

# Cost-effectiveness of oral appliances in the treatment of obstructive sleep apnoea–hypopnoea

Mohsen Sadatsafavi · Carlo A. Marra · Najib T. Ayas · John Stradling · John Fleetham

Received: 3 December 2008 / Revised: 13 January 2009 / Accepted: 25 January 2009  
© Springer-Verlag 2009

## Abstract

**Purpose** Oral appliances (OA) are commonly prescribed for the treatment of obstructive sleep apnoea–hypopnoea (OSAH), but there is limited evidence on their cost-effectiveness.

**Materials and methods** A model was designed to simulate the costs and benefits of treatment of OSAH with OA or continuous positive airway pressure (CPAP) based on their effects on quality of life, motor vehicle crashes, and cardiovascular effects. The primary outcome was the incremental cost-effectiveness ratio (ICER) in terms of costs per one quality-adjusted life year (QALY) gained 5 years after treatment.

**Results** Compared with no treatment, OA results in \$268 higher costs and an incremental QALY of 0.0899 per patient (ICER=\$2,984/QALY). Compared with OA, CPAP resulted in \$1,917 more costs and 0.0696 additional QALYs (ICER=\$27,540/QALY). For the most part in the sensitiv-

ity analyses, CPAP remained cost-effective compared to OA, and OA remained cost-effective with respect to no treatment in almost all scenarios.

**Conclusions** OAs are less economically attractive than CPAP but remain a cost-effective treatment for patients who are unwilling or unable to adhere to CPAP therapy.

**Keywords** Obstructive sleep apnoea · Oral appliances · Continuous positive airway pressure · Economic evaluation · Decision analysis

## Introduction

Obstructive sleep apnoea–hypopnoea (OSAH) is a common syndrome that is characterised by recurrent episodes of partial or complete upper airway obstruction during sleep [1, 2]. OSAH is associated with an increased risk of motor vehicle crashes (MVC) [3], cardiovascular [4] and cerebrovascular [5] events and decreased quality of life [6]. Currently, the primary treatment for OSAH is continuous positive airway pressure (CPAP). However, some patients are unable to tolerate or adhere to CPAP on a long-term basis [7].

Oral appliances (OA) are now widely prescribed for the treatment of OSAH, either as primary therapy or as an alternative for those unwilling or unable to tolerate CPAP [8]. Whilst CPAP has been shown to be more effective than OA [8], there is increasing evidence that OA improves sleepiness, blood pressure and the indices of sleep disordered breathing [9]. In addition, many patients who respond to both treatments often prefer the use of an OA over CPAP [9]. The objective of this study was to evaluate the cost-effectiveness of OA in terms of the incremental cost per quality-adjusted life year (QALY) in patients with

---

M. Sadatsafavi · C. A. Marra  
Collaboration for Outcomes Research and Evaluation,  
Faculty of Pharmaceutical Sciences,  
University of British Columbia,  
Vancouver, BC, Canada

C. A. Marra (✉)  
Centre for Health Evaluation and Outcomes Sciences,  
St. Paul's Hospital,  
620B-1081 Burrard Street,  
Vancouver, BC, Canada V6Z 1Y6  
e-mail: Carlo.marra@ubc.ca

N. T. Ayas · J. Fleetham  
Sleep Disorders Program, Vancouver Acute Hospitals,  
Vancouver, BC, Canada

J. Stradling  
Oxford Centre for Respiratory Medicine,  
University of Oxford, Churchill Hospital,  
Oxford, UK

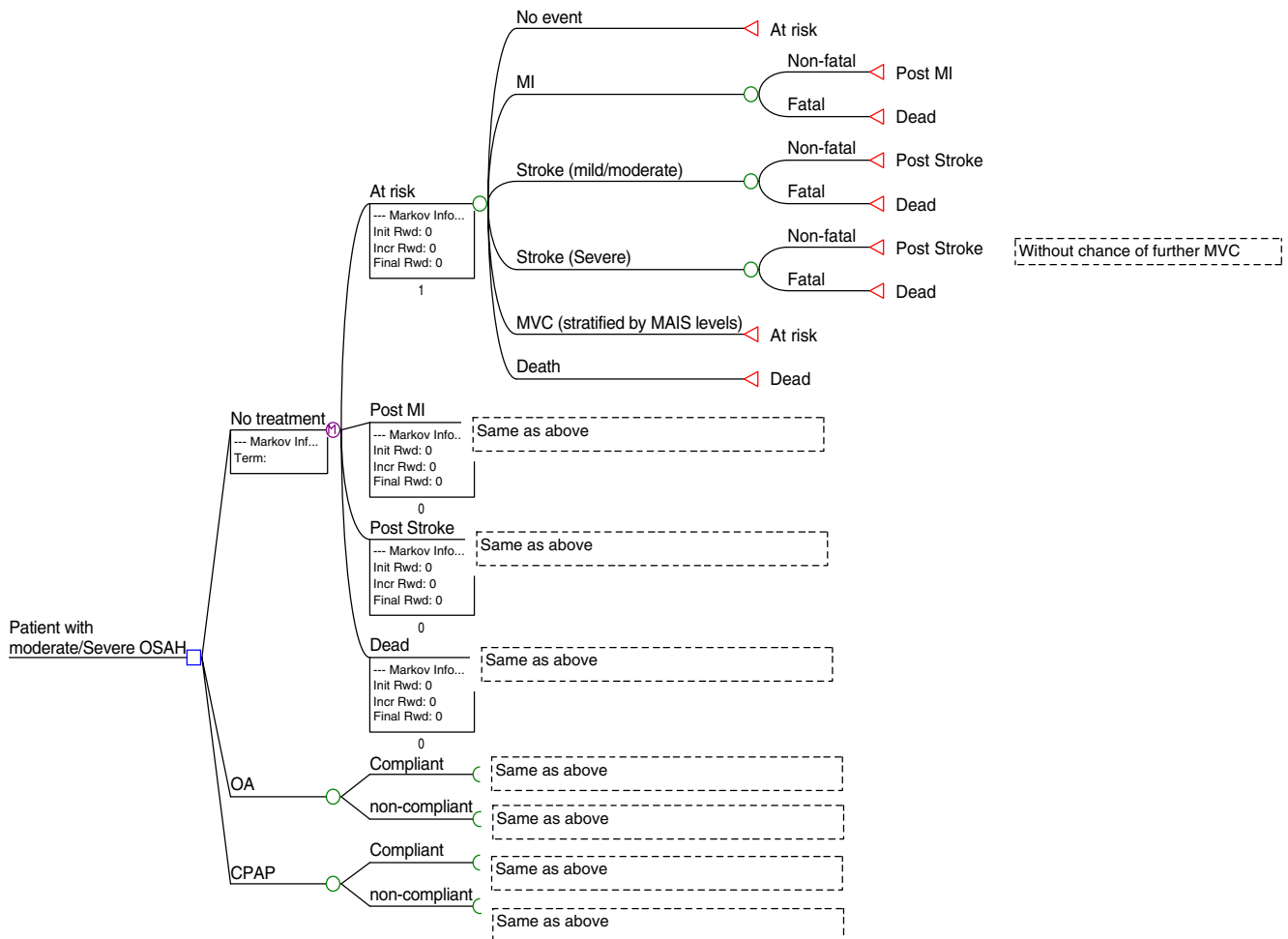
moderate/severe OSAH compared with no treatment and treatment with CPAP from the third-party payer perspective in the USA.

