The impact of pharmaceutical innovation on mortality and hospitalization in Portugal, 2002-2010

Frank R. Lichtenberg
Columbia University and National Bureau of Economic Research

frank.lichtenberg@columbia.edu

21 July 2015

This research was supported by MSD Portugal. The sponsor placed no restrictions or limitations on data, methods, or conclusions and had no right of review or control over the outcome of the research.
The impact of pharmaceutical innovation on mortality and hospitalization in Portugal, 2002-2010

Abstract

Premature mortality has been declining in Portugal, but there has been considerable variation in the rate of decline across diseases. I analyze the effect that pharmaceutical innovation had on premature mortality in Portugal during the period 2002-2010, by investigating whether the diseases that experienced more pharmaceutical innovation had larger declines in premature mortality.

My estimates indicate that premature (before age 70 or 80) mortality from a disease is inversely related to the cumulative number of drugs registered 0-10 years earlier. It is most strongly inversely related to the cumulative number of drugs registered 6 years earlier. This is to be expected, since new drugs diffuse gradually. For low innovation diseases—those with few drugs registered during 1996-2004—premature mortality declined by only 1% between 2002 and 2010, but for high innovation diseases, premature mortality declined by 34% between 2002 and 2010. Premature mortality depends on the number of drugs, not the number of chemical subgroups, which suggests that drugs within the same chemical subgroup are not “therapeutically equivalent.”

Drugs registered during 1995-2000 reduced the hospital discharge rate in 2010 by about 10.7%. For low innovation diseases, the hospital discharge rate increased by 26% between 2005 and 2010, but for high innovation diseases, the hospital discharge rate declined by 5% between 2005 and 2010.

The estimates imply that essentially all of the 25% decline between 2002 and 2010 in premature (before age 70) mortality was due to previous pharmaceutical innovation. Drugs registered during the period 1996-2004 are estimated to have reduced the number of years of potential life lost before ages 70 and 80 in 2010 by 141,300 and 192,028, respectively.

If we do not account for the apparent reduction in hospital expenditure due to previous pharmaceutical innovation, the estimated costs per life-year before ages 70 and 80 gained in 2010 from drugs registered during 1996-2004 are €5483 and €5208, respectively. The cost per life year gained before age 80 from drugs used to treat cancer registered during 1994-2002 is only 7% higher than the cost per life year gained before age 80 from all drugs registered during 1996-2004.

When we account for the apparent reduction in hospital expenditure due to previous pharmaceutical innovation, net 2010 medical expenditure per life-year gained before age 70 and 80 are €1986 and €1868, respectively. According to the World Health Organization, a medical intervention should be considered “very cost-effective” if the cost per quality-adjusted life year gained from that intervention is below a country’s per capita GDP. By this standard, pharmaceutical innovation in Portugal has been extremely cost effective.

Frank R. Lichtenberg
Columbia University
504 Uris Hall
3022 Broadway
New York, NY 10027 USA
frank.lichtenberg@columbia.edu
I. Introduction

Previous authors have argued that “reducing premature mortality is a crucial public health objective” (Renard, Tafforeau, and Deboosere (2014)). A widely used measure of premature mortality is years of potential life lost (YPLL) before a given age (e.g. age 70), i.e. the number of years not lived by an individual who died before that age (Association of Public Health Epidemiologists in Ontario (2015)). Statistics of YPLL are published by the World Health Organization, the OECD, and government agencies of the U.S., Switzerland, and other countries. Burnet et al (2005) argue that YPLL “should be considered when allocating research funds.”

As shown in Figure 1, premature (before age 70) mortality has been declining in Portugal; it declined about 25% between 2002 and 2010. During that period, the population below age 70 declined by 0.5%. But as shown in Figure 2, there has been considerable variation in the rate of decline across diseases. The number of years of potential life lost before age 70 from “other heart diseases” (ICD-10 codes I30-I51) declined by 45%, while the number of years of potential life lost before age 70 from malignant neoplasm of colon, rectosigmoid junction, rectum, anus and anal canal (ICD-10 codes C18-C21) increased by 4%.

In this paper, I will analyze the effect that pharmaceutical innovation had on premature mortality in Portugal during the period 2002-2010. In essence, I will investigate whether the diseases that experienced more pharmaceutical innovation had larger declines in premature mortality. Figure 3 illustrates that the rate of pharmaceutical innovation, as measured by the 1996-2004 increase in the number of drugs ever registered in Portugal, varied considerably across diseases. Sixteen drugs were registered for human immunodeficiency virus [HIV] disease (ICD-10 codes B20-B24), while only 2 drugs were launched for malignant neoplasm of cervix uteri (ICD-10 code C53). The heterogeneous nature of pharmaceutical innovation is also illustrated in Table 1, which lists the drugs used for the treatment of two diseases. Eighteen drugs for the treatment of malignant neoplasm of the stomach have been registered; none were registered after 2001. More than twice as many (38) drugs have been registered for the treatment of acute myocardial infarction; six of these were registered after 2001.

The analysis will be based on aggregate data—longitudinal data on about 45 diseases\(^1\)—rather than patient-level data. Stukel et al (2007) argue that comparisons of outcomes between

\(^1\) The disease classification is the one used in the Eurostat hlth_cd_anr table.
patients treated and untreated in observational studies may be biased due to differences in patient prognosis between groups, often because of unobserved treatment selection biases. I believe that difference-in-differences estimates based on aggregate panel data are much less likely to be subject to unobserved treatment selection biases than estimates based on cross-sectional patient-level data. Moreover, the outcome measures that I analyze (premature mortality rates) are not subject to lead-time bias.

In Section II, I describe econometric models of premature mortality and hospital discharges. The data sources used to construct the data to estimate this model are described in Section III. Empirical results are presented in Section IV. Key implications of the estimates are discussed in Section V. Section VI provides a summary and conclusions.

II. Econometric models of premature mortality and hospital discharges

A. Premature mortality model

In his model of endogenous technological change, Romer (1990) hypothesized an aggregate production function such that an economy’s output depends on the “stock of ideas” that have previously been developed, as well as on the economy’s endowments of labor and capital. The premature mortality model that I will estimate may be considered a health production function, in which premature mortality is an inverse indicator of health output or outcomes, and the cumulative number of drugs approved is analogous to the stock of ideas. The first model will be of the following form:

\[ \ln(YPLL_{70i}) = \beta_k \text{CUM}_{i,t-k} + \alpha_i + \delta_t + \varepsilon_{i,t} \]  

(1)

---

2 Jalan and Ravallion (2001) argued that “aggregation to village level may well reduce measurement error or household-specific selection bias” (p. 10).

