Methodological background

A cost of illness analysis involves the identification, measurement and valuing of all resources related to a specific illness. The perspective of the analysis is fundamental in determining which resources should be considered, and how they should be measured and valued. A health service perspective, for instance, would only consider costs imposed on hospitals and other health care providers. A societal perspective enables a wider analysis, in which all costs are considered, irrespective of who bears them or where they are incurred. Such a perspective not only includes health care costs but also those costs falling outside the health care sector, such as the opportunity costs associated with unpaid (i.e. informal) care to cardiovascular disease (CVD) patients, or productivity losses associated with premature death or morbidity. For this analysis, a societal perspective was adopted.

An annual time frame was adopted for our analysis, in which all costs due to CVD within the most recent year for which data were available were measured, regardless of the time of disease onset. All health care costs were expressed in 2009 prices, and if necessary adjusted using the health consumer price indices of each EU member state.[1] Where applicable, all national currencies were converted to Euro currency using the exchange rate on the last day of 2009.[2]

A “top down” approach was employed to calculate the total expenditure due to CVD across the 27 European Union countries. This approach used aggregate data on morbidity, mortality, hospital admissions, disease related costs, and other health related indicators. An advantage of using this
approach was the readily availability of international and national aggregate data. Given the whole spectrum of diseases under the CVD category, each with various treatment probabilities, complex incidence, and associated costs, a macro approach is likely to produce more accurate results than micro-costing of individual episodes of care.

A variety of international and national sources of epidemiological and health care utilisation data on CVD, CHD and stroke, were used. Among the sources consulted were the World Health Organization (WHO), the OECD, the Statistical Office of the European Communities (EUROSTAT), the World Bank Group, national ministries of health, national statistical institutes, large cohort studies etc. International data were used in preference to national data whenever available, as the former enable cross-country comparisons and are less prone to potential methodological biases. When relevant data could not be obtained from national or international sources, published articles and other literature were consulted. If no data were found for a particular country, extrapolations of resource use and unit costs were performed from similar countries. A country was judged to be similar if it shared comparable gross national income, health care expenditure per capita, general practitioners (GPs) and practising specialists’ density, life expectancy, and approximate location.

The framework used to estimate health care and non-health care costs was similar to the approach by Leal et al. (2006)[3] Luengo-Fernandez (2012)[4] to estimate the economic burden of CVD and dementia in the EU.
Health care expenditure

The categories of CVD health care service included were the following:

- primary care
- accident and emergency care
- hospital inpatient care (including day cases and cardiac rehabilitation services)
- outpatient care
- medications

Other categories of health service were not included, such as school/community based prevention and health education activities, and out-of-pocket expenses incurred by patients in purchasing over the counter medications, aids, home modifications, etc. These were not included in the study due to the difficulties of identifying them in the majority of countries. These excluded categories are likely to represent a very small proportion of the total costs identified.

To account for private spending on health care, in countries where only public resource use was found, cost estimates were inflated using the total proportion of private spending on health care.[5-7]

Health care resource use

Healthcare utilisation data sources are reported in Table 1.
<table>
<thead>
<tr>
<th>Country</th>
<th>Primary care</th>
<th>Outpatient care</th>
<th>A&amp;E</th>
<th>Inpatient care</th>
<th>Medicines</th>
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</thead>
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<td>[10,11]</td>
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</tr>
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<td>[32,34]</td>
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<td>[10,11]</td>
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<td>[37,38]</td>
<td>[10,11]</td>
<td>[6]</td>
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<td></td>
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<td>[10,11]</td>
<td>Using Spain, Greece, Cyprus, Portugal and Italy [6,12,21,55]</td>
</tr>
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<td>[10,11]</td>
<td>Using Bulgaria [18,20]</td>
</tr>
<tr>
<td>Slovakia</td>
<td>Using Czech Rep [9,71]</td>
<td>Using Czech Rep [9,71]</td>
<td>[9,23]</td>
<td>[10,11]</td>
<td>[6]</td>
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<td>[6]</td>
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<td>[9,76]</td>
<td></td>
<td>Using Denmark [9,24,26]</td>
<td>[10,11]</td>
</tr>
<tr>
<td>UK</td>
<td>[78-80]</td>
<td>[9,81-83]</td>
<td>[81,83,84]</td>
<td>[10,11]</td>
<td>[85-88]</td>
</tr>
</tbody>
</table>
Primary care

Primary care activities consisted of CVD-related visits to general practitioners (GPs), together with GP visits to patients’ homes, nurse visits at clinic, and nurse home visits where available.

