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The association between pharmaceutical innovation and both premature mortality and hospital utilization in Switzerland, 1996–2019

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Abstract

We analyze the association that pharmaceutical innovation had with premature mortality from all diseases in Switzerland during the period 1996–2018, and its association with hospital utilization for all diseases in Switzerland during the period 2002–2019. The analysis is performed by investigating whether the diseases that experienced more pharmaceutical innovation had larger subsequent declines in premature mortality and hospitalization. Pharmaceutical innovation is measured by the growth in the number of drugs used to treat a disease ever registered in Switzerland. Utilization of a chemical substance reaches a peak 9–12 years after it was first launched, and then declines. Our estimates indicate that the number of years of potential life lost before ages 85, 75, and 65 is significantly inversely related to the number of chemical substances ever registered 6–9, 3–9, and 0–9 years earlier, respectively. The new chemical substances that were registered during the period 1990–2011 are associated with reductions in the number of years of potential life lost before ages 85, 75, and 65 in 2018 of 257 thousand, 163 thousand, and 102 thousand, respectively. The number of hospital days is significantly inversely related to the number of chemical substances ever registered 8–10 years earlier. The new chemical substances that were registered during the period 1994–2010 are associated with reductions in the number of hospital days in 2019 of 2.07 million. Average length of inpatient hospital stays is significantly inversely related to the number of chemical substances ever registered 2–10 years earlier. The new chemical substances that were registered during the period 1999–2015 are associated with reductions in the average length of stays in 2019 of 0.4 days. Under the assumption that pharmaceutical innovation is exogenous with respect to premature mortality and hospitalization, and that it is uncorrelated with other potential determinants of health outcomes, if we ignore the reduction in hospital utilization associated with previous pharmaceutical innovation, a rough estimate of the cost per life-year before age 85 gained in 2018 is € 14,310. However, about 85% of the 2018 expenditure on drugs registered during the period 1990–2011 may have been offset by the reduction in expenditure on inpatient curative and rehabilitative care. The net cost per life-year before age 85 gained in 2018 may therefore have been € 2201.

Keywords: Prescription drugs, Hospitalization, Longevity, Innovation, Switzerland

1 Introduction

A previous study (Lichtenberg, 2016) analyzed the association that pharmaceutical innovation had with premature mortality from cancer in Switzerland during the period 1995–2012, by investigating whether the cancer sites that experienced more pharmaceutical innovation

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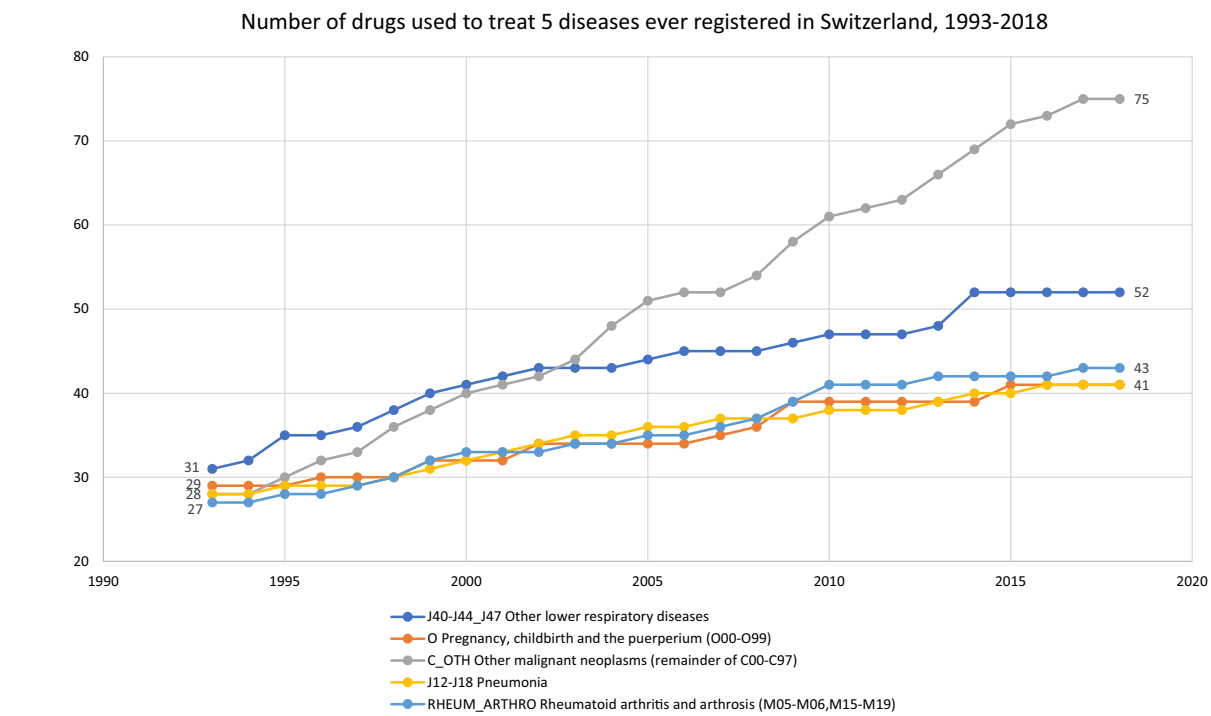

Fig. 1 Number of drugs used to treat 5 diseases ever registered in Switzerland, 1993–2018. *Source*: Author's calculations based on data contained in Swissmedic's Extended list of medicines and Centre National Hospitalier d'Information sur le Médicament's Thériaque database

had larger declines in premature mortality, controlling for the number of people diagnosed and mean age at diagnosis. That study found that premature cancer mortality before ages 75 and 65 was significantly inversely related to the cumulative number of drugs registered 5, 10, and 15 years earlier.

Cancer accounts for only about one-third of the years of potential life lost (YPLL) before age 75 in Switzerland.[1] In the present study, we will use similar methods to analyze the association that pharmaceutical innovation had with premature mortality from *all diseases* in Switzerland during a period that includes more recent years: 1996–2018. There was considerable variation across diseases in the growth in the number of drugs used to treat the diseases ever registered in Switzerland. This is illustrated by Fig. 1, which shows data for 5 diseases, for which fairly similar (between 27 and 31) numbers of drugs had been registered by 1993. During the next 25 years, 16 or fewer drugs were registered for 3 diseases, 21 drugs were registered for "other lower respiratory diseases," and 47 drugs were registered for "other malignant neoplasms."

We will extend the analysis performed in the previous study in two additional ways. We will analyze an additional measure of premature mortality: the number of years of potential life lost before age 85 (as well as before 75 and 65).[2] And, we will analyze the association that pharmaceutical innovation had with hospital utilization for all diseases in Switzerland during the period 2002–2019. In 2018, expenditure on inpatient curative and rehabilitative care was almost three times as great as expenditure on prescribed medicines: €18.0 billion vs. €6.3 billion.

In the next section, we will describe the econometric model that we will use to analyze the association that pharmaceutical innovation had with premature mortality and hospitalization due to all diseases in Switzerland during the period 1996–2019. The data sources used to estimate this model are discussed on Sect. 3. Empirical results are presented in Sect. 4. Some implications of the estimates are discussed on Sect. 5. Section 6 provides a summary.

[1] Association of Public Health Epidemiologists in Ontario (2006) describes the calculation of YPLL.

[2] In 2018, Swiss life expectancy at birth was 83.75 years. The U.S. Centers for Disease Control's WISQARS Years of Potential Life Lost (YPLL) Report website (Centers for Disease Control, 2021) allows the user to calculate YPLL before ages 65, 70, 75, 80, and 85.

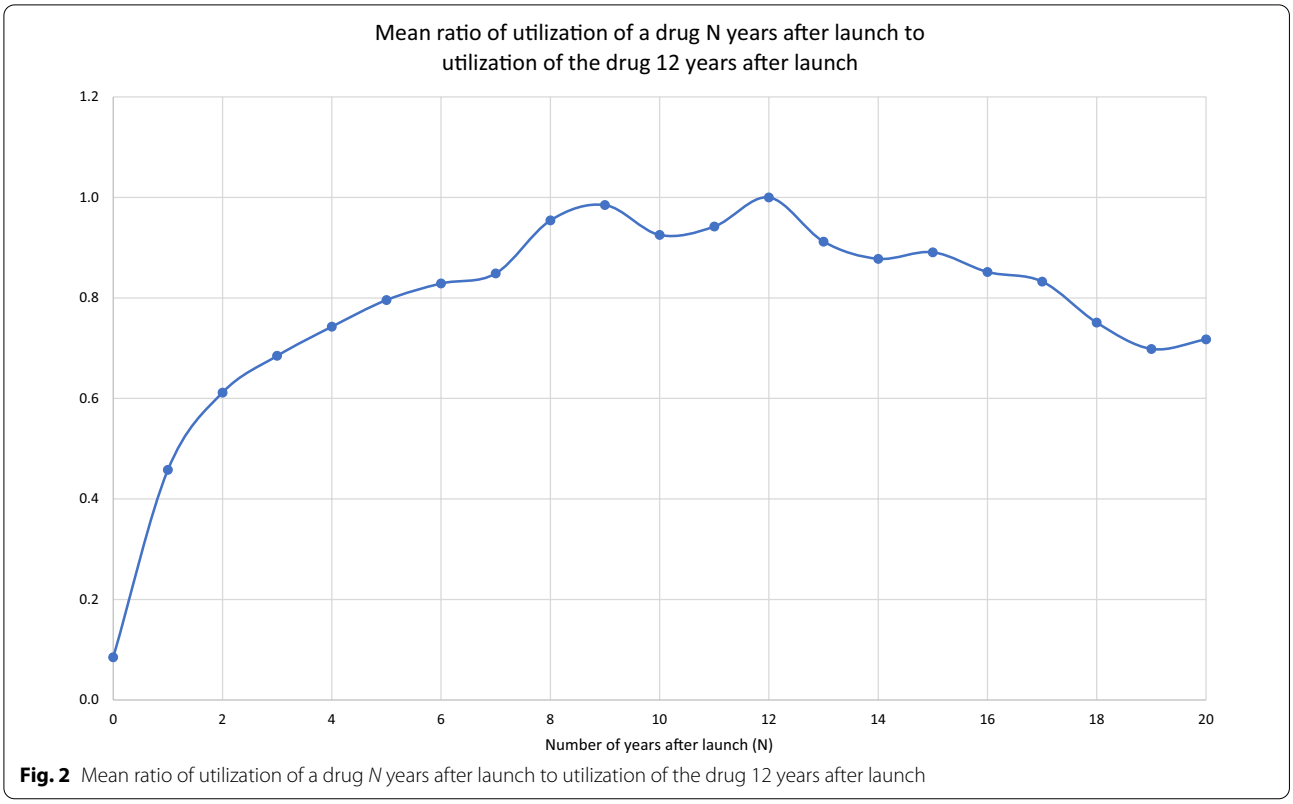

Fig. 2 Mean ratio of utilization of a drug *N* years after launch to utilization of the drug 12 years after launch

2 Econometric model of premature mortality and hospital utilization

We begin with the following general model of the association between health outcomes and the history of pharmaceutical innovation:

$$\ln(Y_{ct}) = \beta \ln\left(\gamma_0 N\_\mathrm{NEW}_{c,t} + \gamma_1 N\_\mathrm{NEW}_{c,t-1} + \gamma_2 N\_\mathrm{NEW}_{c,t-2} + \cdots\right) + \alpha_c + \delta_t + \varepsilon_{ct} \quad (1)$$

where

Y_{ct} a measure of premature mortality or hospital utilization due to medical condition c in year t

$\mathrm{N\_NEW}_{c,t-k}$ the number of new drugs used to treat medical condition c that were approved in year $t-k$ ($k=0, 1, 2, \ldots$);

α_c a fixed effect for medical condition c

δ_t a fixed effect for year t.

According to Eq. (1), premature mortality and hospitalization due to a medical condition depends on the logarithm of a distributed lag function of the number of new drugs approved to treat the disease, controlling for fixed medical condition and year effects. This specification allows the effect of a new drug approval on outcomes to depend upon how long ago the drug was approved. For example, $(\gamma_2/\gamma_1)=2$ would imply that a drug approved 2 years ago has twice as great an impact as a drug approved one year ago.

