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SCIENTIFIC INVESTIGATIONS

Cost-Effectiveness Analysis of the DiagnOSAS Screening Tool Compared With Polysomnography Diagnosis in Dutch Primary Care

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Study Objectives: The growing recognition of obstructive sleep apnea (OSA) as a serious health condition, increasing waiting lists for sleep tests, and a high proportion of unnecessary referrals from general practice highlight the need for alternative diagnostic strategies for OSA. This study's objective was to investigate the cost-effectiveness of DiagnOSAS, a screening tool that strives to facilitate fast and well-informed referral to hospitals and sleep clinics for diagnosis, in The Netherlands.

Methods: A Markov model was constructed to assess cost-effectiveness in men aged 50 years. The diagnostic process of OSA was simulated with and without DiagnOSAS, taking into account the occurrence of hazardous OSA effects: car accidents, myocardial infarction, and stroke. The cost-effectiveness of "DiagnOSAS Strategy" and a "Rapid Diagnosis Scenario," in which time to diagnosis was halved, was assessed.

Results: Base case results show that, within a 10-year time period, DiagnOSAS saves €226 per patient at a negligible decrease (< 0.01) in quality-adjusted life-years (QALYs), resulting in an incremental cost-effectiveness ratio of €56,997/QALY. The "Rapid Diagnosis Scenario" dominates usual care (ie, is both cheaper and more effective). For a willingness-to-pay threshold of €20,000/QALY the probability that the "DiagnOSAS Strategy" and "Rapid Diagnosis Scenario" are cost-effective equals 91.7% and 99.3%, respectively.

Conclusions: DiagnOSAS appears to be a cost-saving alternative for the usual OSA diagnostic strategy in The Netherlands. When DiagnOSAS succeeds in decreasing time to diagnosis, it could substantially improve health outcomes as well.

Keywords: obstructive sleep apnea, obstructive sleep apnea screening, cost-effectiveness analysis, cost-utility analysis

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Current challenges regarding the diagnostic process of obstructive sleep apnea (OSA) ask for alternatives for the current standard of care. Screening tools to rule out OSA in an early phase might be part of the solution. Health economic evaluations of such screening tools, however, are scarce. We evaluate the cost-effectiveness of DiagnOSAS, an OSA screening tool that strives to facilitate fast and well-informed referral to sleep clinics and hospitals for diagnosis.

Study Impact: When accounting for three major negative consequences of OSA, our analysis shows that integration of DiagnOSAS in the diagnostic process is likely to reduce health care cost in The Netherlands. When DiagnOSAS is able to also decrease time to diagnosis, as expected, health outcomes considerably improve as well.

INTRODUCTION

Obstructive sleep apnea (OSA) is a disorder characterized by repeated breathing pauses during sleep. Increased airway resistance results in complete (apnea) or partial (hypopnea) upper airway collapse.[1] OSA severity is measured by the average of apneas and hypopneas per hour of sleep, named the apnea-hypopnea index (AHI).[1] Gold-standard OSA diagnosis takes place via polysomnography (PSG) in sleep clinics or hospitals, where patients undergo a sleep test after referral by their general practitioner (GP).[2] A sleep test is an observation where, during a single night sleep, detailed information on sleep performance, gas exchange, respiration, heartbeat, body position, and muscle contraction and tone is collected.[3] Although OSA can be treated effectively, data suggest that there are still approximately 300,000 patients in whom the condition is undiagnosed and is consequently untreated in The Netherlands.[2] Untreated OSA is associated with an increased risk of accidents, as well as hazardous health effects.[1,4] Examples include cardiovascular diseases, diabetes, and dementia, resulting in significant health loss and high health care costs.[4]

GPs are not always aware of the symptoms associated with OSA.[5] In addition, the differential diagnosis of fatigue is extensive and includes both organic and psychological disorders. Consequently, patients are too often sent home with an alternative diagnosis or advice to improve sleep behavior. In

36% of Dutch patients with OSA, time between first GP visit and final diagnosis was more than 8 years.[6] A second problem regarding diagnosis is incorrect or unnecessary referral by GPs. One-third of the patients referred for sleep tests turn out to be OSA negative.[2] In the future, growing waiting lists for sleep tests are expected as a result of the aging community and an increase in body mass index of the Dutch population.[5] Although at-home polygraphy is the most common diagnostic strategy, supervised PSG monitored by a sleep technician in a sleep clinic or hospital still is the gold standard for diagnosis. The relative proportion of at-home polygraphy in diagnosing OSA in The Netherlands is 50%, compared to 22% for supervised PSG. Other diagnostic modalities used in The Netherlands are at-home PSG (relative proportion 20%) and in-hospital polygraphy (relative proportion 6%).[2] The absence of a simple screening tool currently impedes accessible possibilities to ascertain OSA as the cause for the patient's complaints, resulting in patients in whom the condition is undiagnosed, underdiagnosis in the general population, and long lead times to diagnosis. Consequently, there is an increased interest in alternatives for screening and diagnosis, such as questionnaires and portable sleep test devices, that may offer a rapid and efficient solution for the outlined diagnostic challenges.[7,8]

DiagnOSAS is a new OSA screening tool for GPs to estimate a patient's risk for having OSA. It strives to facilitate fast and well-informed referrals to hospitals or sleep clinics. DiagnOSAS consists of a digital questionnaire and a pulse oximeter. The questionnaire is based on questions extracted from three recognized OSA questionnaires: Berlin Questionnaire, STOP-BANG questionnaire, and Athens Insomnia Scale. Pulse oximetry is used to calculate the oxygen desaturation index (ODI) of a patient during sleep with a portable device. Recent work showed that ODI measurements by modern pulse oximeters were good predictors for excluding OSA.[9] Referral by the GP for further diagnosis in a sleep clinic or hospital depends on the combination of questionnaire answers and pulse oximetry score.

Cost-effectiveness studies permit comparison of health outcomes and costs of different strategies and have been applied to OSA before. However, previous OSA cost-effectiveness studies assumed that patients have already received a diagnosis and have been screened.[7,10] Therefore, consequences of years of no treatment until final diagnosis were not taken into account in existing literature. The significance of this study comes with the scarcity of cost-effectiveness studies incorporating effects of OSA screening. Furthermore, no earlier cost-effectiveness study focused on OSA screening by GPs. The objective of this study is to investigate the cost-effectiveness of DiagnOSAS in Dutch primary care.

