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Cost-effectiveness analysis of universal hypothyroidism screening in the general population aged 30–65 years in Spain

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ABSTRACT

Aims: Hypothyroidism is an endocrine disorder that often begins in a subclinical form but can lead to non-specific symptoms and cardiovascular problems. Its prevalence is higher among women, and a significant proportion of cases remain undiagnosed. While previous studies assessed screening in specific populations (e.g. pregnant women, older adults), this study evaluates the cost-effectiveness of population-wide screening in adults aged 30–65 from the Spanish National Health System (NHS) perspective.

Materials and methods: A cost-effectiveness Markov model was developed, simulating seven health states: subclinical hypothyroidism (undiagnosed and controlled), overt hypothyroidism (undiagnosed and controlled), euthyroid state, cardiovascular event, and death. Two strategies were compared: population-based screening *versus* no screening. Model inputs-transition probabilities, prevalence, costs, utilities, and screening effectiveness-were obtained from published literature. A panel of four clinical experts validated the model structure and assumptions. Lifetime costs and quality-adjusted life-years (QALYs) were estimated, and the incremental cost-effectiveness ratio (ICER) was calculated. Probabilistic, sensitivity, and scenario analyses were conducted.

Results: Population-based screening for hypothyroidism in individuals aged 30–65 resulted in an incremental cost of €34.7 million and 6,037 QALYs gained over 35 years, yielding an ICER of €5,745/QALY, significantly below the Spanish willingness-to-pay threshold (€21,000/QALY). Screening also resulted in 33,215 additional diagnoses of subclinical hypothyroidism and 6,870 fewer cases of overt hypothyroidism. It was cost-effective in 99% of probabilistic simulations and under all tested screening intervals (1–5 years).

Limitations and conclusions: Key limitations include the use of constant transition probabilities and some inputs from international sources. Nonetheless, expert validation supports the model's relevance. The analysis adopts a conservative approach, excluding potential additional benefits like hyperthyroidism detection or integration with routine bloodwork, which could improve cost-effectiveness. Overall, hypothyroidism screening is a cost-effective strategy for the Spanish NHS, improving early detection, preventing progression, and enhancing quality of life in a frequently underdiagnosed population.

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Introduction

Hypothyroidism occurs when the thyroid gland's normal function is reduced, and insufficient thyroid hormone is produced to maintain normal body function[1]. Initially, hypothyroidism may be asymptomatic or present with mild, non-specific symptoms; however, if left untreated, it may progress to more pronounced symptoms and cardiovascular problems[2].

Diagnosis of hypothyroidism cannot be symptom-based and must be accompanied by a blood test to screen patients for the disease, as the symptoms can be similar to those of other health problems[3]. Generally, the condition starts as subclinical hypothyroidism (SH), when thyrotropin hormone (TSH) is increased, but free blood thyroxine (fT4) levels are normal (normal TSH levels: 0.20–5 mIU/L; fT4: 11.0–22.0 pmol/L)[4]. The state in which TSH is notably increased, fT4 is decreased, and symptoms become more evident is known as overt hypothyroidism (OH)[5]. The risk that SH will progress to OH in patients with TSH higher than 8 mIU/L is high, and in 70% of these patients, the TSH level rises to more than 10 mIU/L within 4 years[6]. In women, the prevalence of SH and OH is around 7.9 and 2%, while in men, around 3.43 and 0.15%, respectively[7,8].

The lack of knowledge and understanding of hypothyroidism, as well as the tendency to attribute their symptoms to other causes has led to a delay in its diagnosis[9]. Healthcare professionals need to diagnose or exclude hypothyroidism promptly when faced with a patient displaying the non-specific symptoms associated with this condition, as SH has been proven to be a modifiable risk factor for adverse cardiovascular outcomes[9]. Additionally, undiagnosed hypothyroidism may be associated with other medical conditions[9]. There is a high prevalence of undiagnosed hypothyroidism in patients with sleep-related disorders, metabolic syndrome or obesity, and cardiovascular diseases, among others[9–11]. Also, people with hypothyroidism report having more issues with sleep and social isolation than those without hypothyroidism[12], leading to a poorer quality of life.

Hypothyroidism is associated with significant economic burden. Significantly higher direct costs, indirect costs, and resource utilization have been observed in people with hypothyroidism compared to euthyroid controls[13].

Diagnosed hypothyroidism can be treated with levothyroxine, a daily oral treatment that restores healthy thyroid hormone levels and eliminates symptoms[14]. Importantly, treatment strategies differ between overt and subclinical hypothyroidism: levothyroxine therapy is routinely indicated in overt hypothyroidism, while in subclinical hypothyroidism, pharmacological treatment is typically reserved for patients with severe elevations of TSH (>10 mIU/L) or those exhibiting clear symptoms[14].

In this context, our hypothesis implies that universal screening for hypothyroidism would detect cases of SH and prevent its progression to OH and associated complications, resulting in improved patients' quality of life while reducing healthcare costs. This study aims to evaluate the efficiency of hypothyroidism screening *versus* no screening in the general population aged 30–65 years using a cost-effectiveness model from the perspective of the Spanish National Health System (NHS).

Methods

A pharmacoeconomic Markov model was developed to evaluate the long-term cost-effectiveness (cost-utility, since effectiveness is measured in utility, but referred to as cost-effectiveness from this point forward) of hypothyroidism screening in the general population from 30 to 65 years old. This age range was selected due to the scarcity of cost-effectiveness evidence for hypothyroidism screening specifically targeting this segment of the population. The model included seven health states with different costs and utilities: euthyroid state, undiagnosed subclinical hypothyroidism (uSH), controlled subclinical hypothyroidism (cSH), undiagnosed overt hypothyroidism (uOH), controlled overt hypothyroidism (cOH), cardiovascular event (CVE), and death (absorbing state).

Undiagnosed hypothyroidism (uSH or uOH) refers to patients meeting biochemical criteria for hypothyroidism but who remain unidentified. Controlled hypothyroidism (cSH or cOH) refers to diagnosed patients who receive regular follow-up. In the model, patients transition between states according to transition probabilities. Patients can remain in the same state indefinitely unless they progress, improve, or are diagnosed and transition to a controlled state. An exception is the CVE state, which is transient (Markov tunnel state) and lasts only one cycle.

Patients in the euthyroid state can progress to uSH. Those in uSH can improve to the euthyroid state spontaneously, progress to uOH, or be diagnosed and transition to cSH. Patients in uOH cannot improve without intervention, so they need to be diagnosed to move to cOH, where they will stay indefinitely. Patients in cSH can improve and return to the euthyroid state.

