Utility Indices in Patients with the Obstructive Sleep Apnea Syndrome

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Key Words

Apnea/hypopnea index • Outcome, obstructive sleep apnea • Quality of life • Sleep apnea symptoms • Subjective health perception • Utility indices

Abstract

Background: Utility indices are used in cost-effectiveness analyses as a measure of quality of life reflecting the patient's preference for a given health state on a scale anchored at 0 (corresponding to death) to 1 (perfect health). It is uncertain which utility instruments are most suitable for application in patients with the obstructive sleep apnea syndrome (OSA). **Objectives:** To compare utility indices obtained in OSA patients by various instruments. **Methods:** In 66 untreated OSA patients (median Epworth score 12, apnea/hypopnea index, AHI, 57/h), five different utility instruments were employed. In 34 OSA patients, changes in utility after 4 months of continuous positive airway pressure (CPAP) were retrieved from published SF-36 data. **Results:** In 66 OSA patients, median (quartiles) utility indices were: standard gamble 0.97 (0.89; 0.99); time trade-off 0.94 (0.81; 0.99); EuroQol questionnaire (EQ-5D) 0.92 (0.83; 1.00); Euro-thermometer visual analog scale 0.80 (0.70; 0.90); SF-36 questionnaire (SF-6D) 0.75 (0.69; 0.85; $p < 0.05$ SF-6D and Euro-thermometer utility vs. other indices). Different utility indices were poorly correlated

among each other and with AHI and Epworth scores. SF-6D utility after 4 months of CPAP had changed by 0.04 (0.02; 0.12, $p = 0.026$). **Conclusions:** Utility indices measured by different instruments vary largely and some indices reflect the impaired quality of life in OSA poorly. Interpretation of cost-effectiveness analyses should account for the utility instrument used.

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Introduction

The effectiveness of novel medical treatments is traditionally evaluated in terms of the objective effects on morbidity and mortality. In recent times, increasing emphasis has been placed on subjective outcomes such as quality of life assessed by generic and disease-specific questionnaires that provide profiles of subjective health perception in different domains [1–3]. For cost-effectiveness analysis, quality of life is expressed by a single index measure intended to convey the utility that a person derives from his or her health state [4]. The utility index is defined as the subjective preference of a patient for a given health state and rated on a scale anchored at 0 (corresponding to death) and 1 (corresponding to perfect health) [5, 6]. By multiplying the utility index by the years

spent in a particular health state, quality-adjusted life years are computed. The ratio of increased costs divided by the quality-adjusted life years gained by a medical intervention represents the cost-effectiveness ratio [4]. Decisions on allocation of financial resources for health care are increasingly guided by cost-effectiveness analyses. Since the utility index is a main component of such analyses, its reliable measurement is essential. Various instruments have been used to obtain utility indices *directly* (i.e. the standard gamble and time trade-off methods [5] and the 'Euro-thermometer' visual analog scale [7]), and *indirectly* from questionnaires such as the medical outcome health survey SF-36 [8] or the EuroQol questionnaire [7], which provide the SF-6D and the EQ-5D utility indices, respectively. The performance of different utility instruments in various settings is not well established. Utility indices may be affected by age, gender, socioeconomic status and cultural factors in addition to the individual health preference of a patient with a particular disease [9, 10]. Therefore, utility instruments have to be validated in the specific setting where they are intended to be applied.

The obstructive sleep apnea syndrome (OSA) is a common disorder affecting at least 2–4% of adults in the US population [11], and the prevalence is expected to increase due to the epidemic of obesity. OSA patients are affected by daytime sleepiness, decreased concentration and irritability [12], and the disorder is an independent risk factor for cardiovascular diseases [13, 14] and sleepiness-related traffic and work accidents [15]. Since OSA has a considerable impact on health economics [16], evaluating cost-effectiveness of various treatments such as nocturnal continuous positive airway pressure (CPAP), mandibular advancement devices and surgical interventions would be desirable. However, utility instruments have not been rigorously validated for application in OSA patients. Thus, the objective of this study is to compare utility indices obtained by different instruments in OSA patients and to correlate utility indices with other measures of quality of life, symptoms and the severity of sleep-related breathing disturbances. It was hypothesized that the performance of various utility instruments would vary. Furthermore, we evaluated whether one particular utility instrument, the SF-36 questionnaire-derived SF-6D utility index, reflects changes in quality of life achieved by CPAP therapy in OSA patients. For this purpose, we derived SF-6D utility indices from data collected in a previously published study in OSA patients at baseline and after 4 months of CPAP therapy [17].

