Final report

Cost-of-illness study of Obstructive Sleep Apnea Syndrome (OSAS) in Italy

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Executive summary

Obstructive sleep apnea (OSA) is caused by complete or partial obstruction of the upper airway and has been demonstrated to be a risk factor for several diseases and to be correlated with other non-medical consequences that increase OSA's clinical and economic burden. In Italy the impact of OSA, and its syndrome (OSAS), is highly underestimated by policy-makers, clinicians and general population, also due to substantial diagnosis gaps. To our knowledge, this is the first study aimed at assessing the societal economic burden of OSA(S) in Italy by performing a cost-of-illness (COI) analysis, estimating also the economic consequences of undiagnosed and untreated OSA(S) and assessing the benefits brought by higher diagnosis rates and more appropriate treatment pathway.

Through a literature review and expert opinion, we estimated a prevalence of 12,329,614 moderate-severe OSA(S) patients in Italy (27% of the adult population), of which 65% males, and an overall prevalence of more than 24 million people aged 15 to 74 years old (54% of the adult population). On the basis of expert opinion and data provided by the Italian association of apneic patients, we estimated that only 460,000 moderate-severe patients are diagnosed (4% of the estimated prevalence) and 230,000 treated (2% of the estimated prevalence), suggesting a substantial gap in both diagnosis and treatment.

In order to estimate the burden of OSA(S) in Italy, we first defined the boundaries of OSA(S) in terms of conditions significantly influenced by the disease. We performed a systematic literature review limited to systematic reviews and meta-analyses, whose results were validated and integrated by clinicians from different disciplines involved in a consensus board. Among clinicians, there was high consensus on most of the identified conditions. For some conditions, clinicians reported heterogeneous opinions, reflecting the uncertainty found in the literature around the boundaries of OSA(S). Ultimately, we found 22 clinical (e.g. diabetes) and non-clinical (e.g. car accidents) conditions significantly associated with OSA(S), which were included in COI analysis. Through the population attributable fraction (PAF) methodology, and using the data on the magnitude of association and prevalence of the conditions, we estimated the proportion of each condition that is associated with the presence of OSA(S).

For the purposes of the present study, we considered OSA(S) as a risk factor, among others, of other costly conditions and we estimated all the costs associated with conditions attributable to OSA(S) found in the previous literature step. A comprehensive literature review was conducted to retrieve cost studies for included conditions. According to data availability, we included all direct (healthcare and non-healthcare) and indirect costs. Proportionally to the degree of association of each condition, a part of their estimated total costs was attributed to OSA(S) with a top-down approach using the PAF methodology. Results suggest that the economic burden due to conditions associated with OSA(S) in Italy is substantial and is approximately equal to 31 billion Euros per year, i.e. around 520 Euros per Italian resident. The main drivers of economic burden are direct healthcare costs, which account for 60% of total cost, followed by indirect costs due to morbidity (36%) and direct non-healthcare costs (4%). The mean annual cost per moderate-severe OSA(S) patient is approximately 2,500 Euros. Productivity losses due to premature death (for all causes) related to OSA(S) amount to more than 17 million Euros per year, around 1,570 Euros per dead patient. Literature suggests that the burden of OSA(S) in terms of quality-adjusted life years (QALYs) lost due to OSA(S) is substantial and we estimated that the cost for the society of impaired quality of life due to OSA(S) undertreatment is approximately 9 billion Euros in one year.

Through a comprehensive literature review, we identified studies investigating the effect of continuous positive airway pressure (CPAP) on the conditions included in COI, which found a beneficial and significant impact of CPAP on mortality, risk of stroke, car and work-related accidents. Using data on risk reduction, we simulated different scenarios in order to estimate what would happen to the economic burden influenced by OSA(S) if an increased number of OSA(S) patients were diagnosed and subsequently treated with CPAP. Although an increase in direct healthcare costs could be observed due to increased costs related to higher number of diagnosed and treated of OSA(S) patients, we found that CPAP treatment could diminish the costs of conditions associated, due to lower risk of condition onset. In addition, the more patients treated, the higher the QALYs value gained due appropriate diagnostic and therapeutic pathway, which would ultimately lead to gained value for the whole society.

To summarize, this study aimed at providing reliable estimates of the extent of OSA(S) consequences and its economic burden in Italy. Results suggest that the burden is substantial,

also due to low treatment rates. More appropriate diagnosis rates and clinical pathways for OSA(S) patients, in particular for moderate-severe population, are recommended in order to decrease the clinical and economic burden of disease. The final objective of this study is to increase awareness of the disease burden, both by a clinical and an economic point of view, and inform evidence-based policies, fundamental to ensure appropriate and sustainable therapeutic pathways for patients.

1 Background

Obstructive sleep apnea (OSA) is a respiratory disorder characterized by repeated upper airway partial (hypopnea) or total (apnea) obstruction, causing sleep fragmentation, hypoxemia and consequent daytime fatigue and sleepiness [1, 2]. The term obstructive sleep apnea (OSA) refers to objective laboratory findings, while the term obstructive sleep apnea syndrome (OSA(S)) refers to the combination of the laboratory finding with the clinical consequences related to the disease (e.g. daytime sleepiness) [3]. Diagnosis of OSA(S) usually requires overnight polysomnography (PSG) in order to detect the frequency of disordered breathing events [4]. The number of apnea and hypopnea events per hour of sleep, termed as apnea-hypopnea index (AHI), defines disease severity: the mild form entails 5 to 15 events per hour, moderate 15 to 30 events per hour and severe more than 30 events per hour [5, 6]. OSA(S) is positively correlated with age and male sex and to risk factors such as obesity [6]. Several studies found that OSA(S) is associated with an increased risk of diabetes [7-9], some cancer types [10, 11], and cardiovascular and cerebrovascular diseases [12] such as hypertension [13-16], coronary artery disease [17-19] and stroke [20-23]. Moreover, OSA(S) is associated with decreased quality of life (QoL) [24-26], impaired work performance [27-29] and increased risk of road traffic accidents [30, 31]. According to several population-based studies, prevalence of OSA(S) is relatively high, approximately 3–7% for adult males and 2–5% for adult females in the general population [32-36]. However, methodological differences and difficulties in characterizing this syndrome yielded to variability in estimates [37, 38]. Moreover, it is estimated that only about 40% of patients with OSA(S) are diagnosed, which can lead to underestimation of disease prevalence [39, 40]. Given the high prevalence of the disease, the clinical and economic burden of OSA(S) seems substantial. Several studies assessed the costs of OSA(S) for both treated and untreated patients, and, according to an Australian study, OSA(S) costs amount to more than 7 billion dollars per year [41].

Continuous positive airway pressure (CPAP) represents the gold standard for the treatment of OSA(S) and it can help in reducing costs of untreated disease [42, 43]. When adherence is optimal, CPAP has been demonstrated to reduce symptoms, the possible sequelae of the

disease and to improve self-reported health status [44-47]. Moreover, CPAP has been proved to be cost-effective in patients with moderate to severe OSA(S) compared to other standard medical therapies [48]. However, despite the availability of treatment, the majority of people with OSA(S) remain undiagnosed and untreated.

In the current economic environment, providing reliable estimates of the cost of OSA(S) for the healthcare system is fundamental in order to inform evidence-based policies and ensure appropriate therapeutic pathways for patients.

2 Study objective

In Italy the impact of OSA(S) is highly underestimated by policy-makers, clinicians and general population, also due to substantial diagnosis gaps. The present study aims at assessing the societal economic burden of OSA(S) in Italy by performing a cost-of-illness (COI) analysis, estimating also the economic consequences of undiagnosed and untreated OSA(S) and assessing the benefits brought by higher diagnosis rates and more appropriate treatment pathway. Ultimately, this study aims at increasing awareness of the disease burden, both by a clinical and an economic point of view.

3 Methods

OSA(S) burden was estimated through a cost of illness (COI) approach. COI analysis is one of the earliest form of economic evaluation in the healthcare sector, which allows to identify and measure all the costs of a disease, including direct health and non-healthcare costs and productivity losses (indirect costs). The output, expressed in monetary terms, is an estimate of the total economic burden that the disease imposes to society. COI studies can represent a useful public policy tool to formulate and prioritize health care policies and interventions, suggesting which interventions are more valuable by comparing avoided economic burden [49, 50].

The present study is based on the COI approach, modified with the estimate of alternative scenarios (e.g. different prevalence, etc.), and mainly used literature data and expert opinion.

The COI study entailed different steps:

- Estimation of OSA(S) prevalence in Italy:
    - Definition of OSA(S) boundaries.
- Assessment of total cost of the disease:
    - Identification and valuation of direct and indirect costs.
    - Estimation of the economic consequences of undiagnosed and untreated OSA(S).
- Scenario analysis: definition of alternative scenarios (rate of diagnosis and treatment) and estimation of their impact on disease burden.

A societal perspective was adopted in order to assess the burden of the disease for the Italian population. The study was conducted retrospectively and epidemiological data were selected according to a prevalence-based approach, estimating the costs attributable to all cases occurring in a given year. A prevalence-based approach is preferred to an incidence-based approach for diseases that produce long-term sequelae, such as chronic diseases [50, 51]. Cost data were retrieved according to a comprehensive literature review on a selected scientific database. The methodological approach to cost estimation was top-down.

3.1 Estimation of OSA(S) prevalence in Italy

According to the Italian Ministry of Health, there are no available data on the prevalence of OSA(S) in Italy based on current diagnostic criteria [52]. A review of the literature, both grey and peer-reviewed, was conducted in order to verify this statement. Moreover, expert opinion was elicited in order to complement literature data and obtain reliable and updated estimates of the prevalence of the disease. Finally, on the basis of literature review, documentary analysis and expert opinion, we retrieved data on the number of OSA(S) patients actually diagnosed (i.e. diagnosed prevalence) and treated (i.e. treated prevalence). By comparing these results with the real prevalence, it was possible to estimate the rate of undiagnosed and untreated OSA(S) in Italy, which allows to understand the additional economic burden caused by inappropriate diagnostic and treatment pathway.

3.1.1 Definition of OSA(S) boundaries

A fundamental step in order to understand the burden of OSA(S) in Italy is the definition of the boundaries of the disease, as it is associated with a substantial number of comorbidities (e.g. diabetes, hypertension, etc.). Given the importance of this research phase, it was carried out according to different steps:

1. Preliminary literature review
2. Refinement of the literature review
3. Research board with experts
4. Finalization of the systematic literature review and data extraction

3.1.1.1 *Preliminary literature review*

A preliminary literature review with a systematic approach was conducted to identify all conditions possibly associated with OSA(S) and obtain a first picture of the boundaries of the disease. A search with keywords on one scientific literature database (MEDLINE) and one archive (PubMed) was performed on November 19th, 2018. The search strategies for MEDLINE and PubMed are reported inTable 1. Studies were screened based on titles and abstract by two researchers in parallel (GD, AG) according to the following exclusion criteria:

- Focus on animals.
- Reverse association only, i.e. risk factor for OSA(S).
- Complete absence of information about possible association of OSA(S) with other clinical or non-clinical conditions.

The abstracts included after the screening provided information on the clinical and non-clinical conditions (possibly) associated with OSA(S). Clinical conditions were classified on the basis of the ICD-10 classification system (version 2016) or according to other macro-categories (e.g. diseases in children).

TABLE 1 SEARCH STRATEGY FOR PRELIMINARY LITERATURE REVIEW

MEDLINE	PubMed
1. ("Obstructive Sleep Apn$ea" OR OSAS OR OSA OR OSAHS)[Title] OR ("Sleep Apnea, Obstructive")[MeSH Term] 2. (associate* OR relat* OR connect* OR impos* OR correlate* OR contribut* OR impact* OR cause* OR afflict* OR "risk factor$" OR "odds ratio$" OR effect$ OR consequence$ OR co$morbidit* OR complication$)[Topic] 3. LANGUAGE: English 4. DOCUMENT TYPES: Meta Analysis OR Review 5. SPECIES: Humans 6. only records with abstracts 7. 1 AND 2 AND 3 AND 4 AND 5 AND 6	1. ((associated OR association) OR (related OR relation) OR (connected OR connection) OR impos* OR (correlated OR correlation) OR contribut* OR impact* OR cause* OR afflict* OR (risk factor OR risk factors) OR (odds ratio OR odds ratios) OR (effect OR effects) OR (consequence OR consequences) OR(comorbidity OR comorbidities OR co-morbidity OR co-morbidities) OR (complication OR complications))[Title/Abstract] 2. (Obstructive Sleep Apnea OR Obstructive Sleep Apnoea OR OSA OR OSAS OR OSAHS)[Title] OR Sleep Apnea, Obstructive[MeSH Major Topic] 3. 1 and 2 Filters: Meta-Analysis, Systematic Reviews, Abstract, Humans, English.

3.1.1.2 *Refinement of the literature review*

According to the results obtained from the preliminary review, a systematic literature review was carried out to narrow the search and identify the main conditions that have been demonstrated to be significantly associated with OSA(S). This phase of the systematic review was carried out by two researchers in parallel (GD, AG) and entailed different steps:

- Definition of the research question.
- Definition of the search strategy (database, keywords and inclusion/exclusion criteria) and search performance.
- Titles and abstract screening.

In order to estimate the total economic burden of the disease, it is important to understand which conditions are direct consequences of OSA(S) because a portion of their costs will be attributed to the disease under investigation. Therefore, we declined our research question as: "Which are the clinical and non-clinical conditions that have been demonstrated to be consequences of OSA(S)?". In particular, we seek at finding data on the magnitude of association (e.g. hazard ratio) and the statistical significance of this association (i.e. p-value).

The search was performed in PubMed according to the search strategy presented in Table 1. Studies were excluded based on titles and abstract screening according to stricter exclusion criteria than those applied in the preliminary review, i.e.:

- Focus on animals.
- Reverse association only, i.e. risk factor for OSA(S).
- Complete absence of information about possible association of OSA(S) with other clinical or non-clinical conditions.
- Only association with biomarkers, metabolites, genes or proteins.
- Focus on a very specific population (e.g. indigenous).
- Type of study different from systematic reviews and meta-analyses.

Disagreements between reviewers on study inclusion according to titles and abstracts screening were solved by consensus or by the decision of a third independent reviewer. Again, the abstracts included after the screening provided information on the clinical and non-clinical conditions (possibly) associated with OSA(S). This updated and stricter list of conditions was presented to clinical experts and discussed with them.

3.1.1.3 *Discussion with experts*

A research board with clinicians was organized (December 10th, 2018) in order better inform this research step and integrate the results from the literature with expert opinions. In particular, additional exclusion criteria were discussed, together with the most important associated conditions from a practitioner perspective.

3.1.1.4 *Finalization of the literature review and data extraction*

The discussion with experts allowed to refine both the methods and the results of the literature review. In particular, additional exclusion criteria were added and the systematic literature review was completed according to the following steps:

- Titles and abstract screening (according to the additional exclusion criteria).
- Full-text screening and selection.
- Data extraction and analysis.

After the titles and abstract screening, full-texts of included studies were retrieved and read entirely. The references or citations of the retrieved articles were reviewed for additional articles (citation snowballing). Moreover, a manual search on other sources (e.g., Google Scholar) was carried out to complement the search with keywords. If relevant for the research question, i.e. providing quantitative data on association with OSA(S), the studies were definitely included.

Of the studies included, only some of them were used for data extraction. In particular, if more than one meta-analysis was available for the same condition, we extracted data from the most recent one or, alternatively, from the meta-analysis of higher quality. If two or more meta-analyses for the same condition showed discordant results, they were all included in the analysis. For relevant conditions for which a meta-analysis was not available, we checked whether there was an included systematic review with sufficient quantitative data to carry out a meta-analysis. We discarded those conditions for which a meta-analysis was not available and that were not considered particularly relevant by clinicians involved in the research board.
Data were extracted and reported according to a predefined template, and summary measures of the degree of association between OSA(S) and identified conditions were provided.

Prevalence of included conditions was estimated from published sources.

Population attributable fraction (PAF) methodology was used to calculate the proportion of each condition that is associated with the presence of OSA(S). The PAF can be defined as the proportional reduction in average disease risk that would be achieved by eliminating the exposure to a risk factor [53, 54]. The PAF allows to estimate the amount of disease burden caused by a certain risk factor. In the literature there are different approaches to estimate PAF. In the present analyses, we chose the approach that was deemed more suitable according to the data available. In particular, we used the formula proposed by Levin (1989) [55] when the measure of association provided was relative risk (RR):

$$PAF = \frac{p_{(E)}(RR - 1)}{p_{(E)}(RR - 1) + 1}$$

where $p_{(E)}$ is the prevalence of OSA(S); RR is relative risk.

It is important to highlight that Levin's approach could lead to overestimation of PAF when the measure of association provided is adjusted RR [54]. However, studies included did not provide sufficient data to use alternative approaches, suitable in the presence of confounding, therefore we used Levin's formula for both unadjusted and adjusted RR.

When the measure of association provided was odds ratio (OR), PAF was calculated according to the method based on Eide and Heunch (2001) [56] and used in a recent study by Hillman et al (2018) [57]. By solving simultaneously the following two equations for $p_{(D|E)}$ and $p_{(D|\sim E)}$

$$p_{(D|E)} * p_{(E)} + p_{(D|\sim E)} * p_{(\sim E)} = p_{(D)}$$

$$\left(\frac{p_{(D|E)}}{1 - p_{(D|E)}}\right) / \left(\frac{p_{(D|\sim E)}}{1 - p_{(D|\sim E)}}\right) = OR$$

the formula for PAF calculation is obtained

$$PAF = \frac{\left(p_{(D|E)} - p_{(D|\sim E)}\right) * p_{(E)}}{p_{(D)}}$$

where $p_{(D|E)}$ is the probability of having the particular condition given that an individual has OSA(S); $p_{(D|\sim E)}$ is the probability of having the particular condition given that an individual does not have OSA(S); $p_{(E)}$ is the probability of having OSA(S) (i.e, OSA(S) prevalence); $p_{(\sim E)}$ is the probability of not having OSA(S); $p_{(D)}$ is the probability of having the particular condition; OR is the odds ratio for that condition for individuals with OSA(S).

3.2 Assessment of cost of the disease

To assess the cost of illness, direct and indirect (i.e. productivity losses) costs are the cost categories that should be valued. Direct costs refer to the consumption of healthcare and non-healthcare resources directly attributable to a disease. Direct healthcare costs include costs due to hospitalizations, consultations, laboratory testing, drug or medical device consumption, etc. Direct non-healthcare costs include transportation costs and informal care (i.e. care provided by relatives and friends). Indirect costs refer to productivity losses related to illness or death, and include patients' and informal caregivers' time off work.

As the literature does not provide data on the percentage of OSA(S) patients without any comorbidity, it was not possible to isolate the costs uniquely determined by the sleep disorder. Therefore, for the purposes of the present study, we considered OSA(S) as a risk factor, among

others, of other costly conditions and we estimated all costs associated with conditions attributable to OSA(S) found in the previous literature step. It is worth underlining that for cost calculation we considered only those conditions significantly associated with OSA(S) (i.e. p-value<0.05). A comprehensive literature review was conducted to retrieve cost studies for these conditions. If a cost study for Italy was not available, we included cost studies referred to other countries whose health care systems can be considered comparable to the Italian one. According to data availability, we included all direct (healthcare and non-healthcare) and indirect costs and calculated the mean cost per patient/year. In order to compute the total cost for each condition, we multiplied the mean cost per patient for the condition's prevalence. Then, proportionally to the degree of association of each condition, a part of their costs was attributed to OSA(S) with a top-down approach using the PAF methodology.

All costs were adjusted for inflation to 2018 in their national currency using GDP deflators retrieved from the OECD database [58]. Finally, all costs were adjusted for purchasing power differences using OECD Purchasing Power Parities (PPPs) for GDP for 2018 [59]. PPPs serve both as currency convertors and as spatial price deflators: they convert different currencies to a common currency and, in the process of conversion, equalise their purchasing power by eliminating the differences in price levels between countries. This methodology can ensure better comparability between different currencies. All costs are presented in both the originally published currency and in 2018 Euros.

3.3 Scenario analysis

Starting from the data collected in the previous phases, alternative scenarios were provided to show how costs vary according to different diagnosis rates and different planning and management of treatment pathway (e.g. number of patients using CPAP). Undiagnosed and untreated OSA(S), in fact, can result in significant burden, therefore it is important to estimate its consequences in both clinical and economic terms. A comprehensive literature review was carried out in order to retrieve data on the impact of treating vs not treating OSA(S) on the clinical and non-clinical conditions previously identified. Then, different scenario were estimated by varying the parameters of interest. Ultimately, this allowed to estimate how the

total economic burden of OSA(S) could be reduced with higher diagnosis rates and more appropriate clinical pathway for patients.

4 Results

4.1 Estimation of OSA(S) prevalence in Italy

The review of the literature, both grey and peer reviewed, revealed that there is a lack of updated epidemiological data on OSA(S) for Italy.

Cirignotta et al (1989) carried out an epidemiological survey on 3479 men aged 30 to 69 living in Bologna (north-east of Italy) to estimate the prevalence of snoring and OSA(S) [60]. Unfortunately, only 40 individuals accepted to undergo polysomnography, therefore the results obtained can be hardly considered representative of the Italian population.

Ferini-Strambi et al (1994) estimated the prevalence of sleep-disordered breathing and OSA(S) by means of home-monitoring in a representative sample of 399 adult males in the North of Italy [61]. Results showed that 15.5% of the sample had an AHI>10 and 5% an AHI>20. In another cross-sectional study performed in 1995, Ferini-Strambi et al (1999) assessed the prevalence of sleep-disordered breathing and OSA(S) in a sample of 365 Italian women, aged between 40 and 65 years [62]. The authors found that OSA(S) was common among subjects: 10.7% of the individuals had an AHI between 5 and 9, 7.7% of the individuals had an AHI between 10 and 19, and 2.2% had an AHI≥20. Data of the two studies suggest that in the Italian adult population the prevalence of OSA(S) is higher in male than female, with a ratio of approximately 2-3:1 [63].

At the international level, several epidemiological studies were carried out with the aim of estimating OSA(S) prevalence. In the United States, Young et al (1993) analysed data of a random sample of 602 employed men and women (aged 30 to 60 years old) from the Wisconsin Sleep Cohort Study [1]. The estimated prevalence of OSA(S), defined as an AHI≥5, was 9% for women and 24% for men. A population-based study (HypnoLaus) was recently conducted in Lausanne (Switzerland) by Heinzer and colleagues [64]. The authors analysed data of 2121 patients aged 40-85 who underwent polysomnography. Results showed an OSA overall prevalence (i.e., AHI≥5) equal to 83.8% (95% CI: 81.4–86.0) in men and 60.8% (95% CI: 57.8–63.7)

in women. The prevalence of moderate-to-severe OSA (i.e., AHI≥15) was found to be 49.7% (95% CI: 46.6–52.8) in men and 23.4% (95% CI: 20.9–26.0) in women.

At the European level, a collaborative network of 22 sleep disorder centres, representative of 16 countries, was established in 2005 with the aim of investigating the burden of OSAS(S) in Europe. The project generated a multinational dataset, the European Sleep Apnoea Database (ESADA), containing data from patients referred to sleep centres due to suspected OSA(S). In a paper by Hedner et al (2011), data of 5103 patients (3677 males and 1426 females) with suspected OSA(S) were analysed [65]. Results showed that, among patients with OSA(S), the proportion of severe OSA(S) is substantially higher in male than female, while the opposite is true with mild OSA(S). Table 2 shows the proportion of patients according to OSA(S) severity.

TABLE 2 DISTRIBUTION OF PATIENTS ACCORDING TO OSA(S) SEVERITY

	Female	Male	Total
Mild (5≤AHI<15)	46%	32%	37%
Moderate (15≤AHI<30)	29%	27%	26%
Severe (AHI≥30)	25%	41%	37%

Source: Our elaboration from Hedner et al (2011)

Finally, a systematic review was recently performed by Senaratna et al (2017) in order to determine the prevalence of OSA(S) in the general adult population [66]. The authors included only studies that objectively measured OSA(S) using laboratory instruments and were based on the general population (aged > 18 years). Results suggest a substantial heterogeneity in the estimates provided by the included studies. In fact, the overall prevalence of OSA(S) (AHI≥5) ranged from 9% to 38%. Prevalence was higher in men compared with women. In particular, it varied from 13% to 33% in men and from 6% to 19% in women. Moderate-to-severe OSA(S) (AHI≥15) had a prevalence ranging between 6% and 17% in the overall population.

