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Estimating a cost-effectiveness threshold for healthcare decision-making in the Greek NHS

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ABSTRACT

Background: The introduction of new health technologies improves quality of life and longevity, but also imposes additional strains in the scarce resources of the health system. Consequently, decisions on the adoption of new technologies are typically based, among other criteria, on the difference between costs and outcomes among competing alternatives. This paper aims to estimate a cost-effectiveness threshold that can be used as an input in the decision-making process for the funding (or reimbursement) of health technologies in Greece.
Methods: For a 30-year period, we calculate the Quality-Adjusted Life Expectancy (QALE) of the Greek population and regress it against per capita public health expenditure, using an instrumental variable approach and controlling for a set of covariates. The estimated coefficients of expenditure on QALE are used to inform a cost-effectiveness threshold, estimatead as the cost per QALY gained through a permanent increase in per capita spending.
Results: Based on the estimated coefficient of health expenditure, we estimate a base case cost-effectiveness threshold of €27,117 per QALY gained for the Greek healthcare system, from a third-party payer perspective.
Conclusions: In the Greek healthcare system, which is currently in the stage of establishing a comprehensive health technology assessment process, decision rules which are not based on heuristics or "rules of thumb", are essential.

Introduction

The introduction of new health technologies has profound effects on health systems. Technological innovation substantially contributes to higher life expectancy and better quality of life [1], but is also a key driving force of health spending [2,3].

Faced with growing imbalances between resources and demand, health systems aim to maximize output (i.e. years lived in good health), under the restrictions of finite health budgets. In the context of Health Technology Assessment (HTA), the value dimensions of a health technology are compared by examining the consequences of using the technology versus an established comparator. These dimensions include both positive and normative aspects, among them clinical effectiveness, safety, costs and economic implications, ethical, social, cultural and legal considerations, as well as organizational and environmental aspects [4]. The incremental cost-effectiveness ratio (ICER) or, in other words, the difference in costs divided by the difference in effects/outcomes of the technology under evaluation versus a comparator, is benchmarked against a cut-off point (threshold). This reference value is used as the basis for deciding whether a health technology represents good value for money [5].

Estimating a cost-effectiveness threshold is a country-specific exercise, which follows methodologies that arise from different theoretical foundations and starting points, and require different types of data sources [6,7]. In general, the estimation of a cost-effectiveness threshold (or *CET*) follows either a demand- or a supply-side approach. In the first case, the estimated threshold represents the social demand for health calculated empirically using a variant of a willingness-to-pay (WTP) experiment [8]. The latter forms its basis on representing the opportunity costs of investing in health technologies, within a given budget constraint [9,10]. On the other hand, supply-side CETs are based on the empirical estimation of the relationship between health expenditure and the changes in the health status of the population, assessed in the form of Quality-Adjusted Life Expectancy [11]. This approach is often bounded by data availability. Nevertheless, it has been increasingly used over the past years [12].

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In their seminal report, Claxton et al. [11] estimated a cost-effectiveness threshold (mentioned as "central threshold" in the paper) of £12,936 per QALY gained across the National Health Service in England, by using budgeting data to estimate the relationship between changes in overall NHS expenditure and changes in mortality and quality-adjusted life expectancy [11]. Claxton et al. used an instrumental variable (IV) approach for the empirical estimates. The same strategy was also used by Vallejo-Torres et al. [13], who estimated elasticities of public healthcare spending on quality-adjusted life expectancy, on a regional basis in Spain, returning CET estimates between €22,000 and €25,000 per QALY gained [13]. Supply-side estimates using available data and IV setups have also been reported for Australia, where Edney et al. [14] reported a CET of AUD 28,033 per QALY gained (2017 base year estimates) and Sweden, where Siverskog and Henriksson [15], estimated the marginal cost of a life year in Sweden's public healthcare sector at approximately SEK 370,000 (EUR 39,000) [14,15]. Elasticity estimates between spending and health outcomes are crucial for this approach and they form the basis of calculations. Using elasticity estimates for crude death rates, Edoka and Stacey [16] estimated a CET that reflects the opportunity cost of health spending in South Africa at approximately ZAR 38,500 per DALY averted [16]. Moreover, a marginal productivity approach was used in China for the estimation of a CET, resulting in a threshold of RNB27,923–52,247 (2017 RMB) (central estimate RMB37,446) per DALY averted [17]. Espinosa et al. [18] estimated the supply-side cost-effectiveness elasticity for the healthcare system of Colombia in order to calculate a cost-effectiveness threshold of US$4487.5 per year of life lost avoided and US$5180.8 per quality-adjusted life-year gained [18]. Moler-Zapata et al. [19] estimated that a 1 % increase in the level of health spending in Indonesia reduces under-five mortality by 0,38 % (95 % CI 0.00–0.76) which translates into a cost of averting one DALY of US$235 [19].

