Int. J. of the Economics of Business, 2015
Vol. 22, No. 2, 277–299, http://dx.doi.org/10.1080/13571516.2015.1045743

Pharmaceutical Innovation, Longevity, and Medical Expenditure in Greece, 1995–2010

FRANK R. LICHTENBERG

ABSTRACT *Longitudinal, disease-level data are used to analyze the impact of pharmaceutical innovation on longevity (mean age at death), hospital utilization, and medical expenditure in Greece during the period 1995–2010. The estimates indicate that pharmaceutical innovation increased mean age at death by 0.87 years (10.4 months) – about 44% of the total increase in longevity – and that diseases with larger increases in the cumulative number of drugs launched one to four years earlier had smaller increases in the number of hospital days. Real per capita pharmaceutical expenditure increased rapidly during this period, but 62% of the increase in pharmaceutical expenditure was offset by a reduction in hospital expenditure attributable to pharmaceutical innovation. The baseline estimate of the cost per life-year gained from pharmaceutical innovation in Greece is $17,117, which is a very small fraction of leading economists' estimates of the value of (or consumers' willingness to pay for) a one-year increase in life expectancy.*

Key Words: Pharmaceutical; Innovation; Longevity; Greece; Hospital.

JEL classifications: I12, J11, L65, O33, O52.

1. Introduction

Longevity increase is increasingly recognized by economists to be an important part of economic growth and development (Murphy and Topel, 2006; Nordhaus, 2003). Economists have also come to recognize that, in the long run, the rate of economic "growth … is driven by technological change that arises from intentional [research and development (R&D)] investment decisions made by profit-maximizing agents" (Romer, 1990) and by public organizations such as the National Institutes of Health. In principle, technological change could be either disembodied or embodied in new goods. Solow (1960) hypothesized that most technological change is embodied: to benefit from

This work was supported by MSD Greece. 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.

Frank R. Lichtenberg, Graduate School of Business, Columbia University, 504 Uris Hall, 3022 Broadway, New York, NY 10027, USA; e-mail: frl1@columbia.edu.

technological progress, one must use newer, or later vintage, goods and services. Bresnahan and Gordon (1996) argued that "new goods are at the heart of economic progress." Grossman and Helpman (1991) argued that "almost every product exists on a *quality ladder*, with variants below that may already have become obsolete and others above that have yet to be discovered," and that "each new product enjoys a limited run at the technological frontier, only to fade when still better products come along." Hercowitz (1998, 223) also reached the "conclusion … that 'embodiment' is the main transmission mechanism of technological progress to economic growth."

This article will analyze the impact of pharmaceutical innovation (i.e., the utilization of new drugs) on longevity and medical expenditure in Greece during the period 1995–2010. The medical substances and devices industries are the most research-intensive industries in the economy (National Science Foundation, 2013). Pharmaceuticals are also more research intensive than other types of medical care: in 2007, prescription drugs accounted for 10% of US health expenditure (Center for Medicare and Medicaid Services 2013; Table 2), but more than half of US funding for biomedical research came from pharmaceutical and biotechnology firms (Dorsey et al. 2010). Moreover, new drugs often build on upstream government research (Sampat and Lichtenberg, 2011).

The overall impact of pharmaceutical innovation on longevity and health can be assessed in a variety of ways.[1] Each approach has advantages and disadvantages. One approach is to survey a large number of case studies of specific drugs or classes of drugs. Two problems with this approach are (1) the specific drugs examined may not constitute a representative sample, and (2) different methods and metrics are used in each study, making it difficult to draw general conclusions.

A second approach is to conduct econometric studies of drugs in general. Several types of econometric studies of drugs in general can be performed. One can perform studies using patient-level data to investigate the following question: do patients using newer drugs live longer than patients using older drugs, controlling for their demographic characteristics (age, sex, race, income, education, etc.), medical conditions, behavioral risk factors, and other variables?[2] Alternatively, one can perform studies using aggregate data, preferably longitudinal (panel) data.[3] There are two main types of studies based on aggregate panel data. One can analyze longitudinal *region*-level data to investigate the following question: has life expectancy increased more rapidly in regions (e.g., states or countries) experiencing more pharmaceutical innovation, controlling for changes in income, education, and other variables?[4]

One can also analyze longitudinal *disease*-level data to determine whether life expectancy has increased more rapidly for people with diseases experiencing more pharmaceutical innovation. A potential advantage of this approach is that variation across diseases in the pace of pharmaceutical innovation may be "more exogenous" (e.g., due to heterogeneous scientific opportunity) than variation across individuals or regions. This approach has been applied to US data (Lichtenberg, 2007, 2009).

Several recent studies have shown that prescription drug cost-sharing, which affects the *quantity* of pharmaceutical consumption, has a "spillover effect" on hospital utilization. One study (Chandra, Gruber, and McKnight, 2010) found a "rather modest offsetting rise in hospital care when physician and prescription drug copayments are raised, but … substantial offsets for the

sickest populations with chronic diseases" (p. 211). Another study (Karaca-Mandic et al. 2012) found that "greater cost sharing for asthma medications was associated with a slight reduction in medication use and higher rates of asthma hospitalization among children aged 5 years or older" (p. 1284). Pharmaceutical innovation may have a spillover effect on hospital utilization, because it tends to increase the *quality* (and perhaps also the quantity) of pharmaceutical consumption. Even though pharmaceutical innovation is very likely to increase pharmaceutical expenditure, if it reduces hospital expenditure, it may not increase (and could even reduce) total medical expenditure.[5]

For this study, longitudinal, disease-level data were obtained from several rich databases (Thériaque, the WHO Mortality Database, Greek Statistical Authority, and the IMS Health MIDAS database) to examine the impact of pharmaceutical innovation on longevity, hospital utilization, and medical expenditure in Greece during the period 1995–2010.[6] By combining the estimates of the effect of pharmaceutical innovation on longevity and medical expenditure, the incremental cost-effectiveness (cost per life-year gained) of pharmaceutical innovation in Greece during the period 1995–2010 can be estimated.

In the next section, equations to estimate the impact of pharmaceutical innovation on longevity and hospital utilization will be presented. Data sources are described and descriptive statistics are presented in Section 3. Estimates of econometric models are presented in Section 4. The cost-effectiveness of pharmaceutical innovation in Greece is assessed in Section 5. The final section contains a summary and conclusions.

2. Econometric Models for Estimating the Impact of Pharmaceutical Innovation on Longevity and Hospital Utilization

2.1. Longevity 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 longevity model that will be estimated below may be considered a health production function, in which longevity (age at death) is an indicator of health output or outcomes, and the cumulative number of drugs approved is analogous to the stock of ideas. The model will be of the following form:

$$\text{AGE\_DEATH}_{it} = \beta_k \text{N\_CHEM\_SUBSTANCES}_{i,t-k} + \alpha_i + \delta_t + \varepsilon_{it} \quad (1)$$

where

AGE_DEATH_{it}	=mean age at death from disease i in year t (t = 1995,…,2010)
$\text{N\_CHEM\_SUBSTANCES}_{i,t-k}$	$=\sum_d \text{IND}_{di}\ \text{APP}_{d,t-k}$ = the number of chemical substances (drugs) to treat disease i commercialized by the end of year t–k
IND_{di}	=1 if drug d is used to treat (indicated for) disease i =0 if drug d is not used to treat (indicated for) disease i
$\text{APP}_{d,t-k}$	=1 if drug d was commercialized by the end of year t–k =0 if drug d was not commercialized by the end of year t–k
α_i	= a fixed effect for disease i
δ_t	= a fixed effect for year t.

Inclusion of year and disease fixed effects controls for the overall increase in Greek longevity and for stable between-disease differences in longevity. A positive and significant estimate of β_k in equation (1) would signify that diseases for which there was more pharmaceutical innovation had larger increases in longevity. Equation (1) will be estimated by weighted least squares, weighting by the number of deaths caused by disease i in year t. Standard errors will be clustered within diseases.

If this model is correctly specified, it will enable determination of how much of the increase in mean age at death during the sample period (1995–2010) can be attributed to the introduction of new drugs. The expression (δ_{2010}–δ_{1995}) indicates the 1995–2010 increase in longevity, controlling for (holding constant) the number of drugs, that is, in the absence of pharmaceutical innovation. Suppose equation (1) is estimated, excluding $\text{N\_CHEM\_SUBSTANCES}_{i,t-k}$, and that the year fixed effects from that equation are denoted by δ'_t. Then (δ'_{2010}–δ'_{1995}) indicates the 1995–2010 increase in longevity, not holding constant the number of drugs, that is, in the presence of pharmaceutical innovation, and (δ'_{2010}–δ'_{1995})–(δ_{2010}–δ_{1995}) is an estimate of the 1995–2010 increase in longevity attributable to pharmaceutical innovation.