METHODS

In a pilot study that focused on the effectiveness of DiagnOSAS, held in the Twente region in The Netherlands among patients (n = 77, 71% male) in whom the GP suspected OSA, the mean age of participants was 48 years (standard deviation 13.5 years). Interim results of this pilot show that at least moderate OSA (AHI ≥ 15 events/h), according to in-hospital PSG or polygraphy, was present in 43% of participants. In our study, the expected benefits of DiagnOSAS were simulated for a hypothetical cohort of 1,000 Dutch men aged 50 years in whom the GP suspected OSA. Prevalence of at least moderate OSA in this hypothetical cohort was set to 43%, similar to the observed prevalence. An AHI cutoff point of 15 events/h was used to define the presence of OSA in the main analysis of this study. The reason for this cutoff point, instead of using an AHI cutoff point of 5 events/h, is the lack of consensus about whether patients with an AHI below 15 events/h should be treated and the lack of a gold standard for treating these patients.[11,12] Although the decision analytic model was not optimized for patients with mild OSA, an additional analysis was performed based on DiagnOSAS performance in this subgroup and parameters available in literature for patients with OSA with an AHI of at least 5 events/h.[13,14] Cost-effectiveness was analyzed by estimating the incremental cost-effectiveness ratio (ICER). This ICER reflects a balance between health benefits, in terms of quality-adjusted life-years (QALYs) gained and additional costs required to realize these benefits. Because of the chronic nature of OSA, effects were assessed for 5 years and 10 years.

Model Structure

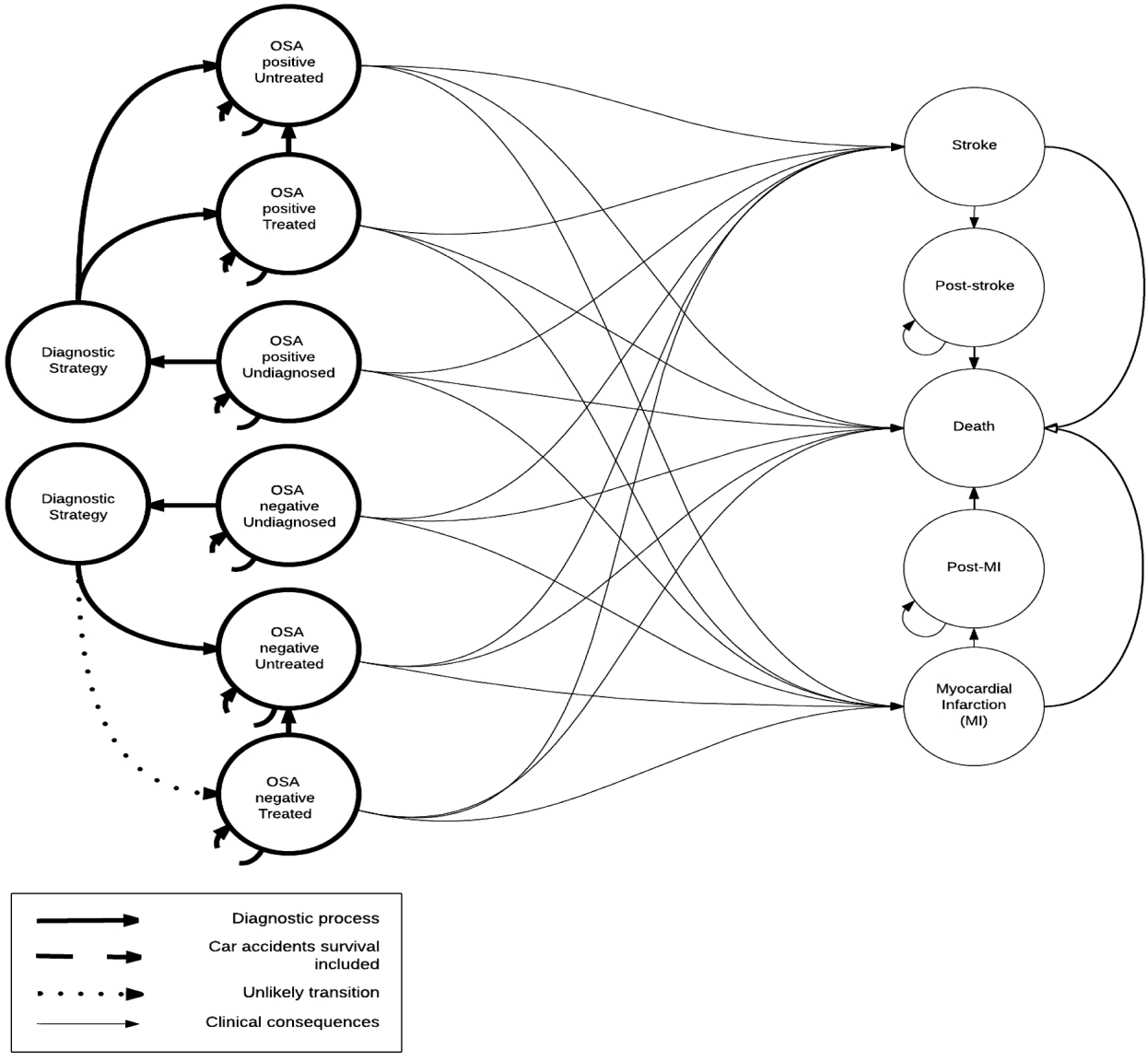
A Markov model was developed to assess cost-effectiveness. Three negative consequences of OSA were included: stroke, myocardial infarction (MI), and car accidents (CA). The model (**Figure 1**) was visualized and implemented to model the process from the time prior to actual diagnosis, followed by diagnostic testing, diagnosis, and treatment.