Beyond the threshold calculation using country- or regional-level data, two studies focusing on the hospital setting have estimated a cost-effectiveness threshold from a supply-side perspective in the Dutch health system. The first calculated a threshold of €73,600 per QALY [20], while the second arrived at a threshold estimate of €41,000 per QALY, based on the marginal returns of cardiovascular spending [21].

Although several health system institutions have been established – including a single payer – Greece has missed out on following the developments in the regulatory path of HTA that took part across European countries during the last decades [22]. Despite several promising attempts since the late-2010s, HTA processes are still underdeveloped and lack some important elements that could promote efficient, transparent, and evidence-based decision-making. Among those, there is currently no context-specific reference/benchmark CET for the health economics evidence used within its HTA process.

This article aims to estimate and report the first supply-side estimate of a cost-effectiveness threshold for Greece, based on the anticipated changes in Quality Adjusted Life Expectancy (QALE) of the population from marginal changes in public health expenditure.

Methods

Empirical approach

Our analysis draws on national and publicly available data from 1990 to 2019 (the last year before the SARS-CoV-2 pandemic). As a first step, we defined a measure of the effect of changes in healthcare spending on the health status of the population. To this end, we used the concept of QALE as a measure of health outcomes (i.e., the change in life expectancy adjusted by relevant changes in health-related quality of life) [23]. To obtain annual estimates of QALE for the Greek population we used the following strategy: first, we created a series of life tables for the Greek population for each year from 1990 to 2019. We used the approach of the Pan-American Health Organization (PAHO) and combined crude mortality estimates (sourced by Eurostat) with population data, both stratified by age band and year [24]. For each age band (0–17 years, 18–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75–84 and 85+), we estimated the average life expectancy (average number of years of life remaining at the beginning of age interval) and multiplied (i.e. *adjusted)* it with the corresponding EQ-5D estimate for the general population of Greece in the given age band in order to obtain the QALE for the age band in a given year. For the EQ-5D norms we used the first publication of EuroQoL for Greece, which collected EQ-5D data from the general population [25]. Third, we calculated a QALE for the entire general population in a given year (QALEgp), through a weighted average of age band QALEs and the share of each age band in the general population. The above steps were iterated for each year in the timeframe of the analysis, in order to create a series of values for the dependent variable (QALEgp).

Using a third-party payer perspective, we used per capita public expenditure for health as our key explanatory variable and the measure of health spending (HEx).[1] We reported expenditure and variables expressed in monetary values in 2019 price levels, after adjusting with the GDP deflator, provided by the World Bank.[2]

In order to examine the link between health spending and QALE, we estimated a linear model with a log-transformed dependent variable of the following form:

$$\log(QALEgp) = a + \beta \log(\mathrm{HEx}_{t-1}) + \gamma_i \mathrm{X}_i + \varepsilon \quad (1)$$

where Xi denotes the vector of covariates in the regression. We used the percentage of people over 65 and the percentage of females in the population as independent variables. We also controlled for the average per capita public expenditure on health in the EU countries, as a proxy of the trends in health spending that are not related to the local health status, but to external factors such as technological advances and price trends in new technologies, among others.

We used a log transformation for QALEgp and HEx, and, thus, the coefficient of HEx represents the elasticity of spending on outcomes. Similar to other studies, the health expenditure variable is lagged by one year, denoting the fact that the effects of spending in health are not expected to be contemporaneous [26].