### Materials and methods

#### The model

A discrete state Markov model was created to simulate the natural course of moderate/severe OSAH [apnoea–hypopnoea index (AHI)  $\geq 15$  events per hour] and the impact of different strategies (no treatment, OA and CPAP) on disease outcomes over a 5-year period. Mild OSAH was not chosen because several fundamental parameters of the model such as the impact of OSAH on MVC, efficacy of CPAP and adherence to treatment have only been evaluated in moderate/severe OSAH. This model was based on a previous economic evaluation conducted by our group on CPAP [10]. However,

to improve the comprehensive treatment effects of both CPAP and OA, cardiovascular and cerebrovascular (CV) events were also modelled. Therefore, in each 1-year cycle of the model, patients could experience a MVC, CV event, die from other causes or remain event-free (Fig. 1). MVCs can result in property damage without injury, injury or death. Injury levels were stratified to five maximum abbreviated injury scale (MAIS) levels [11]. CV events included myocardial infarction (MI) and stroke (ischaemic and haemorrhagic) and could be fatal or non-fatal. Stroke was divided into mild/moderate versus severe. It was assumed that patients with severe injury due to MVC (MAIS 4 or 5) or severe stroke are unable to drive anymore and hence are no longer at risk of further MVCs. Background mortality rates were taken from the US life tables in 2003 [12]. Mortality due to MVC and CV events in this population was deducted from the all-cause mortality estimates. The analyses were performed using Data Pro for Health Care software (TreeAge Software, Williamston, MA, USA).



**Fig. 1** Simplified Illustration of the model\*. \*For simplicity, further stratification of MVCs based on the MAIS levels is omitted from this figure. CPAP continuous positive airway pressure, OA oral appliances,

MVC motor vehicle crash, MAIS maximum abbreviated injury scale, PDO property damage only

**Table 1** Key parameters of the model

Probability/rate	Value (95% CI)		Reference
	Male	Female	
Male/Female prevalence ratio	3.3:1		[14]
Age range (%)			
25–34	10.96	8.43	Sleep Disorders Program, Vancouver Acute Hospitals, Vancouver, British Columbia
35–44	26.71	16.87	
45–54	34.59	44.58	
55–64	27.74	30.12	
Annual probability of MVC in normal population (no OSAH)			
25–34	0.04903	0.03455	[17]
35–44	0.03758	0.02848	
45–54	0.0369	0.02333	
55–64	0.02654	0.01763	
Relative risk of MVC in patients with OSA	7.0 (95% CI 4.2–10)		Meta-analysis of studies reporting the incidence of MVC in OSAH before and after treatment [15, 19–25]
Incidence of MI (per 100,000) in normal population (no OSAH)			
25–34	170	10	[26]
35–44	570	120	
45–54	1170	480	
55–64	1950	920	
Relative risk of MI in untreated OSAH	2.87 (95% CI 1.17–7.51)		[4]
Incidence of stroke (per 100,000) in normal population			
25–34	14	17	[27]
35–44	47	45	
45–54	161	132	
55–64	469	153	
Relative risk of stroke in untreated OSAH	2.87 (95%CI 1.17–7.51)		[4]
Proportion of fatal MIs/total MIs	9.1%	14.8%	[54]
Proportion of fatal strokes/total Strokes	14%	20%	[30]
Proportion of severe strokes/total strokes	0.27		[32]
Adherence to CPAP and OA			
Base case	$EXP(-0.2 \cdot y + 0.025 \times y^2)^a$		[38]
Sensitivity analysis	$EXP(-0.001 \times y + 0.008 \times y^2)$		[37, 39]
Relative efficacy of OA versus CPAP <sup>a</sup>			
Based on AHI	0.56 (95% CI 0.40–0.73)		Meta-analysis of head-to-head studies of OA vs. CPAP with AHI as outcome (see text for details)
Based on ESS	0.56 (0.22–0.88)		
Change in utility for 1 unit change in ESS			
SF-6D utility	-0.0095 (-0.0122, -0.0068)		York economic model of CPAP in OSAH [34]
EQ-5D utility	-0.0097 (-0.0175, -0.0019)		
Proportion of MAIS levels (%)			
Property damage	82.5		[18]
MAIS 0	5.7		
MAIS 1	10.4		
MAIS 2	1.0		
MAIS 3	0.3		
MAIS 4	0.08		
MAIS 5	0.02		
Fatal	0.01		

The confidence interval was calculated based on the number of subjects in the original reports and the assumption of Poisson distribution of AHI. *OSAH* obstructive sleep apnoea/hypopnoea, *CPAP* continuous positive airway pressure, *OA* oral appliances, *MAIS* maximum abbreviated injury scale, *MI* myocardial infarction, *MVC* motor vehicle crash, *AHI* apnoea–hypopnoea index, *ESS* Epworth sleepiness score

<sup>a</sup> y: year after initiation of treatment

Characteristics of the population

Table 1 provides the different data sources used for this analysis. The model was stratified on four age groups (25–34, 35–44, 45–54 and 55–64 years) and gender (male vs. female). The weights assigned to each age group reflect the demographic characteristics of patients with moderate to severe OSAH in our centre which are comparable to that in the USA [13]. We assumed a ratio of 3.3:1 for the prevalence in men vs. women based on a large survey in the USA [14].

Impact of treatment on the incidence of events

Whilst there are some reports on the impact of CPAP treatment on MVC [15] and CV events [4], we are not aware of any data on the impact of treatment with OA on such outcomes. There are several studies evaluating the impact of CPAP and OA on the subjective and objective measures of the severity of OSAH [8] and reports linking the severity of OSAH to MVC and CV events [4, 16]. Therefore, in the absence of direct evidence, we used this indirect evidence to estimate the effect of treatment with CPAP and OA on the events modelled in our analysis. The impact of CPAP and OA on the AHI was used as a surrogate for their effectiveness on reducing other events due to OSAH [8]. We made the assumption that a reduction in the risk of all events for CPAP and OA is proportional to their effect on reducing AHI. Several alternative assumptions were examined in the sensitivity analysis. First, it was assumed that for patients adherent to CPAP, the incidence of all events will be equal to that of the normal population (as suggested by some studies [4, 15]). In alternative scenarios, we assigned lower treatment effect for CPAP and OA and also removed the impact of treatment on individual outcomes (MVC, CV) for both CPAP and OA to evaluate the robustness of our results.

To calculate the relative efficacy of OA versus CPAP, we retrieved data from randomised, parallel-arm and crossover clinical trials comparing CPAP and OA. Details of studies used in the meta-analysis are presented in Table 2. Efficacy was defined as the relative reduction of AHI. For example, if treatment reduced AHI from 24 to 8, its efficacy was  $16/24=0.66$ . The pooled estimate of efficacy of CPAP and OA based on AHI was determined using a joint meta-analysis of AHIs before and after treatment.

