnaire indicated there were no significant differences in symptomatic report and tolerance of the AfH algorithm compared to the AutoSet algorithm. Further studies are needed to assess compliance in the home with the new AfH algorithm.

The strengths of the current study include the use of a randomized controlled crossover design; with patients acting as their own controls to increase study power. In addition, the patients, therapists, and sleep data scorers were blinded to the study intervention. The gold standard of in-laboratory full PSG assessment was used to ascertain the primary study outcomes, and currently recommended definitions for respiratory events were also used. However, the study was not adequately powered to make conclusive statements about secondary outcomes.

Although the study found reduced flow-limited breaths and lower pressure requirements using the AfH algorithm, it is unclear if these changes will translate into measureable clinical benefits to female OSA patients. Further studies, adequately powered for these outcomes, will be needed to answer these questions.

In conclusion, the primary finding of this study is that the efficacy of a novel female-specific (AfH) algorithm among premenopausal women with OSA is noninferior to the standard AutoSet algorithm. The study also suggests the AfH algorithm results in superior control of flow limited breaths in premenopausal women compared to the AutoSet algorithm, and it achieves this at a lower 95th centile pressure.

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Appendix E

Isetta, V.Montserrat, J. M. Santano, R. **Wimms, A. J**. Ramanan, D. Woehrle, H. Navajas, D. Farre, R., Montserrat JM, Santano R, et al. Novel Approach to Simulate Sleep Apnea Patients for Evaluating Positive Pressure Therapy Devices. PLoS One 2016;11:e0151530.

Novel Approach to Simulate Sleep Apnea Patients for Evaluating Positive Pressure Therapy Devices

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Abstract

Bench testing is a useful method to characterize the response of different automatic positive airway pressure (APAP) devices under well-controlled conditions. However, previous models did not consider the diversity of obstructive sleep apnea (OSA) patients' characteristics and phenotypes. The objective of this proof-of-concept study was to design a new bench test for realistically simulating an OSA patient's night, and to implement a one-night example of a typical female phenotype for comparing responses to several currently-available APAP devices. We developed a novel approach aimed at replicating a typical night of sleep which includes different disturbed breathing events, disease severities, sleep/wake phases, body postures and respiratory artefacts. The simulated female OSA patient example that we implemented included periods of wake, light sleep and deep sleep with positional changes and was connected to ten different APAP devices. Flow and pressure readings were recorded; each device was tested twice. The new approach for simulating female OSA patients effectively combined a wide variety of disturbed breathing patterns to mimic the response of a predefined patient type. There were marked differences in response between devices; only three were able to overcome flow limitation to normalize breathing, and only five devices were associated with a residual apnea-hypopnea index of <5/h. In conclusion, bench tests can be designed to simulate specific patient characteristics, and typical stages of sleep, body position, and wake. Each APAP device behaved differently when exposed to this controlled model of a female OSA patient, and should lead to further understanding of OSA treatment.

Introduction

Obstructive sleep apnea (OSA) is a prevalent breathing disorder and is considered a major public health issue, affecting 5–15% of the general population and increasing with both body mass index and age (up to at least 60–65 years) [1,2]. OSA is characterized by repetitive narrowing

collection and analysis, decision to publish, or preparation of the manuscript. The specific roles of these authors are articulated in the 'author contributions' section.

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and closure of the upper airway during sleep [3] that results in brain arousal, intermittent hypoxia, negative intrathoracic pressure swings, and increased sympathetic activity. OSA is associated with a reduction in quality of life, daytime sleepiness, traffic accidents, neurocognitive impairment, metabolic, cardiovascular disease [4] and malignancies [5].

The treatment of choice for OSA is the application of continuous positive airway pressure (CPAP) to the patient's nose or mouth through a mask during sleep at home. This pressure in the mask is transmitted to the pharyngeal area, splinting the collapsible upper airway walls thereby avoiding obstruction. Auto-adjusting positive airway pressure (APAP) devices, which are increasingly being used, are driven by algorithms that measure abnormal sleep breathing events, analyze the patient's breathing pattern and eventually increase the delivered pressure in response to airway obstruction, or decrease pressure when breathing is stable to increase patient comfort [6–11]. In theory, APAP devices should be ideal for treating a range of patients with different characteristics, and for effectively treating OSA despite within-night and night-to-night variations in the upper airway collapsibility experienced by each individual patient [12–16]. However, commercially available APAP devices contain undisclosed proprietary algorithms, and therefore the way that they measure and respond to specific breathing patterns varies [17]. In addition, some APAP manufacturers are introducing new algorithms based on specific patient characteristics. This move towards personalized medicine in the treatment of OSA means greater choice for patients and more variability in APAP algorithms. Therefore, understanding how each device responds to different OSA patterns requires comparative studies using well defined references.