The lag structure of Eq. (1)—in particular, whether recently approved drugs have a smaller or larger impact than drugs approved longer ago—is likely to depend on several factors. Two considerations suggest that recently approved drugs should have a smaller impact. First, utilization of recently-launched drugs tends to be lower than utilization of drugs launched many years earlier. Evidence about the shape of the age (number of years since launch)-utilization profile can be obtained by estimating the following equation:

$$\ln(N\_SU_{mn}) = \rho_m + \delta_n + \varepsilon_{mn} \quad (2)$$

where

$\mathrm{N\_SU}_{mn}$ the number of standard units of chemical substance m sold n years after it was first launched ($n=0, 1, \ldots, 20$)

ρ_m a fixed effect for chemical substance m

δ_n a fixed effect for age n.

The expression $\exp(\delta_n - \delta_{12})$ is a "relative utilization index": it is the mean ratio of the quantity of a drug sold n years after it was launched to the quantity of the same drug sold 12 years after it was launched. We estimated Eq. (2), using annual data for the period 2010–2020 on 1015 chemical substances. Estimates of the "relative utilization index" are shown in Fig. 2. These estimates indicate that utilization of a chemical substance reaches a peak 9–12 years after it was first launched, and then declines. It is used about twice as much 9 years after launch as it was one year after launch. Due to gradual diffusion of new drugs, recently launched drugs may have a smaller impact than previously launched drugs.

A second reason why recently launched drugs may have a smaller impact on outcomes is that some drugs for chronic diseases (e.g. statins) may have to be consumed for several years to achieve full effectiveness.

But there is also a reason why recently launched drugs may have a larger impact than previously launched drugs: quality change. The impact of a drug on disease burden is likely to depend on its quality (or effectiveness) as well as on its quantity (utilization), and drugs launched more recently are likely to be of higher quality than earlier-vintage drugs.[3,4] However, the average annual rate of pharmaceutical quality change is unknown.

Although we think that Eq. (1) is a good theoretical model of the impact of pharmaceutical innovation on outcomes, estimation of that equation is not practical. Without imposing restrictions on the γ_k parameters, Eq. (1) is a nonlinear (and non-log-linear) function of the parameters. Aside from that, to our knowledge, no statistical packages enable estimation of distributed lag models from panel data with clustered standard errors.

However, we think we can obtain some insight about the lag structure by estimating different versions of Eq. (1) under simple, alternative assumptions about γ_k. In the first version, we assume that $\gamma_k = 1$, $\forall\ k$. In this case, the model reduces to $\ln(Y_{ct}) = \beta\ \ln(\text{CUM\_DRUG}_{c,t}) + \alpha_c + \delta_t + \varepsilon_{ct}$, where $\text{CUM\_DRUG}_{c,t} = (\sum_{k=0}\ \text{N\_NEW}_{c,t-k})$. Outcomes in year t depend on the sum of the number of drugs ever launched until the end of year t. In the second version, $\gamma_0 = 0$, $\gamma_k = 1$, $k \geq 1$. In this case, the model reduces to $\ln(Y_{ct}) = \beta\ \ln(\text{CUM\_DRUG}_{c,t-1}) + \alpha_c + \delta_t + \varepsilon_{ct}$, where $\text{CUM\_DRUG}_{c,t-1} = (\sum_{k=1}\ \text{N\_NEW}_{c,t-k})$. Outcomes in year t depend on the sum of the number of drugs ever launched until the end of year $t-1$.

More generally, to assess the association that pharmaceutical innovation had with premature mortality and hospital utilization under 13 different assumed lag structures, we will estimate models based on the following 2-way fixed effects equation:

$$\ln(Y_{ct}) = \beta_k \ln\left(\text{CUM\_DRUG}_{c,t-k}\right) + \alpha_c + \delta_t + \varepsilon_{ct} \tag{3}$$

where Y_{ct} is one of the following variables:

YPLL85_{ct}	the number of years of potential life lost before age 85 due to cause c in year t ($t = 1996, 1997, \ldots, 2018$);
YPLL75_{ct}	the number of years of potential life lost before age 75 due to cause c in year t ($t = 1996, 1997, \ldots, 2018$);
YPLL65_{ct}	the number of years of potential life lost before age 65 due to cause c in year t ($t = 1996, 1997, \ldots, 2018$);
HOSP_DAYS_{ct}	the number of hospital days due to cause c in year t ($t = 2002, 2003, \ldots, 2019$);
ALOS_{ct}	the average length of hospital stays due to cause c in year t ($t = 2002, 2003, \ldots, 2019$)

and

$\text{CUM\_DRUG}_{c,t-k}$	$\sum_m \text{IND}_{mc}\ \text{LAUNCHED}_{m,t-k}$ = the number of chemical substances to treat medical condition c that had been launched in Switzerland by the end of year $t-k$ ($k = 0, 1, 2, \ldots, 12$)[5]
IND_{mc}	= 1 if chemical substance m is used to treat (indicated for) medical

[3] Grossman and Helpman (1991) argued that "innovative goods are better than older products simply because they provide more 'product services' in relation to their cost of production." Bresnahan and Gordon (1996) stated simply that "new goods are at the heart of economic progress," and Bils (2004) said that "much of economic growth occurs through growth in quality as new models of consumer goods replace older, sometimes inferior, models." As noted by Jovanovic and Yatsenko (2012), in "the Spence–Dixit–Stiglitz tradition…new goods [are] of higher quality than old goods."

[4] The impact on disease burden may depend on the *interaction* (quantity * quality) of the two variables. The impact will increase with respect to drug age (time since launch) if the rate of increase of quantity with respect to age is greater than the rate of decline of quality with respect to age; otherwise the impact will decline.

[5] The Swiss process of marketing authorization and reimbursement takes place in two steps. Step one: Drug is reviewed for safety, effectiveness and approval by Swissmedic. If approved, the drug receives market authorization. Step 2: The producer negotiates a price for the drug with the Federal Office of Public Health. Once the price is determined, the drug is put on the Specialty List for reimbursement. Virtually all drugs that receive marketing authorization are put on the Specialty List. This process takes longer for some drugs than it does for others. An intermediary/broker (the Federal Drug Commission (EAK)) is responsible for recommending a price for a newly approved drug. According to Paris and Docteur (2007), "the Swiss tend to be early adopters of new pharmaceutical products."

	condition c[6]
	$=0$ if chemical substance m is not used to treat (indicated for) medical condition c
$\text{LAUNCHED}_{m,t-k}$	1 if chemical substance m had been registered in Switzerland by the end of year $t-k$
	$=0$ if chemical substance m had not been registered in Switzerland by the end of year $t-k$
α_c	a fixed effect for medical condition c
δ_t	a fixed effect for year t

This formulation of the "health production function" (Koç, 2004) is consistent with Romer's (1990) model of endogenous technological change, in which "growth in income per person is tied to growth in the *total stock of ideas*" (Jones (2019, p. 861), emphasis added).

Equation (3) will be estimated by weighted least-squares. For the first four dependent variables, the weight will be $\sum_t Y_{ct}$. For the last dependent variable, the weight will be N_DISCHARGES_{ct} = the number of inpatient hospital discharges due to cause c in year t. Disturbances will be clustered by cause.

The year fixed effects (δ_t 's) in Eq. (3) control for the effects of changes in macroeconomic variables (e.g. population size, GDP, educational attainment), to the extent that those variables have similar effects on mortality and hospitalization caused by different diseases. The year fixed effects capture the change in the dependent variable, holding lagged CUM_DRUG constant, i.e., in the absence of previous pharmaceutical innovation. The ("counterfactual") estimated aggregate value of the dependent variable in year t in the *absence* of previous pharmaceutical innovation is $((\sum_c Y_{c,1996}) \times \exp(\delta_t - \delta_{1996}))$. We can estimate the ("actual") aggregate value of the dependent variable in year t in the *presence* of previous pharmaceutical innovation as $\left(\left(\sum_c Y_{c,1996}\right) \times \exp\left(\delta'_t - \delta'_{1996}\right)\right)$, where δ'_t is the year fixed effect of the following equation[7]:

$$\ln(Y_{ct}) = \alpha'_c + \delta'_t + \varepsilon'_{ct} \tag{4}$$

For each dependent variable, we will estimate 13 versions of Eq. (3): one for each value of the lag length k ($k=0, 1, 2,\ldots,12$). We will also estimate a version that includes multiple lag lengths.

Equation (3) includes a measure of pharmaceutical innovation ($\text{CUM\_DRUG}_{c,t-k}$), but it does not include measures of other types of biomedical innovation (e.g. innovation in diagnostic imaging, surgical procedures, and medical devices). Dorsey (2010) showed that 88% of private U.S. funding for biomedical research came from pharmaceutical and biotechnology firms.[8] Also, some previous research indicated that non-pharmaceutical medical innovation is not positively correlated across diseases with pharmaceutical innovation. Some studies have found no mortality benefit from more intensive screening. For example, data from the Prostate, Lung, Colorectal and Ovarian randomized screening trial showed that, after 13 years of follow up, men who underwent annual prostate cancer screening with prostate-specific antigen testing and digital rectal examination had a 12 percent higher incidence of prostate cancer than men in the control group but the same rate of death from the disease. No evidence of a mortality benefit was seen in subgroups defined by age, the presence of other illnesses, or pre-trial PSA testing (National Cancer Institute, 2012). Also, a large U.S. government study found that drug therapy alone may save the lives of heart disease patients with blocked coronary arteries as effectively as bypass or stenting procedures (Kolata, 2019). Nevertheless, controlling for non-pharmaceutical medical innovation would be desirable, but measuring non-pharmaceutical medical innovation is far more difficult than measuring pharmaceutical innovation.

3 Data sources and descriptive statistics

Data on the Swiss approval dates (1933-present) of molecules (WHO ATC5 chemical substances) were obtained from Swissmedic (2021). Data on approved ICD-10 indications of WHO ATC5 chemical substances were obtained from Thériaque, a database produced by France's Centre National Hospitalier d'Information sur le Médicament (2021). Data on Swiss drug expenditure, by molecule and year (2010–2020), were obtained from the IQVIA MIDAS database. Data on the number of years of potential life lost before ages 85, 75, and 65, by cause and year (1996–2018), were constructed from data contained in the Eurostat hlth_cd_aro and hlth_cd_anr files (European Commission, 2021). Data on population, by age group and year, were obtained from the Eurostat demo_pjangroup file. Data on the number of days of hospital care, by cause and year (2002–2019), were obtained from the Eurostat hlth_co_hosday file. Data on inpatient average length

[6] Many drugs have multiple indications: 50% of drugs have 2 or more indications (causes of disease in the WHO Global Health Estimates disease classification), and 7% of drugs have 5 or more indications.

[7] Both measures control for changes in the distribution of YPLL or hospital utilization, by cause.

[8] Much of the rest came from the federal government (i.e. the NIH), and new drugs often build on upstream government research (Sampat and Lichtenberg 2011). The National Cancer Institute (2021) says that it "has played a vital role in cancer drug discovery and development, and, today, that role continues".

Table 1 Mortality from all causes, 1996–2018

Year	Mortality levels				Population				Premature mortality rates per 100,000 population		
	No. of deaths	YPLL85	YPLL75	YPLL65	Total	< 85	< 75	< 65	YPLL85	YPLL75	YPLL65
1996	62,637	678,896	365,766	199,924	7,062,354	6,935,106	6,586,598	6,018,090	9789	5553	3322
1997	62,838	667,148	357,031	192,713	7,081,346	6,950,862	6,595,723	6,026,239	9598	5413	3198
1998	62,569	653,702	346,199	185,744	7,096,465	6,962,445	6,603,188	6,029,559	9389	5243	3081
1999	62,503	637,552	335,184	178,359	7,123,537	6,986,264	6,621,418	6,043,739	9126	5062	2951
2000	62,527	640,625	338,605	179,822	7,164,444	7,024,097	6,653,572	6,070,181	9120	5089	2962
2001	61,228	619,811	326,724	173,056	7,204,055	7,062,693	6,683,395	6,094,869	8776	4889	2839
2002	61,768	612,010	320,760	168,777	7,255,653	7,109,526	6,718,004	6,124,508	8608	4775	2756
2003	63,070	604,882	313,084	162,107	7,313,853	7,167,551	6,768,515	6,171,374	8439	4626	2627
2004	60,179	586,691	305,981	159,278	7,364,148	7,217,830	6,810,385	6,207,407	8128	4493	2566
2005	61,124	579,391	300,534	155,106	7,415,102	7,266,472	6,849,995	6,240,760	7973	4387	2485
2006	60,283	570,937	295,637	152,249	7,459,128	7,304,488	6,882,484	6,266,663	7816	4295	2430
2007	61,089	564,867	290,267	146,002	7,508,739	7,346,535	6,920,035	6,292,077	7689	4195	2320
2008	61,233	555,458	285,175	142,998	7,593,494	7,425,385	6,992,298	6,348,334	7481	4078	2253
2009	62,431	562,535	288,692	145,640	7,701,856	7,527,656	7,088,899	6,425,411	7473	4072	2267
2010	62,649	549,755	278,545	136,915	7,785,806	7,605,787	7,160,468	6,477,115	7228	3890	2114
2011	62,682	556,477	284,689	142,064	7,870,134	7,691,567	7,241,130	6,540,440	7235	3932	2172
2012	64,805	559,792	285,384	140,979	7,954,662	7,769,860	7,312,969	6,589,510	7205	3902	2139
2013	65,534	558,048	282,933	139,433	8,039,060	7,849,841	7,386,963	6,640,442	7109	3830	2100
2014	64,452	544,088	273,806	133,668	8,139,631	7,945,463	7,475,382	6,706,884	6848	3663	1993
2015	68,279	564,465	282,468	138,385	8,237,666	8,037,466	7,559,383	6,772,101	7023	3737	2043
2016	65,533	541,034	269,709	130,832	8,327,126	8,121,762	7,636,916	6,832,074	6662	3532	1915
2017	67,431	543,475	269,435	131,335	8,419,550	8,207,969	7,711,099	6,896,491	6621	3494	1904
2018	67,621	543,417	268,424	130,084	8,484,130	8,266,991	7,755,618	6,933,765	6573	3461	1876
2018/1996	1.08	0.80	0.73	0.65	1.20	1.19	1.18	1.15	0.67	0.62	0.56

of stay (in days), by cause and year (2002–2019), were obtained from the Eurostat hlth_co_dischls file.