Due to heterogeneity of data provided by the literature, an expert opinion was elicited in order to understand whether, and which, literature data properly reflect the prevalence of OSA(S) in Italy. In particular, we interviewed Prof. Luigi Ferini-Strambi, a clinician specialized in neurology and sleep disorders. On the basis of his clinical experience, he reckoned that the data provided

by the HypnoLaus study [64] are representative of current OSA(S) epidemiology in the Italian population. In particular, data on the prevalence of moderate-severe OSA (i.e., AHI≥15) represent the most reliable estimates and properly reflect the OSA(S) prevalence ratio of 2:1 among men and women actually observed in the Italian adult population [63]. Prof. Ferini-Strambi suggested to consider only moderate-severe patients when assigning costs of other conditions to OSA(S) because usually only more severe patients develop comorbidities. It is worth noting that, according to Prof. Ferini-Strambi, these estimates are not referred to the diagnosed prevalence, which is significantly lower, but to the real/supposed prevalence hypothesizing that every individual with moderate-severe OSA(S) is actually diagnosed. Considering the data from HypnoLaus study and using the distribution of patients between moderate and severe OSA(S) provided by Hedner and colleagues [65] (see Table 2), we derived prevalence rates for population aged 40-85, as shown in Table 3. Throughout the report, we will use prevalence data obtained from mean values provided by Hedner et al. Given the narrow confidence intervals reported in the study, in fact, we may infer that mean values represent sufficiently precise estimates of the true unknown parameter. Using data from ISTAT on the resident population in Italy in 2018 and the prevalence rates, we computed prevalence in absolute terms, i.e. the number of people in Italy aged 40-85 with OSA(S).

TABLE 3 PREVALENCE OF OSA(S) FOR POPULATION AGED 40-85

	Female	Male	Total
Rates			
Mild (5≤AHI<15)	37.4%	34.1%	
Moderate-severe (AHI≥15)	23.4%	49.7%	
Moderate (15≤AHI<30)	12.5%	19.9%	
Severe (AHI≥30)	10.9%	29.8%	
Overall (AHI≥5)	60.8%	83.8%	
Absolute values			
Mild (5≤AHI<15)	6,703,067	5,582,051	12,285,118
Moderate-severe (AHI≥15)	4,193,897	8,135,717	12,329,614
Moderate (15≤AHI<30)	2,236,745	3,260,161	5,496,906
Severe (AHI≥30)	1,957,152	4,875,556	6,832,708
Overall (AHI≥5)	10,896,964	13,717,768	24,614,732

Source. Rates: Our elaboration from Hedner et al (2011) and Heinzer et al (2015). Absolute values: Our elaboration using computed prevalence rates and ISTAT data on Italian resident population aged 40-85 in 2018.

From the prevalence in absolute terms provided in Table 3, we estimated the prevalence rate for the general adult population (aged 15-74) that will be used for PAF calculation. Results are displayed in Table 4 below. It is important to underline that in computing these rates we made a conservative assumption, i.e. that the prevalence between 15 and 39 years old is equal to zero. Therefore, these prevalence rates have to be interpreted carefully. For completeness, in Table 4 we report also prevalence absolute values, already provided in Table 3, as they will be used in the next steps of COI analysis.

TABLE 4 PREVALENCE OF OSA(S) FOR THE GENERAL ADULT POPULATION IN ITALY (AGED 15-74)

	Female	Male	Total
Rates			
Mild (5≤AHI<15)	29%	25%	27%
Moderate-severe (AHI≥15)	18%	36%	27%
Moderate (15≤AHI<30)	10%	14%	12%
Severe (AHI≥30)	9%	22%	15%
Overall (AHI≥5)	48%	61%	54%
Absolute values			
Mild (5≤AHI<15)	6,703,067	5,582,051	12,285,118
Moderate-severe (AHI≥15)	4,193,897	8,135,717	12,329,614
Moderate (15≤AHI<30)	2,236,745	3,260,161	5,496,906
Severe (AHI≥30)	1,957,152	4,875,556	6,832,708
Overall (AHI≥5)	10,896,964	13,717,768	24,614,732

Source: Our elaboration from prevalence values provided in Table 3 and ISTAT data on Italian resident population aged 15-74 in 2018.

4.1.1 Rate of undiagnosed and untreated OSA(S) patients in Italy

The literature reports that OSA(S) is a severely underdiagnosed condition worldwide. Based on a sample of 4,925 employed adults in the United States, Young et al (1997) estimated that 93% of women and 82% of men with moderate-to-severe OSA(S) were not diagnosed [39]. In a prospective observational study performed in an academic hospital on adult surgical patients, Finkel et al (2009) found that, among high-risk patients without diagnosed OSA(S), 82% of them actually had sleep apnea. An Australian study conducted on 793 individuals from the general population provided more conservative estimates: the authors found that the prevalence of undiagnosed moderate-to-severe OSA(S) was approximately 9%, 12.4 % in men and 5.7 % in

women [67]. The reasons underlying poor diagnosis of OSA(S) are several, and start from lack of awareness [68, 69], both among healthcare professionals and general population, to limited routine screening and diagnostic sleep centres [70]. Even when a diagnosis occurred, evidence shows that acceptance and adherence to treatment with CPAP - despite its technological advances - is generally low, ranging from 30 to 60% [71, 72].

According to Prof. Ferini-Strambi, in Italy only 50% of diagnosed OSA(S) patients receive appropriate treatment with CPAP. The treatment should be administered only to patients with moderate to severe OSA(S). On the basis of the data collected by the Italian association of apneic patients (Associazione Apnoici Italiani Onlus), patients currently treated with PAP (both continuous and automatic positive airway pressure) in Italy are approximately 230 000. For the majority of them (138 000, 60%), the cost of the treatment is covered by the NHS. If we apply the estimate provided by Prof. Ferini-Strambi to the number of treated patients, i.e. if we consider that 230 000 patients represent the 50% of moderate-severe OSA(S) diagnoses, we can conclude that the number of diagnosed patients in Italy with moderate-severe OSA(S) are approximately 460 000. By difference, it was possible to estimate the rate of undiagnosed and untreated patients with moderate-severe OSA(S) in Italy, equal to 96% and 98% respectively (Table 5).

TABLE 5 RATE OF DIAGNOSIS AND TREATMENT AMONG PREVALENT MODERATE-SEVERE OSA(S) PATIENTS IN ITALY

Moderate-severe OSA(S)	Total
Prevalence	12,329,614
Diagnosis: Diagnosed patients, n (%) Undiagnosed patients, n (%)	 460,000 (4%) 11,869,614 (96%)
Treatment: Treated patients, n (%) Untreated patients, n (%)	 230,000 (2%) 12,099,614 (98%)

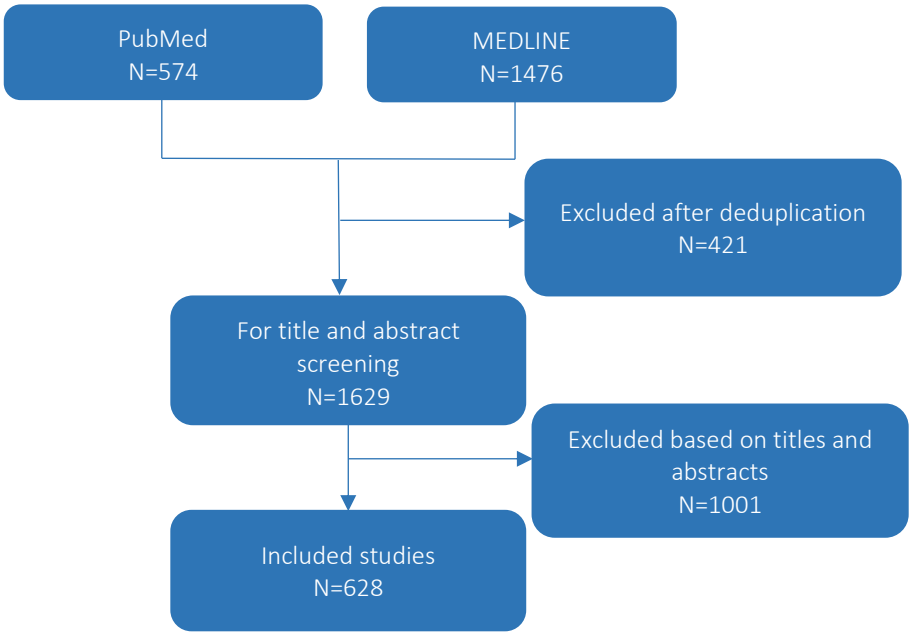
Source. Prevalence: absolute values provided in Table 3. Diagnosis and treatment: Our elaboration from expert opinion and data provided by Italian association of apneic patients (Associazione Apnoici Italiani Onlus).

4.1.2 Definition of OSA(S) boundaries

4.1.2.1 *Preliminary literature review*

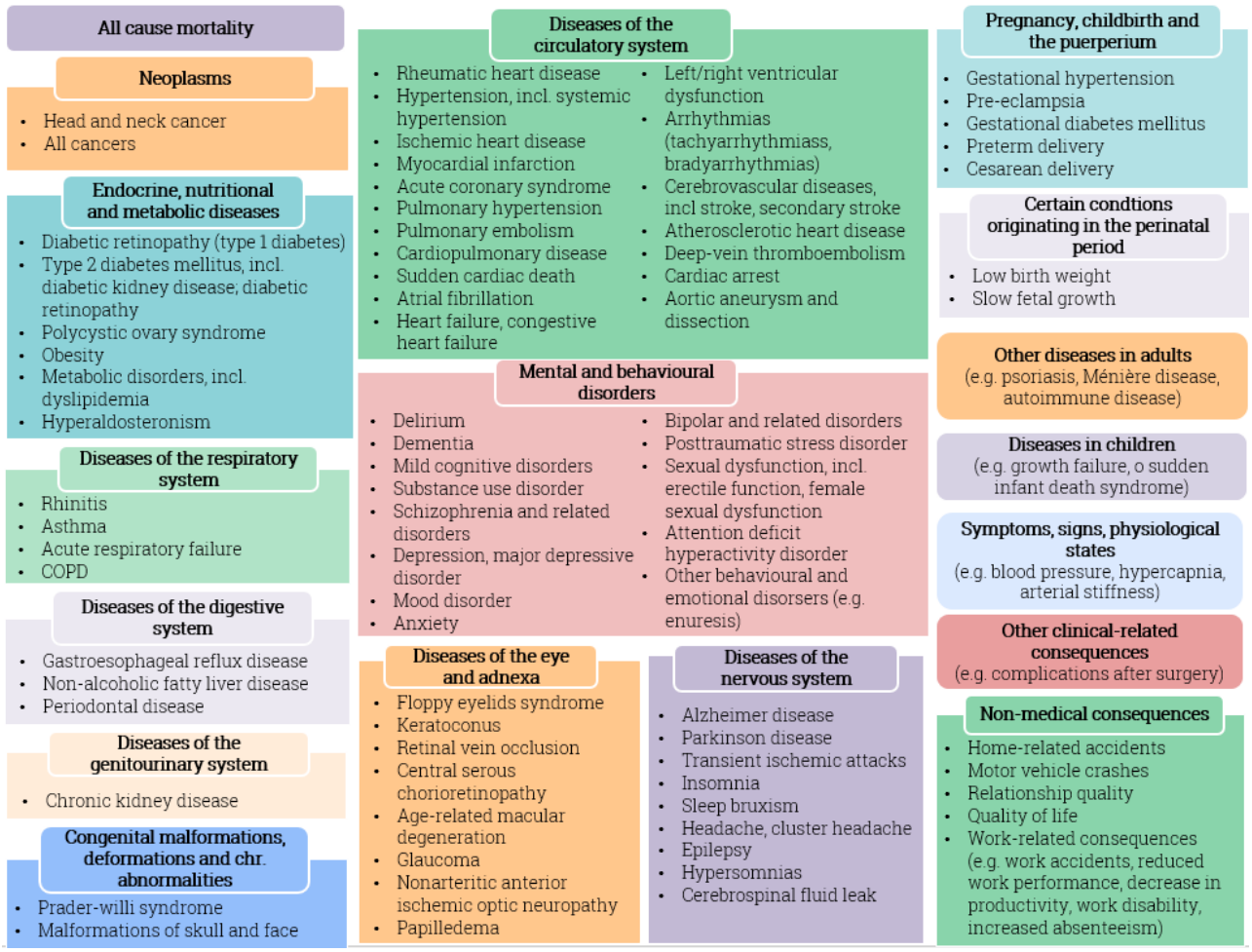
Through the preliminary literature search, we retrieved 2,050 references. After the exclusion of duplicates, 1,629 studies were screened based on titles and abstracts. 628 studies were included and used to map all the conditions possibly associated with OSA(S). Figure 1 illustrates the steps of the screening process.

FIGURE 1 PRELIMINARY LITERATURE REVIEW – SCREENING PROCESS



Although information were extracted only from abstracts and not verified through full-text reading, a substantial number of conditions appear to be associated with OSA(S) (Figure 2). These conditions are extremely heterogeneous and include both clinical and non-medical consequences.

FIGURE 2 PRELIMINARY LITERATURE REVIEW RESULTS - CONDITIONS POSSIBLY ASSOCIATED WITH OSA(S)

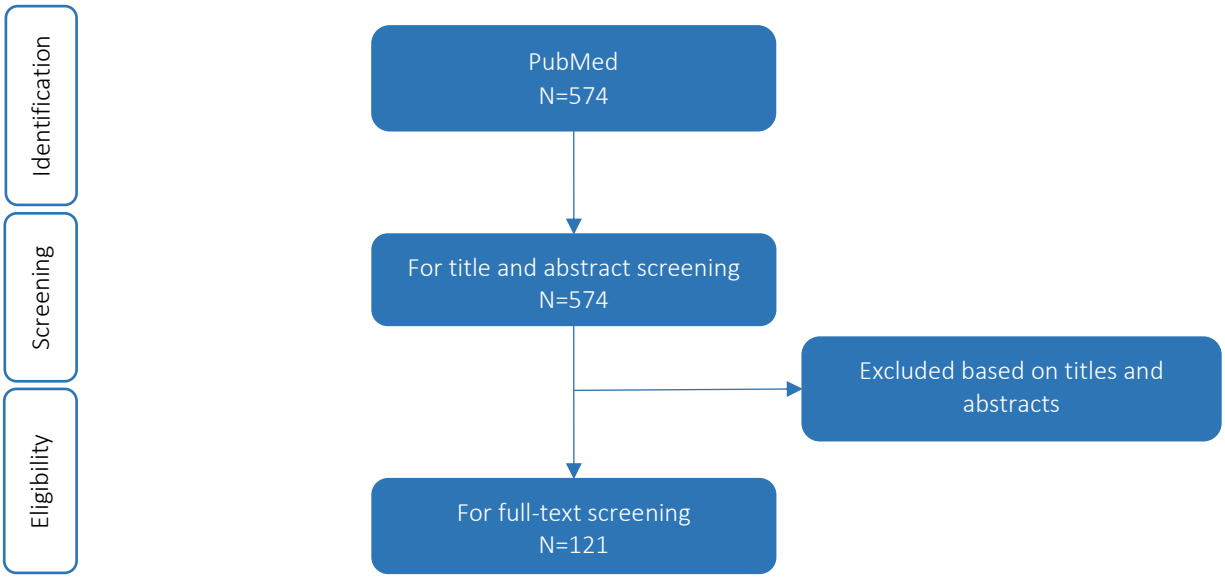


4.1.2.2 *Refinement of the literature review*

Since our aim is to collect quantitative evidence on the association of OSA(S) with other conditions, we decided to narrow the search on the best available evidence and focus our systematic literature review only on systematic reviews and meta-analyses. We carried out the search using PubMed as it provides a special filter that allows to extract these types of study. As anticipated in the method section (see §3.1.1.2), we applied stricter exclusion criteria for the screening of titles and abstracts in the systematic review. It is worth noting that the exclusion criterion on the type of study (i.e. type of study different from systematic reviews and meta-analyses) was added because, despite the applied filter, some non-systematic reviews could be retrieved through the search and thus they have to be excluded manually.

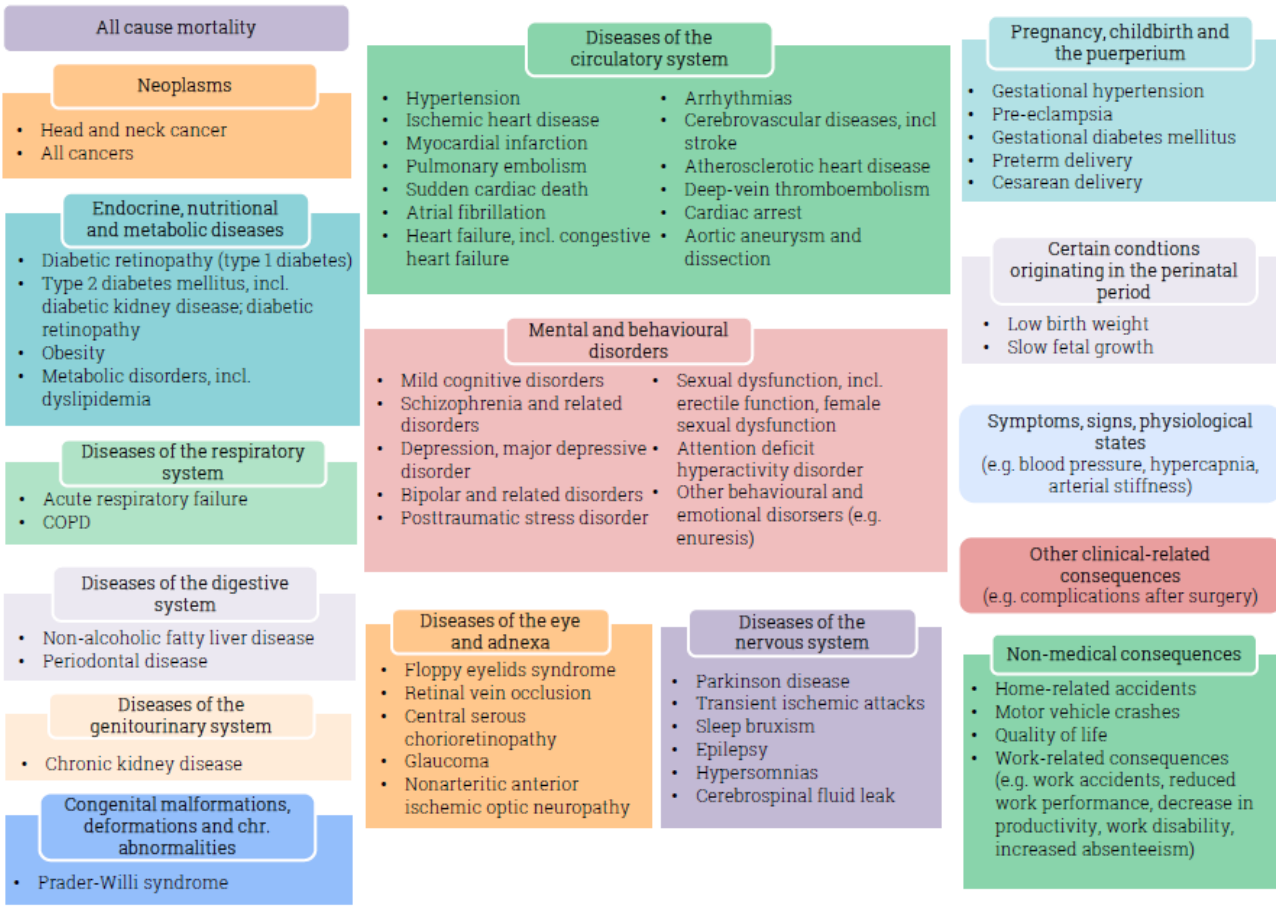
574 titles and abstracts were screened and 121 studies were included for full-text reading (Figure 3).

FIGURE 3 SYSTEMATIC LITERATURE REVIEW – SCREENING PROCESS (PRISMA FLOW DIAGRAM)



According to the information provided in the abstracts, we extracted again a list of conditions possibly associated with OSA(S) (Figure 4). By comparing Figure 4 and Figure 2, it is possible to notice that the systematic review allowed to shrink the list of associated conditions, although the number is still substantial.

FIGURE 4 SYSTEMATIC LITERATURE REVIEW RESULTS– CONDITIONS POSSIBLY ASSOCIATED WITH OSA(S)



4.1.2.3 *Research board with experts*

With the objective of discussing the first results obtained and refine the review, CeRGAS SDA Bocconi organized a board with 4 clinicians (Prof. Luigi Ferini-Strambi, Prof. Livio Luzi, Prof. Nicola Montano, Prof. Roberto Penagini) specialized in different disciplines (i.e. neurology, endocrinology, internal medicine with cardiology specialization, gastroenterology).

First, clinicians were asked, on the basis of their experience and clinical practice, to revise the list of conditions found through the literature review and evaluate whether they were consequences, risk factors or both consequences and risk factors for OSA(S). Moreover, they were asked to indicate whether there were some irrelevant conditions or additional conditions

missing from the list. Their feedbacks were collected with the support of a printed template, reported in the **Appendix 1**.

Clinicians agreed on the exclusion of studies that investigate only symptoms, physiological states or other clinical conditions without providing any association with a specific disease. One additional study on gastroesophageal reflux not retrieved through literature review but highlighted by the clinicians was added to the list. Moreover, stroke was reclassified among the diseases of the nervous system. Dr. Luzi suggested to delete polycystic ovary syndrome and iperaldosteronism. Table 6 provides a synthesis of clinicians' opinion on the list of diseases and non-clinical conditions, each cross indicating a clinician's feedback. While there is high consensus on some conditions, especially for non-medical consequences, clinicians reported heterogeneous opinions for the majority of diseases, reflecting the uncertainty found in the literature around the boundaries of OSA(S). Moreover dr Luzi suggested to identify 5 or 6 diseases related to OSAS and assess prevalence (presumed and real) or a prevalence matching. Despite the heterogeneity, expert opinions will be particularly useful in the next step of the review in order to exclude those conditions that are clearly only risk factors for OSA(S) or are considered irrelevant from a clinical standpoint.

TABLE 6 SYNTHESIS OF CLINICIANS FEEDBACKS ON THE LIST OF CONDITIONS ASSOCIATED WITH OSA(S)

Conditions possibly associated with OSA(S)	Consequence of OSA(S)	Risk factor for OSA(S)	Both consequence and risk factor of OSA(S)	Irrelevant
All-cause mortality	XX			
Neoplasms				X
Head and neck cancer				X
All cancers	X			X
Endocrine, nutritional and metabolic diseases				
Diabetic retinopathy (type 1 diabetes)	XX			
Type 2 diabetes mellitus	X		X	
Diabetic kidney disease	XX			
Diabetic retinopathy	XX			
Obesity *(adults)*		X	XXX	
Obesity *(children)*			XXX	

Conditions possibly associated with OSA(S)	Consequence of OSA(S)	Risk factor for OSA(S)	Both consequence and risk factor of OSA(S)	Irrelevant
Metabolic disorders, incl. dyslipidemia *(adults)*	X		XX	
Metabolic disorders, incl. dyslipidemia *(children)*	X		XX	
Mental and behavioural disorders				
Mild cognitive disorders (e.g. attention, vigilance, processing speed, memory, verbal fluency)	XXX			
Schizophrenia and related disorders		X		XX
Depression, major depressive disorder *(adults)*			XX	X
Depression *(children)*			X	X
Bipolar disorder				XX
Posttraumatic stress disorder			X	X
Sexual dysfunction	XXX			
Erectile dysfunction	XXX			
Female sexual dysfunction	XXX			
Attention deficit hyperactivity disorder	X		X	X
Other behavioural and emotional disorders with onset usually occurring in childhood and adolescence (e.g. enuresis)				
Diseases of the nervous system				
Cerebrovascular diseases, incl. stroke	XX		X	
Parkinson disease		XX		X
Transient ischemic attack	X	X		
Sleep bruxism	X			
Epilepsy *(adults)*	XX		X	
Epilepsy *(children)*	XXX			
Hypersomnias	XX		X	
Cerebrospinal fluid leak				
Diseases of the eye and adnexa				
Floppy eyelids syndrome				
Retinal vein occlusion	XX			
Central serous chorioretinopathy				
Glaucoma	XXX			
Nonarteritic anterior ischemic optic neuropathy				
Diseases of the circulatory system				
Hypertension *(adults)*	X		XX	
Hypertension *(children)*	XX		X	
Ischemic heart disease	XXX			

Conditions possibly associated with OSA(S)	Consequence of OSA(S)	Risk factor for OSA(S)	Both consequence and risk factor of OSA(S)	Irrelevant
Myocardial infarction	XXX			
Pulmonary embolism	X			X
Sudden cardiac death	XXX			
Atrial fibrillation	XX			
Heart failure, incl. congestive heart failure	XXX			
Arrhythmias	XXX			
Atherosclerotic heart disease	XX		X	
Deep-vein thromboembolism	X		X	X
Aortic aneurysm and dissection	XX			
Cardiac arrest	XX			X
Diseases of the respiratory system				
COPD			X	X
Acute respiratory failure			X	
Diseases of the digestive system				
Non-alcoholic fatty liver disease	X		XX	X
Periodontal disease			X	XX
Gastroesophageal reflux disease	X			
Diseases of the genitourinary system				
Chronic kidney disease	X			
Pregnancy, childbirth and the puerperium				
Gestational hypertension	XX			
Pre-eclampsia	XX			
Gestational diabetes mellitus	X		X	X
Preterm delivery	X			X
Cesarean delivery				X
Certain conditions originating in the perinatal period				
Low birth weight	XX			X
Slow fetal growth	XX			X
Congenital malformations, deformations and chromosomal abnormalities				
Prader-Willi syndrome		XX		
Non-medical consequences				
Motor vehicle crashes	XXX			
Quality of life	XXX			
Work-related consequences	XXX			
Work accidents	XXX			
Reduced work performance	XXX			
Decrease in productivity	XXX			

Conditions possibly associated with OSA(S)	Consequence of OSA(S)	Risk factor for OSA(S)	Both consequence and risk factor of OSA(S)	Irrelevant
Decrease in attention	XXX			
Decrease in learning	XXX			
Work disability	XXX			
Increased absenteeism	XXX			

Source: Our elaboration of expert opinions collected during the research board.

