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Pharmaceutical policies: effects of regulating drug insurance schemes.
Cochrane Database of Systematic Reviews 2022, Issue 5. Art. No.: CD011703.
DOI: 10.1002/14651858.CD011703.pub2.

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[Intervention Review]

Pharmaceutical policies: effects of regulating drug insurance schemes

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Editorial group: Cochrane Effective Practice and Organisation of Care Group.
Publication status and date: New, published in Issue 5, 2022.

Citation: Pantoja T, Peñaloza B, Cid C, Herrera CA, Ramsay CR, Hudson J.Pharmaceutical policies: effects of regulating drug insurance schemes. *Cochrane Database of Systematic Reviews* 2022, Issue 5. Art. No.: CD011703. DOI: 10.1002/14651858.CD011703.pub2.

ABSTRACT

Background

Drug insurance schemes are systems that provide access to medicines on a prepaid basis and could potentially improve access to essential medicines and reduce out-of-pocket payments for vulnerable populations.

Objectives

To assess the effects on drug use, drug expenditure, healthcare utilisation and healthcare outcomes of alternative policies for regulating drug insurance schemes.

Search methods

We searched CENTRAL, MEDLINE, Embase, nine other databases, and two trials registers between November 2014 and September 2020, including a citation search for included studies on 15 September 2021 using Web of Science. We screened reference lists of all the relevant reports that we retrieved and reports from the Background section. Authors of relevant papers, relevant organisations, and discussion lists were contacted to identify additional studies, including unpublished and ongoing studies.

Selection criteria

We planned to include randomised trials, non-randomised trials, interrupted time-series studies (including controlled ITS [CITS] and repeated measures [RM] studies), and controlled before-after (CBA) studies. Two review authors independently assessed the search results and reference lists of relevant reports, retrieved the full text of potentially relevant references and independently applied the inclusion criteria to those studies. We resolved disagreements by discussion, and when necessary by including a third review author. We excluded studies of the following pharmaceutical policies covered in other Cochrane Reviews: those that determined how decisions were made about which conditions or drugs were covered; those that placed restrictions on reimbursement for drugs that were covered; and those that regulated out-of-pocket payments for drugs.

Data collection and analysis

Two review authors independently extracted data from the included studies and assessed risk of bias for each study, with disagreements being resolved by consensus. We used the criteria suggested by Cochrane Effective Practice and Organisation of Care (EPOC) to assess the risk of bias of included studies. For randomised trials, non-randomised trials and controlled before-after studies, we planned to report relative effects. For dichotomous outcomes, we reported the risk ratio (RR) when possible and adjusted for baseline differences in the outcome measures. For interrupted time series and controlled interrupted time-series studies, we computed changes along two dimensions: change in level; and change in slope. We undertook a structured synthesis following the EPOC guidance on this topic, describing the range of effects found in the studies for each category of outcomes.

Main results

We identified 58 studies that met the inclusion criteria (25 interrupted time-series studies and 33 controlled before-after studies). Most of the studies (54) assessed a single policy implemented in the United States (US) healthcare system: Medicare Part D. The other four assessed other drug insurance schemes from Canada and the US, but only one of them provided analysable data for inclusion in the quantitative synthesis. The introduction of drug insurance schemes may increase prescription drug use (low-certainty evidence). On the other hand, Medicare Part D may decrease drug expenditure measured as both out-of-pocket spending and total drug spending (low-certainty evidence). Regarding healthcare utilisation, drug insurance policies (such as Medicare Part D) may lead to a small increase in visits to the emergency department. However, it is uncertain whether this type of policy increases or decreases hospital admissions or outpatient visits by beneficiaries of the scheme because the certainty of the evidence was very low. Likewise, it is uncertain if the policy increases or reduces health outcomes such as mortality because the certainty of the evidence was very low.

Authors' conclusions

The introduction of drug insurance schemes such as Medicare Part D in the US health system may increase prescription drug use and may decrease out-of-pocket payments by the beneficiaries of the scheme and total drug expenditures. It may also lead to a small increase in visits to the emergency department by the beneficiaries of the policy. Its effects on other healthcare utilisation outcomes and on health outcomes are uncertain because of the very low certainty of the evidence. The applicability of this evidence to settings outside US healthcare is limited.