3 Survival time for cancer patients is usually measured from the day the cancer is diagnosed until the day they die. Patients are often diagnosed after they have signs and symptoms of cancer. If a screening test leads to a diagnosis before a patient has any symptoms, the patient’s survival time is increased because the date of diagnosis is earlier. This increase in survival time makes it seem as though screened patients are living longer when that may not be happening. This is called lead-time bias. It could be that the only reason the survival time appears to be longer is that the date of diagnosis is earlier for the screened patients. But the screened patients may die at the same time they would have without the screening test. See National Cancer Institute (2015a).
where
\[ YPLL_{70i} = \text{years of potential life lost before age 70 from disease } i \text{ in year } t \text{ (} t = 2002, \ldots, 2010) \]
\[ CUM_{\text{NCE},i,t-k} = \sum_d \text{IND}_{di} \text{REGISTERED}_{d,t-k} = \text{the number of new chemical entities} \]
\[ \text{(drugs) to treat disease } i \text{ that had been registered in Portugal by the end of year } t-k \]
\[ \text{IND}_{di} = 1 \text{ if drug } d \text{ is used to treat (indicated for) disease } i \]
\[ = 0 \text{ if drug } d \text{ is not used to treat (indicated for) disease } i \]
\[ \text{REGISTERED}_{d,t-k} = 1 \text{ if drug } d \text{ was registered in Portugal by the end of year } t-k \]
\[ = 0 \text{ if drug } d \text{ was not registered in Portugal by the end of year } t-k \]
\[ \alpha_i = \text{a fixed effect for disease } i \]
\[ \delta_t = \text{a fixed effect for year } t \]

Inclusion of year and disease fixed effects controls for the overall decline in premature mortality and for stable between-disease differences in premature mortality.\(^4\) A negative and significant estimate of \(\beta_k\) in eq. (1) would signify that diseases for which there was more pharmaceutical innovation had larger declines in premature mortality. The functional form of eq. (1) has the property of diminishing marginal productivity: the absolute reduction in premature mortality declines with each successive increase in the number of drugs.

From estimates of eq. (1), there are two alternative, nearly equivalent, ways to determine how much of the decline in premature mortality during the sample period (2002-2010) can be attributed to the registration of new drugs. The first way is to compute \(\beta_k * \) [mean(CUM_NCE\(_{i,2010-k}\)) - mean(CUM_NCE\(_{i,2002-k}\))]. The second way is based on the year fixed effects. The expression \((\delta_{2010} - \delta_{2002})\) indicates the 2002-2010 decline in premature mortality, controlling for (holding constant) the number of drugs, i.e., in the absence of pharmaceutical innovation. Suppose eq. (1) is estimated, excluding CUM_NCE\(_{i,t-k}\), and that the year fixed effects from that equation are denoted by \(\delta'\). Then \((\delta'_{2010} - \delta'_{2002})\) indicates the 2002-2010 decline in premature mortality, not holding constant the number of drugs, i.e., in the presence of pharmaceutical innovation, and \((\delta'_{2010} - \delta'_{2002}) - (\delta_{2010} - \delta_{2002})\) is an estimate of the 2002-2010 decline in premature mortality attributable to pharmaceutical innovation.

---

\(^4\) The year fixed effects also control for population growth.
The data exhibit heteroskedasticity: diseases with larger total premature mortality during 2002-2010 had smaller (positive and negative) annual percentage fluctuations in YPLL70. Eq. (1) will therefore be estimated by weighted least-squares, weighting by the mean premature mortality rate during 2002-2010 ((∑_t YPLL70_{it}) / 9). The standard errors of eq. (1) will be clustered within diseases.

The measure of pharmaceutical innovation in eq. (1)—the number of chemical substances previously registered to treat a disease—is not the theoretically ideal measure. Premature mortality is presumably more strongly related to the drugs actually used to treat a disease than it is to the drugs that could be used to treat the disease. A preferable measure is the mean vintage of drugs used to treat disease i in year t, defined as VINTAGE_{it} = ∑_d Q_{dit} LAUNCH_YEAR_d / ∑_d Q_{dit}, where Q_{dit} = the quantity of drug d used to treat disease i in year t, and LAUNCH_YEAR_d = the world launch year of drug d. Unfortunately, measurement of VINTAGE_{it} is infeasible: even though data on the total quantity of each drug in each year (Q_{dt} = ∑_i Q_{dit}) are available, many drugs are used to treat multiple diseases, and there is no way to determine the quantity of drug d used to treat disease i in year t. However, Lichtenberg (2014a) showed that in France, there is a highly significant positive correlation across drug classes between changes in the (quantity-weighted) vintage of drugs and changes in the number of chemical substances previously commercialized within the drug class.

Pharmaceutical innovation is not the only type of medical innovation that is likely to reduce premature mortality. Other medical innovation, such as innovation in diagnostic imaging, surgical procedures, and medical devices, is also likely to affect premature mortality. Therefore, measures of these other types of medical innovation should be included in eq. (1). Unfortunately, longitudinal disease-level measures of non-pharmaceutical medical innovation

---

5 According to the Merriam Webster dictionary, one definition of vintage is “a period of origin or manufacture (e.g. a piano of 1845 vintage)”. http://www.merriam-webster.com/dictionary/vintage. Robert Solow (1960) introduced the concept of vintage into economic analysis. Solow’s basic idea was that technical progress is “built into” machines and other goods and that this must be taken into account when making empirical measurements of their roles in production. This was one of the contributions to the theory of economic growth that the Royal Swedish Academy of Sciences cited when it awarded Solow the 1987 Alfred Nobel Memorial Prize in Economic Sciences (Nobelprize.org (2015)).

6 For example, dactinomycin is used to treat C45-C49 connective and soft tissue neoplasms, C51-C58 female genital organ neoplasms, C60-C63 male genital organ neoplasms, and C64-C68 urinary organ neoplasms.

7 Outpatient prescription drug claims usually don’t show the indication of the drug prescribed. Claims for drugs administered by doctors and nurses (e.g. chemotherapy) often show the indication of the drug, but these account for just 15% of drug expenditure. These data are not available for Portugal.
are not available for Portugal. But failure to control for non-pharmaceutical medical innovation is unlikely to bias estimates of the effect of pharmaceutical innovation on premature mortality, for two reasons. First, more than half of U.S. funding for biomedical research came from pharmaceutical and biotechnology firms (Dorsey et al (2010)). Much of the rest came from the federal government (i.e. the NIH), and new drugs often build on upstream government research (Sampat and Lichtenberg (2011)). The National Cancer Institute (2015b) says that it “has played an active role in the development of drugs for cancer treatment for 50 years… [and] that approximately one half of the chemotherapeutic drugs currently used by oncologists for cancer treatment were discovered and/or developed” at the National Cancer Institute.

Second, previous research based on U.S. data indicates that non-pharmaceutical medical innovation is not positively correlated across diseases with pharmaceutical innovation. Lichtenberg (2014a) showed that, in the U.S. during the period 1997-2007, the rate of pharmaceutical innovation was not positively correlated across diseases with the rate of medical procedure innovation and may have been negatively correlated with the rate of diagnostic imaging innovation. Also, Lichtenberg (2014b) found that estimates of the effect of pharmaceutical innovation on U.S. cancer mortality rates were insensitive to the inclusion or exclusion of measures of non-pharmaceutical medical innovation. This suggests that failure to control for other medical innovation is unlikely to result in overestimation of the effect of pharmaceutical innovation on longevity growth.

