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Estimating a cost-effectiveness threshold for the Spanish NHS[*][1]

Laura Vallejo-Torres
(Canary Islands Health Research Foundation (FUNCANIS))

Borja García-Lorenzo
(Servicio de Evaluación del Servicio Canario de la Salud (SESCS))

Pedro Serrano-Aguilar
(Spanish Network of Health Technology and Performance Assessment)

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Canary Islands Health Research Foundation (FUNCANIS)
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Abstract

Background: The mean cost of an additional Quality-Adjusted Life Year (QALY) within a National Health Service (NHS) reveals how much health is lost, on average, when services currently provided by the NHS are displaced. This value has been suggested as a proxy of the average opportunity cost required to set a cost-effectiveness threshold when facing fixed budget constraints. The aim of this paper is to generate information on the marginal cost per QALY in the Spanish NHS that can be used to inform a cost-effectiveness threshold.

Methods: We created a panel of 5 years of data on region-level information across the 17 regional health services in Spain. Our dependent variable is Quality-Adjusted Life Expectancy (QALE). We regress QALE against health spending, and controlling for region and year fixed effects and a comprehensive set of time- and region-variant indicators, applying a one-year lag to expenditure. We use an instrumental variable approach to test for potential remaining endogeneity.

Results: Health expenditure has a positive and significant effect on QALE, with an average spending elasticity of 0.07. This translates into a cost per QALY of between 21,000€ and 24,000€ in Spain, depending on whether we take an average across different age groups or the value derived from the whole population model, respectively.

Conclusions: A cost-effectiveness threshold based on the estimated opportunity cost derived from this study is below the figure of 30,000€ commonly cited in Spain. Further work on societal values of health gains is needed to provide decision makers with the relevant information required in different decision-making contexts.

Introduction

Cost-effectiveness analysis (CEA) provides a framework to compare competing health care alternatives in terms of both their health outcomes and costs. The primary objective of these analyses is to enhance efficiency in the use of health care resources and to maximise total health gains in a population given available funds. Cost-effectiveness results are usually summarised by the incremental cost-effectiveness ratio (ICER), which is defined as the incremental cost divided by the incremental effectiveness of two competing alternatives. The effectiveness unit most widely used and recommended in economic evaluations is the Quality-Adjusted Life Year (QALY).

However, CEA evidence supplied as the incremental cost per QALY gained of competing health technologies is not enough to ultimately make adoption or otherwise recommendations on the basis of cost-effectiveness. For decision-making, the ICER of a technology needs to be compared with a value that indicates the maximum amount considered acceptable to be paid for

health gains in the health system, i.e. the cost-effectiveness threshold. This value is unknown in most health care systems.

There are different views as to what the threshold ought to represent. The two main conceptual perspectives are that the threshold should reflect: i) society's monetary valuation of health gains, or ii) the opportunity cost resulting from the disinvestment required to adopt a new technology (Baker et al., 2011). The former view aims to incorporate population's preferences in making health care choices, while the latter is based on accounting for budget constraints faced by decisions makers.

A recent review of studies that have estimated a cost-effectiveness threshold identified 38 studies (Vallejo-Torres et al, 2016). The review findings suggest that estimates based on the societal value of health gains tend to be higher than those based on the opportunity cost approach. As the authors conclude, "*this suggests that some interventions with positive social net benefits, as informed by individuals' preferences, might not be an appropriate use of resources under current budget constraints*". Some authors have emphasised that when facing a fixed health care budget, information on the opportunity cost of funding decisions is most relevant as it provides a basis to assess whether the health expected to be gained from the use of a new technology exceeds the health expected to be forgone as other services are necessarily displaced (Claxton et al., 2015). This view was shared in a recent consultation to experts in health and welfare economics, where the majority considered that the "*threshold should be estimated using the shadow price approach, as compared to the willingness-to-pay (WTP) approach*" (Karlsberg-Schaffer et al, 2016). A previous consultation among experts in Spain concluded that both approaches, i.e. the WTP and the opportunity cost approach, should be explored in order to inform a cost-effectiveness threshold in Spain (García-Lorenzo et al, 2015).

The aforementioned literature review (Vallejo-Torres et al, 2016) and the associated consultation process (García-Lorenzo et al, 2015) were part of a project commissioned by the Spanish Ministry of Health to provide further evidence on how to estimate a cost-effectiveness threshold for the Spanish context. Following these, in this paper we present a first estimation of the opportunity cost of health care funding decisions in Spain. Research on societal valuations of health gains is currently under development.

In order to provide a measure of the opportunity cost of funding decisions, we aim in this study to estimate the average cost per QALY at which the Spanish National Health Service (SNHS) currently operates. The cost per QALY reveals how much health is lost when services currently provided by the SNHS are displaced, and have been suggested as a proxy of the average opportunity cost value required to set a cost-effectiveness threshold (Claxton et al, 2015).

We used data across the 17 regional health services that compose the SNHS over the period 2008-2012, when health spending experienced considerable cuts due to the economic crisis. We exploited variations between regions and over time to estimate the impact of health spending on health outcomes, measured as quality-adjusted life expectancy. The estimated effect is translated into the cost per QALY of the SNHS providing a measure of the scale of the opportunity cost of health care funding decisions in Spain.

The paper is structured as follows. The next two sub-sections provide a summary of previous research in this field and a summary of the Spanish financing system. The methods section describes the econometric approach and the data used in the analyses. Results are shown in the following section, and the final section provides a discussion and some concluding remarks.

Previous studies

Measuring the average cost per QALY in a health care system involves estimating the impact of health care expenditure on health outcomes, i.e. the health spending elasticity of health. This has been the focus of several previous studies.

Gallet & Doucouliagos (2015) conducted a quantitative review of 65 studies estimating the relationship between health outcomes and health expenditure. The authors estimated meta-regressions on the health spending elasticity. They considered separately studies using mortality rates (infant and overall mortality) and life expectancy (at birth and at an older age, such as age 60 or 80). Health expenditure measures consisted of public as well as private health expenditure, while some papers focused on pharmaceutical spending. Most studies collected panel data across countries, followed by the use of cross-sections of sub-national data and times series. Some studies attempted to correct for the endogeneity of spending, i.e. that health spending is partly determined by the level of health care needs, which are correlated with health outcomes.

Gallet & Doucouliagos (2015) used 885 estimates of the spending elasticity; 629 observations for mortality and 256 observations for life expectancy (LE). Their meta-regressions controlled several studies characteristics: the type of mortality/LE variable (general population versus infant/at birth versus older groups), the type of countries (OECD versus non-OECD countries), the type of health spending (pharmaceutical versus non-pharmaceutical), the source of health spending (public versus private) and the measurement of spending (per capita versus share of overall spending). Additional variables were included to control for data characteristics such as whether the studies used panel data at national aggregated level or sub-national data, and for different specifications, considering the inclusion of variables such as per capita income, lagged health spending or lagged mortality/LE. They also explored the effect of using the instrumental variable (IV) approach as a means to address for the endogeneity of health care spending.