Additionally, patients can transition to CVE state or to death from any state in the model. After experiencing a CVE, patients either transition to death or return to their previous state. However, if a patient was in an undiagnosed state (uSH or uOH) before the CVE, it is assumed they will be diagnosed during the event and transition to the corresponding controlled state (cSH or cOH) if they survive (see Figure 1 for more detail).

The model was designed with the guidance of the expert committee that authored this article to reflect the natural history of the disease. In the model, two distinct arms were simulated. In the first arm (control), there was no population-based screening for hypothyroidism, and the healthcare system diagnosed patients according to current detection rates. In the intervention arm, the cohort underwent population-based screening for hypothyroidism every 5 years. All undiagnosed patients would be identified through screening and transition to the controlled states (cSH or cOH), considering sensitivity and specificity rates.

The model was developed in Microsoft Excel, and costs and quality-adjusted life-years (QALYs) were calculated for each treatment arm at the end of the time horizon (35 years, from 30 to 65 years old). All calculations were performed from the perspective of the Spanish National Health System, and both costs and QALYs were discounted at 3%, following the recommendations for economic evaluations in Spain[15]. Cycles had a duration of one year (reflecting the typical time frame of disease progression, according to the expert committee), and half-cycle corrections were applied to compute total costs and QALYs for each arm[16].

Resource use and costs

Screening for hypothyroidism was proposed as a test for the entire population whose status was unknown to the healthcare system (i.e. those not in cSH, cOH, CVE, or deceased). The expert committee determined that screening would consist of a blood draw and a TSH determination for individuals in an euthyroid state, with the addition of a fT4 determination in cases of uSH and uOH (which does not require an additional blood extraction). Patients in a controlled state (cSH and cOH) or those experiencing a CVE would not undergo screening, as their condition was already managed within the system.

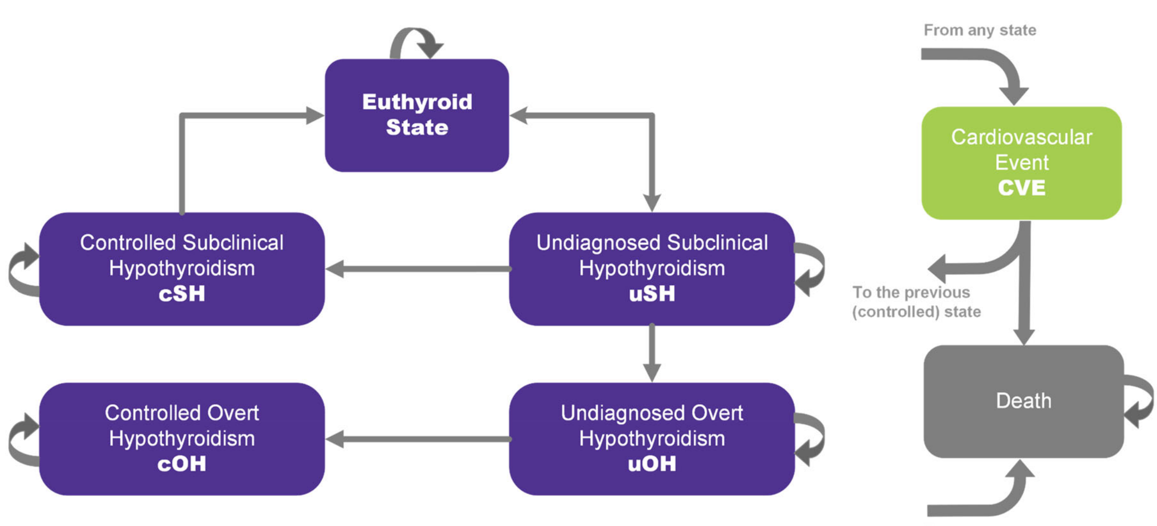

Figure 1. Model structure.

Table 1. Unit costs.

Type of resource	Cost	References
Tests		
TSH determination	€3.35	DOGC[20]
fT4 determination	€3.03	DOGC[20]
Blood extraction	€6.92	Gisbert and Brosa[21]
Treatment		
Levothyroxine 88 µg, 100 tablets	€2.89	Ministry of Health[22]
Levothyroxine 75 µg, 100 tablets	€2.62	Ministry of Health[22]
Visits and CVE management		
Visit to primary healthcare	€67.53	Gisbert and Brosa[21]
Management of CVE	€6,112.78	Ministry of Health[22]

Abbreviations. CVE, cardiovascular event; DOGC, Diari Oficial de la Generalitat de Catalunya; fT4, free thyroxine; TSH, thyroid stimulating hormone.

Table 2. Cost per health state, time, and screening status.

State	Year/screening	Cost
Euthyroid state	Screening	€10.27
uSH	Screening	€13.30
uOH	Screening	€13.30
cSH (women)	First year after diagnosis	€156.61
cSH (women)	Subsequent years	€78.72
cSH (men)	First year after diagnosis	€156.71
cSH (men)	Subsequent years	€78.82
cOH (women)	First year after diagnosis	€165.22
cOH (women)	Subsequent years	€87.33
cOH (men)	First year after diagnosis	€166.21
cOH (men)	Subsequent years	€88.32
CVE	–	€6,112.78
Death	–	€0

Abbreviations. c, controlled; CVE, cardiovascular event; OH, overt hypothyroidism; SH, subclinical hypothyroidism; u, undiagnosed.

Resource use related to disease management differed depending on whether the patient was in the first year after diagnosis or in subsequent years. During the cycle following diagnosis, each controlled patient had two primary care visits and underwent two TSH determination tests. In subsequent cycles, each controlled patient had one scheduled primary care visit and one annual TSH determination test[17]. Conservatively, it was assumed that patients in undiagnosed states did not consume additional resources and, therefore, incurred no additional costs.

Women diagnosed with OH were treated with levothyroxine 75 µg daily while men diagnosed with OH were treated with levothyroxine 88 µg daily[18]. According to the literature and expert consensus, only 10% of patients (TSH $>$ 10 mIU/L) diagnosed with cSH will receive treatment[19]. Additionally, for each CVE, a one-time cost covering all resources associated with the management and treatment of the event was applied.

The cost related to each resource described above can be found in Table 1.

Based on the resource use and the unit costs shown in Table 1, the cost per state, cycle, and patient were calculated and can be observed in Table 2.

Screening efficacy

In the base-case scenario, screening was assumed to occur every five years and was applied to individuals in an euthyroid or undiagnosed hypothyroidism health state (uSH or uOH), with adherence assumed to be 100%.

