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The Impact of Pharmaceutical Innovation on Premature Mortality, Hospital Separations, and Cancer Survival in Australia*

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I analyse the effect that pharmaceutical innovation had on premature (before age 75 and 80) mortality from all diseases in Australia during the period 1998–2011 by investigating whether the diseases that experienced more pharmaceutical innovation had larger declines in premature mortality. My estimates indicate that 60 per cent of the 1998–2011 decline in premature (before age 75) mortality was due to previous pharmaceutical innovation. They also indicate that previous pharmaceutical innovation accounted for 40 per cent of the 1986–2007 increase (from 49.0 per cent to 61.6 per cent) in the 5-year relative cancer survival rate, controlling for mean age at diagnosis and the number of patients diagnosed, and that if no new drugs had been introduced during 1986–1999, the number of hospital separations in 2011 would have been about 13 per cent higher, ceteris paribus. My estimates indicate that new drugs listed on the Pharmaceutical Benefits Scheme during 1989–2002 reduced the number of life-years lost from all diseases before ages 75 and 80 in 2011 by 143,639 and 257,602, respectively, and that the innovation was cost-saving: the reduction in hospital expenditure attributable to it exceeded expenditure on the drugs. Even if it completely ignores the apparent reduction in hospital expenditure, the evidence indicates that pharmaceutical innovation was highly cost-effective.

I Introduction

Previous authors have argued that 'reducing premature mortality is a crucial public health objective' (Renard *et al.*, 2014). A widely used measure of premature mortality is years of potential life lost (YPLL) before a given age (e.g. age 75), that is, the number of years *not* lived by an individual who died before that age (Association of Public Health Epidemiologists in Ontario, 2015). YPLL statistics are published by the World Health Organization (WHO), the Organisation for Economic Co-operation and Development (OECD), and government agencies of the USA, Switzerland, and other countries. Burnet *et al.* (2005) argue that YPLL 'should be considered when allocating research funds'.

The premature (before age 75) mortality rate has been declining in Australia; it declined 24 per

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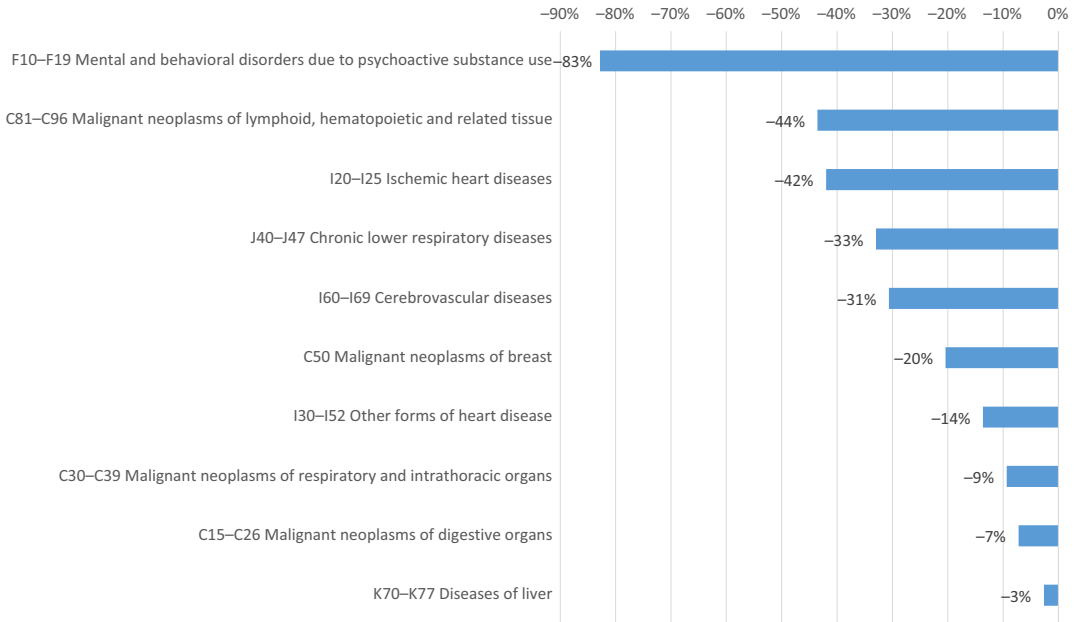
FIGURE 1
Percentage Change in Premature (before Age 75) Mortality Rate, 1998–2011: 10 Diseases (ICD-10 Blocks) with Largest Average Premature Mortality Rates
[Colour figure can be viewed at wileyonlinelibrary.com]



cent between 1998 and 2011 (AIHW 2015c, table S3). But as shown in Figure 1, there has been considerable variation in the rate of decline across diseases. The figure displays data for the 10 diseases (ICD-10 blocks) with the largest average premature mortality rates. The premature mortality rates of three of these diseases declined by more than 40 per cent, while the premature mortality rates of three other diseases declined by less than 10 per cent.

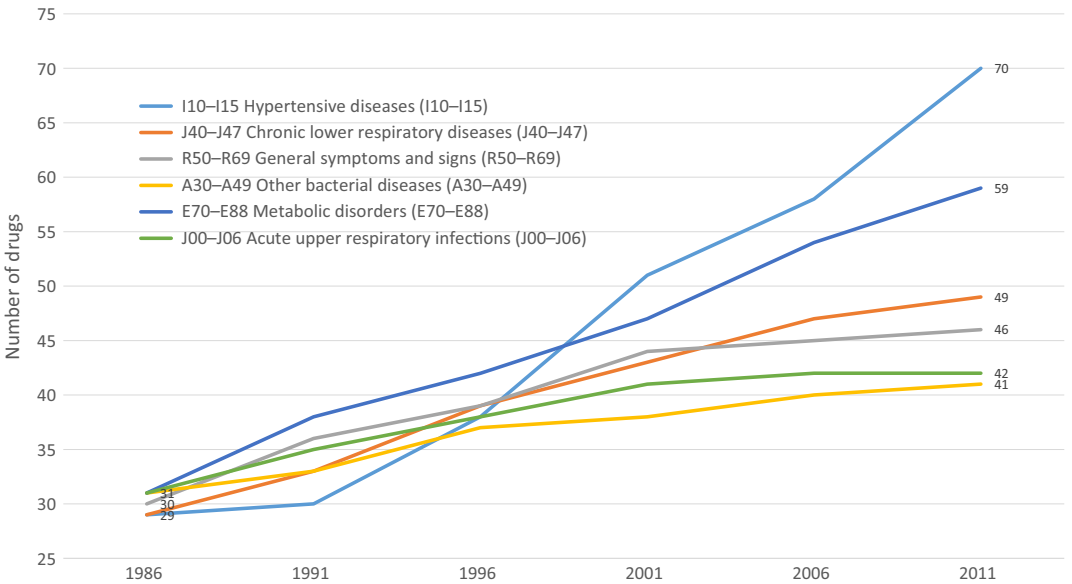
In this paper, I will analyse the effect that pharmaceutical innovation had on premature mortality from all diseases in Australia during the period 1998–2011.[1] In essence, I will investigate whether the diseases that experienced more pharmaceutical innovation had larger declines in premature mortality. Figure 2 illustrates that the rate of pharmaceutical innovation, as measured by the 1986–2011 increase in the number of drugs ever listed in the Pharmaceutical Benefits Scheme (PBS),[2] varied considerably across diseases. Almost the same number of drugs (between 29 and 31) had been listed by 1986 for each of the six diseases shown. During the next 25 years, 41 additional drugs for hypertensive diseases were listed, while only 11 additional drugs were listed for acute upper respiratory infections.[3]

[1] This period was chosen because a consistent cause-of-death classification (ICD-10) was used in these years.

[2] The PBS is a program of the Australian government that provides subsidised prescription drugs to residents of Australia, as well as certain foreign visitors covered by a Reciprocal Health Care Agreement. The PBS seeks to ensure that Australian residents have affordable and reliable access to a wide range of necessary medicines. The scheme assumes responsibility for the cost of drugs to patients in the community setting rather than while in hospital, which is the responsibility of each state and territory. Together with Medicare, the PBS is a key component of health care in Australia.

[3] To illustrate the data on drugs for specific diseases, a list of drugs for acute upper respiratory infections (ICD-10 codes J00–J06), by PBS listing year, is shown in Table A1 in the Appendix.

FIGURE 2
Number of Drugs (Chemical Substances) Ever Listed in Pharmaceutical Benefits Scheme, 5-Year Intervals, 1986–2011: Six Diseases
[Colour figure can be viewed at wileyonlinelibrary.com]



I will analyse the effect that pharmaceutical innovation had on hospital separations as well as on premature mortality from about 170 diseases. Figure 3 shows that there was considerable variation across diseases in the 1998–2012 growth in the number of hospital separations. For example,

FIGURE 3
Number of Hospital Separations, 1998–2012: Six Diseases
[Colour figure can be viewed at wileyonlinelibrary.com]

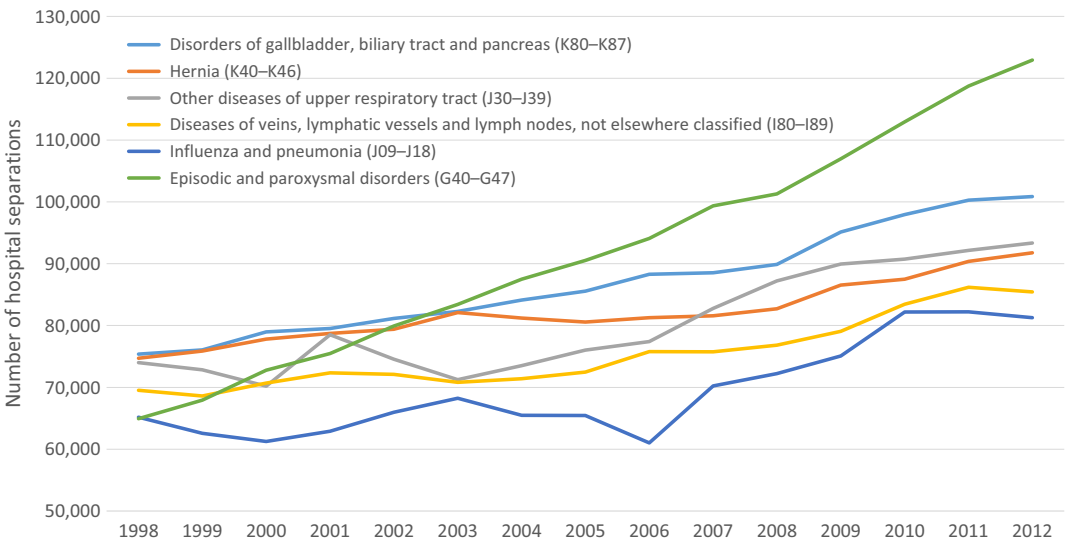
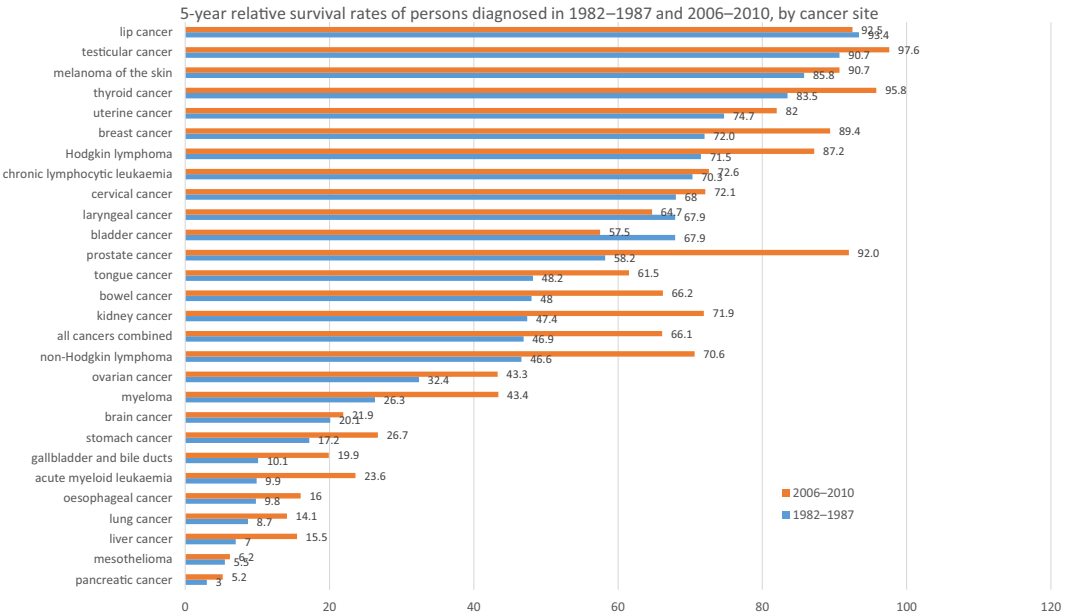