When examining the association between spending and health outcomes, a commonly discussed concern is the potential endogeneity between the two variables, due to reverse causality and omitted variable bias. For example, it might be the case that health spending improves outcomes, but also that poorer health (outcomes) may lead to higher spending. In order to control for potential endogeneity, we used an instrumental variable (IV) approach. Choosing an instrument for this approach is a difficult task, as it should satisfy a set of properties. First, the instrument should be relevant, in the sense that it should be correlated with the potentially endogenous regressor (here, public expenditure for health). Second, the instrument should be valid, and therefore it should not affect the dependent variable, except through the channel of public expenditure on health. In addition, the choice of instrument is bounded by data availability, given that annual estimates of the potential instrument should be available throughout the 30-year period of the analysis.

A series of instruments have been proposed in the relevant studies for the calculation of a supply-side threshold. For example, Claxton et al. [11] tested and used the proportion of the population providing unpaid care, the proportion of households that consist of one pensioner and an index of multiple deprivation [11]. In their study for Australia, Edney et al. [14] also used the proportion of the population providing unpaid care as an instrument for health expenditure [14], whereas,

[1] Eurostat. Health care expenditure by financing scheme. Available at: https://ec.europa.eu/eurostat/databrowser/view/HLTH_SHA11_HF__custom_5075126/default/table?lang=en

[2] World Bank. Inflation, GDP deflator. Available at: https://data.worldbank.or g/indicator/NY.GDP.DEFL.KD.ZG

Vallejo-Torres et al. employed the percentage of total public expenditure assigned to health as an instrument to address endogeneity [13].

Similar to Vallejo-Torres et al. [13], and considering data availability issues in Greece, we also used the share of general government spending allocated to health as an instrumental variable to address potential endogeneity. Although the exogeneity condition cannot be formally tested, the share of government spending allocated to health is expected to mainly influence health through potential changes in health expenditure rather than other channels. Given that instrument validity always entails uncertainty, we further confirmed our results using different instruments and alternative modelling approaches without using an IV. As discussed later, two additional instruments are also used to check the sensitivity of our baseline findings. The validity of the instrument(s) and the 2SLS estimates was assessed through the F-test for weakness of the instruments and Wu-Hausman test for the presence of endogeneity. Calculations were performed in R with the use of the ivreg package (v0.6.1; Fox, Kleiber and Zeileis 2021).

In light of the above, the initial OLS set up is transformed to an instrumental variable (IV) two-stage least-squares regression, where in the first stage HEx is regressed against the IV and all the other covariates, i.e.:

$$\log(\mathrm{HEx}_{t-1}) = a + \delta_1 \mathrm{X_i} + \delta_2 \mathrm{IV} + \varepsilon \quad (2)$$

and, at the second stage, the predicted HEx is used instead of the original HEx values in the initial regression (Eq. (1)).

Estimating the ICER threshold

The second step of our approach involves the transformation of the quantified effects of spending on outcomes into a reference ICER, i.e. into a "cost per QALY gained" metric. To this end, we used the approach proposed by Vallejo-Torres et al. [13] – based on previous work by Lichtenberg [26] - whereby in order for permanent changes to occur in the life expectancy of a population, a permanent change in health expenditure must also occur [13]. The ratio of changes in spending and outcomes is expressed by the elasticity calculated in Eq. (1). This means that a sustained increase of one unit (in our case, one euro) on per capita healthcare expenditure, or, in other words, one euro times the average life expectancy of the population would result to a given increase in the average QALEgp, based on the elasticity estimate. In this sense, the threshold is calculated as the ratio of the above two terms, i.e. (1*averageLE) and ΔQALEgp.

Results

Empirical analysis

Table 1 presents the results of the 2SLS model, for the quantification of the effect of public healthcare expenditure on outcomes, as the latter is represented by the estimates of QALE for the general population. Given that both variables are log-transformed, the coefficient of health expenditure represents the elasticity of spending on outcomes, which is our key parameter of interest.

Table 1
Two-stage least squares analysis results.

Dependent variable: QALEgp	Coefficient	Standard error	*p* value
Covariates			
HEx	0.03617	0.01355	0.009*
Share of females	−0.17931	0.01276	0.000*
Share of people >65	−0.00907	0.00195	0.000*
Avg. public health spending at the EU countries	−0.00003	0.00016	0.025*

* *significant at the 0.05 level.

The diagnostics of the IV model report an F-test of 110.043 and a p-value of <0.001, denoting that the instrument is not weak. The Wu-Hausman test is not significant at the 0.05 level (0.329), not being strongly confirmatory of the presence of endogeneity.