PLAIN LANGUAGE SUMMARY

Effects of policies regulating insurance for drugs

The aim of this Cochrane Review was to find out if drug insurance schemes change people's use of medicines, the amount of money they spend on medicines, their health, and their use of healthcare. Cochrane Review authors collected and analysed all relevant studies to answer this question. They found 58 studies. Most of these studies were from the US assessing a single policy change (Medicare Part D) implemented in January 2006.

Key messages

The USA's Medicare Part D offers free prescription medicines to elderly people. This system may increase the amount of medicines elderly people use, but they may spend less money on medicines. We do not know if this system changes people's health or their use of healthcare services because the certainty of the evidence was very low.

What is a drug insurance scheme?

In a drug insurance scheme, governments or private organisations offer people the medicines they need at a low cost or free of charge. The medicines are usually paid for through government taxes, people's employers, people paying for membership in insurance schemes, or a combination of these systems.

Many countries have mixed systems of public and private drug insurance. Some drug insurance schemes cover everyone in a country or setting. Other schemes only cover certain groups. For instance, some schemes only cover people in work, while other schemes only cover the poor and the elderly.

Successful drug insurance schemes can improve people's health by giving them the medicines they need either free or at a price they can afford. Drug insurance schemes can also save money for governments and private organisations. For instance, people using the right medicines may need fewer healthcare services. Governments and organisations running these schemes can also negotiate better prices with drug companies.

What are the main results of the review?

The review authors found 58 relevant studies. Most of these studies were from the USA and 54 of them assessed one type of drug insurance scheme: Medicare Part D.

Medicare Part D is a drug insurance scheme for elderly people. In this scheme, elderly people who are already on Medicare have free access to their prescription medicines up to a certain sum every year (in 2018, this sum was USD 3750 per person). After this sum is reached, other systems are used. These studies showed the following.

- Medicare Part D may increase the amount of medicines people use (low-certainty evidence).

- Medicare Part D may decrease the amount of money people spend on medicines (low-certainty evidence).

- Medicare Part D may lead to a small increase in the number of emergency department visits by beneficiaries of the scheme (low-certainty evidence).

- We do not know what the effect of Medicare Part D is on people's health or on the use of other healthcare services because the certainty of the evidence was very low.

One of the reasons for our low confidence in these findings is that we do not know how relevant these results are to countries or settings outside the USA.

How up to date is this review?

The review authors searched for studies that had been published up to September 2020.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings

Enrolment in the drug insurance scheme compared to no enrolment in the scheme

Patient or population: People entitled to the drug insurance scheme (elderly and/or poor population)

Settings: United States healthcare system

Intervention: Drug insurance scheme (Medicare Part D or ACA Medicaid expansion)

Comparison: No enrolment, non-eligible for enrolment or low likelihood of enrolment into the drug insurance scheme