Annual data on mortality from all causes during 1996–2018 are shown in Table 1. Between 1996 and 2018, YPLL85 declined by 20%, and the population below age 85 increased by 19%, so the premature (before age 85) mortality rate declined by 33%, from 9789 to 6573 per 100,000 population. The pre-age-75 and pre-age-65 mortality rates declined even more, by 38% and 44%, respectively. Data on mortality by cause in 2018 are shown in Table 5 in Appendix.[9]

Annual data on hospitalization for all causes during 2002–2019 are shown in Table 2. Between 2002 and 2019, the number of hospital days was essentially constant, and the population increased by 18%, so the number of hospital days per 1000 population declined by 15%, despite the aging of the population. The average length of inpatient hospital stays declined even more, by 29%. Data on the number of hospital days and average length of stay, by cause, in 2019 are shown in Table 6 in Appendix.

Data on the number of chemical substances ever registered in Switzerland, by medical condition (hospital classification), 1989–2019, are shown in Table 7 in Appendix.

4 Empirical results

4.1 Premature mortality model estimates

Estimates of β_k from 2-way fixed-effects premature mortality models [Eq. (3)] are presented in Table 3 and plotted in Fig. 3. Each estimate is from a separate model.

Panel A of the table and figure show estimates when the dependent variable is $\ln(\text{YPLL85}_{ct})$. The estimates of β_k are not statistically significant when $k \leq 5$, but they are negative and significant when $6 \leq k \leq 9$: premature (before age 85) mortality is significantly inversely related to the number of chemical substances ever registered 6–9 years earlier. It is most strongly inversely related to the number of chemical substances ever registered

[9] This table (and Table 6 in Appendix) shows data on cause subtotals as well as detailed causes. For example, it shows data on cause E [Endocrine, nutritional and metabolic diseases (E00–E90)] as well as its two components [cause E10–E14 (Diabetes mellitus) and cause E_OTH (Other endocrine, nutritional and metabolic diseases (remainder of E00–E90))]. Our estimates of Eq. (1) are based only on the detailed cause data.

Table 2 Hospital utilization for all causes except V–Z, 2002–2019

Year	No. of hospital days	Population	Hospital days per 1000 population	Average length of stay
2002	11,479,682	7,255,653	1582	11.4
2003	11,424,156	7,313,853	1562	11.3
2004	10,995,761	7,364,148	1493	10.8
2005	10,929,566	7,415,102	1474	10.6
2006	10,677,099	7,459,128	1431	10.2
2007	10,417,517	7,508,739	1387	9.7
2008	10,408,136	7,593,494	1371	9.5
2009	10,444,939	7,701,856	1356	9.2
2010	11,248,330	7,785,806	1445	9.0
2011	11,380,995	7,870,134	1446	8.8
2012	1,1150,469	7,954,662	1402	8.7
2013	11,292,607	8,039,060	1405	8.6
2014	11,388,407	8,139,631	1399	8.5
2015	11,535,738	8,237,666	1400	8.4
2016	11,738,624	8,327,126	1410	8.3
2017	11,612,636	8,419,550	1379	8.2
2018	11,500,553	8,484,130	1356	8.2
2019	11,512,426	8,544,527	1347	8.2
2019/2002	1.00	1.18	0.85	0.71

8 years earlier. This is consistent with the evidence discussed above that utilization of a chemical substance reaches a peak 9–12 years after it was first launched, and that drugs launched more recently are likely to be of higher quality than earlier-vintage drugs.

Panel B of Table 3 and Fig. 3 shows estimates when the dependent variable is $\ln(\text{YPLL75}_{ct})$. In this case, the estimates are negative and significant when $3 \le k \le 9$: the number of years of potential life lost before age 75 is significantly inversely related to the number of chemical substances ever registered 3–9 years earlier. It is most strongly inversely related to the number of chemical substances ever registered 7 years earlier.

Panel C of Table 3 and Fig. 3 shows estimates when the dependent variable is $\ln(\text{YPLL65}_{ct})$. In this case, the estimates are negative and significant when $0 \le k \le 9$: the number of years of potential life lost before age 65 is significantly inversely related to the number of chemical substances ever registered 0–9 years earlier. Once again, it is most strongly inversely related to the number of chemical substances ever registered 7 years earlier. But the finding that YPLL65 is significantly inversely related to the number of chemical substances ever registered just a few years earlier may indicate that access to new drugs for diseases that kill patients at lower ages may occur earlier than access to new drugs for diseases that kill patients at higher ages.

As discussed above, by estimating both Eqs. (3) and (4), we can compute both the ("counterfactual") aggregate value of the dependent variable in year t in the *absence* of previous pharmaceutical innovation, and the ("actual") aggregate value of the dependent variable in year t in the *presence* of previous pharmaceutical innovation. The results of these calculations for the three premature mortality measures are shown in Fig. 4. For each measure, we use the estimate of Eq. (3) in which $\ln(\text{CUM\_DRUG}_{c,t-k})$ is most strongly related to $\ln(\text{Y}_{ct})$.

Panels A and B of Fig. 4 compare the evolution of aggregate YPLL85 $(=\sum_c \text{YPLL85}_{ct})$ controlling for $\text{CUM\_DRUG}_{c,t-7}$ (i.e., if $\text{CUM\_DRUG}_{c,t-7}$ had remained constant) to the actual evolution of aggregate YPLL85. Between 1996 and 2018, YPLL85 declined by 20%, from 679 to 544 thousand. The estimate of β_7 implies that, if $\text{CUM\_DRUG}_{c,t-7}$ had not increased, YPLL85 would have *increased* by 18%, to 801 thousand. As shown in Table 1, during that period, the population below age 85 increased by 19%, which implies that, if $\text{CUM\_DRUG}_{c,t-7}$ had not increased, there would

Table 3 Estimates of β_k from 2-way fixed-effects premature mortality models [Eq. (3)]

Lag (*k*)	Estimate	Standard error	95% Lower confidence	95% Upper confidence	*Z*	Pr>|*Z*|
A. Dependent variable = ln(YPLL85$_{ct}$)						
0	−0.440	0.409	−1.242	0.362	−1.07	0.2827
1	−0.450	0.376	−1.187	0.287	−1.20	0.2317
2	−0.467	0.346	−1.145	0.210	−1.35	0.1766
3	−0.482	0.314	−1.098	0.135	−1.53	0.1257
4	−0.486	0.289	−1.052	0.080	−1.68	0.0926
5	−0.498	0.265	−1.017	0.022	−1.88	0.0605
6	**−0.508**	**0.247**	**−0.992**	**−0.024**	**−2.06**	**0.0395**
7	**−0.514**	**0.233**	**−0.971**	**−0.056**	**−2.20**	**0.0277**
8	**−0.501**	**0.226**	**−0.944**	**−0.058**	**−2.22**	**0.0266**
9	**−0.462**	**0.222**	**−0.896**	**−0.027**	**−2.08**	**0.0374**
10	−0.331	0.200	−0.724	0.062	−1.65	0.0986
11	−0.252	0.183	−0.610	0.106	−1.38	0.1684
12	−0.198	0.171	−0.532	0.136	−1.16	0.2457
B. Dependent variable = ln(YPLL75$_{ct}$)						
0	−0.727	0.477	−1.663	0.208	−1.52	0.1275
1	−0.725	0.433	−1.575	0.124	−1.67	0.0943
2	−0.735	0.385	−1.490	0.021	−1.91	0.0566
3	**−0.717**	**0.351**	**−1.405**	**−0.028**	**−2.04**	**0.0413**
4	**−0.694**	**0.316**	**−1.312**	**−0.076**	**−2.20**	**0.0279**
5	**−0.677**	**0.290**	**−1.245**	**−0.108**	**−2.33**	**0.0197**
6	**−0.669**	**0.271**	**−1.200**	**−0.138**	**−2.47**	**0.0135**
7	**−0.657**	**0.259**	**−1.165**	**−0.149**	**−2.54**	**0.0112**
8	**−0.630**	**0.258**	**−1.135**	**−0.124**	**−2.44**	**0.0147**
9	**−0.565**	**0.266**	**−1.086**	**−0.044**	**−2.13**	**0.0335**
10	−0.398	0.258	−0.904	0.108	−1.54	0.1235
11	−0.287	0.247	−0.770	0.197	−1.16	0.2452
12	−0.204	0.236	−0.666	0.257	−0.87	0.3858
C. Dependent variable = ln(YPLL65$_{ct}$)						
0	**−1.067**	**0.490**	**−2.026**	**−0.107**	**−2.18**	**0.0294**
1	**−1.042**	**0.432**	**−1.890**	**−0.195**	**−2.41**	**0.0159**
2	**−1.025**	**0.371**	**−1.752**	**−0.297**	**−2.76**	**0.0058**
3	**−0.975**	**0.337**	**−1.636**	**−0.314**	**−2.89**	**0.0038**
4	**−0.920**	**0.296**	**−1.500**	**−0.341**	**−3.11**	**0.0019**
5	**−0.878**	**0.271**	**−1.410**	**−0.347**	**−3.24**	**0.0012**
6	**−0.856**	**0.253**	**−1.352**	**−0.361**	**−3.39**	**0.0007**
7	**−0.834**	**0.242**	**−1.309**	**−0.359**	**−3.44**	**0.0006**
8	**−0.799**	**0.247**	**−1.283**	**−0.316**	**−3.24**	**0.0012**
9	**−0.722**	**0.266**	**−1.243**	**−0.201**	**−2.71**	**0.0066**
10	−0.538	0.283	−1.093	0.018	−1.90	0.0579
11	−0.408	0.292	−0.981	0.166	−1.39	0.1634
12	−0.301	0.297	−0.884	0.281	−1.01	0.3105

Estimates in bold are statistically significant (p value < .05)