Life expectancy at birth is probably the most commonly cited measure of longevity, but the measure of life expectancy to be analyzed is mean age at death.[7] The main reason is that life expectancy at birth (or at higher ages) cannot be measured for specific diseases. A more minor "disadvantage" of this indicator is that it is "hypothetical," rather than "actual": it is based on the period life table, which describes what *would* happen to a hypothetical (or synthetic) cohort if it experienced throughout its entire life the mortality conditions of a particular time period (Arias, 2010).

Mean age at death and life expectancy at birth (LE_BIRTH) are both probability-weighted averages of age at death:

$$\text{AGE\_DEATH} = \sum\nolimits_a p_{1a} a$$

$$\text{LE\_BIRTH} = \sum\nolimits_a P_{2a} a$$

where a denotes age at death, and p_{1a} and p_{2a} are probabilities of dying at age a. In the case of AGE_DEATH, the probabilities depend only on the number of deaths at each age: $p_{1a} = \text{N\_DEATHS}_a / \sum_a \text{N\_DEATHS}_a$. In the case of LE_BIRTH, the probabilities depend on the population at each age (POP_a) as well as the number of deaths: $p_{2a} = d_{a-1}$ [$(1-d_0)$ $(1-d_1)$ … $(1-d_{a-2})$], where $d_a = \text{N\_DEATHS}_a / \text{POP}_a$. Since the AGE_DEATH calculation is based only on people who have died, whereas the LE_BIRTH calculation is based on the entire population, AGE_DEATH might be considered a censored measure. Although LE_BIRTH cannot be measured by disease, both measures (and the correlation between them) can be calculated by country and year. Both measures were calculated for 39 European countries during the period 1960–2010. Lichtenberg (2014) showed that there is a very strong positive correlation across countries between LE_BIRTH in 2010 and AGE_DEATH in 2010. The weighted (by total number of deaths) least-squares coefficient from the regression of LE_BIRTH on AGE_DEATH is 1.21 (t-value = 16.6, $R^2 = 0.88$).

There is also a strong positive correlation across countries between the *growth rates* of AGE_DEATH and LE_BIRTH.[8]

The measure of pharmaceutical innovation in equation (1) – the number of chemical substances previously commercialized to treat a disease – is not the theoretically ideal measure. Longevity 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 a disease, defined as $\text{VINTAGE}_{it} = \sum_d Q_{dit}\ \text{LAUNCH\_YEAR}_d / \sum_d Q_{dit}$, 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.[9] Unfortunately, measurement of VINTAGE_{it} is infeasible: although data on the total quantity of each drug in each year ($Q_{d.t} = \Sigma_i\ Q_{dit}$) 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.[10] However, Lichtenberg (2014) 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 contribute to longevity growth. Other medical innovation, such as innovation in diagnostic imaging, surgical procedures, and medical devices, is also likely to affect longevity growth. Therefore, measures of these other types of medical innovation should be included in the longevity model (equation (1)).[11] Unfortunately, longitudinal disease-level measures of nonpharmaceutical medical innovation are not available for Greece. However, longitudinal disease-level measures of nonpharmaceutical and pharmaceutical medical innovation are available for the USA during the period 1997–2007. Lichtenberg (2014) showed that, in the USA, the rate of pharmaceutical innovation is not positively correlated with the rate of medical procedure innovation and may be *negatively* correlated with the rate of diagnostic imaging 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 equation (1), mean age at death from disease i in year t depends on the number of chemical substances (drugs) to treat disease i commercialized by the end of year $t–k$; that is, there is a lag of k years. One would expect there to be a substantial lag because (1) new drugs diffuse gradually – they will not be used widely until years after commercialization, and (2) drugs for chronic conditions (which account for most drug use) may have to be consumed for several years for their full health benefits to be realized. Equation (1) will be estimated for different values of k: $k = 1\ldots,10$.[12] The mean lag between the stock of drugs commercialized for a disease and mean age at death from the disease can be computed as follows, including only the values of k for which β_k is statistically significant: $\text{LAG\_MEAN} = \sum_k \beta_k\, k / \sum_k \beta_k$.

The measure of pharmaceutical innovation, $\text{N\_CHEM\_SUBSTANCES}_{i,t-k} = \sum_d \text{IND}_{di}\ \text{APP}_{d,t-k}$, 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 $t – k$.[13]

2.1. Hospital Utilization Model

To assess the impact of pharmaceutical innovation on hospital utilization, models of the following form will be estimated:

$$\ln(\text{DAYS}_{it}) = \beta_k \ln\left(\text{N\_CHEM\_SUBSTANCES}_{i,t-k}\right) + \alpha_i + \delta_t + \varepsilon_{it} \quad (2)$$

where DAYS_{it} = the number of hospital days for disease i in year t ($t = 2000, \ldots, 2008$). Equation (2) will be estimated by weighted least squares, weighting by $\Sigma_t \text{DAYS}_{it}$. Standard errors will be clustered within diseases.

3. Data Sources and Descriptive Statistics

3.1. Data sources

Calculation of the number of chemical substances (drugs) to treat disease i commercialized by the end of year $t - k$ requires data on drug launch dates and drug indications: $\text{N\_CHEM\_SUBSTANCES}_{i,t-k} = \sum_d \text{IND}_{di}\ \text{APP}_{d,t-k}$. Data on the dates at which drugs were first launched in Greece were obtained from the IMS LifeCycle New Product Focus database.[14] Data on drug indications were obtained from Thériaque (http://www.theriaque.org/) a database of official, regulatory, and bibliographic information on all drugs available in France, intended for health professionals, and funded by the Centre National Hospitalier d'Information sur le Médicament. Thériaque contains data on labeled indications but not off-label indications. According to the FDB MedKnowledge Indications Module, which provides a list of FDA-approved and off-label indications for a given drug, about one in four indications is off-label.

The data necessary to construct mean age at death and the number of deaths, by disease and year, were obtained from the WHO Mortality Database (http://www.who.int/healthinfo/morttables/en/), which covers deaths registered in national civil registration systems, with underlying cause of death as coded by the relevant national authority. Underlying cause of death is

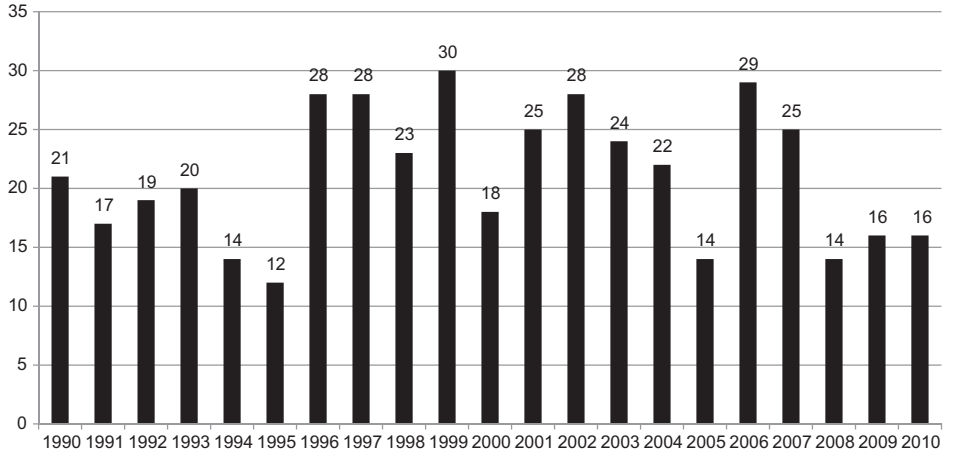


Figure 1. Number of new chemical entities launched in Greece, 1990–2010.

