Does CPAP Use in the First 15 Days Predict its Use after 4 Months? A Prospective French Cohort Study

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Abstract

Objective: Early prediction of which patients with obstructive sleep apnea will not adhere with CPAP can trigger physicians to correct possible causes or offer alternative therapies. This study aims to determine the ability of early CPAP use to predict long-term adherence with CPAP independent from its definition and to test previously described predictors of adherence.

Method: This is a prospective, observational cohort study that was performed in nine sleep disorder centers in France. Patients were newly diagnosed with obstructive sleep apnea and a CPAP was prescribed for the first time. We collected socioeconomic, medical, sleep, and psychological variables to be associated with adherence with CPAP. The patients were evaluated 15 days after CPAP set up and monthly for 4 months until they were adherent. We assessed potential predictors of CPAP adherence at 4 months with emphasis on CPAP use at 15 days. CPAP adherence was defined as an average daily use of at least 3, 4, 5, and 6 hours.

Results: We enrolled 420 patients. Early CPAP use and CPAP use at 4 months were similar. At 4 months, 94% of patients used a CPAP ≥3 hours and 49% of patients used it ≥6 hours. The area under the ROC curve for early CPAP use predicting adherence at 4 months was ≥0.85 for all adherence definitions. The optimal threshold for early CPAP use to predict adherence increased from 3.2 to 6.4 hours as the definition of CPAP adherence increased from 3 to 6 hours. CPAP use at 4 months was higher in older patients.

Conclusions: Early CPAP use was the single best predictor of CPAP adherence and was independent of how adherence was defined. Physicians must assess CPAP use no later than 2 weeks to address its causes or prescribe an alternative therapy.

Keywords: Obstructive sleep apnea (OSA); Continuous positive airway pressure (CPAP); Adherence; predictors

Introduction

Treatment of obstructive sleep apnea (OSA) with continuous positive airway pressure (CPAP) improves sleep quality, reduces sleepiness, enhances quality of life and reduces cardiovascular morbidities [1-3]. As in most medical conditions, the benefits of therapy are reaped only by adherent patients. Unfortunately, and as in other conditions, adherence to the use of a CPAP is suboptimal. In one study which defined adherence arbitrarily as using a CPAP ≥3 hours on 70% of nights, found that 54% of patients were non-adherent [4]. Understanding the barriers to and predictors of CPAP treatment uptake and long-term adherence is therefore critical for successfully establishing and maintaining patients on effective CPAP treatment [5].

It allows physicians to apply interventions that improve adherence early because waiting until patients declare themselves after few months of treatment to be non-adherent might be too late. It also allows physicians to select the patients that need these interventions instead of applying these interventions to all patients at a much higher cost. Knowing which patients are unlikely to adhere to the use of CPAP also prompts physicians to discuss alternative treatments early [6,7].

Socio-economic factors, disease severity, health problems, psychological variables, social variables, testing methods, side effects, and behavioural traits have been associated with adherence to the use of a CPAP. This large number of variables suggests that adherence is a complex process (Appendix 1).

This complexity underscores some of the limitations of published reports. First, the reports focus on one variable or a limited number of variables to predict CPAP adherence. Second, the samples of many of these studies are small. This not only reduces the generalizability of the findings, but also reduces the number of variables that can be reliably tested. Lastly, the sometimes vaguely described follow-up process of the patients reduces the reproducibility of the findings.

Furthermore, the definitions of adherence are arbitrary. The most frequently used definition is 4 hours per night and it is based on the improvement in consequences of OSA in patients that use CPAP for at least 4 hours. There is, however, growing interest in setting CPAP targets based on a patient needs [8-10].

Therefore, we conducted this study to validate a large number of variables as predictors of the adherence to CPAP use in a large sample of patients that were followed meticulously for 4 months. We focused on early use of CPAP and we defined adherence at 4 months in various ways.