In the Markov model, patients were initially distributed over the states: "OSA positive Undiagnosed" and "OSA negative Undiagnosed." This is explained by the difference in risk of events for these two undiagnosed groups, which depends on whether or not OSA is present. Because probabilities for sending home or referral to sleep clinic depended directly on whether the patient had OSA, two diagnostic states were constructed as well. After diagnosis, patients ended up in 1 of the 4 mutually exclusive and collectively exhaustive post-diagnostic states: "OSA positive Untreated," "OSA positive Treated," "OSA negative Untreated" and "OSA negative Treated." Since patients needed a gold standard test before start of treatment, moving from the state "OSA negative Undiagnosed" to "OSA negative Treated" following the diagnostic process was expected to be highly unlikely. The probability of this transition was, therefore, set to zero. However, for the sake of completeness, this state was included in the visual representation of the model. In the four postdiagnostic states, patients were at risk of three negative consequences: CAs, stroke, and MI. After a CA, patients could die or remain in the same state. The assumption was made that patients fully recovered after a nonfatal CA and that the CA did not affect their diagnostic status or condition directly. After a nonfatal stroke or MI, patients ended up in a postevent state, in which they remained until death.

Strategies and Scenario

Two diagnostic strategies and an additional scenario were compared to investigate the cost-effectiveness of DiagnOSAS.

Figure 1—Markov model for the cost-effectiveness evaluation.



This Markov model was used for the cost-effectiveness evaluation of DiagnOSAS. The model represents the process from first OSA-related GP visit to therapy. Two clinical consequences of OSA are included: MI and stroke. Furthermore, car accident risk was included in the undiagnosed, treated and untreated stages. This model was run for the two strategies ("Usual Care Strategy" and "DiagnOSAS Strategy") and the "Rapid DiagnOSAS Scenario" separately. GP = general practitioner, MI = myocardial infarction, OSA = obstructive sleep apnea.

"Usual Care Strategy"

In this strategy, all patients suspected of OSA were referred for the gold-standard diagnostic test: PSG (in a sleep clinic or hospital). Average time to referral was 5.35 years, derived from statistics of the Dutch Apnea Association.[6]

"DiagnOSAS Strategy"

In this strategy all patients suspected of OSA filled in a questionnaire and slept a single night wearing a pulse oximeter in the comfort of their own bed. Referral for further diagnostics based on PSG depended on the combination of questionnaire and overnight pulse oximetry results. Referral for further diagnostics was omitted in patients in whom potential OSA seemed unlikely according to DiagnOSAS' test characteristics (Appendix I, supplemental material). All other patients were referred to a sleep clinic for further diagnostics based on PSG. Time to referral was assumed to be as long as in "Usual Care Strategy," due to the very short duration of the screening pathway and absence of waiting lists.

"Rapid Diagnosis Scenario"

Because DiagnOSAS strives to speed up the diagnostic process, a scenario in which DiagnOSAS would result in 50% shorter time between first GP visit and referral for sleep tests (2.68 years) was evaluated separately. Again, only referral was omitted in patients in whom potential OSA seemed unlikely.

Table 1—Evidence used in the simulation model.

Parameters	Base Case Value	SD	Distribution	Source
Cohort characteristics				
Sex	Male			
Age	50 years			
OSA prevalence (AHI ≥ 15 events/h)	43%	0.06	Beta	DiagnOSAS pilot*
Test characteristics				
Sensitivity PSG	1	Fixed		Gold standard
Specificity PSG	1	Fixed		Gold standard
Sensitivity DiagnOSAS	0.97	0.03	Beta	DiagnOSAS pilot*
Specificity DiagnOSAS	0.47	0.07	Beta	DiagnOSAS pilot*
Average time to diagnosis	5.35 (years)	Fixed		6
Scenario time to diagnosis	2.68 (years)	Fixed**		6
Probabilities				
Car accident	0.0461	0.00006	Beta	19, 20
Probability car accident is fatal	0.00035	0.00003	Beta	19, 28
Stroke (per 1000 person-years)	1.30	0.08	Normal	21
MI (per 1000 person-years)	2.66	0.02	Normal	22
Adjusted all-cause mortality (age- and sex-specific)	0.000574	Fixed		15–18
CPAP nonadherence (annual)	0.023	0.003	Normal	27
OSA-related risks				
Untreated OSA	*Compared to healthy individuals*			
Car accident (relative risk)	2.43	0.36	Log.Norm	14
Stroke (hazard ratio)	3.48	0.03	Log.Norm	23
MI (hazard ratio)	3.06	0.08	Log.Norm	23
CPAP-treated OSA	*Compared to healthy individuals*			
Car accident (risk ratio)	1.29	0.43	Log.Norm	26
	Compared to untreated OSA			
MI (relative risk)	0.54	0.17	Log.Norm	24
Stroke (relative risk)	0.27	0.10	Log.Norm	25
Stroke				
1-year case fatality (probability)	0.21	0.04	Normal	30
All-cause mortality (hazard ratio)	3.9	0.10	Log.Norm	31
MI				
1-year case fatality (probability)	0.07	0.005	Normal	29
All-cause mortality (hazard ratio)	1.47	0.16	Log.Norm	32

* = parameter value is based on the interim results of a DiagnOSAS pilot; final results are not published at the time of writing (October 2017). ** = time to diagnosis in the "Rapid Diagnosis Scenario" was fixed at 2.68 years in nearly all analyses, except for the univariate sensitivity analyses in appendix IV of the supplemental material; here, multiple times to diagnosis were tested. CPAP = continuous positive airway pressure, MI = myocardial infarction, OSA = obstructive sleep apnea, PSG = polysomnography, SD = standard deviation.

Time Horizon

Results were reported for time horizons of 5 and 10 years, applying a 1-year time cycle. Such longer time horizons are necessary when also including years prior to diagnosis and when interested in long-term effects of diagnostic strategies followed by treatment. A lifetime analysis was not performed because of lack of evidence on long-term continuous positive airway pressure (CPAP) adherence and the lack of evidence on age-specific CA risks and fatality in individuals at older age.

Model Parameters

An overview of all model parameters used for the analysis, and the corresponding evidence sources, is shown in **Table 1**. Corresponding utilities and costs used are shown in **Table 2**.