Clinicians were also asked whether the study should consider the general population, divide the population between adults and children, or focus specifically on adults. They suggested to consider only adults, because the disease in children has very different characteristics and also the treatment options are specific for this subpopulation (surgery rather than CPAP).

Finally, clinicians recommended to consider separately those conditions that have been clearly demonstrated to be consequences of OSA(S) and those that present a bidirectional association (i.e. both consequences and risk factors of OSA(S)). For the latter, in fact, it is less straightforward to disentangle the causal relationship of one condition on the other and thus obtain reliable estimates of the magnitude of OSA(S) effect.

4.1.2.4 *Finalization of the systematic literature review and data extraction*

All the hints collected during the research board were integrated in the final steps of the literature review. In particular, studies were screened again on titles and abstracts according to additional exclusion criteria:

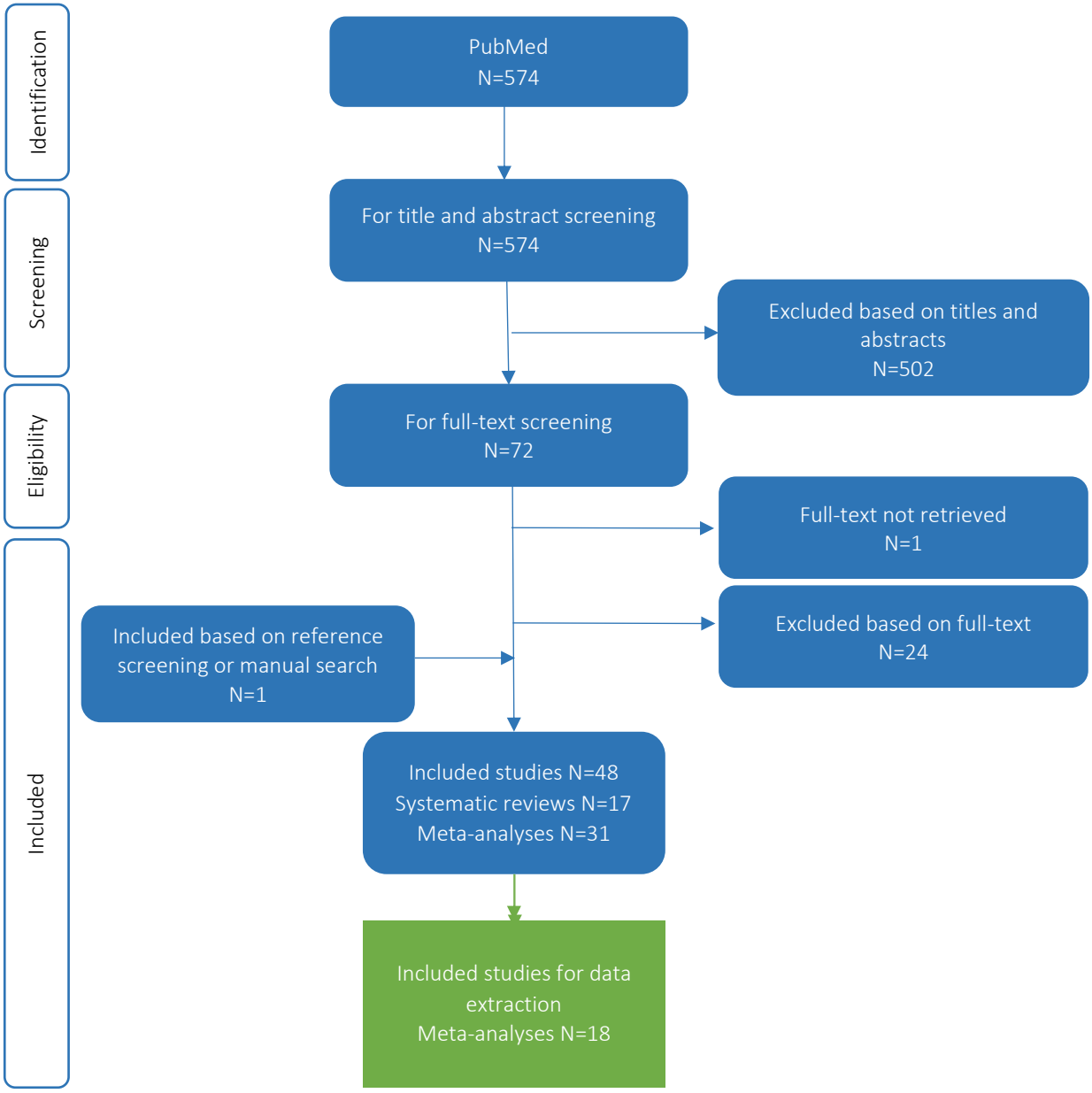
- Focus on children.
- Focus on complications or operative outcomes.
- Focus on symptoms or physiological states.

72 studies were included for full-text reading. It was not possible to retrieve the full-text for one study. 24 full-texts were excluded for one of the following reasons: 1) they investigated OSA(S) exclusively as a consequence of other conditions; 2) they did not provide any quantitative data on the association of OSA(S) with other conditions; 3) they investigated the association of OSA(S)

only with parameters that could eventually identify a clinical condition; 4) they evaluated the risk of having a certain condition only among OSA(S) patients without providing the control group of non-OSA(S) patients; 5) they provided unclear data on the direction of the association between OSA(S) and the condition investigated; 6) they investigated OSA(S) together with other sleep disorders. Through the search on references and on other sources, we found one additional study, which was included in the analysis. Overall, we found 48 relevant articles, of which 31 meta-analysis and 17 systematic reviews.

As anticipated in the method section, only some of the included studies were used for data extraction and/or calculation of association measures. 18 meta-analyses providing summary measure of association (i.e. pooled odds-ratio, relative risk, hazard ratio) were considered. Unfortunately, for some conditions judged relevant by clinicians (e.g. arrhythmias), systematic reviews did not provide sufficient quantitative data to carry out a meta-analysis, therefore they were not included in the analysis. Moreover, for some conditions (e.g. depression), available meta-analyses reported association measures that cannot be used for PAF calculation (e.g. Cohen's d) and therefore were excluded. Finally, no systematic review or meta-analysis investigating quality of life was included as the retrieved studies were focused exclusively on children. Figure 5 displays the entire screening process until data extraction. **Appendix 2** provides the list of the conditions included for data extraction.

FIGURE 5 SYSTEMATIC LITERATURE REVIEW – SCREENING PROCESS AND RESULTS



4.1.2.5 *Clinical and non-clinical conditions associated with OSA(S)*

Table 7 shows, for each condition ultimately included in the analysis, the magnitude of the association with OSA(S) (according to different levels of OSA(S) severity), the range of variation (i.e., confidence interval) and the statistical significance of the association (p-value). It is worth noting that the association coefficients were estimated considering non-OSA(S) patients as the

control group. Results displayed in Table 7 suggest that a substantial number of conditions have been demonstrated to be significantly associated with OSA(S). Some authors provided estimates stratified by OSA(S) severity (i.e., mild, moderate, severe), while other investigated the association with OSA(S) independently from disease severity. In accordance with the elicited expert opinion (see §4.1), a significant association between OSA(S) and clinical conditions is mostly observed for moderate-severe patients, suggesting that the more severe the sleep disorder the higher the probability to develop comorbidities. Moreover, data suggest that severe OSA(S) is associated with an increase in both all-cause and cardiovascular mortality. It is worth noting that, for data extraction, we included two different studies investigating the link between OSA(S) and cancer (see Table 7), which reported discordant results on the statistical significance of association. Despite a study found a non-significant association, we considered cancer in cost estimation for the subsequent COI analysis, thus including the study by Palamaner Subash Shantha et al (2015) which found a statistically significant association between OSA(S) and cancer. This result was recently supported by a multicentre international study [73], which found that the odds of cancer diagnosis were significantly higher in patients with an AHI≥ 5 (OR= 1.35, 95%CI: 1.02-1.79). After stratification for gender, the association remained statistically significant in females but not in males.

TABLE 7 RESULTS OF DATA EXTRACTION: ASSOCIATION BETWEEN OSA(S) AND OTHER CONDITIONS

Condition	OSA(S) severity	Association measure	Magnitude	95% CI	p value	Source
All-cause mortality	Mild	RR	1.26	0.77 - 2.07	NS	Xie et al (2017) [74]
	Moderate	RR	1.04	0.60 - 1.79	NS	
	Severe	RR	1.54	1.21 - 1.97	<0.001	
Cancer mortality	Mild	HR	0.79	0.46 - 1.34	NS	Zhang et al (2017) [75]
	Moderate	HR	1.92	0.63 - 5.88	NS	
	Severe	HR	2.09	0.45 - 9.81	NS	
	Overall	HR	1.38	0.79 - 2.41	NS	
Cardiovascular mortality	Mild	RR	1.80	0.68 - 4.76	NS	Xie et al (2017) [74]
	Moderate	RR	1.11	0.53 - 2.35	NS	
	Severe	RR	2.96	1.45 - 6.01	0.003	
Cancer	Mild	HR	0.91	0.74 - 1.13	NS	Zhang et al (2017) [75]
	Moderate	HR	1.07	0.86 - 1.33	NS	
	Severe	HR	1.03	0.85 - 1.26	NS	
	Overall	HR	1.04	0.92 - 1.16	NS	

Condition	OSA(S) severity	Association measure	Magnitude	95% CI	p value	Source
	Overall	RR	1.40	1.01 - 1.95	0.04	Palamaner Subash Shantha et al (2015) [76]
Diabetic retinopathy	Overall	OR	2.01	1.49 - 2.72	<0.05	Zhu et al (2017) [77]
Diabetic kidney disease	Overall	OR	1.59	1.16 - 2.18	<0.05	Leong et al (2016) [78]
Type 2 diabetes mellitus	Mild	RR	1.22	0.91 - 1.63	NS	Wang et al (2013) [79]
	Moderate-severe	RR	1.63	1.09 - 2.45	0.018	
Metabolic syndrome	Mild	OR	2.39	1.65 - 3.46	<0.05	Xu et al (2015) [80]
	Moderate-severe	OR	3.42	2.28 - 5.13	<0.05	
Erectile dysfunction	Overall (men)	RR	1.82	1.12 - 2.97	<0.05	Liu et al (2015) [81]
Female sexual dysfunction	Overall (women)	RR	2.00	1.29 - 3.08	<0.05	Liu et al (2015) [81]
Stroke	Mild	RR	1.29	0.69 - 2.41	NS	Xie et al (2017) [74]
	Moderate	RR	1.35	0.82 - 2.23	NS	
	Severe	RR	2.15	1.42 - 3.24	<0.001	
Spontaneous cerebrospinal fluid leak	Overall	OR	3.43	1.55 - 7.59	0.002	Bakhsheshian et al (2015) [82]
Floppy eyelids syndrome	Overall	OR	4.70	2.98 - 7.41	<0.001	Huon et al (2016) [83]
Glaucoma	Overall	OR	1.24	1.20 - 1.28	<0.001	Huon et al (2016) [83]
Nonarteritic anterior ischemic optic neuropathy	Overall	OR	6.18	2.00 - 19.11	0.002	Wu et al (2016) [84]
Resistant hypertension	Overall	OR	2.84	1.70 - 3.98	<0.05	Hou et al (2018) [85]
Essential hypertension	Mild	OR	1.18	1.09 - 1.27	<0.05	Hou et al (2018) [85]
	Moderate	OR	1.32	1.20 - 1.43	<0.05	
	Severe	OR	1.56	1.29 - 1.84	<0.05	
Ischemic heart disease	Mild	RR	1.25	0.95 - 1.66	NS	Xie et al (2017) [74]
	Moderate	RR	1.38	1.04 - 1.83	0.026	
	Severe	RR	1.63	1.18 - 2.26	0.003	
Heart failure	Mild	RR	1.02	0.78 - 1.34	NS	Xie et al (2017) [74]
	Moderate	RR	1.07	0.74 - 1.54	NS	
	Severe	RR	1.44	0.94 - 2.21	NS	
Aortic dissection	Mild	OR	1.60	1.01 - 2.53	0.04	

Condition	OSA(S) severity	Association measure	Magnitude	95% CI	p value	Source
	Moderate-severe	OR	4.43	2.59 - 7.59	<0.001	Zhou et al (2018) [86]
Non-alcoholic fatty liver disease	Overall	OR	2.34	1.71 - 3.18	<0.001	Musso et al (2013) [87]
Gastroesophageal reflux disease	Overall	OR	1.57	1.07 - 2.08	<0.05	Wu et al (2018) [88]
Pre-eclampsia	Overall (women)	RR	1.96	1.34 - 2.86	<0.001	Xu et al (2014) [89]
Gestational diabetes mellitus	Overall (women)	RR	1.40	0.62 - 3.19	NS	Xu et al (2014) [89]
Preterm delivery	Overall (women)	RR	1.90	1.24 - 2.91	0.003	Xu et al (2014) [89]
Cesarean delivery	Overall (women)	RR	1.87	1.52 - 2.29	<0.001	Xu et al (2014) [89]
Car accidents	Overall	OR	2.43	1.21 - 4.89	0.013	Tregear et al (2009) [90]
Work accidents	Overall	OR	1.78	1.03 - 3.07	<0.001	Garbarino et al (2016) [91]

Note. Mild: 5≤AHI<15. Moderate: 15≤AHI<30. Severe: AHI≥30. Moderate-severe: AHI≥15. Overall: AHI≥5. RR: relative risk. OR: odds ratio. HR: hazard ratio. 95% CI: confidence interval. NS: not statistically significant (p-value>0.05).

From the data displayed in Table 7 above, we selected for subsequent steps only those conditions for which a statistically significant association was found. Three conditions (i.e. spontaneous cerebrospinal fluid leak, floppy eyelids syndrome, nonarteritic anterior ischemic optic neuropathy) were excluded as it was not possible to retrieve associated cost data (see the following section §4.2). Besides the absence of cost data, the exclusion of these conditions could be justified also through experts' opinion: none of the experts involved, in fact, considered the association of OSA(S) with these conditions relevant from a clinical point of view. Table 8 shows the conditions significantly associated with OSA(S) and the magnitude of their association, which were ultimately used for COI analysis.

TABLE 8 CONDITIONS SIGNIFICANTLY ASSOCIATED WITH OSA(S): MAGNITUDE OF ASSOCIATION

Condition	OSA(S) severity	Magnitude (95% CI)
All-cause mortality	Severe	RR = 1.54 (1.21 - 1.97)
Cardiovascular mortality	Severe	RR = 2.96 (1.45 - 6.01)
Cancer	Overall	RR = 1.40 (1.01 - 1.95)
Diabetic retinopathy	Overall	OR = 2.01 (1.49 - 2.72)
Diabetic kidney disease	Overall	OR = 1.59 (1.16 - 2.18)
Type 2 diabetes	Moderate-severe	RR = 1.63 (1.09 - 2.45)
Metabolic syndrome	Mild	OR = 2.39 (1.65 - 3.46)
	Moderate-severe	OR = 3.42 (2.28 - 5.13)
Erectile dysfunction	Overall (men)	RR = 1.82 (1.12 - 2.97)
Female sexual dysfunction	Overall (women)	RR = 2.00 (1.29 - 3.08)
Stroke	Severe	RR = 2.15 (1.42 - 3.24)
Glaucoma	Overall	OR = 1.24 (1.20 - 1.28)
Resistant hypertension	Overall	OR = 2.84 (1.70 - 3.98)
Essential hypertension	Mild	OR = 1.18 (1.09 - 1.27)
	Moderate	OR = 1.32 (1.20 - 1.43)
	Severe	OR = 1.56 (1.29 - 1.84)
Ischemic heart disease	Moderate	RR = 1.38 (1.04 - 1.83)
	Severe	RR = 1.63 (1.18 - 2.26)
Aortic dissection	Mild	OR = 1.60 (1.01 - 2.53)
	Moderate-severe	OR = 4.43 (2.59 - 7.59)
Non-alcoholic fatty liver disease	Overall	OR = 2.34 (1.71 - 3.18)
Gastroesophageal reflux disease	Overall	OR = 1.53 (1.07 - 2.08)
Pre-eclampsia	Overall (women)	RR = 1.96 (1.34 - 2.86)
Preterm delivery	Overall (women)	RR = 1.90 (1.24 - 2.91)
Cesarean delivery	Overall (women)	RR = 1.87 (1.52 - 2.29)
Car accidents	Overall	OR = 2.43 (1.21 - 4.89)
Work accidents	Overall	OR = 1.78 (1.03 - 3.07)

4.1.2.5.1 *Conditions prevalence and PAF calculation*

For the conditions found to be significantly associated with OSA(S) presented in Table 8 above, we proceeded with the search of prevalence data for Italy using different sources. Results are displayed in Table 9. When prevalence rates were reported, we derived the total number of prevalent cases using ISTAT data on Italian population by age and sex [92]. These data are fundamental in order to calculate PAF and attribute a part of the burden of these conditions to OSA(S). It is worth noting that for stroke and aortic dissection we used incidence data rather than prevalence.

TABLE 9 PREVALENCE OF CONDITIONS SIGNIFICANTLY ASSOCIATED WITH OSA(S)

Condition	Prevalence (adult population aged 15-74)		Source
	n	%	
All-cause mortality	148,527	0.3%	ISTAT (2019) [92]
Cardiovascular mortality	32,471	0.1%	ISTAT (2019) [92]
Cancer†	1,890,000	4.2%	AIOM-AIRTUM (2018) [93]
Diabetic retinopathy	1,191,175	2.6%	AMD et al (2015) [94]
Diabetic kidney disease	688,541	1.5%	AMD-SID (2018) [95] IDF (2017) [96]
Type 2 diabetes	3,098,432	6.8%	IDF (2017) [96]
Metabolic syndrome	14,948,577	33.0%	Tocci et al (2015) [97]
Erectile dysfunction‡	2,243,158	10.0%	Nicolosi et al (2003) [98]
Female sexual dysfunction‡‡	6,653,836	29.0%	Graziottin et al (2007) [99]
Stroke∫	73,116	0.2%	Stevens et al (2017) [100]
Glaucoma¥	811,685	1.8%	Tham et al (2014) [101]
Resistant hypertension	722,517	1.6%	Giampaoli et al (2015) [102] Dovellini (2000) [103]
Essential hypertension	13,727,826	30.3%	Giampaoli et al (2015) [102] Dovellini (2000) [103]
Ischemic heart disease	2,276,838	5.0%	Giampaoli et al (2015) [102]
Aortic dissection∫	1,609	0.004%	Pacini et al (2013)
Non-alcoholic fatty liver disease	9,285,722	20.5%	Younossi et al (2016) [104]
Gastroesophageal reflux disease	4,892,262	10.8%	Darbà et al (2011) [105]
Pre-eclampsia‡‡,*	9,163	0.04%	Fox et al (2017) [106]
Preterm delivery‡‡	27,947	0.1%	Merinopoulou et al (2018) [107]
Cesarean delivery‡‡	165,440	0.7%	OECD (2019) [108]
Car accidents	217,096	0.5%	ISTAT-ACI (2017) [109]
Work accidents **	25,587	0.1%	ISTAT-ACI (2017) [109]

*Note. †Consistently with cost data presented in next section, we considered prevalence of breast, colorectal, prostate, lung and central nervous system cancers. ‡The reference population for the calculation of prevalence rate is Italian male population. ‡‡The reference population for the calculation of prevalence rate is Italian male population. ¥ We used European prevalence data. ∫Incidence data were considered. *We used Irish prevalence data. **We considered the number of commercial motor vehicle crashes as the studies included in Garbarino et al (2016) are mostly focused on these work-related accidents.*

Using data on magnitude of association (i.e. RR or OR) and prevalence of OSA(S) and other conditions, the PAF was calculated for each clinical and non-clinical consequence identified, using the formulas presented in the method section (see §3.1.1.4). The PAF was computed both for mean estimate and the interval of variation (95% CI). It is worth underlining that for car and work accidents the PAF was estimated considering only OSA population with excessive daytime sleepiness (EDS). In particular, we used data provided by Young et al (1993), who estimated a

prevalence of EDS among 30–60 year-old adults with OSA (AHI≥5) equal to 19% [1]. Moreover, for the conditions for which authors reported only the estimate for overall OSA(S), we adopted a conservative approach and provided also estimates referred to moderate-severe subpopulation. This approach is in line with elicited expert opinion, as Prof. Ferini-Strambi suggested that, usually, only moderate-severe patients develop comorbidities. Instead, for the conditions for which authors provided estimates stratified by OSA(S) severity, we considered always the data illustrated in the base-case scenario.

Table 10 provides the results on PAF (using both original estimates and the conservative approach), which can be interpreted as the proportion of each condition influenced by the presence of OSA(S) disease. Table 11 shows PAF estimates ultimately used to calculate the total number of prevalent (incident) cases.

Through the multiplication of PAF by conditions' prevalence (or incidence when appropriate, i.e. stroke and aortic dissection), we obtained the number of prevalent (incident) cases for each condition influenced by OSA(S), stratified by OSA(S) severity (Table 12).

Table 13 provides the total number of prevalent (incident) cases irrespective of OSA(S) severity, obtained according to the conservative approach.