FIGURE 4
Survival Trends, 1982–1987 to 2006–2010
[Colour figure can be viewed at wileyonlinelibrary.com]



Source: AIHW 2012. Cancer survival and prevalence in Australia: period estimates from 1982 to 2010. Cancer series no. 69. Cat. no. CAN 65. Canberra: AIHW. Data for 1988-1993, instead of 1982-1987, are used for liver cancer due to the small number of cases from the earlier time period.

the number of separations due to episodic and paroxysmal disorders (G40–G47) increased by 89 per cent, while the number of separations due to diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified (I80–I89), increased by 23 per cent.

I will also analyse the effect that pharmaceutical innovation had on survival from all (about 30) types of cancer during the period 1986–2007. Cancer is the leading cause of burden of disease in Australia, accounting for about one-fifth of the total burden (AIHW, 2010). With half of Australians developing cancer and one-fifth dying from it before the age of 85, cancer has a major impact on individuals, their families and the health-care system (AIHW, 2012a). In the cancer survival analysis, I will control for the number of people diagnosed (incidence) and the mean age at which they were diagnosed.

Figure 4 presents a summary of trends in 5-year survival rates, by cancer site, between the periods 1982–1987 and 2006–2010. In general, survival from most cancers improved over time. However, the change in survival was not uniform over time and across cancer types. For example, survival from cervical cancer increased until the early 1990s but did not change significantly thereafter. By way of contrast, survival from cancer of unknown primary site remained virtually unchanged until the 2000s when it more than doubled. The cancers that showed the greatest percentage-point increase in survival were: prostate cancer, kidney cancer, and non-Hodgkin lymphoma. Five-year survival from these cancers increased by 24 percentage points or more in absolute terms. Other cancers that showed a greater proportional increase in survival included liver cancer, cancer of unknown primary site, and acute myeloid leukaemia. Five-year survival from these cancers more than doubled between the periods 1982–1987 and 2006–2010, despite remaining lower than the average.

The analysis will be based on aggregate (longitudinal disease-level) data rather than patient-level data. Stukel *et al.* (2007) argue that comparisons of outcomes between 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.[4]

In Section II, I provide theoretical motivation for the main hypothesis, and summarise previous research based on US data. In Section III, I describe econometric models of premature mortality, hospital separations, and cancer survival. The data sources used to construct the data to estimate these models are described in Section IV. Empirical results are presented in Section V. Key implications of the estimates are discussed in Section VI. Section VII provides a summary and conclusions and a discussion of study limitations

II Motivation and Previous Evidence

Longevity increase (or declining mortality rates) is a very important part of economic growth, broadly defined. Nordhaus (2005) argued that 'improvements in health status have been a major contributor to economic welfare over the twentieth century. To a first approximation, the economic value of increases in longevity in the last hundred years is about as large as the value of measured growth in non-health goods and services'. The United Nations Human Development Index is a composite statistic of life expectancy, education, and income per capita indicators, which are used to rank countries into four tiers of human development (United Nations, 2016).

Building on a large collection of previous research by Romer (1990), Grossman and Helpman (1991), Aghion and Howitt (1992), and others, Jones (2002, p. 221) presented a model in which 'long-run growth is driven by the discovery of new ideas throughout the world'. He postulated an aggregate production function in which total output depends on the total stock of ideas available to this economy as well as on physical and human capital. In general, measuring the number of ideas is challenging, but measuring pharmaceutical 'ideas' is considerably easier than measuring ideas in general. The measure of pharmaceutical ideas that I will use is the number of new molecular entities listed on the PBS. Since we have precise information about when those ideas reached the market and the diseases to which they apply, we can assess the impact of those ideas on longevity and hospitalisation in a difference-in-differences framework.

In principle, technological change could be either disembodied or embodied in new goods. Solow (1960) hypothesised that most technological change is embodied: to benefit from 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, p. 223) also reached the 'conclusion ... that "embodiment" is the main transmission mechanism of technological progress to economic growth'.

Several previous studies have investigated the impact of pharmaceutical innovation on longevity growth in the USA. I will briefly summarise three of these studies. Lichtenberg (2011) examined the effect of pharmaceutical and diagnostic imaging innovation on life expectancy in the USA using longitudinal state-level data. Between 1991 and 2004, life expectancy at birth increased 2.37 years. The estimates implied that, during this period, use of newer outpatient prescription drugs increased life expectancy by 0.96–1.26 years; use of newer provider-administered drugs increased life expectancy by 0.48–0.54 years; and the increased use of advanced imaging technology increased life expectancy by 0.62–0.71 years.

Lichtenberg (2013) used patient-level data to analyse the effect of technological change embodied in pharmaceuticals on the longevity of elderly Americans. He investigated the effect of the vintage (year of US Food and Drug Administration approval) of the prescription drugs used by an individual on his or her survival and medical expenditure, controlling for a number of demographic characteristics and indicators and determinants of health status: age, sex, interview year, the mean year the person started taking his or her medications, and dummy variables for activity limitations, race, education,

[4] Jalan and Ravallion (2001, p. 10) argued that 'aggregation to village level may well reduce measurement error or household-specific selection bias'.

family income as a percentage of the poverty line, insurance coverage, Census region, body mass index, smoking, and more than 100 medical conditions. Between 1996 and 2003, the mean vintage of prescription drugs increased by 6.6 years. This is estimated to have increased the life expectancy of elderly Americans by 0.41–0.47 years. This suggests that not less than two-thirds of the 0.6-year increase in the life expectancy of elderly Americans during 1996–2003 was due to the increase in drug vintage.

Lichtenberg (2014b) used longitudinal disease-level data to assess the effect of four types of medical innovation on US cancer mortality rates. The estimates indicated that there were three major sources of the 13.8 per cent decline of the age-adjusted cancer mortality rate during 2000–2009. Drug innovation and imaging innovation are estimated to have reduced the cancer mortality rate by 8.0 per cent and 4.0 per cent, respectively. The decline in incidence is estimated to have reduced the cancer mortality rate by 1.2 per cent.

The Australian health-care system is quite different from the US health-care system. For example, per-capita spending on health care in 2008 was 125 per cent higher in the USA than it was in Australia ($7,538 versus $3,353); the number of new chemical entities launched during 1982–2015 was 49 per cent higher in the USA than it was in Australia (757 versus 507); but the number of doctor consultations per capita in 2008 was 60 per cent higher in Australia than it was in the USA (6.4 versus 4.0) (Squires, 2011). Due to these stark differences, estimates of the effect of pharmaceutical innovation on longevity derived from US data may not be directly applicable to Australia.

III Econometric Models of Premature Mortality, Hospital Separations, and Cancer Survival

(i) Premature Mortality Models

In his model of endogenous technological change, Romer (1990) hypothesised 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 labour 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:

$$\ln(\text{YPLL75}_{it}) = \beta_k \text{CUM\_NCE}_{i,t-k} + \alpha_i + \delta_t + \varepsilon_{i,t} \quad (1)$$

$$\ln(\text{YPLL80}_{it}) = \beta_k \text{CUM\_NCE}_{i,t-k} + \alpha_i + \delta_t + \varepsilon_{i,t} \quad (2)$$

where YPLL75_{it} (YPLL80_{it}) represents YPLL before age 75 (80) from disease i in year t (t = 1998,. . ., 2004, 2006,. . .,2011) per 100,000 population below age 75 (80); $\text{CUM\_NCE}_{i,t-k} = \sum \text{IND}_{di}\text{LISTED\_PBS}_{d,t-k}$ is the number of new chemical entities (drugs) to treat disease i that had been listed on the PBS by the end of year $t - k$, where IND_{di} is 1 (0) if drug d is used (not used) to treat or is (is not) indicated for disease i, and $\text{LISTED\_PBS}_{d,t-k}$ is 1 (0) if drug d was (was not) listed on the PBS by the end of year $t - k$; α_i is a fixed effect for disease i and δ_t is a fixed effect for year t. The diseases are ICD-10 blocks, as defined by the World Health Organization (2015c). Inclusion of year and disease fixed effects controls for the overall decline in premature mortality and for stable between-disease differences in premature mortality. (Some trends may have *increased* premature mortality: between 1995 and 2007, the fraction of the Australian population that was overweight or obese increased from 38.7 per cent to 56 per cent, and the fraction of the Australian population that was obese increased from 10.4 per cent to 21.3 per cent.) Negative and significant estimates of β_k in Equations (1) and (2) would signify that diseases for which there was more pharmaceutical innovation had larger declines in premature mortality. The functional form of (1) and (2) has the property of diminishing marginal productivity: the absolute reduction in premature mortality declines with each successive increase in the number of drugs.

This methodology does not account for cross-disease spill-over effects. A new drug for disease X (e.g. cardiovascular disease) may reduce mortality from disease X but increase mortality from disease Y (e.g. cancer), due to 'competing risks'.[5] However, a new drug for disease X may also reduce mortality from disease Y. For example, Prince *et al.* (2007, p. 859) argue that 'mental

[5] A competing risks model is a duration model where the observed duration is the shortest of a number of latent durations (Honoré & Lleras-Muney, 2006).

disorders increase risk for communicable and non-communicable diseases, and contribute to unintentional and intentional injury. Conversely, many health conditions increase the risk for mental disorder'.

Due to data limitations, the number of new chemical entities is the only disease-specific, time-varying, explanatory variable in Equations (1) and (2). Both a patient-level US study and a longitudinal country-level study have shown that controlling for numerous other potential determinants of longevity does not reduce, and may even increase, the estimated effect of pharmaceutical innovation. The study based on patient-level data (Lichtenberg, 2013) found that controlling for race, education, family income, insurance coverage, Census region, body mass index, smoking, the mean year the person started taking his or her medications, and over 100 medical conditions had virtually no effect on the estimate of the effect of pharmaceutical innovation (the change in drug vintage) on life expectancy. The study based on longitudinal country-level data (Lichtenberg, 2014d) found that controlling for ten other potential determinants of longevity change (real per-capita income, unemployment rate, mean years of schooling, urbanisation rate, real per-capita health expenditure (public and private), the DPT immunisation rate among children aged 12–23 months, HIV prevalence and tuberculosis incidence) *increased* the coefficient on pharmaceutical innovation by about 32 per cent.