Keywords: Obstructive sleep apnea (OSA); Continuous positive airway pressure (CPAP); Adherence; predictors
Materials and Methods

Study design

This prospective cohort study was performed in nine medical centers in the north of France. The protocol was approved by the French Research Ethics Board of The Patient Protection Committee. All patients provided written informed consent before participation.

Study sample

Adult patients (18-75 years old) were recruited from nine centers in France. Each center utilized the same method to recruit and follow their patients in order to avoid any differences between centers (Table 1).

All consecutive patients for whom CPAP had been prescribed for the first time for the treatment of OSA between March 2013 and June 2013 were eligible for the present study. We excluded patients that were cognitively deficient and unable to fill in the questionnaires, patients unable (or refused) to give their informed consent, patients unable to read and/or speak French, and patients with neuromuscular diseases.

Diagnosis of obstructive sleep apnea

The diagnosis was based on a full in-laboratory polysomnogram (PSG) or home sleep test (HST). The PSG was performed with the Alice 5 (Philips, Eindhoven, Netherlands) that included 6 EEG channels, 2 EOG channels, chin EMG, bilateral anterior tibialis EMG, nasal/oral thermistor, nasal pressure transducer, chest and abdominal wall movements, EKG, and pulse oximetry. The PSG scoring was standardized across centers. HST was performed with Embletta polygraph (Resmed, San Diego, CA) that included nasal/oral thermistor, nasal pressure transducer, chest and abdominal wall movements, heart rate, and pulse oximetry.

Sleep was scored with the Rechtschaffen and Kales criteria. Apneas, hypopneas, and arousals were scored according to the American Academy of Sleep Medicine 2007. The apnea hypopnea index that was calculated by dividing the number of apneas and hypopneas by the total sleep time (recording time for HST) in hours.

Prescription of CPAP

CPAP was prescribed if a patient met 1 of 2 conditions: 1) the apnea-hypopnea index (AHI) ≥30 events per hour, or 2) the AHI index was between 15 and 30 events per hour with respiratory arousal >10 per hour and at least 2 symptoms of OSA symptoms (snoring, choking or gasping during sleep, unrefreshing sleep, daytime fatigue, impaired concentration, or nocturia).

CPAP initiation and monitoring

Patients were seen by sleep physicians in consultation and then referred for a sleep study [11-13]. Because knowledge is a pre-condition for health behavior or a change in health behavior, patient were subjected to a specific educational intervention [14]. Before starting CPAP, each patient was educated by a physician and a technician about the health risk of OSA and about the use of the CPAP machine. Patients also watched a 10-min video about the definition of OSA, symptoms of OSA, CPAP machine, the sensation of wearing CPAP, and benefits of using CPAP [15]. The delay between seeing the physician and the sleep study was 15 days and between the sleep study and starting CPAP was less than 48 hours.

The CPAP devices include counters that measure machine-on time using a microprocessor. Patient adherence data was obtained on day 15 and at the end of the first month. Patients with CPAP use ≥3 hours at the end of the first month were evaluated at the end of fourth months. Patients with CPAP use <3 hours at the end of the first month were visited monthly until they became adherent. During each visit, the average nightly use CPAP hours over the last month was recorded (Table 1).

Data collected

Independent variables: The socio-economic variables were age, gender, marital status (married or living as a couple versus living alone), employment status (fulltime, part-time, or unemployed), type of health insurance (government or government insurance with private health insurance). The health variables were infarction, or arrhythmia. The psychological variables were assessed with two scales: The Pichot scale16 and the Epworth Sleepiness Scale (ESS17). The Pichot scale is divided in 2 subscales: depression (13 items) and fatigue (8 items). The ESS measures the level of sleepiness (8 items). OSA related variables were method of diagnosing OSA (PSG or HST), the apnea-hypopnea index (AHI), average nightly use of CPAP in the first 15 days (early CPAP use).

Dependent variable: Adherence was monitored using the smart card technology embedded in the CPAP machines and was defined as the average nightly use of CPAP at the set pressure.