Country-specific overall visits to primary care due to all conditions were obtained for all countries.[6,8,13,16,19,22,26,30,32,36,39,42,43,45,49,50,52-54,57,59,64,67,68,71,72,74,76,78,79] To this we applied the proportion of primary care that was attributable to CVD, which were available for: Belgium,[13] Cyprus,[19] Estonia,[30] Finland,[33] Poland,[60] Romania,[69] Slovenia,[73] Sweden,[77] and the UK.[80]

In France,[37] Germany[40] and the Netherlands,[56] data on ambulatory care expenditure by disease group were used to derive the number of visits due to CVD, CHD and stroke by applying the respective proportions of expenditure, out of all ambulatory expenditure, to the total number of primary care visits.

For the rest of the countries, where the proportion of primary care visits due to CVD was not available, the proportion of overall hospital discharges due to CVD was used,[9] and applied to the total number of primary care visits.

To evaluate the proportion of primary care visits due to CHD and stroke, we obtained the proportion of CVD-related hospital discharges due to CHD and stroke,[9] which was applied to the total number of CVD-related primary care visits. This was undertaken for all countries except France,[37] Germany,[40] the Netherlands[56] and the UK,[80] where this information was available.

Hospital outpatient care

Outpatient care comprised specialist consultations taking place in outpatient wards, clinics, or patients’ homes.

Country-specific overall visits to primary care due to all conditions were obtained for all countries.[6-8,14,16,19,22,26,30,32,36,39,42,43,46,49,50,52,53,57,61,65,67,68,71,72,75,76,81-83] To this we
applied the proportion of outpatient care visits that was attributable to CVD, which were available for: Belgium,[14] Cyprus,[19] Finland,[34] and Slovenia.[73]

In France,[37] Germany,[40] and the Netherlands,[56] data on ambulatory care expenditure by disease group were used to derive the number of visits due to CVD, CHD and stroke by applying the respective proportions of expenditure, out of all ambulatory expenditure, to the total number of outpatient care visits.

For the rest of the countries, where the proportion of outpatient care visits due to CVD was not available, the proportion of overall hospital discharges due to CVD was used,[9] and applied to the total number of outpatient care visits. To evaluate the proportion of outpatient care visits due to CHD and stroke, we obtained the proportion of CVD-related hospital discharges due to CHD and stroke,[9] which was applied to the total number of CVD-related outpatient care visits. This was undertaken for all countries except France,[37] Germany,[40] and the Netherlands,[56] where this information was available.

Accident & Emergency care

Accident and emergency (A&E) consisted of all CVD-related hospital emergency visits. Country-specific overall visits to A&E due to all conditions were obtained for all countries.[3,8,9,15,17,19,23,27,28,30,32,38,41,44,46,48,54,58,62,66,70,75,81,83,84] For five countries (Czech Republic, Latvia, Lithuania, Luxembourg and Sweden) no data on A&E activity was found. As a result, we used the total per capita A&E visits from other countries. Therefore, for: 1) Czech Republic we used estimates from Slovakia;[23] 2) Latvia and Lithuania we used estimates from Estonia;[30] 3) Luxembourg we used estimates from Belgium;[15] and 4) Sweden we used estimates from Denmark;[28]

To the total number of A&E visits we applied the proportion of A&E visits that was attributable to CVD, which were available for: Belgium,[15] Bulgaria,[17] Denmark,[27] Germany,[41] Slovenia,[73] and the UK.[84] In France[37] and the Netherlands,[56] data on A&E expenditure by disease group
were used to derive the number of A&E visits due to CVD, by applying the respective proportions of expenditure to the overall number of A&E visits.

**Hospital inpatient care**

Inpatient care was estimated from the number of CVD-related days in hospital, including day case admissions. The number of days in hospital, which included day cases, was obtained for all countries by primary diagnosis of CVD, CHD and stroke.[10,11]

**Healthcare unit costs**

For all countries, health care resource use was valued using country-specific unit costs, which were derived from published studies, reports, national fee schedules, and WHO CHOosing Interventions that are Cost Effective (CHOICE) country-specific costs.