In eq. (1), premature mortality from disease i in year t depends on the number of new chemical entities (drugs) to treat disease i that had been registered in Portugal by the end of year t-k, i.e. there is a lag of k years. Eq. (1) will be estimated for different values of k: k = 0, 2, 4, 6, 8, 10. One would expect there to be a substantial lag because new drugs diffuse gradually—they won’t be used widely until years after registration. Two kinds of evidence—“within molecule” and “between molecule”—support the gradual diffusion hypothesis. The first kind consists of estimates based on the $\pi_y$ parameters from the following equation:

$$\ln(SU_{my}) = \rho_m + \pi_y + \varepsilon_{my}$$

(2)

where

---

8 A separate model is estimated for each value of k, rather than including multiple values (CUM_NCEi,t-1, CUM_NCEi,t-2, CUM_NCEi,t-3,…) in a single model because CUM_NCE is highly serially correlated (by construction), which would result in extremely high multicollinearity if multiple values were included.)
$SU_{my} = \text{the number of standard units}^9 \text{ of molecule m sold in Portugal y years after registration (y = 0, 1,\ldots, 11)}$

$\rho_m = \text{a fixed effect for molecule m}$

$\pi_y = \text{a fixed effect for age y}$

The expression $\exp(\pi_y - \pi_0)$ is a “relative utilization index”: it is the mean ratio of the number of units of a molecule sold y years after registration to the number of units of the same molecule sold in the year that it was registered. Using annual data on the number of standard units of molecules sold in Portugal during the period 1999-2010, I estimated eq. (2).$^{10}$ Estimates of the “relative utilization index,” based on data on molecules that were registered after 1998, are shown in Figure 4. These estimates indicate that the number of units sold 10 years after registration is about 4.4 times as great as the number of units sold one year after registration. Moreover, Figure 4 provides a conservative estimate of the slope of the age-utilization profile, because there was zero utilization of many of these molecules in the first few years after they were registered.$^{11}$

Figure 5 provides “between-molecule” evidence of gradual diffusion; it shows data on the mean number of retail standard units of drugs sold (in thousands) in Portugal in 2010, by period of registration in Portugal. Mean utilization in 2010 of drugs registered after 2000 is only about half as high as mean utilization of drugs registered before 2001.

The effect of a drug’s registration on premature mortality is likely to depend on both the quality and the quantity of the drug. Indeed, it is likely to depend on the interaction between quality and quantity: a quality improvement will have a greater impact on mortality if drug utilization (quantity) is high. Although newer drugs tend to be of higher quality than older drugs (see Lichtenberg (2014c)), the relative quantity of very new drugs is quite low, so the impact on mortality of very new drugs is lower than the impact of older drugs.

---

$^9$ The number of standard ‘dose’ units sold is determined by taking the number of counting units sold divided by the standard unit factor which is the smallest common dose of a product form as defined by IMS HEALTH. For example, for oral solid forms the standard unit factor is one tablet or capsule whereas for syrup forms the standard unit factor is one teaspoon (5 ml) and injectable forms it is one ampoule or vial. Other measures of quantity, such as the number of patients using the drug, prescriptions for the drug, or defined daily doses of the drug, are not available.

$^{10}$ The data cover retail sales only; hospital sales are not included.

$^{11}$ Since the dependent variable of eq. (2) is logarithmic, observations for which $SU_{my} = 0$ had to be excluded.
The measure of pharmaceutical innovation, $\text{CUM}_\text{NCE}_{i,t-k} = \sum_d \text{IND}_d \text{REGISTERED}_{d,t-k}$, is based on whether drug $d$ had an indication for disease $i$ at the end of 2011. One would prefer to base the measure on whether drug $d$ had an indication for disease $i$ at the end of year $t-k$. FDA data indicate that about one in four new molecular entities has supplemental indications, i.e. indications approved after the drug was initially launched.12

In eq. (1), the measure of premature mortality is the number of years of potential life lost before age 70. To assess the robustness of my results, I will estimate models similar to eq. (1), using the age threshold 80 as well as 70.

Approximately half (21 out of 44) of the diseases in my sample are different forms of cancer. In addition to estimating models using the full set of diseases, I will estimate models on different forms of cancer only.

Chemical substances are divided into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. In the Anatomical Therapeutic Chemical (ATC) classification system developed by the World Health Organization Collaborating Centre for Drug Statistics Methodology, drugs are classified in groups at five different levels. The highest (1st) level is the “anatomical main group” level; there are 14 anatomical main groups. The 2nd, 3rd, 4th, and 5th levels are “therapeutic subgroup,” “pharmacological subgroup,” “chemical subgroup,” and “chemical substance,” respectively.13 Premature mortality from a disease may depend on the number of chemical (or pharmacological) subgroups that have previously been developed to treat the disease rather than, or in addition to,

---

12 Source: Drugs@FDA Data Files
13 For example, the five levels associated with the chemical subgroup “nitrogen mustard analogues” are:

- L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS
- L01 ANTINEOPLASTIC AGENTS
- L01A ALKYLATING AGENTS
- L01AA Nitrogen mustard analogues
  - L01AA01 cyclophosphamide
  - L01AA02 chlorambucil
  - L01AA03 melphalan
  - L01AA05 chloromethine
  - L01AA06 ifosfamide
  - L01AA07 trofosfamide
  - L01AA08 prednimustine
  - L01AA09 bendamustine
the number of chemical substances (drugs) that have previously been developed to treat the disease. This will be investigated by estimating versions of eq. (1) in which CUM_SUBGROUP_{i,t-k} is included in addition to or instead of CUM_NCE_{i,t-k}, where
\[
\text{CUM_SUBGROUP}_{i,t-k} = \sum_g \text{IND_SUBGROUP}_{gi} \text{REGISTERED_SUBGROUP}_{g,t-k}
\]
\[
\text{IND_SUBGROUP}_{gi} = 1 \text{ if any drugs in chemical subgroup } g \text{ are used to treat (indicated for) disease } i
\]
\[
= 0 \text{ if no drugs in chemical subgroup } g \text{ are used to treat (indicated for) disease } i
\]
\[
\text{REGISTERED_SUBGROUP}_{g,t-k} = 1 \text{ if any drugs in chemical subgroup } g \text{ had been registered in Portugal by the end of year } t-k
\]
\[
= 0 \text{ if no drugs in chemical subgroup } g \text{ had been registered in Portugal by the end of year } t-k
\]

B. Hospital discharge model

The hospital discharges model will be of the following form:
\[
\ln(\text{N_HOSP}_{it}) = \beta_k \ln(\text{CUM_NCE}_{i,t-k}) + \alpha_i + \delta_t + \varepsilon_{i,t}
\]  
(3)

where
\[
\text{N_HOSP}_{it} = \text{the number of hospital discharges per 100,000 population for disease } i \text{ in year } t \text{ (} t = 2005, \ldots, 2010\)
\]

The hospital discharge data also exhibit heteroskedasticity: diseases with larger mean hospital discharge rates during 2005-2010 had smaller (positive and negative) annual percentage fluctuations in N_HOSP. Eq. (3) will therefore be estimated by weighted least-squares, weighting by the mean hospital discharge rate during 2005-2010 ((\Sigma_t N_{HOSP}) / 6). The standard errors of eq. (3) will be clustered within diseases.
III. Data

NCE registrations in Portugal (REGISTERED). Data on dates of drug registrations were obtained from INFARMED, the National Authority of Medicines and Health Products, a government agency accountable to the Health Ministry. The data provided by INFARMED includes WHO ATC codes and registration dates of pharmaceutical preparations.

Drug indications (IND). Data on drug indications were obtained from Thériaque, a database of official, regulatory, and bibliographic information on all drugs available in France,\textsuperscript{14} intended for health professionals. This database is produced by the Centre National Hospitalier d'Information sur le Médicament. In this database, drugs are coded according to WHO ATC codes, and diseases are coded according to WHO ICD-10 codes.\textsuperscript{15}

Premature mortality data (YPLL70, YPLL80). Data on years of potential life lost before ages 70 and 80, by disease and year (2002-2010), were constructed from the Eurostat hlth_cd_anr table.