Bench testing is a useful method to characterize the response of different APAP algorithms under well-controlled conditions, thus avoiding the biological variability inherent in clinical trials. However, previously used bench test models have been based on subjecting the APAP device under test to a repetitive string of disturbed breathing patterns, without providing a sufficiently wide spectrum of events. These limitations mean that variety in patient characteristics and phenotypes, or the changes that occur during different sleep stages and body positions over the course of a night's sleep, cannot be taken into consideration. This is particularly relevant given that different

subpopulations of OSA patients (e.g. children, men, women, the elderly) exhibit specific traits in their sleep-related breathing disorders [18].

Therefore, the aims of this proof-of-concept study were: 1) to design a new complex and versatile bench test approach for realistically simulating respiratory events throughout the course of the night in an OSA patient, mimicking breathing disturbances across different phenotypes, and 2) to implement a full night example of a female OSA phenotype and use this to compare the responses of several currently-available APAP devices.

Materials and Methods

The hardware of our new model was based on a previously described bench test [19]. This fully computer-driven model comprises a servo-controlled pump able to deliver a flow that replicates any breathing waveform stored in the computer. An obstruction valve allows the simulation of controlled obstructive events by imposing mechanical impedances previously recorded in patients with OSA. Two other valves can mimic leaks and mouth breathing, and a loudspeaker-in-box system can superimpose simulated snoring onto the breathing flow. The test bench is equipped with two sensors, one to measure pressure at the simulated patient entrance and one to measure the actual flow generated by the patient simulator. A calibrated leak based on a 4-mm internal diameter (ID) orifice [20] mimics the mask leak (exhalation port) in nasal masks. In previous studies, this system was fed by a collection of disturbed breathing events, such as obstructive and central apneas, hypopneas, flow limitation, mask leaks and mouth expiration [19,21].

To design the new OSA simulator model we developed a novel approach aimed at realistically replicating a typical night of sleep for a female patient. With this aim, we considerably expanded our library of disturbed breathing patterns anonymously extracted from polysomnography recordings obtained from real OSA patients and we incorporated several new adjustable features into the simulator. Specifically, the new patient model can be set to react to the pressure delivered by the APAP device (PAP-responsive mode) or to reproduce a fixed scenario of disturbed breathing events (Steady mode), depending on the device characteristics being tested. Moreover, the severity of the simulated OSA profile is now fully modifiable by changing the frequency and duration of each breathing event. Various artefacts were introduced into the event spectrum, such as changes in tidal volume and breath rate, to replicate typical events during wake such as irregular breathing, swallowing, moving and talking. By combining these new features, we aimed to create a new OSA model concept model that can realistically replicate a whole night of sleep, including phases of wake, rapid eye movement (REM) and non-REM sleep, and change in body position, each one designed to mimic different characteristics in terms of upper airway collapsibility.

For this study specifically, as an example of an entire night of sleep-disordered breathing (SDB), the bench test model was set to simulate the disturbed patterns of a female OSA patient with the following characteristics: long sleep latency (45 min), low positive airway pressures (PAPs) required to overcome obstructive events, high proportion of flow limitation events versus apneas, higher apnea-hypopnea index (AHI) during REM sleep, and only minor positional effects on upper airway collapsibility. The features and structure of this female-specific OSA patient simulation are detailed in Table 1. The breathing pattern of the simulated patient depended on the PAP applied by the device under test, with a total duration of 4 hours and 15 minutes. APAP pressure values required to normalize breathing during each stage of the simulation are shown in Fig 1. The simulated night consisted of programming the different stages described in Table 1, starting with 45 minutes of simulated awake stage (sleep onset) followed by a succession of different sleep stages with the features detailed in Table 1 (e.g. breathing frequency, number and types of respiratory events) and a final awake short period. In this way we were able to model a patient exhibiting different sleep breathing characteristics throughout consecutive sleep stages.