Outcomes	Median adjusted[1] relative effect (IQR)	No of studies (N° effect estimates)	Certainty of the evidence (GRADE)	Comments
Drug use	Immediately after policy implementation +3.74% (−9.40% to 22.98%)	8 ITS studies (32 effect estimates)	⊕⊕⊖⊖ **Low[2]**	Drug insurance policies (such as Medicare Part D) may increase drug use immediately after until up to 12 months after the implementation of the policy. However, the range indicates that the policy may slightly decrease or may increase drug use.
	6 to 11 months after policy implementation +8.40% (-2.88% to 25.19%)	9 ITS studies, 1 CBA study (25 effect estimates)	⊕⊕⊖⊖ **Low[2]**	
	1 year or more after policy implementation +14.73% (3.11% to 36.0%)	1 CITS study, 10 ITS and 19 CBA studies (59 effect estimates)	⊕⊕⊖⊖ **Low[3]**	Drug insurance policies (such as Medicare Part D) may increase drug use from 1 year until up to 60 months after the implementation of the policy.
Drug expenditure	Immediately after policy implementation −59.07% (−66.33% to −26.27%)	4 ITS studies (15 effect estimates)	⊕⊕⊖⊖ **Low[4]**	Drug insurance policies (such as Medicare Part D) may decrease drug expenditures immediately and for up to 36 months after the implementation of the policy. When only out-of-pocket expenditures were considered (14, 18 and 39 effect estimates, respectively), there was no change in either the magnitude or variability of the summary effect estimates for any of the 3 outcome time points.
	6 to 11 months after policy implementation −46.96% (−65.98% to −22.98%)	7 ITS studies (19 effect estimates)	⊕⊕⊖⊖ **Low[4]**	
	1 year or more after policy implementation −43.17% (−57.40% to −19.77%)	1 CITS study, 8 ITS studies and 12 CBA studies (48 effect estimates)	⊕⊕⊖⊖ **Low[3]**	
Healthcare utilisation	Emergency Department visits +9.74%	2 ITS studies and 4 CBA studies (14 effect estimates)	⊕⊕⊖⊖ **Low[5]**	Drug insurance policies (such as Medicare Part D) may lead to a small increase in the number or frequency of Emergency Department visits by beneficiaries of the drug insurance scheme.

	(3.29% to 18.64%)			
	Hospital admissions -2.65% (-9.35% to 0.33%)	1 ITS study and 6 CBA studies (8 effect estimates)	⊕⊖⊖⊖ **Very low[6]**	The effects of drug insurance policies (such as Medicare Part D) on hospital admissions, outpatient visits and non-drug medical spending were uncertain because the certainty of the evidence was very low.
	Outpatient visits -28.6% (−69.25% to 22.7%)	3 CBA studies (3 effect estimates)	⊕⊖⊖⊖ **Very low[7]**	
	Non-drug medical spending -11.4% (-11.5% to -8.37%)	1 CITS and 2 CBA studies (3 effect estimates)	⊕⊖⊖⊖ **Very low[8]**	
Health outcomes	Mortality -0.50% (-1.35% to -0.35%)	1 ITS and 2 CBA studies (3 effect estimates)	⊕⊖⊖⊖ **Very low[9]**	The effects of drug insurance policies (such as Medicare Part D) on mortality were uncertain because the certainty of the evidence was very low.
	Non-mortality outcomes: depressive symptoms, activities of daily living (ADL) limitations, change in specific behaviours, self-perception of health: the effects included both small positive and negative impacts for these outcomes.	1 ITS and 6 CBA studies (17 effect estimates)	⊕⊖⊖⊖ **Very low[10]**	The effects of drug insurance policies (such as Medicare Part D) on non-mortality outcomes were uncertain because the certainty of the evidence was very low.

GRADE Working Group grades of evidence

High certainty = This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different** is low.

Moderate certainty = This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different** is moderate.

Low certainty = This research provides some indication of the likely effect. However, the likelihood that it will be substantially different** is high.

Very low certainty = This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different** is very high.

** Substantially different = a large enough difference that it might affect a decision

[1] Adjusted for baseline differences
[2] For these outcomes, because most of the body of evidence came from ITS studies, we started at a moderate grade and downgraded by 1 level because of methodological limitations (uncertainties about incomplete outcome data and the potential presence of other policies at the time when part D was implemented) and some concerns about unexplained inconsistency in the direction of effect.
[3] CBA studies started at a low-certainty grade due to concerns about methodological limitations. There were no additional concerns.