As a sensitivity analysis, we also ran the 2SLS by using two different instruments (a) total government spending per year (sourced by the World Bank database,[3] adjusted in 2019 prices and lagged by 1 year, as in the case of the health expenditure variable) and (b) general government spending on defence. Being a sizable part of government spending, it is expected that in more affluent economic periods both health expenditure and defence expenditure will increase – and the opposite, during a contraction – expressing the capabilities of government spending over time. However, changes in the IV are not expected, reasonably and under normal conditions, to have an effect on the health status of the population. In the first case we find an elasticity of 0.03370 (p=value: 0.042). In the second case, the specification provides an elasticity estimate of 0.02718 (p=value 0.062). Finally, to further assess the robustness of estimates we also estimate the elasticity using a linear probability model estimated by OLS, with the coefficient of interest amounting to 0.04154 (p-value: 0.001).

Calculating the reference ICER

The calculation method of the reference ICER involves the transformation of the elasticity estimate between spending and outcomes, to incremental increases in QALE. The baseline elasticity estimate of 0.03617 implies that a 1 % increase in spending would entail a 0.03617 % increase in QALE. Based on the actual values of the two variables in the end-year of the analysis, an increase of 8.623 euros in public per capita health expenditure would result to an increase in QALE of 0.0144, or, in unitary terms, an increase of 0.00167 per 1 extra euro of spending. Given that this change in expenditure must be permanent for the population in order to achieve a permanent effect on outcomes, this increase must be applied for the remaining life span of the entire cohort, i.e. the average life expectancy, which based on the lifetable calculations is 44.88 years. Thus, the reference ICER is estimated at 27,117 euros per QALY gained.

Table 2 outlines the estimates of the reference ICER under the baseline and scenario sensitivity analysis estimates.

Discussion

In the context of the budget-constraint environment in which health systems typically operate, the ICER threshold represents a "critical ratio", for the resource allocation between alternative actions or in-

Table 2
Results on the reference ICER.

Scenario	Method	Elasticity estimate	Reference threshold (euros/QALY gained)
Baseline	Gov. spending on health as share of total gov. spending as the IV	0.03617	27,117
Alternative 1	Total government spending as the IV	0.03370	29,105
Alternative 2	Spending on defence (per year) as the IV	0.02718	36,086
Alternative 3	No IV: OLS estimates	0.04154	23,612

[3] World Bank. General government final consumption expenditure (current LCU). Available at: https://data.worldbank.org/indicator/NE.CON.GOVT.CN

terventions [27]. Although the ICERs alone cannot serve as the single criterion for decision-making [28], a reference value is considered as an important input in establishing whether a health technology or intervention represents good value for money [29].

The contribution of the study is twofold. First, we provide the first supply-side estimate of a reference ICER for Greece, a country that does its first steps towards evidence-informed decision-making for health technologies. Second, we also add to the relatively small but growing range of literature on identifying a reference ICER for technology appraisals.

Greece is a rather interesting case study, mainly due to the volume and impact of the pharmaceutical policies and measures implemented during the past years. Following a rapid growth of pharmaceutical spending during 1998–2008 (annual growth of 11.3 % in Greece compared to an EU average of 4.7 %), a series of cost-containment measures were implemented during the previous decade in the context of the Economic Adjustment Program (EAP) [30–32]. In particular, price cuts, budget ceilings, rebates, and clawbacks, have been the key policy measures for reducing pharmaceutical expenditure. However, the overreliance on supply-side payback mechanisms, without the concurrent implementation of structural reforms (e.g. demand regulation at the individual level), undermine health system sustainability [22].

The policy relevance of the present study arises from the absence of systematic and robust HTA process, which can guide informed and evidence-based decisions for resource allocation. Greece is a late adopter in HTA implementation and the institutionalization of a dedicated HTA agency is considered a necessity [33]. Additionally, given that there is no official cost-effectiveness threshold in Greece [34], stakeholders currently compare economic evaluation results to assumed thresholds or outdated and less relevant "rules of thumb". Against this background, this study provides an evidence-informed benchmark for health economics practice and HTA.