Diagnostic Performance

Because PSG in a hospital or sleep clinic is the gold standard, its diagnostic performance was assumed to be perfect in terms of sensitivity and specificity. The characteristics of DiagnOSAS were investigated during a pilot. GPs who participated in the pilot were instructed to enroll patients suspected of OSA. After enrollment, the DiagnOSAS team actively contacted patients. Patients who fulfilled inclusion criteria received the DiagnOSAS questionnaire and the pulse oximeter. Based on 24 questions regarding the patient's health state and sleep behavior, the questionnaire resulted in a low, intermediate, or high risk profile. The pulse oximeter provided the patient's ODI, measured during a single night. In practice, the combination of risk profile and ODI would be

Table 2—Utilities and costs used in the simulation model.

Parameters	Base Case Value	SD	Distribution	Source
Utilities				
General Dutch population, age specific	0.86	0.01	Beta	33
Untreated OSA	0.74	0.05	Beta	34
Treated OSA	0.81	0.03	Beta	34
Stroke	0.64	0.02	Beta	35
Poststroke	0.67	0.01	Beta	36
MI	0.67	0.02	Beta	37
Post-MI	0.82	0.01	Beta	37
Costs				
DiagnOSAS costs (one-time)	€120	Fixed		DiagnOSAS board
PSG costs (once)	€1,424	€59	Normal	39
CPAP costs (annually)	€643	€31	Normal	39
Nonfatal car accident costs (once)	€13,446	€3,430	Gamma	40
Fatal car accident costs (once)	€2,371,917	€678,762	Gamma	40
First year costs stroke	€19,081	€2,235	Normal	41
Subsequent years costs stroke (annually)	€3,422	€262	Normal	44
First-year costs MI	€14,561	€1,218	Normal	43
Subsequent years costs MI (annually)	€1,507	€463	Gamma	43

CPAP = continuous positive airway pressure, MI = myocardial infarction, OSA = obstructive sleep apnea, PAP = positive airway pressure, PSG = polysomnography, SD = standard deviation.

used to determine whether referral for an in-hospital sleep study would be necessary, according to DiagnOSAS' test characteristics (Appendix I, supplemental material). However, in the pilot study all included patients underwent a sleep study in the Medisch Spectrum Twente Hospital, Enschede, The Netherlands to enable comparison of screening with and without DiagnOSAS. Performance of the combination of the questionnaire and pulse oximetry was based on a comparison with patients' in-hospital sleep study (PSG or polygraphy) results. The diagnostic performance of a strategy in which DiagnOSAS was used as a screening tool was based on the interim results of this DiagnOSAS pilot, under the assumption that GPs used DiagnOSAS as envisioned by the developers.

Treatment Effect

Mortality risks in healthy individuals were derived from Statistics Netherlands.[15–18] To prevent double counting, the overall risk of dying (from other causes) was corrected for disease-specific mortality risks of stroke and MI, as well as the risk of a fatal CA. When available, age- and sex-specific rates were used. CA risk was based on statistics of the insurers federations and Statistic Netherlands.[19,20] Age- and sex-specific risks of stroke and MI were retrieved from Dutch population studies.[21,22] Based on prior studies on OSA consequences, risks of CAs, stroke, and MI in patients with OSA were calculated.[14,23] All patients with a positive diagnosis of OSA received CPAP treatment. Effects of CPAP on event risk were based on recent literature on the effects of CPAP in patients with OSA.[24–26] Furthermore, a transition from treated to untreated was included in the model, because it has been shown that CPAP adherence is not perfect among patients.[27] The annual probability of stopping CPAP treatment was derived from earlier research on 10-year CPAP adherence.[27] The assumption was made that the annual discontinuation rate was constant across the 10-year period.

Negative Consequences

A literature study was performed in order to investigate negative consequences of OSA. Literature in PubMed and Scopus was searched for OSA-related negative effects. Keywords used included "sleep apnea," "apnea," or "OSAS." To investigate negative consequences, the search terms "effects" and "consequences" were used. In published literature, many connections between OSA and negative consequences are described. However, for only three consequences sufficient data were available to allow incorporation into the Markov model: CA, stroke, and MI. Not all reported negative consequences were therefore included. The probability of having a fatal CA was derived from recent evidence on the number of drivers who died due to a car accident in The Netherlands.[28] Those with stroke or MI could die immediately, die within 1 year following the initial event, or end up in a postevent state. The probability of not surviving the first year was based on large-scale population studies.[29,30] Probabilities of dying in a postevent state were based on all-cause long-term mortality studies in stroke and MI survivors.[31,32]

Health Outcomes

During the simulation, patients moved from undiagnosed states to other states in the model. In these different states, patients experienced different health outcomes. Health outcomes are expressed in QALYs, which are based on quality-of-life values (utilities) combined with the duration for which

a particular quality of life is experienced. Age-specific utilities reported for the Dutch general population were used for the OSA-negative states.[33] To enable calculation of the ICER, health outcomes were expressed in QALYs by multiplying the utilities and person-years spent per state. Utilities for undiagnosed OSA and CPAP-treated OSA were based on literature.[34] Utilities for untreated OSA were considered the same as undiagnosed OSA. OSA-negative undiagnosed and OSA-negative (un)treated patients were assumed to be healthy individuals and were given age-specific general population utilities. Utilities for acute stroke and MI as well as long-term poststroke and post-MI were based on prior studies regarding utility scores among those with MI and stroke.[35–37] When utilities in literature were based on a population with an age different from the age of our study's population, utilities were adjusted by using a ratio based on age-specific utilities in the Dutch general population and disease-specific utilities.[33] Health outcomes were discounted at 1.5% annually according to Dutch guidelines for health economic evaluations.[38]