Patients and Methods

Patients

Successive patients with OSA referred to the Pulmonary Division of the Sleep Disorder Center, University Hospital of Zurich, were asked to participate in the study. OSA was diagnosed based on typical symptoms such as habitual snoring, excessive daytime sleepiness, an Epworth sleepiness scale score ≥ 8 [18] and an apnea/hypopnea index (AHI) $>10/h$ during a cardiorespiratory sleep study. Patients with comorbidities that were thought to significantly affect their quality of life (in particular psychiatric, internal medical and neurologic disorders) were excluded. Informed consent was obtained and the protocol was approved by the hospital ethics committee.

Utility indices were additionally derived from SF-36 questionnaires obtained in 33 OSA patients (median age: 50 years; quartiles: 45 and 58 years) in a previous study [17]. These data included evaluations within 1 month before and 4 months after initiation of CPAP therapy.

Utility Assessment

Three instruments for *direct* utility assessments were employed: the standard gamble, the time trade-off and the visual analog scale ('Euro-thermometer').

Standard Gamble. This test [5] was performed using a custom-made interactive computer application. Patients were asked to choose between two theoretical alternatives presented on the computer screen (fig. 1): either to continue their life in the current health state or to accept an offered therapy. If they chose the therapy, this was associated with a certain chance (probability) of attaining perfect health, but this was also afflicted by a certain risk of immediate death (risk or probability of immediate death = $1 - \text{probability of perfect health}$). By systematically changing the probability of attaining perfect health and its connected risk of immediate death, the point of indifference was determined in an iterative procedure. The probability of perfect health at the point of indifference was taken as the utility of the individual's current health state.

Time Trade-Off. This test [5] was also performed using a custom-made interactive computer application (fig. 1). Patients were asked to choose between two theoretical alternatives: either live for 20 years in their current health state or live in perfect health but for a shorter time period. The number of years the patients were willing to trade off was varied systematically until a point of indifference was reached. The ratio of years at the point of indifference divided by 20 (i.e. the selected time horizon) corresponded to the utility index.

Visual Analog Scale ('Euro-Thermometer'). The Euro-thermometer [7] is part of the EuroQol questionnaire EQ-5D. Patients had to mark their perceived current health state with a pencil on a piece of paper that contained a line with a scale from 0 (corresponding to worst imaginable health or death) to 100 (corresponding to best imaginable, perfect health). The value corresponding to the mark on the scale divided by 100 was taken as the utility index (fig. 1).

In addition, two instruments for *indirect* utility assessments were employed. Utility was derived from answers to questions on various domains of quality of life. The responses were weighted and summed to obtain the utility index according to evaluations obtained in reference populations as described elsewhere [19, 20].

Fig. 1. Utility indices were obtained by the three direct instruments in addition to the indirect utility indices derived from the SF-36 and the EuroQol questionnaires. **a** In the standard gamble test, patients had to select among two options displayed on the computer screen, i.e. to accept a new therapy associated with perfect health but a certain risk of immediate death or to remain in their current health state. The utility index was determined as $[1 - (\% \text{ risk of death}/100)]$ at the point of indifference. **b** In the time trade-off test, patients were asked whether they preferred to live in perfect health but trade off a few years of their life-time (assumed time horizon of 20 years) or to stay in their current health state. The number of years traded off was varied to the point of indifference, and the utility index was taken as the ratio $[1 - (\text{years traded off}/20)]$. **c** In the Euro-thermometer visual analog scale, the patients positioned their current health state on a scale ranging from 0 (worst imaginable health or death) to 100 (best imaginable, perfect health). The value on the scale divided by 100 was taken as the utility index.

Short-Form 6 Dimensions (SF-6D). The SF-6D is derived from the short form of the medical outcome questionnaire SF-36, a generic quality-of-life questionnaire [1, 19]. Patients completed the SF-36 on paper. The answers from 11 of the 36 questions representing six dimensions were used to compute the utility index based on evaluations in a British population [1, 19]. The scores in the eight domains of the SF-36, and the mental and physical component scores were also computed.

EuroQol-5 Dimensions (EQ-5D). The EQ-5D is a generic questionnaire for the evaluation of quality of life encompassing five dimensions. There is one question for each dimension which can be answered by three levels of impairment [2, 20]. Patients completed the questionnaire on paper. The scores for the five domains were computed and the EQ-5D utility index derived according to evaluations in a British population [10, 21].

Protocol

Study participants were asked to perform utility assessment after receiving detailed information on the various tests. An investigator coached the participants performing the computer-based tests and questionnaires. If any participant did not under-

stand how to handle the computer programs or did not understand the questions, the investigator gave additional explanations and, in some cases, the tests were restarted. The time to complete all utility assessments was assessed.