Failure to control for non-pharmaceutical medical innovation (e.g. innovation in diagnostic imaging, surgical procedures, and medical devices) is also unlikely to bias estimates of the effect of pharmaceutical innovation on premature mortality, for two reasons. First, more than half of US 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 National Institutes of Health), and new drugs often build on upstream government research (Sampat & 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 US data (Lichtenberg, 2014a,b) indicates that non-pharmaceutical medical innovation is not positively correlated across diseases with pharmaceutical innovation.

As a robustness check, I will also estimate Equation (1) by instrumental variables (IV). Australia may be considered a 'small open economy' with respect to pharmaceutical research and development (R&D): in 2011, Australia accounted for just 0.45 per cent of global business pharmaceutical R&D expenditure (OECD, 2015). The instrument for pharmaceutical innovation (new drug launches) in Australia that I will use is pharmaceutical innovation in another small open economy, Canada; Canada accounted for only 0.62 per cent of global business pharmaceutical R&D expenditure. The vast majority of drugs launched in both countries were developed in the USA, Europe, and Japan.

From estimates of Equations (1) and (2), there are two alternative, nearly equivalent, ways to determine how much of the decline in premature mortality during the sample period (1998–2011) can be attributed to the registration of new drugs. The first way is to compute β_k[mean(CUM_NCE$_{i,2011-k}$) − mean (CUM_NCE$_{i,1998-k}$)]. The second way is based on the year fixed effects. The expression $\delta_{2011} - \delta_{1998}$ indicates the 1998–2011 decline in premature mortality, controlling for (holding constant) the number of drugs, that is, in the absence of pharmaceutical innovation. Suppose Equation (1) is estimated, excluding CUM_NCE$_{i,t-k}$, and that the year fixed effects from that equation are denoted by δ'_t. Then $\delta'_{2011} - \delta'_{1998}$ indicates the 1998–2011 decline in premature mortality, not holding constant the number of drugs, that is, in the presence of pharmaceutical innovation, and $\delta'_{2011} - \delta'_{1998} - (\delta_{2011} - \delta_{1998})$ is an estimate of the 1998–2011 decline in premature mortality attributable to pharmaceutical innovation.

The data exhibit heteroscedasticity: diseases with larger total premature mortality during 1998–2011 had smaller (positive and negative) annual percentage fluctuations in YPLL75 and YPLL80. Equations (1) and (2) will therefore be estimated by weighted least squares, weighting by the mean premature mortality rate during 1998–2011 (e.g. $\left(\sum_t \text{YPLL75}_{it}\right)/13$). The standard errors of Equations (1) and (2) will be clustered within diseases.

The measure of pharmaceutical innovation in Equations (1) and (2) – 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 $\text{VINTAGE}_{it} = \sum_d Q_{dit}\,\text{LAUNCH\_YEAR}_d / \sum_d Q_{dit}$ where Q_{dit} is the quantity of drug d used to treat disease i in year t, and LAUNCH_YEAR_d is the world launch year of drug d.[6] Unfortunately, measurement of VINTAGE_{it} is infeasible: even though data on the total quantity of each drug in each year ($Q_{d\cdot t} = \sum_i Q_{dit}$) are available, many drugs are used to treat multiple diseases: 49 per cent of drugs are used for more than one indication (ICD-10 block), and the mean number of indications per drug is 2.66. There is no way to determine the quantity of drug *d used to treat disease i* in year t.[7] 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 registered within the drug class.

In Equations (1) and (2), 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 Australia by the end of year $t - k$; that is, there is a lag of k years. Equations (1) and (2) will be estimated for different values of k: $k = 0, 3, 6, 9, 12, 15$. A separate model is estimated for each value of k, rather than including multiple values ($\text{CUM\_NCE}_{i,t}$, $\text{CUM\_NCE}_{i,t-3}$, $\text{CUM\_NCE}_{i,t-5}$,. . .) 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. One would expect there to be a substantial lag because new drugs diffuse gradually: they will not be used widely until years after registration. Data from the *Australian Statistics on Medicines* (ASM; Pharmaceutical Benefits Scheme, 2015) can be used to provide evidence about the process of diffusion of new medicines. I used data from that source linked to data on PBS drug initial listing dates (described below) to estimate the following model:

$$\ln(\text{N\_RX}_{my}) = \rho_m + \pi_y + \varepsilon_{my} \qquad (3)$$

where N_RX_{my} is the number of prescriptions for molecule m sold in Australia y years after it was listed on the PBS ($y = 0, 1, \ldots, 20$), ρ_m is a fixed effect for molecule m, and π_y is a fixed effect for age y. The expression $\exp(\pi_y - \pi_0)$ is a 'relative utilisation index': it is the mean ratio of the number of prescriptions for a molecule y years after it was first listed on the PBS to the number of prescriptions for the same molecule in the year that it was first listed on the PBS. Using annual data on the number of prescriptions for molecules in Australia during the period 2007–2011, I estimated Equation (3). Estimates of the 'relative utilisation index', based on data on molecules that were first listed on the PBS after 1991, are shown in Figure 5. These estimates indicate that it takes about 9 years for a molecule to attain its peak level of utilisation. The number of prescriptions 9 years after first PBS listing is about 2.6 times as great as the number of prescriptions one year after first PBS listing. Moreover, Figure 5 provides a conservative estimate of the slope of the age-utilisation profile, because there was zero utilisation of some molecules in the first few years after they were first listed.[8]

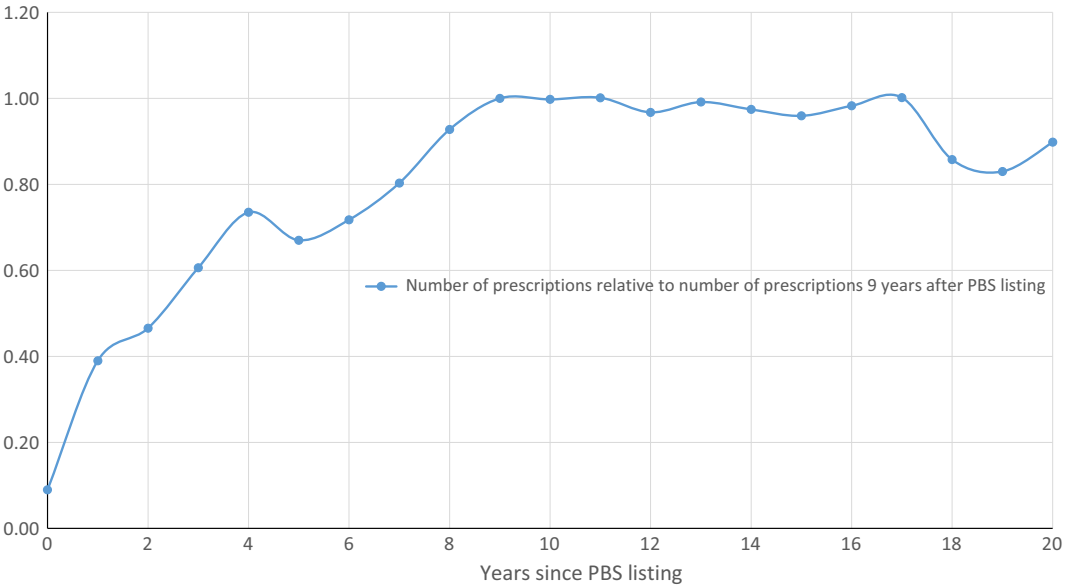
The effect of a drug's PBS listing on premature mortality is likely to depend on both the *quality* and the *quantity* of the drug. Indeed, it is likely to depend on the *interaction* between quality and quantity: a quality improvement will have a greater impact on mortality if drug utilisation (quantity) 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,

[6] According to the Merriam Webster dictionary, one definition of vintage is 'a period of origin or manufacture' (e.g. 'a piano of 1845 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 (2015) cited when it awarded Solow the 1987 Nobel Prize in Economics.

[7] Outpatient prescription drug claims usually do not 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 per cent of drug expenditure. These data are not available for Australia.

[8] Since the dependent variable of Equation (2) is logarithmic, observations for which $\text{N\_RX}_{my} = 0$ had to be excluded.

FIGURE 5
Drug Age–Utilisation Profile
[Colour figure can be viewed at wileyonlinelibrary.com]



The graph shows estimates of $\exp(\delta_y - \delta_9)$ for y = 0, 1,...,20 from the equation $\ln(N\_RX_{dy}) = \alpha_d + \delta_y + \varepsilon_{dy}$, where N_RX_{dy} = the number of prescriptions for drug d y years after PBS listing.

so the impact on mortality of very new drugs is lower than the impact of older drugs.

The measure of pharmaceutical innovation, $CUM\_NCE_{i,t-k} = \sum_d IND_{di} LISTED\_PBS_{d,t-k}$, is based on whether, according to an authoritative French database (described below), drug d had an indication for disease i at the end of 2011. The indications of a drug in Australia are unlikely to differ substantially from its indications in France. If IND_{di} (a dummy variable indicating whether drug d is used to treat (indicated for) disease i in Australia) and therefore $CUM\_NCE_{i,t-k}$ are subject to random measurement errors due to differences between Australia and France in drug indications, estimates of β_k are likely to be biased towards zero, and my estimates are likely to be conservative. One would prefer to base the measure on whether drug d had an indication for disease i at the end of year $t - k$. Calculations based on data published by the US Food and Drug Administration (2015) indicate that about one in four new molecular entities has supplemental indications, that is, indications approved after the drug was initially launched.

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 WHO Collaborating Centre for Drug Statistics Methodology, drugs are classified in groups at five different levels. The highest (first) level is the 'anatomical main group' level; there are 14 anatomical main groups. The second, third, fourth, and fifth levels are 'therapeutic subgroup', 'pharmacological subgroup', 'chemical subgroup', and 'chemical substance', respectively (see Wikipedia, 2016). 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. This will be investigated by estimating versions of Equation (1) in which $CUM\_SUBGROUP_{i,t-k}$ is included in addition to or instead of $CUM\_NCE_{i,t-k}$, where $CUM\_SUBGROUP_{i,t-k} = \sum_g$

IND_SUBGROUP gi LISTED_PBS_SUBGROUP $_{g,t-k}$ in which IND_SUBGROUP$_{gi}$ is 1 (0) if any (no) drugs in chemical subgroup g are used to treat or are indicated for disease I, and LISTED_PBS_SUBGROUP$_{g,t-k}$ is 1 (0) if any (no) drugs in chemical subgroup g had been listed on the PBS by the end of year $t - k$.

(ii) Hospital Separations Model

The hospital separations model I will estimate is:

$$\ln(\text{N\_HOSP}_{it}) = \beta_k \text{CUM\_NCE}_{i,t-k} + \alpha_i + \delta_t + \varepsilon_{i,t} \quad (4)$$

where N_HOSP$_{it}$ is the number of hospital separations due to disease i in year t (t = 1998,. . .,2011). The hospital separations data also exhibit heteroscedasticity: diseases with larger mean hospital separations during 1998–2011 had smaller (positive and negative) annual percentage fluctuations in N_HOSP. Equation (4) will therefore be estimated by weighted least squares, weighting by the mean number of hospital separations during 1998–2011 $\left(\left(\sum_t \text{N\_HOSP}_{it}\right)/14\right)$. The standard errors of Equation (4) will be clustered within diseases.