Baseline rate of events

The annual probability of MVC in individuals without OSAH was determined using data for the year 2005 (200,665,000 licensed motorists) from the National Highway Traffic Safety Administration [17]. Severity of MVC injuries was taken from a technical report on the economic impact of MVCs in the year 2000 [18]. As in our previous report [10], the

**Table 2** Randomised clinical trials comparing AHI in CPAP vs. OA in patients with moderate to severe OSAH

Study	Age mean (SD)	Gender (%male)	Treatment period	Type	Sample size in CPAP arm	CPAP(baseline→ after treatment)	Sample size in OA arm	OA (baseline→ after treatment)
Barnes M et al. [33]	46.4 (1.1)	78.8	3 months	Crossover	89	AHI: 21.3 (17.1)→4.8 (4.7) ESS: 10.7 (5.3)→9.2 (3.77)	85	AHI: 21.3 (17.1)→14.0 (10.1) ESS: 10.7 (5.3)→9.2 (3.77)
Engleman et al. [55]	46 (9)	80	8 weeks	Crossover	48	AHI: 32(29)→8(6) ESS: 15 (3)→8(5)	48	AHI: 30(21)→15.0(16) ESS: 13(4)→12(5)
Randerath et al. [56]	56.5 (10.2)	80	6 weeks	Crossover	20	AHI: 17.5 (7.7)→3.5 (2.9)	20	AHI: 17.5 (7.7)→13.8 (11.1)
Ferguson et al. [57]	44.0 (10.6)	79	4 months	Crossover	20	AHI: 26.8 (11.9)→4.2 (2.2) ESS: 11 (3.8)→5.1 (3.3)	20	AHI: 26.8 (11.9)→13.6 (14.5) ESS: 10.3 (3.1)→4.7 (2.6)
Ferguson et al. [58]	46.2 (10.9)	89	4 months	Crossover	25	AHI: 17.6(13.2)→3.6 (1.7)	25	AHI: 19.7 (13.8)→9.7 (7.3)
Pooled AHI					202	23.5→5.2	198	23.4→13.6
Pooled ESS					157	12.1→8.3	153	11.4→9.5

Numbers in parenthesis are standard deviation

OSAHI obstructive sleep apnoea/hypopnoea, CPAP continuous positive airway pressure, OA oral appliances, AHI apnoea–hypopnoea index

relative risk of MVC in patients with untreated OSAH were calculated based on the meta-analysis of studies that examined MVC rates in patients with OSAH before and after treatment with CPAP [15, 19–25].

The incidence of MI in patients without OSAH for each gender and age group was derived using Framingham equations [26]. The incidence of stroke in patients without OSAH was based on the age- and gender-specific incidence of stroke in year 1996 in the USA [27]. The relative risk of CV events in patients with untreated OSAH was taken from a large observational study [4]. This study did not report the increased risks for MI and stroke separately. Therefore, we assumed that the increased risk was equal for both outcomes and across age groups. We assigned lower risk of CV events (RR=0.7, 95% CI 0.50–0.91) for women relative to men, as reported by Greenberg-Dotan et al. [28]. In an alternative sensitivity analysis, we assumed that the increase in risk of stroke is twice that of cardiovascular events, as suggested by Mar et al. [29]. The proportion of fatal MI and stroke was taken from the Framingham Study and Gusto Trial, respectively [30, 31].

### Quality of life

The effectiveness outcome was the QALY where various health states are adjusted for the quality of life (health utility) of that state and multiplied by the duration of the health state. There are some reports assessing the quality of

life in patients treated with CPAP [29, 32]. However, despite some studies reporting on the quality of life in patients treated with OA using general quality-of-life instruments [33], we are not aware of reports for patients undergoing treatment with OA that enable calculation of health utilities. In the absence of such data, we used the effect of treatment on the Epworth sleepiness score (ESS) to estimate the change in health utility for both treatments. To estimate the change in ESS score due to treatment, we pooled the results (using random-effects meta-analysis) from all randomised parallel-arm and crossover clinical trials comparing the change in ESS in the CPAP and OA arms (Table 3). To convert these changes to change in health utility, we used the results of a regression analysis of ESS to changes in health utility ([34], personal communication). The utility in the original population was measured using two health utility instruments: EuroQol-5D (EQ-5D) and Short form-6D (SF-6D). In the base case analysis, we used the results of the regression analysis based on the latter instrument, as it was based on a larger sample size ( $n=294$  vs. 94).

Health utilities for patients with stroke and MI were taken from the published literature (Table 3). Separate utilities were assigned for the first 6 months after the MI and stroke events and afterwards [35, 36]. Health utility of patients after MI and stroke was assumed to be independent of their OSAH status. The source of the health utilities and the methodology used in calculating utilities for untreated OSAH, the effect of

**Table 3** Utility values in the model

Utility	Value (95% CI)	Reference
OSAH—no treatment	0.74 (0.35–0.97)	[32]
Incremental CPAP	0.0615 (0.00–0.14) <sup>a</sup>	[29, 32]
Incremental OA	Incremental CPAP × relative efficacy of OA (based on ESS)	See text for details
MVC		
MAIS 1	0.93 (0.69–1.00)	[59]
MAIS 2	0.89 (0.67–0.97)	
MAIS 3	0.84 (0.64–0.97)	
MAIS 4	0.93 (0.60–1.00)	
MAIS 5	0.19 (0.15–0.37)	
Myocardial infarction		
First 6 month	0.57 (SD 0.22)	[60]
Afterwards	0.73 (SD 0.22) <sup>b</sup>	
Stroke		
First 6 month	0.31 (SD 0.38)	[36]
Afterwards	0.62 (SD 0.33)	[35]

OSAH obstructive sleep apnoea/hypopnoea, CPAP continuous positive airway pressure, OA oral appliances, MAIS maximum abbreviated injury scale, MI myocardial infarction, MVC motor-vehicle crash, AHI apnoea–hypopnoea index, ESS Epworth sleepiness score

<sup>a</sup> Since one of the studies did not report confidence interval around the difference utilities before and after CPAP, the confidence interval for the probabilistic sensitivity analysis was taken only from [29]

<sup>b</sup> We assumed that disutility due to MI and stroke will be added to the disutility due to OSAH

CPAP and health utilities for different MVC states have been described in our previous economic evaluation [10].

### Adherence

It is difficult to compare adherence to CPAP with that of OA despite the fact that there are rather extensive data on adherence for both treatments [9]. This is because the majority of studies on CPAP adherence are in patients with moderate/severe OSAH, whilst adherence to OA treatment has been mainly studied in mild OSAH. Since the present analysis is for patients with moderate/severe OSAH, we used the data for CPAP adherence and in the main analysis assumed that adherence to CPAP and OA are equal. The reported adherence with CPAP varies [37, 38]. In the main analysis, we used the results of McArdle et al. [38], which reported an adherence of 84% at 1 year and 68% at 5 years. In an alternative scenario, we used the adherence rate of 90% at 3 years as reported by Krieger et al. [37] and 70% at 6 years reported by Lacassagne et al. [39]. For both the base case and sensitivity analysis, we calculated the adherence rate for each year by fitting a quadratic–exponential curve to the adherence rates (Table 1). A two-way sensitivity analysis was performed to evaluate the impact of lower and higher adherence to OA and CPAP on their cost-effectiveness.

### Costs

Table 4 presents the cost estimates used in this analysis. The base case analysis was conducted from the perspective of a third-party payer in the USA, and therefore, only direct costs were considered. The cost of CPAP treatment was modelled as in our previous cost-effectiveness analysis [10]. Non-adherent patients were assumed to incur costs associated with the mask, tubing, headgear and one physician visit plus the rental costs of the CPAP machine and humidifier for their period of treatment. In the USA, patients do not have to cover the cost of the CPAP machine, as it can be returned and used for other patients.