As mentioned before, screening was performed by measuring TSH alone, followed by fT4 testing when needed. For modeling purposes, we assumed a sensitivity of 98% and a specificity of 96% for the screening strategy, regardless of whether it was performed as a single TSH test or as the two-step TSH–fT4 approach[23]. This resulted in two key outcomes. On one hand, 2% of all screened patients with uSH or uOH were not diagnosed. On the other hand, 4% of patients in an euthyroid state received a false positive result. Patients with a false positive result required the same resources as a correctly diagnosed

Table 3. Prevalence rates of hypothyroidism in the Spanish population.

State	Women	Men	References
uSH	5.50%	3.40%	Valdés et al.[4]
uOH	0.60%	0.10%	Valdés et al.[4]
cSH	7.99%	3.43%	Mariscal Hidalgo et al.[7]
cOH	2.00%	0.15%	Pérez Unanua et al.[8]

Abbreviations. c, controlled; OH, overt hypothyroidism; SH, subclinical hypothyroidism; u, undiagnosed.

Table 4. Transition probabilities.

From	To	Women	Men	References
Euthyroid state	uSH	7.73%	2.48%	Mohedano-López et al.[18]
uSH	uOH	2.80%	2.67%	Valdés et al. and Fatourechi[4,25]
Euthyroid state, uSH, cSH, cOH	CVE	0.49%	0.81%	Pérez de la Isla et al. and Comín et al.[26,27]
uSH	Euthyroid state	37.50%	37.50%	Díez et al.[28]
uSH	cSH	37.82%	25.51%	SSO, Gibbons et al.[29,30]
uOH	cOH	88.80%	59.90%	SSO, Gibbons et al.[29,30]
cSH	Euthyroid state	37.50%	37.50%	Díez et al.[28]
All states except CVE and uOH	Death	National life tables by age and sex		SSO[31]
CVE	Death	18.44%	18.44%	Pascual et al.[32]
uOH	CVE	HR*: 1.14	HR*: 1.14	Ning et al.[33]
uOH	Death	HR*: 1.25	HR*: 1.25	Ning et al.[33]

Abbreviations. c, controlled; CVE, cardiovascular event; SSO, Spanish Statistical Office; OH, overt hypothyroidism; SH, subclinical hypothyroidism; u, undiagnosed.
*The HR will be multiplied by the probability of death adjusted for age and sex, extracted from the national life tables.

patient during the first year after diagnosis. In subsequent cycles, patients who had experienced a false positive result no longer consumed additional resources.

In the no screening arm, no formal screening frequency was set, reflecting opportunistic diagnosis in routine clinical practice; consequently, detection rates in this group were modeled according to current transition probability estimates (see next section).

Prevalences and transition probabilities

The model simulated the life course of a cohort of 542,471 individuals aged 30 years old from the Spanish population in January 2024[24], consisting of 267,937 women and 274,534 men. Before the first cycle of the model (cycle zero), patients were distributed among the different health states according to the prevalence rates of these states in the Spanish population (Table 3).

During the course of the cycles, patients transitioned across the different states of the model according to their transition probabilities (Table 4).

Utilities

Women and men in the model had different utility values for the euthyroid state[34]. Utilities for the uSH[35,36] and uOH[37,38] health states were derived from the literature as relative decrements from the euthyroid state, rather than as absolute values. Specifically, the ratio between the reported utility for each hypothyroid state and the corresponding euthyroid value in the source study was applied to the euthyroid utility from García-Gordillo et al.[34]. The utility for the controlled states (cSH and cOH), was assumed to be the same as that of the euthyroid state. Finally, the disutility estimate was derived from the utility of patients with history of cardiovascular disease and CVE $<$ 12 months reported in Ara and Brazier[39] (Table 5).

Model outcomes and sensitivity analysis

After the 35-year time horizon, each arm's costs and QALYs were evaluated. The incremental cost-effectiveness ratio (ICER) of the intervention (screening) relative to the control group (no screening) was calculated as ICER = (Screening Costs − No Screening Costs)/(Screening QALYs − No Screening QALYs) and compared against the Spanish willingness-to-pay (WTP) threshold of €21,000 per QALY[40]. Additionally, the net monetary benefit (NMB) was calculated as incremental QALYs multiplied by the WTP threshold

Table 5. Utilities and disutilities for each healthcare state.

State	Women	Men	References
Euthyroid state	0.867	0.931	García-Gordillo et al.[34]
uSH	0.765	0.822	García-Gordillo et al. and Razvi et al.[34,35]
uOH	0.574	0.617	Hughes et al.[37]
cSH	0.867	0.931	Assumption
cOH	0.867	0.931	Assumption
CVE (disutility)	−0.260	−0.283	Ara and Brazier[39]

Abbreviations. c, controlled; CVE, cardiovascular event; OH, overt hypothyroidism; SH, subclinical hypothyroidism; u, undiagnosed.

Table 6. Scenario analysis.

Parameter	Change	Base case	Scenario analysis	References
Screening frequency (years)	Increased screening frequency (years)	5 years	1, 2, 3, 4 years	Assumption
HR CVE uSH	HR > 1	1	1.19	Bauer et al.[41]
HR CVE uSH	HR > 1	1	1.58	Pascual et al.[32]
10% primary care visits by phone	Lower cost per visit	€67.53	€63.30	Assumption
50% primary care visits by phone	Lower cost per visit	€67.53	€46.28	Assumption
75% adherence to screening	Lower adherence	100%	75%	Assumption
50% adherence to screening	Lower adherence	100%	50%	Assumption

Abbreviations. c, controlled; CVE, cardiovascular event; HR, hazard ratio; OH, overt hypothyroidism; SH, subclinical hypothyroidism; u, undiagnosed.

minus incremental costs, providing a direct monetary estimate of cost-effectiveness. Furthermore, the number of extra diagnoses and the mean number of patients in each health state per year were computed.

In addition to the deterministic results, a univariate sensitivity analysis, a probabilistic sensitivity analysis (PSA), and a scenario analysis were conducted. In the univariate sensitivity analysis (also known as one-way sensitivity analysis, OWSA), each model parameter was varied by its upper and lower 95% confidence interval limit to assess how individual parameter variations impacted the overall results of the model. The results of this analysis are represented using a tornado diagram. For the PSA, a probability distribution was assigned to costs, utilities, and disutilities (Beta for utilities, Gamma for costs, and Lognormal for disutilities—see Supplementary Material, Table SM1), and these parameters were simultaneously varied randomly according to their respective distributions and standard deviations to generate 1,000 scenarios following a Monte Carlo simulation approach. The results of the PSA are presented on an incremental cost-effectiveness plane to illustrate the percentage of interventions falling below the willingness-to-pay threshold.