Statistical analysis

To determine the ability of early CPAP use in predicting adherence with CPAP at 4 months, we calculated the area under the receiver operator characteristic curve (AU-ROC) for 4 adherence definitions (3, 4, 5, 6 hours). We determined the optimal thresholds of early CPAP use to predict adherence based on the Youden Index and calculated the sensitivity (Sn) and specificity (Sp) for these thresholds. We also determined, at each definition of adherence, the thresholds of early CPAP use that had a sensitivity of 90% (Sn90) or a specificity of 90% (Sp90). Bias-corrected bootstrapping of 1000 iterations was used to determine these thresholds and their confidence intervals.

The French government reimburses patients for CPAP if they use it for more than 3 hours per night. Therefore, we used the 3-hour definition for the rest of the analysis, with patients using CPAP ≥ 3 hours per day considered as adherent, patients using CPAP <3 hours considered as non-adherent.

We compared between adherent and non-adherent patients all other variables available for the physician before initiating CPAP (pre-CAP predictors). We used the t-test or chi-squared as indicated by the data type. Differences were significant if the p value is ≤ 0.05. We tested the significant pre-CAP predictors with early CPAP use in a multiple regression analysis to determine the smallest number of independent predictors of adherence.

Results

Patients

We give the study questionnaire to 465 patients: 429 patients responded, 9 were lost during the follow-up, and 420 patients were included in the final analysis (useable response rate of 92%). Most patients were men, obese, and had severe sleep apnea. The majority of patients had private insurance in addition to government insurance (Table 2).

Adherence CPAP use: early CPAP use (5.6 ± 2.0 hours) and CPAP use at 4 months (5.7 ± 1.7 hours) were similar, p=0.09. The correlation
between early CPAP use and CPAP use at 4 months was high ($r=0.71$, $p<0.001$). The linear regression equation for CPAP was use at 4 months (hours)$=2.2 + 0.6 \times$ early use of CPAP (hours).

Early CPAP use was equally predictive of use of CPAP at 4 months no matter what the threshold was (Table 3 and Figure 1). The accuracy of early CPAP in predicting adherence changed with the type of insurance. The AU-ROC was higher when patients had only government insurance than when they had additional private insurance (4-hours: 0.95 ± 0.04 versus 0.86 ± 0.02, $p=0.04$; 5-hours: 0.92 ± 0.06 versus 0.85 ± 0.02, $p=0.2$; 6-hours: 0.96 ± 0.03 versus 0.83 ± 0.02, $p=0.002$). We did not evaluate the 3 hours adherence because the sample was small. The accuracy of early CPAP use in predicting adherence at 4 months was not affected by ESS, age, gender, employment, or marital status.

As the threshold to define CPAP adherence increased from 3 hours to 4 hours, the optimal threshold of early CPAP use increased, then was stable for adherence defined as 4 or 5 hours, and then increased again for adherence define as 6 hours. The ranges of thresholds for Sn90 (3.3-4.6 hours) and for Sp90 (5.5-6.5 hours) were narrow.

When the definition of adherence changes, the distribution of adherence status (remained adherent, became non-adherent, remained non-adherent, became adherent) at 4 months changed. When we used the same threshold to define adherence at 15 days and at 4 months, increasing the threshold for adherence from 3 to 6 hours increased the percentage of patients that remain non-adherent at 4 months and decreased the percentage remained adherent over the 4 month (Figure 2).

### Pre-CPAP predictors of adherence at 4 months

Adherent patients were older than non-adherent patients (57 ± 12 versus 49 ± 11, $p=0.002$). The AU-ROC curve for age as a predictor of adherence was 0.67 and the optimal threshold was 53 years with a sensitivity of 0.62 and a specificity of 0.67. The threshold for a specificity of 90% was 67.

