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SLEEP BREATHING PHYSIOLOGY AND DISORDERS • REVIEW

Economic evaluation of CPAP therapy for obstructive sleep apnea: a scoping review and evidence map

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Abstract

Purpose To synthesize findings of economic evaluations investigating cost-effectiveness of continuous positive airway pressure (CPAP) for obstructive sleep apnea (OSA) and of strategies of organization of care related to CPAP therapy.

Methods Scoping review with searches conducted in MEDLINE, CRD, LILACS, and Embase in August 2020. Eligible studies were economic evaluations comparing CPAP to other alternative or assessing strategies of care for CPAP therapy. Results were presented narratively, and incremental cost-effectiveness ratios (ICER) were presented in evidence maps.

Results Of 34 studies, 3 concluded that CPAP is less costly and more effective when compared to usual care. Most studies indicated that CPAP is associated with better health outcomes, but at higher prices. ICER ranged from USD 316 to 98,793 per quality-adjusted life years (QALY) gained (median 16,499; IQR 8267 to 33,119). One study concluded that CPAP is more costly and less effective, when treatment is applied to all patients, regardless of disease severity. Variability of ICER was mainly due to definition of population and applied time horizons. When CPAP was compared to mandibular advancement device, ICER ranged from USD 21,153 to 361,028 (median 89,671; IQR 26,829 to 295,983), which represents the investment in CPAP therapy required to obtain one extra QALY. Three studies assessed the effects of organizing CPAP therapy in primary care, which was cost-effective or cost-saving.

Conclusions Compared to usual care, CPAP is cost-effective after the second year of treatment, when indicated for moderate-to-severe OSA. CPAP therapy may be even more cost-effective by using different strategies of organization of care. These findings may inform decision making related to CPAP reimbursement in health systems.

Clinical Trial Registration number Not applicable

Keywords Sleep apnea · CPAP · Continuous positive airway pressure · Economic evaluation · Scoping review

Introduction

Obstructive sleep apnea (OSA) is characterized by recurrent episodes of partial or total upper airway obstructions during sleep, commonly associated with snoring, intermittent hypoxia, sleep fragmentation, and daytime symptoms such as excessive daytime sleepiness, irritability, and impairment of cognition [1]. OSA is a highly prevalent condition among the general population, with prevalence estimates ranging from 14 to over 50%, with higher prevalence rates being observed among men [2–4]. Other known risk factors include obesity, older age, craniofacial abnormalities, and diabetes mellitus [5–8].

There is a vast body of evidence indicating that OSA is associated with negative long-term consequences, including hypertension [9], arterial stiffness [10], cardiovascular events

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[11], atrial fibrillation [12], cerebrovascular events [13], and diabetes [14]. These associations are probably mediated by intermediate mechanisms that include chronic intermittent hypoxia and hypercapnia, increased sympathetic activity, inflammation, oxidative stress, among others [15]. OSA is also associated with increased risk of motor vehicle [16] and occupational accidents [17], which is probably explained by excessive daytime sleepiness, increased reaction time, and impairment of other domains of cognition [18].

Aside from being associated with a variety of negative health outcomes, OSA directly jeopardizes quality of life. Individuals with OSA report impaired general health and quality of life [19]. This fact may be explained to some extent by the association of OSA with obesity, comorbid insomnia, and excessive daytime sleepiness[19]. From the economic perspective, OSA has been demonstrated to be associated with increased utilization of healthcare resources [20–22]. Additionally, management of the long-term consequences related to OSA, including stroke, hypertension, and heart failure, impose high costs to health systems [23]. The high proportion of traffic and workplace accidents attributable to OSA and leading to significant healthcare costs and property loss also imposes indirect costs to individuals and society [24].

Continuous positive airway pressure (CPAP) therapy is currently considered standard treatment for moderate-to-severe OSA [25], due to its greater effect on respiratory events, when compared to other alternatives of treatment, such as mandibular advancement device (MAD), airway surgery, positional therapy, and lifestyle modification [26, 27]. In the short term, CPAP therapy reduces daytime sleepiness and improves neurocognitive function [28]. However, effectiveness of CPAP therapy is challenged by issues related to CPAP adherence, which persists relatively low, despite the evolving technology designed to improve comfort [29]. Therefore, there is still need of development and implementation of strategies capable of optimizing adherence.

Considering the high prevalence of OSA and its short- and long-term consequences, OSA should be considered a major issue of public health. Despite being fully treatable with CPAP therapy for most cases, CPAP therapy is not ubiquitously available or effectively reimbursed in health systems worldwide, as it is the case in Brazil [30]. Furthermore, the need of specialized care and the relatively scarce number of qualified health providers in relation to the number of individuals affected by OSA impose important challenges to guarantee appropriate access to treatment [31]. Objectives of this work were to assess the cost-effectiveness of CPAP therapy from previous published economic evaluations and to identify strategies capable of optimizing value in healthcare related to CPAP therapy.

Methods

Study design

This was a scoping review developed in five stages comprised of definition of the research question, elaboration of search strategies, assessment of study eligibility, data extraction, and summary of findings. Scoping reviews are a relatively new approach to synthesize evidence by providing an overview of the available research without producing summary measures to one discrete research question [32]. This methodological framework was proposed by Arksey [33] and Levac [34]. The study report was structured in adherence to PRISMA extension for scoping reviews (PRISMA-ScR) [35]. A protocol was a priori developed and made available at Open Science Framework [36].