Hospital discharge data (N_HOSP). Data on inpatient hospital discharges per 100,000 inhabitants, by diagnosis and year (2005-2010), were obtained from the Eurostat hlth_co_disch2 table.

Drug utilization and expenditure data. Data on the quantity (number of standard units) of and expenditure on drugs in 2010, by molecule, were obtained from IMS Health.

IV. Empirical results

Estimates of CUM_NCE coefficients from models of premature mortality (eq. (1) and similar equations) are presented in Table 2. Panel A of Table 2 shows estimates based on data for all diseases, and where the dependent variable is the log of years of potential life lost before age 70. Models are estimated for 6 alternative assumed values of the lag (in years) from cumulative drug registrations to premature mortality: k = 0, 2, 4, 6, 8, 10. Column F shows the mean change in CUM_NCE between (2002- k) and (2010 – k), which is equivalent to the mean number of drugs registered between (2002 – k) and (2010 – k). For example, column F in line 1 (where k = 0) shows that the mean number of drugs registered for a disease between 2002 and

\textsuperscript{14} A similar database is not available for Portugal, but the indications of drugs are unlikely to differ substantially across countries.\textsuperscript{15} Many drug databases contain information about drug indications, but this information is usually in text form only.
2010 was 3.43, and column F of line 2 (where k = 2) shows that the mean number of drugs registered for a disease between 2000 and 2008 was 5.20. Column G shows the estimated effect of drugs registered between (2002 – k) and (2010 – k) on the log of premature mortality in 2010. For example, column G in line 1 indicates that the drugs registered between 2002 and 2010 reduced premature mortality in 2010 by about 9%.

As shown in lines 1-6, all six estimates of \( \beta_k \) are negative and significant. This signifies that premature (before age 70) mortality from a disease is inversely related to the cumulative number of drugs registered 0-10 years earlier. Life years lost before age 70 is most strongly inversely related to cumulative NCEs registered 6 years earlier: the 2002-2010 decline in premature mortality is most strongly related to the number of drugs registered during 1996-2004. The magnitude of the marginal effect on premature mortality of drugs registered 6 years earlier (-0.039) is 44% larger than that of drugs registered 0 years earlier (-0.027). This is not surprising, since as discussed above, new drugs diffuse gradually. Also, as shown in column F, the mean number of drugs registered during 1996-2004 (6.18) was 80% larger than the mean number of drugs registered during 2002-2010. Consequently, as shown in column G, drugs registered during 1996-2004 reduced premature mortality in 2010 2.7 times as much as drugs registered during 2002-2010: by 24% vs. 9%. This does not necessarily imply that drugs registered during 1996-2004 were more cost-effective than drugs registered during 2002-2010. The relative cost-effectiveness of these two sets of drugs depends on relative expenditure on them as well as on relative mortality reduction attributable to them. In the next section I will provide estimates of the cost (drug expenditure) per life-year gained from both sets of drugs.

An alternative view of the relationship across diseases between the number of drugs registered during 1996-2004 and the log change in premature (before age 70) mortality during 2002-2010 is shown in Figure 6. For each disease, I calculated the number of drugs registered during 1996-2004. I then divided the diseases into three groups (tertiles) of roughly equal size, based on the number of drugs registered during 1996-2004: low, medium, and high innovation groups. Finally, for each of the three groups, I calculated (1) the mean number of drugs registered during 1996-2004, and (2) the mean log change in premature (before age 70) mortality during 2002-2010. For low innovation diseases (for which the mean number of drugs registered was 1.9), the mean log change in premature mortality was only -1%, but for high innovation
diseases (for which the mean number of drugs registered was 11.1), the mean log change in premature mortality was -34%.

Panel B of Table 2 also shows estimates based on data for all diseases, but now the dependent variable is the log of years of potential life lost before age 80. The significance levels of the coefficients in Panel B are not as high as those of the coefficients in Panel A, but 5 of the 6 coefficients in Panel B are significant (p-value < .04), indicating that life years lost before age 80 is also inversely related to the cumulative number of drugs registered 0-10 years earlier. Once again, drugs registered up until 6 years earlier had the largest marginal effect on premature mortality. Drugs registered during 1996-2004 are estimated to have reduced the number of life years lost before age 80 in 2010 by about 18%.

Panel C of Table 2 shows estimates based only on data on different forms of cancer, and the dependent variable is the log of years of potential life lost before age 70. Estimates of $\beta_4$, $\beta_6$, and $\beta_8$ are statistically significant (p-value < .04), but estimates of $\beta_0$ and $\beta_2$ are not. The estimate of $\beta_8$ has the largest magnitude (2.4 times the magnitude of $\beta_0$). A possible explanation for the finding that the lag from NCE registrations to premature mortality reduction is longer for cancer than it is for all diseases is that drugs for cancer diffuse more slowly than drugs for other diseases. As shown in column G of line 17, drugs registered during 1994-2002 are estimated to have reduced the number of life years lost from cancer before age 70 in 2010 by about 6%.

Panel D of Table 2 also shows estimates based only on data on different forms of cancer, but the dependent variable is the log of years of potential life lost before age 80. The pattern of coefficients in panel D is similar to the pattern in panel C. Drugs registered during 1994-2002 are estimated to have reduced the number of life years lost from cancer before age 80 in 2010 by about 6%.

As discussed earlier, in principle, premature mortality from a disease may depend on the number of chemical (or pharmacological) subgroups that have previously been developed to treat the disease rather than, or in addition to, the number of chemical substances (drugs) that have previously been developed to treat the disease. I estimated versions of eq. (1) in which CUM_SUBGROUP$_{i,t-6}$ is included in addition to or instead of CUM_NCE$_{i,t-6}$. Table 3 shows estimates of these models, based on data for all diseases, and where the dependent variable is the log of years of potential life lost before age 70. The equation in column 1 of Table 3 includes only CUM_NCE$_{i,t-6}$; it is identical to the equation in line 4 of Table 2. The equation in column 2
of Table 3 includes only CUM_SUBGROUP\textsubscript{t-6}; the coefficient on this variable is not statistically significant. The equation in column 3 of Table 3 includes both CUM\_NCE\textsubscript{t-6} and CUM\_SUBGROUP\textsubscript{t-6}; only the coefficient on CUM\_NCE\textsubscript{t-6} is significant. Evidently, premature mortality depends on the number of drugs, not the number of chemical subgroups. This suggests that drugs (chemical substances) within the same class (chemical subgroup) are not “therapeutically equivalent,”\textsuperscript{16} i.e. they do not have essentially the same effect in the treatment of a disease or condition. It is also possible that premature mortality depends on the number of chemical subgroups \textit{weighted by their relative importance}, or quality, and that more important chemical subgroups contain larger numbers of drugs.