Finally, a scenario analysis was conducted to evaluate how other assumptions (presented in Table 6) influence the final outcomes. The screening frequency was varied to assess how reducing the interval between screenings would impact the ICER, testing the robustness of the cost-effectiveness under more intensive strategies. Hazard ratios (HRs) were incorporated to explore the impact of relaxing the conservative assumption that patients with uSH have the same risk of transitioning to CVE as those in a euthyroid state. In addition, adherence rates of 75 and 50% were tested to account for more realistic participation in screening programs. Lastly, telemedicine scenarios were introduced to reflect a growing trend in clinical practice, aiming to evaluate the potential effects of reducing costs in primary care.

Results

Without screening, the total cost for the cohort was estimated at €534,750,653, compared to €569,432,005 with screening, resulting in an incremental cost of €34,681,353. Additionally, the cohort without screening accrued 10,070,142 QALYs, whereas the cohort with screening achieved 10,076,179 QALYs, yielding an additional 6,037 QALYs. These results correspond to an ICER of €5,745 per QALY, which is well below the Spanish NHS's cost-effectiveness threshold of €21,000/QALY[40] (Table 7), and a NMB of €92,091,662. For the simulated cohort of 542,471 individuals followed over 35 years, periodic screening would result in 33,215 additional diagnoses of subclinical hypothyroidism and 6,870 fewer diagnoses of overt hypothyroidism compared to the no screening scenario. On average, this translates to an annual increase of 877 patients-year with subclinical hypothyroidism (including both undiagnosed and controlled cases) and a reduction

Table 7. Base case results.

	No screening	Screening	Incremental
Total costs	€534,750,653	€569,432,005	€34,681,353
Screening	€0	€23,122,569	€23,122,569
Visits and testing	€93,265,733	€105,401,507	€12,135,774
Treatment	€4,326,348	€3,784,940	€-541,408
CVE	€437,158,572	€437,122,989	€-35,583
Total costs	€534,750,653	€569,432,005	€34,681,353
Women	€239,275,634	€255,171,584	€15,895,950
Men	€295,475,019	€314,260,421	€18,785,402
Total QALYs	10,070,142	10,076,179	6,037
Women	4,826,657	4,829,571	2,914
Men	5,243,485	5,246,608	3,123
Costs per patient	€985.77	€1,049.70	€63.93
Women	€893.03	€952.36	€59.33
Men	€1,076.28	€1,144.70	€68.43
QALYs per patient	18.5635	18.5746	0.0111
Women	18.0142	18.0250	0.0109
Men	19.0996	19.1110	0.0114
ICER		€5,745/QALY	
Women		€5,456/QALY	
Men		€6,015/QALY	
Net monetary benefit of the intervention		92,091,662	
Diagnoses of subclinical hypothyroidism	346,090	379,305	33,215
Diagnoses of overt hypothyroidism	29,013	22,142	−6,870
Number of patients-year with subclinical hypothyroidism	55,373	56,250	877
Number of patients-year with overt hypothyroidism	21,016	17,350	−3,666
Number of CVE	116,411	116,402	9

Abbreviations. CVE, cardiovascular event; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years.

of 3,666 patients-year with overt hypothyroidism in the cohort undergoing screening every 5 years. Additionally, screening was associated with 9 fewer CVEs over the 35-year period (Table 7).

The OWSA demonstrated that individual variations in parameters were insufficient to shift the ICER beyond the WTP threshold. The most influential parameters were the utilities of healthy or controlled states and, to a lesser extent, the utilities of undiagnosed states, followed by the discount rates for costs and QALYs and the costs of screening (Figure 2).

Meanwhile, the PSA, with a mean ICER of €5,733/QALY, showed that 100% simulations fall within the northeast quadrant, indicating that the screening intervention is more effective but also more costly (Figure 3). Figure 4, which shows the cost-effectiveness acceptability curve, indicates that 99.00% of simulations were cost-effective at a WTP threshold of 21,000 €/QALY.

Lastly, the scenario analysis indicated that all the screening frequencies tested would be cost-effective under the threshold of €21,000 per QALY. Up to biennial screening, ICERs remained very similar, allowing for the implementation of any screening frequency, whereas annual screening proved to be less cost-effective than the others. Notably, among women, triennial screening was slightly more cost-effective than quinquennial screening (Figure 5).

Additionally, the scenario analysis revealed that a higher HR for experiencing a CVE in the uSH state corresponded to a lower ICER. Similarly, reducing the cost of a primary care visit led to a lower ICER for the intervention (Table 8). Finally, lower screening adherence produced only a slight decrease in the ICER because, given the model's cost structure, decreases in adherence translated into nearly proportional reductions in both incremental QALYs and incremental costs. In this context, the change in NMB provides a more informative summary of the welfare impact.

Discussion

The present cost-effectiveness analysis evaluated the efficiency of screening for hypothyroidism *versus* no screening in the general population aged 30–65 years from the perspective of the Spanish NHS.

This analysis has shown that hypothyroidism screening in Spain is a cost-effective intervention for both men and women, with an additional cost of €64 per patient and a QALYs gain of 0.01, resulting in an ICER of €5,745/QALY, well below the Spanish NHS's WTP threshold. In clinical terms, screening has been observed to prevent patients from remaining in the uSH state for extended periods and therefore