Costs

Costs were analyzed based on the third-party payer's perspective and expressed in euros (€). At the time of this writing, one euro was equivalent to 1.17 United States dollars. Only direct medical costs were taken into account. When available, literature based on Dutch data was used for costs.[39–41] All costs were adjusted to 2017 by using the Dutch consumer price index levels as provided by Statistics Netherlands.[42] Costs associated with MI, post-MI, and poststroke in The Netherlands were not available and were therefore obtained from German and Swedish literature.[43,44] First-year stroke costs were based on total health care costs 1 year after stroke as studied in a Dutch population.[41] German research was used for estimating the yearly costs in the post-stroke state.[44] MI costs for the first year and subsequent years were based on Swedish data.[43] The youngest patient group in this study consisted of patients younger than 74 years. Costs for this group were used in the base case population age 50 years. Although costs might be overestimated by using this study, there was a lack of contemporary alternatives that consisted of a more representative population. Swedish costs were converted to euros (€) from Swedish Kronor (SEK) reported by the authors of the original article using exchange rate €1 = SEK 9.33 (2014). Furthermore, German and Swedish costs were corrected for country-specific inflation to obtain 2017 estimates. Costs other than those related to diagnosis, treatment, CA, MI, and stroke were not included. Costs in the undiagnosed and (un)treated states also included the costs of CA, weighted by the actual CA risk. CA costs were derived from the Dutch Ministry of Infrastructure and Environment.[40] Costs of CAs depended on whether the CA was fatal or nonfatal and consisted of medical costs, production loss, material costs, and administration costs. The sum of these costs was divided by the number of car accidents in The Netherlands in order to obtain per-accident costs.[19] Diagnostic costs differed per strategy chosen, depending on the number of patients in whom referral was omitted based on the results of DiagnOSAS. The cost of DiagnOSAS was determined after consultation with the DiagnOSAS developers. Annual treatment costs with CPAP and PSG costs were based on price lists of Dutch hospitals.[39] Price estimations were made by calculating average selling price based on 12 Dutch hospitals of different sizes, selecting one representative hospital per province. Costs were discounted at 4.0% annually according to Dutch guidelines for health economic evaluations.[38]

Sensitivity Analysis

A Monte Carlo simulation with 5,000 samples was performed to generate samples of health outcomes and costs for the "Usual Care Strategy," "DiagnOSAS Strategy" and "Rapid Diagnosis Scenario." For the 5-year and 10-year horizon, average expected costs and health gains per patient were calculated to determine ICERs. The outcomes of the probabilistic sensitivity analyses were plotted in incremental cost-effectiveness planes. When total costs were lower and the health effects in terms of QALYs were larger than in the "Usual Care Strategy," the strategy was considered dominant. To illustrate how the chance that DiagnOSAS is cost-effective varies with the applied willingness-to-pay (WTP) threshold, cost-effectiveness acceptability curves (CEACs) were constructed. These curves were derived from the incremental cost-effectiveness planes and show the proportion of samples that would have an acceptable cost-effectiveness given a specific WTP threshold. Furthermore, the sensitivity of the results to the values of specific parameters was assessed in univariate sensitivity analysis and visualized in tornado diagrams.

RESULTS

Base Case

Table 3 shows the mean values for costs, QALYs, and ICERs for the two diagnostic strategies and the additional scenario. The high ICERs of the "DiagnOSAS Strategy" compared to the "Usual Care Strategy" of €136,827 (after 5 years) and €56,997 (after 10 years) result from a minimal decline in QALYs at a substantial decrease in costs per patient. These cost savings against a minimal QALY change were also seen in the years prior to year 5, see Appendix II in the supplemental material for base case results after 2 years. When the "Rapid Diagnosis Scenario" is compared with "Usual Care Strategy," health gains are realized and costs are saved, after 5 years as well as 10 years. This indicates that when DiagnOSAS implementation speeds up the diagnostic process by 50%, the "Usual Care Strategy" is dominated by the "Rapid Diagnosis Scenario." Base case results for the additional analysis for patients with at least mild OSA (AHI ≥ 5 events/h) are available in Appendix III in the supplemental material.

Incremental Cost-Effectiveness Planes

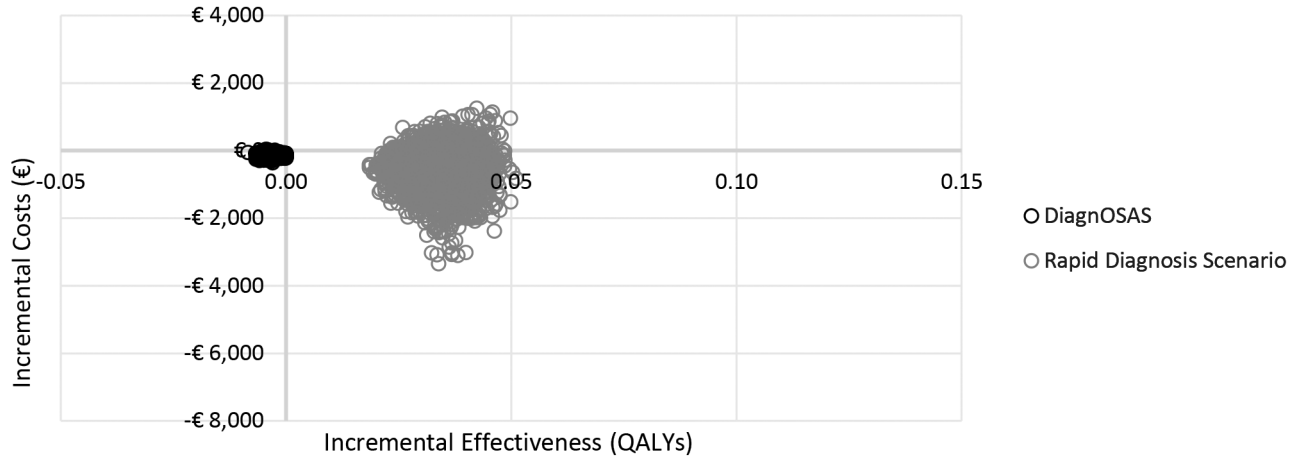
The incremental cost-effectiveness planes are shown in **Figure 2** and **Figure 3**. **Figure 2** displays the comparison of the "DiagnOSAS Strategy" and the "Rapid Diagnosis Scenario" with the "Usual Care Strategy" after 5 years. The "DiagnOSAS Strategy" resulted in lower costs than the "Usual Care Strategy," as most of the simulated samples fell in the lower left

Table 3—Base case results.