Table 1. Drugs used to treat two types of cancer, listed in order of Greek launch year

Drug	World launch year	Greek launch year
C15–C26 Malignant neoplasm of digestive organs and peritoneum		
L01DB03 Epirubicin	1984	1985
H01CB02 Octreotide	1988	1990
J02AC01 Fluconazole	1988	1991
L01CD02 Docetaxel	1995	1996
L01BC05 Gemcitabine	1995	1997
L01XX19 Irinotecan	1994	1998
L01BC06 Capecitabine	1998	1999
L01XC03 Trastuzumab	1998	2000
B03XA02 Darbepoetin alfa	2001	2001
M05BA08 Zoledronic acid	2000	2001
L01XA03 Oxaliplatin	1996	2005
L01XC07 Bevacizumab	2004	2005
L01XC06 Cetuximab	2003	2006
L01XE03 Erlotinib	2004	2006
L01XE04 Sunitinib	2006	2006
L01XE05 Sorafenib	2005	2006
C40–C50 Malignant neoplasm of bone, connective tissue, skin, and breast		
L01DB03 Epirubicin	1984	1985
L01DB07 Mitoxantrone	1984	1987
L03AB05 Interferon alfa-2b	1985	1988
L02AE02 Leuprorelin	1984	1990
L03AB04 Interferon alfa-2a	1986	1990
J02AC01 Fluconazole	1988	1991
L02AE03 Goserelin	1987	1991
L01CD01 Paclitaxel	1992	1994
L02BG02 Formestane	1993	1995
L01CD02 Docetaxel	1995	1996
L01BC05 Gemcitabine	1995	1997
L01CA04 Vinorelbine	1989	1997
L02BA02 Toremifene	1989	1997
L02BG03 Anastrozole	1995	1998
L02BG04 Letrozole	1996	1998
L01BC06 Capecitabine	1998	1999
L01AD05 Fotemustine	1989	2000
L01XC03 Trastuzumab	1998	2000
M05BA06 Ibandronic acid	1996	2000
B03XA02 Darbepoetin alfa	2001	2001
D06BB10 Imiquimod	1997	2001
L02BG06 Exemestane	1999	2001
M05BA08 Zoledronic acid	2000	2001
L01XE01 Imatinib	2001	2002
L01BA04 Pemetrexed	2004	2004
L01XX22 Alitretinoin	1999	2004
L02BA03 Fulvestrant	2002	2004
L01XC07 Bevacizumab	2004	2005
L01XC06 Cetuximab	2003	2006
L01XE07 Lapatinib	2007	2008

defined as "the disease or injury which initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury" in accordance with the rules of the

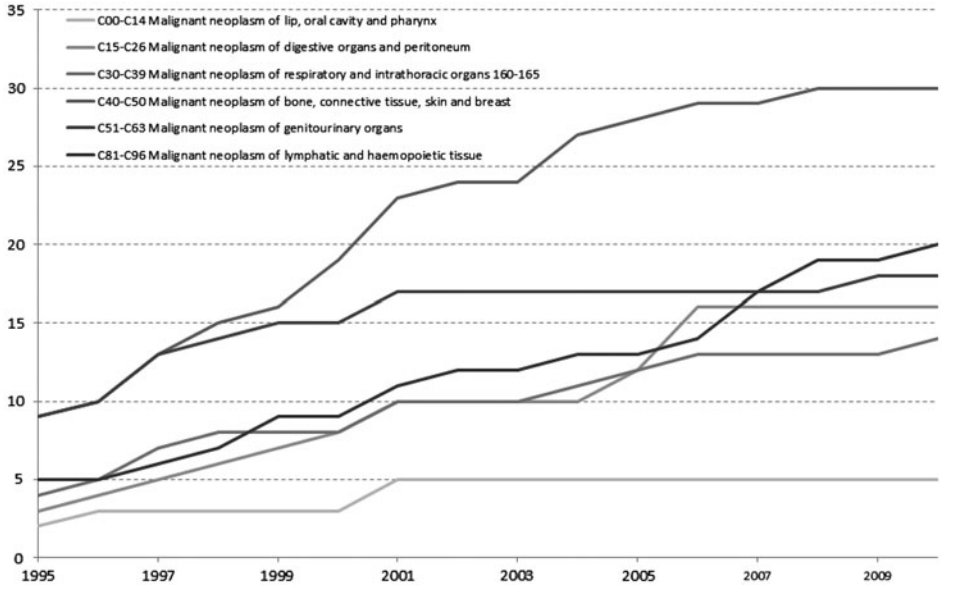


Figure 2. Cumulative number of post-1982 new chemical entities that had ever been launched in Greece, six types of cancer, 1995–2010.

International Classification of Diseases.[15] Data on the number of hospital days, by disease and year, were obtained from the Greek Statistical Authority.

3.2. Descriptive Statistics

Figure 1 shows the number of new chemical entities (NCEs) launched in Greece in each year during the period 1990–2010. The average annual number of NCEs launched was 21. The number ranged from 12 in 1995 to 30 in 1999.

To illustrate the nature of the disease-specific data on pharmaceutical innovation, Table 1 shows the post-1982 drugs used to treat two types of cancer, listed in order of Greek launch year.

There were 16 drugs used to treat malignant neoplasms of digestive organs and peritoneum (ICD-10 codes C15–C26), and 30 drugs used to treat malignant neoplasms of bone, connective tissue, skin, and breast (C40–C50).

Figure 2 illustrates the heterogeneity of diseases with respect to their rates of pharmaceutical innovation. It shows the cumulative number of post-1982 new chemical entities that had previously been launched in Greece to treat six types of cancer during the period 1995–2010. In 1995, there were nine drugs for malignant neoplasms of genitourinary organs (C51–C63), and nine drugs for malignant neoplasms of bone, connective tissue, skin, and breast (C40–C50). The number of drugs for the second disease increased by 21, more than twice as much as the number of drugs for the first disease (by nine).

Table 2 shows data on ten of the leading causes of death in Greece: the number of deaths and mean age at death in 1995 and 2010, and the cumulative number of drugs launched three years earlier. Table 3 shows 2008 hospital statistics, by broad disease category.

Table 2. Data on ten of the leading causes of death in Greece

	Number of deaths		Mean age at death		Cumulative NCEs	
Year	1995	2010	1995	2010	1992	2007
Cause of death						
I60–I69 Cerebrovascular disease	19,024	14,910	80.5	82.0	2	6
I26–I52 Diseases of pulmonary circulation and other forms of heart disease	17,344	18,936	81.4	83.1	10	28
I20–I25 Ischemic heart disease	12,686	11,332	73.5	74.0	8	21
C15–C26 Malignant neoplasm of digestive organs and peritoneum	6,473	7,564	72.5	74.8	3	16
C30–C39 Malignant neoplasm of respiratory and intrathoracic organs 160–165	5,556	6,799	68.5	71.0	3	13
J20–J22, J40–J99 Other diseases of the respiratory system	4,762	7,053	78.6	80.4	11	23
C51–C63 Malignant neoplasm of genitourinary organs	3,271	4,346	73.9	76.3	8	17
K20–K93 Diseases of other parts of the digestive system	2,538	2,576	73.8	74.6	7	23
C40–C50 Malignant neoplasm of bone, connective tissue, skin, and breast	2,118	2,731	67.2	71.2	7	29
C81–C96 Malignant neoplasm of lymphatic and hemopoietic tissue	1,658	1,946	67.9	72.8	5	17

Table 3. 2008 hospital statistics

Categories of diseases	Total patients discharged	Average number of days of treatment per patient	Total number of days of treatment
1. Infectious and parasitic diseases	58,118	5	290,590
2. Neoplasms	244,365	7	1,710,555
3. Endocrine and metabolic diseases, nutritional deficiencies, immunity disorders	48,547	5	242,735
4. Diseases of blood and blood-forming organs	35,087	6	210,522
5. Mental disorders	39,840	76	3,027,840
6. Diseases of the nervous system and sense organs	214,319	3	642,957
7. Diseases of the circulatory system	308,033	6	1,848,198
8. Diseases of the respiratory system	163,786	5	818,930
9. Diseases of the digestive system	223,864	5	1,119,320
10. Diseases of genito-urinary system	173,658	5	868,290
11. Complications of pregnancy, childbirth and the puerperium	165,055	4	660,220
12. Diseases of skin and subcutaneous tissue	43,226	4	172,904
13. Diseases of the musculoskeletal system and connective tissue	97,115	6	582,690
14. Congenital anomalies	13,504	7	94,528
15. Certain conditions originating in the perinatal period	30,276	9	272,484
16. Symptoms, signs and ill-defined conditions	190,522	4	762,088
17. Injury and poisoning	171,810	6	1,030,860
Grand total	*2,221,125*	*7*	*15,547,875*

4. Empirical Results

4.1. Longevity Equation Estimates

Estimates of parameters from longevity (mean age at death) models are presented in Table 4.[16] All models were estimated by weighted least squares, weighting by N_DEATHS_{it}, the number of deaths from disease i in year t. This is appropriate because, due to the inclusion of fixed disease effects, we are in essence analyzing within-disease *changes* in age at death and the variance of these changes is much larger for diseases causing few deaths than it is for diseases causing many deaths.