TABLE 10 POPULATION ATTRIBUTABLE FRACTION – BASE-CASE AND CONSERVATIVE APPROACH

Condition	OSA(S) severity	PAF		PAF – Conservative approach*	
		Mean	95% CI	Mean	95% CI
All-cause mortality	Severe	7.5%	3.1% - 12.7%		
Cardiovascular mortality	Severe	22.7%	6.3% - 42.9%		
Cancer	Overall	17.8%	0.5% - 33.9%	9.7%	0.3% - 20.4%
Diabetic retinopathy	Overall	34.5%	20.4% - 47.2%	20.7%	11.3% - 30.7%
Diabetic kidney disease	Overall	23.8%	7.8% - 38.4%	13.5%	4.1% - 23.7%
Type 2 diabetes	Moderate-severe	14.5%	2.4% - 28.1%		
Metabolic syndrome	Mild	16.4%	9.3% - 23.4%		
	Moderate-severe	23.2%	15.5% - 30.7%		
Erectile dysfunction	Overall (men)	33.3%	6.8% - 54.6%	22.8%	4.1% - 41.5%
Female sexual dysfunction	Overall (women)	32.4%	12.2% - 50.0%	15.3%	5.0% - 27.2%
Stroke	Severe	14.7%	5.9% - 25.1%		

Glaucoma	Overall	11.3%	9.7% - 12.8%	6.0%	5.1% - 6.8%
Resistant hypertension	Overall	49.3%	27.1% - 61.1%	32.5%	15.6% - 43.7%
Essential hypertension	Mild	3.2%	1.7% - 4.6%		
	Moderate	2.4%	1.5% - 3.2%		
	Severe	4.9%	2.7% - 6.8%		
Ischemic heart disease	Moderate	4.4%	0.5% - 9.1%		
	Severe	8.6%	2.6% - 15.9%		
Aortic dissection	Mild	13.9%	0.3% - 29.2%		
	Moderate-severe	48.1%	30.0% - 64.0%		
Non-alcoholic fatty liver disease	Overall	34.7%	22.5% - 45.7%	19.9%	12.2% - 27.5%
Gastroesophageal reflux disease	Overall	20.0%	3.3% - 33.4%	11.0%	1.6% - 19.6%
Pre-eclampsia	Overall (women)	31.5%	14.0% - 47.2%	14.7%	5.8% - 25.1%
Preterm delivery	Overall (women)	30.2%	10.3% - 47.8%	13.9%	4.1% - 25.6%
Cesarean delivery	Overall (women)	29.5%	20.0% - 38.2%	13.5%	8.6% - 18.8%
Car accidents†	Overall	8.2%	1.9% - 12.8%	5.3%	1.0% - 9.7%
Work accidents†	Overall	5.6%	0.3% - 10.0%	3.3%	0.2% - 6.8%

*Note. *The conservative approach provides estimates referred to moderate-severe subpopulation for those conditions for which authors reported only the estimate for overall OSA(S). For the conditions for which authors provided estimates stratified by OSA(S) severity, we considered the data illustrated in the base-case scenario (column "PAF"). † Only OSA population with excessive daytime sleepiness was considered for PAF calculation.*

TABLE 11 POPULATION ATTRIBUTABLE FRACTION USED FOR THE ESTIMATION OF PREVALENT (INCIDENT) CASES

Condition	OSA(S) severity	PAF	
		Mean	95% CI
All-cause mortality	Severe	7.5%	3.1% - 12.7%
Cardiovascular mortality	Severe	22.7%	6.3% - 42.9%
Cancer	Overall*	9.7%	0.3% - 20.4%
Diabetic retinopathy	Overall*	20.7%	11.3% - 30.7%
Diabetic kidney disease	Overall*	13.5%	4.1% - 23.7%
Type 2 diabetes	Moderate-severe	14.5%	2.4% - 28.1%
Metabolic syndrome	Mild	16.4%	9.3% - 23.4%
	Moderate-severe	23.2%	15.5% - 30.7%
Erectile dysfunction	Overall (men)*	22.8%	4.1% - 41.5%
Female sexual dysfunction	Overall (women)*	15.3%	5.0% - 27.2%
Stroke	Severe	14.7%	5.9% - 25.1%
Glaucoma	Overall*	6.0%	5.1% - 6.8%
Resistant hypertension	Overall*	32.5%	15.6% - 43.7%

Essential hypertension	Mild	3.2%	1.7% - 4.6%
	Moderate	2.4%	1.5% - 3.2%
	Severe	4.9%	2.7% - 6.8%
Ischemic heart disease	Moderate	4.4%	0.5% - 9.1%
	Severe	8.6%	2.6% - 15.9%
Aortic dissection	Mild	13.9%	0.3% - 29.2%
	Moderate-severe	48.1%	30.0% - 64.0%
Non-alcoholic fatty liver disease	Overall*	19.9%	12.2% - 27.5%
Gastroesophageal reflux disease	Overall*	11.0%	1.6% - 19.6%
Pre-eclampsia	Overall (women)*	14.7%	5.8% - 25.1%
Preterm delivery	Overall (women)*	13.9%	4.1% - 25.6%
Cesarean delivery	Overall (women)*	13.5%	8.6% - 18.8%
Car accidents†	Overall*	5.3%	1.0% - 9.7%
Work accidents†	Overall*	3.3%	0.2% - 6.8%

*Note. *For these conditions, conservative estimates were reported.*

TABLE 12 NUMBER OF PREVALENT CASES FOR EACH CONDITION INFLUENCED BY OSA(S), STRATIFIED BY OSA(S) SEVERITY

Condition	OSA(S) severity	Condition prevalence (adult population aged 15-74)	# prevalent cases influenced by OSA(S)		# prevalent cases influenced by OSA(S) – Conservative approach*	
			Mean	95% CI	Mean	95% CI
All-cause mortality	Severe	148,527	11,129	4,536 - 18,866		
Cardiovascular mortality	Severe	32,471	7,377	2,053 - 13,932		
Cancer	Overall	1,890,000	335,724	10,151 - 640,826	184,224	5,089 - 385,822
Diabetic retinopathy	Overall	1,191,175	411,019	243,114 - 562,438	246,930	134,940 - 365,156
Diabetic kidney disease	Overall	688,541	164,048	53,940 - 264,652	92,915	28,052 - 163,199
Type 2 diabetes	Moderate-severe	3,098,432	450,426	73,506 - 871,747		
Metabolic syndrome	Mild	14,948,577	2,454,641	1,395,519 - 3,503,557		
	Moderate-severe		3,470,981	2,319,876 - 4,582,779		
Erectile dysfunction	Overall (men)	2,243,158	747,919	153,000 - 1,224,328	511,257	92,892 - 930,756
Female sexual dysfunction	Overall (women)	6,653,836	2,158,001	813,039 - 3,324,254	1,014,992	330,099 - 1,812,570
Stroke†	Severe	73,116	10,757	4,333 - 18,388		
Glaucoma	Overall	811,685	91,503	79,132 - 103,784	48,430	41,554 - 55,365
Resistant hypertension	Overall	722,517	356,158	195,965 -441,401	235,129	113,056 - 315,832
Essential hypertension	Mild	13,727,826	442,561	231,508 - 638,035		
	Moderate		327,235	212,744 - 433,898		
	Severe		673,131	373,788 - 930,531		
Ischemic heart disease	Moderate	2,276,838	99,296	10,877 - 206,232		
	Severe		196,584	59,858 - 361,920		
Aortic dissection†	Mild	1,609	224	4 - 470		
	Moderate-severe		774	483 - 1,030		
Non-alcoholic fatty liver disease	Overall	9,285,722	3,222,264	2,086,183 - 4,244,413	1,844,121	1,136,096 - 2,549,084
Gastroesophageal reflux disease	Overall	4,892,262	978,527	159,057 - 1,635,694	536,097	80,680 - 957,796

Pre-eclampsia	Overall (women)	9,163	2,890	1,286 - 4,322	1,350	528 - 2,298
Preterm delivery	Overall (women)	27,947	8,431	2,887 - 13,367	3,896	1,157 - 7,150
Cesarean delivery	Overall (women)	165,440	48,736	33,046 - 63,266	22,400	14,160 - 31,176
Car accidents	Overall	217,096	17,906	4,181 - 27,877	11,420	2,202 - 21,012
Work accidents	Overall	25,587	1,440	77 - 2,565	845	39 - 1,742

*Note. *The conservative approach provides estimates referred to moderate-severe subpopulation for those conditions for which authors reported only the estimate for overall OSA(S). For the conditions for which authors provided estimates stratified by OSA(S) severity, we considered the data illustrated in the base-case scenario (column "# prevalent cases influenced by OSA(S)").† Incidence data were considered.*

TABLE 13 TOTAL NUMBER OF PREVALENT CASES FOR EACH CONDITION INFLUENCED BY OSA(S)

Condition	# prevalent cases influenced by OSA(S)	
	Mean	95% CI
All-cause mortality	11,129	4,536 - 18,866
Cardiovascular mortality	7,377	2,053 - 13,932
Cancer	184,224	5,089 - 385,822
Diabetic retinopathy	246,930	134,940 - 365,156
Diabetic kidney disease	92,915	28,052 - 163,199
Type 2 diabetes	450,426	73,506 - 871,747
Metabolic syndrome	5,925,622	3,715,395 - 8,086,336
Erectile dysfunction	511,257	92,892 - 930,756
Female sexual dysfunction	1,014,992	330,099 - 1,812,570
Stroke†	10,757	4,333 - 18,388
Glaucoma	48,430	41,554 - 55,365
Resistant hypertension	235,129	113,056 - 315,832
Essential hypertension	1,442,927	818,040 - 2,002,465
Ischemic heart disease	295,880	70,735 - 568,152
Aortic dissection†	998	488 - 1,500
Non-alcoholic fatty liver disease	1,844,121	1,136,096 - 2,549,084
Gastroesophageal reflux disease	536,097	80,680 - 957,796
Pre-eclampsia	1,350	528 - 2,298
Preterm delivery	3,896	1,157 - 7,150
Cesarean delivery	22,400	14,160 - 31,176
Car accidents	11,420	2,202 - 21,012
Work accidents	845	39 - 1,742

Note. Data reported are referred to the base-case scenario for those conditions for which authors provided estimates stratified by OSA(S) severity, while to the conservative approach for those conditions for which authors reported only the estimate for overall OSA(S). † Incidence data were considered.

4.2 Assessment of cost of the disease

Through an extensive literature review, we retrieved cost data for the clinical and non-clinical conditions significantly associated with OSA(S). As anticipated in the previous section, it was not possible to retrieve cost data for three conditions (spontaneous cerebrospinal fluid leak, floppy eyelids syndrome, nonarteritic anterior ischemic optic neuropathy). Figure 6 summarizes the full systematic literature review process and its results, from study screening to final inclusion for COI analysis.

FIGURE 6 SYSTEMATIC LITERATURE REVIEW RESULTS AND STUDIES INCLUDED FOR COI ANALYSIS

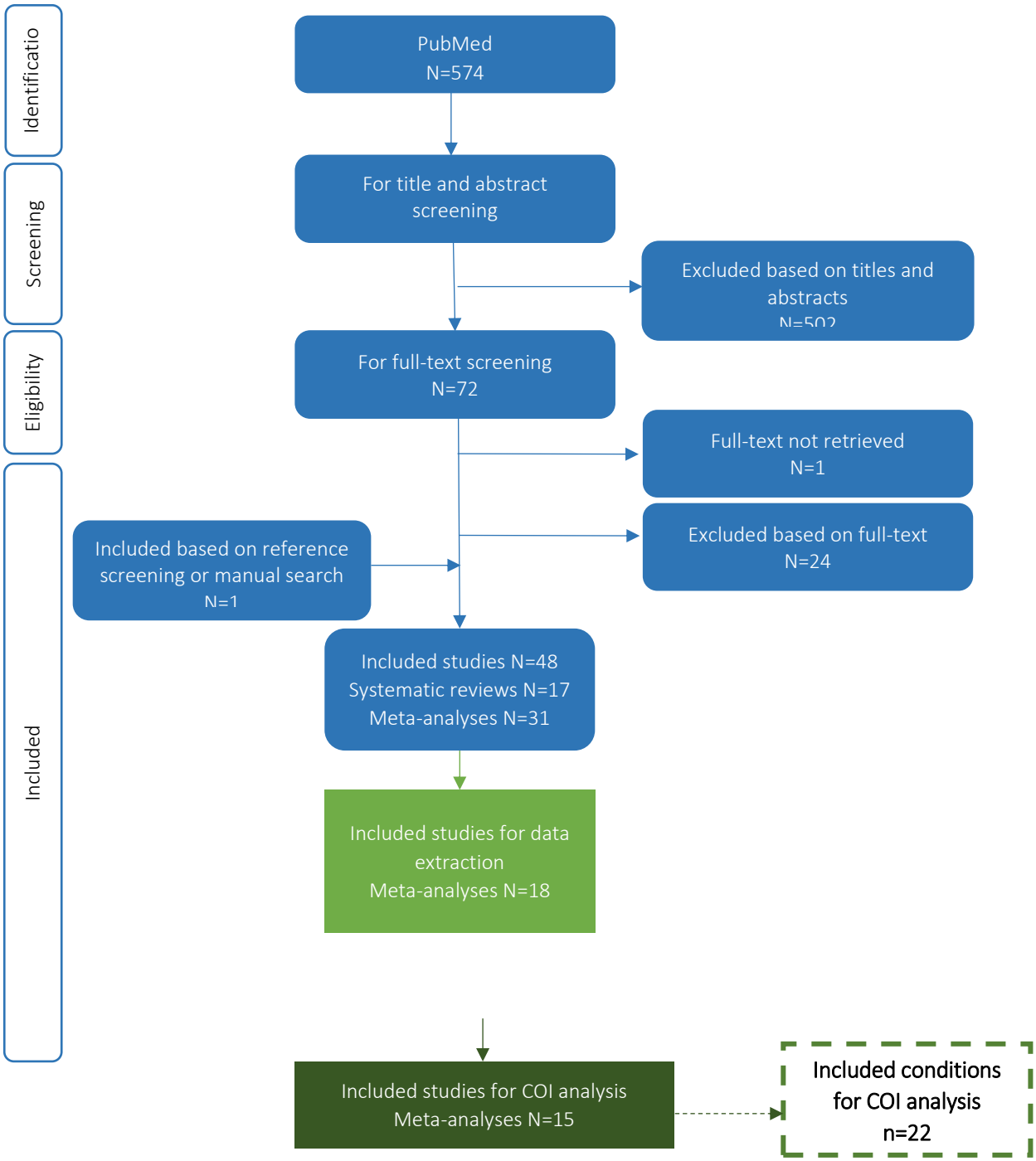


Table 14 displays the costs expressed in 2018 Euros standardized for inflation and PPP. As regards productivity losses, we included only costs due to morbidity, as costs due to all-cause and cardiovascular premature mortality are calculated in the next section (see §4.2.1). The table provided in Appendix 3 shows the cost components per patient/year as retrieved from the literature.

By multiplying the cost per patient by the number of prevalent (or incident) cases due to OSA(S) (presented in Table 13 and calculated adopting the conservative approach in order to avoid overestimation of costs), we obtained the total economic burden influenced by the sleep disorder in Italy in one year. Results on average economic burden associated with OSA(S) are reported in Table 15, while the table in Appendix 4 provides 95% confidence interval estimates of total cost.

Results suggest that the economic burden due to conditions associated with OSA(S) in Italy is substantial and is approximately equal to 31 billion of Euros per year, i.e. around 520 Euros per Italian resident. The main driver of economic burden are direct healthcare costs, which account for 60% of total cost, followed by indirect costs due to morbidity (36%) and direct non-healthcare costs (4%). The mean annual cost per moderate-severe OSA(S) patient is approximately 2500 Euros.

Figure 7 graphically displays the annual cost per OSA(S) patient (panel A) and per resident (panel B), providing both mean and confidence interval estimates. Figure 8 shows the mean direct healthcare cost (per patient and per resident) in comparison to health expenditure per capita in Italy, derived by Armeni et al (2018) [110]. It is worth noting that the cost per resident generated by conditions which are consequences of OSA(S) represents almost the 10% of health expenditure per capita in our country.

TABLE 14 ANNUAL COST PER PATIENT OF CLINICAL AND NON-CLINICAL CONDITIONS ASSOCIATED WITH OSA(S)

Condition	Mean annual cost per patient				Source**
	Direct healthcare cost	Direct non-healthcare cost	Productivity losses cost*	Total cost	
Cancer	€ 5,718	€ 4,581	€ 119	€ 10,418	Luengo-Fernandez et al (2013) [111]
Diabetic retinopathy	€ 307	€ 242	€ 579	€ 1,128	Romero-Aroca et al (2016) [112] Happich et al (2008) [113]
Diabetic kidney disease	€ 797			€ 797	Zhou et al (2017) [114]
Type 2 diabetes	€ 3,866		€ 4,352	€ 8,217	Marcellusi et al (2016) [115]
Metabolic syndrome	€ 1,900		€ 90	€ 1,990	Lucioni et al (2005) [116] Schultz et al (2009) [117]
Erectile dysfunction	€ 407			€ 407	Wilson et al (2002) [118]
Female sexual dysfunction	€ 761			€ 761	Goldmeier et al (2004) [119]
Stroke	€ 13,452	€ 8,490	€ 907	€ 22,848	Fattore et al (2012) [120]
Glaucoma	€ 985			€ 985	Koleva et al (2007) [121]
Resistant hypertension	€ 239			€ 239	Mennini et al (2015) [122]
Essential hypertension	€ 239			€ 239	Mennini et al (2015) [122]
Ischemic heart disease	€ 1,496	€ 348	€ 458	€ 2,303	Leal et al (2006) [123]
Aortic dissection	€ 38,064			€ 38,064	Luebke et al (2014) [124]
Non-alcoholic fatty liver disease	€ 1,197		€ 4,424	€ 5,622	Younossi et al (2016) [104]
Gastroesophageal reflux disease	€ 308		€ 186	€ 494	Darbà et al (2011) [105]
Pre-eclampsia	€ 4,668			€ 4,668	Fox et al (2017) [106]
Preterm delivery	€ 9,025		€ 9,782	€ 18,807	Merinopoulou et al (2018) [107] Institute of Medicine (2007) [125]
Cesarean delivery	€ 2,515		€ 943	€ 3,458	Pizzo (2011) [126]
Car accidents†	€ 9,348		€ 23,834	€ 33,182	Wijnen et al (2017) [127]
Work accidents†‡	€ 9,348		€ 23,834	€ 33,182	Wijnen et al (2017) [127]

*Note. *Only productivity losses due to morbidity are included. *In "Source" column, we reported the references from which cost data were extracted. However, in this table we provide costs already adjusted for inflation and PPP, therefore they may not coincide with those presented in the original studies. ¥ These costs were calculated by estimating the annual quality-adjusted life-years (QALYs) lost due to NAFLD and by applying a monetary value to this QALY estimate. ¥¥ Also direct non-healthcare costs are included in this estimate, but unfortunately from the data provided in the study it was not possible to isolate them. †We adopted a*

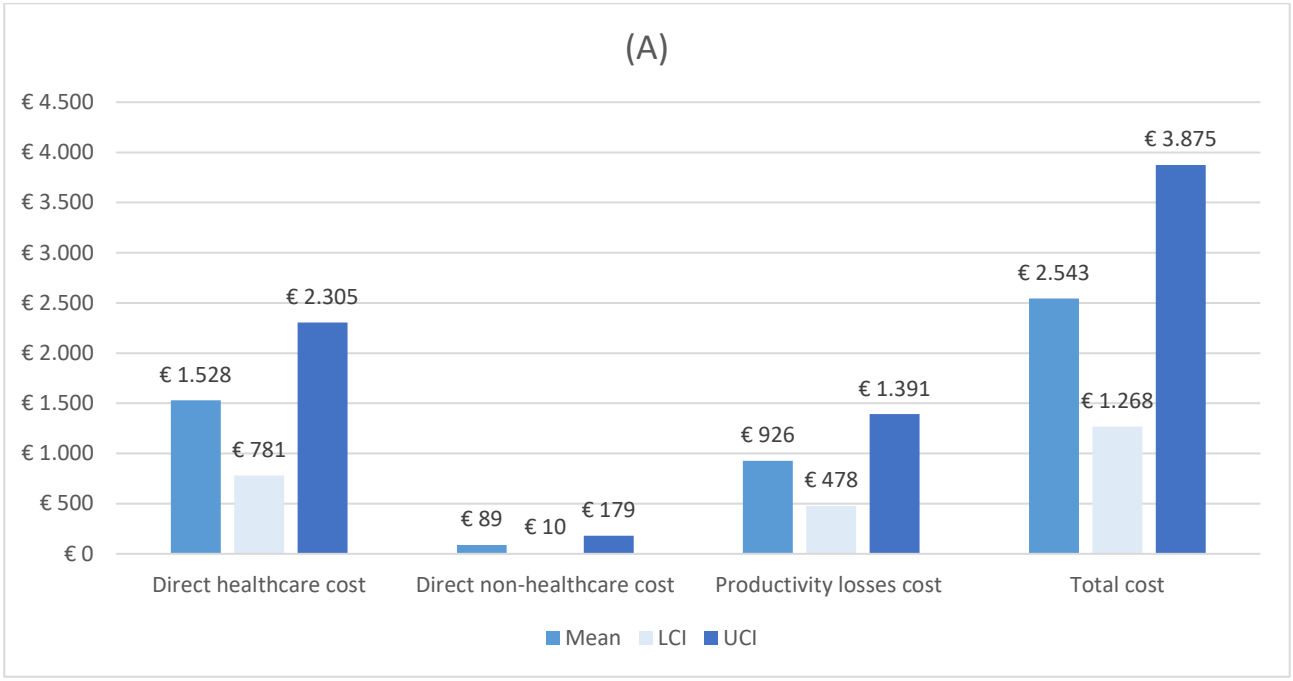
conservative approach and considered only costs due to serious and slight injuries, excluding costs due to fatal crashes. ‡We considered costs due to motor vehicle accidents as the studies included in Garbarino et al (2016) are mostly focused on commercial motor vehicle crashes.

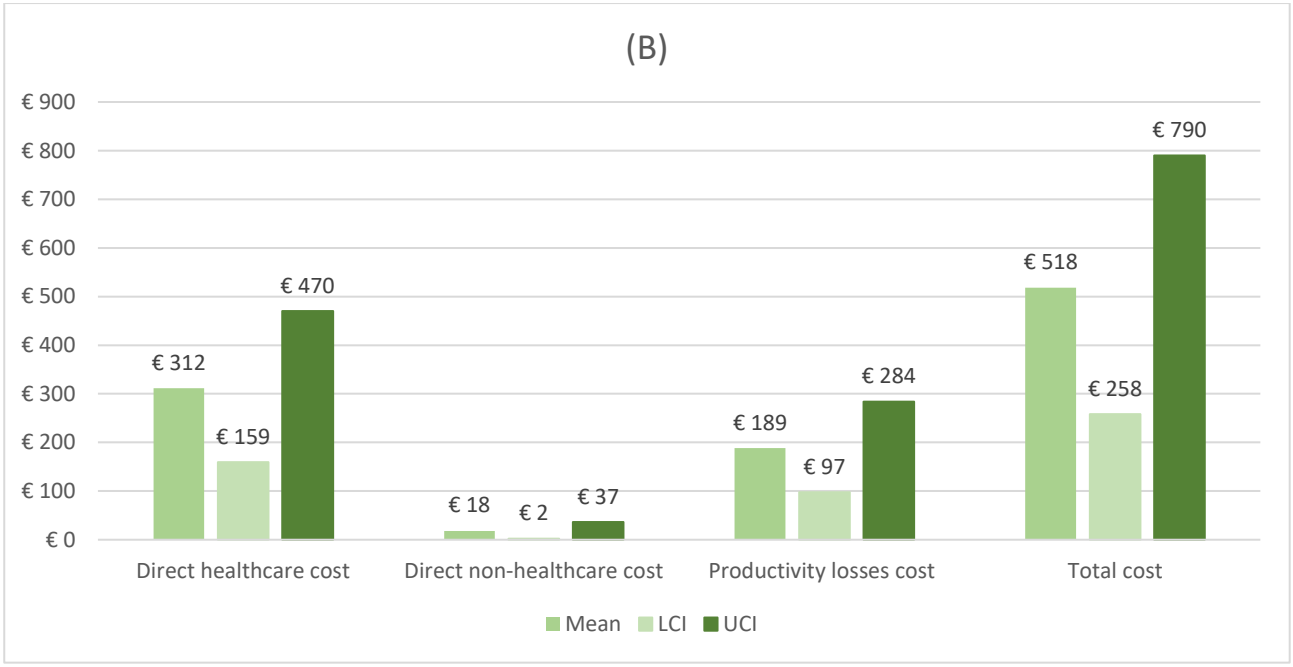
TABLE 15 ANNUAL ECONOMIC BURDEN INFLUENCED BY OSA(S) IN ITALY

Condition	Direct healthcare cost	Direct non-healthcare cost	Productivity losses cost*	Total cost
Cancer	€ 1,053,335,086	€ 843,866,787	€ 21,976,498	€ 1,919,178,370
Diabetic retinopathy	€ 75,903,881	€ 59,787,476	€ 142,872,419	€ 278,563,776
Diabetic kidney disease	€ 74,076,551			€ 74,076,551
Type 2 diabetes	€ 1,741,141,727		€ 1,960,219,449	€ 3,701,361,176
Metabolic syndrome	€ 11,260,422,980		€ 531,818,651	€ 11,792,241,631
Erectile dysfunction	€ 208,151,669			€ 208,151,669
Female sexual dysfunction	€ 772,808,563			€ 772,808,563
Stroke	€ 144,697,413	€ 91,324,306	€ 9,755,712	€ 245,777,431
Glaucoma	€ 47,690,291			€ 47,690,291
Resistant hypertension	€ 56,172,997			€ 56,172,997
Essential hypertension	€ 344,718,771			€ 344,718,771
Ischemic heart disease	€ 442,622,880	€ 103,029,886	€ 135,642,496	€ 681,295,262
Aortic dissection	€ 37,984,396			€ 37,984,396
Non-alcoholic fatty liver disease	€ 2,208,249,940		€ 8,158,942,384	€ 10,367,192,324
Gastroesophageal reflux disease	€ 165,097,914		€ 99,881,300	€ 264,979,215
Pre-eclampsia	€ 6,302,021			€ 6,302,021
Preterm delivery	€ 35,163,957		€ 38,113,552	€ 73,277,509
Cesarean delivery	€ 56,345,557		€ 21,117,043	€ 77,462,600
Car accidents	€ 106,754,952		€ 272,184,561	€ 378,939,513
Work accidents	€ 7,900,413		€ 20,143,051	€ 28,043,464
Total	**€ 18,845,541,959**	**€ 1,098,008,454**	**€ 11,412,667,117**	**€ 31,356,217,529**
Cost per moderate-severe OSA(S) patient †	**€ 1,528**	**€ 89**	**€ 926**	**€ 2,543**
Cost per resident ††	**€ 312**	**€ 18**	**€ 189**	**€ 518**

*Note. *Only productivity losses due to morbidity are included. † Moderate-severe OSA(S) patients=12,329,614 (cfr Table 4). †† Italian resident population= 60,483,973 (source: ISTAT).*

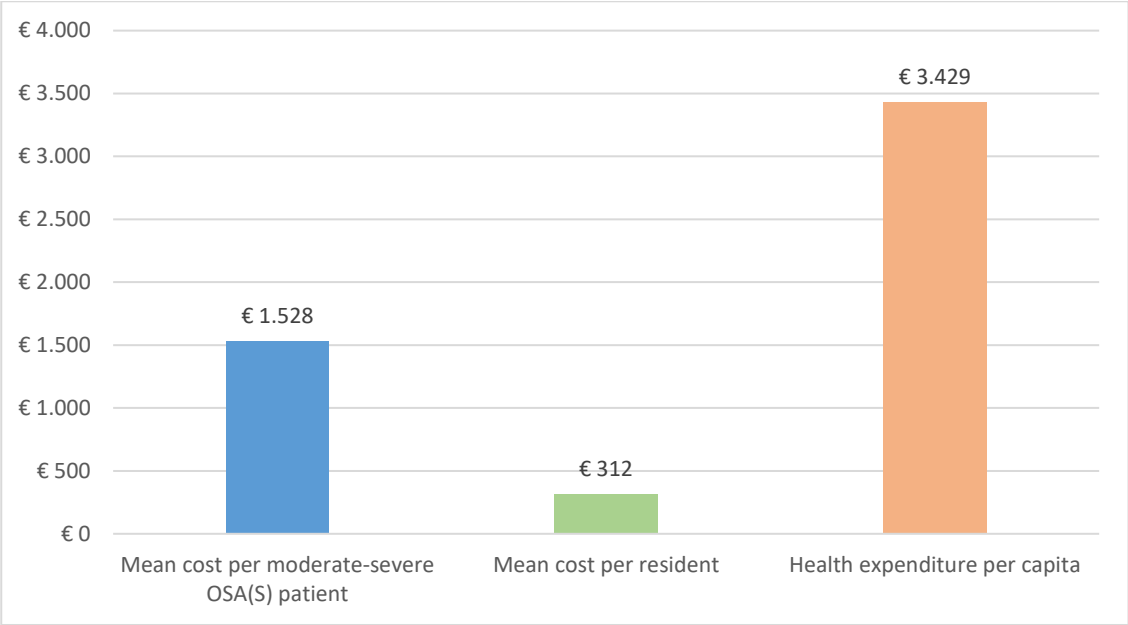
FIGURE 7 AVERAGE ANNUAL COST AND 95%CI PER MODERATE-SEVERE OSA(S) PATIENT (PANEL A) AND PER ITALIAN RESIDENT (PANEL B)





Note. LCI: lower confidence interval. UCI: upper confidence interval.