Definition of the research questions

Research questions were iteratively defined to reflect critical points of decision making related to CPAP therapy for OSA, from the decision of instituting treatment with CPAP in detriment to other strategies of care, to the organization of care related to the initiation of treatment and follow-up of cases.

Search strategies

Search strategies were applied in MEDLINE (via PubMed), the Centre of Review Dissemination (CRD) database, LILACS, and Embase and last updated on August 23, 2020 (**Supplementary information, Table 1**). Additionally, reference lists of included studies were hand searched aiming at identifying potentially eligible studies.

Eligibility criteria, study screening, and data extraction

Inclusion and exclusion criteria were iteratively defined during data extraction, as previously recommended by Arksey and Levac [33, 34].

Any type of full economic evaluation was considered eligible for inclusion, provided they had compared CPAP therapy with other reasonable treatment alternative, such as usual care, lifestyle modification, positional therapy, or oral appliance therapy, regardless of severity, presence or symptoms, and comorbidities. Outcomes of interest included quality-adjusted life years (QALY) or other type or clinically relevant outcomes, such as daytime sleepiness. Measuring QALYs are important in the context of decision making, considering that QALY takes into account both the quantity and the quality of extra life provided by virtually all types of healthcare interventions. Exclusion criteria included unpublished studies, partial economic evaluations, studies in which costs were

reported but no analyses were presented, and studies comparing CPAP therapy to alternatives not usually implemented, as hypoglossal nerve stimulation or bi-level positive airway pressure (BiPAP) therapy. Additionally, studies focusing on the organization of care related to CPAP therapy were also considered for inclusion. There was no restriction related to OSA severity, clinical manifestation, or presence of comorbidities. Both full economic evaluations and partial economic evaluations addressing this research question were considered eligible for inclusion.

Screening of studies was performed at two stages. At the first stage, titles and abstracts were screened independently by two authors, with resolution of disagreements by consensus. At the second stage, full texts were assessed and confronted against the eligibility criteria, as they were iteratively defined. Both stages of study screening were conducted in the Rayyan platform [37]. Reasons for excluding full texts were presented.

Data extraction was performed in a previously piloted spreadsheet, by two authors. Framework for data extraction was a priori defined to reflect the research questions. The final framework was achieved after having incorporated additional aspects approached by included studies that were judged relevant. Accuracy of data extraction was double checked afterwards by one author. Extracted data included author, year of publication, country, type of economic evaluation, type of sources for parameters, perspective of analysis, time horizon, population, intervention, comparator, effectiveness measure, types of costs considered, currency, incremental cost-effective ratio (ICER), and conclusion. Whenever needed and possible, ICERs were calculated.

All economic evaluations reported in the same publication (e.g., applying different perspectives, assessing different populations or comparators) were included. Therefore, unit of analysis was the economic evaluation rather than publications.

Summary of findings

Study screening was documented and presented in a PRISMA flow diagram. Results were presented narratively. Incremental cost-effectiveness ratios (ICER) of CPAP therapy compared to other alternatives of care were analyzed. ICER is calculated from the difference in costs between two alternatives of care, divided by the difference in outcomes between these alternatives, as shown below [38].

$$\mathrm{ICER} = \frac{\text{Cost CPAP} - \text{Cost comparator}}{\text{Effectiveness CPAP} - \text{Effectiveness comparator}}$$

ICER may be interpreted as the investment needed to obtain one unit of effect, such as one QALY. An ICER of U$ 20,000 per QALY means that in order to obtain one extra QALY with a new intervention, an incremental investment of U$ 20,000 must be made.

(ICER) per QALY, whenever reported, were corrected for inflation to 2020 values, and converted to US dollars by using the purchase power parity as estimated by the Organization for Economic Co-operation and Development (OECD), allowing comparisons across different periods and countries [https://eppi.ioe.ac.uk/costconversion/default.aspx]. Lifetime time horizons not specified were calculated by considering life expectancy at the year of publication and the age of the base case.

Main results were additionally presented in evidence maps, describing the type of research question, country, ICER, and other conclusions obtained from included economic evaluations. Evidence maps have been previously used to provide a comprehensive and graphic view of the knowledge on a given field and to provide information on gaps of knowledge still warranting investigation [39]. Evidence maps were produced in R with the package ggplot2 [40].

Considering that the results of economic evaluations are highly dependent of local contexts and that up to present there is no agreed-upon guidance for pooling estimates for costs and resources use, pooled estimates of costs or cost-effectiveness were not calculated [41].

Results

Electronic and additional searches retrieved 645 references. After removing duplicates, titles and abstracts of 588 references were screened, leading to a selection of 48 full texts. Thirty-four studies were included after the assessment of full texts, comprising 51 economic evaluations, since several studies reported more than one economic model. The study flow diagram is presented in **Supplementary information, Figure 1**, as well as the list of excluded studies at the full text stage and reasons for exclusion, **Supplementary information, Table 2**.

