CHEST

The Impact of Treatments for OSA on Monetized Health Economic Outcomes

A Systematic Review

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OBJECTIVE: To review systematically the published literature regarding the impact of treatment for OSA on monetized health economic outcomes.

METHODS: Customized structured searches were performed in PubMed, Embase (Embase.com), and the Cochrane Central Register of Controlled Trials (Wiley) databases. Reference lists of eligible studies were also analyzed. Titles and abstracts were examined, and articles were identified for full-text review. Studies that met inclusion criteria were evaluated in detail, and study characteristics were extracted using a standardized template. Quantitative characteristics of the studies were summarized, and a qualitative synthesis was performed.

RESULTS: Literature searches identified 2,017 nonredundant abstracts, and 196 full-text articles were selected for review. Seventeen studies met inclusion criteria and were included in the final synthesis. Seven studies included formal cost-effectiveness or cost-utility analyses. Ten studies employed cohort designs, and four studies employed randomized controlled trial or quasi-experimental designs. Positive airway pressure was the most common treatment modality, but oral appliances and surgical approaches were also included. The most common health economic outcomes were health-care use (HCU) and quality-adjusted life years (QALYs). Follow-ups ranged from 6 weeks to 5 years. Overall, 15 of 18 comparisons found that treatment of OSA resulted in a positive economic impact. Treatment adherence and OSA severity were positively associated with cost-effectiveness.

CONCLUSIONS: Although study methodologies varied widely, evidence consistently suggested that treatment of OSA was associated with favorable economic outcomes, including QALYs, within accepted ranges of cost-effectiveness, reduced HCU, and reduced monetized costs.

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KEY WORDS: accident risk; CPAP; economics; health-care use; sleep apnea; sleep medicine; treatment; workplace productivity

ABBREVIATIONS: CEA = cost-effectiveness analysis; CUA = cost-utility analysis; HCU = health-care use; HF = heart failure; HrQOL = health-related quality of life; HSAT = home sleep apnea testing; MVC = motor vehicle crash; NOS = Newcastle-Ottawa Scale; OA = oral appliance; PAP = positive airway pressure; PSG = polysomnography; QALY = quality-adjusted life year; RCT = randomized controlled trial; SCD = sickle cell disease; UPPP = uvulopalatopharyngoplasty; USD = US dollars

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OSA is a serious and highly prevalent medical condition with well-documented adverse health consequences. In the United States, approximately 14% of men and 5% of women between the ages of 30 and 70 years have moderate to severe OSA,[1] and the prevalence of the disorder is increasing.[2,3] Relative to healthy control subjects, patients with OSA have numerous adverse health consequences, including increased risk for cardiovascular disease,[4-6] stroke,[7] metabolic syndrome,[8,9] reduced quality of life,[10] and premature death.[11,12]

In addition to these health-related outcomes, OSA is associated with significant economic costs borne by multiple stakeholders, including patients, payers, employers, and society.[13] A white paper commissioned by the American Academy of Sleep Medicine estimated the total societal-level costs of OSA to exceed $150 billion per year in the United States alone, including $86.9 billion because of lost workplace productivity, $30 billion because of increased health-care use (HCU), $26.2 billion because of motor vehicle crashes (MVCs), and $6.5 billion because of workplace accidents and injuries.[14]

Despite consensus that OSA causes substantial economic burden, far less is known about the potential economic benefit of OSA treatment. In the modern health-care climate of rising costs on the one hand and limited resources on the other, such knowledge is required by payers and policy makers to guide evidence-based decision-making regarding allocation of scarce health-care resources. It is thus somewhat surprising that few studies have sought to aggregate extant data or assess the state of the science regarding the health economic impact of OSA treatment (eg, Leger et al[15] and Tarasiuk and Reuveni[16]). Reviews to date have primarily focused on the costs of untreated OSA (eg, Leger et al[15] and Tarasiuk and Reuveni[16]), and a representative literature review included only five studies examining the impact of treatments on HCU.[16] To address this important gap in knowledge, we systematically reviewed the literature of cost-effectiveness and monetized economic impact of OSA treatments. Specifically, this systematic review sought to answer the question, "What is the impact of OSA treatment on monetized health economic outcomes?"

Materials and Methods

This study adheres to reporting requirements as outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[17] To our knowledge, the research protocol is published here for the first time and was not previously registered elsewhere.

Throughout the article, financial costs are adjusted for inflation and presented in 2017 US dollars (USD), with the originally published costs in parentheses. Results originally published in USD were adjusted for inflation by using an online calculator from the Bureau of Labor Statistics (http://www.bls.gov/data/inflation_calculator.htm). Results originally published in non-US currencies were first converted to USD for the publication year by using an online calculator (http://www.oanda.com/currency/converter/) and then adjusted for inflation.

Inclusion Criteria

Empirical studies that employed observational or experimental designs and provided monetized health economic outcomes of OSA treatments based on comparisons with no treatment were eligible for this systematic review. Inclusion criteria for individual studies were as follows: (1) scientific publication in the English language, (2) patients with OSA, (3) patients in whom OSA was treated, (4) comparator group with OSA diagnosis but no OSA treatment, and (5) health economic outcome expressed in monetary units. Exclusion criteria included conference abstracts or proceedings, single case studies, economic modeling studies based on previously published data, and reviews.

Health Economic Outcomes

On the basis of prior literature, several domains of health economic outcome were identified and included in this systematic review, including HCU, costs, workplace productivity, accident risk, and quality-adjusted life years (QALYs). In the broader medical literature, health economic outcomes are often secondary end points in clinical studies, and this was the case in the current systematic review. Given the purpose of this review, our focus was to analyze the impact of OSA treatments on monetized health economic outcomes.

Information Sources

A health sciences librarian (A. G. S.) conducted structured searches of major research databases: PubMed, Embase (Embase.com), and the Cochrane Central Register of Controlled Trials (Wiley).