Diagnostic Strategy	Average Cost Per Patient (€)	Average QALYs Per Patient	Incremental Cost-Effectiveness Ratio: • DiagnOSAS Strategy versus Usual Care Strategy • Rapid Diagnosis Scenario versus Usual Care Strategy
After year 5			
Usual Care Strategy	9,602	4.22	
DiagnOSAS Strategy	9,455	4.22	€136,827/QALY gained
Rapid Diagnosis Scenario	9,136	4.25	Dominant
After year 10			
Usual Care Strategy	21,275	8.76	
DiagnOSAS Strategy	21,049	8.76	€56,997/QALY gained
Rapid Diagnosis Scenario	20,571	8.84	Dominant

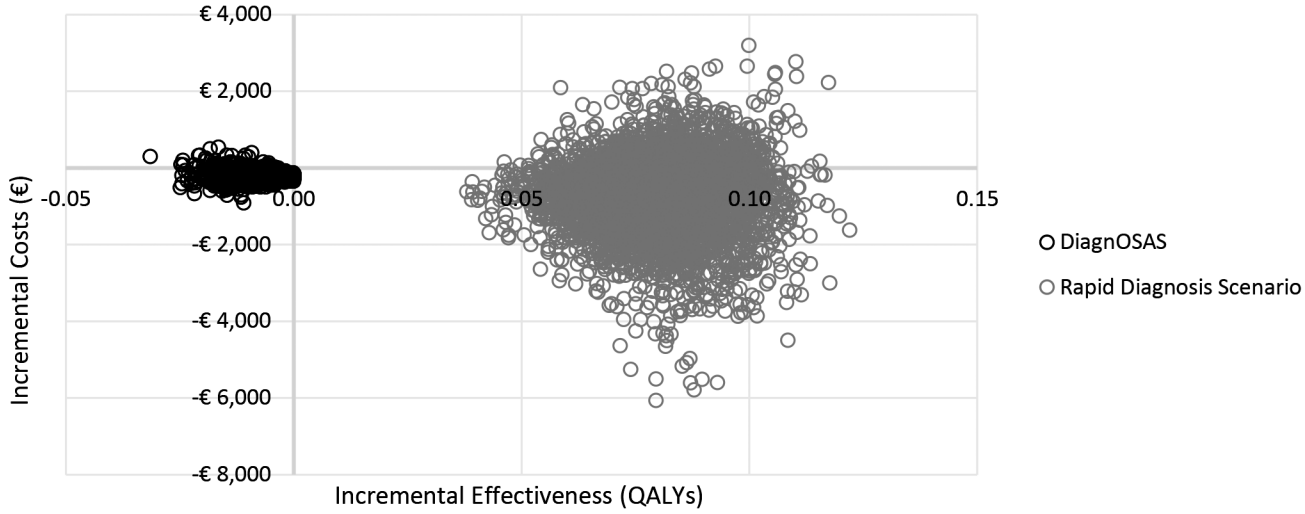
Base case cost-effectiveness of "DiagnOSAS Strategy" and "Rapid Diagnosis Scenario" compared to "Usual Care Strategy," based on 5,000 Monte Carlo simulated samples. QALY = quality-adjusted life year.

Figure 2—Incremental cost-effectiveness plane after 5 years.



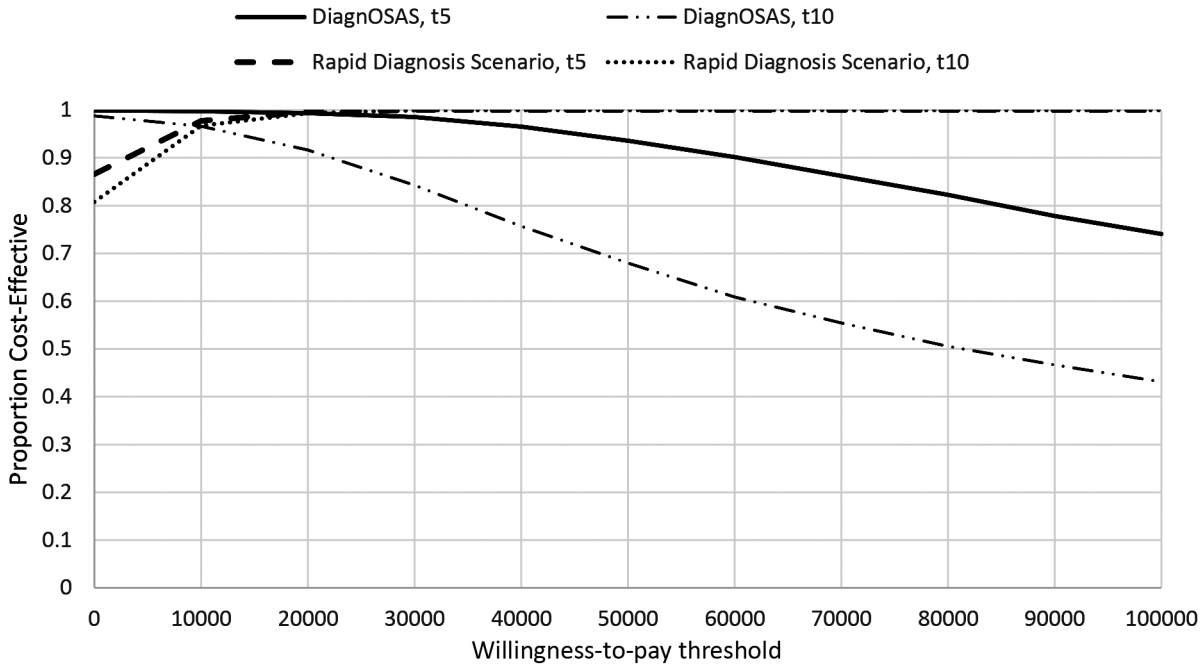
Incremental cost-effectiveness plane of 5,000 Monte Carlo simulated samples comparing "DiagnOSAS Strategy" and "Rapid Diagnosis Scenario" to "Usual Care Strategy" after 5 years. Incremental effectiveness was expressed in quality-adjusted life-years (QALYs), where costs were expressed in euros (€).

Figure 3—Incremental cost-effectiveness plane after 10 years.



Incremental cost-effectiveness plane of 5,000 Monte Carlo simulated samples comparing "DiagnOSAS Strategy" and "Rapid Diagnosis Scenario" to "Usual Care Strategy" after 10 years. Incremental effectiveness was expressed in quality-adjusted life-years (QALYs), where costs were expressed in euros (€).