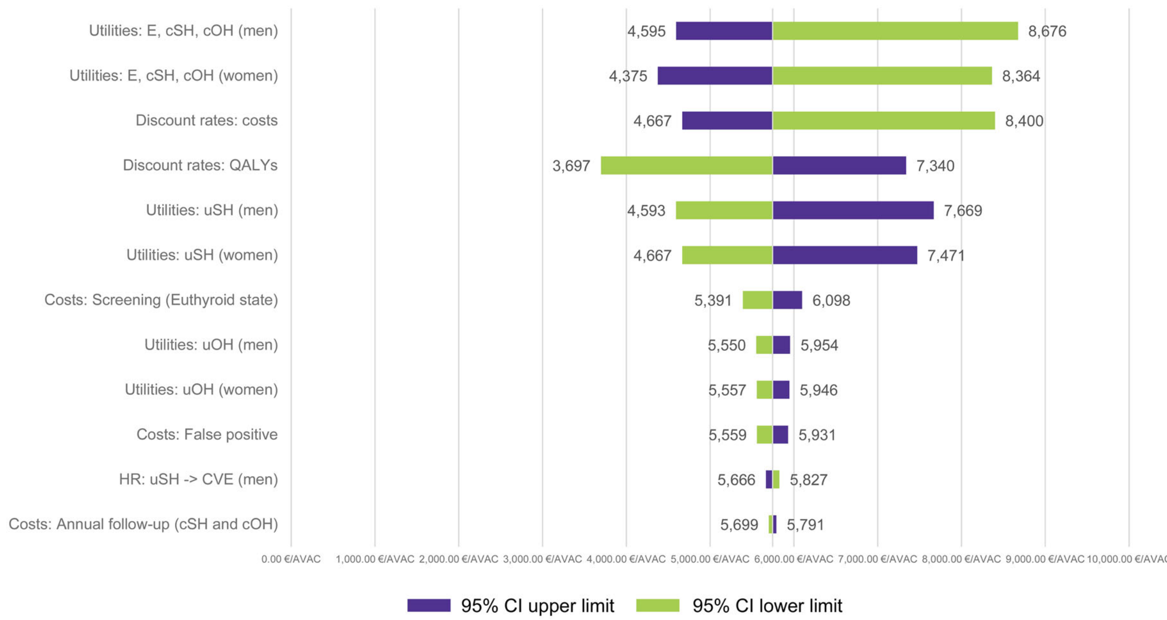

Figure 2. One way sensitivity analysis tornado diagram.

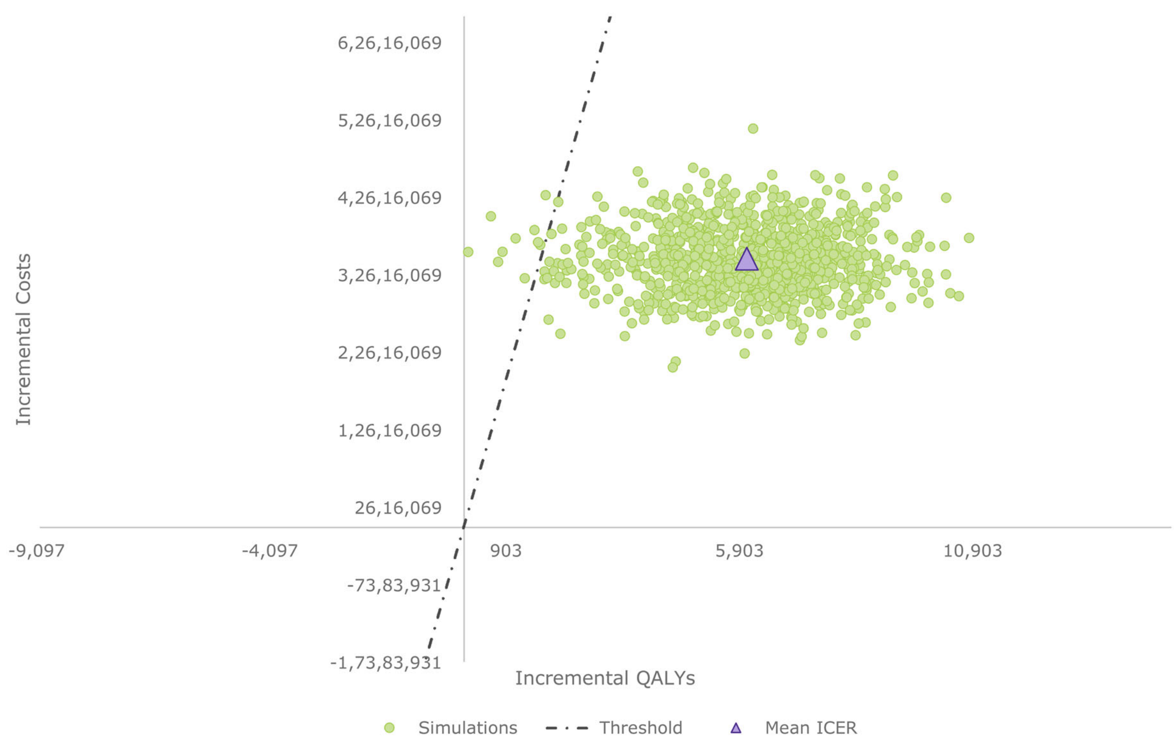

Figure 3. Incremental cost-effectiveness plane.

reduce their risk of transitioning to uOH. This is achieved because, upon screening, patients in the uSH state transition to cSH (a less concerning state). Over time, the screening strategy leads to a progressively larger proportion of patients in the euthyroid state compared to no screening. This relative difference becomes more pronounced in the long term.

The incremental cost associated with screening was mainly driven by testing, additional primary care visits, and laboratory testing following diagnosis; however, the incremental cost per patient remained modest. The improvement in QALYs primarily resulted from enhanced quality of life due to fewer patients progressing to overt hypothyroidism (a reduction of 3,666 patient-years). Conversely, the reduction in CVE contributed minimally (only 9 CVE avoided) because of the conservative approach adopted.

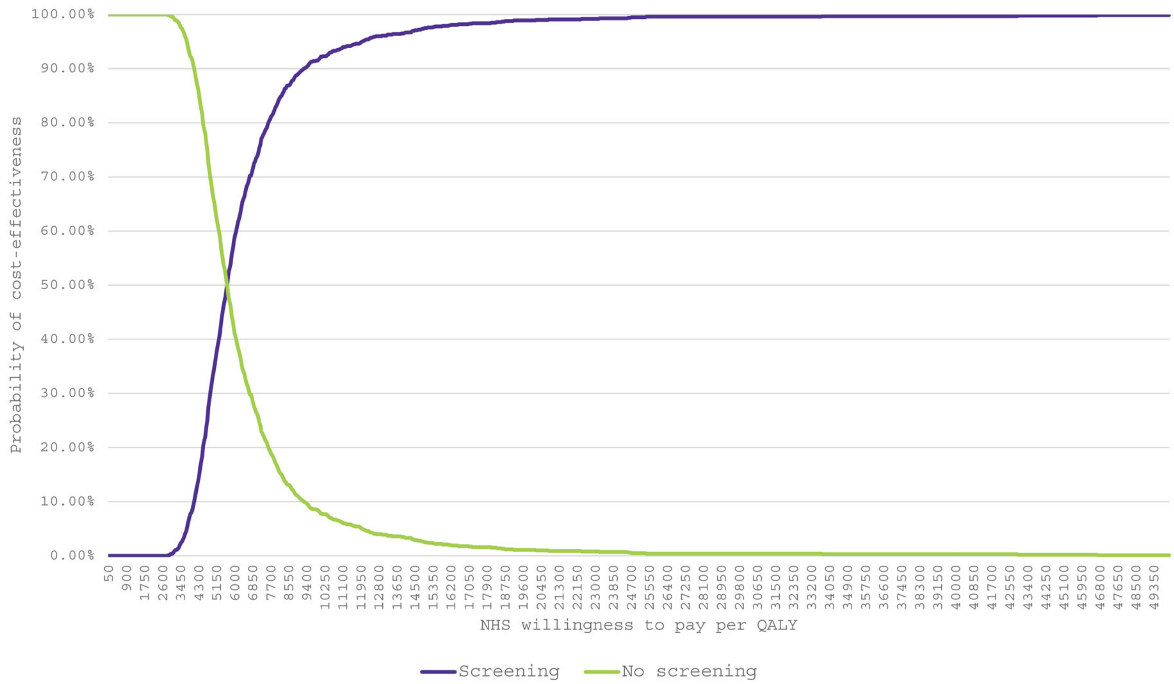

Figure 4. Cost-effectiveness acceptability curve.