We divided patients into 2 groups: older patients>53 years (252 patients), and younger patients ≤53 years (168 patients). In comparison to the older patients, the younger patients had a higher BMI (34 ± 7 versus 31 ± 6), a higher Pichot fatigue score (15 ± 8 versus 14 ± 8, $p=0.01$), and a higher ESS score (11, IQR 8-15 versus 10, IQR 6-14, $p=0.03$), and they used CPAP slightly less in the first 15 days (0.5 ± 0.2 hours). There was also a weak but significant correlation between the Pichot fatigue score and the drop in CPAP use from 15 days to 4 months ($r=0.1$, $p=0.036$).

When age and early use of CPAP were entered in a logistic regression, age became non-significant and early use of CPAP was the only predictor of adherence at 4 months. The odds ratio associated with every hour of early CPAP use for predicting CPAP adherence at 4 months was 2.1 (95% CI: 1.6-2.7, $p<0.001$). On the other hand, in a linear regression model with the hours of CPAP use as the dependent variable, age and early CPAP use were significant and the regression equation was CPAP use at 4 months$=1.5+ [early$ CPAP$ use in hours \times 0.62] + [age in years\times0.01]$.

There was no correlation between CPAP use at 4 months and ESS ($r=-0.05$, $p=0.3$) or between CPAP use and AHI ($r=0.09$, $p=0.06$). Similarly, none of the other pre-CPAP variables (including the methods of diagnosing OSA) was associated with CPAP use at 4 months.

### Discussion

In this relatively large sample of patient with OSA that was followed closely for 4 months, we found that early CPAP use was the strongest predictor of adherence at 4 months independent of its definition. Of the variables available for the physician before starting CPAP, age was the only variable associated, though weakly, with CPAP adherence at 4 months.

Our results complement the results reported by others that long-term CPAP adherence patterns are often established within the first weeks of therapy [15-18]. Bhandari et al. [12] reported that CPAP use by the third day was predictive of CPAP use at 30 days. Popescu et al. [13] reported that CPAP use in the first 2 weeks predicts CPAP adherence at 1 year. Chai-Coetzer et al. [19] reported that adherence at one month predicted CPAP adherence at 1 year. Mcardle et al. [5] reported that CPAP use at 3 months predicts adherence after 2 years. This composite of evidence suggests that adherence to CPAP use must be evaluated early and continuously after initiating therapy.

A novel and interesting finding of our study was the relationship between the area under the ROC curve for early CPAP use and the insurance type. It has been shown in the past that socioeconomic status (especially poverty) is associated with CPAP use (see appendix). In our study, early CPAP use was more predictive of long-term use in patients with government only (suggestive lower income). The type of insurance was not, however, associated the adherence itself. This finding deserves
Socio-economic variables
Men, % 70
Age, years 56 ± 12
Married, % 78
Fully employed, % 59
Government insurance with private health insurance, % 94

Health variables
Body mass index, kg/m² 32 ± 6
Treated Hypertension, % 49
Heart disease (arrhythmia or congestive heart failure), % 12
Stroke, % 12
Myocardial infarction, % 11
Loss of libido, % 32

OSA related variables
AHI 46 ± 19
Diagnosis made with HST, % 38
Daily CPAP use in the first 15 days 5.6±2

Psychological Variables
Epworth Sleepiness Scale 10.7 ± 5
Pichot Fatigue Scale 14.2 ± 7
Pichot Depression Scale 4.7 ± 4

Table 2: Baseline characteristics of the patients at the onset of CPAP therapy (n=420).

<table>
<thead>
<tr>
<th>Definition of adherence at 4 months</th>
<th>Adherence at 4 month based on definition</th>
<th>Threshold at 15 days</th>
<th>Sn</th>
<th>Sp</th>
<th>Sn₉₀</th>
<th>Sp₉₀</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 hours</td>
<td>94%</td>
<td>3.2 (2.2-3.9)</td>
<td>91%</td>
<td>70%</td>
<td>3.3</td>
<td>6.0</td>
</tr>
<tr>
<td>4 hours</td>
<td>81%</td>
<td>5.4 (3.3-5.6)</td>
<td>72%</td>
<td>86%</td>
<td>3.8</td>
<td>5.5</td>
</tr>
<tr>
<td>5 hours</td>
<td>69%</td>
<td>5.5 (5.1-5.5)</td>
<td>77%</td>
<td>83%</td>
<td>4.2</td>
<td>6.2</td>
</tr>
<tr>
<td>6 hours</td>
<td>49%</td>
<td>6.4 (5.7-6.8)</td>
<td>66%</td>
<td>89%</td>
<td>4.6</td>
<td>6.5</td>
</tr>
</tbody>
</table>