Ten different commercially available APAP devices were tested using the new bench test model and the female-specific simulation described above: AirSense 10 (A) and AirSense 10 AutoSet for Her (B) by ResMed; Dreamstar by Sefam (C); Icon by Fisher & Paykel (D);

Resmart by BMC (E); Somnobalance (F) and Prisma 20A (G) by Weinmann; System One by Respironics (H); iCH (I) and XT-Auto by Apex (J). Each APAP device was connected with its own tube to the bench model. Default APAP settings were used (minimum pressure 4 cmH_2O, maximum pressure 20 cmH_2O). Each device was tested twice and the results averaged to obtain the final values.

Results

The new OSA patient simulator could effectively combine a great variety of SDB elements to mimic the response of the predefined patient type. The responses of the assessed APAP devices to the new female-specific bench test model are summarized in Table 2. There was considerable variation among devices, particularly with respect to the mean and maximum nasal pressures applied, and the ability to overcome obstructive events and flow limitation, The residual AHI was calculated as the number of residual obstructive events per hour and the residual flow limitation was measured as the portion of the test in minutes (excluding the initial 45-minute wake period) that the simulated patient remained on flow limitation.

Table 1. Description of the patient simulation implemented in the bench test model.

Stage	Duration	AHI	Features
Sleep onset	45 min	-	
			16 breaths/min
			V_T 500 mL
			Random insertion of changes in breathing rate and V_T, and swallowing
Non-REM cycle 1	60 min	15/h	
			Body position: side
			Apneas (0–5 cmH_2O): event length 12 sec
			Hypopneas (5–7 cmH_2O): event length 16 sec
			Flow limitation (7–9 cmH_2O)
			Normal breathing (>9 cmH_2O)
REM cycle 1	15 min	30/h	
			Apneas (0–8 cmH_2O): event length 18 sec
			Hypopneas (8–10 cmH_2O): event length 16 sec
			Flow limitation (10–12 cmH_2O)
			Normal breathing (>12 cmH_2O)
Non-REM cycle 2	45 min	15/h	
			Body position: side
			Apneas (0–5 cmH_2O): event length 12 sec

			Hypopneas (5–7 cmH_2O): event length 16 sec
			Flow limitation (7–10 cmH_2O)
			Normal breathing (>10 cmH_2O)
REM cycle 2	25 min	30/h	
			Apneas (0–7 cmH_2O): event length 18 sec
			Hypopneas (7–9 cmH_2O): event length 16 sec
			Flow limitation (9–11 cmH_2O)
			Normal breathing (>11 cmH_2O)
Non-REM cycle 3	30 min	15/h	
			Apneas (0–5 cmH_2O): event length 18 sec
			Hypopneas (5–7 cmH_2O): event length 16 sec
			Flow limitation (7–10 cmH_2O)
			Normal breathing (>10 cmH_2O)
REM cycle 3	30 min	30/h	
			Body position: supine
			Apneas (0–9 cmH_2O): event length 18 sec
			Hypopneas (9–11 cmH_2O): event length 16 sec
			Flow limitation (11–13 cmH_2O)
			Normal breathing (>13 cmH_2O)
Awake	5 min	-	Normal breathing

AHI: apnea-hypopnea index; REM: rapid eye movement; V_T: tidal volume.

Breathing normalization with a residual AHI <5/h was only achieved with devices A, B and D; devices E, H, I and J were associated with more than five residual events per hour. Pressure changes of each device throughout the whole test are displayed in Fig 1.

Considering the 45-minute wake period, there was significant variation in the behaviour of the different devices. Table 3 shows the pressure values reached by each tested device at the end of the simulated wake period. Device C did not increase the pressure during wake periods.