FIGURE 8 MEAN DIRECT HEALTHCARE COST (PER PATIENT AND PER RESIDENT) COMPARED TO PUBLIC HEALTH EXPENDITURE PER CAPITA



Note. Source for health expenditure: Armeni et al (2018).

4.2.1 Societal cost due to premature death

Premature death causes substantial production losses, which contribute at increasing the total economic burden of a disease. Results presented in Table 13 suggest that OSA(S) has an important impact on both all-cause and cardiovascular mortality. In order to consider the burden of premature death associated with OSA(S), we estimated productivity costs through the friction method. The friction method assumes that for long term absences, as in the case of premature death, an individual's work can be replaced by the market. Therefore, although a disease may cause loss in production, this loss is limited to a period in which the market adapts to the changed situation, called friction period [128]. This approach is more conservative than the human capital method, which considers earnings lost over a lifetime [129]. The human capital method, in fact, assumes that, if an individual had not died, he would have continued to be productive for a number of years according to his life expectancy. This method has been criticised because it estimates the value of potential rather than actual lost production, without considering the capacity of the market to replace or reallocate employees over jobs [128].

In the present analysis, we considered only productivity losses of employed people, excluding indirect costs of people out of the labor market (e.g. housewives, students). Productivity costs

were estimated for different age groups to account for differences in wages. Age and gender-specific yearly paid production value were drawn from Pradelli and Ghetti (2017) [130]. Employment rates[1] and all-cause mortality data for 2018 (last year available) were retrieved from ISTAT [92]. PAF estimates provided in Table 11 (mean=7.5%, 95%CI: 3.1%-12.7%) were used to identify the number of deaths due to OSA(S) in each age group (in absence of more detailed data, we assumed that the PAF is equal across all age groups). An overview of data used is provided in Table 16.

TABLE 16 DATA FOR PRODUCTION COSTS CALCULATION

Age	# deaths associated with OSA(S)			Employment rate		Annual paid production value	
	Male	Female	Total	Male	Female	Male	Female
15-19	27	10	37	20.8%	14.3%	€ 6,465	€ 3,766
20-24	40	16	56	20.8%	14.3%	€ 7,539	€ 4,368
25-29	46	18	64	69.9%	53.3%	€ 24,001	€ 11,847
30-34	57	27	84	69.9%	53.3%	€ 30,587	€ 14,820
35-39	85	48	133	84.2%	62.6%	€ 30,587	€ 14,820
40-44	173	100	273	84.2%	62.6%	€ 36,498	€ 17,172
45-49	305	189	494	84.1%	60.8%	€ 27,768	€ 11,512
50-54	501	310	811	84.1%	60.8%	€ 32,088	€ 13,293
55-59	732	436	1168	64.2%	43.9%	€ 32,088	€ 13,293
60-64	1067	621	1688	64.2%	43.9%	€ 39,829	€ 15,221
65-69	1647	983	2630	0.0%	0.0%	€ 3,168	€ 507
70-74	2254	1437	3691	0.0%	0.0%	€ 3,168	€ 507

Note. Source for employment rate: ISTAT (2019). Source for annual paid production value: Pradelli and Ghetti (2017).

To our knowledge, there are not available estimates on the friction period for Italy. Therefore, we used the data provided by Oliva and colleagues (2005) for Spain [131]. The authors hypothesized that the cost for the employer of finding and training a replacement for permanent labor leaves is equivalent to the wage paid for the work performed in 75 days (i.e. the friction period). We assumed that the friction period is the same across all age groups.

[1] Employment rates are available until age 64, therefore we assumed an employment rate equal to 0 for people aged 65-74.

Results provided in Table 17 confirm that the productivity losses due to premature death (for all causes) related to OSA(S) are substantial and, on average, amount to more than 17 million Euros for the year considered.

TABLE 17 ANNUAL PRODUCTION COSTS DUE TO PREMATURE DEATH INFLUENCED BY OSA(S)

Age	Production costs due to premature death influenced by OSA(S)	
	Mean	95% CI
15-19	€ 8,541	€ 3,481 - € 14,478
20-24	€ 14,925	€ 6,083 - € 25,300
25-29	€ 182,432	€ 74,350 - € 309,249
30-34	€ 295,315	€ 120,356 - € 500,604
35-39	€ 541,676	€ 220,761 - € 918,223
40-44	€ 1,311,257	€ 534,404 - € 2,222,779
45-49	€ 1,734,865	€ 707,046 - € 2,940,860
50-54	€ 3,293,065	€ 1,342,092 - € 5,582,245
55-59	€ 3,623,670	€ 1,476,831 - € 6,142,671
60-64	€ 6,462,568	€ 2,633,826 - € 10,955,033
Total	**€ 17,468,314**	**€ 7,119,229 - € 29,611,442**
Mean cost per dead OSA(S) patient †	**€ 1,570**	**€ 640 - € 2,661**
Cost per moderate-severe OSA(S) patient ††	**€ 1.4**	**€ 0.6 - € 2.4**
Cost per resident †††	**€ 0.3**	**€ 0.1 - € 0.5**

Note. † Dead patients for all-causes influenced by OSA(S)= 11,129 (cfr Table 13) †† Moderate-severe OSA(S) patients=12,329,614 (cfr Table 4). ††† Italian resident population= 60,483,973 (source: ISTAT).

Using the data on cardiovascular mortality and the corresponding PAF (mean=22.7%, 95% CI: 6.3%-42.9%), we estimated the portion of overall mortality productivity losses due to cardiovascular diseases associated with OSA(S). Results are displayed in Table 18.

TABLE 18 ANNUAL PRODUCTION COSTS DUE TO CARDIOVASCULAR MORTALITY INFLUENCED BY OSA(S)

Age	Production costs due to cardiovascular mortality influenced by OSA(S)	
	Mean	95% CI
15-19	€ 2,063	€ 574 - € 3,895
20-24	€ 3,400	€ 946 - € 6,421
25-29	€ 55,222	€ 15,369 - € 104,284
30-34	€ 134,575	€ 37,453 - € 254,138
35-39	€ 324,025	€ 90,178 - € 611,905
40-44	€ 830,687	€ 231,185 - € 1,568,711
45-49	€ 1,156,147	€ 321,763 - € 2,183,327
50-54	€ 2,285,437	€ 636,051 - € 4,315,937
55-59	€ 2,519,023	€ 701,060 - € 4,757,052
60-64	€ 4,452,966	€ 1,239,288 - € 8,409,209
Total	**€ 11,763,544**	**€ 3,273,867 - € 22,214,880**
Mean cost per dead OSA(S) patient †	**€ 1,595**	**€ 444 - € 3,011**
Cost per moderate-severe OSA(S) patient ††	**€ 1.0**	**€ 0.3 - € 1.8**
Cost per resident †††	**€ 0.2**	**€ 0.1 - € 0.4**

Note. † Dead patients for cardiovascular diseases influenced by OSA(S)=7,377 (cfr Table 13) †† Moderate-severe OSA(S) patients=12,329,614 (cfr Table 4). ††† Italian resident population= 60,483,973 (source: ISTAT).

4.3 Scenario analysis

4.3.1 Consequences of OSA(S) treatment

As reported in Table 5, the number of undiagnosed and untreated patients in Italy is substantial, with negative consequences on economic burden of the disease. Several studies demonstrated that appropriate diagnostic and therapeutic pathways for OSA(S) may have a substantial impact in reducing clinical and non-clinical consequences related to the disease, whereas untreated OSA(S) may result in increased clinical and economic burden [3, 132]. In particular, therapy with CPAP was considered to be effective in preventing and reducing the burden of some of the associated conditions. Through a comprehensive literature review, we identified studies investigating the effect of CPAP therapy on the conditions identified in the previous section. First, we searched for meta-analyses as they provide the best available evidence. If a meta-analysis was not available, we included single studies reporting high quality evidence, e.g. RCTs. Only studies reporting results in terms of OR, RR or HR were included. Unfortunately, for many

conditions (e.g. metabolic syndrome, hypertension, etc), available studies investigated the impact of CPAP only on disease parameters (i.e. on disease severity), with no data on the probability of disease onset. In the absence of reliable data regarding the causal relationship between the use of CPAP and the change in health conditions, we adopted a conservative approach and excluded from this analysis all the conditions for which we could not find in the literature a measure for the causal relationship between the use of CPAP and the probability of disease onset. Results are displayed in Table 19 and suggest a beneficial and significant impact of CPAP on mortality, risk of stroke, car and work-related accidents (all HR/RR/OR<1). It is worth noting that, as reported by authors in the discussion section, the study by McEvoy et al (2016) was not powered to provide definitive answers regarding the effects of CPAP on secondary endpoints, among which diabetes and ischemic heart disease provided in the table below.

TABLE 19 EFFECT OF CPAP ON CONDITIONS ASSOCIATED TO OSA(S)

Condition	Association measure	Magnitude	95% CI	p value	Type of study	Source
All-cause mortality	HR	0.66	0.59 - 0.73	<0.001	Meta-analysis	Fu et al (2017) [133]
Cardiovascular mortality	HR	0.37	0.16 - 0.54	<0.001	Meta-analysis	Fu et al (2017) [133]
Diabetes	HR	0.85	0.61 - 1.19	NS	RCT	McEvoy et al (2016) [134]
Stroke	RR	0.27	0.14 - 0.53	<0.001	Meta-analysis	Kim et al (2016) [135]
Ischemic heart disease	HR	1.07	0.88 - 1.31	NS	RCT	McEvoy et al (2016) [134]
Car accidents	OR	0.30	0.22 - 0.41	<0.001	Meta-analysis	Antonopoulos et al (2011) [136]
Work accidents*	RR	0.28	0.22 - 0.35	<0.001	Meta-analysis	Tregear et al (2010) [137]

*Note. *We considered the impact of CPAP on motor vehicle accidents as the studies included in Garbarino et al (2016) are mostly focused on commercial motor vehicle crashes.*

Considering only the conditions for which a statistically significant effect was found, it was possible to derive the average reduction in the risk of condition onset thanks to CPAP treatment. Results are presented in Table 20 and will be used in scenario analysis. It is important to underline that the exclusion of studies reporting the effect of CPAP on diseases parameters, i.e. on diseases severity, may lead to underestimate the impact of treatment on the clinical and economic burden influenced by OSA(S).

TABLE 20 AVERAGE REDUCTION IN RISK OF CONDITION ONSET AFTER CPAP TREATMENT

Condition	Average reduction in risk of condition onset
All-cause mortality	34%
Cardiovascular mortality	63%
Stroke	73%
Car accidents	70%
Work accidents	72%

Source: Our elaboration from data presented in Table 17

4.3.1.1 *Impact of treating OSA(S) on quality of life*

Several authors investigated the impact of OSA(S) treatment on quality of life (QoL) of both adult patients and their bed partners. Different QoL questionnaires have been used, both generic (e.g. SF-36, EQ-5D) and disease-specific (e.g. SAQLI - Sleep Apnea Quality of Life Index). In the present analysis, we focused on studies providing utility estimates, as they allow to evaluate QoL gains in monetary terms. Utilities are used to represent individuals' preferences for different health states and can take on values from 0 (death) to 1 (perfect health).

In their cross-sectional study performed in Canada, Tousignant et al (1994) [138] found a statistically significant difference ($p<0.001$) in health utility before and after treatment with CPAP, equal to 0.63 and 0.87 respectively. In UK, Jenkinson et al (1997) [139] evaluated the QoL of OSA(S) patients before and after CPAP treatment using three different QoL questionnaires, among which the EQ-5D. In particular, using the EQ-5D, the authors estimated an utility equal to 0.74 (SD=0.21) before treatment and 0.84 (SD=0.25) after 5-7 weeks under treatment, although the difference was not statistically significant. In contrast, results from the Short-Form 36 (SF-36) revealed a statistically significant impact of CPAP on different dimensions of both physical and mental health (Physical Component Score=39.99 vs 46.71 before and after treatment; Mental Component Score=40.40 vs 49.02). Using EQ-5D questionnaire, Chakravorty et al (2002) [140] found a statistically significant change in health utility from 0.73 before treatment to 0.77 after treatment. Moreover, through the standard gamble, the authors found a change from 0.32 before treatment to 0.55 after treatment (these data were also used by Ayas et al (2006) in a cost-effectiveness analysis [141]). In a Spanish study, Mar et al (2003) [142] assessed the cost-effectiveness of CPAP therapy and reported a health utility equal to 0.74 for untreated OSA(S) patients and 0.81 for treated patients. These utility values were used by Guest

and colleagues (2008) [143] to estimate the cost-effectiveness of using CPAP in the treatment of severe OSA(S) in the UK. In another cost-effectiveness study on moderate-severe OSA(S) patients, Català et al (2016) [144] estimated a mean utility value of 0.79 vs 0.84 (p<0.001) before and 1 year after treatment respectively. Moreover, they estimated utility values according to patients' compliance: among compliers, health utility was 0.80 vs 0.87 (p<0.001) before and after treatment; among non-compliers, utility was 0.74 vs 0.70 (p=0.01). In a 12-month multicenter RCT in the UK, McMillan et al (2014) [145] estimated QoL of OSA(S) patients aged 65 years or older receiving CPAP or best supportive care (BSC). For this population, authors found a non significant difference in utility values obtained from EQ-5D questionnaire (0.68 for CPAP patients vs 0.67 for BSC patients), although they found a significant difference in some domains of the SF-36 (e.g. vitality). Moreover, when they assessed QoL with SF-6D (Short-Form 6 Dimensions), CPAP significantly improved QALYs by 0.018.Table 21 provides an overview of the utility values estimated by the studies presented above and the questionnaires used to evaluate OSA(S) patients' quality of life. Further details on the studies are provided in the Appendix 5.

TABLE 21 SUMMARY OF HEALTH UTILITY VALUE ESTIMATED FOR UNTREATED VS TREATED OSA(S) PATIENTS

Study	QoL questionnaire	Health utility values (0-1)			
		Untreated patients	Treated patients	Δ utility (treated-untreated)	p-value
Tousignant et al (1994) [138]	EQ-5D	0.63	0.87	0.24	<0.05
Jenkinson et al (1997) [139]	EQ-5D	0.74	0.84	0.10	NS
Chakravorty et al (2002) [140]	EQ-5D	0.73	0.77	0.04	<0.05
Mar et al (2003) [142] Guest et al (2008) [143]	EQ-5D	0.74	0.81	0.07	n.a.
Català et al (2016) [144]	EQ-5D	0.79	0.84	0.05	<0.001
McMillan et al (2014) [145]	EQ-5D	0.67	0.68	0.01	NS
	SF-6D	-	-	0.02	<0.05

Although some authors have highlighted that the EQ-5D scores may not have sufficient sensitivity to changes in sleepiness due to lack of questions specifically directed at sleepiness or energy, the EQ-5D instrument could still capture the health effects of sleepiness through some of its dimensions, e.g. in terms of its effects on usual activities or anxiety/depression. Moreover, in a HTA study conducted by McDaid and colleagues [146], it has been shown that employing the utility scores calculated from SF-6D, which include a question about energy and vitality, produced very similar results to EQ-5D. Therefore, we feel confident in using EQ-5D derived utilities for the present QoL analysis.

Utility values presented in Table 21 suggest that patients' undertreatment causes a substantial loss in patients' QoL and, ultimately, in quality-adjusted life years (QALYs). QALYs for a single patient can be obtained by multiplying the utility values times the years lived. Since our time perspective is one year, in the present case the QALY for a single patient coincide with the health utility value. Considering the number of untreated patients (see Table 5) and utility values of patients treated vs untreated, it is possible to estimate the amount of QALYs lost due to undertreatment. It is important to consider the QALYs lost both for alive and dead untreated patients. For the latter, we estimated first the proportion of untreated patients among total dead OSA(S) patients in one year (i.e. 11,229, see Table 13) using the HR reported in Table 19. Then, we hypothesized that, on average, the patients died in the middle of the year.

We estimated the amount of QALYs lost due to undertreatment among alive patients according to the formula:

$$QALYs\ lost_{alive} = (utility\ value_{CPAP} - utility\ value_{no\ CPAP}) * \#alive\ untreated\ patients$$

while for dead patients according to the formula:

$$QALYs\ lost_{dead} = \left(utility\ value_{CPAP} - \left(\frac{utility\ value_{no\ CPAP}}{2} + \frac{utility\ value_{dead}}{2}\right)\right) * \#dead\ untreated\ patients$$

For the present analysis, we used the utility values provided by Català and colleagues, which conducted a study with a before-after design. Although RCTs usually represent the best available evidence due to randomization and the presence of a control group, the two RCTs found through literature review present some limitations: the study by Chakravorty et al (2002) had a very small sample of patients (n=57) and a short follow-up (3 months); the study by McMillan et al (2014) focused on older patients (mean age=71) which are not representative of

the patient population considered in the present report (aged 15-74). The selected study by Català and colleagues provides the most recent estimates on QoL, derived from a large sample of patients (n=373) with a sufficiently long follow-up (1 year). A possible drawback of this study is that it considered severe patients (mean AHI=54.3), therefore the health utility gain may be slightly overestimated. However, comparing these results with those provided by Mar et al (2003), which considered less severe patients (mean AHI=41.3) and estimated a utility gain of 0.07, we may conclude that the potential risk of overestimation is acceptable. Using the utility values provided by Català et al, we obtained the following estimates:

$$QALYs\ lost_{alive} = (0.84 - 0.79) * 12{,}092{,}910 = 604{,}645$$

$$QALYs\ lost_{dead} = \left(0.84 - (\frac{0.79}{2} + \frac{0.0}{2})\right) * 6704 = 6{,}704$$

$$QALYs\ lost_{total} = QALYs\ lost_{alive} + QALYs\ lost_{deadl} = 607{,}629$$

Patients' QoL data can be evaluated in monetary terms using a willingness-to-pay (WTP) threshold. The WTP represents a measure of the amount of money a society is willing to invest in order to improve health (in this case, the quality of life of patients). Recently, a WTP threshold for Italy has been empirically estimated by Woods and colleagues [147]. The authors reported a value between 16,712 and 17,928 US dollars, approximately corresponding to 14,860 and 15,940 Euros. Moreover, according to the WHO, an intervention should be considered highly cost-effective if the ICER (Δcost/ΔQALY) is below a country's per-capita gross domestic product (GDP) [148]. Taking into account WHO indications, the threshold for Italy is equal to 26,700 Euros, i.e. the Italian per capita GDP in 2018 (source: Eurostat [149]).

TABLE 22 WILLINGNESS-TO-PAY (WTP) THRESHOLDS FOR ITALY

WTP thresholds	Source
€14,860	Our elaboration from Woods et al (2016)
€15,940	Our elaboration from Woods et al (2016)
€26,700	Our elaboration from WHO and Eurostat

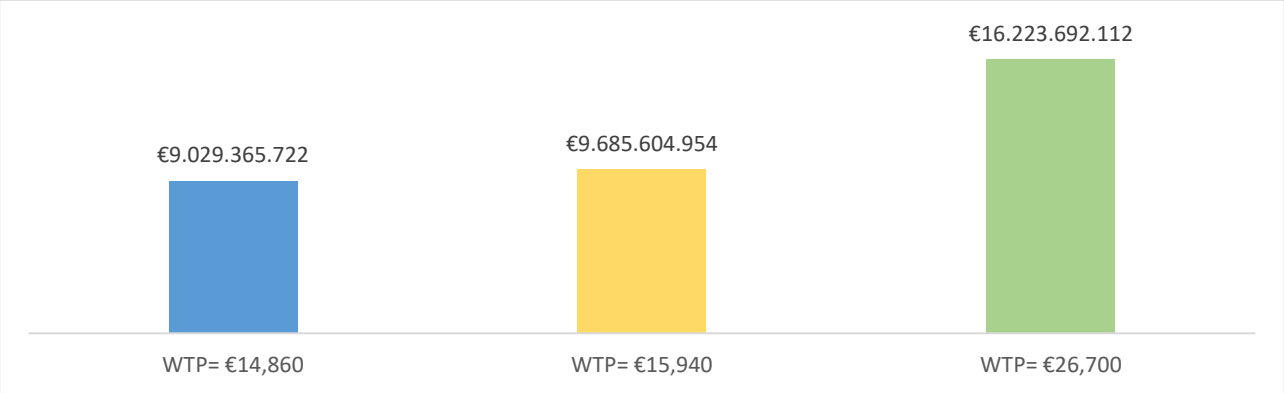
If we multiply WTP thresholds presented in Table 22 to the number of QALYs lost as obtained in the formulas above, it is possible to quantify in monetary terms the cost for the society of impaired quality of life due to OSA(S) undertreatment. Results on QALYs value lost are shown in Table 23.

TABLE 23 QALYS VALUE LOST FOR ALIVE AND DEAD OSA(S) PATIENTS

Untreated patients	QALYs lost due to undertreatment	WTP thresholds for Italy	Value of QALYs lost due to undertreatment
Alive	604,645	€ 14,860	€ 8,985,031,870.32
		€ 15,940	€ 9,638,048,991.45
		€ 26,700	€ 16,144,034,383.42
Dead	2,983	€ 14,860	€ 44,333,851.92
		€ 15,940	€ 47,555,962.29
		€ 26,700	€ 79,657,728.56

Results in Table 23 suggest that the burden in terms of QALYs lost is substantial both for alive and dead patients. Summarizing the estimates for the two groups, we found that the annual QALYs value lost amounts to approximately 9 billion Euros in one year according to the most conservative estimate, as shown in Figure 9.