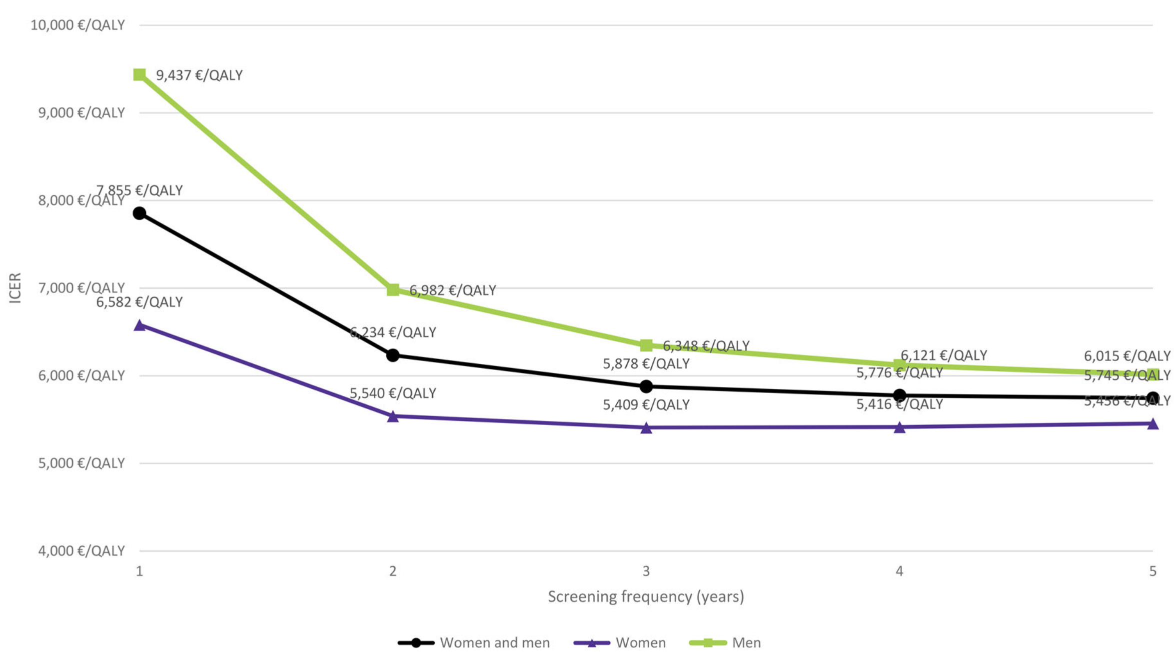

Figure 5. Scenario analysis with screening frequencies (1–4 years).

Correspondingly, most cost-savings originated from avoiding fixed long-term treatment costs and complications related to overt hypothyroidism.

According to the PSA, there is a 99% probability that screening is cost-effective, reinforcing the robustness of these findings. The OWSA demonstrated that the model's results were stable against individual parameter variations. The scenario analysis showed that any screening frequency within the 1–5 year range would constitute a cost-effective intervention for the NHS. Importantly, biennial and triennial screening showed similar cost-effectiveness levels, allowing for flexibility in implementation strategies. However, annual screening was found to be less cost-effective, suggesting that a longer screening interval may balance benefits and costs more efficiently.

Table 8. Scenario analysis results.

Parameter	Change	Base case	Scenario analysis	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)	NMB (€)
Screening frequency	Frequency (years)	5	1	162,095,874	20,636	7,855	271,261,183
Screening frequency	Frequency (years)	5	2	83,275,287	13,358	6,234	197,238,119
Screening frequency	Frequency (years)	5	3	56,957,265	9,690	5,878	146,530,606
Screening frequency	Frequency (years)	5	4	43,426,808	7,519	5,776	114,474,473
HR CVE uSH	HR	1	1.19	34,394,881	6,110	5,630	93,905,457
HR CVE uSH	HR	1	1.58	33,821,263	6,254	5,408	97,507,906
10% primary care visits by phone	Cost per visit	€67.53	€63.30	33,923,663	6,037	5,620	92,848,818
50% primary care visits by phone	Cost per visit	€67.53	€46.28	30,896,462	6,037	5,118	95,877,441
75% adherence	Adherence	100%	75%	25,986,556	4,528	5,740	69,091,551
50% adherence	Adherence	100%	50%	17,308,083	3,018	5,734	46,076,422

Abbreviations. CVE, cardiovascular event; HR, hazard ratio; NMB, net monetary benefit; SH, subclinical hypothyroidism; u, undiagnosed.

To the best of our knowledge, no similar study focused on the general population aged 30–65 years has been published in the last two decades. Most existing cost-effectiveness analyses have targeted specific groups, such as pregnant women[42] or individuals over 60 years old[38], which highlights the need for updated evidence on this topic. These findings suggest that implementing screening could improve early diagnosis rates without placing an excessive financial burden on the healthcare system. Furthermore, these results align with other cost-effective preventive screening programs, such as those for diabetes[43], reinforcing the potential value of integrating hypothyroidism screening into routine primary care assessments.

Our study has some limitations. Firstly, transition probabilities were assumed to be constant over time due to the lack of further evidence published in the literature. However, experts agreed that this assumption was reasonable given the age range considered in the model. Secondly, the model did not adjust for age-related reductions in the upper normal limit of TSH, potentially leading to an overestimation in the number of cases classified as uSH and cSH. Additionally, recent evidence by Feller et al.[44] showed no significant improvements in quality of life or thyroid-related symptoms with thyroid hormone therapy in patients with mild subclinical hypothyroidism (TSH 4.5–10 mIU/L). Nevertheless, our model differs substantially, as pharmacological treatment was restricted to severe cases (TSH $>$ 10 mIU/L), and benefits were projected over a 35-year horizon rather than in the short term. Besides, some parameters were derived from international sources due to the unavailability of equivalent data in Spain. Finally, the disutility of misdiagnosis was not accounted for in cases of false positives. Nevertheless, these estimates were reviewed and validated by local experts to ensure they accurately reflect Spanish clinical practice. Finally, although variations in adherence have little impact on the ICER (because they reduce both incremental costs and incremental QALYs by nearly the same proportion), they do reduce the net monetary benefit (NMB) approximately in line with adherence (e.g. 75% adherence results in an NMB about 25% lower than with 100% adherence).