Estimates of the hospital discharges model (eq. (3)) are shown in Table 4. Models are estimated for 8 alternative assumed values of the lag (in years) from cumulative drug registrations to hospital discharges: k = 0, 2, ..., 12, 14. The estimates in panel A of Table 4 are based on annual data for the period 2005-2010. The estimates in panel B are based on data for the first and last years of this period only; these estimates are quite similar to “long-difference” estimates. McKinnish (2008) argued that when explanatory variables in panel data models are subject to measurement error, long-difference estimates may be less downward biased than fixed-effects estimates,\textsuperscript{17} and that “it seems prudent for researchers to estimate both fixed-effects and long-differences models whenever feasible.”\textsuperscript{18} In panel A, only one of the estimates ($\beta_{10}$) is statistically significant, but four of the estimates in panel B are negative and statistically significant (p-value < .05). Drug registrations in years t-6 and t-8 had the largest (most negative) marginal effects on hospital discharges in year t. The estimate of $\beta_{10}$ in panel B (which is the most significant) implies that drugs registered during 1995-2000 reduced the hospital discharge rate in 2010 by about 10.7%. As shown in Figure 7, between 2005 and 2010, the hospital discharge rate increased by 10.7%. The estimates imply that, if no drugs had been registered

\textsuperscript{16} According to one medical dictionary, drugs that have “essentially the same effect in the treatment of a disease or condition” are therapeutically equivalent. Drugs that are therapeutically equivalent may or may not be chemically equivalent, bioequivalent, or generically equivalent. http://medical-dictionary.thefreedictionary.com/therapeutic+equivalent

\textsuperscript{17} She provides (in her Table 4) an empirical example in which the magnitude of the 7-year long-difference estimate is more than three times the magnitude of the fixed-effects estimate.

\textsuperscript{18} The number of hospital discharges in year t presumably depends more on the number of drugs actually used to treat patients in year t (N\_NCE\_TREAT\textsubscript{t}) than it does on the number of drugs registered by year t (or t-k). (Some drugs are not used until several years after registration.) CUM\_NCE\textsubscript{t-k} might be considered a “noisy indicator” of N\_NCE\_TREAT\textsubscript{t}. In other words, CUM\_NCE\textsubscript{t-k} is subject to measurement error. Measurement error often biases coefficients towards zero.
during 1995-2000, the hospital discharge rate would have increased almost twice as much, by 20.8%.

An alternative view of the relationship across diseases between the 1995-2000 change in the log of the cumulative number of drugs registered and the 2005-2010 change in the log of the hospital discharge rate is shown in Figure 8. For each disease, I calculated the 1995-2000 change in the log of the cumulative number of drugs registered. I then divided the diseases into three groups of roughly equal size, based on the 1995-2000 change in the log of the cumulative number of drugs registered: low, medium, and high innovation groups. Finally, for each of the three groups, I calculated (1) the mean 1995-2000 change in the log of the cumulative number of drugs registered, and (2) the mean 2005-2010 change in the log of the hospital discharge rate. For low innovation diseases (for which the mean 1995-2000 change in the log of the cumulative number of drugs registered was 2.0%), the mean 2005-2010 change in the log of the hospital discharge rate was 26.0%, but for high innovation diseases (for which the mean 1995-2000 change in the log of the cumulative number of drugs registered was 35.9%), the mean 2005-2010 change in the log of the hospital discharge rate was -5.1%.

V. Discussion

Now I will use the estimates of eqs. (1) and (3) to calculate the number of life-years gained in 2010 from previous pharmaceutical innovation and medical expenditure per life-year gained. Figure 9 compares the actual number of years of potential life lost from all diseases before age 70 during 2002-2010 to the estimated number if no drugs had been registered during 1996-2004. The estimates imply that essentially all of the 25% decline between 2002 and 2010 in premature (before age 70) mortality was due to previous pharmaceutical innovation. Drugs registered during the period 1996-2004 are estimated to have reduced the number of years of potential life lost before age 70 in 2010 by 141,300.

The estimates in lines 1 and 4 of Table 6 indicate that the drugs registered during 2002-2010 reduced premature (before age 70) mortality in 2010 only 38% as much as the drugs registered during 1996-2004. However, according to data from IMS Health, 2010 expenditure on drugs registered during 2002-2010 was about 41% as great as 2010 expenditure on drugs
registered during 1996-2004, so the cost per life-year gained in 2010 from drugs registered during these two periods was quite similar.

Figure 10 compares the actual number of years of potential life lost from all diseases before age 80 during 2002-2010 to the estimated number if no drugs had been registered during 1996-2004. Premature (before age 80) mortality declined by 23% between 2002 and 2010. The estimates imply that, if no drugs had been registered during 1996-2004, it would have declined by only 5%. Drugs registered during the period 1996-2004 are estimated to have reduced the number of years of potential life lost before age 80 in 2010 by 192,028.

Figure 11 compares the actual number of years of potential life lost from cancer before age 80 during 2002-2010 to the estimated number if no drugs had been registered during 1994-2002. Premature (before age 80) cancer mortality in 2010 was almost identical to premature cancer mortality in 2002. The estimates imply that if no drugs had been registered during 1994-2002, premature cancer mortality would have increased by about 9%. A substantial decline in the “competing risk” of death from cardiovascular disease could have contributed to increasing premature cancer mortality in the absence of previous pharmaceutical innovation. The estimates imply that drugs registered during the period 1994-2002 reduced the number of years of potential life lost to cancer before age 80 in 2010 by 26,645.

Table 5 shows calculations of medical expenditure per life-year gained from previous pharmaceutical innovation. Data from IMS Health indicate that expenditure in 2010 on all drugs registered during 1996-2004 was €1.13 billion. This is about one third of total pharmaceutical expenditure in 2010 (€3.46 billion). To calculate cost per life-year gained, we need to estimate expenditure by people below ages 70 and 80 in 2010 on all drugs registered during 1996-2004. Data on the age distribution of pharmaceutical expenditure are not available for Portugal, but in Denmark (where reliable data are available from http://medstat.dk/en), people below the ages of 70 and 80 accounted for 69% and 89% of drug expenditure, respectively, in 2013. Assuming that these proportions apply to Portugal, I estimate that people below the ages of 70 and 80 spent €775 million and €1.00 billion, respectively, in 2010 on all drugs registered during 1996-2004. As shown in line 4 of Table 5, if we do not account for the apparent reduction in hospital expenditure due to previous pharmaceutical innovation, the estimated costs per life-year before ages 70 and 80 gained in 2010 from drugs registered during 1996-2004 are €5483 and €5208, respectively.
The innovation-induced reduction in premature (before age 80) mortality in 2010 from cancer is only 14% as large as the innovation-induced reduction in premature (before age 80) mortality in 2010 from all diseases. But according to IMS Health data, 2010 expenditure on drugs used to treat cancer registered during 1994-2002 is only about 15% as great as 2010 expenditure on all drugs registered during 1996-2004. Hence the cost per life year gained before age 80 from drugs used to treat cancer registered during 1994-2002 (€5580) is only 7% higher than the cost per life year gained before age 80 from all drugs registered during 1996-2004.

The estimates in Table 4 imply that drugs registered during 1995-2000 reduced hospital discharges in 2010 by about 10.7%. It therefore seems reasonable to assume that drugs registered during the 8-year period 1992-2000 reduced 2010 hospital discharges by 60% more than drugs registered during the 5-year period 1995-2000, i.e. by 17.1% (= (8/5) *10.7%). According to the OECD, total expenditure on in-patient curative and rehabilitative care was €4.25 billion in 2010. I therefore estimate that drugs registered during the period 1992-2000 reduced hospital expenditure in 2010 by about €728 million (= 17.1% * €4.25 billion). As shown in line 5 of Table 5, people below age 70 and 80 account for 68% and 88%, respectively, of hospital expenditure, so drugs registered during the period 1992-2000 are likely to have reduced 2010 hospital expenditure by people below age 70 and 80 by €494 million (= 68% * €728 million) and €641 million (= 88% * €728 million), respectively. Net 2010 medical expenditure, i.e. 2010 expenditure on drugs registered during 1996-2004 minus the reduction in 2010 hospital expenditure due to these drugs, by people below age 70 and 80 is estimated to be €281 million and €359 million, respectively. Net 2010 medical expenditure per life-year gained before age 70 and 80 are €1986 and €1868, respectively.