Table 3: The percentage of adherent patients at various definitions at four months, the optimal threshold of early use (15 days) to predict adherence based on bootstrap analysis, its sensitivity and specificity, and the threshold of early CPAP use with sensitivity of 90% (Sn₉₀) and specificity of 90% (Sp₉₀).

Figure 1: ROC curves for early CPAP use predicting adherence at the 4 thresholds at 4 months. The area was 0.86 (0.82-0.89) for 3 hours, 0.87 (0.83-0.89) for 4 hours, 0.86 (0.82-0.88) for 5 hours, and 0.85 (0.81-0.88) for 6 hours.

Figure 2: The relation between adherence on day 15 (x-axis) and adherence at 4 months defined with the same hours of CPAP use. When patients were non-adherent at 15 days, they are unlikely to be adherent at 4 months with a decreasing chance of adherence as the threshold for adherence increases. When patients were adherent at 15 days, they were likely to be adherent at 4 month but with a decreasing likelihood as the threshold for adherence increased; but, the lowest adherence rate, which was with a threshold of 6 hours, was still >70%.

Further evaluation because it might reflect a motive behind the use of CPAP such as employment for drivers or just to avoid monetary penalty for not using CPAP.

Because the definition of CPAP adherence is arbitrary and studies have used definitions varying between 2 and 6 hours, we tested 3, 4, 5, and 6 hour thresholds. The AU-ROC curve for early CPAP use predicting later adherence was similar between all definitions of adherence. Therefore, our conclusions can be extended to settings where the criterion of adherence is different from that used in France, especially since Chai-Coetzer and colleagues have shown that the relation between early use and long-term adherence is independent from country [19].

Currently most clinicians rely on a single definition to identify patients not adherent to CPAP use. In the United States, patients are considered adherent if they use a CPAP for more than 4 hours most night of the week. This definition of adherence is required by Medicare to pay for CPAP. Nevertheless, to achieve maximal alertness and cognitive functioning, a reduction in carbon dioxide in patients with obesity hypoventilation syndrome, or a reduction in blood pressure, a patient must use a CPAP for more than 6 hours a day [20-22]. The thresholds we identified can help physicians predict if a patient will meet the required CPAP use. Therefore, for example, if a patient was a commercial driver that required maximal cognitive functioning, early CPAP use of less than 6.5 hours would be concerning and less than 4.5 hours would be very concerning.

Predicting non-adherent patients early helps physicians select patients that need attention and intensive follow-up. Of the patients that were using CPAP ≥3 hours in the first two weeks, 98% were using it ≥3 hours at 4 months. On the other hand, 37% of the patients that were using CPAP < 3 hours at 15 days were still using it <3 hours at 4 months. Thus, when the desired dose of CPAP use is low, only patients with very low early use should probably be followed closely for the first few months.
Because of the correlation between the Pichot fatigue score and age, younger patients were more likely to use a CPAP than younger patients. Sin et al. [23] provided a detailed follow-up of the patients but the sample was small.

Follow-up and adherence in this study was higher than what is reported by others. Two reasons might explain this observation. First, the study had a dedicated physician who was specifically involved in the coordination of data collection to monitor the quality of the collection processing. Second, the French government reimbursed patients for CPAP use if they used it for more than 3 hours per night, which encouraged the patients to use the CPAP. This is slightly different from reimbursement in the United States where Medicare purchases the CPAP machine once the patients is deemed adherent. In fact, the relationship between the accuracy of early CPAP use in predicting adherence and the type of insurance suggests that the reimbursement mechanism might play a role in the change in adherence between the first 15 days and 4 months.