Data Searches

Searches required at least one term to be present from three core concepts: (1) health economics, (2) sleep apnea, and (3) treatment

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(eg, terms such as "positive airway pressure," [PAP] "oral appliance," [OA] and "surgery"). These searches were completed on December 7, 2016, and updated on September 18, 2017. Search strategies used both Medical Subject Headings and text words and were customized to each database (Table 1). In addition to the database searches, reference lists of eligible articles were reviewed.

Study Selection

To identify studies for full-text review, titles and abstracts were independently rated by at least two reviewers. In the case of disagreement, the title and abstract were rated by at least one additional reviewer, and disagreement was resolved through discussion and consensus. Next, studies selected for full-text review were assessed in detail by at least two reviewers.

Data Collection Process

Data were extracted from reports and reviewed for accuracy by a minimum of two reviewers using a standardized extraction template.

Data Items

Depending on the study design, information extracted included (1) study sample or base case; (2) study design; (3) perspective; (4) follow-up duration; (5) OSA diagnostic criteria; (6) OSA treatment and adherence information, when available; (7) health economic outcomes; (8) and key health economic results. A detailed summary of extracted information is included in e-Table 1.

Risk of Bias in Individual Studies

Risk of bias for randomized controlled trials (RCTs) was assessed using the Cochrane risk-of-bias tool based on random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, selective outcome reporting, and incomplete outcome data and other sources of bias. On the basis of the assessment of each domain, risk of bias was judged as high, unclear, or low.[18]

The methodological quality of included observational studies was assessed using the Newcastle-Ottawa Scale (NOS) for nonrandomized trials.[19] The NOS assesses risk of bias in case-control and cohort studies in eight domains, which are broadly categorized into study group selection, comparability, and ascertainment of either the exposure or outcome for case-control or cohort studies, respectively.[19] On the basis of the NOS, each study was scored as being at low risk of bias (studies receiving eight stars), unclear risk of bias (studies receiving seven stars), or high risk of bias (studies receiving fewer than seven stars).

Synthesis of Results

Data from included studies were aggregated and synthesized qualitatively. Data were evaluated for meta-analysis by assessing studies for clinical, geographic, and methodological consistency. On the basis of published guidelines, excessive statistical heterogeneity (ie, defined as $I^2 \geq 70\%$[20]) rendered a planned meta-analysis inappropriate.

TABLE 1] Search Methodology for Systematic Review of Health Economic Outcomes of OSA Treatments

PubMed (1809-present)	(economic*[tiab] OR health care utiliz*[tiab] OR productivity[tiab] OR accident risk [tiab] OR cost[tiab] OR quality adjusted life years[tiab] OR absenteeism[tiab] OR disability adjusted life years[tiab] OR "cost of illness"[MeSH] OR "health expenditures"[MeSH] OR "economics, medical"[MeSH] OR "cost savings"[MeSH] OR "cost-benefit analysis"[MeSH] OR "quality-adjusted life years"[MeSH]) AND (sleep apnea[tiab] OR sleep-related breathing disorder[tiab] OR sleep-disordered breathing[tiab] OR "sleep apnea syndromes"[MeSH]) AND (treatment[tiab] OR therapy[tiab] OR therapeutic[tiab] OR positive airway pressure[tiab] OR cpap[tiab] OR oral appliance[tiab] OR dental device[tiab] OR jaw advancement[tiab] OR bilevel pap[tiab] OR hypoglossal nerve stimulation[tiab] OR weight loss[tiab] OR surgery[tiab] OR "positive-pressure respiration"[MeSH])
Embase (1974-present)	(economic*:ab,ti OR 'health care utiliz*':ab,ti OR productivity:ab,ti OR 'accident risk':ab,ti OR cost:ab,ti OR 'quality adjusted life years':ab,ti OR absenteeism:ab,ti OR 'disability adjusted life years':ab,ti OR 'health economics'/exp OR 'health care utilization'/exp OR 'cost benefit analysis'/exp OR 'cost effectiveness analysis'/exp OR 'cost of illness'/exp OR 'quality adjusted life year'/exp) AND ('sleep apnea':ab,ti OR 'sleep-related breathing disorder*':ab,ti OR 'sleep-disordered breathing':ab,ti OR 'sleep disordered breathing'/exp) AND (treatment:ab,ti OR therapy:ab,ti OR therapeutic:ab,ti OR 'positive airway pressure':ab,ti OR cpap:ab,ti OR 'oral appliance':ab,ti OR 'dental device':ab,ti OR 'jaw advancement':ab,ti OR 'bilevel pap':ab,ti OR 'hypoglossal nerve stimulation':ab,ti OR 'weight loss':ab,ti OR surgery:ab,ti OR 'positive and expiratory pressure'/exp OR 'cpap device'/exp)
Cochrane Central Register of Controlled Trials	(economic* OR health care utiliz* OR productivity OR accident risk OR cost OR quality adjusted life years OR absenteeism OR disability adjusted life years) AND (sleep apnea OR sleep-related breathing disorder OR sleep-disordered breathing) AND (treatment OR therapy OR therapeutic OR positive airway pressure OR cpap OR oral appliance OR dental device OR jaw advancement OR bilevel pap OR hypoglossal nerve stimulation OR weight loss OR surgery)

ab = abstract; exp = explode; MeSH = Medical Subject Headings; pap = positive airway pressure; ti = title.

Results

Study Selection

Literature searches identified 2,670 total (PubMed, 678; Embase, 1,821; Cochrane Central Register of Controlled Clinical Trials, 164) and 2,017 nonredundant abstracts. After abstract review and discussion, 196 full-text articles were selected for review. Of these, 17 studies met inclusion criteria and were included in the final synthesis (Fig 1).

Study Characteristics

Study Design: The most common study design was a retrospective cohort study, which was employed in 10 studies.[21-30] Three studies employed RCT designs,[31-33] and one study employed a quasi-experimental design.[34] Other designs included two case-control studies[35,36] and a prospective cohort study.[37] Three studies included populations with comorbid conditions, including type 2 diabetes mellitus,[35] sickle cell disease (SCD),[29] and heart failure (HF).[25] Tables 2 and 3 summarize key characteristics of included experimental and observational studies, respectively.