According to the World Health Organization, a medical intervention should be considered “very cost-effective” if the cost per quality-adjusted life year (QALY) gained from that intervention is below a country’s per capita GDP. In 2010, Portugal’s GDP per capita was €17,018. Even if we don’t account for the reduction in hospital cost resulting from previous pharmaceutical innovation, our estimates of the cost per life-year gained are about one-third of

---

19 See WHO, Threshold values for intervention cost-effectiveness by region, [http://www.who.int/choice/costs/CER_levels/en/](http://www.who.int/choice/costs/CER_levels/en/)


21 Lichtenberg (2009) demonstrated that the number of QALYs gained from pharmaceutical innovation could be either greater than or less than the number of life-years gained.
per capita GDP. When we do account for the hospital cost reduction, our estimates of the cost per life-year gained from previous pharmaceutical innovation are about one-eighth of per capita GDP.

VI. Summary and conclusions

Premature mortality has been declining in Portugal, but there has been considerable variation in the rate of decline across diseases. I analyzed the effect that pharmaceutical innovation had on premature mortality in Portugal during the period 2002-2010, by investigating whether the diseases that experienced more pharmaceutical innovation had larger declines in premature mortality.

My estimates indicated that premature (before age 70 or 80) mortality from a disease is inversely related to the cumulative number of drugs registered 0-10 years earlier. It is most strongly inversely related to the cumulative number of drugs registered 6 years earlier. This is to be expected, since new drugs diffuse gradually. For low innovation diseases—those with few drugs registered during 1996-2004—premature mortality declined by only 1% between 2002 and 2010, but for high innovation diseases, premature mortality declined by 34% between 2002 and 2010. Premature mortality depends on the number of drugs, not the number of chemical subgroups, which suggests that drugs (chemical substances) within the same class (chemical subgroup) are not “therapeutically equivalent.”

Drugs registered during 1995-2000 reduced the hospital discharge rate in 2010 by about 10.7%. For low innovation diseases, the hospital discharge rate increased by 26% between 2005 and 2010, but for high innovation diseases, the hospital discharge rate declined by 5% between 2005 and 2010.

The estimates implied that essentially all of the 25% decline between 2002 and 2010 in premature (before age 70) mortality was due to previous pharmaceutical innovation. Drugs registered during the period 1996-2004 are estimated to have reduced the number of years of potential life lost before ages 70 and 80 in 2010 by 141,300 and 192,028, respectively. Although the drugs registered during 2002-2010 reduced premature mortality in 2010 only 38% as much as the drugs registered during 1996-2004, the cost per life-year gained in 2010 from drugs registered during these two periods was quite similar.
If we do not account for the apparent reduction in hospital expenditure due to previous pharmaceutical innovation, the estimated costs per life-year before ages 70 and 80 gained in 2010 from drugs registered during 1996-2004 are €5483 and €5208, respectively. The cost per life year gained before age 80 from drugs used to treat cancer registered during 1994-2002 is only 7% higher than the cost per life year gained before age 80 from all drugs registered during 1996-2004.

When we account for the apparent reduction in hospital expenditure due to previous pharmaceutical innovation, net 2010 medical expenditure per life-year gained before age 70 and 80 are €1986 and €1868, respectively.

According to the World Health Organization, a medical intervention should be considered “very cost-effective” if the cost per quality-adjusted life year (QALY) gained from that intervention is below a country’s per capita GDP. By this standard, pharmaceutical innovation in Portugal has been extremely cost effective.

References


The number of years of potential life lost before age 70 in Portugal declined by 25% between 2002 and 2010. During that period, the population below age 70 declined by 0.5%.
Figure 2
Years of potential life lost before age 70, 4 diseases: 2002, 2006, and 2010

C16 - Malignant neoplasm of stomach
I30-I51 - Other heart diseases
C50 - Malignant neoplasm of breast
C18-C21 - Malignant neoplasm of colon, rectosigmoid junction, rectum, anus and anal canal
Figure 3
Number of drugs ever registered in Portugal for 7 diseases: 1996, 2000, and 2004

- **B20-B24** - Human immunodeficiency virus [HIV] disease
- **C18-C21** - Malignant neoplasm of colon, rectosigmoid junction, rectum, anus and anal canal
- **C53** - Malignant neoplasm of cervix uteri
- **C00-C14** - Malignant neoplasm of lip, oral cavity, pharynx
- **F01_F03** - Dementia
- **G20** - Parkinson disease
- **K25-K28** - Ulcer of stomach, duodenum and jejunum
Figure 4
Relative utilization

Years since registration
Figure 5
Mean number of retail standard units of molecules sold in 2010, by year of registration

- 1951-1990 (N = 487 molecules): 14,475
- 2001-2010 (N = 72 molecules): 7,343
There are between 13 and 16 diseases in each innovation level group.
Figure 7
Percentage increase in hospital discharges per 100,000 population, 2005-2010:
Actual vs. estimated if no drugs had been registered in Portugal during 1995-2000

Actual 10.7%

Estimated, if no drugs had been registered in Portugal during 1995-2000 20.8%
Figure 8
% change in hospital discharge rate, 2005-2010, by extent of pharmaceutical innovation during 1995-2000

- Low (mean increase in number of drugs = 2.0%)
- Medium (mean increase in number of drugs = 13.2%)
- High (mean increase in number of drugs = 35.9%)
Figure 9

Years of potential life lost before age 70 in Portugal, 2002-2010: actual vs. estimated, if no drugs had been registered during 1996-2004

Drugs registered during the period 1996-2004 reduced the number of years of potential life lost before age 70 in 2010 by 141,300.
Figure 10
Years of potential life lost **before age 80** in Portugal, 2002-2010: actual vs. estimated, if no drugs had been registered during 1996-2004

Drugs registered during the period 1996-2004 reduced the number of years of potential life lost before age 80 in 2010 by 192,028.
Figure 11

Years of potential life lost to cancer before age 80 in Portugal, 2002-2010: actual vs. estimated, if no drugs had been registered during 1994-2002

Drugs registered during the period 1994-2002 reduced the number of years of potential life lost to cancer before age 80 in 2010 by 26,645.
### Table 1