There are also several assumptions and limitations which may confer a conservative bias to our model. TSH monitoring may offer benefits beyond hypothyroidism, potentially aiding in the detection and management of other thyroid disorders, which would further enhance the overall benefits of the intervention. For example, this screening not only allows doctors to detect hypothyroidism but also hyperthyroidism. Consequently, while the cost component of the model would remain unchanged, the potential benefits could be greater if monitoring and treatment of hyperthyroidism were also considered. Furthermore, it is important to note that the model's estimation is conservative, as the cost of blood sample collection is only assessed in relation to its benefits for hypothyroidism. However, screening could be incorporated into routine blood tests requested in primary care, thereby substantially reducing the costs attributable to hypothyroidism screening alone.

Despite its limitations, the model has several key strengths. The parameters used in the model represent Spanish clinical practice due to the involvement of the scientific committee. In the same way, the model's design allows for a better understanding of the mechanism behind underdiagnosis and the existence of patients experiencing a poorer quality of life.

Conclusions

Our analysis demonstrates that hypothyroidism screening is a cost-effective intervention for the Spanish National Health System, providing health benefits at a reasonable cost. These findings suggest that implementing screening as a preventive measure could improve early detection, prevent disease progression, and enhance patients' quality of life.

Given that hypothyroidism is a prevalent yet frequently underdiagnosed condition, these findings provide valuable insights into the potential benefits of a systematic screening approach.

Transparency

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Author contributions

Zafón Lopis, O. Vicente López, Mª A. Cruz Martos, and JM. Cucalón contributed to the conceptualization, investigation, and methodology, as well as the writing-review, and editing of the manuscript.

B. Alcalá Revilla contributed to the conceptualization, investigation, and methodology, and served as the project administration manager. She also contributed to the validation, as well as the writing-review, and editing of the manuscript.

H. De los Santos Real contributed to the conceptualization and methodology, as well as the writing-review, and editing of the manuscript.

B. Citoler Berdala contributed to the conceptualization, formal analysis, investigation, methodology, and supervision. She also contributed to the validation and visualization of the data, as well as the original draft writing and the writing-review, and editing of the manuscript.

D. Pérez Troncoso contributed to the conceptualization, data curation, formal analysis, investigation, and methodology. He also contributed to the validation and visualization of the data, as well as the original draft writing and the writing-review, and editing of the manuscript.

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References

[1] McDermott M. Hypothyroidism. Ann Intern Med. 2020;173(1):ITC1–ITC16. doi: 10.7326/AITC202007070.

[2] Chiovato L, Magri F, Carlé A. Hypothyroidism in context: where we've been and where we're going. Adv Ther. 2019;36(Suppl 2):47–58. doi: 10.1007/s12325-019-01080-8.

[3] Jansen H, Boelen A, Heijboer A, et al. Hypothyroidism: the difficulty in attributing symptoms to their underlying cause. Front Endocrinol. 2023;14:1130661. doi: 10.3389/fendo.2023.1130661.

[4] Valdés S, Maldonado-Araque C, Lago-Sampedro A, et al. Population-based national prevalence of thyroid dysfunction in Spain and associated factors: diabetes study. Thyroid. 2017;27(2):156–166. doi: 10.1089/thy.2016.0353.

[5] Parretti H, Okosieme O, Vanderpump M. Current recommendations in the management of hypothyroidism: developed from a statement by the British Thyroid Association Executive. Br J Gen Pract. 2016;66(651):538–540. doi: 10.3399/bjgp16X687493.

[6] Azim S, Nasr C. Subclinical hypothyroidism: when to treat. Cleve Clin J Med. 2019;86(2):101–110. doi: 10.3949/ccjm.86a.17053.

[7] Mariscal Hidalgo AI, Lozano Alonso JE, Vega Alonso T. Hipotiroidismo subclínico en una muestra oportunista de la población de Castilla y León. Gac Sanit. 2015;29(2):105–111. 2015/03/01/doi: 10.1016/j.gaceta.2014.10.007.

[8] Pérez Unanua MP, Mateo Pascual C, Muñoz González Y, et al. UPDATE IN FAMILY MEDICINE: management of thyroid disorders in primary care I. Thyroid disease screening. Hypothyroidism. Med Fam SEMERGEN. 2008; 34(9):450–454. doi: 10.1016/S1138-3593(08)75204-3.

[9] Gottwald-Hostalek U, Schulte B. Low awareness and under-diagnosis of hypothyroidism. Curr Med Res Opin. 2022;38(1):59–64. doi: 10.1080/03007995.2021.1997258.

[10] Zhong L, Liu S, Yang Y, et al. Metabolic syndrome and risk of subclinical hypothyroidism: a systematic review and meta-analysis. Front Endocrinol. 2024;15:1399236. doi: 10.3389/fendo.2024.1399236.

[11] Yoshinaka A, Akatsuka M, Yamamoto S, et al. Sudden cardiac arrest associated with myxedema coma due to undiagnosed hypothyroidism: a case report. BMC Endocr Disord. 2021;21(1):229. doi: 10.1186/s12902-021-00894-4.

[12] Ellegard L, Krantz E, Trimpou P, et al. Health-related quality of life in hypothyroidism—a population-based study, the WHO MONICA project. Clin Endocrinol. 2021;95(1):197–208.

[13] Hepp Z, Lage MJ, Espaillat R, et al. The direct and indirect economic burden of hypothyroidism in the United States: a retrospective claims database study. J Med Econ. 2021;24(1):440–446. doi: 10.1080/13696998.2021.1900202.

[14] Jonklaas J, Bianco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association Task Force on thyroid hormone replacement. Thyroid. 2014;24(12):1670–1751. doi: 10.1089/thy.2014.0028.

[15] Eslava AO, Gil RM, Fuentes MDF, et al. Guideline for economic evaluation and budget impact in drug assessment reports. Madrid: SEFH, Sociedad Española de Farmacia Hospitalaria; 2017.

[16] Naimark DM, Bott M, Krahn M. The half-cycle correction explained: two alternative pedagogical approaches. Med Decis Making. 2008;28(5):706–712. doi: 10.1177/0272989X08315241.

[17] Olloqui Mundet J, Ochoa Prieto J. Family medicine in the monitoring of hypothyroidism. Aten Primaria. 2002; 29(1):36–38. doi: 10.1016/s0212-6567(02)70498-8.