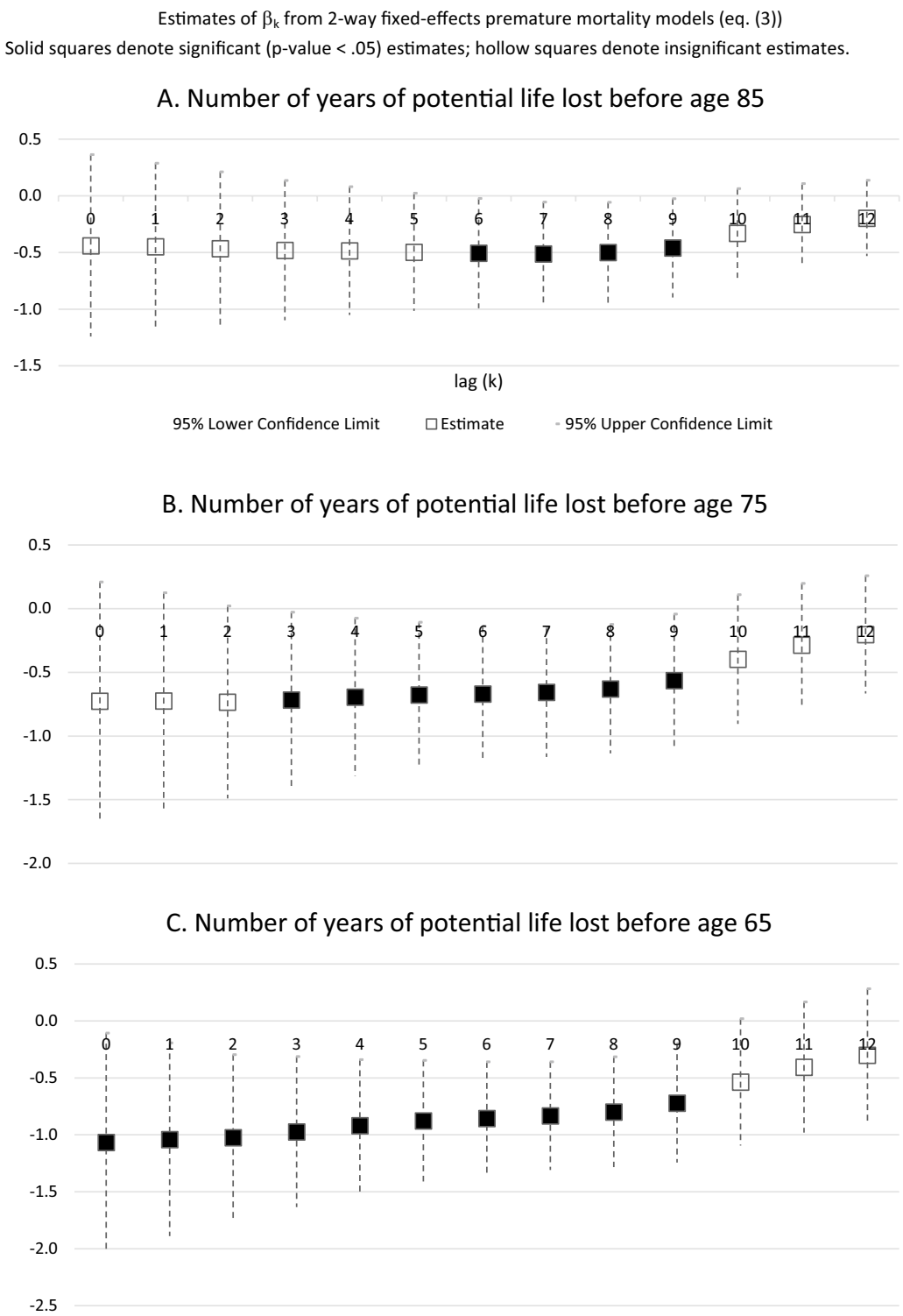

Fig. 3 Estimates of β_k from 2-way fixed-effects premature mortality models [Eq. (3)] Solid squares denote significant (p value < .05) estimates; hollow squares denote insignificant estimates

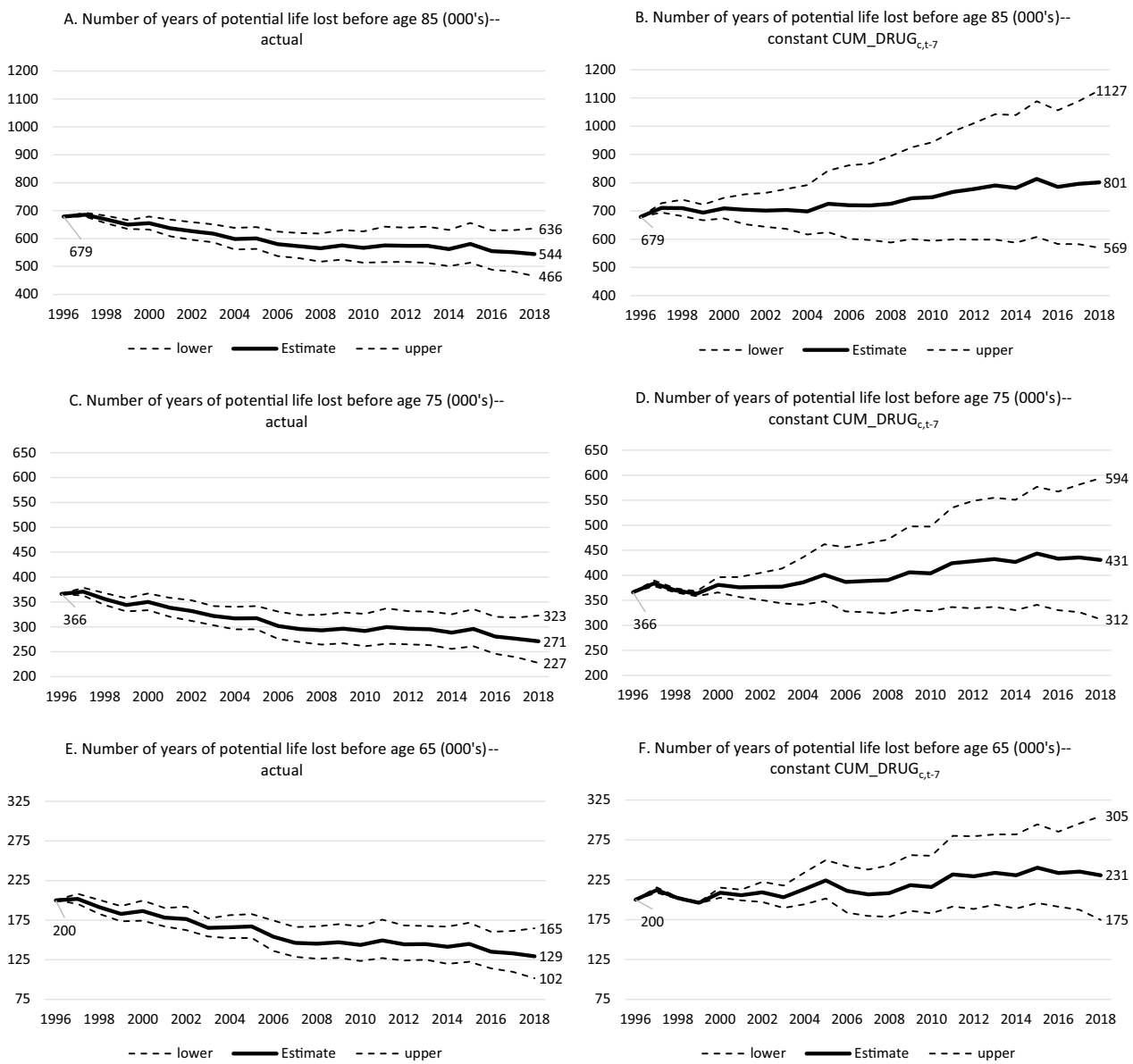

Fig. 4 The evolution of the aggregate number of years of potential life lost: actual versus estimated, in the absence of previous pharmaceutical innovation

have been almost no change in the premature (before age 85) mortality rate.[10] The new chemical substances that were registered during the period 1990–2011 are associated with a reduction in the number of years of potential life lost before age 85 in 2018 of 257 thousand (= 801 thousand–544 thousand).

[10] Between 1997 and 2017, some non-medical determinants of health improved, but others declined. The fraction of the population aged 15 + who were daily smokers declined from 28.9 to 19.1%, but the fraction of the population who were obese (self-reported) increased from 6.8 to 11.3% (Organisation for Economic Co-operation and Development, 2021).

Panels C and D of Fig. 4 show similar calculations for YPLL75. Between 1996 and 2018, YPLL75 declined by 26%, from 366 to 271 thousand. The estimate of β_7 implies that, if $CUM\_DRUG_{c,t-7}$ had not increased, YPLL75 would have *increased* by 18%, to 431 thousand. As shown in Table 1, during that period, the population below age 75 increased by 18%, which implies that, if $CUM\_DRUG_{c,t-7}$ had not increased, there would have been almost no change in the premature (before age 75) mortality rate. The new chemical substances that were registered during the period 1990–2011 are associated with a reduction in the number of years of potential life lost before age 75 in 2018 of 163 thousand (=430 thousand−267 thousand).

Panels E and F of Fig. 4 show similar calculations for YPLL65. Between 1996 and 2018, YPLL65 declined by 35%, from 200 to 129 thousand. The estimate of β_7 implies that, if $CUM\_DRUG_{c,t-7}$ had not increased, YPLL65 would have *increased* by 16%, to 231 thousand. As shown in Table 1, during that period, the population below age 65 increased by 15%, which implies that, if $CUM\_DRUG_{c,t-7}$ had not increased, there would have been almost no change in the premature (before age 65) mortality rate. The new chemical substances that were registered during the period 1990–2011 are associated with a reduction in the number of years of potential life lost before age 65 in 2018 of 102 thousand (=231 thousand−129 thousand).

As stated earlier, we also estimated a version of Eq. (3) that includes multiple lag lengths: $CUM\_DRUG_{c,t}$, $CUM\_DRUG_{c,t-8}$, and $CUM\_DRUG_{c,t-12}$. These estimates are shown in Table 8 in Appendix. In model 1 in that table, the dependent variable is $\ln(YPLL85_{ct})$. The coefficient on $CUM\_DRUG_{c,t-8}$ is negative and significant (p value = 0.0025); the coefficients on $CUM\_DRUG_{c,t}$ and $CUM\_DRUG_{c,t-12}$ are insignificant. The magnitude of the coefficient on $CUM\_DRUG_{c,t-8}$ is slightly (8%) larger than the coefficient shown in Table 3 (reproduced in model 2 of Table 8 in Appendix). In models 3 and 4 of Table 8 in Appendix, the dependent variable is $\ln(YPLL75_{ct})$; in models 5 and 6, the dependent variable is $\ln(YPLL65_{ct})$. In those models as well, the coefficient on $CUM\_DRUG_{c,t-8}$ is negative and significant, and the coefficients on $CUM\_DRUG_{c,t}$ and $CUM\_DRUG_{c,t-12}$ are insignificant.

4.2 Hospital utilization model estimates

Estimates of β_k from 2-way fixed-effects hospital utilization models [Eq. (3)] are presented in Table 4 and plotted in Fig. 5.

Panel A of the table and figure shows estimates when the dependent variable is $\ln(HOSP\_DAYS_{ct})$. The estimates of β_k are negative and significant when $8 \le k \le 10$: the number of hospital days is significantly inversely related to the number of chemical substances ever registered 8–10 years earlier. (The estimates of β_7 and β_{11} are marginally significant (p value < 0.07).) It is most strongly inversely related to the number of chemical substances ever registered 9 years earlier.

Panel B of the table and figure shows estimates when the dependent variable is $\ln(ALOS_{ct})$. The estimates of β_k are negative and significant when $2 \le k \le 10$: average length of stay is significantly inversely related to the number of chemical substances ever registered 2–10 years earlier. It is most strongly inversely related to the number of chemical substances ever registered 4 years earlier. This relatively short lag might be due to more rapid diffusion of new drugs in the hospital sector than in the retail sector, which is the case in the U.S.

Panels A and B of Fig. 6 compare the actual evolution of aggregate hospital utilization to the estimated evolution, in the absence of previous pharmaceutical innovation. Between 2002 and 2019, controlling for the changing mix of causes of hospitalization, HOSP_DAYS increased by 4%, from 11.5 million to 12.0 million. The estimate of β_9 implies that, if $CUM\_DRUG_{c,t-9}$ had not increased, HOSP_DAYS would have *increased* by 22%, to 14.0 million. As shown in Table 2, during that period, the population increased by 18%, which implies that, if $CUM\_DRUG_{c,t-9}$ had not increased, there would have been a small (3%) increase in the number of hospital days per 1000 population. The new chemical substances that were registered during the period 1994–2010 are associated with a reduction inthe number of hospital days in 2019 by 2.07 million (=14.02 million−11.95 million).

Panels C and D of Fig. 6 compare the actual evolution of the average length of inpatient hospital stays to the estimated evolution, in the absence of previous pharmaceutical innovation. Between 2002 and 2019, controlling for the changing mix of causes of hospitalization, ALOS declined by 3.3 days, from 11.4 to 8.1 days. The estimate of β_4 implies that, if $CUM\_DRUG_{c,t-4}$ had not increased, ALOS would have declined by 2.9 days, to 8.5 days. The new chemical substances that were registered during the period 1999–2015 are associated with a reduction in ALOS in 2019 of 0.4 (=8.5–8.1) days.