Drugs used for the treatment of two diseases

<table>
<thead>
<tr>
<th>C16 - Malignant neoplasm of stomach</th>
<th>I21_I22 - Acute myocardial infarction including subsequent myocardial infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>H02AB02 Dexamethasone 1959</td>
<td>B01AA03 Warfarin 1962</td>
</tr>
<tr>
<td>H02AB01 Betamethasone 1962</td>
<td>B01AC07 Dipyridamole 1962</td>
</tr>
<tr>
<td>H02AB04 Methylprednisolone 1965</td>
<td>C08DA01 Verapamil 1966</td>
</tr>
<tr>
<td>L01XA01 Cisplatin 1980</td>
<td>A03BA01 Atropine 1967</td>
</tr>
<tr>
<td>L01DB03 Epirubicin 1984</td>
<td>B01AD01 Streptokinase 1967</td>
</tr>
<tr>
<td>L01DC03 Mitomycin 1984</td>
<td>N02BA01 Acetylsalicylic acid 1970</td>
</tr>
<tr>
<td>V03AF03 Calcium folinate 1985</td>
<td>B01AB01 Heparin 1975</td>
</tr>
<tr>
<td>B03XA01 Erythropoietin 1988</td>
<td>C07AB03 Atenolol 1977</td>
</tr>
<tr>
<td>J02AC01 Fluconazole 1988</td>
<td>C07AB02 Metoprolol 1978</td>
</tr>
<tr>
<td>H01CB02 Octreotide 1989</td>
<td>C01CA07 Dobutamine 1980</td>
</tr>
<tr>
<td>L01DB01 Doxorubicin 1991</td>
<td>B01AC06 Acetylsalicylic acid 1981</td>
</tr>
<tr>
<td>B01AB04 Dalteparin 1992</td>
<td>C09AA01 Captorpril 1981</td>
</tr>
<tr>
<td>L01CD02 Docetaxel 1995</td>
<td>C01DA02 Glyceryl trinitrate 1984</td>
</tr>
<tr>
<td>V03AF04 Calcium levofolinate 1996</td>
<td>B01AD03 Anistreplase 1988</td>
</tr>
<tr>
<td>L01XC03 Trastuzumab 2000</td>
<td>C09AA03 Lisinopril 1989</td>
</tr>
<tr>
<td>B03XA02 Darbepoetin alfa 2001</td>
<td>B01AB06 Nadroparin 1990</td>
</tr>
<tr>
<td>L01BC06 Capecitabine 2001</td>
<td>B01AD02 Alteplase 1990</td>
</tr>
<tr>
<td>M05BA08 Zoledronic acid 2001</td>
<td>C09AA04 Perindopril 1990</td>
</tr>
<tr>
<td></td>
<td>B01AB05 Enoxaparin 1991</td>
</tr>
<tr>
<td></td>
<td>C09AA05 Ramipril 1991</td>
</tr>
<tr>
<td></td>
<td>C10AA03 Pravastatin 1991</td>
</tr>
<tr>
<td></td>
<td>B01AB04 Dalteparin 1992</td>
</tr>
<tr>
<td></td>
<td>C01BB01 Lidocaine 1992</td>
</tr>
<tr>
<td></td>
<td>B01AC13 Abciximab 1996</td>
</tr>
<tr>
<td></td>
<td>B01AD07 Reteplase 1996</td>
</tr>
<tr>
<td></td>
<td>C10AA04 Fluvastatin 1996</td>
</tr>
<tr>
<td></td>
<td>B01AC04 Clopidogrel 1998</td>
</tr>
<tr>
<td></td>
<td>B01AC16 Eptifibatide 1999</td>
</tr>
<tr>
<td></td>
<td>B01AC17 Tirofiban 1999</td>
</tr>
<tr>
<td></td>
<td>B01AC30 Combinations 1999</td>
</tr>
<tr>
<td></td>
<td>C09AA15 Zofenopril 1999</td>
</tr>
<tr>
<td></td>
<td>B01AD11 Tenecteplase 2001</td>
</tr>
<tr>
<td></td>
<td>B01AX05 Fondaparinux 2002</td>
</tr>
<tr>
<td></td>
<td>C10AA07 Rosuvastatin 2003</td>
</tr>
<tr>
<td></td>
<td>B01AE06 Bivalirudin 2004</td>
</tr>
<tr>
<td></td>
<td>C03DA04 Eplerenone 2004</td>
</tr>
<tr>
<td></td>
<td>C10BX02 Pravastatin and acetylsalicylic acid 2005</td>
</tr>
<tr>
<td></td>
<td>B01AC22 Prasugrel 2009</td>
</tr>
</tbody>
</table>
### Table 2
Estimates of $\beta_k$ parameters from premature mortality model (eq. (1))

<table>
<thead>
<tr>
<th>Col.</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
</tr>
</thead>
<tbody>
<tr>
<td>Line</td>
<td>Parameter</td>
<td>Estimate</td>
<td>Std. Error</td>
<td>Z</td>
<td>Pr &gt;</td>
<td>( \text{mean}(\Delta \text{CUM}_NCE_k) )</td>
<td>( \frac{\beta_k}{\text{mean}(\Delta \text{CUM}_NCE_k)} )</td>
</tr>
<tr>
<td>1</td>
<td>$\beta_0$</td>
<td>-0.027</td>
<td>0.008</td>
<td><strong>-3.21</strong></td>
<td>0.001</td>
<td>3.43</td>
<td>-0.09</td>
</tr>
<tr>
<td>2</td>
<td>$\beta_2$</td>
<td>-0.030</td>
<td>0.008</td>
<td><strong>-3.54</strong></td>
<td>0.000</td>
<td>5.20</td>
<td>-0.15</td>
</tr>
<tr>
<td>3</td>
<td>$\beta_4$</td>
<td>-0.028</td>
<td>0.012</td>
<td><strong>-2.28</strong></td>
<td>0.023</td>
<td>5.77</td>
<td>-0.16</td>
</tr>
<tr>
<td>4</td>
<td>$\beta_6$</td>
<td>-0.039</td>
<td>0.009</td>
<td><strong>-4.35</strong></td>
<td>&lt;0.001</td>
<td>6.18</td>
<td>-0.24</td>
</tr>
<tr>
<td>5</td>
<td>$\beta_8$</td>
<td>-0.029</td>
<td>0.008</td>
<td><strong>-3.69</strong></td>
<td>0.000</td>
<td>7.45</td>
<td>-0.22</td>
</tr>
<tr>
<td>6</td>
<td>$\beta_{10}$</td>
<td>-0.026</td>
<td>0.008</td>
<td><strong>-3.44</strong></td>
<td>0.001</td>
<td>5.89</td>
<td>-0.15</td>
</tr>
<tr>
<td>7</td>
<td>$\beta_0$</td>
<td>-0.019</td>
<td>0.009</td>
<td><strong>-2.08</strong></td>
<td>0.038</td>
<td>3.43</td>
<td>-0.06</td>
</tr>
<tr>
<td>8</td>
<td>$\beta_2$</td>
<td>-0.021</td>
<td>0.010</td>
<td><strong>-2.13</strong></td>
<td>0.033</td>
<td>5.20</td>
<td>-0.11</td>
</tr>
<tr>
<td>9</td>
<td>$\beta_4$</td>
<td>-0.018</td>
<td>0.013</td>
<td><strong>-1.33</strong></td>
<td>0.185</td>
<td>5.77</td>
<td>-0.10</td>
</tr>
<tr>
<td>10</td>
<td>$\beta_6$</td>
<td>-0.029</td>
<td>0.010</td>
<td><strong>-2.78</strong></td>
<td>0.006</td>
<td>6.18</td>
<td>-0.18</td>
</tr>
<tr>
<td>11</td>
<td>$\beta_8$</td>
<td>-0.021</td>
<td>0.008</td>
<td><strong>-2.51</strong></td>
<td>0.012</td>
<td>7.45</td>
<td>-0.16</td>
</tr>
<tr>
<td>12</td>
<td>$\beta_{10}$</td>
<td>-0.020</td>
<td>0.007</td>
<td><strong>-2.83</strong></td>
<td>0.005</td>
<td>5.89</td>
<td>-0.12</td>
</tr>
<tr>
<td>13</td>
<td>$\beta_0$</td>
<td>-0.005</td>
<td>0.004</td>
<td><strong>-1.24</strong></td>
<td>0.215</td>
<td>2.00</td>
<td>-0.01</td>
</tr>
<tr>
<td>14</td>
<td>$\beta_2$</td>
<td>-0.006</td>
<td>0.004</td>
<td><strong>-1.65</strong></td>
<td>0.100</td>
<td>4.05</td>
<td>-0.02</td>
</tr>
<tr>
<td>15</td>
<td>$\beta_4$</td>
<td>-0.006</td>
<td>0.003</td>
<td><strong>-2.12</strong></td>
<td>0.034</td>
<td>3.95</td>
<td>-0.02</td>
</tr>
<tr>
<td>16</td>
<td>$\beta_6$</td>
<td>-0.011</td>
<td>0.005</td>
<td><strong>-2.18</strong></td>
<td>0.029</td>
<td>3.52</td>
<td>-0.04</td>
</tr>
<tr>
<td>17</td>
<td>$\beta_8$</td>
<td>-0.012</td>
<td>0.004</td>
<td><strong>-3.26</strong></td>
<td>0.001</td>
<td>5.24</td>
<td>-0.06</td>
</tr>
<tr>
<td>18</td>
<td>$\beta_{10}$</td>
<td>-0.007</td>
<td>0.005</td>
<td><strong>-1.32</strong></td>
<td>0.185</td>
<td>2.95</td>
<td>-0.02</td>
</tr>
<tr>
<td>19</td>
<td>$\beta_0$</td>
<td>-0.005</td>
<td>0.004</td>
<td><strong>-1.10</strong></td>
<td>0.269</td>
<td>2.00</td>
<td>-0.01</td>
</tr>
<tr>
<td>20</td>
<td>$\beta_2$</td>
<td>-0.006</td>
<td>0.004</td>
<td><strong>-1.63</strong></td>
<td>0.104</td>
<td>4.05</td>
<td>-0.02</td>
</tr>
<tr>
<td>21</td>
<td>$\beta_4$</td>
<td>-0.007</td>
<td>0.003</td>
<td><strong>-2.37</strong></td>
<td>0.018</td>
<td>3.95</td>
<td>-0.03</td>
</tr>
<tr>
<td>22</td>
<td>$\beta_6$</td>
<td>-0.011</td>
<td>0.003</td>
<td><strong>-3.34</strong></td>
<td>0.001</td>
<td>3.52</td>
<td>-0.04</td>
</tr>
<tr>
<td>23</td>
<td>$\beta_8$</td>
<td>-0.012</td>
<td>0.003</td>
<td><strong>-3.86</strong></td>
<td>0.000</td>
<td>5.24</td>
<td>-0.06</td>
</tr>
<tr>
<td>24</td>
<td>$\beta_{10}$</td>
<td>-0.008</td>
<td>0.006</td>
<td><strong>-1.46</strong></td>
<td>0.145</td>
<td>2.95</td>
<td>-0.02</td>
</tr>
</tbody>
</table>