The results showed that "*spending elasticity for mortality is in the neighborhood of -0.10, whereas it is roughly equal to 0.02 for life expectancy*". The health outcome and expenditure measures used affected the results, indicating that, for instance, there was a greater impact on LE when measured from an older age compared to LE at birth, and the impact of public expenditure was larger than for pharmaceutical and private spending. Furthermore, the estimates were found, in some cases, to be sensitive to model specification, such as the inclusion of income and whether the study controlled for the potential endogeneity of health care spending.

There are also a series of studies that have used an estimated health spending elasticity to arrive at a cost per Life Year (LY). For example, Lichtenberg (2004) estimated a cost of $11,000 per LY in the USA using time series data from 1960-1997. In Spain, Puig-Junoy & Merino-Castello (2004) applied a similar methodology using health spending and LE at birth from 1960-2001, and estimated a cost per LY less than 13,000€.

Some studies have adjusted the estimated impact on mortality to account for Health Related Quality of Life (HRQoL) in order to approximate the estimation to the marginal cost of a QALY. For example, Martin et al. (2008; 2011) measured the cost per QALY for specific diseases in England using administrative data for Primary Care Trusts in England. The most recent of these papers used spending data from 2005/06 for five diseases. Their results ranged from £12,593 for cardiovascular diseases to £47,069 for diabetes. Claxton et al. (2015) used a similar approach but provided an estimate for each of the 23 disease programmes using expenditure data from 2008/09 and combined the disease-specific values to arrive at a central estimate of £12,936 per QALY in England.

Spanish health financing system

The Spanish NHS experienced a decentralisation process that started in the early 1980's and was completed in 2002, when all seventeen regions, named Autonomous Communities (ACs), that form the country were responsible for planning and delivery of their own health services. Therefore, the SNHS consists of 17 different regional health services that hold over 92% of the overall national health budget.

Health care is financed through general taxation collected by both the central and regional governments. The central government then allocates a budget across regions to meet the provision of the following public services for which ACs are responsible: health, education, social services and other general services such as culture, housing and infrastructure. There is an allocation mechanism to compute the corresponding shares transferred from the central administration to each region, except for the Basque Country and Navarre which account for a specific financing system, and for Ceuta and Melilla, which are centrally managed due to their small size. The allocation mechanism is based on a set of weighting indicators that take into account demographic and geographical factors. Demographics factors consists of measures of the quantity and intensity of the demand of services in each region, based on the population size, the school-aged population, the population aged 65 and over and the population under the coverage of SNHS. The latter is divided in seven age groups according to the estimated relative health expenditure per capita in each group. Geographical indicators consist of region size, dispersion of the population and insularity (de la Fuente, 2015). Each region decides how to allocate their budget across the public services above mentioned.

Over the period of analysis, health spending was substantially reduced in Spain as a consequence of the economic crisis and stringent requirement for ACs to meet deficit reduction goals. As a result, health spending has decreased by nearly 10% between 2009 and 2012[1]. There was however variation in spending reductions in health across regions. In this study we exploit the variation in health spending observed between regions and over time to estimate the marginal cost of a QALY in the SNHS.

Methods

Econometric approach

Fixed effect models

We created a longitudinal panel of 5 years of data (2008-2012) of region-level information across ACs in Spain. We run Ordinary Least Squares (OLS) models controlling for region and year fixed effects, and a comprehensive set of time- and region-variant indicators. The model takes the form:

$$log(H_{jt}) = \beta log(Exp_{jt-1}) + \delta X_{jt-1} + \gamma_t + \mu_j + \varepsilon_{jt} \qquad \text{Eq. 1}$$

- H_{jt} is the population health variable observed for region j at time t,
- Exp_{t-1} is the lagged health expenditure variable of region j in year t-1,
- X_{jt-1} is a set of other lagged attributes of region j in year t-1,
- γ_t is a fixed effect for year t,

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1 Available from
http://www.msssi.gob.es/estadEstudios/estadisticas/inforRecopilaciones/gastoSanitario2005/home.htm

- μ_j is a fixed effect for region j,
- ε_{it} is a disturbance term.

H and *Exp* have been log transformed, and therefore the *β* parameter estimate can be interpreted as an elasticity.

Region fixed effects control for unobserved determinants of health outcomes that vary between regions but are stable over time, while the year fixed effects control for unobserved determinants of health outcomes that change over time but are invariant between regions. The control variables account for observed characteristics that vary across both regions and time. The lag structure allow for the fact that the impact on health is not likely to occur contemporaneously with expenditure, as a delay in accruing a health benefit is expected.

IV models

Fixed effects are used as a means of addressing endogeneity. However, these models may not capture all sources of variation within regions and years that correlate with expenditure and health outcomes; in that case some degree of endogeneity might remain. We use an IV approach to test and address for this potential endogeneity problem by applying a two-stage least squares (2SLS) model. 2SLS involves replacing the potentially endogenous variable in the health outcome equation with its predicted values from an OLS model which regresses the endogenous variable against a set of covariates including a subset of instruments. Instruments that are good predictors of the endogenous variable (health spending) but are not independently correlated with the outcome (health status) are able to purge the bias in the estimation of the causal relationship of interest. However, the performance of the IV estimators critically relies on the validity of the instruments, which have to satisfy two properties: they have to be highly correlated with the variables being instrumented (relevance of instruments); and, they must be uncorrelated with the error term of the health outcomes equation conditional on the other covariates in the model (orthogonality requirement). We test for the relevance property based on an F-test of the significance of the instruments in the first-stage equation. The orthogonality requirement cannot be formally tested and mainly relies on face validity arguments. If a larger number of instruments than endogenous variables are available, then a test of overidentifying restrictions can partly explore the validity of such set of instruments (e.g., Hansen-Sargan test). We test for exogeneity using auxiliary regressions (Davidson & MacKinnon, 1993). If we fail to reject the null hypothesis of exogeneity then, assuming the instruments are valid, OLS models will yield consistent parameter estimates.

We use the percentage of total public expenditure assigned to health as an instrument to test for the potential remaining endogeneity. This variable is expected to influence how much a region spends on health per capita, as the larger the percentage of total public expenditure that is allocated to health, the larger the per capita health expenditure a region would be able to incur, all else equal. Conditionally on the model covariates, the percentage of public expenditure allocated to health should not affect the health of the population, rather than via the impact that this has on variations in health expenditure per capita. For instance, it might be the case that spending proportionally more on health is correlated with lower/higher expenditures on other public services that also affect population health, such as education or social deprivation policies. However, our models include a comprehensive series of indicators (see below) controlling for this potential correlation, such as educational attainment, poverty risk, unemployment rates, GDP, etc. as well as regional and year effects.