(iii) Cancer Survival Model

I now describe how I will analyse the effect that pharmaceutical innovation had on survival from all types of cancer during the period 1986–2007. The survival measure I will use is the 5-year relative survival rate. Five-year survival reflects the probability of being alive for at least 5 years after cancer diagnosis. It is a standard indicator used in reporting to reflect the prognosis of cancer and to compare survival across different cancers, time periods, and groups of people.

Relative survival is the standard approach for measuring population-based cancer survival (Coleman *et al.*, 2011). It is calculated from two measures of crude survival: observed and expected survival. Observed survival refers to the proportion of people alive for a given amount of time after a diagnosis of cancer and is calculated from population-based cancer data. Expected survival refers to the proportion of people in the general population alive for a given amount of time and is calculated from life tables of the entire Australian population, assumed to be cancer-free. Relative survival is calculated from observed survival divided by expected survival, where the numerator and denominator have been matched for sex, age, calendar year, and, where applicable, remoteness and socioeconomic status.

One of the advantages of relative survival is that it does not require information on the cause of death. By adjusting the survival of individuals with cancer for the underlying mortality that they would have experienced in the general population, relative survival reflects the net survival associated with cancer. In other words, relative survival is an inverse measure of the excess mortality attributed, either directly or indirectly, to a diagnosis of cancer.

The relative survival data I will analyse were calculated using the period method (Brenner & Gefeller, 1996). The period method calculates survival from a given follow-up or at-risk time period. Survival estimates are based on the survival experience of people who were diagnosed before or during this period, and who were at risk of dying during this period. Because the period method allows recent years of follow-up to be selected, it produces up-to-date survival estimates that reflect recent changes in cancer survival trends (Brenner, 2002; Brenner & Hakulinen, 2002a,b). The period method is an alternative to the traditional cohort method, which focuses on a group of people diagnosed with cancer in a past time period, and follows these people over time.

The US National Cancer Institute (2015a) says that 'certain factors may cause survival times to look like they are getting better when they are not. . . . These factors include lead-time bias and overdiagnosis':

> *Lead-time bias*. 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.*Overdiagnosis*.

> Sometimes, screening tests find cancers that don't matter because they would have gone away on their own or never caused any symptoms. These cancers would never have been found if not for the screening test. Finding these cancers is called overdiagnosis. Overdiagnosis can make it seem like more people are surviving cancer longer, but in reality, these are people who would not have died from cancer anyway.

To guard against the risk that lead-time bias and overdiagnosis could bias my estimates of the effect of pharmaceutical innovation on cancer survival, I will control for (changes in) the number of people diagnosed (incidence) and the mean age at which they were diagnosed.

The cancer survival model I will estimate is

$$\ln(\text{ODDS}_{st}) = \beta_k \text{CUM\_NCE}_{s,t-k} + \pi \text{AGE\_DIAG}_{st} + \gamma \ln(\text{N\_CASES}_{st}) + \alpha_s + \delta_t + \varepsilon_{st} \quad (5)$$

where $\text{ODDS}_{st} = \text{RELSURV5}_{st}/(1 - \text{RELSURV5}_{st})$ in which RELSURV5_{st} is the 5-year relative survival rate from cancer at site s in year t (t = 1986,. . .,2007); $\text{CUM\_NCE}_{s,t-k} = \sum_d \text{IND}_{ds}\text{LISTED\_PBS}_{d,t-k}$ is the number of new chemical entities (drugs) to treat cancer at site s that had been listed on the PBS by the end of year $t - k$; AGE_DIAG_{st} is the mean age at which patients were diagnosed with cancer at site s in year t; and N_CASES_{st} is the number of patients diagnosed with cancer at site s in year t. Equation (5) will be estimated by weighted least squares, weighting by N_CASES_{st}. The standard errors will be clustered within cancer sites.

IV Data Sources

Initial PBS listing dates of drugs. Dates of first listing of PBS items (from which LISTED_PBS was computed) and their WHO ATC codes were provided by the PBS Information Management Section of the Pharmaceutical Policy Branch of the Pharmaceutical Benefits Division of the Department of Health.

Drug indications (IND). Data on drug indications were obtained from Thériaque (2015), a database of official, regulatory, and bibliographic information on all drugs available in France, 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.

Premature mortality data (YPLL75, YPLL80). Data on YPLL before ages 75 and 80, by disease and year (1998–2004 and 2006–2011), and population by age and year were constructed from the *WHO Mortality Database* (World Health Organization, 2015a). Mortality data are reported in 5-year age groups. I assume that deaths in a 5-year age group occur at the midpoint of the age group. For example, I assume that deaths at age 35–39 years occurred at age 37.5. The Association of Public Health Epidemiologists in Ontario (2015) uses this method.

Hospital separations data (N_HOSP). Data on inpatient hospital separations, by principal diagnosis and year (2005–2010), were obtained from the *AIHW Principal Diagnosis Data Cubes* (AIHW, 2015a). The principal diagnosis is defined as the diagnosis established after study to be chiefly responsible for occasioning the patient's episode of care in hospital.

Cancer survival data (RELSURV5). Data on 5-year relative survival rates, by cancer site and year (1986–2007), were obtained from *Cancer survival and prevalence in Australia: period estimates from 1982 to 2010* (AIHW, 2012b).

Cancer incidence and age at diagnosis data (N_CASES and AGE_DIAG) were constructed from data contained in *Australian Cancer Incidence and Mortality (ACIM) books* (AIHW, 2015b).

Drug utilisation and expenditure data. Data on the number of prescriptions for and expenditure on drugs, by molecule and year (2007–2011), were obtained from the *Australian Statistics on Medicines* (Pharmaceutical Benefits Scheme, 2015), an annual publication produced by the Drug Utilisation Sub-committee of the Pharmaceutical Benefits Advisory Committee. The data available in the ASM represent estimates of the aggregate community use of prescription medicines in Australia.

V Empirical Results

(i) Premature Mortality Model Estimates

Estimates of CUM_NCE coefficients from models of premature mortality caused by all diseases (Eqns 1 and 2) are presented in panels A and B of Table 1. Panel A shows estimates of Equation (1), where the dependent variable is the log of YPLL before age 75 per 100,000 people below age 75. Models are estimated for six

TABLE 1
Estimates of CUM_NCE Coefficients from Premature Mortality Equations (1) and (2)

Line	Parameter	Estimate	Standard error	Z	$P > \|Z\|$
(A) Equation (1)					
1	β_0	−0.0147	0.0107	−1.37	0.1696
2	β_3	−0.0147	0.0090	−1.64	0.1013
3	β_6	**−0.0153**	**0.0072**	**−2.11**	**0.0352**
4	β_9	**−0.0136**	**0.0057**	**−2.38**	**0.0175**
5	β_{12}	−0.0121	0.0069	−1.75	0.0800
6	β_{15}	−0.012	0.0090	−1.34	0.1806
(B) Equation (2)					
7	β_0	−0.0177	0.0116	−1.53	0.1261
8	β_3	−0.0187	0.0098	−1.91	0.0556
9	β_6	**−0.0189**	**0.0081**	**−2.32**	**0.0203**
10	β_9	**−0.0171**	**0.0062**	**−2.75**	**0.0059**
11	β_{12}	**−0.0154**	**0.0074**	**−2.08**	**0.0373**
12	β_{15}	−0.0157	0.0092	−1.70	0.0889

Notes: $YPLL75_{it}$ = years of potential life lost before age 75 from disease i in year t per 100,000 population below age 75. $YPLL80_{it}$ = years of potential life lost before age 80 from disease i in year t per 100,000 population below age 80. $CUM\_NCE_{i,t-k}$ = the number of new chemical entities (drugs) to treat disease i that had been listed on the PBS by the end of year $t - k$. α_i = a fixed effect for disease i. δ_t = a fixed effect for year t. Each estimate is from a different model. Estimates in bold are statistically significant ($P < 0.05$). N = 1,788. All models include 170 fixed disease effects and 13 fixed year effects. Models were estimated via weighted least-squares. Weight used in lines 1–6 was $((\Sigma_t\ YPLL75_{it})/13)$; weight used in lines 7–12 was $((\Sigma_t\ YPLL80_{it})/13)$. Standard errors were clustered within diseases.

alternative assumed values of the lag (in years) from the number of drugs ever listed on the PBS to premature mortality: k = 0, 3, 6, 9, 12, 15. As shown in lines 1 and 2, the estimates of β_0 and β_3 are not statistically significant. However, as shown in lines 3 and 4, the estimates of β_6 and β_9 are negative and statistically significant ($P < 0.04$). This signifies that the number of life-years lost before age 75 is inversely related to the number of drugs that had been listed on the PBS up until 6–9 years earlier. Since, as shown in Figure 5, drugs are used much less frequently during the first few years after they are first listed on the PBS than they are later on, it is not surprising that it takes 6–9 years for the addition of new drugs to the PBS formulary to have a significant negative effect on premature mortality. The non-significance of β_{12} and β_{15} may be due to the fact that newer drugs (e.g. drugs listed 9 years earlier) are of higher quality than older drugs (e.g. drugs listed 15 years earlier).

Panel B shows estimates of Equation (2), where the dependent variable is the log of YPLL before age 80 per 100,000 people below age 80. Once again, the estimates of β_0 and β_3 are not statistically significant ($P > 0.05$), although the estimate of β_3 is nearly significant ($P = 0.056$). As shown in lines 9–11 of Table 1, the estimates of β_6, β_9, and β_{12} are all negative and statistically significant: the number of life-years lost before age 80 is inversely related to the number of drugs that had been listed on the PBS up until 6–12 years earlier.

As a robustness check, I also estimated the model in line 10 of Table 1 by IV. The instrument for pharmaceutical innovation in Australia that I used is pharmaceutical innovation in Canada. The first stage of the two-stage least-squares procedure was (unweighted) estimation of the model $CUM\_NCE\_AUSTRALIA_{i,t} = \theta\ CUM\_NCE\_CANADA_{i,t} + \alpha_i + \delta_t + \varepsilon_{i,t}$. The estimate of θ was 0.596 (standard error 0.047; $Z = 12.59$; $P < 0.0001$). The IV estimate of β_9 in the second stage equation, $\ln(YPLL70_{it}) = \beta_9\ CUM\_NCE\_AUSTRALIA_{i,t-9} + \alpha_i + \delta_t + \varepsilon_{i,t}$ was −0.023 (standard error 0.010; $Z = 2.27$; $P = 0.0235$). This is 36 per cent *larger* than the ordinary least-squares (OLS) estimate in line 10 of Table 1: −0.017 (standard error 0.006; $Z = 2.75$; $P = 0.0059$), although the difference between the IV and OLS estimates may not be

statistically significant.[9] This finding suggests that my estimates are not biased away from zero by reverse causality or other specification errors.[10]

As discussed above, the reduction in premature mortality attributable to previous pharmaceutical innovation can be estimated by comparing the year fixed effects from a model including a CUM_NCE measure to the year fixed effects from a similar model that excludes the CUM_NCE measure. I have done this for the model shown in line 4 of Table 1: $\ln(\text{YPLL75}_{it}) = \beta_9\ \text{CUM\_NCE}_{i,t-9} + \alpha_i + \delta_t + \varepsilon_{i,t}$. (Mortality before ages 75 and 80 are both most strongly inversely related to the number of drugs ever listed 9 years earlier.) Estimates of parameters of models of $\ln(\text{YPLL75}_{it})$ and $\ln(\text{YPLL80}_{it})$ including and excluding $\text{CUM\_NCE}_{i,t-9}$ are shown in Table A2 in the Appendix. The calculations are depicted in Figure 6. In 1998, the number of potential years of life lost before age 75 per 1,000 population under age 75 years was 54.7 (AIHW, 2015c, table S3). Between 1998 and 2011, the premature (before age 75) mortality rate declined by 11.7, to 43.0. (This decline controls for changes in the distribution of deaths, by cause; when these are not controlled for, the decline is slightly greater, from 54.7 to 41.6.) The estimates indicate that if no new drugs had been listed on the PBS during 1989–2002, the premature mortality rate would have declined by only 4.7, from 54.7 to 50.0, ceteris paribus, that is, assuming that other factors that might have compensated for the absence of innovation did not change. Hence 60 per cent (= 1 − 4.7/11.7) of the decline in premature mortality was due to previous pharmaceutical innovation.