Methodological Quality and Risk of Bias: The methodological quality of the three included RCTs was generally high, and all RCTs showed low risk of bias in most of the Cochrane risk-of-bias domains. One RCT was open label, so blinding of participants and study personnel was absent.[33] In another, blinding of participants and study personnel was unclear.[32] Allocation concealment was not reported in two RCTs.[32,33]

On the basis of the NOS, risk of bias across all included observational studies was low. Six studies, including five cohort studies[21,23,25,26,29] and one case-control study[35] scored nine stars and were deemed to have low risk of bias. Seven other cohort studies did not adjust for important covariates; thus, risk of bias was deemed unclear, and these studies were scored seven stars.[22,24,27,30,34,36,37] A final cohort study[28] did not clarify representativeness of the sample and was also scored seven stars.

Participants: As presented in Tables 2 through 5, the number of participants in empirical studies ranged from 19[28] to 30,719[25] and differed substantially by recruitment strategy. Among clinic-based studies, sample sizes ranged from 19[28] to 414.[22] Among administrative claims review studies, sample sizes ranged from 740[36] to 30,719.[25] Studies were published between the years of 1994[28] and 2016.[30] Study locations included the United Studies (n = 4),[23-25,29] the United

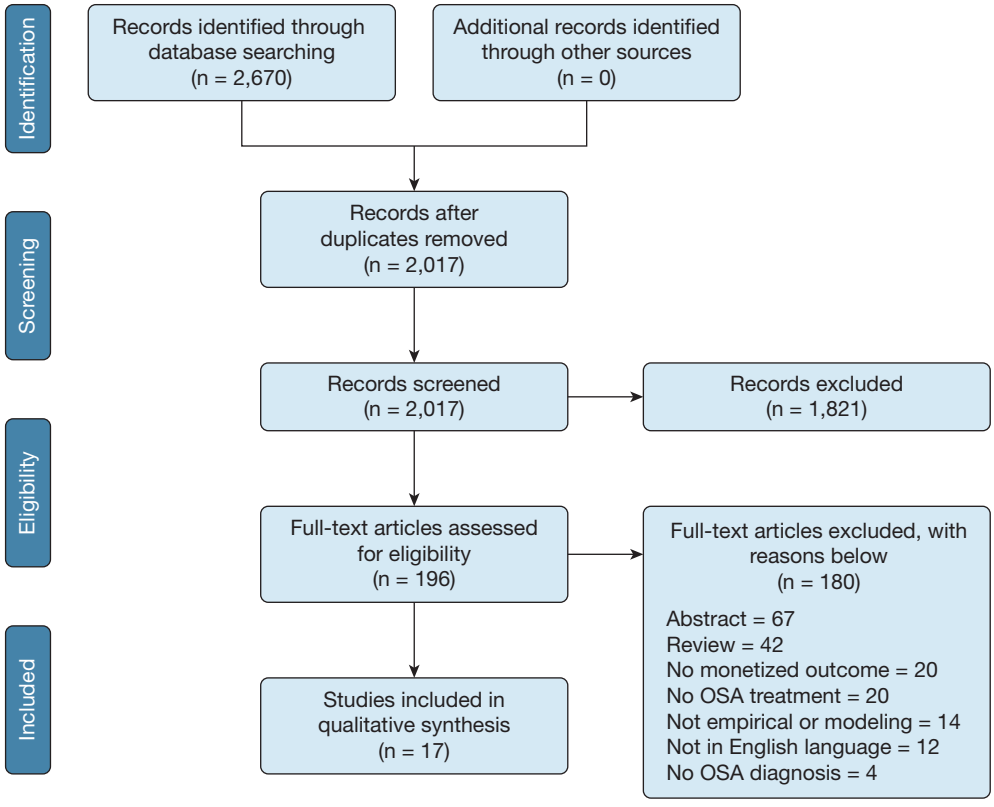

Figure 1 – *Flowchart of search results.*

TABLE 2] Summary of Studies Evaluating the Cost-effectiveness of OSA Treatment

Study/Year (Country)	No. of Participants (Mean Age, y; Male, %)	Study Design	OSA Treatment (Adherence)	Comparison Group	Economic Outcome	Main Findings
Experimental						
Pelletier-Fleury et al[32]/ 2004 (France)	171 (53; 82)	Multicenter RCT	CPAP (O)	6 mo delayed treatment	HCU: total costs CEA	Severe OSA: Reduced costs ($414 vs $876 [€263 vs €556 in 2004 Euros]; $P < .0001$) over 6 mo and was cost-effective Moderate OSA: Increased costs ($961 vs $467 [€610 vs €297 in 2004 Euros]; $P < .0001$) and was not cost-effective
McMillan et al[31]/ 2014 (United Kingdom)	278 (71; 79)	Multicenter RCT	APAP (O)	Supportive care	HrQOL: EQ-5D and SF-6D CEA	0.018 SF-6D QALYs gained (EQ-5D QALYs were similar between groups), reduced costs (−$61 [−£35 in 2014 GBP]) over 1 y and was marginally cost-effective
Quinnell et al[33]/ 2014 (United Kingdom)	90 (51; 80)	Crossover RCT	OA	No treatment	HrQOL: FOSQ, SAQLI CEA	0.009 to 0.018 QALYs gained, reduced costs −$26 to $46 (−£15 to £26 in 2014 GBP) over 1 y, ICERs of −$29,964 to $26,062 (−£17,104 to £14,876 in 2014 GBP)
Lojander et al[34]/ 2008 (Finland)	78 (56; 71)	Prospective quasi-experiment	CPAP, APAP, or BPAP with LC (O)	CPAP	HrQOL: 15 d CEA	LC: 0.37 QALYs gained (0.386 ± 1.16 to 0.016 ± 2.34), reduced costs −$1,166 ($448 −$1,615 [€848 (€326-€1,174) in 2010 Euros]), ICER of $1,166 (€845 in 2010 Euros) over 6.8 mo PAP: 0.016 ± 2.34 QALYs gained, ICER of $100,912 (€73,375 in 2010 Euros)
Nonexperimental						
Català et al[30]/ 2016 (Spain)	373 (56; 85)	Retrospective cohort study	CPAP (O)	1 y pretreatment	HCU: total costs; medical costs for MVCs and workplace accidents CEA	0.05 QALYs gained (0.07 among adherers and −0.04 among nonadherers), ICER of $57,774 (€51,147 in 2016 Euros) in y 1 and projected ICER of $1,744 (€1,544 in 2016 Euros) in y 2
Tousignant et al[28]/ 1994 (Canada)	19 (57; 74)	Retrospective cohort study	CPAP (NR)	Pretreatment	HrQOL: S-G CEA	5.4 QALYs and 0.24 (0.63-0.87) utility gained, at an incremental cost of $955 ($800 in 1994 CAD) over 9 mo, ICER of $22,248 ($18,637 in 1994 CAD)