There are several limitations in this study. The first limitation is that we did not test side effects. Early complaints of side effects have previously been associated with long-term non-adherence with CPAP [19]. We assume that they were addressed with the patients during the frequent visits and should have been resolved by the fourth months of follow-up. The second limitation is that we did not test coping, locus of control, and self-efficacy, which have previously been shown to predict adherence [19,20,21,26-29]. They are probably mechanisms that lead to early non-adherence that ultimately continues long-term. Once a patient is identified early on to be at risk of non-adherence, the clinician must evaluate that patient's coping and self-efficacy. Lastly, our follow-up was 4 months only. The longer the follow-up, the more events that can affect adherence: seasonal allergy, mask failure, change work hours, etc. The 4 month follow-up is probably optimal to reduce external events that can affect adherence.

In conclusion, CPAP use in the first 15 days is the best predictor of adherence to the use of a CPAP at 4 months and it was more accurate in patients than in government only insured patients. The threshold of early CPAP use should be adjusted based on the desired long term adherence. These observations might assist physicians identify early the young, fatigued patients gradually reduced their CPAP use because they did not feel better with it. This observation is also concerning because younger patients will live longer than older ones, and if they remain non-adherent, they are likely to suffer cardiovascular complications at a younger age, further leading to a larger societal impact of OSA.

Many investigators have reported that AHI [4,13] and the ESS4, [25] predicted adherence. We did not find such a relationship. This is not due to spectrum bias because the distribution of both AHI and ESS were wide. A larger sample size might have resulted in a weak correlation between AHI and adherence, but it would have been too weak to be useful predictor. Yet, patients with high AHI and ESS should receive special attention from physicians because they are more likely to benefit when they adhere to CPAP use than patients with lower AHI or ESS.

In contrast, 76% of patients using a CPAP more than 6 hours at 15 days were still doing so at 4 months and only 24% of patients using a CPAP less than 6 hours increased above this threshold. Therefore, when the desired dose of CPAP is high, as in drivers and patients with obesity hyperventilation, all patient should be followed closely.

Age was the only pre-CPAP variable predictor of adherence: older patients were more likely to use a CPAP than younger patients. Sin et al. [23] reported a similar relation between age and CPAP adherence. In fact they reported that CPAP use increased by 0.24 hours per decade, fact they reported that CPAP use increased by 0.24 hours per decade, etc. The 4 four month follow-up is probably optimal to reduce external events that can affect adherence.

Although they were more fatigued and sleepy, younger patients used a CPAP less than older ones. This profile is similar to that report by Pepin et al. [24] as a predictor of residual sleepiness after treatment with a CPAP. Because of the correlation between the Pichot fatigue score and the drop in CPAP use from 15 days to 4 months, it is plausible that these young, fatigued patients gradually reduced their CPAP use because they did not feel better with it. This observation is also concerning because younger patients will live longer than older ones, and if they remain non-adherent, they are likely to suffer cardiovascular complications at a younger age, further leading to a larger societal impact of OSA.
patients that will not meets their target of CPAP use and these patients will be suitable for intensive follow-up or alternative therapy.

**Contributions**

Study conception and design: Thibaut Gentina. Thibaut Gentina designed the research plan and organized the study.

Acquisition of data: François Jounieux, Catherine Lamblin and François Codron developed the methodology, participated in the collection of data and coordinated the data-analysis.

Analysis and interpretation of data: Elodie Dancoine and Aiman Tulaimat performed the analyses.

Drafting of manuscript: Thibaut Gentina, Elodie Dancoine and Aiman Tulaimat contributed to the writing of the manuscript.

Critical revision: Elodie Dancoine and Aiman Tulaimat.

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**Conflict of Interest**

There is not conflict of interest in this research.