[4] For these outcomes, because most of the body of evidence came from ITS studies, we started at a moderate grade and downgraded by 1 level because of methodological limitations (uncertainties about incomplete outcome data and the potential presence of other policies at the time when Part D was implemented).
[5] Starting at a low grade (as most of the contributing evidence came from CBA studies), we did not have any additional concerns.
[6] Starting at a low grade (as most of the contributing evidence came from CBA studies), we downgraded by 1 level because of some concerns about methodological limitations and some concerns about unexplained inconsistency in the direction of effect.
[7] Starting at a low grade (as all of the contributing evidence came from CBA studies), we downgraded by 1 level because of some concerns about unexplained inconsistency in the direction of effect and some imprecision.
[8] Starting at a low grade (as most of the contributing evidence came from CBA studies), we downgraded by 1 level because of concerns about indirectness.
[9] Starting at a low grade (as most of the contributing evidence came from CBA studies), we downgraded by 1 level because of concerns about imprecision.
[10] Starting at a low grade (as most of the contributing evidence cane from CBA studies), we downgraded by 1 level because of concerns about imprecision.
CBA = Controlled before-after study
ITS = Interrupted time-series study

BACKGROUND

Pharmaceuticals are an essential part of modern medicine, playing a major role in protecting, maintaining and restoring people's health. The provision of appropriate medicines of assured quality in adequate quantities and at reasonable prices is therefore a concern of both global and national policy makers around the world.

Description of the condition

One significant challenge in this field has been the increase in spending on drugs during the last decade. According to the World Health Organization (WHO) National Health Accounts data in 2006, the mean expenditures on pharmaceuticals as a share of total expenditures on health was 24.9% across all countries, but ranged from 30.4% for low-income countries to 19.7% for high-income countries (Lu 2011). In 2017, spending on retail pharmaceuticals in countries included in the Organization for Economic Co-operation and Development (OECD) averaged USD 564 per person, ranging from USD 175 (Costa Rica) to USD 1220 (USA) per capita per year. Most spending on retail pharmaceuticals is for prescription medicines (75%) with the remainder spent on over-the-counter (OTC) medicines (19%) and medical non-durables (5%). This type of expenditure accounted for almost one-fifth of all healthcare expenditure, and represented the third largest spending component in OECD countries after inpatient and outpatient care (OECD 2019).

Along with growth of spending on pharmaceuticals, there is increasing consumption of drugs due to changes in medical practice and the appearance of more expensive drugs. Although this consumption has grown in all countries, in the non-hospital sector, the relative growth between 2000 and 2008 has been higher in low-income countries (29.3%) than in high-income countries (18.6%) (Hoebert 2011). For example, consumption of anti-diabetic drugs in OECD countries increased from 37 defined daily doses (DDD) per 1000 people per day in 2000 up to 68 DDD per 1000 people per day in 2017; and consumption of antidepressants increased from 32 DDD per 1000 people per day in 2000 up to 63 DDD per 1000 people per day in 2017 (OECD 2019).

Despite the rise in spending and consumption, people in many countries do not have sufficient access to medicines. A study of accessibility of the 15 most commonly used drugs in 50 countries showed that the availability of generics in the private sector ranged between 60.7% and 76.3%, while in the public sector it ranged from 27% to 44.3% (Cameron 2008). The availability of original drugs in the private sector was between 22.3% and 61.8%.

The proportion of the total cost for drugs paid for by out-of-pocket (OOP) payments by patients is an important indicator of barriers to access to medicines. In 2006, private expenditure on medicines as a share of total pharmaceutical expenditure per capita was 61.2%, 66.5% and 76.9% in upper-middle-income, lower-middle-income and low-income countries, respectively (Lu 2011). This reflects the reality that OOP expenditure is the major source of pharmaceutical payments in all but high-income countries. These OOPs might lead to 'catastrophic' payments, defined as paying more than 40% of household income directly on healthcare after basic needs have been met (Murray 2003). Catastrophic payments are well documented (Van Doorslaer 2007), and are usually focused on spending on healthcare in general, rather than on pharmaceuticals specifically. Payments for medicines are often, however, a high proportion of OOP spending. Moreover, high OOP payments might lead to discontinuation of essential medicines when people cannot afford to pay for them.

Description of the intervention

Drug insurance schemes, which are systems that provide access to medicines on a prepaid basis, could potentially address some of the problems currently faced by many health systems regarding medicines, such as rising costs and inappropriate OOP payments. They may have multiple — although sometimes conflicting — goals including:

- ensuring that everyone has access to essential medicines;
- ensuring equitable access to drugs;
- reducing or eliminating OOP payments for essential medicines;
- preventing catastrophic payments for drugs;
- containing the amount of public funds that are spent on drugs, for example, by negotiating better prices and reducing inappropriate use of drugs; and
- ensuring the appropriate use of drugs.