(Continued)

TABLE 2] (Continued)

Study/Year (Country)	No. of Participants (Mean Age, y; Male, %)	Study Design	OSA Treatment (Adherence)	Comparison Group	Economic Outcome	Main Findings
Comorbid OSA						
Guest et al[35]/ 2014 (United Kingdom)	300 with T2DM (54; 82)	Case-control study	CPAP (SR)	Matched patients with T2DM and untreated OSA	HCU: total costs HrQOL: previous literature CEA	0.27 QALYs gained over 5 y, at an incremental cost of $7,255 (£4,141 in 2014 GBP) over 5 y, ICER of $26,301 (£15,337 in 2014 GBP)

Adherence reported for positive airway pressure only. APAP = auto-adjusting positive airway pressure; BPAP = bilevel positive airway pressure; CAD = Canadian dollars; CEA = cost-effectiveness analysis; EQ-5D = EuroQol-5D; FOSQ = Functional Outcomes of Sleep Questionnaire; GBP = Great Britain pounds; HCU = health-care use; HrQOL = health-related quality of life; ICER = incremental cost-effectiveness ratio; LC = lifestyle counseling; MVC = motor vehicle crash; NR = not reported; O = objective; OA = oral appliance; QALY = quality-adjusted life year; RCT = randomized controlled trial; SAQLI = Calgary Sleep Apnea Quality of Life Index; SF-6D = Short-Form Six-Dimension; S-G = Standard-Gamble; SR = self-report; T2DM = type 2 diabetes mellitus.

Kingdom (n = 3),[31,33,35] Canada (n = 4),[21,22,28,37] and one each from Denmark,[26] Finland,[34] France,[32] Israel,[36] Spain,[30] and Sweden.[27] Although one study each included all-male[21] and all-female[22] samples, most empirical studies were sex-mixed and included > 70% male participants. The majority of studies included middle-aged adults, with two studies focusing on older adults[25,31] and two studies including children < 20 years of age.[26,36]

Perspective: All seven cost-effectiveness analysis (CEA) or cost-utility analysis (CUA) studies reported results from the perspective of the payer.

Follow-up Duration: Follow-ups ranged from 6 weeks[33] to 5 years,[21,35] with most studies having follow-ups of 6 months to 2 years.

OSA Diagnostic Criteria: OSA diagnoses varied by study setting. In clinic-based studies, OSA was diagnosed during overnight polysomnography (PSG; n = 9),[21,22,27,28,32,33,36,37,38] home sleep apnea testing (HSAT; n = 1),[31] or mixed approaches such as HSAT followed by PSG if necessary (n = 2).[30,34] In administrative review studies, OSA diagnosis was operationalized by diagnostic, procedural, or equipment-related codes indicative of OSA (n = 6).[23-26,29,35]

OSA Treatments: In the vast majority of studies, the OSA treatment was PAP, including CPAP, auto-adjusting PAP, and bilevel PAP. PAP adherence was reported in all but five studies,[23-25,28,39] with a roughly equal number of studies employing objective (eg, machine counter or Secure Digital download)[30-34] and subjective (eg, patient or bed-partner report)[21,22,27,35,37] measures of adherence. Other treatment modalities included surgical approaches (n = 3)[26,29,36] and OAs (n = 1).[33]

Health Economic Outcomes: The most common economic outcome was HCU (n = 17). Some studies included measures of health-related quality of life (HrQOL; ie, QALYs) and CEA or CUA (n = 7),[28,30-35] accident and injury-related costs (n = 3),[30-32] and measures of lost workplace productivity such as costs of days missed from work and costs of short-term disability (n = 3).[24,26,30]

Results of Individual Studies

Cost-effectiveness of OSA Treatments: Seven studies, including six studies of PAP[28,30-32,34,35] and one study of OA,[33] evaluated the impact of OSA treatment on HrQOL (ie, QALY) and included CEA or CUA. Six of