FIGURE 9 ANNUAL ECONOMIC VALUE OF QALYS LOST DUE TO UNDERTREATMENT OF OSA(S)



Finally, although all the studies reported were conducted in countries different from Italy, it is interesting to compare the health utility values provided in those studies with EQ-5D population reference data (or normative data) for Italy. Normative data, in fact, allow to compare health profiles of patients with specific conditions with data for the average person of the same age and/or gender in the general population, and thus identify the burden of disease in a particular patient population. For Italy, EQ-5D index population norms (based on European VAS value set) are 0.969 for age 18-24, 0.956 for age 25-34, 0.943 for age 35-44, 0.910 for age 45-54, 0.877 for age 55-64 and 0.823 for age 65-74, with a mean equal to 0.913 [150].

By comparing these data with health utilities before CPAP treatment, it is possible to conclude that OSA(S) patients have impaired quality of life compared to age-matched normative values, which may significantly improve after CPAP therapy.

Although some studies analyzed the impact of CPAP on bed partners' QoL, none of them provided health utility values. Therefore, it was not possible to quantify in monetary terms the loss of QALYs for bed partners. However, for the sake of completeness, we reported the main findings of the studies retrieved in the literature. Using a non-validated questionnaire, Kiely and McNicholas (1997) found that bed partners experienced benefits in terms of sleep quality, daytime alertness, mood, overall quality of life and personal relationship after CPAP therapy [151]. The study by McArdle et al (2001) reported that partners' subjective sleep quality was significantly better when OSA(S) patients were treated with CPAP than with placebo [152]. Parish and Lyng (2003) evaluated the QoL before and after CPAP treatment using two questionnaires, i.e. SF-36 and SAQLI. The authors found that bed partners registered significant improvements in several domains of SF-36 (role-physical, vitality, social functioning, and mental health) and in almost all domains of SAQLI (daily functioning, social interactions and emotional functioning) after CPAP treatment of their OSA(S) partners [26]. In a prospective study, Doherty et al (2003) administered the SF-36 and HADS (hospital anxiety and depression scale) to both OSA(S) patients and their bed partners. They found that, after CPAP therapy, bed partners' HADS anxiety scores improved significantly, as well as the SF-36 domains of physical problems, emotional problems, social functioning, mental health and energy and vitality [153].

4.3.2 Scenarios estimation

In this section, different scenarios are simulated in order to estimate what would happen to the economic burden influenced by OSA(S) if an increased number of OSA(S) patients were diagnosed and subsequently treated with CPAP.

Philips S.p.A. provided us with data on the cost of treating an OSA(S) patient with CPAP. In particular, in Italy the device is usually rented by the National Health Service (NHS), at a cost of approximately €0.70 per day. As reported in §4.1.1, in Italy the cost of CPAP treatment is covered by the NHS in the 60% of cases. We assume that the cost is the same for patients for

whom the NHS does not cover CPAP cost. Therefore, for the present analysis we hypothesize that the cost per treated patient is approximately €256 per year[2].

According to a study conducted by the ESADA (European Sleep Apnoea Database) group, in Italy the current practice for diagnosis of OSA(S) patients entails both cardio-respiratory polygraphy (CRPG) and polysomnography (PSG) [154]. The golden standard for objective assessment of OSA(S) is in-hospital, technician-attended polysomnography (PSG). However, the use of this diagnostic test is limited by its high cost and limited accessibility to sleep centres. Therefore, unattended portable PSG and CRPG are often used.

Unfortunately, there are no studies published on peer-reviewed journals providing data on the cost of different diagnostic pathway for OSA(S) in Italy. Based on the data reported in a cost-effectiveness analysis conducted by Català and colleagues [144], we assumed that OSA(S) diagnosis is performed by standard PSG monitored in the hospital in 32.4% of cases. In the rest of cases (67.6%), we assume that half of the patients undergo outpatient PSG and CRPG respectively, in both cases after an initial visit with a specialist (e.g. neurologist). For in-hospital PSG costs, we considered the data provided by a preliminary study conducted by the Sleep Centre of San Raffaele hospital (Milan, Italy) and published on an Italian newspaper (Sanità24 - Il Sole 24 Ore). We assume that the cost for initial visit with a specialist is already included in the costs provided. The cost for inpatient diagnosis can be either covered by NHS or paid by the patient. On the basis of a recent estimate published in OASI (Observatory on Healthcare Organizations and Policies in Italy) report, we assume that costs are not covered by the NHS in the 26% of cases [155]. For outpatient diagnostic pathway, we considered the unit cost (tariff) for diagnostic exams (i.e. PSG and CRPG) and the cost for a consultation with a specialist retrieved from "Nomenclatore dell'assistenza specialistica ambulatoriale", an official document freely accessible from the Italian Ministry of Health website [156]. Figure 10 shows the distribution of patients according to different diagnostic pathways, while Table 24 provides a summary of the cost for OSA(S) diagnosis in Italy. Considering patients distribution across diagnostic pathways and the costs associated with them, OSA(S) diagnosis costs amount to approximately €381 per patient.

[2] €0.70 * 365 days

FIGURE 10 DISTRIBUTION OF PATIENTS BY DIAGNOSTIC PATHWAY

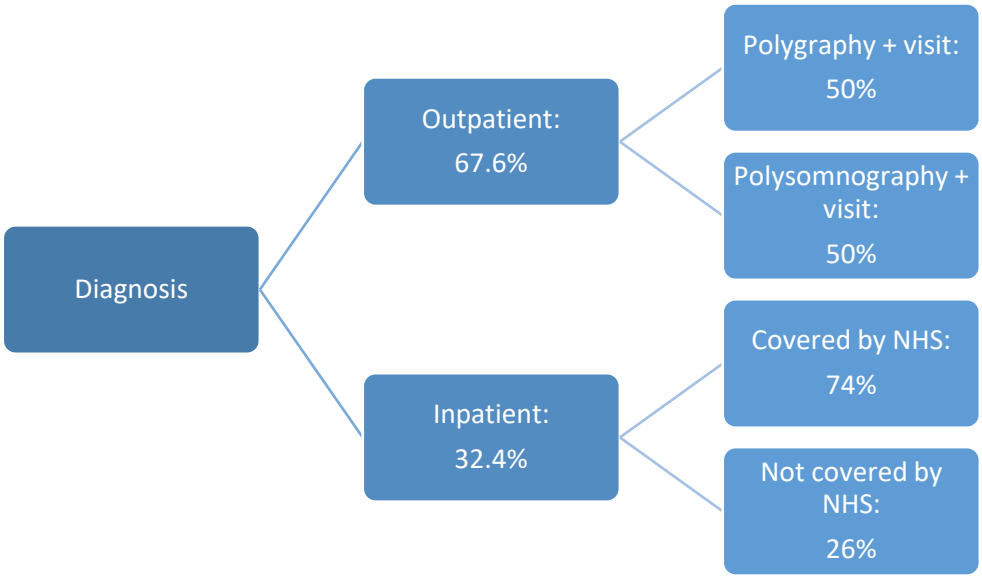


TABLE 24 OSA(S) DIAGNOSTIC TESTS: UNIT COST IN ITALY

Diagnostic test		Unit cost	Source
Outpatient	Initial visit with a specialist	€20.66	Nomenclatore dell'assistenza specialistica ambulatoriale
	Polysomnography	€139.44	
	Polygraphy	€51.13	
Inpatient	Polysomnography covered by NHS	€880	Sanità24 - Il Sole 24 Ore
	Polysomnography not covered by NHS	€1090	

Data presented in Table 20 allow to estimate the potential savings following CPAP treatment, as it has been demonstrated that CPAP helps reducing the onset (and thus costs) of some conditions associated with OSA(S). Moreover, according to utility values provided by Català et al (2016) (see Table 21) and using the three different WTP thresholds provided in Table 22, we are able to estimate the QALYs value gained thanks to CPAP therapy.

Table 25 provides a synthetic overview of the parameters used for scenario analysis and the variation of each parameter with respect to the status quo (i.e. the current scenario) or other scenarios. In each scenario we hypothesize an increasing rate of diagnosis and/or treatment with respect to the previous one, with the objective of reaching around 1 million moderate-severe patients diagnoses and treated, who represent the 8% of moderate-severe OSA(S)

population. Starting from the assumption that the incidence of OSA(S) is quite low, in our models we hypothesize that no new cases arise in the next few years. Moreover, we make the assumption that all patients undergoing diagnosis are true positive and that all patients assigned to treatment actually adhere to CPAP.

TABLE 25 SCENARIOS SUMMARY

	Current scenario	Scenario 1	Scenario 2	Scenario 3
Variation in parameter	-	All diagnosed patients in the current scenario are treated	+50% diagnoses with respect to scenario 1, all newly diagnosed patients are treated	+50% diagnoses with respect to scenario 2, all newly diagnosed patients are treated
# OSA(S) moderate-severe patients	12,329,614			
# diagnosed	460,000	460,000	690,000	1,035,000
# treated with CPAP	230,000	460,000	690,000	1,035,000

Table 26 shows the impact of the three simulated scenarios on cost components. It is worth noting that results reported in the table are related, for each scenario, to the variation of costs with respect to the previous scenario (i.e. they do not report cumulative variation in costs).

Figure 11 provides a graphical representation of the results obtained in Table 26, highlighting the total avoided and rising costs following increased diagnosis and treatment rates of OSA(S) patients. In Appendix 6, figures showing avoided and rising costs per moderate-severe patient are reported.

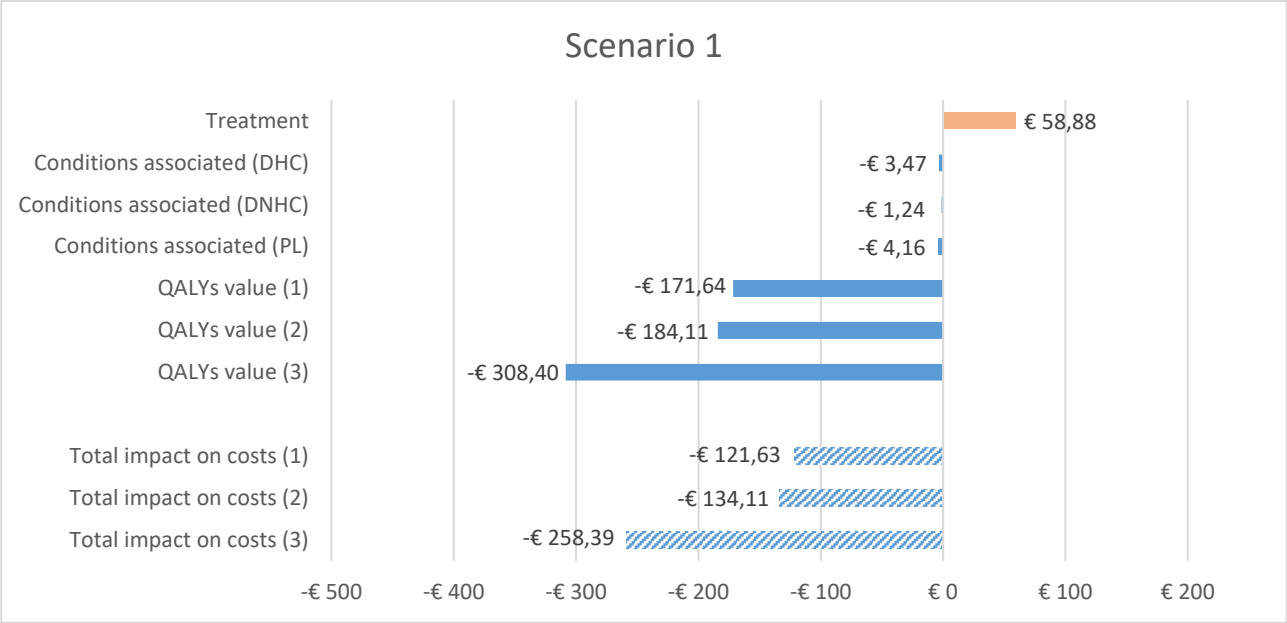
TABLE 26 IMPACT OF SIMULATED SCENARIOS ON COSTS

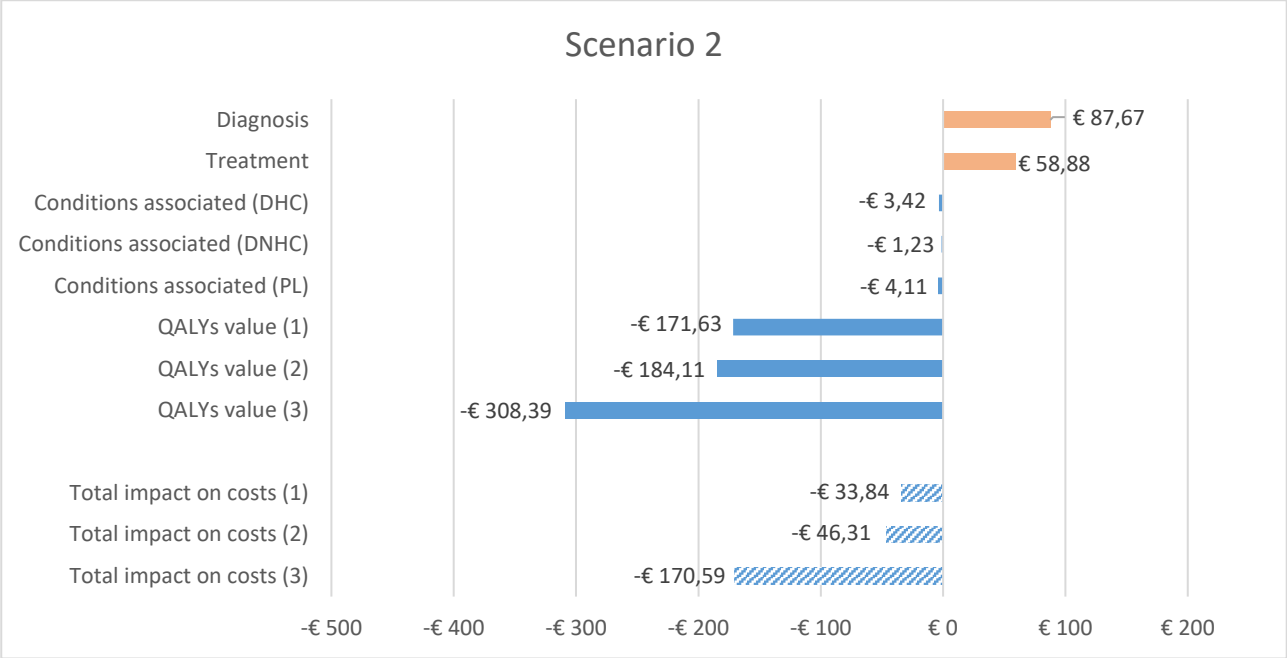
Scenario 1 (all diagnosed patients in the current scenario are treated)				
Rising costs				
Treatment	€ 58,880,000			
Potential savings due to avoided conditions	***Direct healthcare cost***	***Direct non-healthcare cost***	***Productivity losses cost***	***Total cost***
All-cause mortality	€ 0	€ 0	€ 64,524	€ 64,524
Cardiovascular mortality	€ 0	€ 0	€ 138,238	€ 138,238
Stroke	€ 1,970,513	€ 1,243,655	€ 132,862	€ 3,346,883
Car accidents	€ 1,393,995	€ 0	€ 3,554,180	€ 4,948,175
Work accidents	€ 106,093	€ 0	€ 270,498	€ 376,591
QALYs value gained from increased treatment				
QALYs value (1)	€ 171,640,174			
QALYs value (2)	€ 184,114,695			
QALYs value (3)	€ 308,397,890			

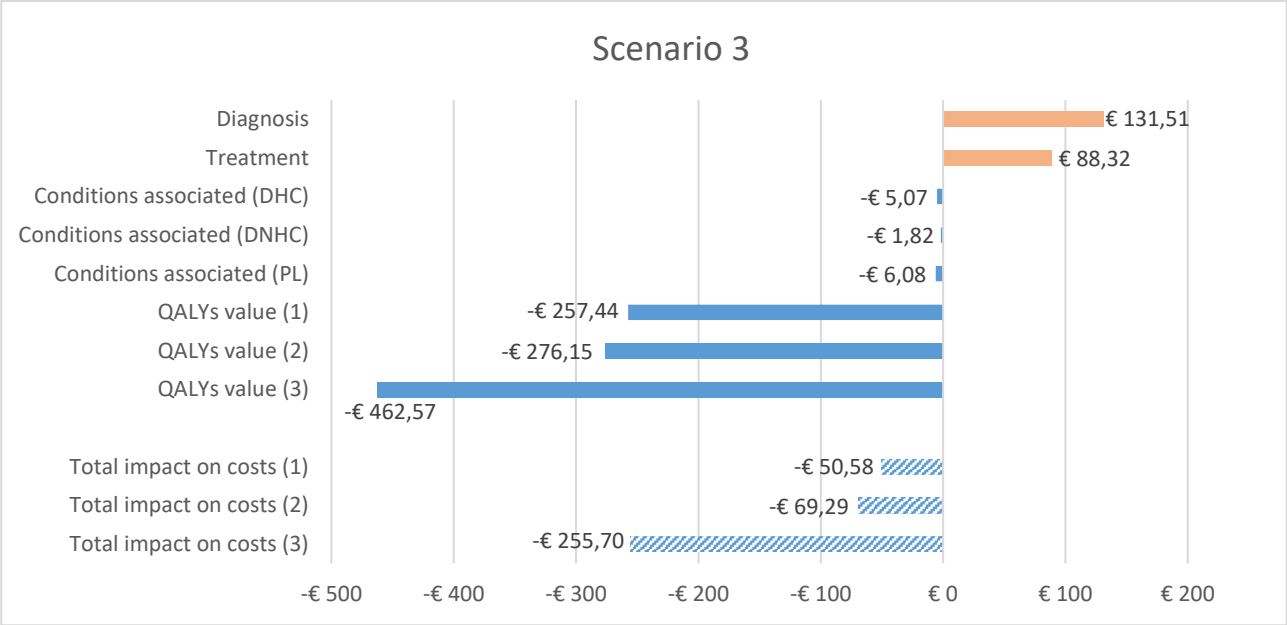
Scenario 2 (+50% diagnoses with respect to scenario 1, all newly diagnosed patients are treated)				
Rising costs				
Diagnosis	€ 87,673,521			
Treatment	€ 58,880,000			
Potential savings due to avoided conditions	***Direct healthcare cost***	***Direct non-healthcare cost***	***Productivity losses cost***	***Total cost***
All-cause mortality	€ 0	€ 0	€ 64,658	€ 64,658
Cardiovascular mortality	€ 0	€ 0	€ 136,614	€ 136,614
Stroke	€ 1,943,679	€ 1,226,720	€ 131,052	€ 3,301,307
Car accidents	€ 1,375,792	€ 0	€ 3,507,770	€ 4,883,562
Work accidents	€ 104,668	€ 0	€ 266,865	€ 371,533
QALYs value gained from increased treatment				
QALYs value (1)	€ 171,634,696			
QALYs value (2)	€ 184,108,820			
QALYs value (3)	€ 308,388,048			

Scenario 3 (+50% diagnoses with respect to scenario 2, all newly diagnosed patients are treated)				
Rising costs				
Diagnosis	€ 131,510,281			
Treatment	€ 88,320,000			
Potential savings due to avoided conditions	***Direct healthcare cost***	***Direct non-healthcare cost***	***Productivity losses cost***	***Total cost***
All-cause mortality	€ 0	€ 0	€ 97,178	€ 97,178
Cardiovascular mortality	€ 0	€ 0	€ 202,512	€ 202,512
Stroke	€ 2,875,816	€ 1,815,022	€ 193,902	€ 4,884,526
Car accidents	€ 2,036,741	€ 0	€ 5,192,948	€ 7,229,689
Work accidents	€ 154,893	€ 0	€ 394,921	€ 549,815
QALYs value gained from increased treatment				
QALYs value (1)	€ 257,443,893.18			
QALYs value (2)	€ 276,154,485.69			
QALYs value (3)	€ 462,567,425.84			

FIGURE 11 AVOIDED AND RISINGS COSTS FOLLOWING INCREASED DIAGNOSIS AND TREATMENT OF OSA(S) PATIENTS (IN MILLION EUROS)


Scenario 1
Treatment
Conditions associated (DHC)
Conditions associated (DNHC)
Conditions associated (PL)
QALYs value (1)
QALYs value (2)
QALYs value (3)
Total impact on costs (1)
Total impact on costs (2)
Total impact on costs (3)
€ 58,88
-€ 3,47
-€ 1,24
-€ 4,16
-€ 171,64
-€ 184,11
-€ 308,40
-€ 121,63
-€ 134,11
-€ 258,39
-€ 500
-€ 400
-€ 300
-€ 200
-€ 100
€ 0
€ 100
€ 200

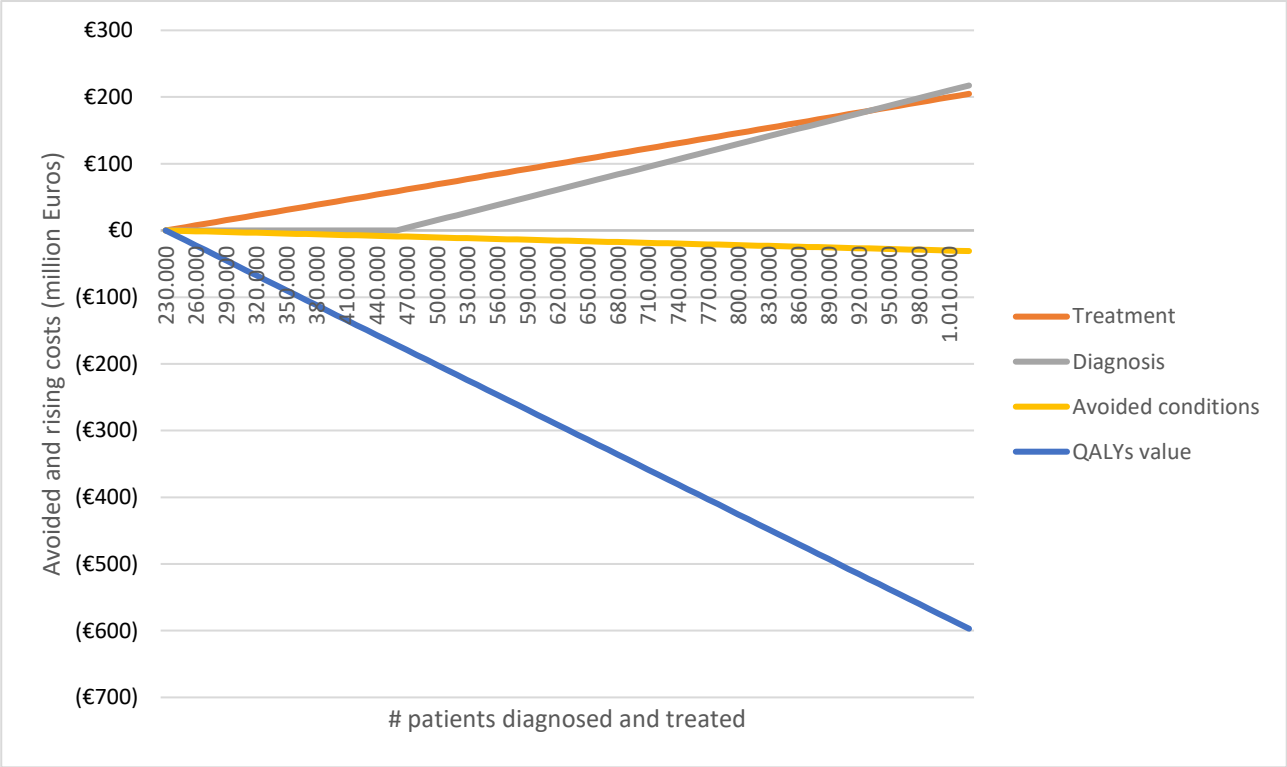

Scenario 2
Diagnosis
Treatment
Conditions associated (DHC)
Conditions associated (DNHC)
Conditions associated (PL)
QALYs value (1)
QALYs value (2)
QALYs value (3)
Total impact on costs (1)
Total impact on costs (2)
Total impact on costs (3)
€ 87,67
€ 58,88
-€ 3,42
-€ 1,23
-€ 4,11
-€ 171,63
-€ 184,11
-€ 308,39
-€ 33,84
-€ 46,31
-€ 170,59
-€ 500
-€ 400
-€ 300
-€ 200
-€ 100
€ 0
€ 100
€ 200



Note. DHC: direct healthcare costs. DHNC: direct non-healthcare costs. PL: productivity losses.