Data

Health variable

Our measure of health is Quality-Adjusted Life Expectancy (QALE). QALE provides a comprehensive measure of health outcomes that is relevant for all SNHS activities, and allows the estimation of the impact of expenditure on mortality as well as on HRQoL. Information on Life Tables by region and year are available from the Office of National Statistics (ONS) of Spain[2]. This data is then combined with information on HRQoL to adjust LE by health status. The most widely used methodology to apply this adjustment is the Sullivan method (Sullivan, 1971), where disability prevalences from survey data are used to compute disability-free life expectancies using a dichotomous disability variable. We use a similar approach but applied data on EQ-5D weights to undertake this adjustment. This allows us to create a LE variable adjusted for HRQoL on a QALY scale. To do this we adjusted the number of years lived in each age range from Life Tables, multiplying them by the average EQ-5D scores by age and gender (Gaminde & Roset, 2001).

QALE values provide the expected number of healthy years that individuals of a certain age are expected to live. We computed regressions of QALE at each age ($QALE_x$, x = 0, 1, 5, 10,…, 95). In addition to estimating the impact of health expenditure on QALE at given ages, we also estimated the impact on the average QALE of the population. The latter is computed as follows, where w_x is the share of the population in age group x (Lichtenberg, 2004):

$$QALE_{pop} = \sum w_x \, QALE_x \qquad\qquad\qquad \text{Eq. 2}$$

Quality of life variable

The only source of Spanish nationally representative EQ-5D data is the Spanish Health Survey (SHS) conducted in 2011/12. There are other surveys, such as the SHS in 2006/07 and the European Health Interview Survey (EHIS) conducted in Spain in 2009/10, which did not include EQ-5D but included a series of other health and socioeconomic indicators. We used these surveys[3] to generate predicted EQ-5D values that allow us to create a time-variant HRQoL indicator used to adjust LE information.

EQ-5D models were stratified by gender and age groups (15-44, 45-64 and 65 or more years). In each case we used generalised linear models (GLM) with log link function and gaussian variance on HRQoL decrements, i.e. on 1 minus reported EQ-5D values. The models take the form:

$$(1 - EQ5D_i) = \alpha + \rho H_i + \tau Soc_i + \varepsilon_i \qquad\qquad\qquad \text{Eq. 3}$$

- $EQ5D_i$ is the EQ-5D score of individual *i*

- H_i is a set of health-related indicators of individual *i*

- Soc_i is a set of socioeconomic characteristics of individual *i*

- ε_i is a disturbance term.

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[2] Available from http://www.ine.es/jaxi/menu.do?type=pcaxis&path=%2Ft20%2Fp319a&file=inebase&L=0
[3] Available from http://www.msssi.gob.es/estadisticas/microdatos.do

The predictors included in the models were: age; self-assessed health based on responses to the question: 'How is your health in general? Would you say it was: very good, good, fair, bad or very bad?'; whether or not the individual has one of the 7 longstanding illnesses that were included across all surveys; and whether or not the respondent experienced no limitations, moderate or severe limitations on daily activities in the past 6 months.

Individuals between and within areas might report different levels of EQ-5D due to differences in reporting behaviour not related to differences in their underlying health status but due to, for instance, their socioeconomic characteristics. Therefore, we also include in these models a series of socioeconomic indicators that consist of: nationality (Spanish versus non-Spanish); marital status (married, single, widow, separated, divorced); educational attainment (illiterate, primary school, lower secondary, upper secondary, post-secondary non-tertiary, short-cycle tertiary, tertiary high education); and economic activity (working, disabled, unemployed, retired, student, taking care of home and family, other activity). When predicting EQ-5D scores we fixed the socioeconomic variables at the sample mean value for every respondent with the aim of removing any socioeconomic-related reporting bias. As a result, our HRQoL indicator depends on the purged effect of health problems on HRQoL, and on the varying levels of these indicators across regions and across time.

We then computed the HRQoL indicator as the mean value of the predicted EQ-5D scores by region and year for each gender and age group. EQ-5D estimates constructed using SHS 2006/07 were used to adjust LE data in 2008, while estimates using data from EHIS 2009/10 were linked to LE for 2009 and 2010 and the remaining years (2011-2013) were linked to SHS 2011/12 estimates. EQ-5D data on individuals younger than 15 years is not available in the SHS, thus the values estimated in the youngest available age group (15-44) were used for these individuals.

Expenditure data

Our measure of spending is health expenditure per person per year. We use total public health expenditure by region and by year as provided by the Ministry of Health statistics database[4]. We computed expenditure per capita by dividing total expenditure by the size of the population in the corresponding year according to the population statistics published by the ONS in Spain. Data were taken from 2008 to 2012 and adjusted for inflation using GDP deflator estimates for Spain provided by the World Bank[5]. Values were expressed in €2012.

Other indicators

We included a comprehensive list of variables capturing region- and time-variant differences in needs for health care resources. For this we assembled a unique dataset of demographic, socioeconomic, health and environmental factors. Appendix 1 presents a summary of the variables included and their sources.

Demographic variables included information on the size of the population; the proportion of the population who are males; and the proportion in each age group, defined as 0-14, 15-44, 45-64, 65-84, and 85 years and over[6]. We also included a comprehensive list of health variables that aim to control for health spending needs over and above age and gender characteristics. These

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4 Available from
http://www.msssi.gob.es/estadEstudios/estadisticas/inforRecopilaciones/gastoSanitario2005/home.htm
5 Available from http://data.worldbank.org/indicator/NY.GDP.DEFL.KD.ZG
6 Note that different age groups were used on EQ-5D models due to the fact that age groups defined the stratifications models and a finer categorization would have led to few observations being included in each model.

consisted of prevalences of major diseases proxied by age/sex adjusted hospitalisation rates by ICD9 groups; individuals on incapacity benefits; individuals with disability; number of traffic accident victims; individuals on retirement benefits; and proportion of smokers. A series of regional socioeconomic indicators were also included that consist of GDP per capita; unemployment rate; poverty risk; individuals educational attainment; and number of immigrants by country of origin. We also tried to control for unavoidable variations in health spending such as differences on the cost of providing care proxied by the cost of floor space in squared metres and mean salaries. Finally, we took into account the number of individuals in each region who have health insurance cover provided by other public administrations.

Results

Descriptive statistics

Table 1 provides the mean values of health expenditure per capita, and LE and QALE at birth in each region and year. On average, health expenditure decreases over the period of analysis, particularly in 2012. The extent of these decreases varies by region, with a special case in Cantabria region where expenditure increased in 2012. This issue is explored in sensitivity analyses.