Our estimate of the cost of OA was based on a survey of 124 dentists across USA [40]. We assumed that both CPAP and OA will be functional for an average of 5 years. For OA, we assumed that 2.5 follow-up visits during a 5-year treatment period would be needed [40]. Unlike CPAP, patients unable to use OA would have to cover the full cost of the OA as it is custom-made for each patient. A univariate sensitivity analysis was performed to study the impact of different cost values for OA on the results.

Direct medical costs of MVC for each MAIS group were obtained from the year 2000 report of the National Traffic Safety Administration [18]. The estimated costs in that report are the lifetime cost of MVC. Similar to our previous analysis [10], we assumed that such costs are uniformly

**Table 4** Cost estimates (year 2004 US \$)

Cost	Value	Reference
CPAP		
Mask	117.64	[10]
Tubing	41.02	
Headgear	37.16	
CPAP rental per month	96.99	
Heated humidifier per month	30.11	
OA		
Initial cost	1,233	[40], Medicare (2004)
Follow-up visit (2.5 in 5 years)	59.62	
Myocardial infarction		
Initial (fatal)	11,107	[41]
Initial (non-fatal)	15,649	
Annual	1,246	
Stroke		
Initial (fatal)	9,811	[41]
Initial (non-fatal)	66,781	
Annual <sup>a</sup>	12,987	
MVC costs (direct)		
PDO	995	[18]
MAIS0	685	
MAIS1	5,565	
MAIS2	29,986	
MAIS3	85,449	
MAIS4	203,775	
MAIS5	485,760	
FATAL	168,056	

CPAP continuous positive airway pressure, OA oral appliances, MVC motor vehicle crash, MAIS maximum abbreviated injury scale, PDO property damage only

<sup>a</sup> Includes the cost of rehabilitation

distributed over the average of 40 years, and hence, only 5/40=12.5% of costs fall within the time horizon of the model. An alternative analysis considered 50% of lifetime costs to be incurred at the first 5 years. Two exceptions were costs of fatal MVCs and MVCs causing only property damage, for which all costs were taken into account. All cost components were inflated to year 2004 using the medical component of the consumer price index.

We used the same approach as Sarasin et al. [41] in modelling cost of stroke and MI. The cost of stroke consisted of the costs related to hospitalisation and inpatient rehabilitation and ongoing treatment for all stroke survivors. The cost of MI included the cost of hospitalisation due to the event and annual treatment cost up to the time horizon of the study.

### Cost-effectiveness analysis

The main (base case) analysis and one-way and two-way sensitivity analyses were performed by running the model

with the point estimates of the probabilities, utilities and costs. Cost, QALYs and the 5-year incidence of the events were estimated. The incremental cost-effectiveness ratio (ICER) was calculated for OA versus no treatment and for CPAP versus OA. In the base case analysis, an annual discount rate of 3% was assigned to the future costs and QALYs, whilst the effect of higher discount (6%) and no discounting was evaluated in the sensitivity analysis.

In addition to the one-way sensitivity analyses described earlier, a probabilistic sensitivity analysis (PSA) was performed by drawing a random number from the corresponding distributions for each parameter and running the model 1,000 times. Results of the PSA are presented as the cost-effectiveness acceptability curve [42], which presents the probability of each treatment being the best option at a given value that the decision maker is willing to pay to obtain one QALY (i.e. equivalent of one healthy year of life). Since none of the cost estimates were accompanied by any measure of uncertainty, uncertainty around costs was modelled by assigning a triangular distribution to the costs with lower and upper bound of 25% of the point estimate. All sensitivity analyses were done using QALY as the effectiveness outcome.

## Results

### Relative efficacy of OA versus CPAP

Results of the meta-analysis of the relative efficacy of OA and CPAP are presented in Table 2. AHI was decreased by 18.3 (95% CI 14.1–22.0) in the CPAP group and by 9.7

(95% CI 6.4–12.8) in the OA group, and the relative efficacy of OA versus CPAP based on their ability to reduce AHI was estimated to be 0.53 (95% CI 0.38–0.77). CPAP reduced the ESS score by 3.91 (95% CI 2.29–8.10), whilst OA reduced ESS by 2.20 (95% CI 0.69–6.84).

### Outcomes

The annual incidence of MVC and CV events in a simulated cohort of 1,000 patients in each intervention arm and also in the normal population is presented in Table 5. The most common event in the model was MVC. However, the majority of such MVCs would result in property damage only, and the incidence of MVC excluding property-damage-only crashes was 22.8 in the no treatment, 16.1 in the OA and 7.2 in the CPAP group (in 1,000 patient-years).

### Cost-effectiveness analysis

The results of base case analysis are shown in the first row of Table 6. Compared with no treatment, OA resulted in an incremental cost of \$268 with an incremental QALY of 0.0899 per individual, resulting in an ICER of \$2,984 per QALY. Compared with OA, CPAP resulted in \$1,917 more costs and 0.0696 additional QALYs, yielding an ICER of \$27,540 per QALY. Results of the one-way sensitivity analysis are shown in Table 6 and Fig. 2. Results were generally robust to different assumptions, as OA remained a cost-effective strategy against no treatment in all scenarios. CPAP was cost-effective compared with OA in the majority of scenarios, with one exception: when the gain in utility

**Table 5** Incidence of MVC, CHD, and CV events (per 1,000 patient-years)

	No treatment <sup>a</sup>		OA		CPAP		Normal population <sup>a</sup>	
	Male	Female	Male	Female	Male	Female	Male	Female
MVC <sup>b</sup>								
25–34	34.5	26.8	18.0	14.3	12.0	8.8	9.9	7.1
Averaged over 5 years (time horizon of the model)								
35–44	29.2	23.0	16.6	13.3	8.7	7.6	7.2	5.6
45–54	24.8	17.4	15.5	11.3	8.5	5.7	7.5	4.5
CPAP continuous positive airway pressure, OA oral appliances, MI myocardial infarction, MVC motor-vehicle crash								
55–64	19.3	14.2	10.5	8.8	7.6	4.5	5.3	3.7
MI								
25–34	5.3	1.9	2.7	1.1	0.9	0.4	0.3	0.0
35–44	16.1	4.5	8.7	2.3	3.2	0.8	1.3	0.3
45–54	30.1	14.2	16.3	7.5	6.3	2.9	2.4	0.3
55–64	44.9	22.0	25.5	12.1	10.2	4.5	3.9	1.8
Stroke								
25–34	0.3	0.5	0.1	0.3	0.1	0.0	0.0	0.0
35–44	1.3	1.3	0.6	0.6	0.3	0.2	0.2	0.1
45–54	4.0	3.2	2.1	1.7	0.9	0.5	0.4	0.2
55–64	10.4	8.1	5.5	4.5	2.2	1.7	1.1	0.7

<sup>a</sup> For 'No treatment' and 'Normal population', the rates are taken from the literature.