Estimates of hospital utilization models that include multiple lag lengths ($CUM\_DRUG_{c,t}$, $CUM\_DRUG_{c,t-8}$, and $CUM\_DRUG_{c,t-12}$) are shown as models 7 and 9 in

Table 4 Estimates of β_k from 2-way fixed-effects hospital utilization models [Eq. (3)]

Lag (k)	Estimate	Standard error	95% Lower confidence	95% Upper confidence	*Z*	Pr>|*Z*|
A. Dependent variable = ln(HOSP_DAYS$_{ct}$)						
0	0.076	0.267	−0.448	0.600	0.28	0.776
1	0.002	0.263	−0.513	0.518	0.01	0.9929
2	−0.071	0.269	−0.598	0.456	−0.27	0.7907
3	−0.155	0.281	−0.706	0.396	−0.55	0.5816
4	−0.219	0.279	−0.766	0.329	−0.78	0.434
5	−0.251	0.267	−0.774	0.272	−0.94	0.3467
6	−0.326	0.224	−0.766	0.114	−1.45	0.1462
7	−0.356	0.195	−0.738	0.026	−1.83	0.0675
8	**−0.369**	**0.179**	**−0.719**	**−0.019**	**−2.07**	**0.0388**
9	**−0.370**	**0.172**	**−0.707**	**−0.033**	**−2.15**	**0.0315**
10	**−0.326**	**0.160**	**−0.641**	**−0.012**	**−2.03**	**0.042**
11	−0.288	0.150	−0.580	0.006	−1.92	0.0544
12	−0.233	0.141	−0.508	0.043	−1.66	0.0977
B. Dependent variable = ln(ALOS$_{ct}$)						
0	−0.070	0.052	−0.171	0.032	−1.35	0.1779
1	−0.097	0.054	−0.203	0.009	−1.79	0.0734
2	**−0.123**	**0.057**	**−0.235**	**−0.010**	**−2.14**	**0.0324**
3	**−0.151**	**0.060**	**−0.269**	**−0.032**	**−2.49**	**0.0127**
4	**−0.164**	**0.061**	**−0.283**	**−0.045**	**−2.70**	**0.0069**
5	**−0.160**	**0.061**	**−0.279**	**−0.041**	**−2.63**	**0.0086**
6	**−0.154**	**0.060**	**−0.272**	**−0.036**	**−2.55**	**0.0108**
7	**−0.156**	**0.060**	**−0.275**	**−0.038**	**−2.59**	**0.0096**
8	**−0.153**	**0.062**	**−0.275**	**−0.031**	**−2.46**	**0.0137**
9	**−0.141**	**0.063**	**−0.263**	**−0.018**	**−2.24**	**0.0251**
10	**−0.122**	**0.062**	**−0.243**	**−0.001**	**−1.97**	**0.0491**
11	−0.116	0.062	−0.238	0.007	−1.85	0.0638
12	−0.114	0.063	−0.238	0.010	−1.81	0.0708

Estimates in bold are statistically significant (p value < .05)

Table 8 in Appendix. In model 7, the dependent variable is ln(HOSP_DAYS$_{ct}$). The coefficient on CUM_DRUG$_{c,t}$ is *positive* and significant. Perhaps this is due to reverse causality: an exogenous increase in hospital utilization for a medical condition could stimulate an acceleration or increase in new drug approvals for that condition. The coefficient on CUM_DRUG$_{c,t-8}$ remains negative and significant; its magnitude is 25% larger than the coefficient shown in Table 4 (reproduced in model 8 of Table 8 in Appendix). The coefficient on CUM_DRUG$_{c,t-12}$ is insignificant. In model 9, the dependent variable is ln(ALOS$_{ct}$). The coefficient on CUM_DRUG$_{c,t-8}$ is negative and significant; the coefficients on CUM_DRUG$_{c,t}$ and CUM_DRUG$_{c,t-12}$ are insignificant.

5 Discussion

As shown in Panels A and B of Fig. 4, the new chemical substances that were registered during the period 1990–2011 are associated with a reduction in the number of years of potential life lost before age 85 in 2018 of 257 thousand. Now we will obtain rough estimates of the incremental cost-effectiveness (cost per life-year before age 85 gained) of those chemical substances in 2018. First, we will estimate cost-effectiveness if we ignore the reduction in hospital utilization attributable to previous pharmaceutical innovation. Then, we will estimate cost-effectiveness if we account for this reduction in hospital utilization.

As noted above, according to Eurostat, expenditure on prescribed medicines in Switzerland in 2018 was € 6288 million. Data from the IQVIA MIDAS database indicate

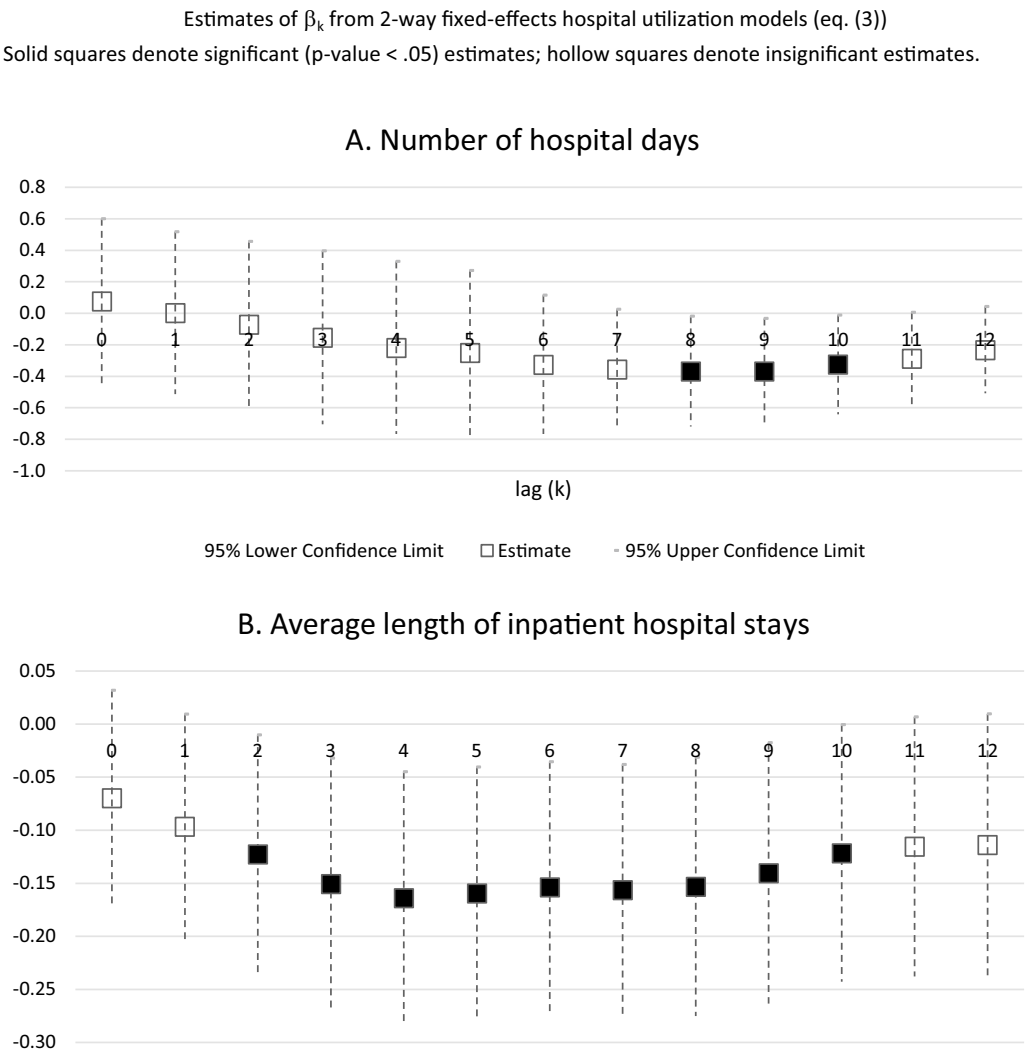

Fig. 5 Estimates of β_k from 2-way fixed-effects hospital utilization models [Eq. (3)] Solid squares denote significant (p value < .05) estimates; hollow squares denote insignificant estimates

that 58.5% of 2018 expenditure on prescribed medicines was on new chemical substances that were registered during the period 1990–2011. These figures imply that, in 2018, € 3678 million (= 58.5% × € 6288 million) was spent on new chemical substances that were registered during the period 1990–2011. Therefore, if we ignore the reduction in hospital utilization attributable to previous pharmaceutical innovation, a rough estimate of the cost per life-year before age 85 gained in 2018 is € 14,310 (= € 3678 million/257,000 life-years).[11]

As noted by Bertram et al (2016), authors writing on behalf of the WHO's *Choosing Interventions that are Cost–Effective* project (WHO-CHOICE) suggested in 2005 that "interventions that avert one disability-adjusted life-year (DALY) for less than average per capita income for a given country or region are considered very cost–effective; interventions that cost less than three times average per capita income per DALY averted are still considered cost–effective." Switzerland's per capita GDP in 2018 was € 73,436, so the new chemical substances that were registered during the period 1990–2011 appear to have been very cost–effective overall, even if we ignore the reduction in hospital utilization attributable to previous pharmaceutical innovation.

[11] Part of the € 3678 million expenditure was on patients above age 85, so the true cost per life-year before age 85 gained was lower.

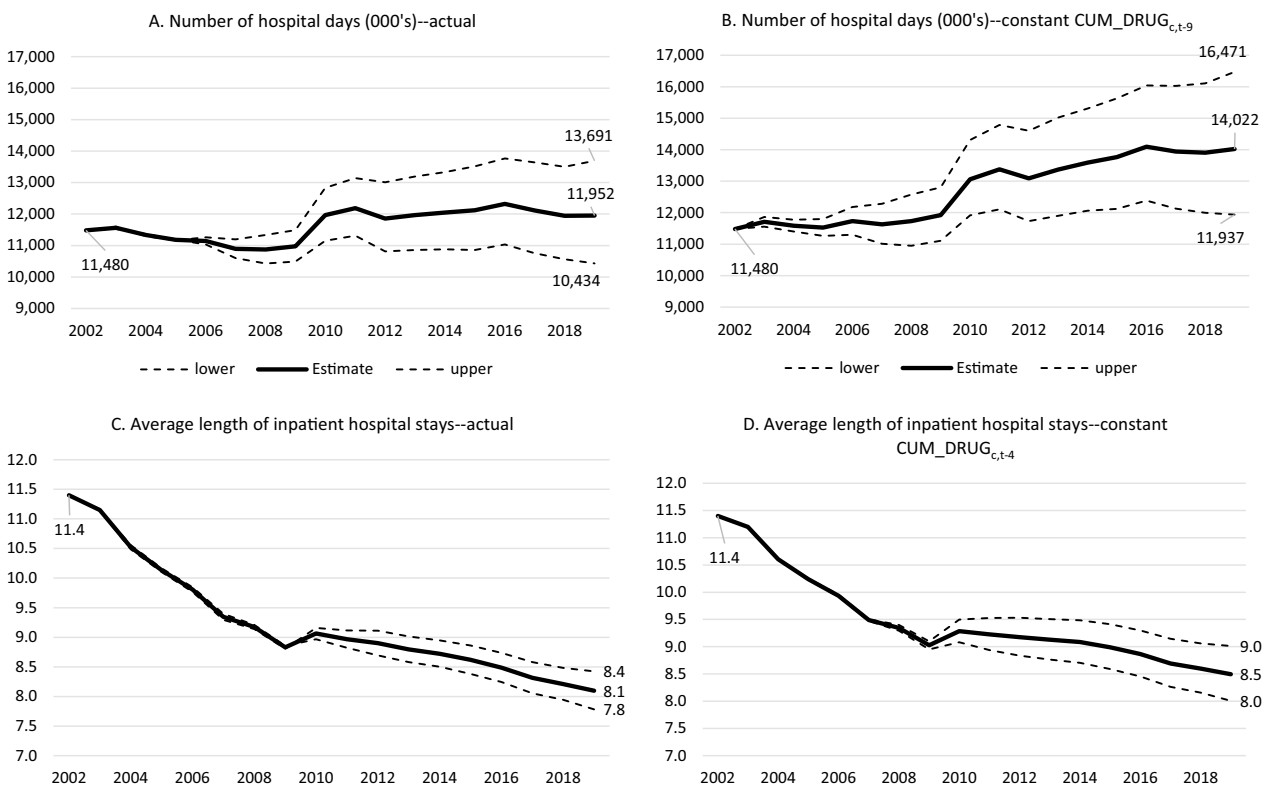

Fig. 6 The evolution of aggregate hospital utilization: actual versus estimated, in the absence of previous pharmaceutical innovation

As shown in Panels A and B of Fig. 6, the new chemical substances that were registered during the period 1994–2010 are associated with a reduction in the number of hospital days in 2019 of 2.07 million (=14.02 million–11.95 million). In other words, if no new chemical substances had been registered during the period 1994–2010, the number of hospital days might have been 17.3% (=(14.02 million/11.95 million)−1) higher in 2019. It is plausible that expenditure on inpatient curative and rehabilitative care would also have been 17.3% higher. According to Eurostat, expenditure on inpatient curative and rehabilitative care in 2018 was € 17,965 million. Therefore, we estimate that, if no new chemical substances had been registered during the period 1994–2010, expenditure on inpatient curative and rehabilitative care in 2018 might have been € 3112 million (=17.3% × € 17,965 million) higher. About 85% (=€ 3112 million/€ 3678 million) of the 2018 expenditure on drugs registered during the period 1990–2011 may have been offset by the reduction in expenditure on inpatient curative and rehabilitative care. The net cost per life-year before age 85 gained in 2018 may have been € 2201 (=(1–85%) × € 14,309).[12]

6 Summary and conclusions

In this study, we analyzed the association that pharmaceutical innovation had with premature mortality from all diseases in Switzerland during the period 1996–2018, and its association with hospital utilization for all diseases in Switzerland during the period 2002–2019. Most private biomedical research funding comes from pharmaceutical and biotechnology firms.