To gather utility indices before and after 4 months of CPAP therapy, SF-36 questionnaires from OSA patients who had participated in a previous study [17] were reanalyzed and the change in the SF-6D utility index with introduction of treatment was evaluated.

Data Analysis and Statistics

Results were summarized by medians (quartiles) or means (SD) for non-normally and normally distributed outcomes, respectively. Utility values obtained in the same participant by different instruments were compared by identity plots, by computing Spearman correlation coefficients and by Wilcoxon matched pair tests. Data from different groups were compared by the Mann-Whitney U test. Spearman correlations were computed between utility indices and the AHI and the Epworth sleepiness score. A probability of $p < 0.05$ was considered statistically significant.

Table 1. Patient characteristics and multidimensional, generic quality of life

Number of patients (female)	66 (8)	
Age, years	55 (47; 61)	
AHI, events/h	57 (38; 72)	
Epworth score	12 (10; 15)	
SF-36 quality of life		norm
Physical function	85 (65; 90)*	[90]
Role physical	75 (50; 100)*	[96]
Bodily pain	100 (62; 100)	[78]
General health	72 (57; 82)	[72]
Vitality	55 (35; 70)*	[66]
Social function	100 (75; 100)*	[99]
Role emotional	100 (67; 100)*	[100]
Mental health	80 (64; 88)	[80]
Physical component summary	49 (40; 54)	[50]
Mental component summary	52 (45; 56)	[50]
EQ-5D quality of life		
Mobility	1 (1; 1)	
Self-care	1 (1; 1)	
Usual activities	1 (1; 1)	
Pain/discomfort	1 (1; 2)	
Anxiety/depression	1 (1; 1)	

Medians (lower quartile; upper quartile). Transposed SF-36 scores are presented with a range from 0 to 100, with higher values corresponding to better quality of life. EQ-5D domains are rated on a scale from 1 (no impairment) to 3 (maximal impairment). * $p < 0.005$ vs. norm [median of the value observed in a US reference population of corresponding age and gender].

Results

Sixty-six OSA patients participated in the study (table 1). In some patients, utility indices could not be obtained by some of the five methods because of technical failures or incomplete questionnaire data and, in 1 patient, because he did not understand the principles of the standard gamble test. Therefore, the number of available utility indices collected by the different instruments varies between 56 and 66. OSA patients required a mean ($\pm$ SD) time of 20 ± 8 min to complete utility assessments by all five instruments. Most patients required detailed explanations before they were able to perform the standard gamble and time trade-off tests while they were generally able to complete the SF-36, the EQ-5D and the Euro-thermometer tests after brief instructions.

Patient characteristics are summarized in table 1 along with multidimensional quality of life assessed by the generic questionnaires SF-36 and EQ-5D. The OSA patients had moderate/severe sleep-related breathing disturbances and moderate subjective daytime sleepiness. Com-

Table 2. Utility indices measured by different instruments in OSA patients

Standard gamble utility index (SG)	(n = 65)
	0.97 (0.89; 0.99)
Time trade-off utility index (TTO)	(n = 56)
	0.94 (0.81; 0.99)
EQ-5D utility index	(n = 57)
	0.92 (0.83; 1.00)*, **
Euro-thermometer visual analog scale utility index (VAS)	(n = 65)
	0.80 (0.70; 0.90)*, **
SF-6D utility index	(n = 66)
	0.75 (0.69; 0.85)**

* $p < 0.05$, VAS utility vs. EQ-5D, and EQ-5D vs. TTO; ** $p < 0.001$, SF-6D utility vs. TTO; SF-6D vs. SG; SF-6D vs. EQ-5D; VAS vs. TTO; VAS vs. SG, and EQ-5D vs. SG.

pared to a US reference population of corresponding age and gender reported by Ware et al. [1], their SF-36 quality of life was reduced in several domains, whereas the medians of the EQ-5D domains had a value of 1, suggesting no impairment.

Results of utility assessments are summarized in table 2. Figure 2 shows histograms of utility indices and AHI in the OSA patients. The median SF-6D utility index in OSA patients was significantly lower than the corresponding values obtained by all other instruments with the exception of the Euro-thermometer utility index that was similarly low (table 2). In contrast, the standard gamble and time trade-off utility indices were higher than those obtained by all other instruments and their value was close to 1, suggesting a ceiling effect in these two indices (fig. 2).

In table 3, Spearman rank order correlations of utility indices obtained by the five different instruments are presented.