Included studies addressed different research questions in two domains, namely cost-effectiveness of CPAP therapy compared with usual care, lifestyle modification, positional therapy, MAD [42–60]; and organization of care related to CPAP therapy [61–75].

Characteristics of studies focusing on cost-effectiveness of CPAP

Countries

Included studies were conducted in Europe, North America, South America, and Oceania. In Europe, five studies were conducted in the UK [45, 53, 54, 57, 58], two studies in Spain [43, 56], one in France [52], one in Finland [55], one in Greece [44], and one in the Netherlands [48]. In North America, three studies were conducted in Canada [42, 50,

60], two in the USA [49, 51], and one in Mexico [46]. The other studies were conducted in Brazil [47] and in Australia [59].

Types of economic evaluations

Eighteen studies presented full economic evaluations, six presented cost-effectiveness analysis (CEA) [43, 44, 46, 53, 59, 60], and 13 presented cost-utility analysis (CUA) [42, 45, 47–52, 54–58].

Perspective of economic evaluations

Included economic evaluations were conducted under different perspectives, namely the healthcare provider perspective in 11 studies [44, 46–48, 50, 51, 53–57]; healthcare provider and patient perspective in one study [52]; healthcare provider and societal perspective in four studies [43, 45, 59, 67]; third-party payer in two studies [42, 49]; and third-party payer and societal perspective in one study [60].

Time horizons

There was a great variability across studies regarding the applied time horizon for estimating costs and effects. As expected, economic evaluations with data collected alongside the study applied shorter time horizons from 6 months [55] to 2 years [43]. Studies that developed modeling to estimate cost and effects projected longer time horizons, from 5 years [42] to lifetime time horizons [45, 47, 50].

Types of population

Included studies focused on different subtypes of OSA, defined as any severity of OSA plus symptoms in three studies [45, 55, 57]; mild-to-moderate OSA in two studies [52, 58]; moderate OSA in one study [48]; moderate-to-severe OSA in six studies [42, 49–51, 59, 60]; moderate-to-severe OSA plus symptoms in one study [43]; severe OSA in one study [47]; severe OSA plus symptom in two studies [44, 53]; unspecified OSA in three studies [46, 56, 67]; OSA plus diabetes mellitus in one study [54].

Types of interventions

To be included in this scoping review, one of the treatment alternatives necessarily had to involve CPAP therapy. Therefore, all studies compared CPAP therapy to another strategy of care.

Types of comparators

Comparators involved no treatment in 13 studies, commonly described as usual care [42–44, 46, 47, 49, 50, 53, 54, 56, 57, 59, 60]; lifestyle advice in one study [55]; MAD in two studies [48, 58]; no treatment or MAD in two studies [45, 51]; no treatment, MAD, or lifestyle advice in one study [52].

Types of measures of effectiveness

The most assessed measure of effectiveness were QALYs, assessed in 14 studies as the sole measure of effectiveness or alongside other outcome measures, such as excessive daytime sleepiness [45, 47–53, 55–57]. Two studies reported life years gained [44, 46].

Types of assessed costs

Fifteen studies assessed direct medical costs including a mix of products and services, such as equipment purchase or rental, costs related to diagnosis, positive pressure titration, and follow-up [44, 46–58, 67]. Shelf life of CPAP was 5 to 7 years. Four studies assessed indirect costs, in addition to direct medical costs [42, 45, 59, 60] and Catalá et al. provided a more comprehensive approach by assessing direct medical and non-medical costs, as well as indirect costs [43].

Main characteristics of included studies focusing on cost-effectiveness of CPAP therapy are presented in Table 1.

Characteristics of studies focusing on organization of care

Countries

Included studies were conducted in Europe and North America. In Europe, six studies were conducted in Spain [61, 69, 70, 72, 73, 75], one in Finland [64], one in Germany [68], and one in France [71]. In North America, four studies were conducted in the USA [62, 63, 65, 66] and one conducted in Canada [74].

Types of economic evaluations

Amongst full economic evaluations, four of the included studies reported CUA [62, 69, 70, 72]; three reported CEA [71, 74, 75]; three conducted cost-minimization analysis [61, 63, 73]; and two performed cost-benefit analysis [68]. Three studies provided partial economic evaluations, by only analyzing costs [64, 66] of by analyzing effectiveness and costs separately [65].

Table 1 Characteristic of included economic evaluations focusing on CPAP therapy compared to other strategies of care