[12] To our knowledge, no studies have provided estimates of the average cost-effectiveness of other broad categories of medical innovations, such as surgical or diagnostic imaging innovations. As stated earlier, measuring non-pharmaceutical medical innovation is far more difficult than measuring pharmaceutical innovation.

The analysis was performed by investigating whether the diseases that experienced more pharmaceutical innovation had larger declines in premature mortality and hospitalization. Pharmaceutical innovation was measured by the growth in the number of drugs used to treat a disease ever registered in Switzerland. We allowed the association of innovation to be subject to a substantial lag because utilization of recently-launched drugs tends to be lower than utilization of drugs launched many years earlier. Utilization of a chemical substance reaches a peak 9–12 years after it was first launched, and then declines.

Our estimates indicated that the number of years of potential life lost before ages 85, 75, and 65 is significantly inversely related to the number of chemical substances ever registered 6–9, 3–9, and 0–9 years earlier, respectively. The new chemical substances that were registered during the period 1990–2011 are associated with reductions inthe number of years of potential life lost before ages 85, 75, and 65 in 2018 of 257 thousand, 163 thousand, and 102 thousand, respectively.

The number of hospital days is significantly inversely related to the number of chemical substances ever registered 8–10 years earlier. The new chemical substances that were registered during the period 1994–2010 are associated with a reduction inthe number of hospital days in 2019 of 2.07 million. Average length of inpatient hospital stays is significantly inversely related to the number of chemical substances ever registered 2–10 years earlier. The new chemical substances that were registered during the period 1999–2015 are associated with a reduction inALOS in 2019 of 0.4 days.

If we ignore the reduction in hospital utilization attributable to previous pharmaceutical innovation, a rough estimate of the cost per life-year before age 85 gained in 2018 is € 14,310.

Moreover, about 85% of the 2018 expenditure on drugs registered during the period 1990–2011 may have been offset by the reduction in expenditure on inpatient curative and rehabilitative care. The net cost per life-year before age 85 gained in 2018 may therefore have been € 2201.

Our estimates are predicated on the assumption that pharmaceutical innovation is exogenous with respect to premature mortality and hospitalization, and that it is uncorrelated with other potential determinants of health outcomes. For several reasons, this assumption could be violated.[13]

One reason is that Switzerland implemented a mandatory health insurance system in 1996, with several reforms since then that affected the quality of health services and the drug admission process. The potential endogeneity of pharmaceutical innovation in Switzerland due to changes in the Swiss health insurance system might be addressed by using an instrument for the number of new drugs approved for a disease in Switzerland. One potential instrument is the number of new drugs approved in the U.S.[14] (There is a very strong positive correlation across 58 diseases between the 1996–2018 growth in number of drugs ever approved in the USA and Switzerland: $R^2 = 0.59$; p value < 0.0001.) We estimated Eq. (3) using instrumental variables (IV); the instrument for the number of new drugs ever approved for a disease in Switzerland was the number of new drugs ever approved for a disease in the United States three years earlier. While the IV and OLS estimates had different magnitudes and lag structures, both sets of estimates revealed highly significant inverse associations across diseases between both premature mortality and hospital days and the lagged number of drugs ever registered.

A second potential reason for violation of the assumption is implementation of non-pharmaceutical medical innovations (e.g. medical devices) and new disease-specific treatment guidelines. A previous study (Lichtenberg, 2014) indicated that controlling for non-pharmaceutical medical innovation did not affect estimates of the effect of pharmaceutical innovation on U.S. cancer mortality. We are not aware of evidence for the hypothesis that, in general, changes in guidelines have reduced mortality or hospitalization, or that they are correlated across diseases with new drug approvals. Future studies of Swiss mortality and hospitalization should attempt to control for non-pharmaceutical medical innovation and for changes in guidelines.

Appendix

Tables 5 , 6 , 7 and 8.

[13] Some violations of the exogeneity assumption would render our estimates *conservative*. For example, an exogenous increase in the prevalence of a disease would be likely to increase both mortality from the disease and the number of registrations of new drugs that treat the disease.

[14] In 2017, US drug expenditure was 41 times as large as Swiss drug expenditure (316 billion versus 8 billion USD). It is highly implausible that reforms to Switzerland's mandatory health insurance system had any effect on U.S. drug approvals.

Table 5 Mortality by cause in 2018

icd10	No. of deaths	YPLL85	YPLL75	YPLL65
A–R_V–Y All causes of death (A00–Y89) excluding S00–T98	67,621	543,417	268,424	130,084
A15–A19_B90 Tuberculosis	25	340	213	120
ACC Accidents (V01–X59, Y85, Y86)	2912	38,666	25,848	17,076
ACC_OTH Other accidents (W20–W64, W75–X39, X50–X59, Y86)	478	8924	5929	3801
A_B Certain infectious and parasitic diseases (A00–B99)	823	6280	3275	1693
A_B_OTH Other infectious and parasitic diseases (remainder of A00–B99)	723	4258	1975	1015
B15–B19_B942 Viral hepatitis and sequelae of viral hepatitis	13	223	140	75
B180–B182 Chronic viral hepatitis B and C	9	203	133	75
B20–B24 Human immunodeficiency virus [HIV] disease	22	598	390	208
C Malignant neoplasms (C00–C97)	17,650	203,475	93,248	34,870
C00–C14 Malignant neoplasm of lip, oral cavity, pharynx	453	6533	3025	950
C00–D48 Neoplasms	18,216	206,715	94,502	35,337
C15 Malignant neoplasm of oesophagus	449	5818	2598	758
C16 Malignant neoplasm of stomach	568	7850	3980	1648
C18–C21 Malignant neoplasm of colon, rectosigmoid junction, rectum, anus and anal canal	1733	18,665	8523	3110
C22 Malignant neoplasm of liver and intrahepatic bile ducts	748	9140	3998	1330
C25 Malignant neoplasm of pancreas	1451	17,010	7373	2398
C32 Malignant neoplasm of larynx	77	1008	435	133
C33_C34 Malignant neoplasm of trachea, bronchus and lung	3375	44,498	19,408	5583
C43 Malignant melanoma of skin	289	3880	2040	938
C50 Malignant neoplasm of breast	1447	18,548	9620	4260
C53 Malignant neoplasm of cervix uteri	77	1603	1005	523
C54_C55 Malignant neoplasm of other parts of uterus	212	2243	970	303
C56 Malignant neoplasm of ovary	403	5165	2405	885
C61 Malignant neoplasm of prostate	1410	7245	1953	325
C64 Malignant neoplasm of kidney, except renal pelvis	321	3762	1777	737
C67 Malignant neoplasm of bladder	577	4175	1505	438
C70–C72 Malignant neoplasm of brain and central nervous system	568	11,640	6800	3565
C73 Malignant neoplasm of thyroid gland	65	598	245	85
C81–C86 Hodgkin disease and lymphomas	550	4933	2045	873
C88_C90_C96 Other malignant neoplasm of lymphoid, haematopoietic and related tissue	380	2903	1035	315
C91–C95 Leukaemia	622	6751	3281	1621
C_OTH Other malignant neoplasms (remainder of C00–C97)	1875	19,513	9231	4098
D00–D48 Non-malignant neoplasms (benign and uncertain)	566	3240	1255	467
D50–D89 Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	213	1336	743	486
E Endocrine, nutritional and metabolic diseases (E00–E90)	1721	12,362	5952	2920
E10–E14 Diabetes mellitus	1163	6630	2570	895
E_OTH Other endocrine, nutritional and metabolic diseases (remainder of E00–E90)	558	5732	3382	2025
F Mental and behavioural disorders (F00–F99)	5686	18,205	7468	3528
F01_F03 Dementia	4860	6800	833	85
F10 Mental and behavioural disorders due to use of alcohol	181	3345	1753	670
F_OTH Other mental and behavioural disorders (remainder of F00–F99)	556	4898	2605	1338
G20 Parkinson disease	757	2985	523	60
G30 Alzheimer disease	1518	3648	643	110
G_H Diseases of the nervous system and the sense organs (G00–H95)	3655	25,873	11,581	5538
G_H_OTH Other diseases of the nervous system and the sense organs (remainder of G00–H95)	1380	19,241	10,416	5368
I Diseases of the circulatory system (I00–I99)	20,910	93,417	36,667	13,692
I20–I25 Ischaemic heart diseases	6962	37,240	14,930	5195
I20_I23–I25 Other ischaemic heart diseases	4712	19,380	6888	2193

Table 5 (continued)

icd10	No. of deaths	YPLL85	YPLL75	YPLL65
I21_I22 Acute myocardial infarction including subsequent myocardial infarction	2250	17,860	8043	3003
I30–I51 Other heart diseases	5860	22,278	8873	3683
I60–I69 Cerebrovascular diseases	3539	16,065	5942	2172
I_OTH Other diseases of the circulatory system (remainder of I00–I99)	4549	17,834	6922	2642
J Diseases of the respiratory system (J00–J99)	4671	25,812	9072	2784
J09–J11 Influenza (including swine flu)	323	1950	845	360
J12–J18 Pneumonia	1409	5035	1847	727
J40–J44_J47 Other lower respiratory diseases	2029	13,535	4340	938
J40–J47 Chronic lower respiratory diseases	2133	14,610	4985	1293
J45_J46 Asthma and status asthmaticus	104	1075	645	355
J_OTH Other diseases of the respiratory system (remainder of J00–J99)	806	4218	1395	405
K Diseases of the digestive system (K00–K93)	2497	20,829	9589	3739
K25–K28 Ulcer of stomach, duodenum and jejunum	120	553	163	58
K70_K73_K74 Chronic liver disease	607	10,958	5818	2285
K72–K75 Chronic liver disease (excluding alcoholic and toxic liver disease)	188	2420	1157	457
K_OTH Other diseases of the digestive system (remainder of K00–K93)	1770	9319	3609	1396
L Diseases of the skin and subcutaneous tissue (L00–L99)	119	505	150	45
M Diseases of the musculoskeletal system and connective tissue (M00–M99)	722	3867	1507	635
M_OTH Other diseases of the musculoskeletal system and connective tissue (remainder of M00–M99)	507	3132	1295	575
N Diseases of the genitourinary system (N00–N99)	1293	3928	1078	278
N00–N29 Diseases of kidney and ureter	807	2533	705	188
N_OTH Other diseases of the genitourinary system (remainder of N00–N99)	486	1395	373	90
O Pregnancy, childbirth and the puerperium (O00–O99)	6	305	245	185
P Certain conditions originating in the perinatal period (P00–P96)	160	13,520	11,920	10,320
Q Congenital malformations, deformations and chromosomal abnormalities (Q00–Q99)	250	12,122	9802	7709
R Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00–R99)	2575	23,253	12,986	6848
R95 Sudden infant death syndrome	6	507	447	387
R96–R99 Ill-defined and unknown causes of mortality	1893	21,736	12,176	6304
RHEUM_ARTHRO Rheumatoid arthritis and arthrosis (M05–M06, M15–M19)	215	735	213	60
R_OTH Other symptoms, signs and abnormal clinical and laboratory findings (remainder of R00–R99)	676	1010	363	158
TOXICO Drug dependence, toxicomania (F11–F16, F18–F19)	89	3163	2278	1435
V01–Y89 External causes of morbidity and mortality (V01–Y89)	4104	75,091	51,891	34,351
V01–Y89_OTH Other external causes of morbidity and mortality (remainder of V01–Y89)	19	315	180	85
V_Y85 Transport accidents (V01–V99, Y85)	337	10,605	7730	5410
W00–W19 Falls	1870	10,617	5782	3395
W65–W74 Accidental drowning and submersion	64	2066	1529	1094
X40–X49 Accidental poisoning by and exposure to noxious substances	163	6455	4880	3377
X60–X84_Y870 Intentional self-harm	1047	32,040	22,888	15,175
X85–Y09_Y871 Assault	43	1686	1286	929
Y10–Y34_Y872 Event of undetermined intent	77	2245	1607	1052