The effects on premature mortality of both the number of drugs and the number of chemical subgroups (drug classes) for the disease ever listed 9 years earlier are investigated in Table 2. Six models are presented in the table. The dependent variable in the first three models (lines 4, 4a, and 4b) is the log of the premature (before age 75) mortality rate. The model in line 4 of Table 2 is identical to the model in line 4 of Table 1: the only regressor (aside from disease and year fixed effects) is $\text{CUM\_NCE}_{i,t-9}$. In line 4a, the only regressor is $\text{CUM\_SUBGROUP}_{i,t-9}$. The coefficient on this variable is non-significant. The model in line 4b includes both $\text{CUM\_NCE}_{i,t-9}$ and $\text{CUM\_SUBGROUP}_{i,t-9}$. Only the coefficient on $\text{CUM\_NCE}_{i,t-9}$ is significant.

The dependent variable in the last three models (lines 10, 10a, and 10b) is the log of the premature (before age 80) mortality rate. The model in line 10 of Table 2 is identical to the model in line 10 of Table 1. In line 10a, the only regressor is $\text{CUM\_SUBGROUP}_{i,t-9}$. The coefficient on this variable is non-significant. The estimates of the first five models in Table 2 support the hypothesis that premature mortality depends only on the number of drugs ever listed on the PBS, not on the number of drug classes. This would be the case if drugs within the same class are not 'therapeutically equivalent'.[11] In the model in line 10b, the coefficient on $\text{CUM\_NCE}_{i,t-9}$ is negative and significant, and the coefficient on $\text{CUM\_SUBGROUP}_{i,t-9}$ is positive and significant. High collinearity between these two variables may account for this. Moreover, the net effect of growth of the number of drugs and the number of drug classes is to reduce premature mortality.

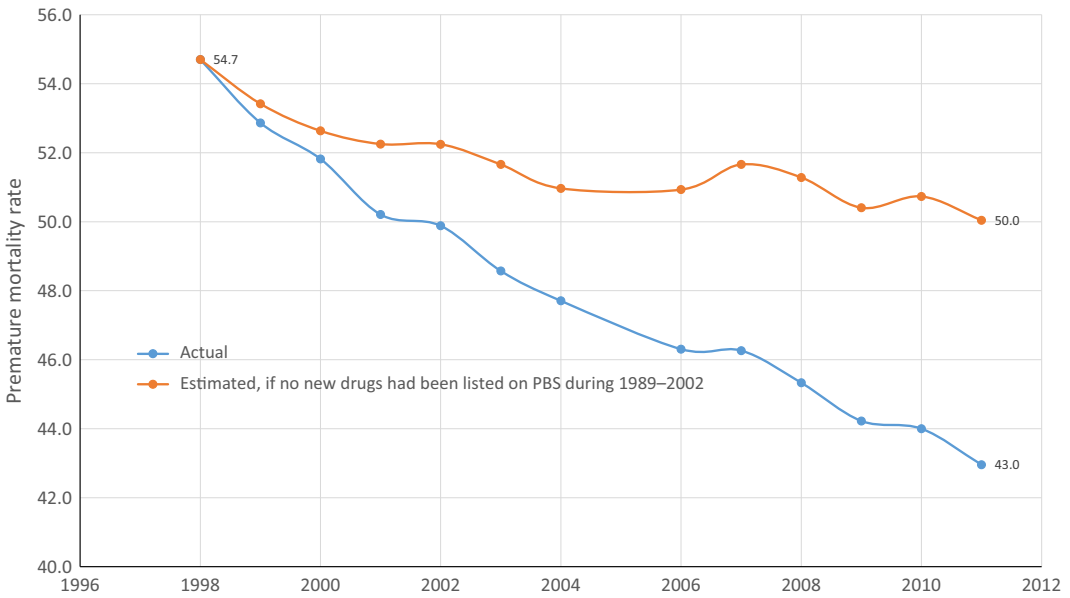
One possible interpretation of the non-significance of the number of drug classes is that mortality depends on the number of drug classes, but some drug classes may be more important or valuable than other drug classes.

[9] In a study based on longitudinal disease-level data for the USA, Lichtenberg (2014c) also found that IV estimates of the percentage reductions in work loss days, school loss days, and inpatient events attributable to pharmaceutical innovation were larger than the corresponding OLS estimates. That study used a different instrument for pharmaceutical innovation (developed by Acemoglu & Linn, 2004): the potential size of the market for drugs for a medical condition. The IV estimates of the percentage reductions in work loss days, school loss days, and inpatient events attributable to pharmaceutical innovation were about 2.4 times as large as the corresponding OLS estimates.

[10] The IV estimate might be larger than the OLS estimate because the latter (but not the former) might be biased towards zero by reverse causality: high (expected) future mortality might stimulate more PBS drug listings. However, this potential explanation for the difference between the IV and OLS estimates presumes a considerable amount of foresight. The most significant correlations are with a 9-year lag. (The contemporaneous correlations are insignificant.) It seems quite implausible that premature mortality in year t should cause PBS drug listings in year $t - 9$.

[11] Drugs are considered to be therapeutically equivalent if they have essentially the same effect in the treatment of a disease or condition.

FIGURE 6
Percentage (before Age 75) Mortality Rate, Australia, 1998–2011: Actual versus Estimated, If No New Drugs Had Been Listed on PBS during 1989–2002
[Colour figure can be viewed at wileyonlinelibrary.com]



The premature mortality rate is the number of years of potential life lost before age 75 per 1,000 population under age 75 years.

Moreover, drug classes that are more important or valuable are likely to have larger numbers of drugs. In other words, mortality is inversely related to the number of drug classes, weighted by their relative importance, and the number of drugs in a class may be a good indicator of the relative importance of the class. This could explain why mortality is related to the number of drugs rather than the number of drug classes.

(ii) Hospital Separations Model Estimates

Estimates of CUM_NCE coefficients from models of hospital separations caused by all diseases (Eqn 4) are presented in Table 3. As shown in line 13, the number of hospital separations in year t is not significantly related to the number of drugs ever listed on the PBS in year t. However, as shown in lines 14–18, the number of hospital separations is significantly inversely related to the number of drugs ever listed on the PBS 3–15 years earlier. The number of hospital separations is most strongly inversely related to the number of drugs ever listed on the PBS 12 years earlier. The reduction in hospital separations attributable to previous pharmaceutical innovation can be estimated by comparing the year fixed effects from a model including a CUM_NCE measure to the year fixed effects from a similar model that excludes the CUM_NCE measure. I have done this for the model shown in line 17 of Table 3: $\ln(\text{N\_HOSP}_{it}) = \beta_{12}\,\text{CUM\_NCE}_{i,t-12} + \alpha_i + \delta_t + \varepsilon_{i,t}$. Estimates of parameters of models of $\ln(\text{N\_HOSP}_{it})$ including and excluding $\text{CUM\_NCE}_{i,t-12}$ are shown in Table A3. The results are displayed in Figure 7. Between 1998 and 2011, the number of hospital separations increased by 47 per cent, from 5.7 million to 8.4 million. (This increase controls for changes in the distribution of separations, by principal diagnosis; when these are not controlled for, the increase is greater, from 5.7 million to 9.3 million. The population of Australia increased by 21 per cent during this period.) The estimates indicate that if no new drugs had been listed on the PBS during 1986–

TABLE 2
Effects of the Number of Drugs and the Number of Chemical Subgroups on Premature Mortality

Line	Dependent variable		Regressor: $CUM\_NCE_{i,t-9}$	Regressor: $CUM\_SUBGROUP_{i,t-9}$
4	log of premature (before age 75) mortality rate	Estimate	**−0.0136**	
		Standard error	**0.0057**	
		Z	**−2.38**	
		$P > \|Z\|$	**0.0175**	
4a	log of premature (before age 75) mortality rate	Estimate		−0.0016
		Standard error		0.0144
		Z		−0.11
		$P > \|Z\|$		0.9115
4b	log of premature (before age 75) mortality rate	Estimate	**−0.0172**	0.0193
		Standard error	**0.0052**	0.0138
		Z	**−3.34**	1.4
		$P > \|Z\|$	**0.0008**	0.1624
10	log of premature (before age 80) mortality rate	Estimate	**−0.0171**	
		Standard error	**0.0062**	
		Z	**−2.75**	
		$P > \|Z\|$	**0.0059**	
10a	log of premature (before age 80) mortality rate	Estimate		0.003
		Standard error		0.0133
		Z		0.23
		$P > \|Z\|$		0.8192
10b	log of premature (before age 80) mortality rate	Estimate	**−0.0217**	**0.0272**
		Standard error	**0.0048**	**0.011**
		Z	**−4.48**	**2.47**
		$P > \|Z\|$	**<0.0001**	**0.0135**

Notes: $CUM\_NCE_{i,t-9}$ = the number of new chemical entities (drugs) to treat disease *i* that had been listed on the PBS by the end of year $t - 9$. $CUM\_SUBGROUP_{i,t-9}$ = the number of chemical subgroups to treat disease *i* that had been listed on the PBS by the end of year $t - 9$. Estimates in bold are statistically significant (*p*-value < .05).