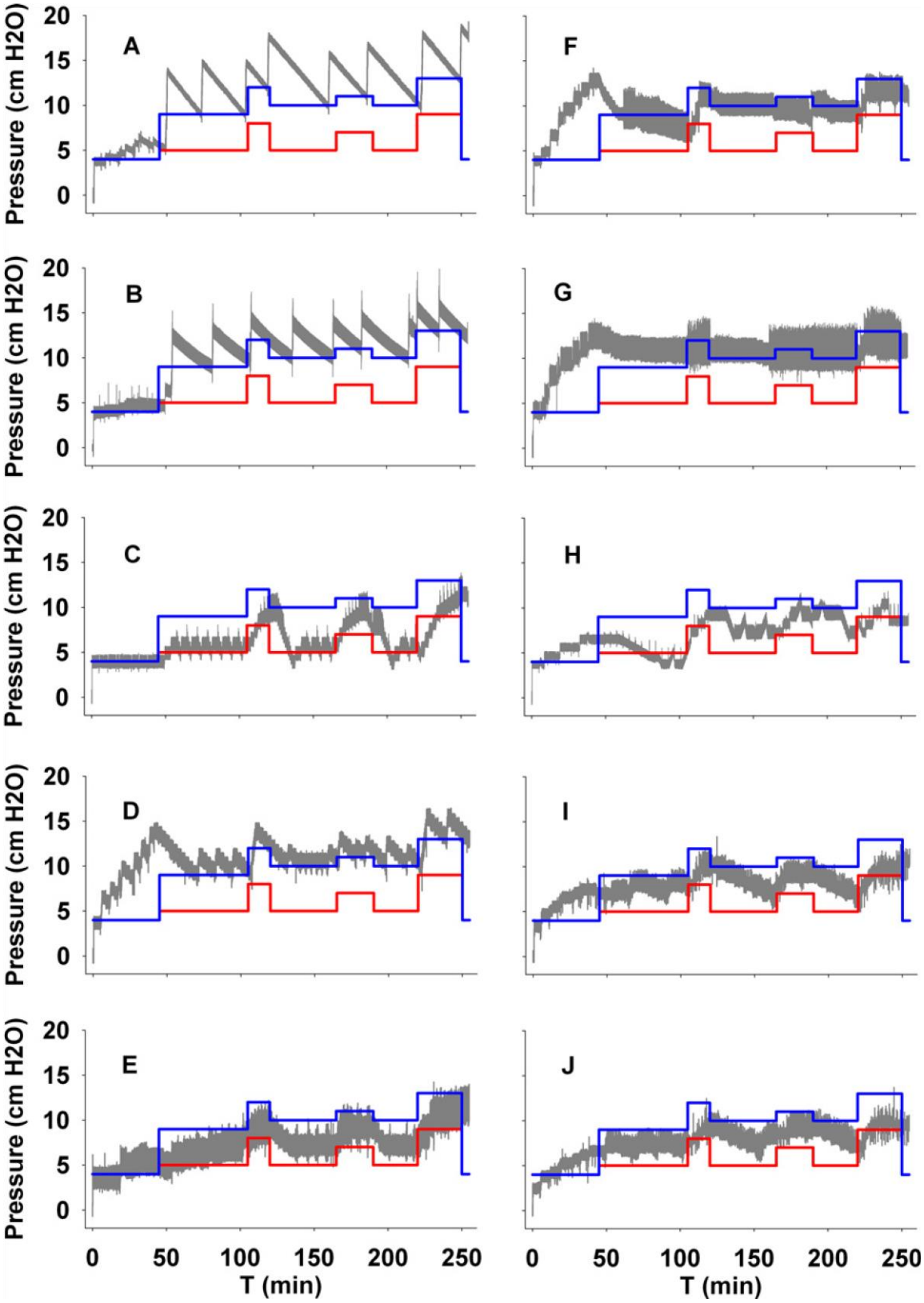

Fig 1. Pressure trends over a full simulated night (grey line) for all APAP devices tested. A device that delivered pressures above the blue line achieves full breathing normalization, while if it delivered pressures just above the red line only obstructive apneas were overcome.

Table 2. Reponses of automatic CPAP devices to a specific simulated OSA patient.

Device	Pmax cmH_2O	Pmean cmH_2O	Residual AHI AHI,/h	Overcome obstructive events?	Overcome flow limitation?	Residual flow limitation, min (% sleep time)
A	18.65	13.25	0.7	Yes	Yes	4 (2%)
B	15.4	11.8	0.7	Yes	Yes	4 (2%)
C	11.4	6.75	16.5	No	No	24 (12%)
D	15.3	11.3	0.6	Yes	Yes	24.5 (12%)
E	11.35	7.7	11.9	No	No	81 (40%)
F	12.6	9.5	2.4	Yes	No	167 (81%)
G	12.1	10.05	1.6	Yes	No	122 (60%)
H	12.45	7.75	10	No	No	76 (37%)
I	10.6	8.3	6.5	Yes	No	142 (69%)
J	10.1	8.2	8.5	No	No	132.5 (65%)

AHI: apnea-hypopnea index; P_{max}: maximum positive airway pressure applied; P_{mean}: mean positive airway pressure; A: AirSense 10 by ResMed; B: AirSense 10 AutoSet for Her by ResMed; C: Dreamstar by Sefam; D: Icon by Fisher & Paykel; E: Resmart by BMC; F: omnobalance by Weinmann; G: Prisma 20A by Weinmann; H: System One by Respironics; I: iCH by Apex; J: XT-Auto by Apex.