Table 6 Hospital days and average length of stay, by cause, in 2019

Cause	hosday	los
A–T_Z All causes of diseases (A00–Z99) excluding V00–Y98	11,816,124	8.2
A–T_Z_XNB All causes of diseases (A00–Z99) excluding V00–Y98 and Z38	11,631,919	8.4
A00–A08 Intestinal infectious diseases except diarrhoea	34,235	4.5
A09 Diarrhoea and gastroenteritis of presumed infectious origin	19,502	3.7
A15–A19_B90 Tuberculosis	6898	16.2
A40_A41 Septicaemia	148,320	11.6
ABORT_OTH Other pregnancy with abortive outcome (O00–O03, O05–O08)	4204	1.7
ARTHROPAT_OTH Other arthropathies (M00–M15, M18–M22,M24–M25)	167,601	4.8
A_B Certain infectious and parasitic diseases (A00–B99)	313,242	7.8
A_B_OTH Other infectious and parasitic diseases (remainder of A00–B99)	102,717	7.4
B20–B24 Human immunodeficiency virus [HIV] disease	1570	15.5
C00–D48 Neoplasms	1,039,818	8.0
C18–C21 Malignant neoplasm of colon, rectosigmoid junction, rectum, anus and anal canal	109,394	11.6
C33_C34 Malignant neoplasm of trachea, bronchus and lung	101,286	10.5
C43_C44 Malignant neoplasms of skin	17,985	5.4
C50 Malignant neoplasm of breast	60,829	5.6
C53–C55 Malignant neoplasm of uterus	17,304	7.7
C56 Malignant neoplasm of ovary	19,003	10.2
C61 Malignant neoplasm of prostate	53,122	6.5
C67 Malignant neoplasm of bladder	46,711	5.7
C_OTH Other malignant neoplasms (remainder of C00–C97)	499,662	9.9
D00–D09 In situ neoplasms	10,029	3.8
D00–D48_OTH Other in situ neoplasms, benign neoplasms and neoplasms of uncertain or unknown behaviour (remainder of D00–D48)	78,572	5.2
D12 Benign neoplasm of colon, rectum, anus and anal canal	7876	4.0
D25 Leiomyoma of uterus	18,045	3.1
D50–D64 Anaemias	25,328	6.7
D50–D89 Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	46,391	7.1
D65–D89 Other diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	21,063	7.6
E Endocrine, nutritional and metabolic diseases (E00–E90)	169,286	7.1
E10–E14 Diabetes mellitus	73,749	9.8
E_OTH Other endocrine, nutritional and metabolic diseases (remainder of E00–E90)	95,537	5.9
F Mental and behavioural disorders (F00–F99)	2,800,678	26.7
F00–F03 Dementia	51,487	20.0
F10 Mental and behavioural disorders due to use of alcohol	298,672	17.9
F11–F19 Mental and behavioural disorders due to psychoactive substance use	146,157	23.1
F20–F29 Schizophrenia, schizotypal and delusional disorders	555,997	36.8
F30–F39 Mood [affective] disorders	965,750	31.7
F_OTH Other mental and behavioural disorders (remainder of F00–F99)	782,615	23.2
G Diseases of the nervous system (G00–G99)	496,052	12.8
G30 Alzheimer disease	54,081	26.9
G35 Multiple sclerosis	35,210	17.9
G40_G41 Epilepsy, status epilepticus	85,158	10.4
G45 Transient cerebral ischaemic attacks and related syndromes	17,872	3.8
G_OTH Other diseases of the nervous system (remainder of G00–G99)	303,731	13.9
H00–H59 Diseases of the eye and adnexa	27,595	2.3
H00–H59_OTH Other diseases of the eye and adnexa (remainder of H00–H59)	24,594	2.5
H25_H26_H28 Cataract	3001	1.6
H60–H95 Diseases of the ear and mastoid process	26,236	3.4
I Diseases of the circulatory system (I00–I99)	1,347,121	8.5

Table 6 (continued)

Cause	hosday	los
I10–I15 Hypertensive diseases	22,811	4.7
I20 Angina pectoris	19,975	3.4
I21_I22 Acute myocardial infarction including subsequent myocardial infarction	121,883	6.3
I23–I25 Other ischaemic heart disease	84,861	5.6
I26–I28 Pulmonary heart disease and diseases of pulmonary circulation	40,421	7.1
I44–I49 Conduction disorders and cardiac arrhythmias	75,728	4.0
I50 Heart failure	244,219	10.7
I60–I69 Cerebrovascular diseases	408,650	14.7
I70 Atherosclerosis	73,163	8.1
I83 Varicose veins of lower extremities	10,440	2.9
INJ_HEAD_OTH Other injuries to the head (S00–S05, S07–S09)	26,524	3.1
INJ_OTH Other injuries (S10–S51, S53–S71, S73–S81, S83–T14, T79)	461,583	6.3
INTESTINE_OTH Other diseases of intestine (K55, K58–K59, K63)	36,428	7.3
I_OTH Other diseases of the circulatory system (remainder of I00–I99)	244,970	9.3
J Diseases of the respiratory system (J00–J99)	591,185	6.5
J00–J11 Acute upper respiratory infections and influenza	53,769	4.7
J12–J18 Pneumonia	192,878	8.4
J20–J22 Other acute lower respiratory infections	38,266	4.0
J35 Chronic diseases of tonsils and adenoids	14,053	2.2
J40–J44_J47 Other lower respiratory diseases	135,744	10.4
J45_J46 Asthma and status asthmaticus	18,626	6.7
J60–J99 Other diseases of the respiratory system	106,344	10.3
K Diseases of the digestive system (K00–K93)	648,439	5.5
K00–K08 Disorders of teeth and supporting structures	3628	3.0
K09–K14 Other diseases of oral cavity, salivary glands and jaws	9146	4.3
K20–K23 Diseases of oesophagus	18,497	5.5
K25–K28 Ulcer of stomach, duodenum and jejunum	24,992	8.5
K29–K31 Dyspepsia and other diseases of stomach and duodenum	18,970	5.4
K35–K38 Diseases of appendix	40,489	3.3
K40 Inguinal hernia	28,214	2.2
K41–K46 Other abdominal hernia	52,298	4.8
K50_K51 Crohn disease and ulcerative colitis	16,826	8.7
K52 Other noninfective gastroenteritis and colitis	12,690	6.4
K56 Paralytic ileus and intestinal obstruction without hernia	56,539	7.9
K57 Diverticular disease of intestine	76,212	7.1
K60–K62 Diseases of anus and rectum	18,540	3.1
K70 Alcoholic liver disease	26,864	12.8
K71–K77 Other diseases of liver	26,296	10.7
K80 Cholelithiasis	73,062	4.3
K81–K83 Other diseases of gallbladder and biliary tract	19,630	6.8
K85–K87 Diseases of pancreas	37,935	8.2
K_OTH Other diseases of the digestive system (remainder of K00–K93)	51,183	6.6
L Diseases of the skin and subcutaneous tissue (L00–L99)	108,916	6.7
L00–L08 Infections of the skin and subcutaneous tissue	47,653	4.9
L20–L45 Dermatitis, eczema and papulosquamous disorders	13,912	7.8
L_OTH Other diseases of the skin and subcutaneous tissue (remainder of L00–L99)	47,351	10.2
M Diseases of the musculoskeletal system and connective tissue (M00–M99)	1,260,110	7.1
M16 Coxarthrosis [arthrosis of hip]	190,749	8.1
M17 Gonarthrosis [arthrosis of knee]	240,539	9.0

Table 6 (continued)

Cause	hosday	los
M23 Internal derangement of knee	15,824	2.2
M30–M36 Systemic connective tissue disorders	18,495	9.3
M40–M49 Deforming dorsopathies and spondylopathies	192,585	9.8
M50_M51 Cervical disc disorders, other intervertebral disc disorders	96,232	6.7
M53_M80–M99 Other disorders of the musculoskeletal system and connective tissue	150,166	9.1
M54 Dorsalgia	78,871	10.1
M60–M79 Soft tissue disorders	109,048	4.5
N Diseases of the genitourinary system (N00–N99)	337,409	4.1
N00–N16 Glomerular and renal tubulo-interstitial diseases	71,916	4.5
N17–N19 Renal failure	41,461	8.6
N20–N23 Urolithiasis	25,446	2.3
N25–N39 Other diseases of the urinary system	83,579	5.4
N40 Hyperplasia of prostate	33,504	4.1
N41–N51 Other diseases of male genital organs	21,038	3.6
N60–N64 Disorders of breast	4029	2.4
N70–N77 Inflammatory diseases of female pelvic organs	5618	3.4
N91–N95 Menstrual, menopausal and other female genital conditions	4852	2.4
N_OTH Other diseases of the genitourinary system (remainder of N00–N99)	45,966	3.0
O Pregnancy, childbirth and the puerperium (O00–O99)	401,713	4.0
O04 Medical abortion	1428	1.6
O10–O48 Complications of pregnancy predominantly in the antenatal period	158,301	4.5
O60–O75 Complications of labour and delivery	203,351	3.9
O80 Single spontaneous delivery	13,772	3.0
O81–O84 Other delivery	4402	4.2
O85–O92 Complications predominantly related to the puerperium	5390	3.6
O95–O99 Other obstetric conditions	10,865	3.8
P Certain conditions originating in the perinatal period (P00–P96)	186,457	6.1
P07 Disorders related to short gestation and low birth weight, not elsewhere classified	22,400	7.6
P_OTH Other conditions originating in the perinatal period (remainder of P00–P96)	164,057	5.9
Q Congenital malformations, deformations and chromosomal abnormalities (Q00–Q99)	61,355	6.1
R Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00–R99)	327,700	7.4
R07 Pain in throat and chest	6135	2.2
R10 Abdominal and pelvic pain	12,820	2.9
R69 Unknown and unspecified causes of morbidity	49,220	80.0
R_OTH Other symptoms, signs and abnormal clinical and laboratory findings (remainder of R00–R99)	259,525	7.1
S06 Intracranial injury	109,959	5.2
S52 Fracture of forearm	47,750	3.6
S72 Fracture of femur	280,120	14.0
S82 Fracture of lower leg, including ankle	121,737	8.6
S_T Injury, poisoning and certain other consequences of external causes (S00–T98)	1,321,657	7.0
S_T_OTH Other and unspecified effects of external causes (remainder of S00–T98)	8533	2.7
T20–T32 Burns and corrosions	8658	8.2
T36–T65 Poisonings by drugs, medicaments and biological substances and toxic effects	4706	1.7
T80–T88 Complications of surgical and medical care, not elsewhere classified	251,591	7.8
T90–T98 Sequelae of injuries, of poisoning and of other consequences of external causes	496	24.8
UPRESPIR_OTH Other diseases of upper respiratory tract (J30–J34, J36–J39)	31,505	2.3

Table 7 No. of chemical substances ever registered in Switzerland, by medical condition (hospital classification), 1989–2019