Both LE and QALE at birth have increased overtime, from over 81 years in 2009 to nearly 83 years of LE in 2013. The number of years that individuals are expected to live in good health has increased from 73 to 75 years in this period in Spain. Summary statistics of region- and time-variant control variables are presented in Appendix 2.

Quality of life models

The coefficients of the health and socioeconomic variables included in the regression models of EQ-5D decrements stratified by age and gender using the SHS 2011/12 are presented in Table 2. Some covariates are excluded from the regression models due to small numbers or counter-intuitive signs due to collinearity. Mean values of the included covariates across the SHS 2006/07, EHIS 2009/10 and SHS 2011/12 are also shown in Table 2. Health variables performed as expected, with a particular stronger gradient with respect to self-assessed health and limitations on daily activities.

Information on the coefficients estimated using the SHS 2011/12 and sample means of these variables available in the other surveys were used to derive out of sample predictions of EQ-5D values for the years where EQ-5D data was not available. These predictive EQ-5D values were used to adjust LE information by area, year of data and sex and age group to create QALE variables, as explained above.

Health expenditure models

Table 3 summarises the main results of the health spending elasticities for QALE in Spain based on the estimations derived from models described in Equation 1. We run separate models for the average QALE of the population as well as for QALE at given ages (i.e. QALE at birth, 1 year, 5 years, 10 years,…, 95 years). The effect of the control variables in the model of average QALE are presented in Appendix 2. The same covariates were included in every model.

The first row in Table 4 shows the results for the model of the average QALE of the whole population. The estimated elasticity of 0.0699 (second column) indicates that a 1% increase in

per capita annual health expenditure increases average QALE in 0.0699%. This is a positive and statistically significant effect of health expenditure on population health. When evaluating this result at sample means, this finding implies that, on average, an increase in 1€ in health expenditure per person per year leads to a QALE increase of 0.0018 years or 0.65 days (third column). In other words, a 10€ extra spending per person per year in health would be related to, on average, an increased life expectancy of 6.5 days in perfect health.

When looking at the QALE models at given ages, the estimated effects of health spending are positive in every case, and statistically significant at early ages as well as in the oldest age group. The results also show that while expenditure elasticity appears to increase with age, the marginal effects are lower at older ages, showing that the absolute impact of health spending on healthy years is lower as the individual ages (Figure 1).

Cost per QALY estimation

In order to transform the marginal effect of annual health expenditure on QALE into a cost per QALY we take into account the LE of the relevant group. For instance, the estimated effect on average QALE of 0.0018 healthy years will be accrued by increasing health expenditure in 1€ per year, and thus, considering the average life expectancy of this population of 44.31 years (fourth column), the cost per QALY is estimated in 24,222€ (= 44.31/0.0018; fifth column). This calculation assumes that the estimated effect on QALE pertain to a permanent increase in spending per head of 1€ per year. We interpret this to mean an increase in spending across the life expectancy of the relevant population (which across the whole population is 44.31 years). Hence, we interpret the coefficient as meaning that a lifetime increase in spending of 1€ per year (e.g., for 44.31 years) will produce 0.0018 QALYs. Therefore a permanent increase in lifetime spending of 1€ per year, e.g., 44.31€ in total, will produce 0.0018 QALYs over the average lifetime, and therefore the cost to gain one QALY is 44.31/0.0018.

Similarly, this transformation is equivalent to estimating the annual health gain corresponding to a 1€ increase in that given year. This is computed by dividing the estimated overall QALE gain by the number of years that the individual is expected to live, arriving at the same cost per QALY of 24,222€ (=1/(0.0018/44.31).

The fifth column in Table 3 shows the cost per QALY for the average population as well as the cost per QALY at different ages. These results are shown graphically in Figure 1. The mean cost per QALY following from the age specific models, weighted to account for population sizes for different age groups in Spain (sixth column), is estimated in 22,314€. Alternatively, we estimated an overall cost per QALY of 21,023€ as the ratio between the sum of incremental annual health expenditures across age groups and the sum of the incremental annual health gains in each age group using the following formulae:

$$Cost\ per\ QALY = \frac{\sum_{x=1}^{j}(n_x * \Delta Exp_x)}{\sum_{x=1}^{j}\left(\frac{n_x * \Delta QALE_x}{LE_x}\right)} \qquad \text{Eq. 6}$$

- n_x is the population size of age group x

- ΔExp_x is the incremental annual expenditure in age group x ($\Delta 1$ € per capita)

- $\Delta QALE_x$ is the incremental effect on QALE in age group x

- LE_x is life expectancy of age group x

IV Models

The last two columns of Table 3 show the results for the IV models. There is a strongly significant correlation between the instrument and the potentially endogenous variable (F-test 31.30; p-value<0.0001) indicating that the instrument meets the relevance requirement. We cannot empirically test for the orthogonality criterion; the partial test of overidentification cannot be conducted as the number of instruments available is not higher than the potentially endogenous variables.

The IV results are very similar to the OLS models estimates and, assuming that the instrument is valid, the exogeneity tests fail to reject the exogeneity of health expenditure in every model. Therefore OLS estimates presented in the previous section are preferred to the 2SLS model estimates.

Additional analyses

Table 4 presents additional analyses that were conducted to explore a series of issues. For simplicity, we use the model of average QALE as the base case to allow comparisons across different models and/or specifications.

Firstly, we tested for different functional forms of the health expenditure variable by including second- and third-order polynomial functions (without log transformation). The squared and cubic terms were non-significant.

Ministry of Health statistics on health expenditure included a note indicating that Cantabria health spending information included for the first time in 2012 payments made through the "extraordinary supplier payment" mechanism, amounting to 256,767,398€. Excluding this amount implies a reduction in health spending per capita from 1,766€ to 1,333€ in Cantabria in 2012, in line with the pattern observed in other regions. This, however, does not have a significant effect on the overall model results. The estimated marginal cost of a QALY using this adjusted figure for Cantabria is 24,841€.

We experimented with applying a 3% discount rate to QALE gains and to the corresponding lifetime health spending investment, assuming that health gains are proportional over time and linear with respect to increases in expenditure. The cost per QALY using this approach was estimated to be 23,868€.

In addition, Table 4 shows how the estimated impact of expenditure on QALE changes as increasingly more sets of covariates are included in the model. Controlling only for age and gender characteristics yields an observed negative relationship between expenditure and health outcomes. However, after controlling for differences in underlying health factors, the relationship between spending and QALE becomes positive. The estimated effect increases as controls for socioeconomic, environmental and population covered by insurance are added. This highlights that differences in needs and other unavoidable factors play an important role when estimating the causal relationship of expenditure on health.

We also estimated the impact of expenditure on QALE without allowing for a lag between spending and health outcomes, i.e. including QALE as contemporaneous with health expenditure. We found that in this case the effect of expenditure is considerably smaller and non-significant, suggesting that there is a delay in accruing health benefits related to higher spending. This might also reflect a larger degree of endogeneity between contemporaneous health and health spending.