Figure 12 shows the cumulative variation in costs due to increased diagnosis and treatment rates with respect to the status quo. The figures reported in Appendix 7 show in more detail the impact of increasing treatment rates on the conditions associated to OSA(S), both in terms of avoided cases and potential savings generated.

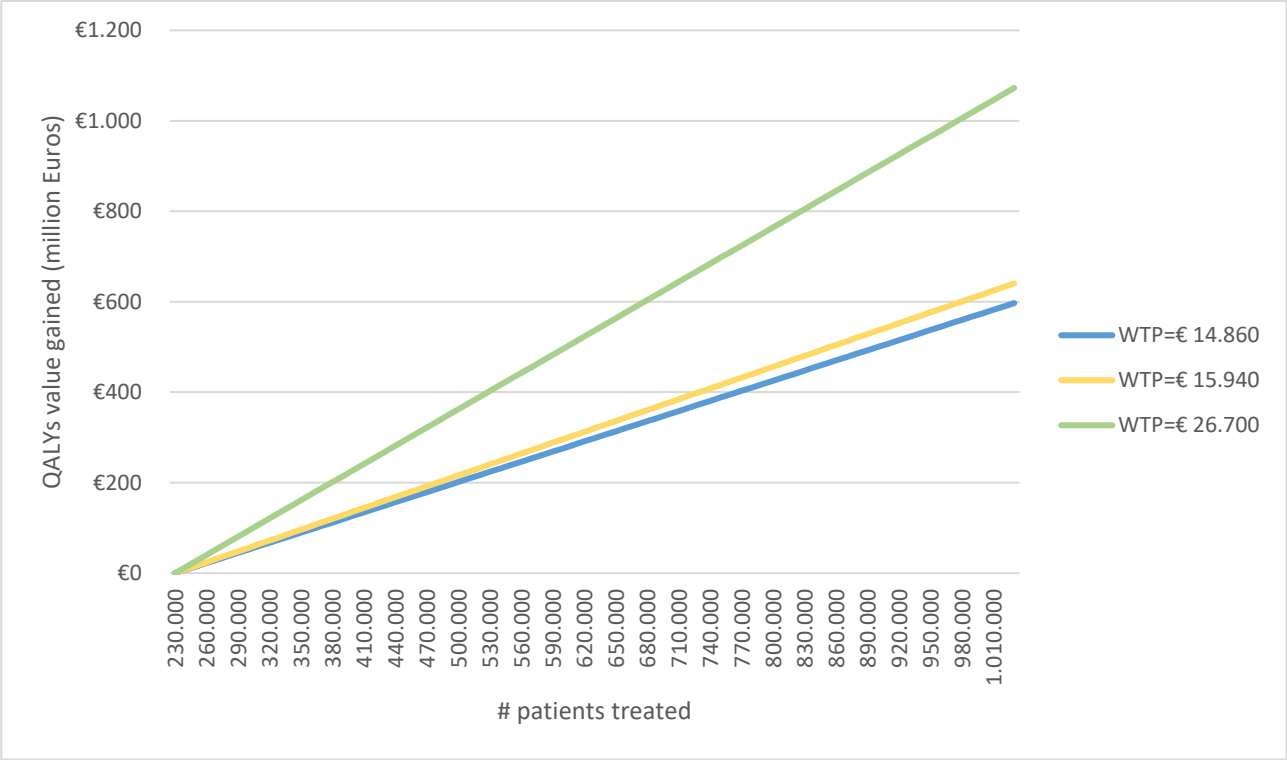
FIGURE 12 SUMMARY RESULTS OF SCENARIO ANALYSIS – CUMULATIVE AVOIDED AND RISINGS COSTS FOLLOWING INCREASED DIAGNOSIS AND TREATMENT OF OSA(S) PATIENTS (IN MILLION EUROS)



Note. (i) Rising costs are above the horizontal axis, while avoided costs (or potential saving) are below the horizontal axis. (ii) In this figure, QALYs value was calculated using the most conservative WTP estimate.

It is worth noting that, although an increment in direct healthcare costs could be observed due to increased costs related to higher number of diagnosed and treated of OSA(S) patients, CPAP treatment could generate potential savings in direct healthcare, non-healthcare and productivity losses costs of conditions associated with OSA(S) due to a reduction in their onset. In addition, the more patients treated, the lower the QALYs value lost due inappropriate diagnostic and therapeutic pathway. In all three scenarios, we can observe that potential savings due increased QoL (thanks to decreased OSA(S) morbility) obtained with higher rates of CPAP treatment substantially overcome rising costs of diagnosis and treatment. Figure 13 shows how QALYs value substantially increases with increasing number of OSA(S) patients treated, ultimately leading to gained value for the society.

FIGURE 13 QALYS VALUE GAINED WITH INCREASING TREATMENT RATES (IN MILLION EUROS)


€1.200
€1.000
€800
€600
€400
€200
€0
QALYs value gained (million Euros)
230.000
260.000
290.000
320.000
350.000
380.000
410.000
440.000
470.000
500.000
530.000
560.000
590.000
620.000
650.000
680.000
710.000
740.000
770.000
800.000
830.000
860.000
890.000
920.000
950.000
980.000
1.010.000
# patients treated
WTP=€ 14.860
WTP=€ 15.940
WTP=€ 26.700

5 Conclusions

This study aimed at providing reliable estimates of the extent of OSA(S) consequences in Italy, both from a clinical and economic point of view. We estimated a prevalence of 12,329,614 moderate-severe OSA(S) patients (27% of the adult population), of which only 460,000 are diagnosed (4% of the estimated prevalence) and 230,000 treated (2% of the estimated prevalence), suggesting a substantial gap in both diagnosis and treatment. The systematic literature review revealed that the boundaries of OSA(S) are wide: several clinical and non-clinical conditions were found to be significantly associated with OSA(S). Overall, 22 conditions were included in COI analysis, performed adopting a societal perspective, and a part of their cost was attributed to OSA(S) through the population attributable fraction methodology. Results of COI revealed that the economic burden due to conditions associated with OSA(S) in Italy is very high, approximately 31 billion Euros per year (2,500 Euros per moderate-severe patient). The main drivers of economic burden are direct healthcare costs (60% of total cost), followed by indirect costs due to morbidity (36%) and direct non-healthcare costs (4%). Productivity losses due to premature death (for all causes) related to OSA(S) amount to more than 17 million Euros per year. Moreover, the cost for the society of impaired quality of life due to OSA(S) undertreatment is approximately 9 billion Euros in one year. Different scenarios were simulated in order to estimate what would happen to the economic burden influenced by OSA(S) if an increased number of OSA(S) patients were diagnosed and subsequently treated with CPAP. Although an increase in direct healthcare costs could be observed due to higher diagnosis and treatment, CPAP treatment could diminish the costs of conditions associated, due to lower risk of condition onset. In addition, the more patients treated, the lower the QALYs value lost due inappropriate diagnostic and therapeutic pathway, which would ultimately lead to gained value for the society.

In summary, results suggest that the burden of OSA(S) is substantial, also due to low treatment rates. More appropriate diagnosis rates and clinical pathways for OSA(S) patients, in particular for moderate-severe population, are recommended in order to decrease the clinical and economic burden of disease.

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Appendix 1

Template used to elicit expert opinions on the list of conditions identified through the systematic literature review

Conditions possibly associated with OSA(S)	Consequence of OSA(S)	Risk factor for OSA(S)	Both consequence and risk factor of OSA(S)	Irrelevant
All-cause mortality				
Neoplasms				
Head and neck cancer				
All cancers				
Endocrine, nutritional and metabolic diseases				
Diabetic retinopathy (type 1 diabetes)				
Type 2 diabetes mellitus				
Diabetic kidney disease				
Diabetic retinopathy				
Obesity *(adults)*				
Obesity *(children)*				
Metabolic disorders, incl. dyslipidemia *(adults)*				
Metabolic disorders, incl. dyslipidemia *(children)*				
Mental and behavioural disorders				
Mild cognitive disorders (e.g. attention, vigilance, processing speed, memory, verbal fluency)				
Schizophrenia and related disorders				
Depression, major depressive disorder *(adults)*				
Depression *(children)*				
Bipolar disorder				
Posttraumatic stress disorder				
Sexual dysfunction				
Erectile dysfunction				
Female sexual dysfunction				
Attention deficit hyperactivity disorder				
Other behavioural and emotional disorders with onset usually occurring in childhood and adolescence (e.g. enuresis)				
Diseases of the nervous system				
Parkinson disease				
Transient ischemic attack				
Sleep bruxism				
Epilepsy *(adults)*				

Conditions possibly associated with OSA(S)	Consequence of OSA(S)	Risk factor for OSA(S)	Both consequence and risk factor of OSA(S)	Irrelevant
Epilepsy *(children)*				
Hypersomnias				
Cerebrospinal fluid leak				
Diseases of the eye and adnexa				
Floppy eyelids syndrome				
Retinal vein occlusion				
Central serous chorioretinopathy				
Glaucoma				
Nonarteritic anterior ischemic optic neuropathy				
Diseases of the circulatory system				
Hypertension *(adults)*				
Hypertension *(children)*				
Ischemic heart disease				
Myocardial infarction				
Pulmonary embolism				
Sudden cardiac death				
Atrial fibrillation				
Heart failure, incl. congestive heart failure				
Arrhythmias				
Atherosclerotic heart disease				
Deep-vein thromboembolism				
Aortic aneurysm and dissection				
Cerebrovascular diseases, incl. stroke				
Cardiac arrest				
Diseases of the respiratory system				
COPD				
Acute respiratory failure				
Diseases of the digestive system				
Non-alcoholic fatty liver disease				
Periodontal disease				
Diseases of the genitourinary system				
Chronic kidney disease				
Pregnancy, childbirth and the puerperium				
Gestational hypertension				
Pre-eclampsia				
Gestational diabetes mellitus				
Preterm delivery				
Cesarean delivery				
Certain conditions originating in the perinatal period				
Low birth weight				

Conditions possibly associated with OSA(S)	Consequence of OSA(S)	Risk factor for OSA(S)	Both consequence and risk factor of OSA(S)	Irrelevant
Slow fetal growth				
Congenital malformations, deformations and chromosomal abnormalities				
Prader-Willi syndrome				
Symptoms, signs, physiological states				
Blood pressure				
Hypercapnia				
Arterial stiffness				
Other amnesia (e.g. episodic memory loss)				
Pulmonary arterial pressure				
Interventricular septum thickness				
Right ventricular dimension				
Insulin resistance *(adults)*				
Insulin resistance *(children)*				
Visceral abdominal fat				
Adiponectin				
Endothelial dysfunction				
Chronic inflammation				
Choroidal thickness				
Oxygen saturation				
Energy balance regulation				
Retinal nerve fiber layer thickness				
Subfoveal choroidal thickness				
Abnormal activation and grey matter loss				
Vascular endothelial growth factor levels				
Other clinical-related consequences (not classified)				
Perioperative risk				
Postoperative complications (general, cardiac or bariatric surgery)				
Respiratory complications *(adults)*				
Respiratory complications *(children)*				
Cardiac complications				
Cardiopulmonary complications				
Neurological complications				
Postoperative desaturation				
Reintubation				
Unplanned ICU admission *(adults)*				

Conditions possibly associated with OSA(S)	Consequence of OSA(S)	Risk factor for OSA(S)	Both consequence and risk factor of OSA(S)	Irrelevant
Unplanned NICU admission *(children)*				
Hemorrhage *(children)*				
Infection or sepsis				
Mortality				
Increased LOS				
Executive functioning				
Cognitive functioning				
Renal functioning				
Non-medical consequences				
Motor vehicle crashes				
Quality of life				
Work-related consequences				
Work accidents				
Reduced work performance				
Decrease in productivity				
Decrease in attention				
Decrease in learning				
Work disability				
Increased absenteeism				

Please indicate other conditions that, according to your experience, are consequences of OSA(S) but were not retrieved through literature review.

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Appendix 2

List of list of conditions associated with OSA(S) included in the analysis

Conditions associated with OSA(S)
Mortality
All-cause mortality
Cancer mortality
Cardiovascular mortality
Neoplasms
All cancers
Endocrine, nutritional and metabolic diseases
Type 2 diabetes mellitus
Diabetic kidney disease
Diabetic retinopathy
Metabolic disorders
Mental and behavioural disorders
Erectile dysfunction
Female sexual dysfunction
Diseases of the nervous system
Stroke
Spontaneous cerebrospinal fluid leak
Diseases of the eye and adnexa
Floppy eyelids syndrome
Glaucoma
Nonarteritic anterior ischemic optic neuropathy
Diseases of the circulatory system
Hypertension
Ischemic heart disease
Heart failure
Aortic dissection
Diseases of the digestive system
Non-alcoholic fatty liver disease
Diseases of the genitourinary system
Gastroesophageal reflux disease
Pregnancy, childbirth and the puerperium
Pre-eclampsia
Gestational diabetes mellitus
Preterm delivery
Cesarean delivery
Non-medical consequences
Motor vehicle crashes
Work-related consequences (work accidents)

Appendix 3

Annual cost per patient of clinical and non-clinical conditions associated with OSA(S) – Original results

Condition	Mean annual cost per patient				Year	Country	Source
	Direct healthcare cost	Direct non-healthcare cost	Productivity losses cost*	Total cost			
Cancer	€ 5,217	€ 4,180	€ 109	€ 9,506	2009	Italy	Luengo-Fernandez et al (2013)
Diabetic retinopathy	€ 273			€ 273	2014	Spain	Romero-Aroca et al (2016)
		€ 213	€ 509	€ 1,434	2002	Germany	Happich et al (2008)
Diabetic kidney disease	$1,108			$1,108	2016	United States	Zhou et al (2017)
Type 2 diabetes	€ 3,640		€ 4,098	€ 7,738	2012	Italy	Marcellusi et al (2016)
Metabolic syndrome	€ 1,522			€ 1,522	2003	Italy	Lucioni et al (2005)
			$106	$106	2006	United States	Schultz et al (2009)
Erectile dysfunction	£286			£286	2000	United Kingdom	Wilson et al (2002)
Female sexual dysfunction	£551			£551	2002	United Kingdom	Goldmeier et al (2004)
Stroke	€ 11,747	€ 7,414	€ 792	€ 19,953	2007	Italy	Fattore et al (2012)
Glaucoma	€ 789			€ 789	2003	Italy	Koleva et al (2007)
Resistant hypertension	€ 222			€ 222	2011	Italy	Mennini et al (2015)
Essential hypertension	€ 222			€ 222	2011	Italy	Mennini et al (2015)
Ischemic heart disease	€ 1,198	€ 279	€ 64	€ 1,541	2003	Italy	Leal et al (2006)
Aortic dissection	€ 49,915			€ 49,915	2012	United States	Luebke et al (2014)
Non-alcoholic fatty liver disease	€ 1,163		€ 4,297	€ 5,460	2015	Italy	Younossi et al (2016)
Gastroesophageal reflux disease	€ 281		€ 170	€ 451	2009	Italy	Darbà et al (2011)
Pre-eclampsia	€ 5,243			€ 5,243	2016	Ireland	Fox et al (2017)
Preterm delivery	€ 8,684			€ 8,684	2014	Italy	Merinopoulou et al (2018)
			$11,214	$11,214	2005	United States	Institute of Medicine (2007)
Cesarean delivery	€ 2,336		€ 876	€ 3,212	2011	Italy	Pizzo (2011)
Car accidents†	€ 9,079		€ 23,148	€ 32,227	2015	Italy	Wijnen et al (2017)
Work accidents†*	€ 9,079		€ 23,148	€ 32,227	2015	Italy	Wijnen et al (2017)

*Note. *Only productivity losses due to morbidity are included.† We adopted a conservative approach and considered costs due to serious and slight injuries, while costs due to fatal crashes were excluded. *We considered costs due to motor vehicle accidents as the studies included in Garbarino et al (2016) are mostly focused on commercial motor vehicle crashes.*

Appendix 4

Confidence interval estimates of economic burden influences by OSA(S) in Italy

	Lower confidence interval				Upper confidence interval			
Condition	**Direct healthcare cost**	**Direct non-healthcare cost**	**Productivity losses cost***	**Total cost**	**Direct healthcare cost**	**Direct non-healthcare cost**	**Productivity losses cost***	**Total cost**
Cancer	€ 29,098,815	€ 23,312,167	€ 607,110	€ 53,018,092	€ 2,206,009,772	€ 1,767,318,304	€ 46,025,591	€ 4,019,353,666
Diabetic retinopathy	€ 41,479,266	€ 32,672,119	€ 78,075,626	€ 152,227,010	€ 112,245,483	€ 88,412,792	€ 211,277,517	€ 411,935,792
Diabetic kidney disease	€ 22,364,250			€ 22,364,250	€ 130,111,086			€ 130,111,086
Type 2 diabetes	€ 284,139,682		€ 319,891,323	€ 604,031,005	€ 3,369,778,422		€ 3,793,778,015	€ 7,163,556,437
Metabolic syndrome	€ 7,060,342,250		€ 333,452,988	€ 7,393,795,238	€ 15,366,415,550		€ 725,740,623	€ 16,092,156,173
Erectile dysfunction	€ 37,819,567			€ 37,819,567	€ 378,945,036			€ 378,945,036
Female sexual dysfunction	€ 251,335,383			€ 251,335,383	€ 1,380,079,552			€ 1,380,079,552
Stroke	€ 58,289,698	€ 36,788,952	€ 3,929,977	€ 99,008,627	€ 247,353,089	€ 156,114,395	€ 16,676,909	€ 420,144,393
Glaucoma	€ 40,919,088			€ 40,919,088	€ 54,519,370			€ 54,519,370
Resistant hypertension	€ 27,009,377			€ 27,009,377	€ 75,452,971			€ 75,452,971
Essential hypertension	€ 195,431,790			€ 195,431,790	€ 478,393,824			€ 478,393,824
Ischemic heart disease	€ 105,816,430	€ 24,631,024	€ 32,427,616	€ 162,875,070	€ 849,929,363	€ 197,839,130	€ 260,462,224	€ 1,308,230,716
Aortic dissection	€ 18,559,409			€ 18,559,409	€ 57,110,790			€ 57,110,790
Non-alcoholic fatty liver disease	€ 1,360,422,639		€ 5,026,428,272	€ 6,386,850,912	€ 3,052,411,389		€ 11,277,912,071	€ 14,330,323,461
Gastroesophageal reflux disease	€ 24,846,297		€ 15,031,568	€ 39,877,865	€ 294,965,268		€ 178,448,738	€ 473,414,006
Pre-eclampsia	€ 2,466,688			€ 2,466,688	€ 10,728,260			€ 10,728,260
Preterm delivery	€ 10,444,918		€ 11,321,050	€ 21,765,968	€ 64,529,766		€ 69,942,600	€ 134,472,366
Cesarean delivery	€ 35,617,912		€ 13,348,790	€ 48,966,701	€ 78,420,953		€ 29,390,404	€ 107,811,357
Car accidents	€ 20,582,278		€ 52,476,987	€ 73,059,265	€ 196,419,343		€ 500,794,685	€ 697,214,027
Work accidents	€ 364,941		€ 930,461	€ 1,295,402	€ 16,281,558		€ 41,511,786	€ 57,793,344
Total	**€ 9,627,350,678**	**€ 117,404,262**	**€ 5,887,921,768**	**€ 15,632,676,708**	**€ 28,420,100,843**	**€ 2,209,684,621**	**€ 17,151,961,162**	**€ 47,781,746,627**

Cost per moderate-severe OSA(S) patient †	**€ 781**	**€ 10**	**€ 478**	**€ 1,268**	**€ 2,305**	**€ 179**	**€ 1,391**	**€ 3,875**
Cost per resident ††	**€ 159**	**€ 2**	**€ 97**	**€ 258**	**€ 470**	**€ 37**	**€ 284**	**€ 790**

*Note. *Only productivity losses due to morbidity are included. † Moderate-severe OSA(S) patients=12,329,614 (cfr Table 4). †† Italian resident population= 60,483,973 (source: ISTAT).*

Appendix 5

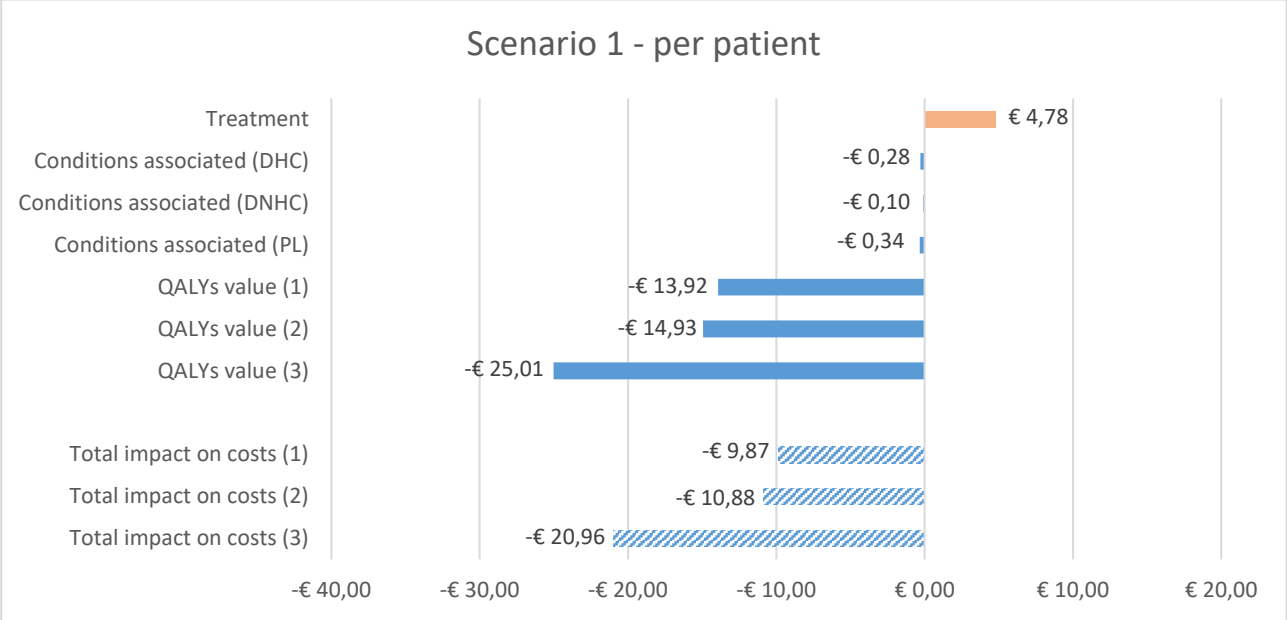
Characteristics of studies considered for QoL analysis