A&E visit unit costs were not identified for eight countries (Bulgaria, Cyprus, Czech Republic, Latvia, Lithuania, Poland, Romania and Slovakia). As a result, unit costs for these countries were predicted from the linear regression analysis of the unit costs of the remaining countries on the respective number of curative hospital beds, healthcare expenditure and total hospital beds per capita. For Cyprus, the unit cost of an inpatient day was predicted from the linear regression analysis of the unit cost of the other countries on the respective total number of curative hospital beds and on healthcare expenditure per capita. The unit cost of an outpatient visit in Malta was predicted from the linear regression analysis of the unit costs of the other countries on healthcare expenditure per capita. Sources of unit costs per country and resource use category are reported in **Table 2**.
<table>
<thead>
<tr>
<th>Country</th>
<th>Primary care</th>
<th>Outpatient care</th>
<th>A&amp;E</th>
<th>Inpatient care</th>
</tr>
</thead>
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<td>[92]</td>
<td>[93]</td>
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<td>Cyprus</td>
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<td>[94]</td>
<td>Regression</td>
<td>Regression</td>
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<td>[100]</td>
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<td>[107]</td>
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<td>[111]</td>
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<td>UK</td>
<td>[125]</td>
<td>[126]</td>
<td>[126]</td>
<td>[126]</td>
</tr>
</tbody>
</table>
Expenditure on Medications

The costs related to consumption of CVD-related medication were included in the analysis. CVD-related medications were defined as those coded under the Anatomical Therapeutic Chemical (ATC) Classification Code C (Cardiovascular System).


For Lithuania, Malta and Romania no data on CVD-related pharmaceutical expenditure was identified. Therefore, for: 1) Lithuania we used the average from estimates from Estonia and Latvia,[31,51] 2) Malta we used the average from Cyprus,[21] Greece,[6] Italy,[12] Portugal,[55] and Spain[6] and 3) Romania we used estimates from Bulgaria.[18] Finally, to estimate the expenditure on CHD and stroke pharmaceuticals, data on the proportion of CVD-related expenditure that was due to these two conditions, was obtained from Germany,[40] France[37] and the Netherlands,[56] and averaged proportions from these countries were applied to the remaining countries.

Non-health care expenditure

The categories of non-health care expenditure included in the study were the following:

- Informal care
- Productivity costs due to mortality
- Productivity costs due to morbidity

Informal care costs

Informal care costs were equivalent to the opportunity cost of unpaid care. This opportunity cost is a measure of the amount of money that carers forgo to provide unpaid care for their spouses, friends or relatives suffering from CVD, CHD or stroke. It was hypothesised that only those people being severely limited in daily activities due to cardiovascular diseases would receive informal care.
In order to estimate informal care costs due to CVD, CHD and stroke we made use of the Survey of Health, Ageing and Retirement in Europe (SHARE).[127] SHARE is a multidisciplinary and cross-national panel database of micro data on health, socio-economic status and social and family networks, freely available to researchers, in which all data are collected via face-to-face, computer-aided personal interviews, supplemented by self-completion paper and pencil questionnaires. For our analysis, we used data collected in 2006 as part of SHARE wave 2, which included over 32,000 respondents resident in 13 EU countries (Austria, Belgium, Czech Republic, Denmark, France, Germany, Greece, Ireland, Italy, Netherlands, Poland, Spain and Sweden). For countries not in SHARE, we combined data from similar countries that were in SHARE to obtain estimates for the 14 remaining countries. Therefore, for Bulgaria, Estonia, Hungary, Latvia, Lithuania, Romania, Slovakia and Slovenia we used combined data from the Czech Republic and Poland. For Finland we used combined data from Denmark and Sweden. For Cyprus, Malta and Portugal we used combined data from Greece, Italy and Spain. Finally, for Luxembourg and the UK we used combined data from Austria, Belgium, France, Germany, Ireland, Luxembourg, and the Netherlands.

To evaluate the amount of informal care provided was estimated by calculating the sum of the age and sex-specific products of the following:

1) Prevalence of CVD, CHD and stroke in the population.