[18] Mohedano López E, Sanchís Osuna LM, González Vargas JM, et al. Epidemiological characteristics of hypothyroidism in a southern Spanish area (Seville). Rev Clín Med Fam. 2020;13(2):123–130.

[19] Donnay S, Balsa JA, Álvarez J, et al. Disease burden attributable to subclinical hypothyroidism in the Spanish population. Rev Clin Esp. 2013;213(8):363–369. doi: 10.1016/j.rceng.2013.07.002.

[20] Resolución SLT/4326/2023, de 20 de diciembre. Diari Oficial de la Generalitat de Catalunya, número 9067 de 27 de diciembre de 2023; 2023.

[21] Gisbert R, Brosa M. Base de datos de costes sanitarios y ratios coste-efectividad españoles: eSalud Barcelona. Oblikue ConsultingSL; 2018 [cited 2024 Apr]. Available from: http://www.oblikue.com/bddcostes/

[22] Ministry of Health. Nomenclator: information on products included in the pharmaceutical provision of the NHS; 2024.

[23] Medrano Ortiz de Zárate ME, de Santillana-Hernández SP, Torres-Arreola L, et al. Diagnóstico y tratamiento del hipotiroidismo primario en adultos. Rev Med IMSS. 2012;50(1):71–80.

[24] Spanish Statistical Office. Resident population by date, sex, and age; 2024 [cited 2024 Apr]. Available from: https://www.ine.es/jaxiT3/Tabla.htm?t=59589

[25] Fatourechi V, editor. Subclinical hypothyroidism: an update for primary care physicians. Mayo Clinic Proceedings. Elsevier; 2009.

[26] Pérez de Isla L, Arroyo-Olivares R, Alonso R, et al. Incidence of cardiovascular events and changes in estimated risk and treatment of familial hypercholesterolemia: the SAFEHEART registry. Rev Esp Cardiol. 2020; 73(10):828–834. doi: 10.1016/j.rec.2019.10.028.

[27] Comín E, Solanas P, Cabezas C, et al. [Estimating cardiovascular risk in Spain using different algorithms]. Rev Esp Cardiol. 2007;60(7):693–702. doi: 10.1016/S1885-5857(08)60004-3.

[28] Díez JJ, Iglesias P, Burman KD. Spontaneous normalization of thyrotropin concentrations in patients with subclinical hypothyroidism. J Clin Endocrinol Metab. 2005;90(7):4124–4127. doi: 10.1210/jc.2005-0375.

[29] Spanish Statistical Office. GP consultation in the last 4 weeks by age group, 2020; 2020. Available from: https://ine.es/dynt3/inebase/es/index.htm?type=pcaxis&path=/t00/mujeres_hombres/tablas_1/&file=pcaxis&dh=0&capsel=0

[30] Gibbons V, Lawrenson R, Sleigh P, et al. Investigating the pathways in primary practice leading to the diagnosis of central hypothyroidism. N Z Med J. 2012;125(1364):83–90.

[31] Spanish Statistical Office. National results by autonomous communities and provinces. Mortality tables by year, sex, age and functions; 2024 [cited 2024 Apr]. Available from: https://www.ine.es/jaxiT3/Tabla.htm?t=27153

[32] Pascual I, Hernandez-Vaquero D, Almendarez M, et al. Observed and expected survival in men and women after suffering a STEMI. J Clin Med. 2020;9(4):1174.

[33] Ning Y, Cheng YJ, Liu LJ, et al. What is the association of hypothyroidism with risks of cardiovascular events and mortality? A meta-analysis of 55 cohort studies involving 1,898,314 participants. BMC Med. 2017;15(1):21. doi: 10.1186/s12916-017-0777-9.

[34] Garcia-Gordillo MA, Adsuar JC, Olivares PR. Normative values of EQ-5D-5L: in a Spanish representative population sample from Spanish Health Survey, 2011. Qual Life Res. 2016;25(5):1313–1321. doi: 10.1007/s11136-015-1164-7.

[35] Razvi S, Ingoe LE, McMillan CV, et al. Health status in patients with sub-clinical hypothyroidism. Eur J Endocrinol. 2005;152(5):713–717. doi: 10.1530/eje.1.01907.

[36] Ara R, Brazier J. Deriving an algorithm to convert the eight mean SF-36 dimension scores into a mean EQ-5D preference-based score from published studies (where patient level data are not available). Value Health. 2008;11(7):1131–1143. doi: 10.1111/j.1524-4733.2008.00352.x.

[37] Hughes DA, Skiadas K, Fitzsimmons D, et al. Liothyronine for hypothyroidism: a candidate for disinvestment or in need of further research? A value of information analysis. BMJ Open. 2021;11(12):e051702. doi: 10.1136/bmjopen-2021-051702.

[38] Bona M, Santini F, Rivolta G, et al. Cost effectiveness of screening for subclinical hypothyroidism in the elderly. Pharmacoeconomics. 1998;14(2):209–216. 1998/08/01 doi: 10.2165/00019053-199814020-00009.

[39] Ara R, Brazier J. Health related quality of life by age, gender and history of cardiovascular disease: results from the Health Survey for England. Sheffield: University of Sheffield; 2009.

[40] Vallejo-Torres LG-LB, Castilla I, Valcárcel Nazco C, et al. Monetary value of a quality-adjusted life year: empirical estimation of opportunity cost in the Spanish National Health System. Madrid: Ministerio de Sanidad, Servicios Sociales e Igualdad; 2015.

[41] Bauer BS, Azcoaga-Lorenzo A, Agrawal U, et al. The impact of the management strategies for patients with subclinical hypothyroidism on long-term clinical outcomes: an umbrella review. PLOS One. 2022;17(5):e0268070. doi: 10.1371/journal.pone.0268070.

[42] Donnay Candil S, Balsa Barro JA, Álvarez Hernández J, et al. [Cost-effectiveness analysis of universal screening for thyroid disease in pregnant women in Spain]. Endocrinol Nutr. 2015;62(7):322–330. doi: 10.1016/j.endoen.2015.08.002.

[43] Kahn R, Alperin P, Eddy D, et al. Age at initiation and frequency of screening to detect type 2 diabetes: a cost-effectiveness analysis. Lancet. 2010;375(9723):1365–1374. doi: 10.1016/S0140-6736(09)62162-0.

[44] Feller M, Snel M, Moutzouri E, et al. Association of thyroid hormone therapy with quality of life and thyroid-related symptoms in patients with subclinical hypothyroidism: a systematic review and meta-analysis. JAMA. 2018;320(13):1349–1359. doi: 10.1001/jama.2018.13770.