Country	Study	Economic evaluation	Source of data	Perspective of analysis	Population	Comparator	Outcome measures	Costs
Australia	Streatfeild 2019	Cost-effectiveness	Modeling	Healthcare provider Societal	Moderate-to-severe OSA	Usual care	DALY	Direct medical costs Indirect costs
Brazil	Luccheta 2019	Cost-utility	Modeling	Healthcare provider	Severe OSA	Usual care	QALY	Direct medical costs
Canada	Ayas 2006	Cost-utility	Modeling	Third-party payer Societal	Moderate-to-severe OSA	Usual care	QALY	Direct medical costs Indirect costs
	Tan 2008	Cost-effectiveness	Modeling	Third-party payer Societal	Moderate-to-severe OSA	Usual care	QALY	Direct medical costs Indirect costs
	Tousignant 1994	Cost-utility	Mixed	Healthcare provider	Moderate-to-severe OSA	Usual care	QALY	Direct medical costs
Finland	Lojander 2008	Cost-utility	Primary study	Healthcare provider	Any severity of OSA plus symptoms	Lifestyle advice	QALY	Direct medical costs
France	Poullié 2016	Cost-utility	Modeling	Healthcare provider Patient	Mild OSA with low cardiovascular risk Moderate OSA with low cardiovascular risk Mild-to-moderate OSA with high cardiovascular risk	Usual care MAD Lifestyle advice	QALY	Direct medical costs
Greece	Trakada 2015	Cost-effectiveness	Modeling	Healthcare provider	Severe OSA plus symptoms	Usual care	Life years gained	Direct medical costs
Netherlands	Giannopoulou 2013	Cost-utility	Modeling	Healthcare provider	Moderate OSA	MAD	QALY	Direct medical costs
Spain	Catalá 2016	Cost-effectiveness	Primary study	Healthcare provider Societal	Moderate-to-severe OSA plus symptoms	Usual care	QALY	Direct medical costs Direct non-medical costs Indirect costs
	Mar 2003	Cost-utility	Modeling	Healthcare provider	Unspecified OSA	Usual care	QALY	Direct medical costs
U.K.	Guest 2008	Cost-effectiveness	Modeling	Healthcare provider	Severe OSA plus symptoms	Usual care	QALY	Direct medical costs
	Guest 2014	Cost-utility	Registry	Healthcare provider	OSA plus DM	Usual care	QALY	Direct medical costs
	McDaid 2009	Cost-utility	Modeling	Healthcare provider Societal	Any severity of OSA plus symptoms	Usual care MAD	QALY	Direct medical costs Indirect costs
	McMillan 2015	Cost-utility	Mixed	Healthcare provider provider	Any severity of OSA plus symptoms	Usual care	QALY	Direct medical costs
	Sharples 2014	Cost-utility	Mixed	Healthcare provider	Mild-to-moderate OSA	MAD	QALY	Direct medical costs
U.S.	Sadatsafavi 2009	Cost-utility	Modeling	Healthcare provider	Moderate-to-severe OSA	Usual care MAD	QALY	Direct medical costs

DALY, disability-adjusted life years; *EDS*, excessive daytime sleepiness; *MAD*, mandibular advancement device; *OSA*, obstructive sleep apnea; *QALY*, quality-adjusted life years

Perspective of economic evaluations

Seven studies adopted the perspective of healthcare provider [61, 62, 64, 65, 68, 72, 73]; one employed the healthcare provider and patient perspectives [75]; two applied the healthcare provider and societal perspectives [70, 71]; two applied the societal perspective [69, 74]; and two applied the third-party payer perspective [63, 66].

Time horizon

Most studies assessed or projected effectiveness and costs for short time horizons, of 3 [65, 70, 75] or 6 months [61, 69, 71–73]. One study employed a time horizon of 1 year [68] and three employed a time horizon of 5 years [62, 64, 74].

Strategies for optimizing healthcare related to CPAP therapy

Care setting Three studies assessed the effects of organizing CPAP therapy within primary care facilities, compared to specialized care [61, 72, 73]. One study conducted in Germany assessed screening for OSA in healthcare facilities dedicated to patients suffering from chronic diseases [68]. Home-based diagnosis followed by unattended positive pressure titration was compared to traditional in laboratory pathway by Kim et al. [63]. Telehealth

strategies compared to healthcare delivered by face-to-face meetings were assessed in three studies [69, 70, 75].

Strategies to optimize adherence Adding follow-up with respiratory therapists was compared to traditional care in one study [65]. Telemonitoring to address CPAP compliance versus usual care was approached by Ekroos et al. [64]. Patient engagement by the use of patient decision aids (PDA) was assessed in one study [74].

Other types of strategies Different policies of reimbursement for Medicare beneficiaries were addressed in Billings 2013 [62]. One reimbursement policy involved coverage with CPAP therapy, regardless of 90-day trial adherence provided follow-up visits occurred every 3 months. After 13 months, CPAP supplies would only be covered if an adherence threshold were documented in at least one visit. For the other alternative, CPAP rental or supply costs were not reimbursed if adherence thresholds were not observed in the first 90 days. Sequential trials were allowed for those undergoing another polysomnogram and clinic visit.

Time of institution of CPAP therapy was assessed in one study, in which immediate institution of CPAP therapy was compared to a 6-month postponement [71]. Effects of delayed treatment on daytime sleepiness, cognitive function, quality of life, and healthcare expenditure were assessed.

Previous trial with positional device before CPAP initiation was assessed by Ramos 2015 [66]. Participants with positional OSA, defined by non-supine apnea–hypopnea index <5 events/h were given a trial with a positional device, while participants presenting obstructive events even in the lateral position immediately received CPAP therapy.

Types of measures of effectiveness

Four studies reported QALY [61, 62, 69, 72] and/or adherence to CPAP therapy [65, 69, 72, 75]. Other effectiveness measures included daytime sleepiness [61, 71, 73, 75], quality of life [74, 75], and utilities [73]. Effectiveness measures were not reported in studies focusing on partial economic evaluations [63, 64, 66, 68].