The extent to which a demand-side approach [35,36] or a supply-side estimate is preferable for the estimation of the reference ICER has been extensively discussed in existing literature. It appears that supply-side thresholds may be more relevant in the context of a constrained budget where displacements must occur in order to introduce (and fund) new health interventions [37–39]. This renders the need for a context-specific threshold, which would incorporate and reflect the local health system characteristics, in order to enhance its social acceptance [40,41].

In order to estimate a reference ICER for Greece, we used a methodology that centers around the elasticity of spending on health outcomes. This approach has been applied in previous studies for other countries, including England, Spain, Australia and South Africa [11,13,14,16]. Another approach which has been proposed by Al-Jedai et al., uses an existing elasticity from an analysis of cross-country data from another paper, and applies it to Saudi Arabia [42]. Our empirical strategy differs, however, in a series of elements, most notably the use of a time-series approach, instead of a panel data specification for the 2SLS.

Nevertheless, the results of this analysis share common ground with previous evidence. The size of the estimated elasticity using Greek data is close to the cross-country estimates for other high-income countries [43]. In addition, our CET estimate is in the lower bound of the range of the CETs currently used across European countries ($ 23,604 - $ 80,549), as reported by a recent study [44].

This study has some limitations. First, similar to other studies, we begin with the hypothesis that the objective of health spending is to generate benefits in the form of QALYs [45]. Nevertheless, QALY maximization may not capture the full spectrum of benefits from health interventions for individual and societal welfare. There is indeed an enduring debate regarding the extent to which QALY is an adequate measure of welfare [46–48]. Nonetheless, the "cost/QALY gained" criterion remains a mainstay in resource allocation decisions in health care and has been widely applied across countries, including Greece. Second, although we created a series of life tables for all the years for the first time in Greece, we could not find EQ-5D scores over time, due to data availability constraints for relevant health-related quality of care estimates. The time point EQ-5D estimate may lead to the underestimation of the effect of expenditure on QALYs. There is some evidence that population norms regarding health-related quality of life may change over time. As such, annual EQ-5D data could result in QALE estimates of higher robustness through the years. Last, the model estimates of the elasticity for Greece are based on a limited number of country-level observations, due to data availability constraints. This is an important limitation, which cannot be addressed given the existing data sources in Greece. Future research should focus on this limitation and provide updated estimates either by employing longer time-series or by using regional-level panel data over time, conditional on data availability. The CET estimate thus serves as a placeholder, until more granular data will be available, allowing us for arriving at elasticity estimates based on a larger number of observations.

Similar to previous literature, this study provides an estimate of the reference ICER for resource allocation decisions from a third-party payer perspective. These estimates are more well-founded compared to rules of thumb, such as the *30,000 Euros/QALY gained* threshold that is typically used in the absence of a better estimate [13]. They also have advantages over less context-specific approaches, such as the *1 to 3 GDP per capita per QALY gained (or DALY avoided) threshold* originally proposed by the WHO, which has been criticized [40], for being blunt or lacking adequate empirical or theoretical justification [49]. However, it should be acknowledged that this estimate should be revised on a regular basis [42] in order to better reflect resource availability, the overall technical efficiency of the system and the changes in service demand, among other things [50]. Nevertheless, this CET estimate can serve as the basis of future efforts that will re-evaluate the reference ICER or, perhaps, provide varying estimates for different diseases, patient subgroups or levels of service provision [51]. The latter is a topical issue, since many decision-making bodies appear to use multiple thresholds, or threshold ranges or modifiers in their decisions. However, the justification for doing so is currently a topic of ongoing debate [37]. Going beyond cost-effectiveness, decision making must also incorporate other elements, which are normative in nature, reflect population values and preferences and consider ethical and societal aspects in the assessment and appraisal of health technologies [52].

Availability of data and materials

All data used are publicly available in international sources, such as the World Bank, Eurostat and OECD databases.

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CRediT authorship contribution statement

Kostas Athanasakis: Conceptualization, Methodology, Data curation, Formal analysis, Writing – original draft. **Giannis Agorastos:** Conceptualization, Methodology, Data curation, Formal analysis, Writing – review & editing. **Ilias Kyriopoulos:** Conceptualization, Methodology, Data curation, Formal analysis, Writing – review & editing.

Declaration of competing interests

None.

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