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### Appendix 1

<table>
<thead>
<tr>
<th>Reference</th>
<th>Factors associated with compliance</th>
<th>Country</th>
<th>Sample (n)</th>
<th>threshold value to be adherent (/ night)</th>
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<tr>
<td><strong>Socio-economic variables</strong></td>
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<tr>
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## Factors associated with compliance

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Krieger et al. (1996)
Young et al. (1993)
Pelletier et al. (2001)
Gagnadoux et al. (2011)
Loredo et al. (2007)
Wild et al. (2004)
Olsen et al. (2008)
Redenius et al. (2008)
Sugiera et al. (2007)
Reishten et al. (2010)
Margel et al. (2005)
McArdle et al. (1999)
Hung et al. (1990)
Philips et al. (2013)
Palombini et al. (2006)
Martínez-Garcia et al. (2012) | BMI     | England  | 209        | 2 hours                                |
<p>|           |                                   | BMI     | France     | 728                                    | 4 hours                                |
|           |                                   | BMI     | U.S.       | 602                                    | 4 hours                                |
|           |                                   | BMI     | France     | 163                                    | 3 hours                                |
|           |                                   | BMI     | France     | 1141                                   | 4 hours                                |
|           |                                   | BMI, heart disorder | U.S. | 76                                    | 6 hours                                |
|           |                                   | BMI     | United Kingdom | 119                              | 3 hours                                |
|           |                                   | BMI     | Australia  | 77                                     | 4 hours                                |
|           |                                   | BMI     | U.S.       | 309                                    | 4 hours                                |
|           |                                   | BMI     | Japan      | 77                                     | 5 hours                                |
|           |                                   | Erectile dysfunction | U.S. and Canada | 123                                | Not indicated                         |
|           |                                   | Erectile dysfunction | Israel   | 60                                     | Not indicated                         |
|           |                                   | Treated Hypertension, heart disorder          | U.K.   | 1211                                   | 2 hours                                |
|           |                                   | Treated Hypertension, myocardial infarction  | Australia | 101                               | Not indicated                         |
|           |                                   | Treated Hypertension                          | Spain  | 725                                    | 4 hours                                |
|           |                                   | Stroke                                          | Italy   | 50                                     | 4 hours                                |
|           |                                   | Stroke, myocardial infarction                 | Italy   | 223                                    | 4 hours                                |
|           | osa related variables             | AHI     | U.K.       | 1211                                   | 2 hours                                |
|           |                                   | AHI     | England    | 209                                    | 2 hours                                |
|           |                                   | AHI     | France     | 728                                    | 4 hours                                |
|           |                                   | AHI     | France     | 163                                    | 3 hours                                |
|           |                                   | AHI     | France     | 1141                                   | 4 hours                                |
|           |                                   | AHI     | United Kingdom | 119                              | 3 hours                                |
|           |                                   | AHI     | Italy      | 50                                     | 4 hours                                |
|           |                                   | AHI     | China      | 112                                    | 4 hours                                |
|           |                                   | AHI     | France     | 233                                    | Not indicated                         |
|           |                                   | AHI     | France     | 44                                     | 5 hours                                |
|           |                                   | AHI     | Synthetical article |       | Not indicated                        |
|           | psychological/behavioral variables | Epworth Sleepiness, Pichot Fatigue Scale | U.K.   | 1211                                   | 2 hours                                |
|           |                                   | Epworth Sleepiness                            | France | 728                                    | 4 hours                                |
|           |                                   | Epworth Sleepiness                            | France | 163                                    | 3 hours                                |
|           |                                   | Epworth Sleepiness                            | United Kingdom | 82                               | 4 hours                                |
|           |                                   | Epworth Sleepiness                            | U.S.   | 91                                     | 4 hours                                |
|           |                                   | Epworth Sleepiness, self-efficacy             | Canada  | 296                                    | 4 hours                                |</p>
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<td>Balachandran et al.(2013)</td>
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Appendix References