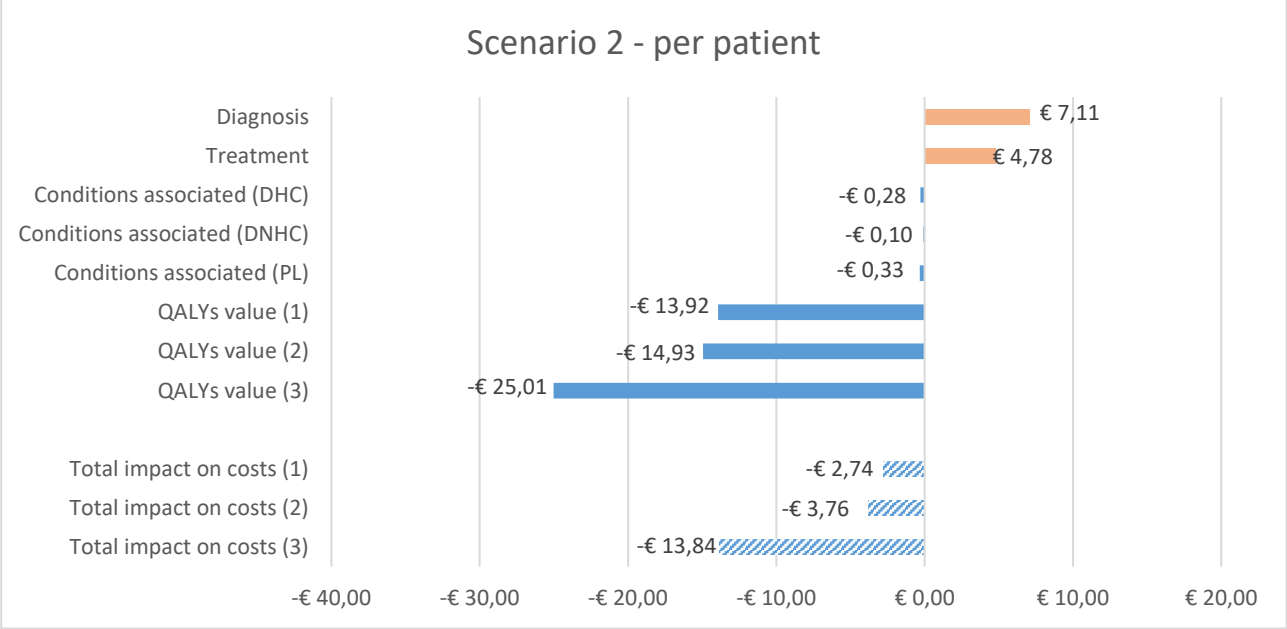
Study	Country	Study design	Sample size	OSA(S) severity at baseline	Mean age (SD)	Male gender (%)	Follow-up
Tousignant et al (1994)	Canada	Retrospective before-after	19	Mean AHI=67.6	57 (10.2)	74%	9.5 months
Jenkinson et al (1997)	UK	Before-after	108	Mean ESS=14.0	50 (9.8)	100%	5-7 weeks
Chakravorty et al (2002)	UK	RCT	57 (CPAP=32; no CPAP=21)	Mean AHI=49 Mean ESS=14	50 (11)	n.a.	3 months
Mar et al (2003)	Spain	Before-after	46	Mean AHI=41.3 Mean ESS=13.8	53 (12)	87%	3 months
Català et al (2016)	Spain	Retrospective before-after	373	Mean AHI=54.3	56 (10.2)	85%	1 year
McMillan et al (2014)	UK	RCT	278 (CPAP=138; no CPAP=140)	Mean ESS=11.6	71 (4.6)	82%	3-12 months

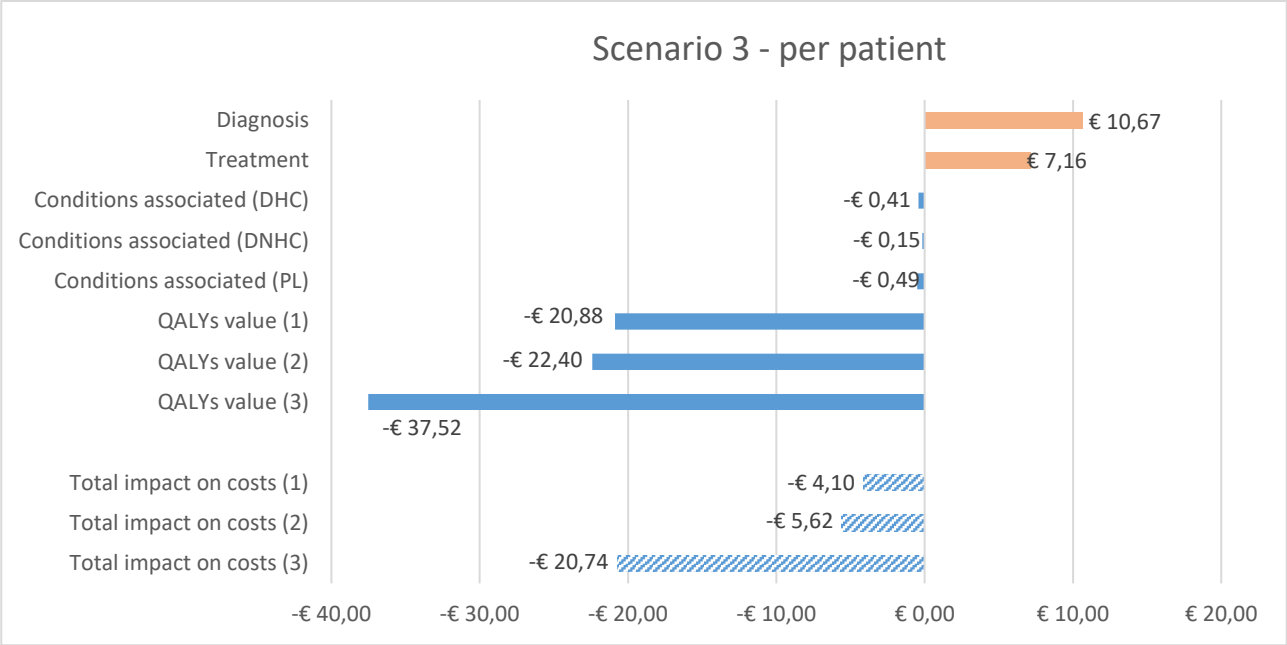
Note: Since the study by Guest et al (2008) did not provide original QoL estimates but used utility values provided by Mar et al (2003), the detail of Guest et al are not provided in the present table.

Appendix 6

Results of scenario analysis - Avoided and risings costs following increased diagnosis and treatment per moderate-severe OSA(S) patient

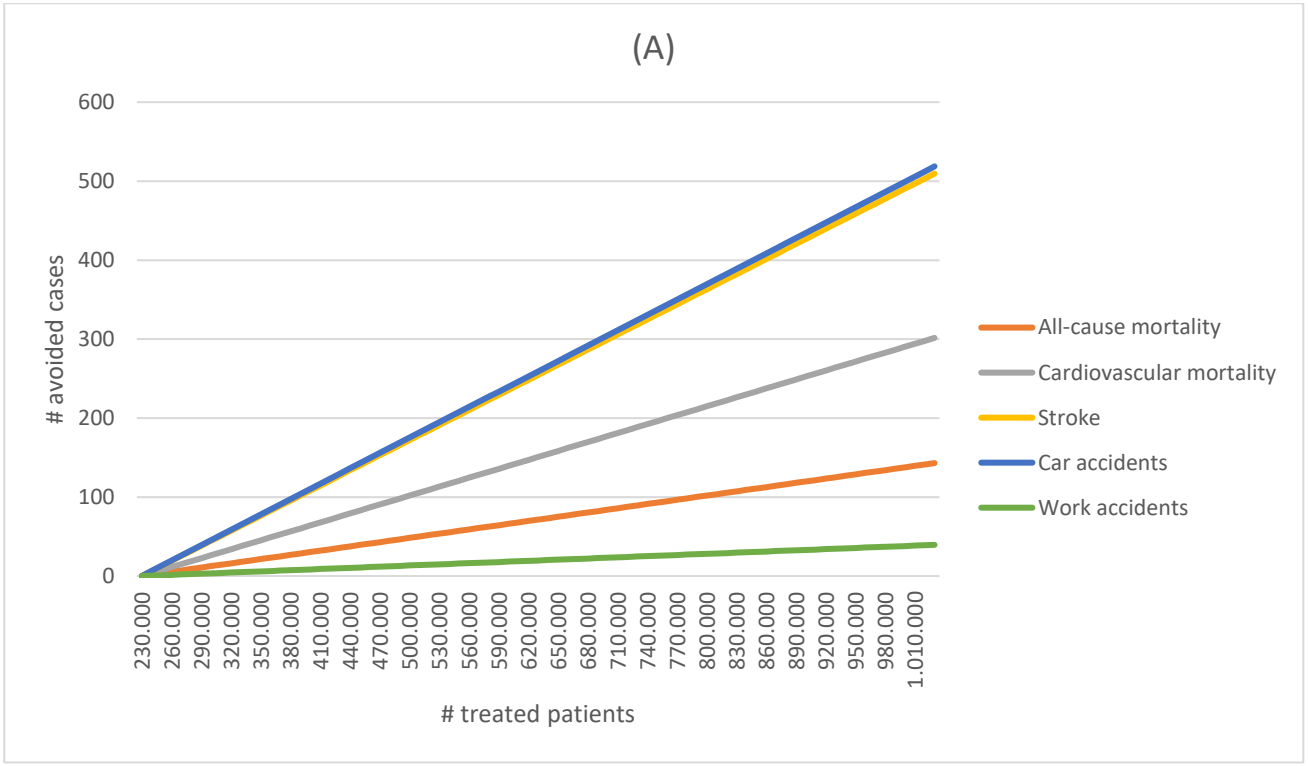


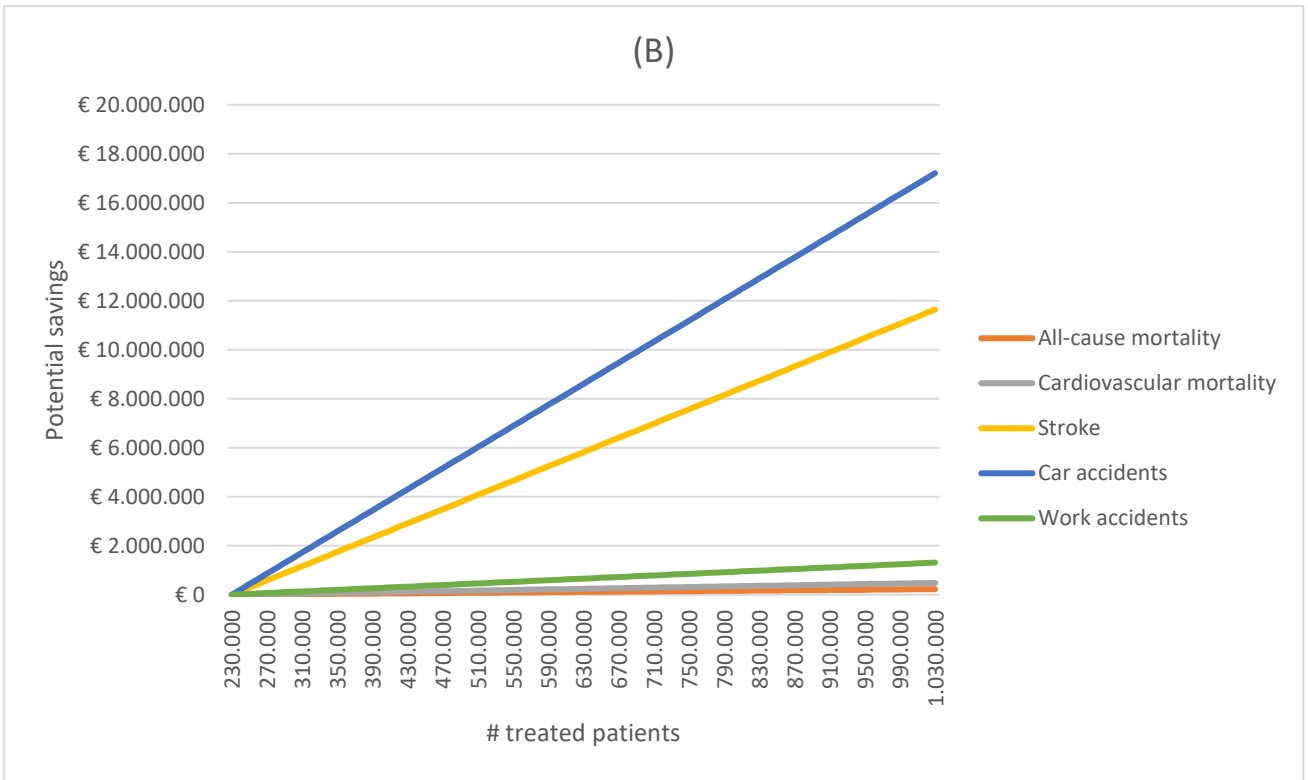



Scenario 3 - per patient
Diagnosis
Treatment
Conditions associated (DHC)
Conditions associated (DNHC)
Conditions associated (PL)
QALYs value (1)
QALYs value (2)
QALYs value (3)
Total impact on costs (1)
Total impact on costs (2)
Total impact on costs (3)
€ 10,67
€ 7,16
-€ 0,41
-€ 0,15
-€ 0,49
-€ 20,88
-€ 22,40
-€ 37,52
-€ 4,10
-€ 5,62
-€ 20,74
-€ 40,00
-€ 30,00
-€ 20,00
-€ 10,00
€ 0,00
€ 10,00
€ 20,00

Appendix 7

Results of scenario analysis – Number of avoided cases among newly treated patients (panel A) and potential savings due to avoided cases (panel B)





Appendix 8

Overview of the main results

RESULTS SYNTHESIS 1 PREVALENCE OF OSA(S) FOR THE GENERAL ADULT POPULATION IN ITALY (AGED 15-74)

Prevalence	Female	Male	Total
Rates			
Mild (5≤AHI<15)	29%	25%	27%
Moderate-severe (AHI≥15)	18%	36%	27%
Moderate (15≤AHI<30)	10%	14%	12%
Severe (AHI≥30)	9%	22%	15%
Overall (AHI≥5)	48%	61%	54%
Absolute values			
Mild (5≤AHI<15)	6,703,067	5,582,051	12,285,118
Moderate-severe (AHI≥15)	4,193,897	8,135,717	12,329,614
Moderate (15≤AHI<30)	2,236,745	3,260,161	5,496,906
Severe (AHI≥30)	1,957,152	4,875,556	6,832,708
Overall (AHI≥5)	10,896,964	13,717,768	24,614,732

RESULTS SYNTHESIS 2 RATE OF DIAGNOSIS AND TREATMENT AMONG PREVALENT MODERATE-SEVERE OSA(S) PATIENTS IN ITALY

Moderate-severe OSA(S)	Total
Prevalence	12,329,614
Diagnosis: Diagnosed patients, n (%) Undiagnosed patients, n (%)	 460,000 (4%) 11,869,614 (96%)
Treatment: Treated patients, n (%) Untreated patients, n (%)	 230,000 (2%) 12,099,614 (98%)

RESULTS SYNTHESIS 3 CONDITIONS SIGNIFICANTLY ASSOCIATED WITH OSA(S): MAGNITUDE OF ASSOCIATION

Condition	OSA(S) severity	Magnitude (95% CI)
All-cause mortality	Severe	RR = 1.54 (1.21 - 1.97)
Cardiovascular mortality	Severe	RR = 2.96 (1.45 - 6.01)
Cancer	Overall	RR = 1.40 (1.01 - 1.95)
Diabetic retinopathy	Overall	OR = 2.01 (1.49 - 2.72)
Diabetic kidney disease	Overall	OR = 1.59 (1.16 - 2.18)
Type 2 diabetes	Moderate-severe	RR = 1.63 (1.09 - 2.45)
Metabolic syndrome	Mild	OR = 2.39 (1.65 - 3.46)
	Moderate-severe	OR = 3.42 (2.28 - 5.13)
Erectile dysfunction	Overall (men)	RR = 1.82 (1.12 - 2.97)
Female sexual dysfunction	Overall (women)	RR = 2.00 (1.29 - 3.08)
Stroke	Severe	RR = 2.15 (1.42 - 3.24)

Glaucoma	Overall	OR = 1.24 (1.20 - 1.28)
Resistant hypertension	Overall	OR = 2.84 (1.70 - 3.98)
Essential hypertension	Mild	OR = 1.18 (1.09 - 1.27)
	Moderate	OR = 1.32 (1.20 - 1.43)
	Severe	OR = 1.56 (1.29 - 1.84)
Ischemic heart disease	Moderate	RR = 1.38 (1.04 - 1.83)
	Severe	RR = 1.63 (1.18 - 2.26)
Aortic dissection	Mild	OR = 1.60 (1.01 - 2.53)
	Moderate-severe	OR = 4.43 (2.59 - 7.59)
Non-alcoholic fatty liver disease	Overall	OR = 2.34 (1.71 - 3.18)
Gastroesophageal reflux disease	Overall	OR = 1.53 (1.07 - 2.08)
Pre-eclampsia	Overall (women)	RR = 1.96 (1.34 - 2.86)
Preterm delivery	Overall (women)	RR = 1.90 (1.24 - 2.91)
Cesarean delivery	Overall (women)	RR = 1.87 (1.52 - 2.29)
Car accidents	Overall	OR = 2.43 (1.21 - 4.89)
Work accidents	Overall	OR = 1.78 (1.03 - 3.07)

RESULTS SYNTHESIS 4 ANNUAL ECONOMIC BURDEN INFLUENCED BY OSA(S) IN ITALY

Condition	Direct healthcare cost	Direct non-healthcare cost	Productivity losses cost	Total cost
Cancer	€ 1,053,335,086	€ 843,866,787	€ 21,976,498	€ 1,919,178,370
Diabetic retinopathy	€ 75,903,881	€ 59,787,476	€ 142,872,419	€ 278,563,776
Diabetic kidney disease	€ 74,076,551			€ 74,076,551
Type 2 diabetes	€ 1,741,141,727		€ 1,960,219,449	€ 3,701,361,176
Metabolic syndrome	€ 11,260,422,980		€ 531,818,651	€ 11,792,241,631
Erectile dysfunction	€ 208,151,669			€ 208,151,669
Female sexual dysfunction	€ 772,808,563			€ 772,808,563
Stroke	€ 144,697,413	€ 91,324,306	€ 9,755,712	€ 245,777,431
Glaucoma	€ 47,690,291			€ 47,690,291
Resistant hypertension	€ 56,172,997			€ 56,172,997
Essential hypertension	€ 344,718,771			€ 344,718,771
Ischemic heart disease	€ 442,622,880	€ 103,029,886	€ 135,642,496	€ 681,295,262
Aortic dissection	€ 37,984,396			€ 37,984,396
Non-alcoholic fatty liver disease	€ 2,208,249,940		€ 8,158,942,384	€ 10,367,192,324
Gastroesophageal reflux disease	€ 165,097,914		€ 99,881,300	€ 264,979,215
Pre-eclampsia	€ 6,302,021			€ 6,302,021
Preterm delivery	€ 35,163,957		€ 38,113,552	€ 73,277,509
Cesarean delivery	€ 56,345,557		€ 21,117,043	€ 77,462,600
Car accidents	€ 106,754,952		€ 272,184,561	€ 378,939,513
Work accidents	€ 7,900,413		€ 20,143,051	€ 28,043,464
Total	**€ 18,845,541,959**	**€ 1,098,008,454**	**€ 11,412,667,117**	**€ 31,356,217,529**
Cost per moderate-severe OSA(S) patient †	**€ 1,528**	**€ 89**	**€ 926**	**€ 2,543**
Cost per resident ††	**€ 312**	**€ 18**	**€ 189**	**€ 518**

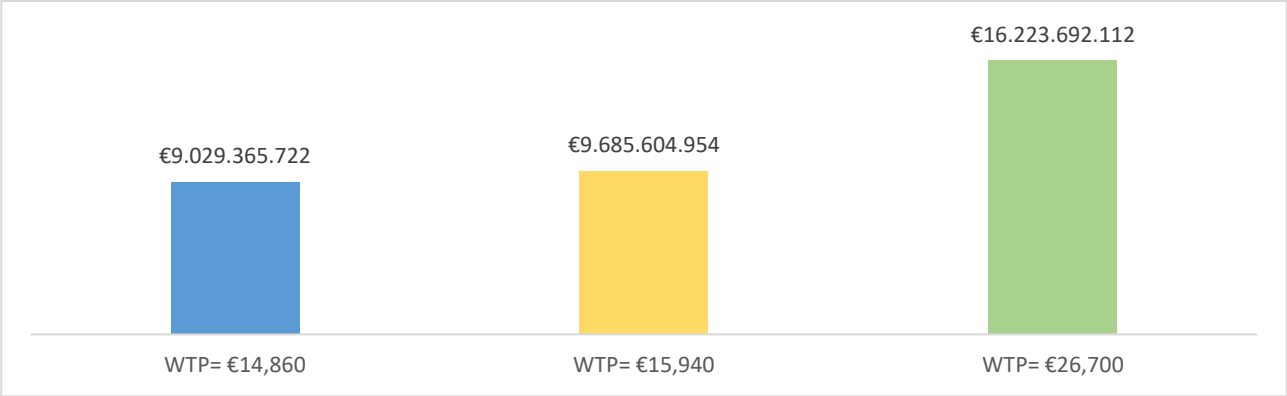
RESULTS SYNTHESIS 5 ANNUAL PRODUCTION COSTS DUE TO PREMATURE DEATH INFLUENCED BY OSA(S)

Age	Production costs due to premature death influenced by OSA(S)	
	Mean	95% CI
15-19	€ 8,541	€ 3,481 - € 14,478
20-24	€ 14,925	€ 6,083 - € 25,300
25-29	€ 182,432	€ 74,350 - € 309,249
30-34	€ 295,315	€ 120,356 - € 500,604
35-39	€ 541,676	€ 220,761 - € 918,223
40-44	€ 1,311,257	€ 534,404 - € 2,222,779
45-49	€ 1,734,865	€ 707,046 - € 2,940,860
50-54	€ 3,293,065	€ 1,342,092 - € 5,582,245
55-59	€ 3,623,670	€ 1,476,831 - € 6,142,671
60-64	€ 6,462,568	€ 2,633,826 - € 10,955,033
Total	**€ 17,468,314**	**€ 7,119,229 - € 29,611,442**
Mean cost per dead OSA(S) patient †	**€ 1,570**	**€ 640 - € 2,661**
Cost per moderate-severe OSA(S) patient ††	**€ 1.4**	**€ 0.6 - € 2.4**
Cost per resident †††	**€ 0.3**	**€ 0.1 - € 0.5**

RESULTS SYNTHESIS 6 AVERAGE REDUCTION IN RISK OF CONDITION ONSET AFTER CPAP TREATMENT

Condition	Average reduction in risk of condition onset
All-cause mortality	34%
Cardiovascular mortality	63%
Stroke	73%
Car accidents	70%
Work accidents	72%

RESULTS SYNTHESIS 7 ANNUAL ECONOMIC VALUE OF QALYS LOST DUE TO UNDERTREATMENT OF OSA(S)



RESULTS SYNTHESIS 8 IMPACT OF SIMULATED SCENARIOS ON COSTS

Scenario 1 (all diagnosed patients in the current scenario are treated)				
Rising costs				
Treatment	€ 58,880,000			
Potential savings due to avoided conditions	***Direct healthcare cost***	***Direct non-healthcare cost***	***Productivity losses cost***	***Total cost***
All-cause mortality	€ 0	€ 0	€ 64,524	€ 64,524
Cardiovascular mortality	€ 0	€ 0	€ 138,238	€ 138,238
Stroke	€ 1,970,513	€ 1,243,655	€ 132,862	€ 3,346,883
Car accidents	€ 1,393,995	€ 0	€ 3,554,180	€ 4,948,175
Work accidents	€ 106,093	€ 0	€ 270,498	€ 376,591
QALYs value gained from increased treatment				
QALYs value (1)	€ 171,640,174			
QALYs value (2)	€ 184,114,695			
QALYs value (3)	€ 308,397,890			

Scenario 2 (+50% diagnoses with respect to scenario 1, all newly diagnosed patients are treated)					
Rising costs					
Diagnosis	€ 87,673,521				
Treatment	€ 58,880,000				
Potential savings due to avoided conditions	***Direct healthcare cost***		***Direct non-healthcare cost***	***Productivity losses cost***	***Total cost***
All-cause mortality	€ 0		€ 0	€ 64,658	€ 64,658
Cardiovascular mortality	€ 0		€ 0	€ 136,614	€ 136,614
Stroke	€ 1,943,679		€ 1,226,720	€ 131,052	€ 3,301,307
Car accidents	€ 1,375,792		€ 0	€ 3,507,770	€ 4,883,562
Work accidents	€ 104,668		€ 0	€ 266,865	€ 371,533
QALYs value gained from increased treatment					
QALYs value (1)	€ 171,634,696				
QALYs value (2)	€ 184,108,820				
QALYs value (3)	€ 308,388,048				

Scenario 3 (+50% diagnoses with respect to scenario 2, all newly diagnosed patients are treated)					
Rising costs					
Diagnosis	€ 131,510,281				
Treatment	€ 88,320,000				
Potential savings due to avoided conditions	***Direct healthcare cost***		***Direct non-healthcare cost***	***Productivity losses cost***	***Total cost***
All-cause mortality	€ 0		€ 0	€ 97,178	€ 97,178
Cardiovascular mortality	€ 0		€ 0	€ 202,512	€ 202,512
Stroke	€ 2,875,816		€ 1,815,022	€ 193,902	€ 4,884,526
Car accidents	€ 2,036,741		€ 0	€ 5,192,948	€ 7,229,689
Work accidents	€ 154,893		€ 0	€ 394,921	€ 549,815
QALYs value gained from increased treatment					
QALYs value (1)	€ 257,443,893.18				
QALYs value (2)	€ 276,154,485.69				
QALYs value (3)	€ 462,567,425.84				

Rapporto di ricerca realizzato con il contributo incondizionato di