The standard gamble and the time trade-off utility indices were correlated among themselves but not with any of the other utility indices. The EQ-5D and the Euro-thermometer VAS were correlated among themselves and with the SF-6D index. We further evaluated whether utility indices were correlated with selected measures of quality of life that were impaired in OSA patients (table 2). This analysis revealed that the SF-36 physical component summary was significantly correlated with utility indices from the EQ-5D, the Euro-thermometer visual analog scale and the SF-6D (table 3). The EQ-5D pain/discomfort domain was significantly correlated with utility indices from the EQ-5D, the Euro-thermometer and the SF-6D

Fig. 2. Distribution of the utility indices obtained by the various instruments and the AHI in 66 OSA patients. There is a ceiling effect in the standard gamble and time trade-off utility indices.

Fig. 3. Correlations among utility indices obtained by various instruments and the AHI with the SF-6D utility index in 66 OSA patients. The Spearman rank order correlation coefficient R is indicated. The dashed lines represent identity.

(table 3). Except for a weak correlation between the Epworth sleepiness score and the standard gamble and time trade-off utility indices, none of the utility indices were correlated with measures of disease severity, e.g. the Epworth sleepiness score or the AHI (table 3).

In 34 patients participating in our previous study [17], SF-36 data were re-analyzed to obtain SF-6D utility (table 4). The baseline SF-6D utility index was similar (me-

dian value of 0.74) to the corresponding value observed in the 66 patients in the current study (median value of 0.75, table 2). Computation of SF-6D utility indices after 4 months of CPAP therapy in patients from the previous study revealed a significant improvement by a median of 0.04 to 0.79 points (table 4). Over the same time period, the AHI and the Epworth sleepiness score had also significantly improved (table 4).

Table 3. Correlations between utility indices, generic quality of life, Epworth sleepiness score and AHI in OSA patients

	Standard gamble utility index	Time trade-off utility index	EQ-5D utility index	Euro-thermometer VAS utility index	SF-6D utility index
Standard gamble utility index		0.50***	-0.09	0.15	0.12
Time trade-off utility index	0.50***		-0.01	0.21	0.07
EQ-5D utility index	-0.09	-0.01		0.50***	0.55***
Euro-thermometer VAS utility index	0.15	0.21	0.50***		0.41***
SF-6D utility index	0.12	0.07	0.55***	0.41***	
SF-36 physical function	-0.03	0.01	0.53***	0.43***	0.48***
SF-36 role physical	0.09	0.12	0.32*	0.37**	0.65***
SF-36 vitality	0.01	0.12	0.35**	0.30*	0.68***
EQ-5D pain/discomfort domain	0.14	0.02	-0.88***	-0.4**	-0.49***
Epworth sleepiness score	-0.28*	-0.31*	0.05	0.00	-0.17
AHI	-0.16	0.01	0.13	0.05	-0.00

Values are Spearman rank order correlations (R). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$; VAS = visual analog scale. Horizontal dashed lines separate direct from indirect utility indices and measures of disease severity, respectively.

Table 4. SF-6D utility indices in OSA patients before and 4 months after initiating CPAP therapy

	Baseline	4 months on CPAP	Change
Epworth score	15.0 (11.0; 17.0)	7.0 (4.0; 9.5)	7.0 (5.0; 9.0)**
AHI (events/h)	49.8 (34.8; 59.4)	5.0 (3.1; 8.6)	37.8 (26.2; 54.7)**
SF-6D utility index	0.74 (0.66; 0.81)	0.79 (0.68; 0.85)	0.04 (-0.02; 0.12)*

SF-6D utility was derived from data collected in a previous trial [17] in 33 OSA patients; values are medians (quartiles). * $p = 0.026$, ** $p < 0.000001$.

Discussion

We evaluated subjective health perception by several direct and indirect utility instruments in OSA patients and found that utility indices derived from the five different instruments tested differed significantly and were only weakly correlated among themselves and with other generic measures of quality of life and with measures of disease severity, e.g. the Epworth sleepiness score and AHI. Utility indices obtained by the standard gamble and the time trade-off methods showed ceiling effects and seemed not to reflect the burden of disease in OSA patients. The Euro-thermometer visual analog scale and the SF-6D utility indices revealed the lowest values in OSA patients and the SF-6D utility index improved significantly with CPAP therapy. Therefore, of the five instruments tested, the SF-6D and the Euro-thermometer util-

ity indices seem to be the most suitable to reflect the impaired quality of life in OSA patients.