Three devices (A, B and E) displayed only mild pressure increases (<2 cmH_2O). Moderate pressure increases (2.5–3 cmH_2O) were displayed by three devices (H, I and J), and significant pressure increases (>7 cmH_2O) were seen from three devices (D, F and G). Three examples of different responses during the simulated wake period are presented in Fig 2, together with the flow signal generated by the simulator during the initial awake phase, which consisted of normal breathing with some events inserted simulating flow alterations due to irregular breathing (E) and swallowing (S). Devices A, B and D contain algorithms aimed at automatically detecting sleep onset (for A, B AutoRamp mode and for D SenseAwake mode). Devices A and B showed similar pressure increases with AutoRamp mode turned off, while device D responded with higher pressure increases when the SenseAwake mode turned off.

To assess whether the observed variations in pressure during wake had an influence on the results of testing, a subset of devices that showed a moderate to significant pressure increase during sleep onset (D, G, H and I) were retested without the wake phase of the test. In this

Table 3. Pressure values reached by each device after 45 minutes of simulated wake.

Device	APAP pressure after 45 mins of simulated wake (cmH_2O)
A	5.4 (5.8 with AutoRamp OFF)
B	4.8 (5.2 with AutoRamp OFF)
C	4.0
D	11.2 (14.5 with SenseAwake OFF)
E	4.6
F	11.8
G	11.7
H	6.5
I	6.8
J	6.9

A: AirSense 10 by ResMed; B: AirSense 10 AutoSet for Her by ResMed; C: Dreamstar by Sefam; D: Icon by Fisher & Paykel; E: Resmart by BMC; F: Somnobalance by Weinmann; G: Prisma 20A by Weinmann; H: System One by Respironics; I: iCH by Apex; J: XT-Auto by Apex.