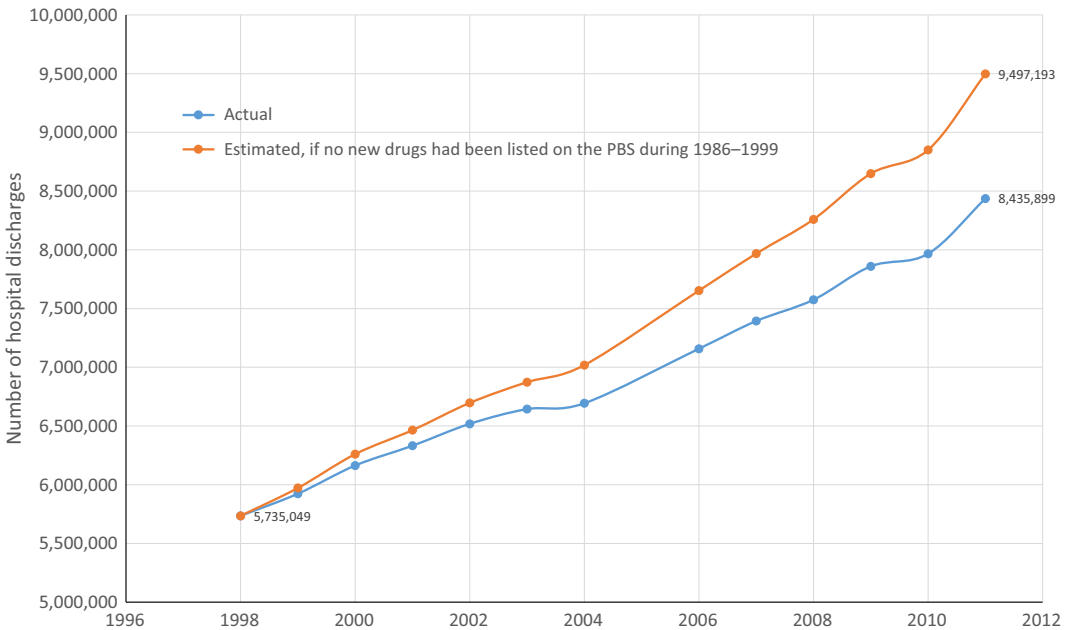
1999, the number of hospital separations would have increased by 66 per cent, from 5.7 million to 9.5 million, assuming that other factors that might have compensated for the absence of innovation did not change. The number of hospital separations in 2011 would have been 12.6 per cent higher: 1.06 million additional separations.

TABLE 3
Estimates of CUM_NCE Coefficients from Hospital Separations Equation (4)

Line	Parameter	Estimate	Standard error	*Z*	$P > \|Z\|$
13	β_0	−0.0138	0.0088	−1.57	0.1161
14	β_3	**−0.0154**	**0.0074**	**−2.09**	**0.0370**
15	β_6	**−0.0161**	**0.0063**	**−2.57**	**0.0103**
16	β_9	**−0.0144**	**0.0052**	**−2.80**	**0.0051**
17	β_{12}	**−0.0164**	**0.0056**	**−2.94**	**0.0033**
18	β_{15}	**−0.0147**	**0.0065**	**−2.28**	**0.0227**

Notes: N_HOSP_{it} = the number of hospital separations due to disease *i* in year *t*. $CUM\_NCE_{i,t-k}$ = the number of new chemical entities (drugs) to treat disease *i* that had been listed on the PBS by the end of year $t - k$. α_i = a fixed effect for disease *i*. δ_t = a fixed effect for year *t*. Each estimate is from a different model. Estimates in bold are statistically significant ($\boldsymbol{P} < 0.05$). N = 1,662. All models include 170 fixed disease effects and 13 fixed year effects. Models were estimated via weighted least-squares. Weight used was $((\Sigma_t\ N\_HOSP_{it})/13)$. Standard errors were clustered within diseases.

FIGURE 7
Number of Hospital Discharges, 1998–2011: Actual versus Estimated, If No New Drugs Had Been Listed on PBS during 1986–1999
[Colour figure can be viewed at wileyonlinelibrary.com]



(iii) Cancer Survival Model Estimates

Estimates of CUM_NCE coefficients from models of cancer survival (Eqn 5) are presented in Table 4. AGE_DIAG_{st} and $\ln(N\_CASES_{st})$ were included as covariates in all models. For simplicity, the coefficients on these variables are not shown in Table 4; both were highly significant and had the expected signs, and were very similar for different values of k. For example, when $k = 9$, the coefficient on AGE_DIAG_{st} is −0.0954 (standard error 0.0199; $Z = 4.80$), and the coefficient on $\ln(N\_CASES_{st})$ is 0.6123 (standard error 0.1488; $Z = 4.11$). Thus reductions in mean age at diagnosis and increases in the number of patients diagnosed are associated with increases in survival rates.

As shown in lines 19–23, the cancer survival rate is significantly positively related to the number of drugs that had ever been listed on the PBS 0–12 years earlier, controlling for mean age at diagnosis and the number of patients diagnosed. The cancer survival rate is most strongly positively related to the number of drugs that had ever been listed on the PBS 9 years earlier.

The increase in the cancer survival rate attributable to previous pharmaceutical innovation can be estimated by comparing the year fixed effects from a model including a CUM_NCE measure to the year fixed effects from a similar model that excludes the CUM_NCE measure. I have done this for the model shown in line 22 of Table 4: $\ln(ODDS_{st}) = \beta_9\, CUM\_NCE_{s,t-9} + \pi\, AGE\_DIAG_{st} + \gamma \ln(N\_CASES_{st}) + \alpha_s + \delta_t + \varepsilon_{st}$. Estimates of parameters of models of $\ln(ODDS_{st})$ including and excluding $CUM\_NCE_{s,t-9}$ are shown in Table A4. The results are displayed in Figure 8; since the dependent variable in Equation (5) is $\ln(ODDS_{st})$, where $ODDS_{st} = RELSURV5_{st}/(1 - RELSURV5_{st})$, Figure 8 shows the following function of the year fixed effects: $1/(1 + (1/\exp(\delta_t)))$. Between 1986 and 2007, the 5-year relative survival rate increased from 49.0 per cent to 61.6 per cent, controlling for mean age at diagnosis, the number

TABLE 4
Estimates of CUM_NCE Coefficients from Cancer Survival Equation (5)

Line	Parameter	Estimate	Standard error	Z	$P > \|Z\|$
19	β_0	**0.0131**	**0.0063**	**2.08**	**0.0379**
20	β_3	**0.0136**	**0.0054**	**2.52**	**0.0118**
21	β_6	**0.0135**	**0.0058**	**2.35**	**0.0190**
22	β_9	**0.0182**	**0.0067**	**2.72**	**0.0066**
23	β_{12}	**0.0230**	**0.0114**	**2.02**	**0.0435**
24	β_{15}	0.0187	0.0139	1.35	0.1769

Notes: $\text{ODDS}_{st} = \text{RELSURV5}_{st}/(1 - \text{RELSURV5}_{st})$. RELSURV5_{st} = the 5-year relative survival rate from cancer at site s in year t. $\text{CUM\_NCE}_{s,t-k}$ = the number of new chemical entities (drugs) to treat cancer at site s that had been listed on the PBS by the end of year $t - k$. AGE_DIAG_{st} = the mean age at which patients were diagnosed with cancer at site s in year t. N_CASES_{st} = the number of patients diagnosed with cancer at site s in year t. α_i = a fixed effect for cancer at site s. δ_t = a fixed effect for year t. Each estimate is from a different model. Estimates in bold are statistically significant ($P < 0.05$). $N = 525$. All models include 30 fixed cancer site effects and 30 fixed year effects. Models were estimated via weighted least-squares. Weight used was N_CASES_{st}. Standard errors were clustered within cancer sites.

of patients diagnosed, and changes in the distribution of patients diagnosed, by cancer site. (When these factors are not controlled for, the increase in the cancer survival rate was larger, from 49.0 per cent in 1986 to 64.2 per cent in 2007.) The estimates indicate that if no new drugs had been listed on the PBS during 1977–1998, the 5-year relative survival rate would have increased from 49.0 per cent to 56.5 per cent, ceteris paribus. Hence previous pharmaceutical

FIGURE 8
Five-year Relative Cancer Survival Rate, 1986–2007: Actual versus Estimated, If No New Drugs Had Been Listed on PBS during 1977–1998
[Colour figure can be viewed at wileyonlinelibrary.com]

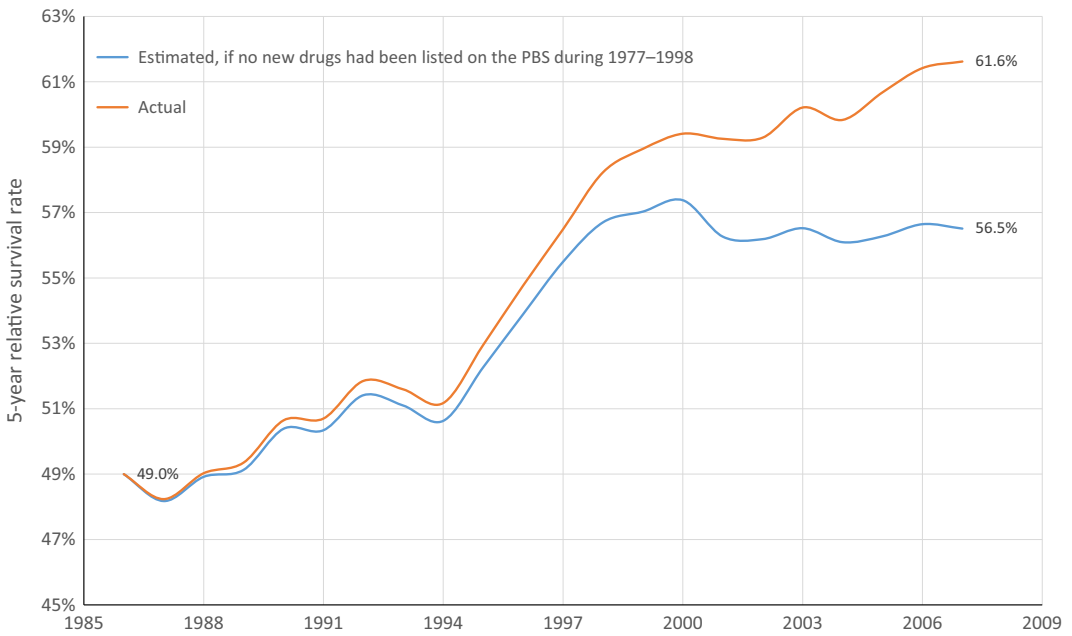


TABLE 5
Estimates of the Number of Life-Years Gained in 2011 from Previous Pharmaceutical Innovation and Medical Expenditure per Life-Year Gained

	Before age 75	Before age 80
Life years gained in 2011	143,639	257,602
Total expenditure on drugs age 9–22 in 2011	$5,768,556,127	$5,768,556,127
% of 2011 US outpatient drug expend that is by patients below age 75/80	86%	92%
Estimated expend on drugs age 9–22 in 2011 by people below age 75/80	$4,975,693,434	$5,296,292,926
Estimated reduction in 2010–2011 hospital expenditure (all ages) due to drugs age 9–22	$6,846,596,600	$6,846,596,600
% of 1998–1999 to 2007–2008 Australian hospital separations of patients below age 75 or 80	81%	89%
Estimated reduction in 2010–2011 hospital expenditure (patients below age 75 or 80) due to drugs age 9–22	$5,561,844,228	$6,119,478,688
Cost per life-year gained based on:		
100% of hospital cost offset	−$4,081	−$3,196
50% of hospital cost offset	$15,280	$8,682
0% of hospital cost offset	$34,640	$20,560

innovation is estimated to have accounted for 40 per cent (= 1 − (56.5 per cent − 49.0 per cent)/(61.6 per cent − 49.0 per cent)) of the 1986–2007 increase in the 5-year relative survival rate.

VI Discussion

I will now use the estimates of Equations (1), (2), and (4) to calculate the number of life-years gained in 2011 from previous pharmaceutical innovation, and medical expenditure per life-year gained. The calculations are summarised in Table 5. According to AIHW (2015c) (table S3), 870,672 years of potential life were lost before age 75 in 2011.[12] The difference between the two estimates of the 1998 year fixed effect in line 2 of Table A2 imply that if no new drugs had been listed on the PBS during 1989–2002, the number of YPLL before age 75 in 2011 would have been 143,639 (16.5 per cent = exp (0.2417 − 0.0890) − 1) higher. I also estimate that 1,170,597 years of potential life were lost before age 80 in 2011.[13] The difference between the two estimates of the 1998 year fixed effect in line 16 of Table A2 implies that if no new drugs had been listed on the PBS during 1989–2002, the number of YPLL before age 80 in 2011 would have been 257,602 (22.0 per cent = exp (0.2482 − 0.0493) − 1) higher.