For OA and CPAP arms; they are estimated from the results of the meta-analysis on the AHI and ESS scores

<sup>b</sup> Not including MVCs resulting only in property damage

**Table 6** Base case and univariate sensitivity analysis

Assumption	No treatment		OA		CPAP		ICER (OA vs. no treatment)	ICER (CPAP vs. OA)	ICER (CPAP vs. no treatment)
	Cost	QALY	Cost	QALY	Cost	QALY			
Base case analysis	\$4,216	3.3367	\$4,484	3.4266	\$6,401	3.4962	2,984	27,540	13,698
MVC effects removed	\$3,342	3.3444	\$3,867	3.4320	\$5,967	3.4999	5,990	30,915	16,874
MI effects removed	\$1,704	3.3710	\$2,601	3.4543	\$4,943	3.5182	10,774	36,619	22,000
Stroke effects removed	\$3,507	3.3523	\$3,963	3.4382	\$6,019	3.5050	5,306	30,809	16,460
Zero utility gain for OA	\$4,216	3.3367	\$4,484	3.3525	\$6,401	3.4962	16,988	13,337	13,698
Utility gain of OA equal to CPAP	\$4,216	3.3367	\$4,484	3.4839	\$6,401	3.4962	1,823	155,539	13,698
Discount rate 6%	\$3,958	3.1605	\$4,281	3.2464	\$6,162	3.3129	3,762	28,275	14,456
Discount rate 0%	\$4,506	3.5344	\$4,713	3.6288	\$6,671	3.7019	2,191	26,787	12,925
CPAP treatment bringing events to normal range	\$4,216	3.3367	\$4,484	3.4266	\$5,367	3.5108	2,984	10,480	6,609
Efficacy of treatment with CPAP/OA <sup>a</sup>									
25% lower	\$4,216	3.3367	\$4,951	3.3831	\$7,052	3.4419	15,841	26,958	35,731
40% lower	\$4,216	3.3367	\$5,448	3.3613	\$7,781	3.4099	49,964	48,665	48,005
RR for stroke twice that of MI	\$4,894	3.3214	\$4,886	3.4172	\$6,592	3.4910	-86	23,138	13,489
ESS to utility (EQ-5D)	\$4,216	3.3367	\$4,484	3.4280	\$6,401	3.4987	2,939	27,113	11,906
Lower adherence to CPAP and OA $EXP(-0.035 \times y)$	\$4,208	3.3385	\$4,319	3.4436	\$6,434	3.5255	1,058	25,829	12,366
50% of lifetime MVC costs incurred within the first 5 years	\$4,623	3.3367	\$4,765	3.4266	\$6,596	3.4962	1,577	26,304	26,944

Note that all analyses are generated by running the model with the point-estimates of parameters, and hence the uncertainty around the model outcomes is not reported

CPAP continuous positive airway pressure, OA oral appliances, MI myocardial infarction, MVC motor vehicle crash, QALY quality-adjusted life years, ICER incremental cost-effectiveness ratio

<sup>a</sup> Efficacy of CPAP in reducing MVC and CV rates was assumed to be 75% and 60% of the value used in the base case analysis. Since OA efficacy is modelled as relative to CPAP, this will also reduce the OA efficacy

was assumed to be equal between OA and CPAP, in which case the ICER of CPAP vs. OA surpassed the cost-effectiveness threshold of \$50,000/QALY.

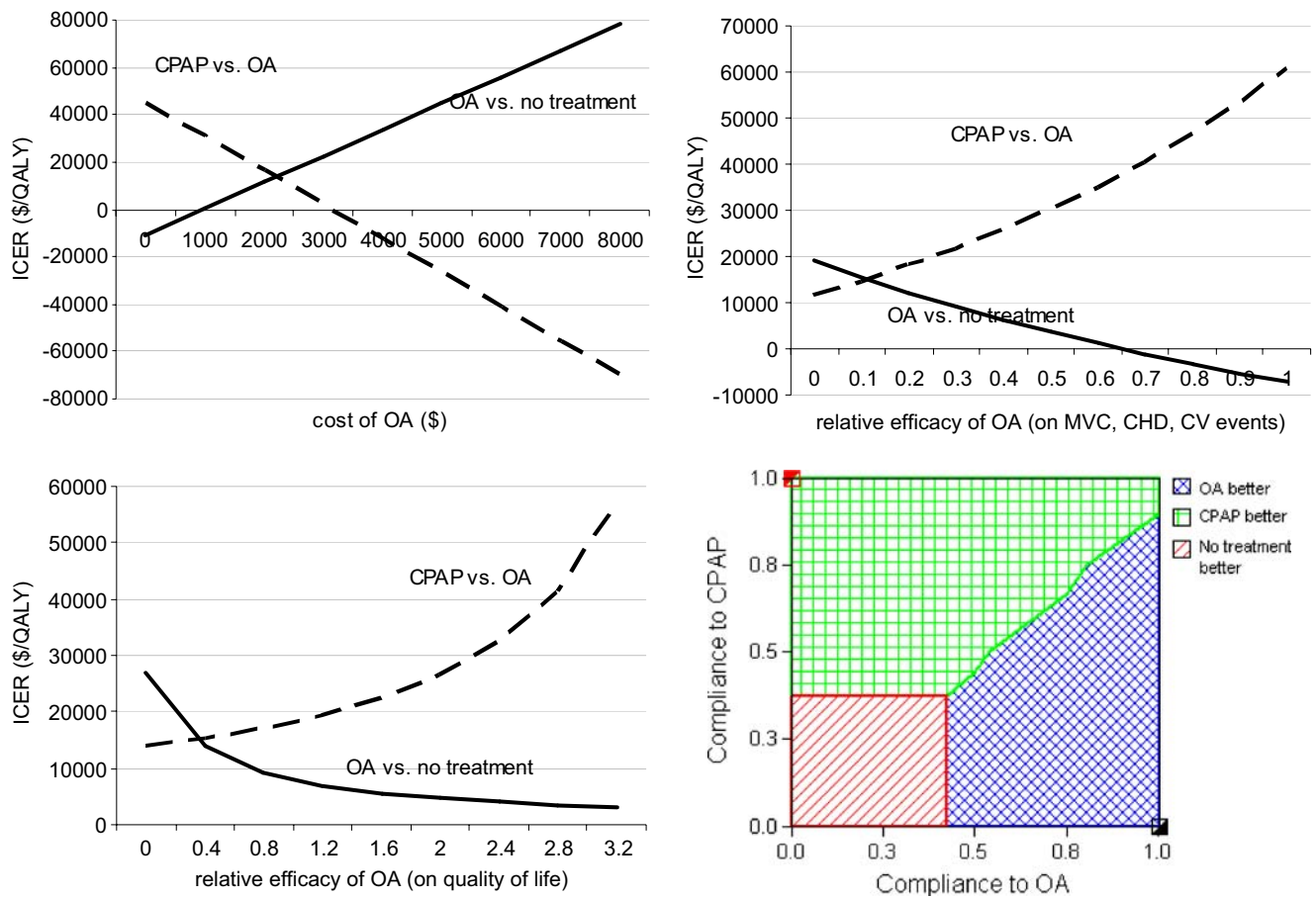
Figure 2 shows the impact of four variables (cost of OA, relative efficacy of OA as measured by its effect on AHI and ESS, and adherence to OA and CPAP) on the results of the cost-effectiveness analysis. OA became cost-saving (compared with no treatment) as if its initial cost fell below 964\$ and remained cost-effective as long as its initial costs were less than \$5,710. OA became cost-saving compared to no treatment also when it was assumed to be at least 65% effective on reducing MVC, MI and stroke. When OA was assumed to have no impact on MVC and CV events, it remained cost-effective (vs. no treatment) purely due to its effect on quality of life. Likewise, whilst the improvement in quality of life due to OA was set to zero, OA was still cost-effective through reducing the incidence of MVC and CV events. Result of the two-way sensitivity analysis on the adherence of OA and CPAP is presented in the bottom-right panel of Fig. 2. At 70% adherence (i.e. 30% non-adherence per year) for CPAP, OA became the best option if adherence to OA was at least 80%. No treatment became

the preferred strategy only when adherence to both CPAP and OA was less than 46% per year.