TABLE 3] Summary of Studies Evaluating the Impact of OSA Treatment on HCU

Study/Year (Country)	No. of Participants (Mean Age, y; Male, %)	Study Design	OSA Treatment (Adherence)	Comparison Group	HCU Measures	Authors' Main Findings
Albarrak et al[21]/2005 (Canada)	34 (48; 100)	Retrospective cohort study	CPAP (SR)	1 y pretreatment	Outpatient visits, physician costs	Reduced outpatient visits (−1.03 visits; $P < .001$) and physician costs (−$14.23 [−13.92 in 2005 CAD]; $P = .0009$) over 5 y
Bahammam et al[37]/1999 (Canada)	344 (49; 100)	Prospective cohort study	CPAP or BPAP (SR)	2 y prediagnosis	Physician costs, hospitalizations	Among adherers, reduced physician costs ($P < .05$) and hospitalizations ($P = .05$) over 2 y
Banno et al[22]/2006 (Canada)	414 (49; 0)	Retrospective cohort study	CPAP or BPAP (SR)	2 y prediagnosis	Outpatient visits, physician costs	Reduced outpatient visits (−1.48 visits; $P < .0001$) and physician costs (−$37.26 [−$37.96 in 2006 CAD]; $P < .0001$) over 2 y
Cai et al[23]/2012 (United States)	15,424 (48; 70)	Retrospective cohort study	CPAP (NR)	1 y prediagnosis	Total costs, all-cause, and OSA-related hospitalizations	Reduced total costs ($792 vs $883 [$705 PMPM vs $786 PMPM in 2010]; $P < .001$) and rates of all-cause (19% vs 24.2%; $P < .001$) and OSA-related (8% vs 11.3%; $P < .001$) hospitalizations over 2 y
Hoffman et al[24]/2010 (United States)	248 (44; 99)	Retrospective cohort study	CPAP or BPAP (NR)	1 y prediagnosis	Total costs	Reduced HCU costs over 2 y (y 1: −$3,062 [−$2,727 in 2010 USD], $P = .002$; y 2: −$3,465 [−$3,086 in 2010 USD], $P = .008$)
Jennum and Kjellberg[26]/2011 (Denmark)	19,438 (10% children < 20, mean age, NR; 78)	Retrospective cohort study	CPAP (NR), UPPP	2 y prediagnosis	Total costs	Neither CPAP nor UPPP reduced HCU costs over 2 y.
Peker et al[27]/1997 (Sweden)	82 (55; 82)	Retrospective cohort study	CPAP (SR)	2 y prediagnosis	Hospital costs	Reduced CVPD-related hospitalization costs (−$80,680 vs +$11,134 [−$52,900 vs +$7,300 in 1997 USD]) over 2 y
Tarasiuk et al[36]/2004 (Israel)	740 (children < 18, 5.6; 37)	Prospective, longitudinal case-control study	TA	1 y prediagnosis	Total costs	Reduced total costs (−32.5%; $P < .0004$) over 1 y
Comorbid OSA						
Javaheri et al[25]/2011 (United States)	30,719 with HF (range, 67.1-76.5; 43)	Retrospective cohort study	CPAP (NR) and oxygen use	Untreated	Total costs	Costs were lowest for those tested, given a diagnosis, and treated ($6,465 per quarter [$5,758 in 2010 USD]) and highest for those not tested, given a clinical diagnosis, and not treated ($12,080 per quarter [$10,759 in 2010 USD])

(Continued)

TABLE 3] *(Continued)*

Study/Year (Country)	No. of Participants (Mean Age, y; Male, %)	Study Design	OSA Treatment (Adherence)	Comparison Group	HCU Measures	Authors' Main Findings
Tripathi et al[29]/2011 (United States)	2,194 with SCD (NR; 60.2)	Retrospective cohort study	TA	Matched children with SCD who did not undergo TA	Outpatient visits, ED visits, hospitalization, and total costs	Reduced outpatient visits for OSA and cerebrovascular events and lowered mean acute service costs over 3 y

Adherence reported for positive airway pressure only. CVPD = cardiovascular-pulmonary disease; PMPM = per member per month; TA = adenotonsillectomy; UPPP = uvulopalatopharyngoplasty. See Table 2 legend for expansion of other abbreviations.

seven studies found that OSA treatment was beneficial in terms of CEA or CUA results. In one study, CPAP was cost-effective among patients with severe but not moderate OSA.[32] Contrary to these authors, Lojander and colleagues[34] conducted a prospective quasi-experimental treatment study and found that, compared with CPAP, lifestyle counseling was associated with greater improvements in HrQOL, lower costs, and a much more favorable incremental cost-effectiveness ratio (ie, cost per QALY gained). Results are presented in Table 2 (with additional detail presented in e-Table 1).

Impact of OSA Treatment on HCU: Eight observational studies evaluated the impact of PAP therapies alone on HCU expressed in USD.[21-27,37] Seven of eight studies found that, compared with no treatment, PAP was associated with reduced HCU and costs. Conversely, Jennum and Kjellberg[26] conducted a large administrative review in Denmark and found that relative to 1 year prior to diagnosis, neither CPAP nor uvulopalatopharyngoplasty (UPPP) was associated with reductions in HCU within 2 years.

In addition, three observational studies evaluated the impact of OSA surgeries on HCU[26,29,36]: Two evaluated the economic impact of surgical approaches for OSA among children and adolescents and one among adults. One of the two studies conducted among children involved children with SCD, and both studies found that, compared with no treatment, adenotonsillectomy was associated with reductions in total cost, hospitalizations, and ED visits, as well as fewer outpatient visits among those with SCD. A third study evaluated UPPP among adults with OSA and found no benefit from UPPP on HCU or costs.[26] Results are presented in Table 3 (with additional detail presented in e-Table 1).

Impact of OSA Treatment on Workplace Productivity and Absenteeism: Three studies[24,26,30] evaluated the impact of OSA treatment on workplace productivity and days missed from work. In a case-crossover study, Català and colleagues[30] found that relative to 1 year prior to treatment, CPAP was associated with a significant reduction in days missed from work at 1-year follow-up (7.5 vs 4.2 days missed; $P < .001$). Notably, reductions in days missed were greater among PAP adherers than among nonadherers ($P < .001$), who demonstrated a significant increase in days missed from baseline to 1 year follow-up (5.2 vs 20.8 days missed; $P < .001$).[30] In a cohort study

TABLE 4] Summary of Studies Evaluating the Impact of OSA Treatment on Workplace Productivity

Study/Year (Country)	No. of Participants (Mean Age, y; Male, %)	Study Design	OSA Treatment (Adherence)	Comparison Group	Workplace Costs	Authors' Main Findings
Català et al[30]/ 2016 (Spain)	373 (56; 85)	Retrospective cohort study	CPAP (O)	1 y prediagnosis	Costs of days missed from work because of medical care	Reduced days missed from work (−3.3 d) over 1 y; PAP adherence was associated with greater reductions in days missed from work over 1 y
Hoffman et al[24]/ 2010 (United States)	248 (44; 99)	Retrospective cohort study	CPAP or BPAP (NR)	1 y pretreatment	Disability costs	Reduced short-term disability costs (−$593 [−$528 in 2010 USD]) and fewer days missed from work (−6.9 d) over 2 y
Jennum and Kjellberg[26]/ 2011 (Denmark)	19,438 (10% children < 20, mean age, NR; 78)	Retrospective cohort study	CPAP (NR), UPPP	2 y prediagnosis	Lost productivity	Neither CPAP nor UPPP was associated with reductions in workplace costs within 2 y.