Assessed costs

Types of assessed costs reported included only direct medical costs in most studies [61–66, 73, 74]. Direct medical and non-medical costs were assessed in one study [72]. A combination of direct and indirect costs was reported in five studies [68–71, 75].

Main characteristics of included studies focusing on the organization of care related to the institution of CPAP therapy or follow-up of cases are presented in Table 2.

Cost-effectiveness of CPAP therapy and of strategies for optimizing care

Cost-effectiveness of CPAP therapy compared to usual care

Three studies concluded that CPAP therapy is a dominant strategy when compared to usual care. In the study conducted by Gay et al. in Mexico, CPAP therapy led to incremental savings per patient of USD 4386 and an incremental effectiveness of 0.496 life years gained [46]. In the study conducted by McMillan, CPAP therapy reduced the average costs per patient by—USD 589 and was associated with improvement in quality of life of 0.051 QALYs. In the study conducted by Trakada in Greece, CPAP therapy was considered a dominant strategy among males, with costs savings of USD 8497 and a gain in life expectancy of 0.074 years. When both sexes were taken into account in the model, CPAP therapy was considered cost-effective but not dominant.

For studies in which CPAP therapy led to gain of QALYs but at higher costs, incremental cost-effectiveness ratios (ICER) of CUA comparing CPAP therapy to usual care ranged from USD 316 to USD 98,793 per QALY (median = US$ 16,499; IQR = US$ 8267 to 33,119). Medians and IQR per continent were US$ 24,603 ± 56,137 for Europe; US$ 3385 ± 11,978 for North America; US$ 18,776 for Oceania (one study); and US$ 1547 in South America (one study). Results were statistically significant different (Kruskal-Wallis x^2 = 9.0792, p value = 0.028), with pairwise comparisons pointing differences between Europe and North America (Wilcoxon rank-sum test, p value 0.05). ICER across different types of population was not statistically significant.

When only CUA in which population was defined as moderate-to-severe OSA and time horizon surpassed the first year of treatment were considered, ICER ranged from US$ 316 to US$ 18,776 (median US$ 10,272; IQR US$ 2872 to US$ 16,884). There were no statistically significant differences between continents (Kruskal-Wallis x^2 = 4.7363, df = 3, p value = 0.1922).

Evidence map depicting results of ICER by countries and types of population is presented in Fig. 1.

In the study by Lojander et al., in which the effect of CPAP therapy on QALY was compared to lifestyle advice for participants with OSA, regardless of the disease severity, CPAP was considered a dominated strategy [55]. QALYs gained was 0.016 ± 2.34 in the CPAP group and 0.386 ± 1.16 in the lifestyle guidance group. Mean cost per QALY gained was USD 103,153 for the CPAP therapy group and USD 1187 for the lifestyle guidance group.

Cost-effectiveness of CPAP therapy compared to MAD

Studies comparing CPAP therapy to MAD, estimated ICERs ranging from USD 21,153 to USD 361,028 (median = US$ 89,671, IQR = USD 26,829 to USD 295,983).

Table 2 Characteristic of included economic evaluations focusing on organization of care related to the institution of treatment with CPAP or follow-up of cases

Country	Study	Economic evaluation	Source of data	Perspective of analysis	Population	Intervention	Comparator	Outcome measures	Costs
Canadá	Trenaman 2014	Cost-effectiveness	Modeling	Societal	Moderate OSA	CPAP plus patient decision aid	CPAP	Quality of life	Direct medical costs
France	Pelletier-Fleury 2004	Cost-effectiveness	Primary study	Public healthcare provider Societal	Moderate-to-severe OSA plus symptoms	Immediate CPAP treatment	Postponed CPAP treatment	Quality of life EDS cognition	Direct medical costs Indirect costs
Germany	Fisher 2002	Cost-benefit	Primary study	Publlic healthcare provider	Suspected OSA	Screening for OSA among patients with chronic conditions	Specialized care	Economic benefit	Direct medical costs Indirect costs
Spain	Isetta 2015	Cost-utility	Primary study	Societal	Unspecified OSA	Telehealth	Face-to-face follow-up	QALY CPAP adherence	Direct medical costs Direct non-medical costs Indirect costs
	Lugo 2019	Cost-utility	Primary study	Public healthcare provider Societal	OSA	Telehealth	Face-to-face follow-up	EDS Quality of life	Direct medical costs Direct non-medical costs Indirect costs
	Sanchez-De-La-Torre 2015	Cost-utility	Primary study	Publlic healthcare provider	Unspecified OSA	Primary care	Specialized care	QALY CPAP adherence	Direct medical costs
	Sanchez Quiroga 2018	Cost-minimization	Primary study	Publlic healthcare provider	Suspected OSA	Primary care	Specialized care	QALY EDS	Direct non-medical costs
	Tarraubella 2018	Cost-minimization	Primary study	Publlic healthcare provider	Suspected OSA	Primary care	Specialized care	Utility EDS	Medical direct costs
	Turino 2017	Cost-effectiveness	Primary study	Public healthcare provider Patient	Unspecified OSA	Telehealth	Face-to-face follow-up	Quality of life CPAP adherence Symptom improvement	Direct medical costs Indirect costs
U.S.	Billings 2013	Cost-utility	Modeling	Publlic health provider	Moderate-to-severe OSA	Clinic-only policy of reimbursement	MEDICARE policy for reimbursement	QALY	Direct medical costs
	Kim 2012	Cost-minimization	Primary study	Third-party payer	Moderate-to-severe OSA	Home-based diagnosis and unattended APAP titration	Traditional in-hospital pathway	Not reported	Direct medical costs
	Vega 2019	Cost analysis	Primary study	Third-party payer	Unspecified OSA	Trial with posicional device for positional OSA before CPAP	CPAP therapy	EDS	Direct medical costs