Finally, we estimated a health spending elasticity for average LE of 0.0203 and for LE at birth in 0.0107 (Table 4). This was found to be in line with previous research (see Gallet & Doucouliagos, 2015). However, our estimates were found to be non-significant.

Discussion

In this study we provide an estimate of the marginal cost of a QALY in the NHS in Spain that allows us to infer how much health, on average, is lost when resources currently provided by the health care system are displaced. This value indicates the average opportunity cost of incorporating health technologies in the SNHS when disinvestment is required to fund new interventions. This figure was estimated to lie between 21,000€ and 24,000€ per QALY, depending on whether we use the average across the estimates provided by different age groups or the value derived from the average population model, respectively.

The methodology applied in this paper builds on previous work by Claxton et al, 2015. However, in this study we used panel data on expenditure and health outcomes for the same regions over multiple time periods, which allows us to control for the effects of unobservable factors based on fixed effect specifications rather than relying on, what often are, controversial instruments. Moreover, Claxton et al, estimated the effect of health spending on mortality alone and assumed that HRQoL improves in proportion to the estimated mortality improvement. In this paper we have used a health outcome variable capturing differences in mortality and morbidity in order to directly estimate the impact of health expenditure on mortality as well as on HRQoL. On the other hand, information on health spending across disease programmes is not available in Spain, and therefore, cost per QALY was estimated using overall health spending and population health outcomes, as opposed to the disease-specific models conducted in Claxton et al, 2015. While our approach does not allows for the flexibility on the estimations across diseases conducted in Claxton et al, it provides us with an average estimate across the overall SNHS, which is the ultimate aim of this research. It is also worth noting that our period under analysis, characterised by disinvestments across all regions, provides us with a potentially more accurate estimate of the amount of health displaced by disinvestment, i.e. the opportunity costs, than estimates based on periods of growing spending. This is because, other things being equal, more expenditure would increase health but at a diminishing rate (Claxton et al, 2015).

We acknowledge a series of limitations of this study. Firstly, there are data restrictions, especially with respect to HRQoL of the Spanish population that was collected using the EQ-5D instrument only in 2011/12. We attempted to overcome this limitation by generating predicted values based on the impact that health problems have on HRQoL purged from reporting bias and the varying degree of these health problems over time and across regions. While this approach might provide more appropriate HRQoL indicators than observed from raw data, we had to rely on the estimated effects based on a single year of EQ-5D data to derive out-of-sample predictions across a number of surveys that did not fully cover our period of analysis. Routinely collecting EQ-5D information in health surveys conducted in Spain in an ideally yearly basis would help solving this limitation. Secondly, the exogeneity test indicating that spending is not endogenous in our models, conditional to the fixed effects and other covariates, relies on the validity of the instrument we used. While the instrument met the relevance requirement, the orthogonality criterion could not be formally tested, yielding some uncertainty about the validity of the instrument. Finding appropriate instruments continues to be one of the hardest tasks to assess the relationship between spending and health. Thirdly, the transformation we applied to translate the spending elasticity for QALE into a cost per QALY assumes that health gains

estimated over the person life expectancy in our models are achieved when the corresponding extra annual health spending is sustained over the lifetime. The reason is that while the dependent variable is expressed as a life expectancy indicator, the health spending variable pertains to annual expenditure in health. This transformation imposes linearity between expenditure investment and QALY gains over time.

The estimate provided in this paper suggests that the most commonly cited threshold value of 30,000€ per LY/QALY used in Spain is higher than the estimated threshold derived from the opportunity cost approach. The 30,000€ figure was not based on any empirical estimation but simply reflected the findings from a review of the Spanish economic evaluation literature showing that authors of published papers were likely to recommend adoption of the intervention under study when the ICER was below this value (Sacristán et al., 2004). The result from this review was not intended to inform a cost-effectiveness threshold, and despite of not being formally adopted by the SNHS, it has since then generated a path-dependency issue in the scientific literature.

In this paper we have aimed to generate information on the cost per QALY of the SNHS on the basis that, under fixed budget constraints that characterise most health services, information on the opportunity cost is what matters to make allocation decisions. A serious danger with using such approach alone, however, is that it might perpetuate the belief that the opportunity cost threshold reflects the marginal benefits of health care, and decision makers would not be made aware of the series of technologies whose benefits offset their costs according to society's view. A society-value threshold allows for the identification of such interventions and this information might have implications for the size of the budget by identifying health care interventions that are desirable but not currently feasible. Furthermore, while fixed budgets and displacements are likely to define many decision-making situations, this is not necessarily the case in every instance. Budgets might not be fixed – especially when new tax revenue becomes available for the health care system. The opportunity costs of allocating new funds to health do not fall within the NHS, but across other alternative uses of public spending. Therefore, the estimates provided in this paper will not be relevant to guide such decisions. Society's value of health gains would arguably better reflect the strengths of preferences across different alternative of consumptions of the public, providing a more relevant threshold value. There are some previous studies within the Spanish context that have used the WTP approach to inform a cost-effectiveness threshold (Pinto-Prades et al, 2009; Donaldson et al, 2011; Abellán-Perpiñán et al, 2011; Martín-Fernández et al, 2014). The sensitivity of the WTP values to the assumptions and techniques applied in their analyses characterise the finding of these studies. Further work to overcome these limitations on the societal valuation of a QALY is currently underway.

Further work on the opportunity costs approach implies the recognition that the threshold defined by the cost per QALY is a dynamic figure that needs to be updated frequently to account for changes in the budget and efficiency over time. The identification and/or development of new routinely collected data sources is required to refine and update the estimates currently provided, and further work is needed to account for any remaining source of endogeneity.

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Table 1. Mean values of health expenditure, life expectancy and quality-adjusted life expectancy at birth across regions and over time