Figure 4—Cost-effectiveness acceptability curves.



Cost-effectiveness acceptability curves of the "DiagnOSAS Strategy" and the "Rapid Diagnosis Scenario" after 5 and 10 years compared to the "Usual Care Strategy" at different willingness-to-pay thresholds (expressed in QALYs, quality adjusted life years). The complement of each cost-effectiveness acceptability curve is equal to the "Usual Care Strategy" probability of being cost-effective at a specific threshold. QALY = quality-adjusted life-year, t5 = 5 years, t10 = 10 years.

quadrant, indicating lower costs at lower effectiveness. In almost all simulated samples, the "DiagnOSAS Strategy" saves several hundred euros (mean cost saving €147), whereas health outcomes remained similar (mean reduction 0.001 QALYs). When comparing the "Rapid Diagnosis Scenario" to the "Usual Care Strategy," the "Rapid Diagnosis Scenario" was more effective (mean increase 0.03 QALYs) and less expensive (mean cost saving €465) in most simulated samples. When a 10-year time horizon is applied (**Figure 3**), simulated samples displayed more variation. However, most of the "DiagnOSAS Strategy" outcomes (99%) still save costs against a minimal reduction in effectiveness. When comparing the "Rapid Diagnosis Scenario" to the "Usual Care Strategy" after 10 years, again, most of the simulated samples (81%) indicated higher effectiveness at lower costs. The remaining simulated samples fell in the upper right quadrant and thus also indicated health benefits. Tornado diagrams of the results' sensitivity to the values of specific parameters are visualized in Appendix IV in the supplemental material.

Cost-Effectiveness Acceptability Curves

The CEACs in **Figure 4** illustrate how the probability that the "DiagnOSAS Strategy" is cost-effective varies with the applied WTP threshold. The proportion of simulated samples deemed cost-effective were plotted against WTP thresholds ranging from €0 to €100,000 per QALY. In The Netherlands, a €20,000/QALY WTP threshold is advised for illnesses with a low burden of disease.[45] At this WTP, the probability that the "DiagnOSAS Strategy" is cost-effective equals 99.3% and 91.7% at 5 and 10 years, respectively.[45] For an €80,000/QALY WTP threshold, advised for illnesses with a high burden of disease, these probabilities are 82.2% and 50.6%, respectively.[45] Looking at the CEACs for the "Rapid Diagnosis Scenario," 99.6% and 99.3% of the simulated samples are cost-effective at a WTP threshold of €20,000/QALY for years 5 and 10, respectively. Furthermore, all simulated samples (100%) are cost-effective at the €80,000/QALY threshold at 5 and 10 years for the "Rapid Diagnosis Scenario."

DISCUSSION

The growing recognition of OSA as a serious health condition, increasing waiting lists for sleep tests, and a high proportion of unnecessary referrals by GPs all are factors that indicate the urgent need for alternative diagnostic strategies for OSA to lower costs and improve access to treatment.[2,5,6] The objective of this study was to investigate the cost-effectiveness of DiagnOSAS, a screening tool that strives to facilitate accurate and fast referral to hospitals and sleep clinics for OSA diagnosis in The Netherlands. By applying a Markov model, this study showed that implementing DiagnOSAS in the GP's practice can lead to significant cost savings of over €200/patient without compromising health outcomes. This was confirmed in incremental cost-effectiveness planes, where most simulated samples for the "DiagnOSAS Strategy" fell in the lower half. In addition, the 95% confidence interval of the simulated samples after 10 years had 0.01 QALYs loss as lower boundary

(ie, highest loss). Even more promising were the results of the "Rapid Diagnosis Scenario," in which DiagnOSAS was assumed to halve the time to diagnosis. The "Rapid Diagnosis Scenario" not only resulted in noteworthy cost reductions, but also in substantial health gains.

Cost-effectiveness acceptability curves showed that DiagnOSAS has high chance of being cost-effective at relative low WTP thresholds, even if it would not affect time to diagnosis. At higher WTP thresholds, however, the chance that the "DiagnOSAS Strategy" would be cost-effective decreases somewhat. Conversely, in the "Rapid Diagnosis Scenario," this chance increased to 100% with increasing WTP. The drop of the "DiagnOSAS Strategy" curves can be explained by the fact that the diagnostic performance of a strategy in which DiagnOSAS is used as screening tool is slightly worse than that of the gold standard. Although the "DiagnOSAS Strategy" leads to cost reductions, such cost savings have limited effect for higher societal WTP thresholds, where strategies only appear favorable if they have 100% chance to result in health improvements.

The fact that DiagnOSAS performs slightly worse than PSG in hospitals and sleep clinics deserves further explanation. At the moment, PSG under the supervision of a sleep technician is the gold standard for OSA diagnosis. Because the performance of DiagnOSAS was measured in a direct comparison with the gold standard, by definition, DiagnOSAS could not outperform the gold standard in terms of sensitivity and specificity. This is why DiagnOSAS cannot, in our analysis, lead to improved health outcomes (QALY gains), unless shorter time to diagnosis is assumed. It should be noted that, without exception, the observed discrepancies were due to minor differences in AHI as interpreted by DiagnOSAS and PSG. Yet, in patients with an AHI near the cutoff value (AHI ≥ 15 events/h), even subtle differences could easily result in false-negative and false-positive results. Future research should show to what extent diagnostic strategies in which DiagnOSAS is used as a screening tool are, in fact, inferior to current gold-standard diagnoses, or if they may be superior instead. For now, however, the results show that even with a slightly lower diagnostic performance than the gold standard, the "DiagnOSAS Strategy" and "Rapid Diagnosis Scenario" are very likely to be cost-effective compared to usual care.

Prior studies have evaluated OSA screening as well. Different studies validated the use of questionnaires and monitoring devices in potential patients with OSA.[7,46] Most studies focused on the accuracy of screening methods and concluded that OSA screening can be of great value in the future. Yet, the comparison of cost and effects of different OSA screening strategies is rarely made. Because most OSA cost-effectiveness studies start at the point where patients have already received a diagnosis, the role of the GP in OSA diagnosis and screening is often ignored. In France, however, research has been conducted into the cost-effectiveness of a screening strategy in which the GP and community pharmacists collaborated closely.[10] Patients were screened by community pharmacists before visiting their GP. The collaboration was considered to be cost-effective by the researchers and indicated that there is potential in improving the process prior to the final diagnosis, as also corroborated by our results.