CPAP, continuous positive airway pressure; *EDS*, excessive daytime sleepiness; *OSA*, obstructive sleep apnea; *QALY*, quality-adjusted life years

Fig. 1 Evidence map of studies comparing CPAP therapy to usual care

Median values of ICERs of studies conducted in Europe were USD 145,977 ± 321,335. One additional study conducted in North America reported an ICER of USD 33,366 (Fig. 2).

Cost-effectiveness of strategies focusing on the organization of care

Most studies focusing on strategies to optimize organization of care employed effectiveness measures other than QALY; therefore, it was not possible to make confrontations of values of ICER across studies. Results of the economic evaluations were assessed in accordance with authors' conclusions, into the following pre-defined categories: dominated, not cost-effective, cost-effective, and dominant strategy.

Included studies approached different interventions that were mapped onto three major categories, namely, types of care setting, strategies to optimize CPAP adherence, and a miscellaneous category, including strategies of reimbursement and time of institution of CPAP therapy. All studies concluded that the investigated intervention was considered either cost-effective or cost-saving (Fig. 3).

Discussion

Our findings evinced great variability of measures of cost-effectiveness of CPAP therapy. The broad range of obtained ICER was justified, considering that economic evaluations were contextualized to reflect local specificities. Variability of results may reflect true differences in terms of costs or of effectiveness across different locations. However, a few methodological elements could explain the differences of ICER estimates. Definition of the population approached in economic evaluation comparing CPAP therapy to usual care exerted an important influence on ICER estimates. When considered only economic evaluations that considered mild OSA, ICER estimates reached figures as high as USD 98,793 per QALY gained. This may reflect the fact that clinical benefit of instituting CPAP therapy for less severe cases is low, in terms of improving quality of life or reducing the risk of long-term negative consequences, such as road traffic accidents or cerebrovascular events. The same was observed for studies that stratified analysis according to cardiovascular risk. CPAP therapy was not considered cost-effective for populations with low cardiovascular risk.