Data from the ASM linked with information on the dates of first listing of PBS items indicate that expenditure in 2011 on drugs that were first listed on the PBS during 1989–2002 was A$5769 million.[14] I need to estimate how much of the expenditure on these drugs was made by, or on behalf of, patients below the ages of 75 and 80. I do not have any data on the distribution of drug expenditure by age group for Australia, but I do have this kind of data for the USA, from the Medical Expenditure Panel Survey (Agency for Healthcare Research and Quality, 2015). In 2011, 86 per cent of US outpatient drug expenditure was for patients below age 75; 92 per cent was for patients below age 80. Assuming that the same fractions apply to expenditure on PBS drugs, expenditure in 2011 for patients below age 75 and 80 on drugs that were first listed on the PBS during 1989–2002 was A$4,976 million and A $5,296 million, respectively.

>The difference between the two estimates of the 1998 year fixed effect in line 2 of Table A3 implies that if no new drugs had been listed on the PBS during

[12] This figure is 2.3 per cent higher than my estimate (851,295) based on data in the WHO Mortality Database.

[13] This figure is 2.3 per cent higher than my estimate (1,144,545) based on data in the WHO Mortality Database.

[14] This is just over half (52 per cent) of the total cost (government and patient contribution) of PBS drugs in 2011 (A$11,145) reported in ASM. The latter figure is 8.6 per cent higher than the figure for total pharmaceutical sales reported in the OECD Health database (A $10,261), which is surprising since, as noted earlier, the PBS does not assume responsibility for the cost of drugs to patients while they are in hospital.

1986–1999, the number of hospital separations in 2011 would have been 13.1 per cent (= exp (−0.3812 − (−0.5044)) − 1) higher. I will assume that hospital expenditure in 2011 would also have been 13.1 per cent higher. Total expenditure on public hospital services and private hospitals in 2011 was A $52,220 million (AIHW, 2014, Table A1).[15] Hence I estimate that if no new drugs had been listed on the PBS during 1986–1999, hospital expenditure in 2011 would have been A$6,847 million (= 13.1 per cent × A$52,220 million) higher. People below age 75 and 80 account for 81 per cent and 89 per cent, respectively, of Australian hospital separations.[16] This implies that if no new drugs had been listed on the PBS during 1986–1999, hospital expenditure in 2011 on people below ages 75 and 80 would have been A $5,562 million (= 81 per cent × A$6,847 million) and A$6,119 million (= 89 per cent × A$6,847 million) higher, respectively.

These calculations imply that previous pharmaceutical innovation reduced the number of life-years lost before ages 75 and 80 in 2011 by 143,639 and 257,602, respectively, and that the innovation was *cost-saving*: the reduction in hospital expenditure attributable to it exceeded expenditure on the drugs.[17] Even if one discounts or completely ignores the apparent reduction in hospital expenditure, the evidence indicates that pharmaceutical innovation was highly cost-effective. If the true reduction in hospital expenditure was only 50 per cent as large as I have estimated, the cost per life-year gained before age 75 and 80 was A$15,280 and A$8,682, respectively. If there was *no* reduction in hospital expenditure, the cost per life-year gained before age 75 and 80 was A $34,640 and A$20,560, respectively.

The WHO considers interventions whose cost per quality-adjusted life-year (QALY) gained is less than 3 times per-capita GDP to be cost-effective, and those whose cost per QALY gained is less than per-capita GDP to be highly cost-effective (World Health Organization, 2015b); Australia's per-capita GDP in 2011 was A $66,608.[18] Also, Hirth *et al.* (2000) performed a search of the value-of-life literature, and identified 41 estimates of the value of life from 37 articles based on data from a number of countries. From estimates of the value of life, they calculated estimates of the value of a QALY. Four types of methods were used to produce those estimates: revealed preference/job risk, contingent valuation, revealed preference/non-occupational safety, and human capital. Even if we completely ignore the apparent reduction in hospital expenditure, the cost per life-year gained from previous pharmaceutical innovation is well below the vast majority of estimates from the value-of-life literature of the value of a life-year.

VII Summary and Conclusions

Premature (before age 75 and 80) mortality has been declining in Australia, but there has been considerable variation in the rate of decline across diseases. I first analysed the effect that pharmaceutical innovation had on premature mortality from all diseases in Australia during the period 1998–2011 by investigating whether the diseases that experienced more pharmaceutical innovation had larger declines in premature mortality. My estimates indicated that 60 per cent of the 1998–2011 decline in premature (before age 75) mortality was due to previous pharmaceutical innovation. This estimate is broadly consistent with estimates of the impact of pharmaceutical innovation on longevity in the USA and other countries.

This estimate might be conservative, for two reasons: omitted variable bias and reverse causality. Due to data limitations, we were unable to control for non-pharmaceutical medical innovation. There is some evidence from the US healthcare system that pharmaceutical and non-pharmaceutical medical innovation are inversely correlated across diseases: diseases that had greater innovation in self-administered drugs had (statistically significant) less imaging innovation. But other evidence suggests that the two types of

[15] This figure is the average of the 2010–2011 and 2011–2012 figures, A$50,931 and A$53,509 million, respectively.

[16] These figures are based on hospital separations during the period 1998–1999 to 2007–2008 (AIHW, 2015a).

[17] A previous study (Lichtenberg, 2014c) found that pharmaceutical innovation was cost-saving in the USA. In that study, the measure of pharmaceutical innovation was the mean vintage of drugs. An instrument for pharmaceutical innovation (the potential size of the market for drugs for a medical condition) was used. The value of the benefits of pharmaceutical innovation (primarily reduction in hospital expenditure and work-loss days) implied by the IV estimates was about 30 per cent larger than the value implied by the OLS estimates.

[18] 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.

innovation are uncorrelated across diseases in the USA, and the relationship between them may be different in Australia. With regard to the second reason for potential downward bias, innovation and mortality may be related not only because innovation reduces mortality, but also because mortality 'reverse-causes' innovation: high (expected) future mortality might stimulate more PBS drug listings. The inverse relationship between innovation and morality that we estimate may be the *sum* (or net effect) of the negative effect of innovation on mortality and the positive effect of mortality on innovation. However, the latter effect presumes a considerable amount of foresight. The most significant correlation between innovation and morality has a 9-year lag. It seems quite implausible that premature mortality in year t should cause PBS drug listings in year $t - 9$. But due to the gradual diffusion of drugs documented in Figure 5, it is easy to see why drug listings in year $t - 9$ should affect premature mortality in year t.

The estimates generally supported the hypothesis that premature mortality depends on the number of drugs ever listed on the PBS, not on the number of drug classes. This may indicate that drugs within the same class are not 'therapeutically equivalent'. It is also possible that mortality is inversely related to the number of drug classes, weighted by their relative importance, and that the number of drugs in a class is a good indicator of the relative importance of the class.

Next, I analysed the effect that pharmaceutical innovation had on hospital separations from all diseases during the period 1998–2011. The estimates indicated that if no new drugs had been listed on the PBS during 1986–1999, the number of hospital separations in 2011 would have been about 13 per cent higher.

Lastly, I analysed the effect that pharmaceutical innovation had on survival from all types of cancer during the period 1986–2007, controlling for mean age at diagnosis, the number of patients diagnosed, and changes in the distribution of patients diagnosed, by cancer site. I estimated that previous pharmaceutical innovation accounted for 40 per cent of the 1986–2007 increase (from 49.0 per cent to 61.6 per cent) in the 5-year relative survival rate.

My estimates indicated that new drugs listed on the PBS during 1989–2002 reduced the number of life-years lost from all diseases before ages 75 and 80 in 2011 by 143,639 and 257,602, respectively, and that the innovation was *cost-saving*: the reduction in hospital expenditure attributable to it exceeded expenditure on the drugs. Even if one discounts or completely ignores the apparent reduction in hospital expenditure, the evidence indicates that pharmaceutical innovation was highly cost-effective. If the true reduction in hospital expenditure was only 50 per cent as large as I have estimated, the cost per life-year gained before age 75 and 80 was A$15,280 and A$8682, respectively. If there was *no* reduction in hospital expenditure, the cost per life-year gained before age 75 and 80 was A$34,640 and A$20,560, respectively. According to the World Health Organization, an intervention whose cost per QALY gained is less than A$66,608 should be considered highly cost-effective.

Because new drugs diffuse gradually, premature mortality is most strongly inversely related to the number of drugs that had ever been listed 9 years earlier. Therefore, if we assume that the relationship between pharmaceutical innovation and premature mortality remains the same until the year 2020, we can estimate the number of life-years that will be gained in that year from previous (until 2011) pharmaceutical innovation. I estimate that new drugs listed on the PBS during the period 1989–2011 will reduce the number of life-years lost before age 80 in the year 2020 by 308,245.

This study was subject to a number of limitations, including the following:

- The methodology did not account for cross-disease spill-over effects, that is, for the possibility that a new drug for disease X may either increase or reduce mortality from disease Y.
- The number of new chemical entities was the only disease-specific, time-varying, explanatory variable in the premature mortality and hospitalisation models. Both a patient-level US study and a longitudinal country-level study have shown that controlling for numerous other potential determinants of longevity does not reduce, and may even increase, the estimated effect of pharmaceutical innovation. However, we cannot rule out the possibility that, *in Australia*, other potential determinants of longevity are correlated across diseases with pharmaceutical innovation.
- The measure of pharmaceutical innovation we used (the number of chemical substances previously registered to treat a disease) is not the theoretically ideal measure.
- The estimates are based on the assumption that the indications of a drug in Australia are the same as its indications in France.

- The estimates of the (counterfactual) decline in premature mortality in the absence of pharmaceutical innovation are based on the assumption that other factors that might have compensated for the absence of innovation did not change.

Hopefully future research based on new and improved data sources will overcome these limitations.