Table 4 shows estimates of β_k ($k = 1,\ldots,10$) from equation (1). Each estimate is from a separate model.[17] The estimates of β_k are positive and significant for $1 \le k \le 7$. This indicates that an increase in the number of chemical substances for a disease has a positive effect on mean age at death from the disease one to seven years later.

As noted earlier, our estimates enable us to determine how much of the increase in mean age at death during the sample period (1995–2010) can be attributed to the introduction of new drugs. As shown in Figure 3, between 1995 and 2010, mean age at death increased by 2.0 years, from 74.7 to 76.7. Estimates of equation (1) where $k = 3$ imply that, in the absence of

Table 4. Weighted least-squares estimates of β_k from the model $AGE\_DEATH_{it} = \beta_k\ N\_CHEM\_SUBSTANCES_{i,t-k} + \alpha_i + \delta_t + \varepsilon_{it}$ each estimate is from a separate model weight = $\Sigma_t\ N\_DEATHS_{it}$ disturbances are clustered within diseases

Parameter	Estimate	Empirical standard error estimates	95% Lower confidence limit	95% Upper confidence limit	Z	Pr > | Z |
β_1	0.0600	0.0273	0.0066	0.1135	2.20	0.0278
β_2	0.0630	0.0265	0.0112	0.1149	2.38	0.0172
β_3	0.0669	0.0246	0.0188	0.1151	2.72	0.0065
β_4	0.0704	0.0264	0.0187	0.1222	2.67	0.0077
β_5	0.0722	0.0274	0.0186	0.1259	2.64	0.0084
β_6	0.0716	0.0279	0.0169	0.1263	2.57	0.0103
β_7	0.0634	0.0292	0.0061	0.1206	2.17	0.0302
β_8	0.0508	0.0295	−0.007	0.1085	1.72	0.0848
β_9	0.0401	0.0324	−0.0233	0.1036	1.24	0.2152
β_{10}	0.0343	0.0336	−0.0316	0.1002	1.02	0.3077

AGE_DEATH_{it} = mean age at death from disease i in year t.
$N\_CHEM\_SUBSTANCES_{i,t-k}$ = the number of chemical substances (drugs) to treat disease i commercialized in Greece by the end of year $t - k$.
N_DEATHS_{it} = the number of deaths caused by disease i in year t.

pharmaceutical innovation, mean age at death would have increased by 1.1 years, from 74.7 to 75.8. In other words, pharmaceutical innovation increased longevity in Greece by 0.87 years during the period 1995–2010 – 44% of the total increase.

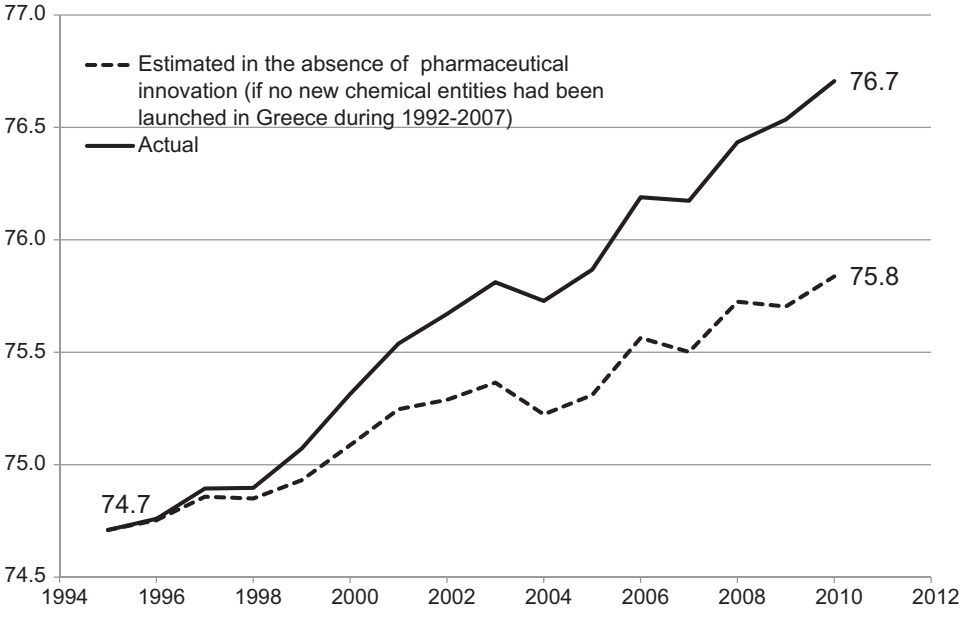


Figure 3. Mean age at death, Greece, 1995–2010: actual versus estimated in the absence of pharmaceutical innovation.

4.2. Hospital Utilization Equation Estimates

Estimates of parameters from hospital utilization models are presented in Table 5.[18] Four of the estimates (for $1 \le k \le 4$) are negative and significant ($p < 0.06$). This indicates that diseases with larger increases in the cumulative number of NCEs one to four years earlier had smaller increases in the number of hospital days.

As shown in Figure 4, between 2000 and 2008, the number of hospital days fell slightly, from 14.0 million to 13.9 million. Estimates of equation (2) where

Table 5. Weighted least-squares estimates of β_k from the model $\ln(DAYS_{it}) = \beta_k \ln(N\_CHEM\_SUBSTANCES_{i,t-k}) + \alpha_i + \delta_t + \varepsilon_{it}$ each estimate is from a separate model weight = Σ_t $DAYS_{it}$ disturbances are clustered within diseases

Parameter	Estimate	Empirical standard error estimates	95% Lower confidence limit	95% Upper confidence limit	Z	Pr > | Z |
β_1	−0.1411	0.0396	−0.2187	−0.0636	−3.57	0.0004
β_2	−0.1364	0.0600	−0.2540	−0.0188	−2.27	0.023
β_3	−0.1811	0.0950	−0.3673	0.0052	−1.91	0.0567
β_4	−0.2198	0.1019	−0.4194	−0.0201	−2.16	0.031
β_5	−0.1102	0.0774	−0.2620	0.0415	−1.42	0.1545
β_6	−0.0061	0.0479	−0.1000	0.0879	−0.13	0.8994
β_7	−0.0481	0.0474	−0.1411	0.0449	−1.01	0.3109
β_8	−0.0709	0.0445	−0.1582	0.0163	−1.59	0.1109
β_9	−0.0939	0.0695	−0.2302	0.0424	−1.35	0.177
β_{10}	−0.0438	0.0575	−0.1565	0.0690	−0.76	0.4468

$DAYS_{it}$ = the number of hospital days for disease i in year t.
$N\_CHEM\_SUBSTANCES_{i,t-k}$ = the number of chemical substances (drugs) to treat disease i commercialized in Greece by the end of year $t - k$.

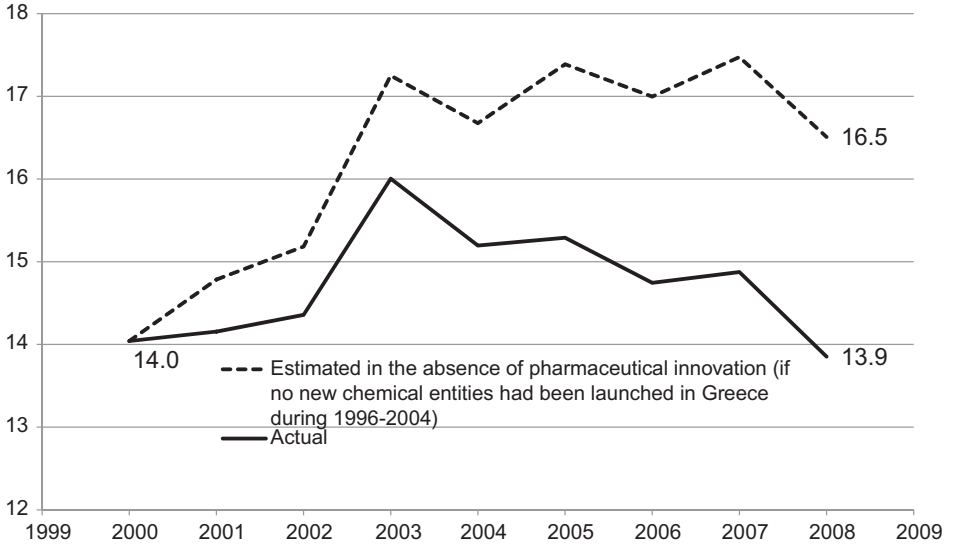


Figure 4. Millions of hospital days, Greece, 2000–2008: actual versus estimated in the absence of pharmaceutical innovation.