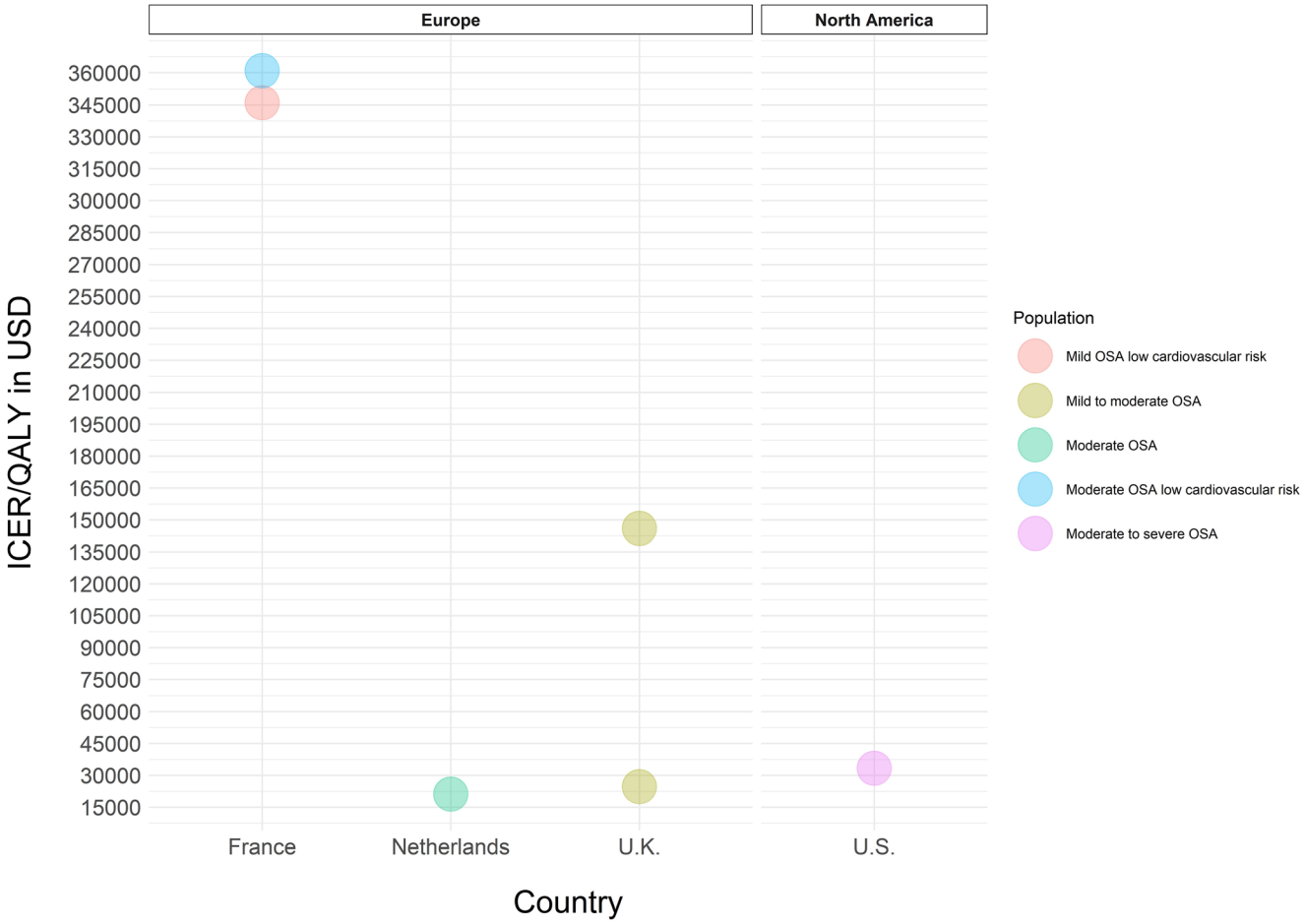

Fig. 2 Evidence map of studies comparing CPAP therapy to MAD

Conversely, for studies considering moderate-to-severe OSA as the population of interest in the model, CPAP therapy was associated with much lower ICER estimates, with maximum value near USD 19,000 per QALY gained. Exception cases were economic evaluations that applied time horizons of 1 year. For this analysis, CPAP therapy was overall not considered cost-effective, which would be expected, considering the multiple resources consumed by patients initiating CPAP therapy, such as sleep studies for diagnosis and positive pressure titration, and the short period of time for capturing savings related to avoided complications.

Comparisons of ICER across continents showed statistically significant differences, with higher values observed in Europe in comparison to those observed in North America. However, when ICER estimates of studies involving only moderate-to-severe cases after the second year were considered, differences across continents lost statistical significance. This suggests that the main factors associated to variability in ICER estimates are not elements related to local contexts, but to methodological issues, such as the definition of the population and the time horizon applied in models. This fact has been observed by other authors. Moro et al. concluded that time horizons is one of the most important issues in determining cost-effectiveness of different strategies for diagnosing OSA [76].

When compared to MAD, results showed some inconsistencies. Even considering only mild-to-moderate cases, ICER estimates showed great variability (USD 21,153 to USD 361,028), with some estimates indicating CPAP therapy to be cost-effective and others indicating ICER values high above cost-effectiveness thresholds (e.g., U.K. £ 20,000 to 30,000; USD 50,000). This was especially true for models in which population was stratified to reflect the cardiovascular risk. For mild-to-moderate OSA with low cardiovascular risk, ICER estimates were above USD 340,000, indicating that, for this specific population, MAD could be considered more cost-effective.

Identified strategies for the organization of care of OSA included replacing care from specialized units to primary care units as well as strategies to optimize CPAP adherence, by adding follow-up with respiratory therapists or by utilizing telemonitoring and patient engagement. All investigated strategies were considered cost-effective or cost-saving, which indicates that the way health care is organized may further optimize cost-effectiveness of CPAP therapy.