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Appendix

TABLE A1
Drugs for Acute Upper Respiratory Infections (ICD-10 Codes J00–J06), by PBS Listing Year

Drug	PBS listing year	Drug	PBS listing year
H02AB01 betamethasone	1964	A01AD11 various	1983
H02AB02 dexamethasone	1964	B05CB01 sodium chloride	1983
H02AB04 methylprednisolone	1964	R01AA05 oxymetazoline	1983
H02AB06 prednisolone	1964	R01AD01 beclometasone	1983
H02AB07 prednisone	1964	R01BA02 pseudoephedrine	1983
H02AB09 hydrocortisone	1964	J01CR02 amoxicillin and enzyme inhibitor	1986
J01AA07 tetracycline	1964	N02BA51 acetylsalicylic acid, combinations excl. psycholeptics	1986
J01CA01 ampicillin	1964	N02BE51 paracetamol, combinations excl. psycholeptics	1986
J01CE01 benzylpenicillin	1964	R05CA10 combinations	1986
J01CE02 phenoxymethylpenicillin	1964	J01DD04 ceftriaxone	1987
J01CE30 combinations	1964	J01MA02 ciprofloxacin	1988
J01FA01 erythromycin	1964	J01CR03 ticarcillin and enzyme inhibitor	1989
J01AA02 doxycycline	1968	J01DC04 cefaclor	1989
J01AA05 metacycline	1969	J01FA06 roxithromycin	1992
J01GB03 gentamicin	1969	J01FA10 azithromycin	1995
H02AB08 triamcinolone	1970	J01FA09 clarithromycin	1996
J01EE01 sulfamethoxazole and trimethoprim	1970	J01CF01 dicloxacillin	1997
J01DB01 cefalexin	1971	J01DC02 cefuroxime	1999
J01XA01 vancomycin	1972	J01DE01 cefepime	1999
M01AE01 ibuprofen	1973	J01MA14 moxifloxacin	2002
J01CA04 amoxicillin	1974	R01AA03 ephedrine	.
J01GB01 tobramycin	1976		

TABLE A2
Estimates of Parameters of Premature Mortality Models Including and Excluding CUM_NCE$_{i,t-9}$

			CUM_NCE$_{i,t-9}$ included				CUM_NCE$_{i,t-9}$ excluded			
Line	Parameter		Estimate	Standard error	Z	$P > \|Z\|$	Estimate	Standard error	Z	$P > \|Z\|$
(A) Equation (1)										
1	CUM_NCE$_{i,t-9}$		−0.0136	0.0057	−2.38	0.0175				
2	Year	1998	0.089	0.0873	1.02	0.3078	0.2417	0.0621	3.89	<.0001
3	Year	1999	0.0653	0.0807	0.81	0.4183	0.2076	0.0581	3.57	0.0004
4	Year	2000	0.0505	0.081	0.62	0.5328	0.1876	0.0543	3.46	0.0005
5	Year	2001	0.0432	0.0568	0.76	0.4469	0.156	0.0442	3.53	0.0004
6	Year	2002	0.0431	0.0541	0.8	0.4255	0.1495	0.0377	3.96	<.0001
7	Year	2003	0.0318	0.0471	0.68	0.499	0.1229	0.0337	3.65	0.0003
8	Year	2004	0.0183	0.0399	0.46	0.6468	0.1049	0.0296	3.54	0.0004
9	Year	2006	0.0176	0.029	0.61	0.5431	0.0751	0.0213	3.52	0.0004
10	Year	2007	0.0318	0.0221	1.44	0.1495	0.0742	0.0145	5.1	<.0001
11	Year	2008	0.0245	0.0172	1.42	0.1556	0.0538	0.0162	3.32	0.0009
12	Year	2009	0.0072	0.0145	0.5	0.6188	0.0291	0.0133	2.19	0.0289
13	Year	2010	0.0137	0.0123	1.12	0.2628	0.024	0.0103	2.33	0.0198
14	Year	2011	0	0	.	.	0	0	.	.
(B) Equation (2)										
15	CUM_NCE$_{i,t-9}$		−0.0171	0.0062	−2.75	0.0059				
16	Year	1998	0.0493	0.0811	0.61	0.5434	0.2482	0.0685	3.62	0.0003
17	Year	1999	0.0318	0.0755	0.42	0.6736	0.2174	0.0638	3.41	0.0007
18	Year	2000	0.0149	0.0753	0.2	0.8428	0.1934	0.0583	3.32	0.0009
19	Year	2001	0.0178	0.0527	0.34	0.7353	0.1648	0.0509	3.24	0.0012
20	Year	2002	0.0196	0.0518	0.38	0.705	0.1582	0.0429	3.69	0.0002
21	Year	2003	0.0086	0.0443	0.19	0.8458	0.1275	0.038	3.35	0.0008
22	Year	2004	−0.0057	0.0392	−0.14	0.8852	0.107	0.0341	3.14	0.0017
23	Year	2006	−0.0034	0.0296	−0.12	0.9076	0.0713	0.0225	3.16	0.0016
24	Year	2007	0.0133	0.0217	0.61	0.5391	0.0684	0.0157	4.35	<.0001
25	Year	2008	0.014	0.016	0.88	0.3789	0.0521	0.0171	3.04	0.0024
26	Year	2009	−0.0031	0.0129	−0.24	0.8111	0.0252	0.013	1.93	0.0531
27	Year	2010	0.0066	0.0107	0.61	0.5402	0.0198	0.0084	2.36	0.0185
28	Year	2011	0	0	.	.	0	0	.	.

Notes: YPLL75$_{it}$ = years of potential life lost before age 75 from disease i in year t per 100,000 population. YPLL80$_{it}$ = years of potential life lost before age 80 from disease i in year t per 100,000 population. CUM_NCE$_{i,t-k}$ = the number of new chemical entities (drugs) to treat disease i that had been listed on the PBS by the end of year $t - k$. α_i = a fixed effect for disease i. δ_t = a fixed effect for year t.

TABLE A3
Estimates of Parameters of Hospital Separations Model Including and Excluding CUM_NCE$_{i,t-12}$
ln (N_HOSP_{it}) = $\beta_{12} CUM\_NCE_{i,t-12} + \alpha_i + \delta_t + \varepsilon_{i,t}$

			CUM_NCE$_{i,t-12}$ included				CUM_NCE$_{i,t-12}$ excluded			
Line	Parameter		Estimate	Standard error	Z	$P > \|Z\|$	Estimate	Standard error	Z	$P > \|Z\|$
1	CUM_NCE$_{i,t-12}$		−0.0164	0.0056	−2.94	0.0033				
2	Year	1998	−0.5044	0.0553	−9.12	<.0001	−0.3812	0.0485	−7.86	<.0001
3	Year	1999	−0.4639	0.053	−8.75	<.0001	−0.3454	0.0461	−7.49	<.0001
4	Year	2000	−0.4168	0.0496	−8.4	<.0001	−0.3008	0.0442	−6.81	<.0001
5	Year	2001	−0.3847	0.0446	−8.62	<.0001	−0.2677	0.0367	−7.29	<.0001
6	Year	2002	−0.3494	0.042	−8.32	<.0001	−0.239	0.0364	−6.56	<.0001
7	Year	2003	−0.3234	0.0387	−8.35	<.0001	−0.2174	0.034	−6.39	<.0001
8	Year	2004	−0.3025	0.0335	−9.02	<.0001	−0.2251	0.0318	−7.07	<.0001
9	Year	2006	−0.216	0.0257	−8.41	<.0001	−0.1641	0.0288	−5.69	<.0001
10	Year	2007	−0.1756	0.0231	−7.59	<.0001	−0.1232	0.0238	−5.18	<.0001
11	Year	2008	−0.1397	0.0149	−9.38	<.0001	−0.1173	0.0171	−6.87	<.0001
12	Year	2009	−0.0936	0.0121	−7.74	<.0001	−0.0717	0.0176	−4.06	<.0001
13	Year	2010	−0.0706	0.0233	−3.03	0.0024	−0.0443	0.015	−2.96	0.0031
14	Year	2011	0	0	.	.	0	0	.	.

Notes: N_HOSP$_{it}$ = the number of hospital separations due to disease i in year t. CUM_NCE$_{i,t-k}$ = the number of new chemical entities (drugs) to treat disease i that had been listed on the PBS by the end of year $t - k$. α_i = a fixed effect for disease i. δ_t = a fixed effect for year t.

TABLE A4
Estimates of Parameters of Cancer Survival Model Including and Excluding CUM_NCE$_{s,t-9}$
$\ln(\text{ODDS}_{st}) = \beta_9\text{CUM\_NCE}_{s,t-9} + \pi\text{AGE\_DIAG}_{st} + \gamma\ln(\text{N\_CASES}_{st}) + \alpha_s + \delta_t + \varepsilon_{s,t}$

			CUM_NCE$_{s,t-12}$ included				CUM_NCE$_{s,t-12}$ excluded			
Line	Parameter		Estimate	Standard error	Z	$P > \|Z\|$	Estimate	Standard error	Z	$P > \|Z\|$
1	CUM_NCE$_{s,t-9}$		0.0182	0.0067	2.72	0.0066				
2	AGE_DIAG$_{st}$		−0.0954	0.0199	−4.8	<.0001	−0.1061	0.0193	−5.51	<.0001
3	ln(N_CASES$_{st}$)		0.6123	0.1488	4.11	<.0001	0.5769	0.1497	3.85	0.0001
4	Year	1986	−0.3019	0.152	−1.99	0.0471	−0.5135	0.1385	−3.71	0.0002
5	Year	1987	−0.3349	0.1264	−2.65	0.008	−0.5441	0.1275	−4.27	<.0001
6	Year	1988	−0.3052	0.1368	−2.23	0.0257	−0.5124	0.1355	−3.78	0.0002
7	Year	1989	−0.2967	0.1394	−2.13	0.0334	−0.4994	0.1363	−3.66	0.0002
8	Year	1990	−0.2464	0.1388	−1.78	0.0758	−0.4477	0.1363	−3.28	0.001
9	Year	1991	−0.2482	0.1319	−1.88	0.0599	−0.4455	0.1281	−3.48	0.0005
10	Year	1992	−0.2053	0.1308	−1.57	0.1165	−0.3994	0.1251	−3.19	0.0014
11	Year	1993	−0.218	0.1431	−1.52	0.1278	−0.4098	0.1463	−2.8	0.0051
12	Year	1994	−0.2367	0.1299	−1.82	0.0684	−0.4265	0.1305	−3.27	0.0011
13	Year	1995	−0.1711	0.0967	−1.77	0.0768	−0.3553	0.0921	−3.86	0.0001
14	Year	1996	−0.1059	0.0853	−1.24	0.2147	−0.2822	0.0652	−4.33	<.0001
15	Year	1997	−0.0412	0.0798	−0.52	0.6057	−0.2124	0.0579	−3.67	0.0002
16	Year	1998	0.0078	0.0714	0.11	0.9133	−0.1412	0.0589	−2.4	0.0165
17	Year	1999	0.0212	0.0637	0.33	0.7392	−0.1116	0.0477	−2.34	0.0193
18	Year	2000	0.0354	0.0632	0.56	0.576	−0.0924	0.044	−2.1	0.0356
19	Year	2001	−0.01	0.0547	−0.18	0.8555	−0.0989	0.0475	−2.08	0.0373
20	Year	2002	−0.0131	0.0475	−0.28	0.7821	−0.0974	0.043	−2.27	0.0235
21	Year	2003	0.0005	0.0475	0.01	0.9919	−0.0591	0.0486	−1.22	0.2239
22	Year	2004	−0.0169	0.0451	−0.38	0.7075	−0.0749	0.0359	−2.09	0.0368
23	Year	2005	−0.0096	0.0273	−0.35	0.725	−0.0397	0.0252	−1.58	0.1149
24	Year	2006	0.0055	0.0207	0.27	0.7907	−0.0085	0.0187	−0.45	0.6511
25	Year	2007	0	0	.	.	0	0	.	.

Notes: ODDS$_{st}$ = RELSURV5$_{st}$/(1 − RELSURV5$_{st}$). RELSURV5$_{st}$ = the 5-year relative survival rate from cancer at site s in year t. CUM_NCE$_{s,t-k}$ = the number of new chemical entities (drugs) to treat cancer at site s that had been listed on the PBS by the end of year $t - k$. AGE_DIAG$_{st}$ = the mean age at which patients were diagnosed with cancer at site s in year t. N_CASES$_{st}$ = the number of patients diagnosed with cancer at site s in year t. α_i = a fixed effect for cancer at site s. δ_t = a fixed effect for year t.