$k = 4$ imply that, in the absence of pharmaceutical innovation, the number of hospital days would have increased by 2.5 million, from 14.0 million to 16.5 million. In other words, pharmaceutical innovation reduced hospital utilization at an average annual rate of 2.1%.

5. The Cost-Effectiveness of Pharmaceutical Innovation in Greece

Now I will use estimates of the effect of pharmaceutical innovation on mean age at death (Table 4) and hospital utilization (Table 5) to calculate the incremental cost-effectiveness of pharmaceutical innovation, that is, the cost per life year gained from the introduction of new drugs. The incremental cost-effectiveness ratio (ICER) is defined as follows:[19]

$$\text{ICER} = (\text{LE}_{\text{actual}} * \text{MedExpend}_{\text{actual}}) - \left(\text{LE}_{\text{no\_innovation}} * \text{MedExpend}_{\text{no\_innovation}}\right)$$

$$LE_{actual} - LE_{no\_innovation}$$

Where

$\text{MedExpend}_{\text{actual}}$	=actual per capita medical expenditure in 2007
$\text{MedExpend}_{\text{no\_innovation}}$	=estimated per capita medical expenditure in 2007 in the absence of seven prior years of pharmaceutical innovation
$\text{LE}_{\text{actual}}$	=actual life expectancy in 2007
$\text{LE}_{\text{no\_innovation}}$	=estimated life expectancy in 2007 in the absence of seven prior years of pharmaceutical innovation

Table 6 shows a "baseline" calculation of the ICER. Line 1 shows the actual value of life expectancy (mean age at death) in 2007 (76.49 years), and the estimated value (76.04 years, derived from the estimate of β_3 in Table 4) in the absence of (lagged) pharmaceutical innovation during the period 2000–2007. The estimates indicate that life expectancy would have been 0.45 years (5.4 months) lower in 2007 in the absence of pharmaceutical innovation. Lines 2–4 show three components of medical expenditure, and line 5 shows their sum, total medical expenditure. The 2007 actual values (expressed in USD PPP) were obtained from Economou (2010) and http://stats.oecd.org/.[20] Pharmaceutical expenditure is considered first, in line 2. During this period, real per capita pharmaceutical expenditure increased at an average annual rate of 11.1% (OECD Table 7.4.3). To be conservative, we will assume that pharmaceutical innovation was responsible for the entire 11.1% annual growth in real per capita pharmaceutical expenditure, that is, it increased per capita pharmaceutical expenditure by \$222 (from \$204 to \$427) between 2000 and 2007.

Hospital expenditure is considered next, in line 3. The estimate of β_4 in Table 5 implied that, in the absence of lagged pharmaceutical innovation during 2000–2007, the number of hospital days would have been 16.5% ($=1.022^7-1$) higher in 2007. Evidence based on US data indicates that the elasticity of hospital expenditure with respect to the number of hospital days is

Table 6. Baseline estimate of cost per life-year gained from pharmaceutical innovation

Line	Variable	Actual values, 2007 (Y_{actual})	Estimated values in 2007 in the absence of seven prior years of pharmaceutical innovation ($Y_{no\_innovation}$)	Difference ($Y_{no\_innovation} - Y_{actual}$)
1	Life expectancy (mean age at death) Per capita medical expenditure in 2007, USD PPP	76.49[a]	76.04	−0.45
2	Prescription drug expenditure	$427[b]	204[c]	–$222
3	Hospital expenditure	$1,053[b]	$1,191	$138
4	Other medical expenditure	$1,244	$1,244	$0
5	Total medical expenditure	$2,724[d]	$2,639	–$84
6	Lifetime medical expenditure (= life expectancy × total medical expenditure in 2007)	$208,372	$200,670	–$7,702

[a]WHO Mortality Database.
[b]Tables 3.2 and 3.4, Economou C. (2010) Greece: Health system review. Health Syst Transit 12(7): 1–177, xv–xvi, http://www.euro.who.int/__data/assets/pdf_file/0004/130,729/e94660.pdf.
[c]Estimate based on assumption that pharmaceutical innovation was responsible for the entire 11.1% (OECD Table 7.4.3) annual growth in real per capita pharmaceutical expenditure.
[d]OECD Table 7.1.1.

about 0.81. If it is assumed that this also applies to Greece, then hospital expenditure would have been 12.3% (=0.81 × ln(1.022^7)) higher in 2007 in the absence of lagged pharmaceutical innovation during 2000–2007. Hence, per capita hospital pharmaceutical expenditure in 2007 would have been $138 higher ($1,191 instead of $1,053). Longitudinal disease-level data on expenditure on or utilization of other medical services are not available, so it is assumed (in line 4) that pharmaceutical innovation had no effect on other medical expenditure. As shown in line 5, under these assumptions, per capita medical expenditure in 2007 would have been $84 lower in the absence of prior pharmaceutical innovation, because the estimated increase in hospital expenditure would have been smaller than the estimated reduction in pharmaceutical expenditure. Lifetime medical expenditure would have been $7,702 lower in the absence of prior pharmaceutical innovation, due to the reductions in life expectancy and annual medical expenditure. The calculations in Table 6 imply that the cost per life-year gained from the introduction of new drugs was $17,117 (= –$7,702/–0.45 years), which is a very small fraction of leading economists' estimates of the value of (or consumers' willingness to pay for) a one-year increase in life expectancy. Aldy and Viscusi (2008) estimate that the average value of (willingness to pay for) an American life-year is $300,000.

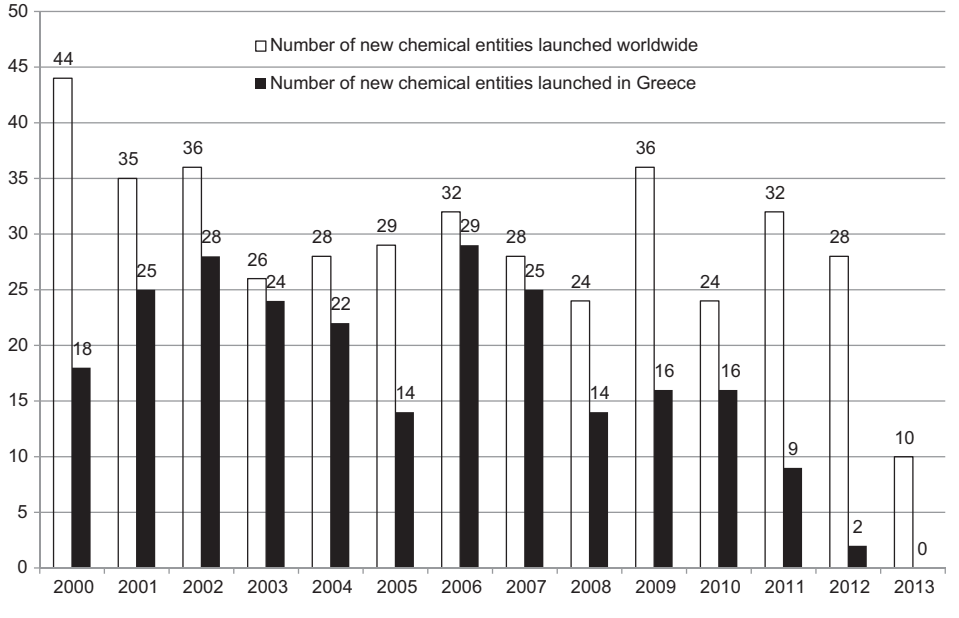
There are several good reasons to think that the calculations in Table 6 lead to an overestimate of the ICER. First, the increase in life expectancy attributable to pharmaceutical innovation may be underestimated. The increase in life expectancy at birth during 1995–2010 was 13% larger than the increase in mean age at death (2.81 years vs. 2.48 years). Second, some of the increase

in pharmaceutical expenditure may be attributable to factors other than pharmaceutical innovation. Third, in Table 6, it is assumed that pharmaceutical innovation had no effect on other medical expenditure, but it may have reduced other medical expenditure – especially nursing home expenditure – as it appears to have reduced hospital expenditure.

This study is subject to several limitations. One limitation is that the estimates do not capture between-disease spillover effects, because the relationship analyzed is between pharmaceutical innovation related to a disease and the mean age of deaths caused by the disease. These effects appear to be fairly modest in practice, but accounting for these spillover effects would certainly be desirable.