The cost-effectiveness acceptability curve comparing the three strategies is presented in Fig. 3. If the third-party payer is willing to pay less than \$32,000 for each QALY gained, OA was the best strategy, whereas for all higher willingness-to-pay values, CPAP had the highest chance of being the best option. At very low values of willingness-to-pay (<\$6,000), no treatment became the best option. Overall, in 35% of simulations, OA was less costly and more effective with respect to no treatment. In almost all other simulations, OA resulted in higher costs and effectiveness, but the ICER was still below \$50,000/QALY. Compared with OA, CPAP was cost-effective (ICER < \$50,000/QALY) in 90% of instances.

## Discussion

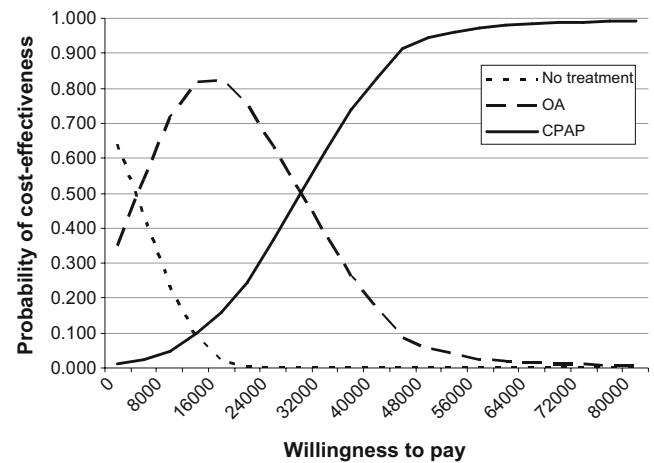
This is the first analysis where the relative cost-effectiveness of OA and CPAP in the treatment of patients with moderate/severe OSAH has been determined. We found



**Fig. 2** Results of the one-way and two-way sensitivity analysis\*. *Top left*, One-way sensitivity analysis of the cost of OA. *Top right*, One-way sensitivity analysis of the relative efficacy of OA versus CPAP based on AHI. *Bottom left*, One-way sensitivity analysis of the relative efficacy of OA versus CPAP based on ESS. *Bottom right*, Two-way sensitivity analysis of the adherence to OA and CPAP: Each shaded

area presents the range of adherence for which that treatment option is the most cost-effective at the willingness-to-pay of \$50,000/QALY. OA oral appliances, CPAP continuous positive airway pressure, ICER incremental cost-effectiveness ratio, AHI apnoea-hypopnoea index, ESS Epworth sleepiness score

that OA and CPAP are both highly cost-effective treatments for OSAH when compared to no treatment, with CPAP being the best option. These results corroborate the current recommendations on the use of CPAP as the primary treatment for moderate/severe OSAH, with OA the preferred treatment in patients unwilling or unable to use CPAP [43]. In the USA, it is currently recommended that treatments that result in less than \$50,000 costs per one additional QALY be adopted, whilst some suggest that this value should be as high as 100,000\$/QALY [44]. Based on these standards, the ICER of \$2,984 for OA and \$13,698 for CPAP versus no treatment are highly favourable. Our confidence in the benefits of treating patients with moderate/severe OSAH based on our analysis is very high, with only a 1% chance that not treating is the most economically attractive decision. The one-way sensitivity analyses also indicate that the conclusions are robust to the underlying assumptions, the most important of which are probably with regard to the efficacy of CPAP and OA on



**Fig. 3** Cost-effectiveness acceptability curve of three alternative strategies in treating OSAH: no treatment (solid line), OA (dashed line) and CPAP (dotted line). Willingness-to-pay: The amount of money that the third-party payer accepts to pay in order to obtain 1 QALY (i.e. equivalent of one year of health) in a patient with OSAH. OA oral appliances, CPAP continuous positive airway pressure

reducing untoward events and improving quality of life. Both treatments remained cost-effective when MVC or CV events were individually removed from the model or when the efficacy of both CPAP and OA in reducing these events was lowered to 60% of the value used in the main analysis.

Several studies have examined the economic impact of treatment with CPAP [29, 45, 46], but to our knowledge, this study is the first economic evaluation of OA in OSAH. Our finding regarding the cost-effectiveness of CPAP versus no treatment are in agreement with previous studies which have found CPAP to be highly cost-effective. This is despite several differences in the methods and assumptions. In our previous cost-effectiveness analysis [10], we estimated an ICER of \$17,250/QALY for CPAP (third-party payer perspective, EQ5D-derived health utilities). The lower ICER observed here is due to the incorporation of CV events in the present analysis. In the study performed by Mar et al. [29], the ICER of CPAP versus no treatment after 5 years of treatment was estimated to be 7,861€ (year 2000), which is also close to our estimates.

This study has several limitations. Given lack of evidence on many aspects of the model, we made assumptions regarding the effect of OA using indices of disease severity as a surrogate. The treatment efficacy for OA in our model was based on its relative effect compared with CPAP on an objective and a subjective measure of the severity of the disease, which both yielded an effect close to 55% of that of CPAP. The relationship between measures of severity and model outcomes and quality of life may not be linear, though there are some reports that support this assumption. In a cross-sectional study by Shahar et al. [47] and a case-control study by Hung et al. [48], a direct relationship between quartiles of AHI and cardiovascular events has been observed. Furthermore, recent studies have suggested other objective outcomes as better indicators of cardiovascular disease. For example, the Sleep and Heart Health Study has reported that hypopnoeas associated with an arterial oxygen desaturation (of 4% or more) is a better predictor of CVD than apnoea/hypopnoea index alone [49]. However, we could not incorporate desaturation in our analysis as few studies have reported the impact of treatment on arterial oxygen desaturation.

The base case analysis considered equal adherence to CPAP and OA. It is difficult to compare adherence between the two treatments as adherence to CPAP can be determined through objective monitoring, whereas adherence to OA treatment can only be determined by self-reports. In the few crossover studies comparing CPAP and OA treatment in the same patients, the subjective preference for OA has generally been higher than that of CPAP. Hoffstein [9] reviewed seven crossover studies and found that OA treatment was preferred in five studies, whilst in one study, neither treatment was preferred and in one study, CPAP was the preferred treatment. In this latter study, although

patients' subjective preference was in favour of CPAP, 76% adhered to OA versus only 43% to CPAP to the point that the treatment could be deemed as effective (i.e. at least 4 h per night on at least 70% nights) [33]. A survey of 124 dentists in the USA showed that only 10% of patients with OSAH cannot tolerate long-term use with OA [40]. Therefore, it seems that adherence to OA is unlikely to be lower than that of CPAP. The possible higher adherence to OA might explain the comparable improvements in outcome between CPAP and OA in the intention-to-treat analysis of clinical trials [50]. This, combined with the fact that non-adherence is associated with significant usage of resources without appreciable health benefits, makes adherence an important parameter affecting the cost-effectiveness of treatments in OSAH. Based on our results, if adherence to OA is 10% or higher above that of CPAP, OA becomes the most favourable treatment in patients with moderate/severe OSAH.