In our additional analysis on patients with mild OSA (AHI = 5–15 events/h), with DiagnOSAS sensitivity reduced to 86% compared with 97% in the original analysis, a more prominent reduction in effectiveness and higher costs was found for the "DiagnOSAS Strategy" compared with "Usual Care Strategy." For the "Rapid Diagnosis Scenario," however, results for mild OSA were quite similar to those for severe OSA. However, caution in the interpretation of these results is necessary, as our model was not optimized for patients with mild OSA. When optimal treatment of mild OSA is agreed upon, an additional cost-effectiveness study of DiagnOSAS in this population is of interest and could be performed rapidly.

The performed model-based analysis has some limitations. Our study focused on a hypothetical cohort of 1,000 men aged 50 years in whom the GP suspected OSA. Characteristics of this cohort and the performance of DiagnOSAS in this cohort were compiled on the basis of a previously performed DiagnOSAS study. The analysis therefore did not include patients who were asymptomatic or did not recognize OSA symptoms (and therefore did not visit a GP), women, children, and elderly persons. Therefore, caution is required for this study's generalizability to other populations. Additional research into the performance and cost-effectiveness of DiagnOSAS in these excluded patient groups would thus be of added value. This is especially true for patients with OSA who are asymptomatic or do not recognize their symptoms being related to OSA. Indeed, of the white-collar employees in whom OSA was confirmed using PSG following in-company OSA screening in The Netherlands, up to 78% had not recognized their symptoms beforehand.[47] Moreover, data from a study in a randomly selected population of 1,522 employed participants (aged 30–60 years, 55% male) suggested that more than half of the participants with moderate to severe OSA did not recognize their symptoms.[48] These studies suggest that screening might also be promising for early OSA diagnostics in patients without manifested OSA-related complaints. Especially, patients with multiple risk factors for OSA may be an attractive subgroup for OSA screening in asymptomatic individuals.

An additional study on the performance of DiagnOSAS in a population with participants who do not recognize or do not have OSA-related symptoms would be interesting. In particular, given the potential selection bias that might have occurred in our study, the DiagnOSAS screening tool was used by patients in whom the GP already suspected OSA. Furthermore, one could question the added value of the questionnaire in this preselected population, that it is likely to have affirmative answers in the questionnaire. Testing DiagnOSAS as a screening tool in a broader population might thus be useful to prevent selection bias and could be meaningful in order to evaluate the utility of the questionnaire as well.

Another limitation was the necessary use of assumptions in our analysis, with the core assumption being that GPs would use DiagnOSAS for decision-making and referral as envisioned by the developers. This means that DiagnOSAS is used in all patients with OSA-related complaints, and referral is dependent on the results that follow from the questionnaire and pulse oximetry. It is conceivable, however, that GPs would use DiagnOSAS differently. For example, by not using the tool in all patients with OSA-related complaints, but using

DiagnOSAS only when GPs themselves feel uncertain about the risk of OSA, may affect cost-effectiveness outcomes. The only way to find out whether the assumptions on DiagnOSAS use are reasonable is to perform a pragmatic health economic trial focusing on the actual use of DiagnOSAS by GPs in their daily working environment. In addition to the assumptions on DiagnOSAS use by GPs, CPAP treatment was assumed to be provided to all patients with OSA. In patients with mild and moderate OSA, however, mandibular repositioner appliance treatment is used as well.[12] Because studies show that both treatments do not differ widely in effectiveness, this assumption might at most have led to an overestimation of treatment costs, as CPAP is more expensive than mandibular repositioner appliance treatment.[12,49,50] Because DiagnOSAS leads to more patients being treated with CPAP when time to diagnosis is reduced, the overestimation of treatment costs might have led to an underestimation of the total cost reduction in this scenario.

The beneficial effects of timely OSA diagnosis and treatment are in a direct way experienced by the patient through improved sleep quality and reduced exposure to OSA-related risks, resulting in a higher quality of life. Because OSA is still undiagnosed in approximately 300,000 patients in The Netherlands, the savings of several hundreds of euros per patient and potential health gains induced by DiagnOSAS emphasize the importance of implementation of timely diagnosis.[5] In addition, on a societal level, accessible OSA screening is expected to reduce the number of CAs through offering adequate treatment to patients with OSA in whom the condition was previously undiagnosed. In addition to saving lives, societal costs could be reduced substantially as well given the fact that total costs of CAs in the Netherlands were €12.5 billion in 2009.[40] The model used in this article only included stroke and MI as clinical consequences of OSA. Recent studies, however, also showed a possible relationship between OSA and depression, type 2 diabetes, hypertension, and heart disease other than MI.[4] Therefore, it is likely that the health gains and cost reductions reported here partly underestimate the true benefits of DiagnOSAS in practice. Because literature on these relationships did not contain all necessary quantitative evidence, these consequences could not yet be included in our analysis.

In conclusion, the cost-effectiveness analysis presented in this article investigates the process from first OSA-related GP visit to OSA therapy, taking into account OSA-related negative consequences CA, MI, and stroke. Implementation of DiagnOSAS appears to be a cost-saving addition to the usual diagnostic strategy in The Netherlands. Taking into account that DiagnOSAS might realize a decrease in time to diagnosis, this screening tool could substantially improve health outcomes as well. Furthermore, when future research shows that the performance of DiagnOSAS is not inferior to the current gold standard, the expected benefits of DiagnOSAS would increase even further.

ABBREVIATIONS

AHI, apnea-hypopnea index
CA, car accident
CEAC, cost-effectiveness acceptability curve
CPAP, continuous positive airway pressure
GP, general practitioner
ICER, incremental cost-effectiveness ratio
MI, myocardial infarction
ODI, oxygen desaturation index
OSA, obstructive sleep apnea
PSG, polysomnography
QALYs, quality-adjusted life-years
SEK, Swedish Kronor
WTP, willingness-to-pay

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