A second limitation is that the outcome measure analyzed is the number of life-years, not the number of *quality-adjusted* life-years (QALYs). As argued in Lichtenberg (2009), even though quality of life is generally far from perfect toward the end of life, the increase in QALYs attributable to innovation could be either greater than or less than the increase in life-years.

A third limitation is that controlling for other types of medical innovation, such as innovation in diagnostic imaging, surgical procedures, and medical devices, was infeasible, since longitudinal disease-level measures of nonpharmaceutical medical innovation are not available for Greece. Such data are available for the USA during the period 1998–2007, and they suggest that failure to control for other medical innovation is unlikely to result in overestimation of the effect of pharmaceutical innovation on longevity growth, but further research on this issue is clearly warranted.



Note: 2013 data do not cover the entire year.

Figure 5. Number of new chemical entities launched worldwide and in Greece, 2000–2013.
Source: Author's calculations based on IMS Health New Product Focus database.

6. Summary and Conclusions

In this article, longitudinal, disease-level data were used to analyze the impact of pharmaceutical innovation on longevity (mean age at death), hospital utilization, and medical expenditure in Greece during the period 1995–2010. The estimates imply that pharmaceutical innovation increased mean age at death by 0.87 years during this period – about 44% of the total increase in longevity. Pharmaceutical innovation may have increased real per capita pharmaceutical expenditure by $222 during the period 2000–2007, but we estimate that 62% of this increase was offset by a reduction in hospital expenditure. The baseline estimate of the cost per life-year gained from pharmaceutical innovation in Greece during 2000–2007 is about $17,117.

As shown in Figure 5, the number of new drugs launched in Greece has declined dramatically in recent years. During the period 2000–2007, the number of new drugs launched in Greece was 72% as high as the number of new drugs launched worldwide. During the period 2008–2013, the number of new drugs launched in Greece was only 37% as high as the number of new drugs launched worldwide. The evidence presented in this article indicates that reduced access to new drugs would have adverse long-term effects on longevity and other aspects of health.

Notes

1. For a review of the literature on the impact of medical innovation in general, see the 604-page report prepared by the Australian Productivity Commission (2005).
2. Lichtenberg et al. (2009) studied the impact of pharmaceutical innovation on longevity using patient-level data on elderly residents of Quebec, and Lichtenberg (2013) studied this issue using patient-level data on elderly Americans.
3. Grunfeld and Griliches (1960, 1) showed that "aggregation of economic variables can, and in fact frequently does, reduce … specification errors. Hence, aggregation does not only produce an aggregation error, but may also produce an aggregation gain." In particular, patient-level data are surely more subject to selection effects (the sickest patients might get the newest – or oldest – treatments) than aggregate data.
4. Lichtenberg (2011) studied the impact of pharmaceutical innovation on longevity using longitudinal state-level US data, and Lichtenberg (2012a) studied this issue using longitudinal state-level German data.
5. Newhouse (1992) observed that "technological change is not necessarily expenditure-increasing" (p. 11), and that "hospital expenditure is the single largest component of the overall expenditure increase" (p. 12).
6. Patient-level and longitudinal region-level data for Greece are not available.
7. Government agencies such as the Australian Institute of Health and Welfare (2013), Statistics Canada (http://www.cbc.ca/news/canada/story/2008/01/14/death-stats.html), and the Arizona Department of Health Services (http://www.azdhs.gov/plan/report/ahs/ahs2010/pdf/2d1.pdf) publish data on mean age at death.
8. In a weighted (by total number of deaths) least-squares regression of the form $\text{LE\_BIRTH}_{ct} = \beta\ \text{AGE\_DEATH}_{ct} + \alpha_c + \delta_t + \varepsilon_{ct}$, where $\text{LE\_BIRTH}_{ct} = \text{LE\_BIRTH}$ in country c in year t, the estimate of β is 0.523 ($Z = 5.39$, p-value < 0.0001).
9. 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.

10. Outpatient prescription drug claims usually do n'ot 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 Greece.
11. However, the number of people exposed to pharmaceutical innovation tends to be much larger than the number of people exposed to other types of medical innovation. In 2007, 62% of Americans consumed prescription drugs, while only 8% of Americans were admitted to hospitals. (Source: Agency for Healthcare Research and Quality, MEPS HC-113: 2007 Full Year Consolidated Data File, http://meps.ahrq.gov/mepsweb/data_stats/download_data_files_detail.jsp?cboPufNumber=HC-113)
12. A separate model is estimated for each value of k, rather than including multiple values ($N\_CHEM\_SUBSTANCES_{i,t-1}$, $N\_CHEM\_SUBSTANCES_{i,t-3}$, $N\_CHEM\_SUBSTANCES_{i,t-5}$,…) in a single model because N_CHEM_SUBSTANCES is highly serially correlated (by construction), which would result in extremely high multicollinearity if multiple values were included.
13. About one in four new molecular entities has supplemental indications.
14. This database covers products launched worldwide since 1982. Good coverage of Greece began in 1990.
15. Greek deaths are classified by ICD 9th revision, Basic Tabulation List.
16. The estimates in the article are based on the default covariance structure of multivariate responses: independent. I obtain identical estimates when I specify the covariance structure to be exchangeable. I also estimated the model when the covariance structure was specified as first-order autoregressive. These estimates seem much less plausible than the estimates based on the independent covariance structure, because they are less consistent with a smoothness prior: the hypothesis that physical properties in a neighborhood of space or in an interval of time present some coherence and generally do not change abruptly.
17. Estimates of all parameters of the model $AGE\_DEATH_{it} = \beta_3\ N\_CHEM\_SUBSTANCES_{i,t-3} + \alpha_i + \delta_t + \varepsilon_{it}$ are shown in Appendix Table A1.
18. Estimates of all parameters of the model $\ln(DAYS_{it}) = \beta_4\ \ln(CUM\_NCE_{i,t-4}) + \alpha_i + \delta_t + \varepsilon_{it}$ are shown in Appendix Table A2.
19. $LE_{actual} \times MedExpend_{actual}$ = actual (undiscounted) lifetime medical expenditure; $LE_{no\_innovation} \times MedExpend_{no\_innovation}$ = estimated (undiscounted) lifetime medical expenditure in the absence of nine prior years of pharmaceutical innovation.
20. The 2007 actual values depend on the age/gender and health of the Greek population.

References

Aldy, Joseph E., and W. Kip Viscusi. 2008. Adjusting the Value of a Statistical Life for Age and Cohort Effects. *Review of Economics and Statistics* 90 (3): 573–581.

Arias, Elizabeth. 2010. United States Life Tables. 2006. National Vital Statistics Reports; vol 58 no 21. National Center for Health Statistics. Hyattsville, MD.

Australian Institute of Health and Welfare. 2013. National GRIM (General Record of Incidence of Mortality) Books, http://www.aihw.gov.au/national-grim-books/.

Australian Productivity Commission. 2005. Impacts of Advances in Medical Technology in Australia, Research Report, Melbourne, http://www.pc.gov.au/__data/assets/pdf_file/0003/17193/medicaltechnology.pdf.

Bresnahan, Timothy F., and Robert J. Gordon. 1996. *The Economics of New Goods*. Chicago, IL: University of Chicago Press.

Center for Medicare and Medicaid Services. 2013. National Health Expenditure Data, http://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/Downloads/tables.pdf.

Chandra, Amitabh, Jonathan Gruber, and Robin McKnight. 2010. Patient Cost-sharing and Hospitalization Offsets in the Elderly. *American Economic Review* 100 (1): 193–213.

Dorsey, E. Ray, Jason de Roulet, Joel P. Thompson, Jason I. Reminick, Ashley Thai, Zachary White-Stellato, Christopher A. Beck, Benjamin P. George, and Hamilton Moses, III. 2010. Financial Anatomy of Biomedical Research, 2003–2008. *Journal of the American Medical Association* 303 (2): 137–143.

Economou, Charalampos. 2010. Greece: Health System Review. *Health Syst Transit* 12 (7): 1–177, xv–xvi. http://www.euro.who.int/__data/assets/pdf_file/0004/130729/e94660.pdf.

Grossman, Gene M., and Elhanan Helpman. 1991. Quality Ladders in the Theory of Growth. *The Review of Economic Studies* 58 (1): 43–61.

Grunfeld, Yehuda, and Zvi Griliches. 1960. Is Aggregation Necessarily Bad? *Review of Economics and Statistics* 42 (1): 1–13.