Region / Year	Health expenditure per capita (€)					LE at birth					QALE at birth				
	2008	2009	2010	2011	2012	2009	2010	2011	2012	2013	2009	2010	2011	2012	2013
Andalucía	1,279	1,257	1,213	1,135	1,101	80.35	80.81	80.95	80.96	81.61	70.86	71.19	73.04	73.07	73.56
Aragón	1,442	1,535	1,485	1,528	1,521	82.02	82.25	82.39	82.74	83.16	75.02	75.20	76.11	76.42	76.75
Asturias	1,458	1,632	1,557	1,602	1,541	81.09	81.21	81.37	81.55	82.23	72.81	72.89	72.24	72.40	72.93
Baleares	1,267	1,339	1,553	1,453	1,175	81.16	81.63	82.00	81.92	82.69	74.02	74.39	74.82	74.76	75.38
Canarias	1,443	1,485	1,399	1,325	1,208	81.01	81.57	81.41	81.58	82.33	72.33	72.77	71.38	71.53	72.05
Cantabria	1,349	1,396	1,463	1,301	1,766	82.02	82.14	82.50	82.57	83.08	74.36	74.43	75.79	75.85	76.25
Castilla La Mancha	1,423	1,540	1,541	1,464	1,241	82.33	82.76	82.83	82.73	83.17	73.35	73.66	75.52	75.45	75.77
Castilla y León	1,435	1,395	1,423	1,311	1,362	82.73	82.98	83.24	83.20	83.57	75.45	75.63	76.67	76.65	76.95
Cataluña	1,360	1,420	1,438	1,350	1,261	81.94	82.33	82.61	82.53	83.08	74.26	74.57	75.71	75.64	76.09
Comunidad Valenciana	1,254	1,341	1,368	1,346	1,221	81.33	81.61	81.83	81.91	82.50	71.97	72.17	74.86	74.93	75.40
Extremadura	1,534	1,605	1,578	1,539	1,409	81.09	81.22	81.79	81.45	81.89	71.50	71.58	74.13	73.90	74.22
Galicia	1,391	1,475	1,424	1,325	1,274	81.51	82.02	82.19	82.29	82.69	71.38	71.74	74.34	74.42	74.74
Madrid	1,204	1,277	1,158	1,319	1,193	82.98	83.48	83.72	83.74	84.26	74.65	75.03	77.11	77.11	77.55
Murcia	1,513	1,573	1,546	1,556	1,444	80.92	81.63	81.73	81.73	82.35	69.87	70.35	74.21	74.21	74.68
Navarra	1,497	1,611	1,581	1,553	1,435	82.95	83.76	83.55	83.48	83.63	75.82	76.47	77.18	77.12	77.23
País Vasco	1,559	1,667	1,659	1,636	1,579	82.02	82.49	82.52	82.79	83.22	74.27	74.63	75.64	75.88	76.22
La Rioja	1,498	1,470	1,463	1,442	1,307	82.58	83.00	82.91	82.69	83.63	74.60	74.99	75.99	75.82	76.57
Total	1,406	1,472	1,462	1,423	1,355	81.77	82.17	82.33	82.34	82.89	73.32	73.63	74.98	75.01	75.43

Note: LE = Life expectancy; QALE = Quality-adjusted life expectancy

Table 2. Coefficients on EQ-5D decrements across gender and age groups models

	Mean	Females 15-44	Females 45-64	Females 65+	Males 15-44	Males 45-64	Males 65+
Health indicators							
Age	51.13	0.025***	0.007***	0.021***	0.012***	0.024***	0.018***
Self-assessed general health							
Very good	0.158	-1.660***	-1.876***	-0.868***	-1.959***	-1.850***	-1.552***
Good	0.493	-0.836***	-1.143***	-0.658***	-1.735***	-0.548***	-0.869***
Fair	0.247	-0.532***	-0.580***	-0.328***	-0.981***	-0.098***	-0.351***
Bad	0.078		-0.356***	-0.158***	-0.263***		-0.233***
Very bad	0.024	Omitted category					
Longstanding illnesses							
Hypertension	0.249	0.350***	0.028		0.062		0.051*
Myocardial infarction	0.025	0.670***			0.444***		
Chronic cervical pain	0.201		0.301***	0.085***	0.100**	0.194***	
Chronic back pain	0.220	0.430***	0.010	0.093***	0.250***		0.152***
Chronic bronchitis	0.057		0.067**		0.034		
Diabetes	0.080			0.077***	0.546***	0.008**	0.107***
Ulcer stomach / duodenum	0.055						
Incontinence	0.050	0.147*	0.008	0.111***	0.102		0.069**
Depression/anxiety	0.149	0.534***	0.419***	0.134***	0.244***	0.225***	0.241***
Stroke	0.016	0.252***	0.268***	0.191***	0.436***	0.397***	0.203***
Migraine	0.116		0.036				0.056
Osteoporosis	0.068	0.224***				0.054	
Limitation on daily activities							
Severe limitations	0.053	1.671***	1.091***	2.180***	2.583***	2.004***	1.535***
Moderate limitations	0.206	0.951***	0.692***	1.092***	1.183***	1.334***	0.852***
No limitations	0.741	Omitted category					
Socioeconomic variables							
Nationality							
Non-Spanish	0.066	0.012	0.106	-0.185**	0.489***	0.785***	-0.113
Spanish	0.934	Omitted category					

Marital status

Single	0.263	0.068**	0.207***	-0.113**	0.173***	0.221***	-0.119*
Widowed	0.128	0.093**	-0.284***	-0.024	-0.529	-0.938***	-0.100**
Separated	0.027	0.074	-0.194***	-0.108	0.641***	0.503***	0.547***
Divorced	0.032	-0.079	0.014	-0.294	-0.579	-0.096	-0.355*
Married	0.548	Omitted category					

Educational attainment

No primary education	0.128	0.627***	-0.108**	-0.078***	-1.214***	-0.146*	0.073
Primary education	0.253	0.576***	-0.201***	-0.151***	-1.429***	-0.211**	0.143*
Lower secondary	0.186	0.636***	-0.026	-0.099***	-1.098***	-0.123*	0.037
Upper secondary	0.095	0.860***	-0.393***	-0.111*	-0.716***	-0.324***	0.111
Post-secondary non-tertiary	0.098	0.329***	-0.352***	-0.243***	-0.779***	-0.020	0.281**
Short-cycle tertiary	0.059	0.660***	-0.358***	-0.124	-1.447***	-0.326**	-0.139
Tertiary high education	0.155	0.164	-0.249***	-0.290***	-1.274***	-0.717***	0.102
Illiterate	0.024	Omitted category					

Employment status

Unable to work	0.020	0.609***	0.430***	0.500**	0.382***	0.658***	0.728
Unemployed	0.094	0.134***	0.122***	-0.372	-0.548***	0.129**	
Retired	0.270	0.148	0.187***	0.131***	-0.321	0.259***	0.442
Student	0.048	-0.112	0.445	-4.280	0.333***	-7.140	
Taking care of home and family	0.158	-0.028	0.100***	0.031	-0.422	-0.202	0.030
Other activity	0.006	0.117	-0.218***	0.354**	0.589***	0.094	-5.726
Working	0.439	Omitted category					
Sample size	72,524	4,100	3,529	3,663	4,137	3,216	2,211

Note: *p-value<0.10. **p-value<0.05. ***p-value<0.01. Negative coefficients mean the variable increases HRQoL and viceversa.