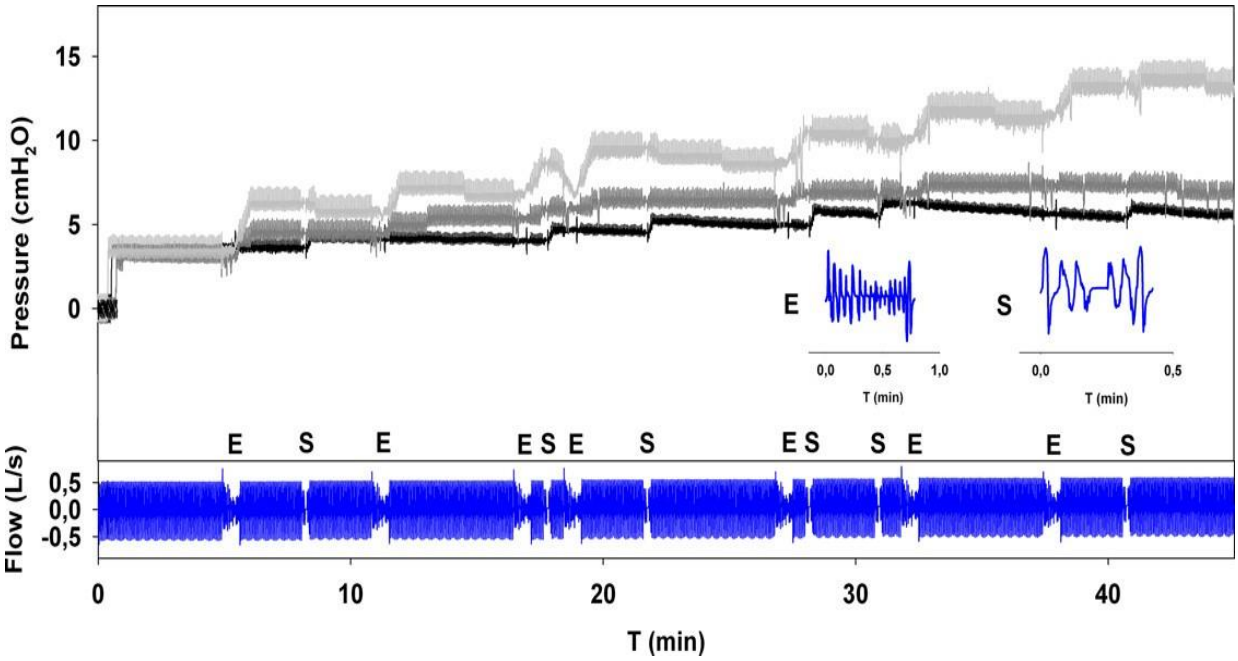

Fig 2. Pressure trends for three different APAP devices tested during the initial 45-minute simulated wake period. Device A (black line) showed a mild pressure increase (< 2 cmH_2O), device I (dark grey line) showed a moderate pressure increase (2.5–3 cmH_2O), while device D (light grey line) showed a high pressure increase (>7 cmH_2O) in response to the breathing pattern simulating 45 minutes of wake period (blue line). E: erratic breathing; S: swallowing.

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additional analysis (Table 4), the responses of the tested devices were relatively similar to the ones in the previous tests that included the 45-minute sleep onset phase. The largest change was seen in device D, where the residual AHI increased from 0.6 to 6 events per hour.

Discussion

We successfully developed and carried out a proof-of-concept test of a novel optimized bench model easily adaptable to simulate different SDB patterns found in OSA, including periods of wake, periods representing different sleep stages and phases of more or less severe SDB events. This tool can be useful to objectively evaluate bench test performance of different APAP devices with realistic breathing patterns covering a wide range of patient phenotypes. In its "Steady mode", the simulator could also assess the capacity of APAP, as well as CPAP, devices to estimate treatment duration and detect residual respiratory events of a fixed predefined disturbed breathing scenario.

The presentation and severity of OSA varies greatly depending on patient characteristics such as gender, age, body mass index, and craniofacial structure [18,22]. Specific patient

Table 4. Results of device re-testing without the sleep onset period.

Device	Pmax cmH_2O	Pmean cmH_2O	Residual AHI, /h	Overcome events	Overcome flow limitation	Residual flow limitation, min (% sleep time)
D	14.6	8.95	6	Yes	Yes	9 (4%)
G	11.65	9.25	2.6	Yes	No	164 (80%)
H	11.45	7.35	6.6	No	No	70 (34%)
I	11.3	7.9	9.6	Yes	No	107.5 (52%)

AHI: apnea-hypopnea index; NA: not available; P_{max}: maximum positive airway pressure applied; P_{mean}: mean positive airway pressure; D: Icon by Fisher & Paykel; G: Prisma 20A by Weinmann; H: System One by Respironics; I: iCH by Apex.

subgroups have been gaining a lot of attention recently because of their clinical relevance. At one end of the age spectrum, elderly patients tend to present with severe OSA and snoring becomes less common. In addition, the frequency of central events increases, although obstructive events still predominate [23]. In contrast, children with OSA have frequent snoring, restless sleep, mouth breathing, apneas, gasping, and laboured or paradoxical breathing [24]. With the growing trend

towards personalized therapy, specific patient breathing patterns will be increasingly studied as manufacturers work to design the most optimal treatment for each phenotype.

One good example of this is OSA in females versus males. It is well-known that the polysomnographic features of female OSA are different from those of male OSA. Overall, women have less severe OSA with, on average, a lower AHI [25] and shorter apneas [26]. Women also have more episodes of upper airway events during REM sleep [25]. Body position is far less important for the severity of OSA in women, while OSA severity in men is based more on position than sleep state [25]. Furthermore, women may take longer to fall asleep, but have fewer awakenings during sleep [27]. Regardless of the patient's gender, there is also significant night-to-night variation in OSA, based on factors such as body posture, sleep stages, and previous drug or alcohol intake [28]. Besides OSA pathophysiology, gender influences also patients' PAP requirements [29], as generally female patients require lower pressures. Such considerable variability between phenotypes highlights the relevance of the simulation approach taken in this study. In our optimized bench test we implemented a dynamic pattern ("PAP-responsive") simulating a female patient phenotype (although an individual male patient may also present with this OSA pattern), which included long periods of flow limitation, low AHI, and short, low-severity obstructive events. Only three of the APAP devices tested were able to achieve full breathing normalization by overcoming all types of disturbed events including flow limitation. Considering the potential for increased flow limitation in female patients, which may lead to breathing disturbances, the effectiveness of treatment in patients presenting with a high component of flow limitation should be carefully examined.