We limited the study population to patients with moderate/severe OSAH despite the fact that OAs can be prescribed for mild OSAH [43]. As the benefit of treatment is likely to be higher in patients with the moderate/severe disease, the results of this analysis cannot be extrapolated to mild OSAH. Another limitation was that the estimated effect of OSAH on CV was based on an observational study [4], which could be prone to selection bias due to difference between patients who seek treatment and those who do not. Similarly, the effect of OSAH on MVC was based on the meta-analysis of studies that had a before/after design. It is thus possible that some patients may have been sent for assessment of suspected OSAH breathing because of an MVC, causing a referral bias.

Our analysis did not appreciate the potential difference in costs, treatment effect and adherence of the various types of OA (e.g. tongue retaining vs. mandibular advancement and fixed vs. adjustable devices). We found it very difficult to synthesise the evidence from the literature by subtypes of OA. Further studies are needed to examine the differences in efficacy, adherence and costs of the various types of OA. We also did not model potential adverse events of OA in this study. Short-term side effects such as excessive salivation, mouth and teeth discomfort are the most commonly reported adverse effects of OA treatment and are usually self-limited and unlikely to adversely affect quality of life. However, OA might be associated with long-term dental side effects [51, 52]. Future research should determine the rate of such events and their impact on patient's quality of life.

Another limitation of the present work is lack of access to a better cost data especially for OA. Our estimates for cost of OA are based on a survey of non-representative population of dentists published in 1997 which might be outdated. Other authors have reported large variations in the cost of OA. For example, cost of the custom-made device is reported to range

from \$100 to over \$600, and dentists' service fee varies between \$200 and \$2,500 [53]. Fortunately, our results are robust with regard to cost of OA, as the superiority of CPAP vs. OA and OA vs. no treatment is preserved when cost of OA varies from zero to more than \$5,000 (Fig. 2).

We acknowledge that our assumptions and the uncertainty in the evidence may limit the generalisability of our findings. Our focus on direct healthcare costs makes our study more vulnerable to the different patterns of healthcare usage (e.g. costs of OA and treatment reimbursement plans in different settings). We believe that the results of our sensitivity analyses should be reassuring given that the overall conclusions remain the same despite a wide range of scenarios. There remains a lack of evidence in several aspects of the effectiveness of OA therapy. Additional studies are required to assess the long-term impact of OA treatment on MVCs, CV, quality of life, side effects and resource utilisation.

## References

- Kales A, Vela-Bueno A, Kales JD (1987) Sleep disorders: sleep apnea and narcolepsy. *Ann Intern Med* 106(3):434–443
- Patil SP et al (2007) Adult obstructive sleep apnea: pathophysiology and diagnosis. *Chest* 132(1):325–337 doi:10.1378/chest.07-0040
- Howard ME et al (2004) Sleepiness, sleep-disordered breathing, and accident risk factors in commercial vehicle drivers. *Am J Respir Crit Care Med* 170(9):1014–1021 doi:10.1164/rccm.200312-1782OC
- Marin JM et al (2005) Long-term cardiovascular outcomes in men with obstructive sleep apnoea–hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet* 365(9464):1046–1053
- Yaggi HK et al (2005) Obstructive sleep apnea as a risk factor for stroke and death. *N Engl J Med* 353(19):2034–2041 doi:10.1056/NEJMoa043104
- Moyer CA et al (2001) Quality of life in obstructive sleep apnea: a systematic review of the literature. *Sleep Med* 2(6):477–491 doi:10.1016/S1389-9457(01)00072-7
- Zozula R, Rosen R (2001) Compliance with continuous positive airway pressure therapy: assessing and improving treatment outcomes. *Curr Opin Pulm Med* 7(6):391–398 doi:10.1097/00063198-200111000-00005
- Lim J et al (2006) Oral appliances for obstructive sleep apnoea. *Cochrane Database Syst Rev* (1):CD004435
- Hoffstein V (2007) Review of oral appliances for treatment of sleep-disordered breathing. *Sleep Breath* 11(1):1–22 doi:10.1007/s11325-006-0084-8
- Ayas NT et al (2006) Cost-effectiveness of continuous positive airway pressure therapy for moderate to severe obstructive sleep apnea/hypopnea. *Arch Intern Med* 166(9):977–984 doi:10.1001/archinte.166.9.977
- Association for the Advancement of Automotive Medicine C.o.I.S (1990) The Abbreviated Injury Scale-1990 Revision (AIS-90). Available from [http://www.carcrash.org/publications\\_books.htm](http://www.carcrash.org/publications_books.htm). Cited 2007 2007/12/19
- Arias E (2006) United States life tables, 2003. *Natl Vital Stat Rep* 54(14):1–40
- Young T, Peppard PE, Gottlieb DJ (2002) Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med* 165(9):1217–1239 doi:10.1164/rccm.2109080
- Bixler EO et al (2001) Prevalence of sleep-disordered breathing in women: effects of gender. *Am J Respir Crit Care Med* 163(3 Pt 1):608–613
- George CF (2001) Reduction in motor vehicle collisions following treatment of sleep apnoea with nasal CPAP. *Thorax* 56(7):508–512 doi:10.1136/thorax.56.7.508
- Young T et al (1997) Sleep-disordered breathing and motor vehicle accidents in a population-based sample of employed adults. *Sleep* 20(8):608–613
- National Highway Traffic Safety Administration N.C.f.S.a.A. US Department of Transportation (2006) Traffic safety facts 2005. Available from <http://www.nrd.nhtsa.dot.gov/pdf/nrd-30/NCSA/TSFAnn/TSF2005.pdf>. Cited 2007 2007/12/19
- Blincoe L, S.L., Zaloshnja L, Miller T, Romano E, Luchter S, Spicer R (2000) Economic impact of motor vehicle crashes, 2000. National Highway Traffic Safety Administration 2000. National Highway Traffic Safety Administration, Washington, DC
- Findley L et al (2000) Treatment with nasal CPAP decreases automobile accidents in patients with sleep apnea. *Am J Respir Crit Care Med* 161(3 Pt 1):857–859
- Krieger J et al (1997) Accidents in obstructive sleep apnea patients treated with nasal continuous positive airway pressure: a prospective study. The Working Group ANTADIR, Paris and CRESGE, Lille, France. *Association Nationale de Traitement a Domicile des Insuffisants Respiratoires*. *Chest* 112(6):1561–1566 doi:10.1378/chest.112.6.1561
- Engleman HM et al (1996) Self-reported use of CPAP and benefits of CPAP therapy: a patient survey. *Chest* 109(6):1470–1476 doi:10.1378/chest.109.6.1470
- Horstmann S et al (2000) Sleepiness-related accidents in sleep apnea patients. *Sleep* 23(3):383–389
- Cassel W et al (1996) Risk of traffic accidents in patients with sleep-disordered breathing: reduction with nasal CPAP. *Eur Respir J* 9(12):2606–2611 doi:10.1183/09031936.96.09122606
- Yamamoto H et al (2000) Long-term effects nasal continuous positive airway pressure on daytime sleepiness, mood and traffic accidents in patients with obstructive sleep apnoea. *Respir Med* 94(1):87–90 doi:10.1053/rmed.1999.0698
- Suratt P, Findley L (1992) Effect of nasal CPAP treatment on automobile driving simulator performance and on self-reported automobile accidents in subjects with sleep apnea. *Am Rev Respir Dis* 145:A69
- Anderson KM et al (1991) Cardiovascular disease risk profiles. *Am Heart J* 121(1 Pt 2):293–298 doi:10.1016/0002-8703(91)90861-B
- Williams GR (2001) Incidence and characteristics of total stroke in the United States. *BMC Neurol* 1:2 doi:10.1186/1471-2377-1-2
- Greenberg-Dotan S et al (2007) Gender differences in morbidity and health care utilization among adult obstructive sleep apnea patients. *Sleep* 30(9):1173–1180
- Mar J et al (2003) The cost-effectiveness of nCPAP treatment in patients with moderate-to-severe obstructive sleep apnoea. *Eur Respir J* 21(3):515–522 doi:10.1183/09031936.03.00040903
- Carandang R et al (2006) Trends in incidence, lifetime risk, severity, and 30-day mortality of stroke over the past 50 years. *JAMA* 296(24):2939–2946 doi:10.1001/jama.296.24.2939
- Lee KL et al (1995) Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction. Results from an international trial of 41,021 patients. GUSTO-I Investigators. *Circulation* 91(6):1659–1668
- Jenkinson C, Stradling J, Petersen S (1998) How should we evaluate health status? A comparison of three methods in patients presenting with obstructive sleep apnoea. *Qual Life Res* 7(2):95–100 doi:10.1023/A:1008845123907
- Barnes M et al (2004) Efficacy of positive airway pressure and oral appliance in mild to moderate obstructive sleep apnea. *Am J Respir Crit Care Med* 170(6):656–664 doi:10.1164/rccm.200311-1571OC