Hercowitz, Zvi. 1998. The 'Embodiment' Controversy: A Review Essay. *Journal of Monetary Economics* 41 (1): 217–224.

Karaca-Mandic, Pinar, Anupam B. Jena, Geoffrey F. Joyce, and Dana P. Goldman. 2012. Out-of-pocket Medication Costs and Use of Medications and Health Care Services among Children with Asthma. *Journal of the American Medical Association* 307 (12): 1284–1291.

Lichtenberg, Frank R. 2007. The Impact of New Drugs on U.S. Longevity and Medical Expenditure, 1990–2003. *American Economic Review* 97 (2): 438–443.

Lichtenberg, Frank R. 2009. The Effect of New Cancer Drug Approvals on the Life Expectancy of American Cancer Patients, 1978–2004. *Economics of Innovation and New Technology* 18 (5): 407–428.

Lichtenberg, Frank R. 2011. The Quality of Medical Care, Behavioral Risk Factors, and Longevity Growth. *International Journal of Health Care Finance and Economics* 11 (1): 1–34.

Lichtenberg, Frank R. 2012a. The Contribution of Pharmaceutical Innovation to Longevity Growth in Germany and France, 2001–2007. *PharmacoEconomics* 30 (3): 197–211.

Lichtenberg, Frank R. 2013. The Effect of Pharmaceutical Innovation on Longevity: Patient Level Evidence from the 1996–2002 Medical Expenditure Panel Survey and Linked Mortality Public-use Files. *Forum for Health Economics and Policy* 16 (1): 1–33.

Lichtenberg, Frank R. 2014. The Impact of Pharmaceutical Innovation on Longevity and Medical Expenditure in France, 2000–2009. *Economics and Human Biology* 13: 107–127.

Lichtenberg, Frank R., Paul Grootendorst, Marc Van Audenrode, Dominick Latremouille-Viau, and Patrick Lefebvre. 2009. The Impact of Drug Vintage on Patient Survival: A Patient-level Analysis Using Quebec's Provincial Health Plan Data. *Value in Health* 12 (6): 847–856.

Murphy, Kevin M., and Robert H. Topel. 2006. The Value of Health and Longevity. *Journal of Political Economy* 114 (5): 871–904.

National Science Foundation. 2013. U.S. Corporate R&D: Volume 1: Top 500 Firms in R&D by Industry Category, Accessed 26 January 2013. http://www.nsf.gov/statistics/nsf00301/expendit.htm#intensity.

Newhouse, Joseph P. 1992. Medical Care Costs: How Much Welfare Loss? *Journal of Economic Perspectives* 6 (3): 3–21.

Nordhaus, William D. 2003. The Health of Nations: The Contribution of Improved Health to Living Standards. In *Measuring the Gains from Medical Research: An Economic Approach*, edited by Kevin M. Murphy and Robert H. Topel, 41–73. Chicago, IL: University of Chicago Press.

Romer, Paul. 1990. Endogenous Technological Change. *Journal of Political Economy* 98 (S5, Part 2): S71–S102.

Sampat, Bhaven N., and Frank R. Lichtenberg. 2011. What Are the Respective Roles of the Public and Private Sectors in Pharmaceutical Innovation? *Health Affairs* 30 (2): 332–339.

Solow, Robert M. 1960. Investment and Technological Progress. In *Mathematical Methods in Social Sciences 1959*, edited by Kenneth Arrow, Samuel Karlin, and Patrick Suppes, 89–104. Stanford: Stanford University Press.

Appendix

Table A1. Estimates of all parameters of the model $AGE\_DEATH_{it} = \beta_3\ N\_CHEM\_SUBSTANCES_{i,t-3} + \alpha_i + \delta_t + \varepsilon_{it}$

Parameter	Level 1	Estimate	Standard error	Z	Pr > | Z |
cum_nce3		0.0669	0.0246	2.72	0.0065
Year	1995	−1.1273	0.3715	−3.03	0.0024
Year	1996	−1.0838	0.3759	−2.88	0.0039
Year	1997	−0.9795	0.3491	−2.81	0.005
Year	1998	−0.9875	0.2746	−3.6	0.0003
Year	1999	−0.9059	0.2912	−3.11	0.0019
Year	2000	−0.75	0.2905	−2.58	0.0098
Year	2001	−0.5906	0.2661	−2.22	0.0265
Year	2002	−0.5484	0.2131	−2.57	0.0101
Year	2003	−0.472	0.196	−2.41	0.016
Year	2004	−0.6136	0.1569	−3.91	<0.0001
Year	2005	−0.5272	0.1499	−3.52	0.0004
Year	2006	−0.2729	0.146	−1.87	0.0617
Year	2007	−0.3356	0.0831	−4.04	<0.0001
Year	2008	−0.1123	0.1164	−0.96	0.3347
Year	2009	−0.1336	0.0698	−1.91	0.0558
Year	2010	0	0	.	.
Cause	A00–A09 Intestinal infectious diseases	7.3743	0.2779	26.54	<0.0001
Cause	A15–A19 Tuberculosis	15.6621	0.3192	49.07	<0.0001
Cause	A20–A79 Other bacterial diseases	20.1831	0.0632	319.36	<0.0001
Cause	A80–B34 Viral diseases	5.3896	0.0717	75.2	<0.0001
Cause	C00–C14 Malignant neoplasm of lip, oral cavity, and pharynx	12.3417	0.2557	48.27	<0.0001
Cause	C15–C26 Malignant neoplasm of digestive organs and peritoneum	16.9134	0.1493	113.32	<0.0001
Cause	C30–C39 Malignant neoplasm of respiratory and intrathoracic organs 160–165	13.1754	0.1461	90.17	<0.0001
Cause	C40–C50 Malignant neoplasm of bone, connective tissue, skin, and breast	12.0989	0.1211	99.88	<0.0001
Cause	C51–C63 Malignant neoplasm of genitourinary organs	18.2847	0.0433	422.4	<0.0001
Cause	C81–C96 Malignant neoplasm of lymphatic and hemopoietic tissue	14.4887	0.1183	122.47	<0.0001
Cause	D00–D09 Carcinoma *in situ*	17.1639	0.2283	75.2	<0.0001
Cause	D10–D36 Benign neoplasm	14.4894	0.2219	65.3	<0.0001
Cause	D50–D89 Diseases of blood and blood-forming organs	9.9988	0.1357	73.67	<0.0001
Cause	E00–E35, E70–E90 Endocrine and metabolic diseases, immunity disorders	15.4685	0.4612	33.54	<0.0001
Cause	E40–E68 Nutritional deficiencies	0.1183	0.2625	0.45	0.6522
Cause	F00–F99 Mental disorders	17.953	0.1003	179.04	<0.0001
Cause	G00–G99 Diseases of the nervous system	11.6561	0.3364	34.65	<0.0001
Cause	H00–H59 Disorders of the eye and adnexa	2.9784	0.0873	34.13	<0.0001
Cause	H60–H95 Diseases of the ear and mastoid process	11.4428	0.1542	74.22	<0.0001
Cause	I00–I09 Rheumatic fever and rheumatic heart disease	15.1964	0.2801	54.25	<0.0001
Cause	I10–I15 Hypertensive disease	22.9013	0.2442	93.79	<0.0001

(*Continued*)

Table A1. (*Continued*).