Published data comparing different APAP algorithms is scarce, particularly for devices recently launched into the market. Pevernagie et al examined two APAP devices and found that the residual apnea-hypopnea index (AHI) was lower during use of one device compared with the other (3.5±5.6/h vs 9.9±31.0/h), and that the amount of snoring during the night was significantly higher with one device [30]. A similar study by Nolan et al compared three commercially available devices. The authors found that mean pressure and patient compliance were significantly lower on one of the APAP devices [17]. Differences between algorithms combined with a lack of information regarding how different auto-adjusting devices work has led to the perception that auto-adjusting devices are a 'black box' which should be used with caution [31]. In this study, we also found considerable variation among devices in both the magnitude of response to obstructive events, the time taken to increase pressure during disrupted breathing, and device behaviour during the simulated wake period. With the exception of one device, which did not increase the pressure at all,

most devices at least slightly increased pressure during simulated wakefulness. Some devices showed quite an intense pressure response during the wake period of the test, with one reaching almost 14 cmH_2O and two reaching 12 cmH_2O. Due to the potential impact this could have on patient comfort, pressure changes during wake periods should be assessed in clinical practice, particularly in patients who report difficulties falling asleep while using PAP therapy or issues with comfort at higher PAP pressures.

As stated above, our finding of considerable variability in the response of APAP devices when subjected to the same breathing pattern under well-controlled conditions is in agreement with previous reports [19,21,32]. These variations can be attributed to the individual algorithms within each APAP device. Each algorithm analyses flow and pressure to determine whether there is a breathing disturbance, and then initiates the most appropriate response to correct such a disturbance. For instance, it is interesting to note that, as we explained previously [21], the simulated hypopneas in our model were defined according to specific values of a flowlimitation pattern index initially introduced by Teschler et al [33]. Therefore, it could be possible that automatic CPAP devices set to detect hypopneas using this index, or something similar, could be more suitable for detecting our simulated events than other devices that use other metrics to define and detect hypopneas. Another reason for the observed different response in the automatic CPAP devices tested is that the optimal rate of pressure increase after detection of obstructive events has not been clinically defined. In fact, APAP devices are designed to normalize breathing at a rate which treats actual SDB, avoiding any response to false events, thereby unnecessarily modifying pressure. The results of this bench test have shown that, under well-controlled conditions, there are marked variations in response by different APAP devices, and that there may be high residual AHI or uncontrolled flow limitation in some female patients on some APAP devices. Therefore, all APAP devices should not be considered equal, and efficacy and patient comfort should be carefully examined following APAP initiation.

It must be noted that our results are restricted to the specific patterns of disturbed breathing used in this bench test to simulate a specific OSA patient. It is possible that the response of the tested devices would have been different from the ones reported here if SBD was simulated using different patterns or patient phenotypes. In addition, a limitation of this study is that one device of each type was used. Hence, a more complete assessment would require testing of a larger number of each type of device randomly obtained from those available in the market. Finally, it should be stressed that although bench testing is a useful way to investigate the behaviour of different devices, testing

outcomes may vary in clinical practice due to the almost unlimited spectrum of events and phenotypes found in real life. Indeed, crucial factors such as changes in loop gain, and upper airway compliance and pharyngeal critical pressure are not considered in our model. Accordingly, bench testing should be considered as a preliminary assessment before clinical evaluation in patients.

In conclusion, this study showed that a dynamic bench model tailored to represent specific OSA patient phenotypes, incorporating a variety of disturbed breathing events within the same simulated night, including different degrees of severity along sleep stages, and a period of wakefulness, can be useful to characterize treatment responses of commercially-available APAP devices. This demonstrates that bench testing can be modified to better represent a "real" patient, and that APAP devices can show markedly different responses to the same simulated breathing patterns. Realistically mimicking OSA patients during bench testing is useful as a first step to aid in the understanding of actual APAP device responses observed in the clinical setting, and can be helpful in selecting the device that best meets the individual needs of each patient, thereby improving comfort and increasing adherence to therapy, which is essential for effective treatment and reducing the consequences of OSA [34].

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Author Contributions

Conceived and designed the experiments: VI JMM RS AJW DR HW DN RF. Performed the experiments: VI RS RF. Analyzed the data: VI RS RF. Contributed reagents/materials/analysis tools: JMM AJW HW DN RF. Wrote the paper: VI JMM AJW HW DN RF.

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