Adherence reported for PAP only. PAP = positive airway pressure. See Tables 2 and 3 legends for expansion of other abbreviations.

among a self-insured employee population of commercial drivers, Hoffman and colleagues[24] found that relative to 1 year prior to treatment, PAP therapy was associated with a $528 reduction in short-term disability costs over 2 years ($368 reduction in year 1, $P = .002$; $160 reduction in year 2, $P = .302$). By comparison, untreated control subjects demonstrated increased short-term disability costs during this same period. Similarly, relative to 1 year prior to diagnosis, PAP was also associated with fewer days missed from work over 2 years (4.4 fewer days missed in year 1, $P = .004$; 2.5 fewer days missed in year 2, $P = .2$). Finally, as part of the aforementioned retrospective review of a Danish national patient registry, Jennum and Kjellberg[26] found CPAP to be unrelated to a proxy measure of labor market income. Results are presented in Table 4 (with additional detail presented in e-Table 1).

Impact of OSA Treatment on Accident Risk: Two studies sought to examine the economic impact of OSA treatments on accident risk, including the risk for MVCs. In a case-crossover study, Català and colleagues[30] reported a reduction in MVC from 1 year pretreatment to 1 year posttreatment, but this reduction was not statistically significant (2.1 vs 1.3 MVC). Subgroup analyses among PAP adherers and nonadherers were also not significant. In a multicenter RCT of OSA treatments among older adults, McMillan and colleagues[31] found no differences between patients treated with PAP or best supportive care in home accidents, MVC, or all accidents. Notably, Pelletier-Fleury and colleagues[32] sought to include work accidents, home accidents, and MVCs in estimates of OSA costs. However, no such accidents were reported during the 6-month follow-up, so differences between groups could not be evaluated.[32] Results are presented in Table 5 (with additional detail presented in e-Table 1).

Synthesis of Results

As detailed previously and presented throughout Tables 2 through 5, there was substantial between-study heterogeneity in most key study characteristics. In particular, studies varied widely in their assessment of economic outcomes: HCU, total costs, and number of days missed from work were not defined consistently across studies. Even when studies were stratified by geographic region, between-study variability presented substantial challenges to pooling outcomes. For example, when we attempted

to pool data from two studies conducted in Europe[30,35] by using random effects meta-analysis, we found that the pooled estimates for HCU and QALYs demonstrated statistically significant heterogeneity (99.3%; $P < .001$ for HCU; 90%; $P < .01$ for QALYs) as measured by both the Cochran Q test and the I^2 statistic.[20] Similarly, when we attempted to pool studies conducted in North America,[21,23,37] we found that the pooled effect size was driven nearly entirely by one study,[23] which contributed 99.95% of the weight of the effect size. From a quantitative perspective, the available data were clearly inappropriate for statistical aggregation.

In addition to these contraindications to the quantitative combining of results, the studies were conducted in many different countries and were designed to address questions of relevance to those localized health systems. Thus, any final pooled estimate would not reflect the economic realities of any one country and would be of limited value for informing health-care service planning and resource allocation decisions globally. In most cases, such policy-level decisions are highly specific to location, country, and system, and meta-analytic approaches are often inappropriate.[40-42] Given these practical barriers and theoretical contraindications for a quantitative analysis, qualitative synthesis was employed to aggregate results of individual studies included in this systematic review.

In total, 17 separate studies tested 18 OSA treatments. Thirteen studies compared PAP with no treatment, standard care, or lifestyle and weight-loss counseling, and one study tested immediate PAP with delayed PAP.[32] Among non-PAP studies, the most common comparator was no treatment, including studies of surgical approaches (n = 3)[26,29,36] and OAs.[33] Overall, 15 of 18 OSA treatments were associated with a positive health economic outcome. In terms of specific treatment modalities, CPAP was associated with a positive health economic outcome in 12 of 14 studies, with some positive findings being limited to specific subpopulations (ie, only patients with severe OSA[32]). OAs were associated with a positive health economic outcome in one study.[33] Surgical approaches were associated with a positive health economic outcome in two studies[29,36] and related to a negative economic outcome in one study.[26] Four studies found PAP adherence to enhance economic outcomes,[22,27,30,37] and one study detected no relationship between adherence and outcomes.[34]

Discussion

Based on this comprehensive systematic review of the literature, the overwhelming majority of evidence supports the beneficial economic impact of OSA treatments. Studies to date have been conducted in North America, Europe, and Israel and employed a wide range of research methodologies, including retrospective and prospective cohort designs, case-control designs, and CEAs nested within RCTs. Irrespective of study design, PAP was the most frequently studied OSA therapy. Nearly all comparisons found that relative to no treatment, PAP was associated with favorable economic outcomes, including increased cost-effectiveness, reduced HCU, and improved workplace productivity and reduced days missed from work. OA and surgical approaches were less frequently studied, and results were somewhat more equivocal when compared with results with PAP. Non-PAP therapies might also be cost-effective, but extant data are scant; future studies are clearly warranted.