As part of wave 2, participants in SHARE were asked to report if they suffered any health condition, including heart attack, stroke or hypertension. For this specific analysis, due to lack of further information on other cardiovascular conditions, CVD was defined as either having suffered a heart attack, stroke and/or hypertension, and CHD as having suffered a heart attack.

2) Probability of being severely limited in daily activities due to CVD, CHD or stroke.

Participants in SHARE were asked whether they had no, moderate or severe limitations in daily activities. Using a logistic regression analysis we estimated the probability of a respondent being severely limited by controlling for age, gender, presence of CVD, CHD or stroke, presence of other health conditions, and country of residence.
3) Probability of receiving informal care due to CVD, CHD or stroke.

Participants in SHARE were asked whether they received unpaid care from relatives/friends living with them or from outside the household. Using two logistic regression analyses (one for help from inside household and another one for help outside the household), we estimated the probability of a respondent receiving unpaid care by controlling for age, gender, presence of CVD, CHD or stroke, limitations in daily living, presence of other health conditions, and country of residence.

4) Amounts of informal care received.

Participants in SHARE who received informal care were further asked whether they received care: almost daily, almost weekly, almost every month, or less often. Using an ordered logistic regression we estimated the amounts of care received by controlling for age, gender, presence of CVD, CHD or stroke, limitations in daily living, presence of other health conditions, and country of residence.

Participants in SHARE were further asked the hours of unpaid care received either daily, weekly, monthly or annually. Conditional on how often they received care, the hours of care received did not vary by condition, age and gender, so, for each country, average hours of care received daily, weekly, monthly or annually were estimated without controlling for other characteristics.

5) Probability of unpaid care provided by employed or non-employed relatives or friends.

Participants in SHARE who received informal care were asked who provided the care (e.g. spouse, sibling, offspring, parent friend etc...). We assumed that spouses, siblings and friends providing the care would typically be aged 65 years of age or more, and therefore be retired. If care was being provided by either the patients' children or their children's spouses, then it was assumed that these informal carers would be under 65 years of age. Using gender-specific economic activity and unemployment rates for each country,[128] we then determined the proportion of these carers who were employed or unemployed/economically inactive.

6) Monetary value for hour of care provided.

The average net hourly wage rate was applied to informal care provided by those carers in working age and who were economically active and in employment. Annual earnings were obtained,[129-134] and then adjusted to hourly wage rates, assuming there were 230 working days each year, and each
day consisted of 8 hours of work. For those carers in retirement, unemployed, or economically inactive, the national hourly minimum wage was applied.\textsuperscript{[135]} For those countries with no official minimum wage rate (Cyprus,\textsuperscript{[132]} Denmark,\textsuperscript{[136]} Finland,\textsuperscript{[137]} Germany,\textsuperscript{[137]} Italy\textsuperscript{[137]} and Sweden\textsuperscript{[137]}), the worst paid sector in the economy was proxied as a minimum wage.

**Productivity costs due to mortality**

The costs associated with lost productivity due to mortality comprised the foregone earnings from premature death due to the diseases under analysis. Age and gender specific deaths due to each of the three cardiovascular disease categories were obtained for all countries from the EUROSTAT mortality database.\textsuperscript{[138]}

For all countries we assumed an initial working age of 15. The number of working years lost due to premature mortality was estimated both for males and females combining the previous information together with the number of deaths broken down by age and gender. Number of working years lost was then multiplied by gender-specific average annual earnings.\textsuperscript{[129-134]} However, this estimate would overestimate these costs as not everyone will be economically active (i.e. either working or actively searching for work) or employed. Therefore, age- and gender-specific unemployment and activity rates for each of the 27 countries were applied to the potential foregone earnings due to premature mortality.\textsuperscript{[128]}

As these productivity costs would be incurred in future years, all future foregone earnings were discounted using a 3.5\% rate per annum following current UK HM Treasury recommendations.\textsuperscript{[139]}

**Productivity costs due to morbidity**

The costs associated with lost productivity due to morbidity were the costs associated with absence of work due to CVD, CHD and stroke. Morbidity losses could occur due to: individuals taking absence from leave for a defined period of time; or due to individuals being declared incapacitated or disabled due to their condition, and therefore leaving the labour market.