Table 3. Main model results: elasticities, marginal effects and costs per QALY estimates

Dependent variable (1)	Elasticity (2)	ME (3)	LE (4)	Cost/QALY (5)	Population (6)	Elasticity IV models	Durbin-Wu-Hausman (p-value)
QALE$_{pop}$	0.0699**	0.0018**	44.31	24,222 €	46,512,199	0.0731**	(0.8739)
QALE at 0	0.0527**	0.0029**	82.29	28,044 €	424,881	0.0407**	(0.3530)
QALE at 1	0.0577**	0.0032**	81.53	25,635 €	1,895,731	0.0488**	(0.4822)
QALE at 5	0.0586**	0.0031**	77.58	25,321 €	2,478,498	0.0515**	(0.5931)
QALE at 10	0.0588**	0.0029**	72.62	25,350 €	2,267,843	0.0522**	(0.6365)
QALE at 15	0.0618**	0.0028**	67.65	24,235 €	2,140,570	0.0569**	(0.7425)
QALE at 20	0.0654**	0.0027**	62.71	23,036 €	2,374,617	0.0609**	(0.7793)
QALE at 25	0.0662**	0.0025**	57.79	22,915 €	2,749,308	0.0625**	(0.8331)
QALE at 30	0.0679**	0.0023**	52.88	22,531 €	3,456,208	0.0653**	(0.8950)
QALE at 35	0.0727**	0.0023**	47.98	21,236 €	4,032,770	0.0696**	(0.8841)
QALE at 40	0.0775*	0.0021*	43.13	20,179 €	3,858,819	0.0752*	(0.9235)
QALE at 45	0.0857*	0.0021*	38.35	18,549 €	3,689,866	0.0855*	(0.9947)
QALE at 50	0.0891*	0.0019*	33.69	18,058 €	3,333,372	0.0856*	(0.9059)
QALE at 55	0.0830	0.0015	29.18	19,717 €	2,877,803	0.0721	(0.7448)
QALE at 60	0.0936	0.0014	24.81	17,895 €	2,491,892	0.0630	(0.4456)
QALE at 65	0.0904	0.0011	20.61	19,186 €	2,327,434	0.0387	(0.3047)
QALE at 70	0.0825	0.0008	16.58	20,935 €	1,809,958	0.0185	(0.2110)
QALE at 75	0.0944	0.0007	12.79	18,195 €	1,652,238	0.0194	(0.1486)
QALE at 80	0.0677	0.0004	9.42	25,169 €	1,403,260	0.0055	(0.2527)
QALE at 85	0.0700	0.0003	6.63	24,128 €	825,182	0.0149	(0.3326)
QALE at 90	0.0826	0.0002	4.58	20,189 €	333,079	0.0648	(0.7614)
QALE at 95	0.3023**	0.0006**	3.31	5,452 €	88,871	0.2022	(0.1969)
Average Cost per QALY				21,023 €[1]	22,314 €[2]		
F-test of relevance of instrument (p-value)						31.30 (<0.0001)	

Note: *p-value<0.10. **p-value<0.05. ***p-value<0.001. LE = Life expectancy; ME = Marginal effect.

1 Based on the population-weighted mean of the cost per QALY across age groups

2 Based on the ratio between the sum of incremental annual health expenditures across age groups and the sum of the incremental annual health gains in each age group (Equation 6).

Table 4. Additional analyses results

Expenditure functional form	Coefficient	(p-value)	
Expenditure per capita	-0.05344	(0.551)	
Expenditure per capita squared	0.00003	(0.590)	
Expenditure per capita cubic	0.000000	(0.645)	
	Elasticity	**ME**	**Cost/QALY**
Base case (QALE$_{pop}$ model)	**0.0699****	**0.0018**	**24,222 €**
Adjusted Cantabria expenditure	0.0682*	0.0018	24,841 €
Applying 3% discount rate	-	-	23,868 €
Set of control variables			
Only demographic controls	-0.0004	-0.00001	-
Plus health indicators controls	0.0323	0.0008	52,425 €
Plus socioeconomic controls	0.0576	0.0015	29,427 €
Plus environmental controls	0.0650*	0.0017	26,052 €
Plus insurance controls (base case)	0.0699**	0.0018	24,222 €
Not allowing for lagged effect	0.0328	0.0009	41,298 €
Not adjusting for HRQoL (LE$_{pop}$)	0.0203	0.0006	66,743 €
Not adjusting for HRQoL (LE at birth)	0.0107	0.0006	126,800 €

Note: *p-value<0.10. **p-value<0.05. ***p-value<0.001. ME = Marginal effect

Figure 1. Cost per QALY and marginal effect at given ages
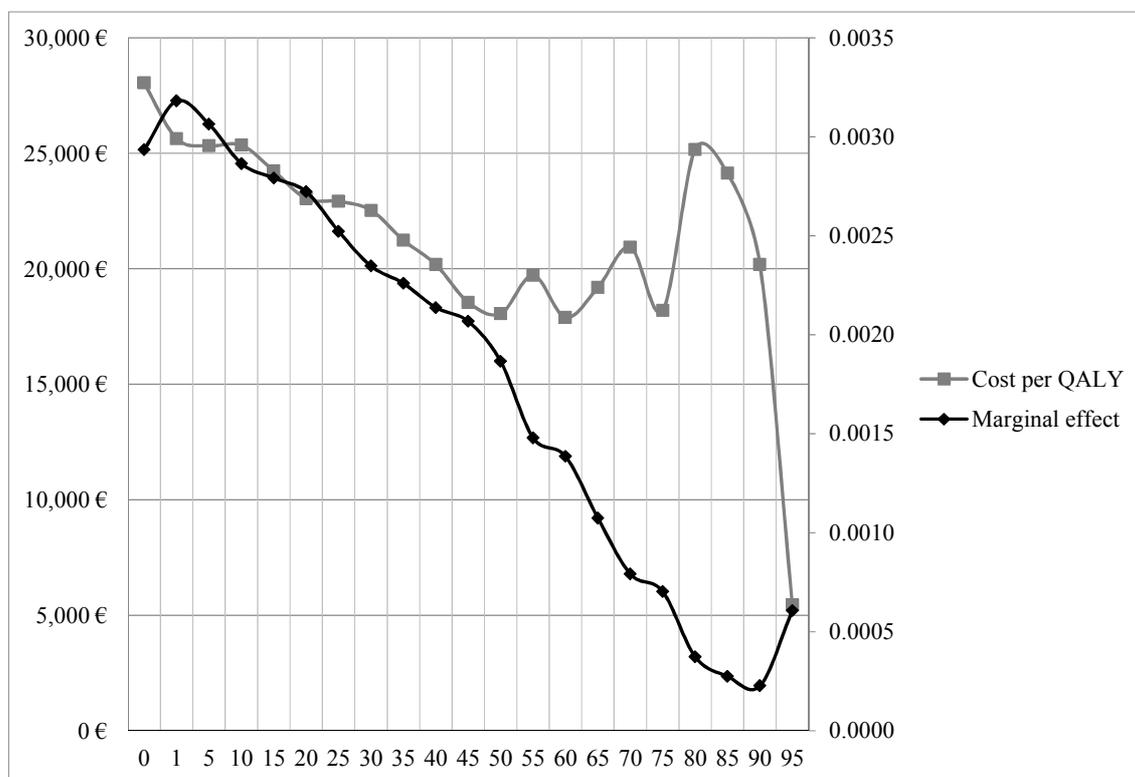
Appendix 1. List of control variables and sources