Using standardized methodologies, we consistently found OSA treatments to be cost-effective from the

TABLE 5] Summary of Studies Evaluating the Impact of OSA Treatment on Accident Risk

Study/Year (Country)	No. of Participants (Mean Age, y; Male, %)	Study Design	OSA Treatment (Adherence)	Comparison Group	Accident Costs	Authors' Main Findings
Català et al[30]/ 2016 (Spain)	373 (56; 85)	Retrospective cohort study	CPAP (O)	1 y prediagnosis	Medical costs for MVCs and workplace accidents	No significant reductions within 2 y
McMillan et al[31]/2014 (United Kingdom)	278 (71; 79)	Multicenter RCT	APAP (O)	Supportive care	Home accidents, MVCs, all accidents	No significant reductions within 1 y

Adherence reported for PAP only. See Table 2 legend for expansion of abbreviations.

payer perspective. Five of six studies found that PAP resulted in improvements in HrQOL within commonly accepted ranges of cost-effectiveness (eg, $50,000 USD or thresholds defined by localized health systems). Unexpectedly, Lojander and colleagues[34] found in a prospective quasi-experiment that relative to PAP, lifestyle counseling had greater impact on HrQOL and at lower cost, which resulted in much greater cost-effectiveness (ie, incremental cost-effectiveness ratios of $1,166 [€845 in 2010 Euros] and $100,912 [€73,375 in 2010 Euros], respectively). This study population included patients with mild OSA, and although controversial, the beneficial effects of CPAP on HrQOL are diminished among patients with mild disease.[43,44] Another possible explanation for the surprising finding is that the study might have been underpowered to detect effects of PAP in this sample. In addition, treatment was assigned based on clinical judgment rather than randomization, and the potential impact on results was not assessed. Despite the findings of the quasi-experimental study of the study by Lojander and colleagues,[34] the preponderance of evidence suggests that, compared with no treatment, CPAP is cost-effective, especially among patients with moderate to severe OSA.

In addition to PAP, OA therapy was cost-effective. In a single RCT among patients with mild to moderate OSA, Quinnell and colleagues[33] found that relative to no treatment, self-molded, semibespoke, and fully bespoke mandibular advancement devices were cost-effective over a 6-week time frame. Semibespoke devices were the most cost-effective and suggested by the authors as a first treatment option. Although this single study requires replication with diverse OSA samples and longer follow-ups, it is highly promising that OA therapy can provide economic in addition to clinical benefit. Dental sleep medicine is a rapidly expanding domain of sleep medicine. OAs are preferred by many patients and are an accepted treatment alternative for patients with mild to moderate OSA or who are unable to tolerate PAP.[45]

In addition to the CEAs, the vast majority of studies found OSA treatments to reduce HCU. Specifically, relative to no treatment, seven of eight comparisons of PAP and two of three comparisons of OSA surgeries found treatment to reduce outpatient visits, hospitalizations, ED visits, and costs. Samples included adults and children, for whom adenotonsillectomy is considered first-line treatment for OSA, as well as populations with comorbid conditions, including HF and SCD. Null findings regarding the impact of PAP and surgery on HCU were both reported in the same study, a large administrative review study conducted by Jennum and Kjellberg.[26] Three possible explanations for these null findings seem likely. First, no efforts were made to quantify or confirm PAP adherence, an inherent challenge to an administrative review methodology. Second, UPPP is an expensive procedure that does not reliably normalize the apnea-hypopnea index.[46] Finally, the 2-year time frame might have been insufficient to detect beneficial economic effect. In the current review, longer follow-ups were typically associated with more favorable economic outcomes. The authors briefly mentioned a subgroup analysis in which CPAP was associated with reduced costs during year 2, although costs remained higher than before diagnosis. However, these results were not formally reported and thus could not be assessed in detail. In summary, nine of 10 comparisons found OSA treatments to reduce HCU across the continents, ages, and populations with comorbid conditions evaluated. The findings regarding cost-effectiveness of OSA treatments and impact on HrQOL will be of particular interest to payers and policy makers charged with allocation of scarce health-care resources.

Studies also assessed the economic impact of OSA treatment on outcomes that matter to employers. Both Hoffman and colleagues[24] and Català and colleagues[30] found that, relative to 1 year prior to treatment, PAP was associated with reduced absenteeism over 2 years. Furthermore, Hoffman and colleagues[24] found that PAP was associated with reduced HCU and reduced short-term disability costs among a self-insured employee population of commercial truck drivers. These data speak directly to the needs of employers concerned with improving workplace productivity and reducing health-care spending as means to enhance business performance.[13,47] Although Jennum and Kjellberg[26] detected no economic benefit from CPAP or UPPP, the dependent measure of labor market income was not measured directly. Furthermore, in light of the pattern of results in the study by Jennum and Kjellberg,[26] the result regarding lack of economic benefit is not surprising. Overall, evidence from two studies suggests that OSA treatments are associated with fewer days missed from work.[24,30]

In the broader sleep medicine literature, it is well-documented that OSA treatments are associated with reduced accident risk (eg, MVC).[48-50] However, in the present review, no study found a beneficial effect from OSA treatment on monetized accident risk. These null findings can likely be attributed to the low frequency of

this outcome in the included studies and to our inclusion criteria requiring outcomes to be expressed in monetary units. Additional empirical studies are clearly needed to understand the economic impact of OSA treatments from a societal perspective, which includes all direct and indirect costs, including accidents.

Through this review, results suggest that cost-effectiveness is closely linked to clinical effectiveness of OSA treatment. It is thus perhaps not surprising that the economic benefit of PAP related directly to PAP adherence. Although PAP is highly effective, many patients struggle to acclimate to the therapy, resulting in suboptimal long-term adherence that is comparable with adherence to medication therapies in other chronic diseases.[51] Of studies that evaluated the economic impact of PAP adherence, a clear majority (four of five) found PAP adherence to be associated positively with enhanced economic outcomes.[22,27,30,37] Thus, the present results support maximizing PAP adherence as a clinical, public health, and economic imperative.