*Temporary absence from work due to sickness*
Country-specific overall annual days of sickness leave due to all conditions was obtained for all countries.\textsuperscript{6,30,72,76,134,140-159} To this we applied the proportion of sickness leave that was attributable to CVD, which was available in Austria,\textsuperscript{140} Belgium,\textsuperscript{141} Czech Republic,\textsuperscript{143} Estonia,\textsuperscript{160} France,\textsuperscript{161} Germany,\textsuperscript{162} Italy,\textsuperscript{163} Luxembourg,\textsuperscript{151} Netherlands,\textsuperscript{164} Poland,\textsuperscript{153} Slovenia,\textsuperscript{165} Spain,\textsuperscript{166} and Sweden.\textsuperscript{167} For Finland\textsuperscript{168} and the UK,\textsuperscript{169} we used the proportion of overall permanent absence from work due to CVD.

For countries where we could not establish the proportion of sickness leave attributable to CVD, we used proportions from other countries. Therefore, for: 1) Bulgaria, Hungary and Romania we used estimates from Poland;\textsuperscript{153} 2) Cyprus, Greece and Portugal we used estimates from Spain;\textsuperscript{166} 3) Denmark we used estimates from Sweden;\textsuperscript{167} 4) Ireland we used estimates from the UK;\textsuperscript{169} 5) Latvia and Lithuania we used estimates from Estonia;\textsuperscript{160} 6) Malta we used estimates from Italy;\textsuperscript{163} and 7) Slovakia we used estimates from the Czech Republic.\textsuperscript{143}

Except for Austria,\textsuperscript{140} the Czech Republic,\textsuperscript{143} Finland,\textsuperscript{168} France,\textsuperscript{161} Germany,\textsuperscript{162} Slovenia,\textsuperscript{165} and the UK\textsuperscript{169} where the proportion of sickness leave/incapacity attributable to CHD and stroke was available, for all other countries the proportion of CVD days due to CHD and stroke was obtained by assuming that this would be the same as the proportion of overall days in hospital due to CHD or stroke in the working age population.\textsuperscript{10} We hypothesised that the higher the number of days spent in hospital, the higher the number of working days lost due to illness.

**Permanent absence from work due to incapacity or disability**

Country-specific information on the numbers of working-age individuals receiving incapacity or disability benefits and not being able to work conditions was obtained for all countries.\textsuperscript{53,54,72,76,140,141,146,152,154,158,168-178,178-182} To this we applied the proportion of was attributable to CVD, which was available in Finland,\textsuperscript{168} France,\textsuperscript{179} the Netherlands,\textsuperscript{152} Slovenia,\textsuperscript{165} and the UK.\textsuperscript{169} For Austria,\textsuperscript{140} Belgium,\textsuperscript{141} Czech Republic,\textsuperscript{143} Estonia,\textsuperscript{160} Germany,\textsuperscript{162} Italy,\textsuperscript{163} Luxembourg,\textsuperscript{151} Poland,\textsuperscript{153} Spain,\textsuperscript{166} and Sweden\textsuperscript{167} we applied the proportion of sickness leave that was attributable to CVD. For countries where we could not not
establish the proportion of sickness leave attributable to CVD, we used proportions from other countries using the methodology to estimate temporary absence from work due to sickness.

For those countries where the proportion of sickness leave/incapacity attributable to CHD and stroke was unavailable, the proportion of CVD days due to CHD and stroke was obtained by assuming that this would be the same as the proportion of overall days in hospital due to CHD or stroke in the working age population.[10]

Valuing absence from work

The average annual earnings identified when estimating informal care and mortality costs were converted to average daily earnings. The product of working days lost and average daily earnings provided the productivity losses associated with CVD, CHD and stroke morbidity. However, absent workers after a certain period are likely to be replaced at work by other workers, and so the total morbidity loss as computed above is likely to be an upper limit of the “real” loss from CVD, CHD and stroke. Hence, we estimated the “friction period”, i.e. the period of employee’s absence from work due to illness before he or she is replaced by another worker, which is estimated to be 90 days in Europe.[183] Therefore, for all new permanent cases of disability/incapacity, and/or the average spell of temporary sickness leave was more than 90 days, only the first 90 days of absence from work were assigned a monetary value.
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