Variable	Source
Demographic characteristics	
Size of the population	ONS statistics
Proportion of males	ONS statistics
Proportion of individuals by age group (0-14, 15-44, 45-64, 65-84, 85+)	ONS statistics
Health indicators	
Prevalence of major diseases (proxied by adjusted hospitalisation rates by ICD9 groups)	Ministry of Health statistics
Individuals on incapacity benefits	IMSERSO
Individuals with disability	BEDPD
Traffic accident victims	DGT
Individuals on retirement benefits	Ministry of Labour and Social Security statistics
Proportion of smokers	SHS 2006/07, EHIS 2009/10 and SHS 2011/12
Deprivation indicators	
GDP per capita	ONS statistics
Unemployment rates	Economically Active Population Survey, ONS
Poverty risk	Quality of Life Survey, ONS
Educational attainment	Economically Active Population Survey, ONS
Immigrants by country of origin	ONS statistics
Environmental indicators	
Price per floor squared metre	Ministry of Development statistics
Labour cost	Quarterly Labour Cost Survey
Health insurance coverage	
Number of individuals on ISFAS health insurance	Ministry of Defence
Number of individuals on MUGEJU health insurance	Ministry of Justice
Number of individuals on MUFACE health insurance	Ministry of the Finance and Public Administrations

Note: ONS = Office of Natinal Statistics; IMSERSO = Instituto for the eldery and social services; BEDPD = National database of persons with disability; DGT = General Department of Traffic; SHS = Spanish Health Survey; EHIS = European Health Survey Interview

Appendix 2. Mean values and coefficients of covariates

Variable	Mean	SD	Minimu	Maximum	Coefficient
QALE$_{pop}$ (Dependent variable)	35.13	1.92	38.62	30.22	-
Expenditure per capita	1,423	139	1,766	1,101	0.0699**
Size of the population	2,718,847	2,424,730	316,192	8,377,809	-0.0000004***
Males (%)	49.538	0.7574	47.9622	50.6947	-0.1291**
Individuals aged 0-14 (%)	14.414	1.7623	10.2846	17.6587	-13.2188*
Individuals aged 15-44 (%)	42.316	2.8555	36.5234	48.1285	-13.1944*
Individuals aged 45-64 (%)	25.505	1.7458	21.4179	29.7670	-13.1791*
Individuals aged 65-84 (%)	15.294	2.2783	11.4876	19.4273	-13.1308*
Individuals aged 85 or more (%)	49.538	0.7574	47.9622	50.6947	-13.2784*
Individuals on incapacity benefits (%)	17.2865	2.3452	10.9400	23.7700	0.0021
Individuals with disability (%)	71.9345	8.8989	52.3000	86.5700	0.0050**
Traffic accident victims (%)	14.2942	2.1491	10.9100	21.2200	-0.0048
Individuals on retirement benefits (%)	7.6756	1.4499	4.8900	12.9900	-0.0016
Hospitalisation rates CIE-1	18.0931	4.2469	10.6900	28.8300	0.0024
Hospitalisation rates CIE-2	28.0434	5.5599	18.3000	44.8400	0.0017
Hospitalisation rates CIE-3	85.6839	8.8983	65.7600	108.6800	-0.0022**
Hospitalisation rates CIE-4	90.2626	14.1187	54.5000	117.0500	-0.0013
Hospitalisation rates CIE-5	95.8742	13.8312	58.8800	116.6000	-0.0019
Hospitalisation rates CIE-6	47.6111	8.6283	30.1700	62.5000	0.0030
Hospitalisation rates CIE-7	105.5381	13.3298	79.6100	136.6700	-0.0009
Hospitalisation rates CIE-8	8.5531	1.7140	4.8900	11.7100	0.0013
Hospitalisation rates CIE-9	55.5948	17.6231	26.3300	104.7600	0.0001
Hospitalisation rates CIE-10	11.2044	1.7278	7.5700	15.1200	-0.0048
Hospitalisation rates CIE-11	21.7442	5.1583	13.1900	33.5600	0.0033*
Hospitalisation rates CIE-12	34.1458	8.0871	14.1100	54.5900	0.0011
Hospitalisation rates CIE-13	67.3052	9.0706	43.5100	89.3000	-0.0008
Hospitalisation rates CIE-14	5.6652	7.0636	0.0400	39.7600	-0.0003
Hospitalisation rates CIE-15	0.0227	0.0085	0.0047	0.0390	3.0394***
Hospitalisation rates CIE-16	0.0574	0.0185	0.0298	0.1126	-0.5663
Hospitalisation rates CIE-17	0.0023	0.0008	0.0007	0.0045	-24.0641*
Hospitalisation rates CIE-18	15,038	14,782	989	60,182	0.0000***
Proportion of smokers	0.2798	0.0303	0.2142	0.3378	-0.2739**
GDP per capita	22,790	4,353	15,133	30,947	0.0000
Unemployment rates (%)	0.1774	0.0659	0.0662	0.3435	-0.2569
Poverty index	0.2538	0.0833	0.0880	0.4210	0.0236
Individuals with university degree (%)	0.2002	0.0437	0.1345	0.3046	0.4397
Individual illiterate (%)	0.0819	0.0404	0.0189	0.1635	0.1378
Immigrants Africa (%)	0.0013	0.0009	0.0002	0.0050	7.6490
Immigrants America (%)	0.0029	0.0017	0.0007	0.0105	-8.1533**
Immigrants Asia (%)	0.0006	0.0005	0.0001	0.0027	-21.4360**
Immigrants no EU (%)	0.0004	0.0002	0.0000	0.0011	13.2507
Labour cost (€)	2,421	239	2,030	2,987	-0.0001
Price floor square meter (€)	227.6	95.1	67.0	523.6	0.0000
ISFAS	36,002	38,911	4,767	151,692	0.0000
MUGEJU	4,450	4,332	345	17,043	0.0000
MUFACE	90,370	85,003	10,018	317,901	0.0000
Year 2009	0.2000	0.4024	0.0000	1.0000	-0.0072
Year 2010	0.2000	0.4024	0.0000	1.0000	-0.0153
Year 2011	0.2000	0.4024	0.0000	1.0000	-0.0470
Year 2012	0.2000	0.4024	0.0000	1.0000	-0.0790
N	85	85	85	85	85

Note: *p-value<0.10. **p-value<0.05. ***p-value<0.001