Parameter	Level 1	Estimate	Standard error	*Z*	Pr > | *Z* |
Cause	I20–I25 Ischemic heart disease	16.701	0.0327	510.96	<0.0001
Cause	I26–I52 Diseases of pulmonary circulation and other forms of heart disease	24.9027	0.1066	233.67	<0.0001
Cause	I60–I69 Cerebrovascular disease	24.7121	0.2387	103.54	<0.0001
Cause	I70–I99 Other diseases of the circulatory system	18.8488	0.2242	84.06	<0.0001
Cause	J00–J18, J30–J39 Diseases of the upper respiratory tract	23.1765	0.2196	105.53	<0.0001
Cause	J20–J22, J40–J99 Other diseases of the respiratory system	21.9118	0.096	228.13	<0.0001
Cause	K00–K14 Diseases of oral cavity, salivary glands, and jaws	17.3414	0.2983	58.14	<0.0001
Cause	K20–K93 Diseases of other parts of the digestive system	16.7264	0.0547	305.54	<0.0001
Cause	N00–N39 Diseases of urinary system	21.3178	0.1658	128.56	<0.0001
Cause	N40–N51 Diseases of male genital organs	15.6726	0.0631	248.54	<0.0001
Cause	N60–N99 Diseases of female genital organs	0	0	.	.
Intercept		56.7021	0.4977	113.94	<0.0001

Table A2. Estimates of all parameters of the model $\ln(DAYS_{it}) = \beta 4 \ln(N\_CHEM\_SUBSTANCES_{i,t-4}) + \alpha_i + \delta_t + \varepsilon_{it}$

Parameter	Level 1	Estimate	Standard error	Z	Pr > |Z|
lcum_nce4		−0.2198	0.1019	−2.16	0.031
Year	2000	−0.1619	0.0811	−2	0.0458
Year	2001	−0.1103	0.0854	−1.29	0.1962
Year	2002	−0.0837	0.08	−1.05	0.2952
Year	2003	0.0439	0.0583	0.75	0.4516
Year	2004	0.01	0.0484	0.21	0.8364
Year	2005	0.0519	0.0495	1.05	0.2944
Year	2006	0.0291	0.0516	0.56	0.5722
Year	2007	0.0569	0.0329	1.73	0.0843
Year	2008	0	0	.	.
Group	A00	1.0456	0.0215	48.55	<0.0001
Group	A15	−0.0249	0.0167	−1.49	0.1355
Group	A20	−1.7136	0.1134	−15.11	<0.0001
Group	A30	1.2693	0.2531	5.02	<0.0001
Group	A50	−2.1005	0.2369	−8.87	<0.0001
Group	A65	−3.7693	0.0215	−175	<0.0001
Group	B20	−1.2543	0.1909	−6.57	<0.0001
Group	B35	−2.5657	0.2746	−9.34	<0.0001
Group	B50	−2.8248	0.0771	−36.62	<0.0001
Group	C00	0.1009	0.1548	0.65	0.5148
Group	C15	−1.0051	0.1548	−6.49	<0.0001
Group	C16	1.0433	0.1995	5.23	<0.0001
Group	C17	−3.1438	0.0699	−45	<0.0001
Group	C18	1.5814	0.1254	12.61	<0.0001
Group	C19	0.4932	0.1254	3.93	<0.0001
Group	C22	0.215	0.1503	1.43	0.1524
Group	C23	−0.5621	0.1503	−3.74	0.0002
Group	C25	0.5816	0.1761	3.3	0.001
Group	C30	−1.5224	0.1548	−9.83	<0.0001
Group	C32	0.1072	0.0699	1.54	0.1247
Group	C33	2.2944	0.2359	9.73	<0.0001
Group	C40	−1.0449	0.0699	−14.96	<0.0001
Group	C43	−0.6784	0.1663	−4.08	<0.0001
Group	C44	−1.0424	0.0903	−11.54	<0.0001
Group	C45	−0.2433	0.1826	−1.33	0.1826
Group	C50	1.9021	0.2945	6.46	<0.0001
Group	C53	−0.5014	0.1062	−4.72	<0.0001
Group	C54	−0.0686	0.0699	−0.98	0.3262
Group	C56	0.4574	0.2212	2.07	0.0387
Group	C58	−6.1049	0.0699	−87.39	<0.0001
Group	C60	0.4257	0.1219	3.49	0.0005
Group	C61	1.1126	0.2471	4.5	<0.0001
Group	C62	−1.3281	0.0699	−19.01	<0.0001
Group	C67	1.3201	0.1503	8.79	<0.0001
Group	C71	0.6447	0.113	5.7	<0.0001
Group	C81	−0.8381	0.1219	−6.88	<0.0001
Group	C82	1.7234	0.2104	8.19	<0.0001
Group	C91	1.7942	0.2285	7.85	<0.0001
Group	D00	−3.8818	0.1505	−25.79	<0.0001
Group	D10	0.7921	0.1415	5.6	<0.0001
Group	D25	−0.1562	0.0215	−7.25	<0.0001

(*Continued*)

Table A2. (*Continued*)

Parameter	Level 1	Estimate	Standard error	Z	Pr > |Z|
Group	D34	−2.9133	0.075	−38.85	<0.0001
Group	D50	1.3647	0.2231	6.12	<0.0001
Group	D60	1.3677	0.0517	26.45	<0.0001
Group	E10	1.8706	0.281	6.66	<0.0001
Group	E65	−1.294	0.0353	−36.65	<0.0001
Group	E70	−2.2629	0.2162	−10.47	<0.0001
Group	F20	3.409	0.1179	28.92	<0.0001
Group	F30	2.8989	0.2652	10.93	<0.0001
Group	F40	1.406	0.2403	5.85	<0.0001
Group	F70	2.1003	0.092	22.83	<0.0001
Group	G00	−0.4452	0.1837	−2.42	0.0154
Group	G20	−0.2453	0.1755	−1.4	0.162
Group	G35	−0.3603	0.1323	−2.72	0.0065
Group	G40	0.8444	0.2001	4.22	<0.0001
Group	H00	0.9163	0.2048	4.47	<0.0001
Group	H04	−2.376	0.0215	−110.32	<0.0001
Group	H10	−3.9111	0.2519	−15.53	<0.0001
Group	H40	−0.76	0.1909	−3.98	<0.0001
Group	H49	−2.7257	0.0085	−319.79	<0.0001
Group	H65	−0.2071	0.161	−1.29	0.1984
Group	I00	−5.4773	0.0232	−235.62	<0.0001
Group	I05	−3.8066	0.0232	−163.75	<0.0001
Group	I10	1.7462	0.3453	5.06	<0.0001
Group	I20	3.1907	0.2686	11.88	<0.0001
Group	I21	1.9182	0.2179	8.8	<0.0001
Group	I26	−0.2474	0.0232	−10.64	<0.0001
Group	I60	−0.8378	0.0364	−23.04	<0.0001
Group	I61	0.5443	0.0232	23.41	<0.0001
Group	I63	−0.3234	0.0699	−4.63	<0.0001
Group	I64	2.9525	0.0763	38.69	<0.0001
Group	I70	−0.3442	0.0235	−14.62	<0.0001
Group	I71	1.1464	0.1315	8.72	<0.0001
Group	I74	−1.6058	0.0235	−68.22	<0.0001
Group	I80	0.2972	0.0232	12.78	<0.0001
Group	I83	−0.6599	0.0232	−28.39	<0.0001
Group	I84	−0.7641	0.0232	−32.87	<0.0001
Group	J00	0.5101	0.274	1.86	0.0627
Group	J09	−3.9719	0.0444	−89.47	<0.0001
Group	J12	1.9576	0.2803	6.98	<0.0001
Group	J20	1.034	0.2781	3.72	0.0002
Group	J30	0.0726	0.1848	0.39	0.6947
Group	J31	−0.9308	0.2057	−4.52	<0.0001
Group	J33	0.4669	0.0215	21.68	<0.0001
Group	J40	2.428	0.2889	8.4	<0.0001
Group	J80	2.4768	0.0906	27.34	<0.0001
Group	K00	−0.1067	0.0828	−1.29	0.1974
Group	K20	0.2262	0.231	0.98	0.3275
Group	K50	3.1417	0.1874	16.76	<0.0001
Group	K55	−0.8339	0.0906	−9.21	<0.0001
Group	K70	0.832	0.0562	14.8	<0.0001
Group	L00	1.3812	0.2626	5.26	<0.0001
Group	L10	1.7329	0.3036	5.71	<0.0001
Group	M00	2.7793	0.309	8.99	<0.0001

(*Continued*)

Table A2. (*Continued*)

Parameter	Level 1	Estimate	Standard error	Z	Pr > |Z|
Group	M40	2.2359	0.1869	11.97	<0.0001
Group	M80	−0.5344	0.2185	−2.45	0.0145
Group	N00	3.6792	0.3284	11.2	<0.0001
Group	N40	1.6461	0.1821	9.04	<0.0001
Group	N41	0.5307	0.2382	2.23	0.0259
Group	N46	−4.1802	0.075	−55.74	<0.0001
Group	N70	−1.8539	0.0594	−31.19	<0.0001
Group	N71	−1.1125	0.2179	−5.1	<0.0001
Group	N80	1.6696	0.161	10.37	<0.0001
Group	N97	−4.0472	0.0887	−45.64	<0.0001
Group	O03	−0.1824	0.0215	−8.47	<0.0001
Group	Q10	0.1989	0.0215	9.24	<0.0001
Group	Q20	0	0	.	.
Intercept		10.3275	0.0372	277.36	<0.0001