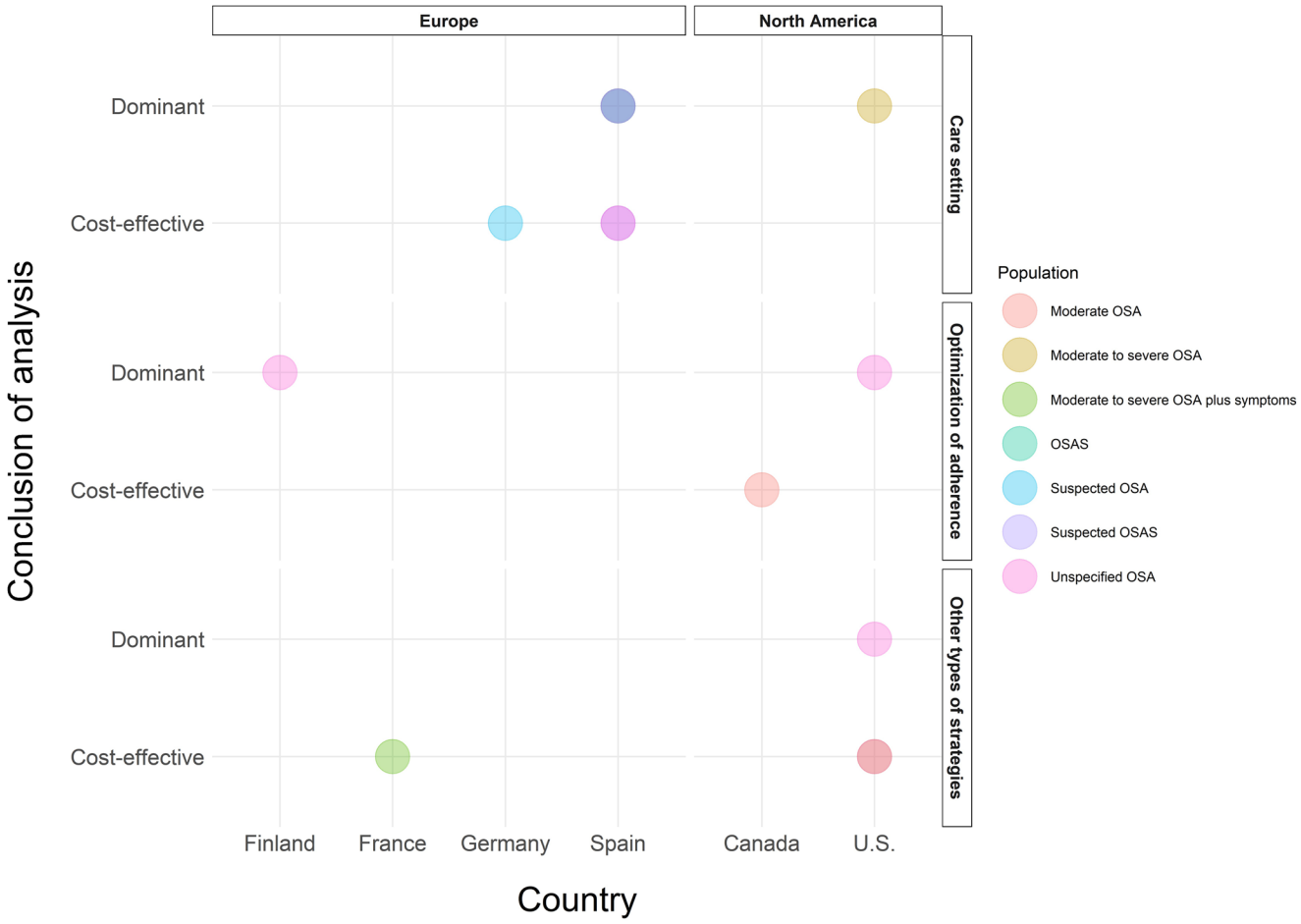

Fig. 3 Evidence map of strategies for optimizing CPAP therapy

To the best of our knowledge, this study represents the most complete synthesis of economic evaluations assessing the cost-effectiveness of CPAP therapy and the cost-effectiveness of strategies for organizing care related to CPAP therapy. In the recent systematic review conducted by Wickwire et al. [77], 17 studies were included in qualitative synthesis. Authors concluded that OSA treatment is associated with favorable clinical and economic outcomes, within accepted ranges of cost-effectiveness. Toraldo et al. conducted a narrative review of cost-effectiveness strategies in OSA management[78], from strategies of diagnosis to models of care for managing OSA. Authors concluded that cost-effectiveness should not be interpreted independently from other measures, such as diagnosis accuracy and outcomes related to OSA treatment. None of these studies explored the variability of ICER estimates across continents or countries, or in relation to methodological aspects of the economic evaluation. Therefore, we could not confront our results to the ones of these studies.

Our study has several strengths. Firstly, a comprehensive search was conducted in several databases to identify studies that have assessed cost-effectiveness of CPAP therapy in comparison to strategies usually applied in real life. Additionally, we also take a step further to assess the strategies for organizing care capable of optimizing the cost-effectiveness of CPAP therapy. We also followed a structured methodology for conducting scoping reviews and produced evidence maps to help clarifying variability related to ICER estimates. To achieve this, we converted different currencies to USD, by applying purchase power parity and corrected values for inflation to current values. Lastly, most of the included economic evaluations performed CUA, thus using QALY as the effectiveness measure. CUA is recommended by methodological guidelines and indicated by health technology assessment (HTA) agencies such as the National Institute for Health and Care Excellence (NICE) and the Scottish Medicine Consortium (SMC) [79, 80], mostly because CUA encompasses patient's perspective by considering quality of life over time, and this is highly appropriate, especially for diseases that directly impact on quality of life, such as OSA.

One of the limitations of our study is that we considered the results for the base cases of the included studies and did not account for the results of deterministic or probabilistic sensitivity analysis, due to the complexity of taking all these

elements into consideration. We could not confront results from high-income countries to upper middle or lower middle–income countries due to the scarcity of studies conducted in countries belonging to these last categories. We also did not have the intention to generalize results from one context to another; therefore, we did not analyze the transferability of results.

Conclusion

When compared to usual care, CPAP therapy was considered a cost-effective modality of care for moderate-to-severe OSA after the second year of treatment in all studies, with ICER estimates below commonly applied cost-effectiveness thresholds. CPAP therapy may be even more cost-effective by the use of different strategies for the organization of care, such as treating patients in primary care facilities and promoting CPAP adherence with telemonitoring.

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Authors' contributions DVP developed the study protocol. DVP and AR performed searches, screened references, and extracted data. DVP, AMB, and AR performed narrative synthesis and developed and revised the manuscript. ALE and LFD contributed to study design and revised the manuscript critically.

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Data availability Relevant data is presented in Supplemental material.

Declarations

Conflict of interest DVP, ALE, and LFD have been developing consulting activities for ResMed Brasil. AMB and AR declare no potential conflict of interest.

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