Few previous studies have measured utility indices by various instruments in OSA patients. In a retrospective analysis of 19 OSA patients, Tousignant et al. [22] reported a mean standard gamble utility index of 0.63 before treatment and of 0.87 after several months of CPAP therapy. In a randomized trial, Chakravorty et al. [23] recorded a mean standard gamble utility index in 32 OSA patients of 0.32 before and of 0.55 during CPAP therapy. The utility indices of untreated OSA patients in the two cited studies [22, 23] are lower than the corresponding values of 0.97 and 0.94 obtained with the standard gamble and time trade-off methods in the current study (table 2). We have no definitive explanation for this discrepancy since disease severity assessed by the AHI in our patients (median of 57/h, table 1) was similar to that of

the patients in the studies cited (mean values of 67/h [22] and 55/h [23] before treatment), although socioeconomic patient characteristics and aspects of the protocol and test application might have differed between the studies.

In four studies [23–26] comprising a total of 260 OSA patients, the mean EQ-5D utility indices before initiation of treatment were between 0.73 and 0.79, i.e. lower than the value of 0.92 observed in the current study (table 2). In only one of these studies [23], initiation of CPAP therapy was associated with a significant increase in the EQ-5D utility index of 0.04 while CPAP had no significant effect on the index in the other three studies [24–26]. Therefore, the authors concluded that the EQ-5D questionnaire might not capture the relevant quality-of-life domains affected in OSA patients [24, 25]. Consistent with this interpretation, we found that EQ-5D quality of life was normal in OSA patients apart from a trend to a minor impairment in the pain/discomfort domain (table 1) and, accordingly, the EQ-5D utility indices were relatively high, suggesting a ceiling effect as previously observed in other patient groups [27] (table 2).

In two of the studies cited [23, 24], the Euro-thermometer visual analog scale has also been employed along with other utility instruments. In untreated OSA patients, the Euro-thermometer utility index was 0.67 [24] and 0.59 [23], which increased by 0.04 and 0.11, respectively, with CPAP therapy. In the current study, the Euro-thermometer utility index was higher (median: 0.80, table 2) than the baseline value in the studies cited but lower than corresponding values derived in the same patients by the standard gamble, the time-trade-off and the EQ-5D questionnaire (table 2), suggesting that the Euro-thermometer visual analog scale was able to better express the patients' impaired quality of life.

Our study is the first to include SF-6D utility indices in quality-of-life assessment in OSA patients. The SF-6D indices were lower than those obtained by all other instruments (table 2) and there was a significant improvement in SF-6D utility of 0.04 with CPAP therapy (table 4). This value falls well within the range of minimally important differences of 0.011–0.097 computed for SF-6D utility in patients with various diseases other than OSA (e.g. COPD and back pain) [28]. Since SF-6D utility indices in the current study were correlated with quality of life assessed by the physical component summary of the SF-36 and with the pain/discomfort domain of the EQ-5D as well as with the EQ-5D utility index and the Euro-thermometer-derived utility index, the SF-6D index seems promising as a sensitive generic instrument for

evaluation of utility and its changes with treatment in OSA patients.

In line with divergent utility indices obtained by the EQ-5D and other instruments in previous studies in OSA [22–26] and other diseases [27, 28], we found only a weak or no correlation among utility indices obtained by different instruments (table 3). This was in part related to the ceiling effect observed in the standard gamble and time trade-off indices (fig. 2). In our experience, the OSA patients in the current study did not perceive their disorder as directly life-threatening and were therefore reluctant to accept even a minor risk of immediate death in the standard gamble, or to give up a portion of their lifetime in the time trade-off test. The weak or absent correlation between several utility indices and other measures of generic quality of life (i.e. SF-36 domains or the EQ-5D pain/discomfort domain) and with measures of OSA severity such as the Epworth sleepiness scale or the AHI suggests that certain utility indices might not appropriately reflect the burden of disease in OSA. Similarly, generic quality of life was poorly correlated with sleep-related breathing disturbances in OSA patients in previous studies [29]. Further prospective trials are required to evaluate which utility instruments are most suitable to track treatment effects in OSA.

In conclusion, we demonstrated that utility indices derived by different instruments in OSA patients vary largely and are poorly correlated among themselves. Therefore, the interpretation of cost-effectiveness analysis based on utility assessment in OSA has to carefully account for the instruments used. Instruments established in other settings, such as the standard gamble and the time trade-off methods, provided relatively high utility indices (between 0.9 and 1.0) even in moderate/severe OSA. Apparently, these indices do not appropriately reflect the impaired quality-of-life domains of OSA patients and the improvement by treatment. Therefore, the SF-6D utility index and the Euro-thermometer visual analog scale that revealed lower values that were correlated with other measures of generic quality of life seem better suited to reflect the disease state of OSA patients, and to track treatment-induced changes (by the SF-6D).

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