34. Mc-Daid C G.S., Weatherly H, Durée K, van der Burgt M, van Hout S, Akers J, Davies RJO, Sculpher M, Westwood M (2007) The continuous positive airway pressure for the treatment of obstructive sleep apnoea–hypopnoea syndrome: a systematic review and economic analysis. CRD/CHE Technology Assessment Group (Centre for Reviews and Dissemination/Centre for Health Economics), University of York, pp 120–126
35. Pickard AS, Johnson JA, Feeny DH (2005) Responsiveness of generic health-related quality of life measures in stroke. *Qual Life Res* 14(1):207–219 doi:10.1007/s11136-004-3928-3
36. Bradley CJ, Kroll J, Holmes-Rovner M (2000) The health and activities limitation index in patients with acute myocardial infarction. *J Clin Epidemiol* 53(6):555–562 doi:10.1016/S0895-4356(99)00219-X
37. Krieger J et al (1996) Long-term compliance with CPAP therapy in obstructive sleep apnea patients and in snorers. *Sleep* 19(9): S136–S143
38. McArdle N et al (1999) Long-term use of CPAP therapy for sleep apnea/hypopnea syndrome. *Am J Respir Crit Care Med* 159(4 Pt 1):1108–1114
39. Lacassagne L et al (2000) Results of 248 patients with sleep apnea syndrome treated by continuous positive pressure ventilation between 1990 and 1995. A study of compliance and outcome of the apnea–hypopnea index. *Rev Mal Respir* 17(2): 467–474
40. Loube MD, Strauss AM (1997) Survey of oral appliance practice among dentists treating obstructive sleep apnea patients. *Chest* 111(2):382–386 doi:10.1378/chest.111.2.382
41. Sarasin FP, Gaspoz JM, Bounameaux H (2000) Cost-effectiveness of new antiplatelet regimens used as secondary prevention of stroke or transient ischemic attack. *Arch Intern Med* 160(18):2773–2778 doi:10.1001/archinte.160.18.2773
42. O’Hagan A, Stevens JW, Montmartin J (2000) Inference for the cost-effectiveness acceptability curve and cost-effectiveness ratio. *Pharmacoeconomics* 17(4):339–349 doi:10.2165/00019053-200017040-00004
43. Kushida CA et al (2006) Practice parameters for the treatment of snoring and obstructive sleep apnea with oral appliances: an update for 2005. *Sleep* 29(2):240–243
44. Hirth RA et al (2000) Willingness to pay for a quality-adjusted life year: in search of a standard. *Med Decis Making* 20(3):332–342 doi:10.1177/0272989X0002000310
45. Albarrak M et al (2005) Utilization of healthcare resources in obstructive sleep apnea syndrome: a 5-year follow-up study in men using CPAP. *Sleep* 28(10):1306–1311
46. Tousignant P et al (1994) Quality adjusted life years added by treatment of obstructive sleep apnea. *Sleep* 17(1):52–60
47. Shahar E et al (2001) Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. *Am J Respir Crit Care Med* 163(1):19–25
48. Hung J et al (1990) Association of sleep apnoea with myocardial infarction in men. *Lancet* 336(8710):261–264 doi:10.1016/0140-6736(90)91799-G
49. Punjabi NM et al (2008) Sleep-disordered breathing and cardiovascular disease: an outcome-based definition of hypopneas. *Am J Respir Crit Care Med* 177(10):1150–1155 doi:10.1164/rccm.200712-1884OC
50. Gotsopoulos H, Kelly JJ, Cistulli PA (2004) Oral appliance therapy reduces blood pressure in obstructive sleep apnea: a randomized, controlled trial. *Sleep* 27(5):934–941
51. Marklund M (2006) Predictors of long-term orthodontic side effects from mandibular advancement devices in patients with snoring and obstructive sleep apnea. *Am J Orthod Dentofacial Orthop* 129(2):214–221 doi:10.1016/j.ajodo.2005.10.004
52. Almeida FR et al (2006) Long-term sequelae of oral appliance therapy in obstructive sleep apnea patients: part 2. Study-model analysis. *Am J Orthod Dentofacial Orthop* 129(2):205–213 doi:10.1016/j.ajodo.2005.04.034
53. Ferguson KA et al (2006) Oral appliances for snoring and obstructive sleep apnea: a review. *Sleep* 29(2):244–262
54. Malacrida R et al (1998) A comparison of the early outcome of acute myocardial infarction in women and men. The Third International Study of Infarct Survival Collaborative Group. *N Engl J Med* 338(1):8–14 doi:10.1056/NEJM199801013380102
55. Engleman HM et al (2002) Randomized crossover trial of two treatments for sleep apnea/hypopnea syndrome: continuous positive airway pressure and mandibular repositioning splint. *Am J Respir Crit Care Med* 166(6):855–859 doi:10.1164/rccm.2109023
56. Randerath WJ et al (2002) An individually adjustable oral appliance vs continuous positive airway pressure in mild-to-moderate obstructive sleep apnea syndrome. *Chest* 122(2):569–575 doi:10.1378/chest.122.2.569
57. Ferguson KA et al (1997) A short-term controlled trial of an adjustable oral appliance for the treatment of mild to moderate obstructive sleep apnoea. *Thorax* 52(4):362–368
58. Ferguson KA et al (1996) A randomized crossover study of an oral appliance vs nasal-continuous positive airway pressure in the treatment of mild-moderate obstructive sleep apnea. *Chest* 109(5):1269–1275 doi:10.1378/chest.109.5.1269
59. Graham JD et al (1997) The cost-effectiveness of air bags by seating position. *JAMA* 278(17):1418–1425 doi:10.1001/jama.278.17.1418
60. Mahoney EM et al (2002) Cost and cost-effectiveness of an early invasive vs conservative strategy for the treatment of unstable angina and non-ST-segment elevation myocardial infarction. *JAMA* 288(15):1851–1858 doi:10.1001/jama.288.15.1851