Each estimate is from a separate model. All models include fixed disease effects and fixed year effects. Models were estimated by weighted least-squares, weighting by the mean premature mortality rate during 2002-2010. The standard errors are clustered within diseases.
### Table 3

Estimates of the effects of $\text{CUM\_NCE}_{i,t-6}$ and/or $\text{CUM\_SUBGROUP}_{i,t-6}$ on premature (before age 70) mortality.

<table>
<thead>
<tr>
<th>Column</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{CUM_NCE}_{i,t-6}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimate</td>
<td>-0.039</td>
<td>-0.046</td>
<td></td>
</tr>
<tr>
<td>Standard Error</td>
<td>0.009</td>
<td>0.010</td>
<td></td>
</tr>
<tr>
<td>$Z$</td>
<td>-4.35</td>
<td>-4.49</td>
<td></td>
</tr>
<tr>
<td>Pr &gt; $</td>
<td>Z</td>
<td>$</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>$\text{CUM_SUBGROUP}_{i,t-6}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimate</td>
<td>-0.034</td>
<td>0.027</td>
<td></td>
</tr>
<tr>
<td>Standard Error</td>
<td>0.021</td>
<td>0.024</td>
<td></td>
</tr>
<tr>
<td>$Z$</td>
<td>-1.68</td>
<td>1.15</td>
<td></td>
</tr>
<tr>
<td>Pr &gt; $</td>
<td>Z</td>
<td>$</td>
<td>0.093</td>
</tr>
</tbody>
</table>
### Table 4

Estimates of $\beta_k$ parameters from hospital discharges model (eq. (3))

| Line | k  | Parameter | Estimate | Std. Err. | Z  | Pr > | Z  | | mean(Δln(CUM_ NCEi)) | mean(Δln(CUM_ NCEi)) |
|------|----|-----------|----------|-----------|-----|-------|-----|----------------|---------------------|
| 1    | 0  | $\beta_0$ | -0.480   | 0.614     | -0.78| 0.434 | -0.697 | 0.728 | -0.96 | 0.339 | 0.049 | -0.034 |
| 2    | 2  | $\beta_2$ | -0.333   | 0.423     | -0.79| 0.431 | -0.523 | 0.516 | -1.01 | 0.311 | 0.058 | -0.030 |
| 3    | 4  | $\beta_4$ | -0.343   | 0.242     | -1.42| 0.157 | -0.377 | 0.260 | -1.45 | 0.148 | 0.084 | -0.031 |
| 4    | 6  | $\beta_6$ | -0.257   | 0.194     | -1.32| 0.186 | -0.891 | 0.441 | -2.02 | 0.043 | 0.100 | -0.089 |
| 5    | 8  | $\beta_8$ | -0.331   | 0.242     | -1.37| 0.172 | -0.885 | 0.373 | -2.38 | 0.018 | 0.128 | -0.113 |
| 6    | 10 | $\beta_{10}$ | -0.569  | 0.257     | -2.22| 0.027 | -0.628 | 0.255 | -2.46 | 0.014 | 0.170 | -0.107 |
| 7    | 12 | $\beta_{12}$ | -0.438  | 0.248     | -1.76| 0.078 | -0.601 | 0.304 | -1.97 | 0.048 | 0.146 | -0.088 |
| 8    | 14 | $\beta_{14}$ | -0.290  | 0.258     | -1.13| 0.260 | -0.331 | 0.261 | -1.27 | 0.204 | 0.167 | -0.055 |
Table 5

Calculation of cost per life year gained in 2010 from drugs for all diseases registered during 1996-2004

<table>
<thead>
<tr>
<th>Age group</th>
<th>Below age 70</th>
<th>Below age 80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated % of 2010 expenditure on drugs registered during 1996-2004</td>
<td>69%</td>
<td>89%</td>
</tr>
<tr>
<td>Estimated 2010 expenditure on drugs registered during 1996-2004</td>
<td>€ 774,679,568</td>
<td>€ 1,000,048,688</td>
</tr>
<tr>
<td>Estimated life-years gained</td>
<td>141,300</td>
<td>192,028</td>
</tr>
</tbody>
</table>

**Without allowance for hospital cost offset**

| Cost (pharmaceutical expenditure) per life-year gained | € 5,483 | € 5,208 |

**With allowance for hospital cost offset**

| Estimated % of 2010 expenditure on hospitals | 68%      | 88%      |
| Estimated reduction in 2010 expenditure on hospitals | € 494,048,894 | € 641,323,356 |
| Drug expenditure net of hospital cost reduction | € 280,630,674 | € 358,725,332 |
| Cost (net medical expenditure) per life-year gained | € 1,986  | € 1,868  |