Cost-effectiveness is also strongly related to costs. Direct medical costs associated with OSA typically include outpatient encounters (ie, generalist or specialist consultation), diagnostic testing (ie, PSG or HSAT), treatment initiation and equipment (ie, in-laboratory or at-home PAP titration, OA titration, surgery, and so on), and ongoing medical oversight and supplies (ie, outpatient encounters, PAP mask, tubing, and filter resupply, replacement OAs, and so on). These costs typically decrease over time. To guide economic decision-making, one must weigh initial costs against the costs of untreated OSA, including increased HCU, diminished workplace productivity, increased disability rates, and increased accident risk, which could be expected to increase over time.

In addition to costs, sleep apnea severity and time horizon are important determinants of health economic decision-making.[52] In the present review, cost-effectiveness was greatest among patients with severe OSA. Furthermore, although follow-ups were highly variable, longer time horizons were associated with more favorable economic outcomes. Because OSA costs are higher at the time of diagnosis and initiation of therapy, it can take several years for these costs to be recouped via reduced HCU. Time horizon is arguably even more important when considering comorbid OSA. In these instances, OSA treatments might not be powerful enough to overcome rapidly the combined up-front costs of OSA treatment along with costs associated with other comorbid conditions. Thus, researchers must strive to define the optimal time horizon for evaluating the cost-effectiveness of OSA treatments, as well as to identify other key outcomes for evaluating OSA comorbid with other costly conditions. Finally, perspective is central to the time horizon required because broader perspectives (eg, societal perspectives) that include direct and indirect costs of untreated OSA will allow for recouping costs more quickly.

Limitations

Although this systematic review captures the current state of the science, a number of limitations must be noted. First, this review included only studies examining cost-effectiveness or impact on monetized health economic outcomes. Many studies in the literature examine nonmonetized outcomes closely related to costs and cost savings, such as physician encounters, hospital readmissions, and MVCs. Relatively fewer studies examine the impact of OSA treatment on workplace productivity and disability, another key health economic outcome and a central outcome from the employer perspective. Second, our analyses were limited to publications in the English language. A large number of germane abstracts were excluded, and several studies not in the English language were excluded. Some of these abstracts may be developed into peer-reviewed publications. Similarly, including publications not in the English language could provide much-needed insight into the cost-effectiveness of OSA treatments around the globe, where important data are lacking. Third, the current project did not consider the costs associated with OSA diagnosis, which are substantial. OSA diagnosis is increasingly linked to OSA treatment through OSA pathways reflecting more intensive levels of care (eg, attended diagnosis and PAP titration vs HSAT and auto-adjusting PAP). Evaluation of care pathways will become increasingly important as sleep medicine payment models transition from volume to value and population health.[13]

Future Directions

Results of the current project suggest several important areas for future research (Table 6). First and most important, we strongly recommend that future OSA trials include measures of direct and indirect OSA costs. Second, sleep researchers should include both general and disease-specific measures of HrQOL in OSA trials to evaluate the cost-effectiveness of OSA treatments within commonly accepted thresholds (ie, $50,000 per QALY). Third, studies of the economic aspects of treating OSA

TABLE 6] Key Actionable Recommendations to Advance Health Economic Understanding of OSA Treatments

Domain	Recommendation
Include health economic end points	Include measures of direct and indirect costs of OSA in all future OSA trials
Evaluate cost-effectiveness	Include measures of both general and disease-specific measures of health-related quality of life in all future OSA trials
Study-specific populations	Conduct health economic analyses among women, older adults, and children; among different ethnic groups; and among patients with varying OSA severities
Understand comorbid OSA	Study economic impact of OSA and OSA treatments in costly and chronic comorbid disease states such as heart failure, type 2 diabetes mellitus, and depression
Increase adherence	Study economic cost-benefit of interventions designed to increase treatment adherence, including cognitive-behavioral treatment, telehealth and remote monitoring, automated approaches, and other interventions
Adopt employer perspective	Evaluate cost-benefit of OSA treatments from employer perspective: impact on lost workplace productivity (ie, absenteeism) and workplace accident and injury risk
Evaluate global impact	Evaluate cost-effectiveness of treating OSA worldwide in various health-care delivery systems
Compare economic effectiveness	Compare economic effectiveness between OSA treatments to empower stakeholders to make evidence-based decisions regarding allocation of scare health-care resources

should include diverse populations, especially women, older adults, and children; different ethnic and racial groups; people with varying levels of OSA; and people with high-cost comorbidities (eg, HF, COPD, type 2 diabetes mellitus, depression).[53] Fourth, future studies should examine the linear dose-response relationship between PAP use and cost-effectiveness. Fifth, greater insight is needed into the cost-effectiveness of interventions designed to increase PAP use in diverse populations. Sixth, greater insight into the employer perspective is essential because roughly one-half of OSA indirect costs are associated with lost workplace productivity (ie, absenteeism) and workplace accident and injury risk. Greater insight into the cost-benefit ratio of treating OSA is likely to be of particular interest to the increasing number of large ($N > 1,000$) self-insured employers.[54] Seventh, given that a great majority of extant data are from select developed nations, studies including a wider variety of health-care delivery systems are warranted. Finally, in light of the rapidly expanding number of alternate OSA treatment modalities, comparative effectiveness analyses between OSA treatments will empower stakeholders to make evidence-based decisions regarding allocation of scare health-care resources.

Conclusions

OSA is a common and costly condition, with well-documented adverse impacts on HrQOL and economic outcomes. Total societal-level expenditures associated with OSA are estimated at $160 billion per year in the United States alone.[14] Results of this systematic review indicate not only that the great majority of evidence supports the cost-effectiveness of PAP therapy for the treatment of OSA but also that other OSA treatments might be cost-effective. Health-care costs, physician visits, and days missed from work were all reduced from use of CPAP. In the modern health-care climate, patients, payers, and policy makers are increasingly attuned to not only the health outcomes but also the economic aspects of medical care. Thus, in light of the increasing prevalence of OSA and the significant adverse health consequences associated with the disease, these results should encourage payers and policy makers to expand access to sleep medicine care.

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