	1989	1994	1999	2004	2009	2014	2019
All medical conditions	590	729	917	1068	1229	1401	1588
A00–A08 Intestinal infectious diseases except diarrhoea	11	13	13	13	16	17	17
A09 Diarrhoea and gastroenteritis of presumed infectious origin	4	4	4	4	4	4	4
A15–A19_B90 Tuberculosis	9	10	10	10	11	12	12
A40_A41 Septicaemia	16	17	18	20	22	23	23
ABORT_OTH Other pregnancy with abortive outcome (O00–O03, O05–O08)	4	4	5	5	5	5	6
ARTHROPAT_OTH Other arthropathies (M00–M15, M18–M22,M24–M25)	45	47	54	56	62	66	69
A_B_OTH Other infectious and parasitic diseases (remainder of A00–B99)	80	96	115	129	146	152	157
B20–B24 Human immunodeficiency virus [HIV] disease	2	3	8	16	26	31	35
C18–C21 Malignant neoplasm of colon, rectosigmoid junction, rectum, anus and anal canal	8	8	12	16	19	24	26
C33_C34 Malignant neoplasm of trachea, bronchus and lung	16	18	22	26	30	33	37
C43_C44 Malignant neoplasms of skin	7	7	10	15	15	20	25
C50 Malignant neoplasm of breast	19	23	32	37	43	49	50
C53–C55 Malignant neoplasm of uterus	12	12	14	17	18	20	20
C56 Malignant neoplasm of ovary	16	18	21	24	26	28	29
C61 Malignant neoplasm of prostate	11	13	17	19	19	27	27
C67 Malignant neoplasm of bladder	12	14	16	18	19	22	22
C_OTH Other malignant neoplasms (remainder of C00–C97)	33	38	53	64	87	109	127
D00–D09 In situ neoplasms	6	8	11	14	20	25	26
D00–D48_OTH Other in situ neoplasms, benign neoplasms and neoplasms of uncertain or unknown behaviour (remainder of D00–D48)	11	13	21	26	34	40	42
D12 Benign neoplasm of colon, rectum, anus and anal canal	2	2	3	4	4	4	4
D25 Leiomyoma of uterus	2	2	3	4	4	4	4
D50–D64 Anaemias	15	16	18	20	23	25	25
D65–D89 Other diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	22	29	33	39	46	51	52
E10–E14 Diabetes mellitus	7	10	20	25	36	39	40
E_OTH Other endocrine, nutritional and metabolic diseases (remainder of E00–E90)	87	99	116	131	150	154	163
F00–F03 Dementia	6	6	8	9	9	9	9
F10 Mental and behavioural disorders due to use of alcohol	18	18	19	20	21	22	22
F11–F19 Mental and behavioural disorders due to psychoactive substance use	9	9	11	14	17	17	17
F20–F29 Schizophrenia, schizotypal and delusional disorders	11	12	15	16	18	18	19
F30–F39 Mood [affective] disorders	16	24	28	31	32	34	37
F_OTH Other mental and behavioural disorders (remainder of F00–F99)	46	55	61	69	79	81	85
G30 Alzheimer disease	0	1	3	4	5	5	5
G35 Multiple sclerosis	8	11	14	15	17	20	22
G40_G41 Epilepsy, status epilepticus	17	20	23	24	29	30	30
G45 Transient cerebral ischaemic attacks and related syndromes	3	5	7	7	8	11	11
G_OTH Other diseases of the nervous system (remainder of G00–G99)	55	58	72	82	93	97	99
H00–H59_OTH Other diseases of the eye and adnexa (remainder of H00–H59)	34	41	53	61	66	68	71
H25_H26_H28 Cataract	1	1	1	1	1	1	1
H60–H95 Diseases of the ear and mastoid process	21	22	23	24	24	25	25
I10–I15 Hypertensive diseases	22	35	50	55	67	72	74
I20 Angina pectoris	15	20	22	23	25	27	27
I21_I22 Acute myocardial infarction including subsequent myocardial infarction	14	16	20	24	28	30	30
I23–I25 Other ischaemic heart disease	15	16	19	23	24	24	24
I26–I28 Pulmonary heart disease and diseases of pulmonary circulation	6	8	9	14	16	20	21
I44–I49 Conduction disorders and cardiac arrhythmias	13	16	18	19	23	26	26
I50 Heart failure	13	17	22	24	27	28	30
I60–I69 Cerebrovascular diseases	7	10	14	14	15	18	18

Table 7 (continued)

	1989	1994	1999	2004	2009	2014	2019
I70 Atherosclerosis	0	1	2	2	3	5	5
I83 Varicose veins of lower extremities	4	6	6	6	6	6	6
INJ_OTH Other injuries (S10–S51, S53–S71, S73–S81, S83–T14, T79)	14	15	15	16	16	17	17
INTESTINE_OTH Other diseases of intestine (K55, K58–K59, K63)	33	37	41	41	43	46	49
I_OTH Other diseases of the circulatory system (remainder of I00–I99)	53	60	65	67	72	75	77
J00–J11 Acute upper respiratory infections and influenza	43	48	55	56	58	59	59
J12–J18 Pneumonia	23	28	31	35	37	40	42
J20–J22 Other acute lower respiratory infections	19	23	25	27	30	31	32
J40–J44_J47 Other lower respiratory diseases	28	32	40	43	46	52	55
J45_J46 Asthma and status asthmaticus	15	17	23	26	29	32	33
J60–J99 Other diseases of the respiratory system	19	20	20	21	21	21	25
K00–K08 Disorders of teeth and supporting structures	19	19	19	20	20	20	20
K09–K14 Other diseases of oral cavity, salivary glands and jaws	15	15	16	17	17	17	17
K20–K23 Diseases of oesophagus	5	7	10	11	11	12	12
K25–K28 Ulcer of stomach, duodenum and jejunum	5	7	11	13	13	14	15
K29–K31 Dyspepsia and other diseases of stomach and duodenum	10	10	10	10	11	12	12
K50_K51 Crohn disease and ulcerative colitis	8	9	10	11	11	13	14
K52 Other noninfective gastroenteritis and colitis	0	1	2	2	2	2	2
K56 Paralytic ileus and intestinal obstruction without hernia	2	2	2	2	2	2	2
K60–K62 Diseases of anus and rectum	1	1	1	1	2	2	2
K70 Alcoholic liver disease	5	6	7	9	10	10	10
K71–K77 Other diseases of liver	12	15	16	18	20	20	22
K80 Cholelithiasis	1	1	1	1	2	2	2
K81–K83 Other diseases of gallbladder and biliary tract	5	5	5	5	6	6	6
K85–K87 Diseases of pancreas	3	3	3	3	3	3	3
K_OTH Other diseases of the digestive system (remainder of K00–K93)	22	26	26	26	29	29	30
L00–L08 Infections of the skin and subcutaneous tissue	19	23	27	30	32	33	33
L20–L45 Dermatitis, eczema and papulosquamous disorders	38	41	46	50	54	57	61
L_OTH Other diseases of the skin and subcutaneous tissue (remainder of L00–L99)	52	61	67	74	80	85	86
M16 Coxarthrosis [arthrosis of hip]	21	21	23	23	24	24	24
M17 Gonarthrosis [arthrosis of knee]	21	21	23	23	24	24	24
M23 Internal derangement of knee	11	11	12	12	12	12	12
M30–M36 Systemic connective tissue disorders	13	13	16	19	20	22	23
M40–M49 Deforming dorsopathies and spondylopathies	12	13	16	18	18	20	21
M50_M51 Cervical disc disorders, other intervertebral disc disorders	6	6	7	8	8	8	8
M53_M80–M99 Other disorders of the musculoskeletal system and connective tissue	31	33	37	43	46	47	47
M54 Dorsalgia	22	23	25	26	26	26	26
M60–M79 Soft tissue disorders	28	29	30	31	32	32	32
N00–N16 Glomerular and renal tubulo-interstitial diseases	21	23	27	28	29	29	32
N17–N19 Renal failure	11	13	16	20	23	23	25
N20–N23 Urolithiasis	3	3	3	4	5	5	5
N25–N39 other diseases of the urinary system	31	39	44	48	53	55	57
N40 Hyperplasia of prostate	2	5	7	9	10	11	12
N41–N51 other diseases of male genital organs	14	15	19	20	21	21	21
N60–N64 disorders of breast	4	4	4	4	4	4	4
N70–N77 Inflammatory diseases of female pelvic organs	18	20	21	21	22	22	22
N91–N95 Menstrual, menopausal and other female genital conditions	22	23	29	33	35	36	36
N_OTH Other diseases of the genitourinary system (remainder of N00–N99)	8	10	14	16	17	19	19
O04 Medical abortion	3	3	4	4	4	4	5

Table 7 (continued)

	1989	1994	1999	2004	2009	2014	2019
O10–O48 Complications of pregnancy predominantly in the antenatal period	13	13	15	15	17	17	17
O60–O75 Complications of labour and delivery	6	7	7	8	10	10	10
O80 Single spontaneous delivery	0	0	0	1	2	2	2
O81–O84 Other delivery	2	2	2	3	4	4	4
O85–O92 Complications predominantly related to the puerperium	8	9	9	9	9	9	10
P07 Disorders related to short gestation and low birth weight, not elsewhere classified	4	5	5	5	5	5	5
P_OTH Other conditions originating in the perinatal period (remainder of P00–P96)	14	15	15	16	17	17	18
Q Congenital malformations, deformations and chromosomal abnormalities (Q00–Q99)	7	12	13	14	16	16	19
R07 Pain in throat and chest	11	11	11	11	12	12	12
R10 Abdominal and pelvic pain	9	10	10	10	10	11	11
R_OTH Other symptoms, signs and abnormal clinical and laboratory findings (remainder of R00–R99)	112	127	140	150	168	172	180
S06 Intracranial injury	4	4	4	4	4	4	4
S72 Fracture of femur	0	0	0	3	4	4	4
S82 Fracture of lower leg, including ankle	0	0	0	1	1	1	1
S_T_OTH Other and unspecified effects of external causes (remainder of S00–T98)	13	17	17	17	18	19	19
T20–T32 Burns and corrosions	13	14	15	16	16	17	17
T36–T65 Poisonings by drugs, medicaments and biological substances and toxic effects	11	12	12	14	18	20	21
T80–T88 Complications of surgical and medical care, not elsewhere classified	20	23	29	33	37	38	38
UPRESPIR_OTH Other diseases of upper respiratory tract (J30–J34, J36–J39)	34	41	50	54	57	59	59

Table 8 Estimates of models that include multiple lag lengths ($CUM\_DRUG_{c,t}$, $CUM\_DRUG_{c,t-8}$, and $CUM\_DRUG_{c,t-12}$)

Model	Dependent variable	Lag (*k*)	Estimate	Std. err	95% Lower confidence	95% Upper confidence	*Z*	Pr>|*Z*|
1	$\ln(YPLL85_{ct})$	0	0.249	0.224	−0.191	0.688	1.11	0.2676
		8	−0.544	0.180	−0.896	−0.191	−3.02	0.0025
		12	0.014	0.166	−0.312	0.339	0.08	0.9344
2	$\ln(YPLL85_{ct})$	8	−0.501	0.226	−0.944	−0.058	−2.22	0.0266
3	$\ln(YPLL75_{ct})$	0	0.115	0.264	−0.402	0.632	0.44	0.6617
		8	−0.691	0.213	−1.109	−0.273	−3.24	0.0012
		12	0.148	0.222	−0.288	0.584	0.67	0.5048
4	$\ln(YPLL75_{ct})$	8	−0.630	0.258	−1.135	−0.124	−2.44	0.0147
5	$\ln(YPLL65_{ct})$	0	−0.022	0.385	−0.776	0.733	−0.06	0.9553
		8	−0.893	0.236	−1.355	−0.431	−3.79	0.0001
		12	0.264	0.325	−0.373	0.902	0.81	0.4164
6	$\ln(YPLL65_{ct})$	8	−0.799	0.247	−1.283	−0.316	−3.24	0.0012
7	$\ln(HOSP\_DAYS_{ct})$	0	0.749	0.271	0.218	1.281	2.76	0.0058
		8	−0.460	0.218	−0.888	−0.033	−2.11	0.0348
		12	−0.199	0.134	−0.462	0.065	−1.48	0.1389
8	$\ln(HOSP\_DAYS_{ct})$	8	−0.369	0.179	−0.719	−0.019	−2.07	0.0388
9	$\ln(ALOS_{ct})$	0	0.031	0.067	−0.100	0.163	0.47	0.6415
		8	−0.120	0.047	−0.212	−0.027	−2.54	0.0112
		12	−0.061	0.058	−0.175	0.052	−1.06	0.2891
10	$\ln(ALOS_{ct})$	8	−0.153	0.062	−0.275	−0.031	−2.46	0.0137

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Availability of data and materials
All data, except IQVIA MIDAS data, are publicly available. The IQVIA MIDAS data are not publicly available but are available from the corresponding author on reasonable request.

Declarations

Competing interests
The authors declare that they have no competing interests.

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