Approaches to drug insurance vary substantially between countries for several reasons, including differences in prioritising the above goals; political differences, for example, the extent of social solidarity; and economic differences. These approaches are a reflection of the way in which governments choose to regulate the governance, financing and provision of drug insurance schemes through determining:

- who can provide drug insurance;
- who receives drug insurance;
- who pays for drug insurance; and
- who makes decisions regarding which conditions and which drugs are covered.

Such regulations may apply specifically to drug insurance or may apply more generally to health insurance (with or without drug insurance).

Who can provide drug insurance

Drug insurance can either be provided publicly by the government or privately by non-governmental organisations. Private insurance, in turn, can be either for-profit or not-for-profit (non-profit).

Private insurance can be a substitute for public insurance; can supplement public insurance by providing coverage for drugs beyond that covered by public insurance; or can be in competition with public health insurance by providing alternatives to public drug insurance. Most countries have mixed systems of public and private drug insurance. There is wide variation in the rules set by governments and, consequently, in the extent of public and private insurance, the mix of for-profit and not-for-profit drug insurance, and the mix of substitute, supplementary and competitive private drug insurance schemes (WHO 2004a; WHO 2004b; World Bank 2007).

Who receives drug insurance

Drug insurance may be universal, that is, covering everyone in a jurisdiction; or only available to certain groups, such as the poor

or the elderly (WHO 2004b). Regulations can require that drug insurance is:

- universal, meaning that everyone in a jurisdiction is covered;
- compulsory, meaning that individuals must have drug insurance, but not everyone is covered by public insurance, and public insurance is not provided automatically to everyone;
- provided to specific groups, for example, the poor, the elderly or the employed; or
- optional, meaning that the government can also regulate who can or cannot be excluded from enrolling in drug insurance schemes.

Who pays for drug insurance

Premiums (pre-payments) for drug insurance can be paid out of general tax revenues, earmarked taxes, by employers, or directly by those who are insured (Savedoff 2004). Many countries have mixed systems in which premiums are partially paid by two or more of these sources or where different sources pay the premiums for different groups of people.

Who makes decisions regarding which conditions and which drugs are covered

Decisions about coverage can be made by the government, by independent bodies to which the government has allocated authority, or by the owners of private health insurance schemes. There can also be mixed systems where some types of decisions are, for example, made by the government and others are left to the owners of private insurance schemes. In federal systems some decisions may be made by the federal government and others by sub-national governments or authorities.

How the intervention might work

Who can provide drug insurance

Approaches to the provision of drug insurance operate in different ways and may vary considerably in achieving the goals of drug insurance (Savedoff 2004; WHO 2004a; WHO 2004b; WHO 2010; World Bank 2007). Thus, from society's perspective, public drug insurance might facilitate pursuing all the suggested goals (Table 1). Private for-profit drug insurance, on the other hand, might have disadvantages of limited coverage and lack of protection for vulnerable populations, but might be more effective for cost containment in terms of public spending. Advocates of private for-profit insurance argue that the creation of a parallel system of private finance can ensure the sustainability of the public system by reducing public cost pressures, and improve quality in the public system through competition. Opponents of parallel private finance argue that it will create a 'two-tiered' system, which would increase costs, compromise equity, and reduce quality and access as those with the financial means (and often the strongest voice) choose private insurance instead of public insurance.

Private not-for-profit drug insurance schemes may not differ significantly from for-profit schemes, although they might provide better coverage if resources that would have gone to profits were instead used for the benefit of the insured. Public, private not-for-profit and for-profit insurance schemes can all utilise various mechanisms for cost containment, for example, centralised procurement, price negotiation and co-payments (OOP payment done by beneficiaries on top of payments by insurance schemes). Their motivations for using these mechanisms may differ, however.

Who receives drug insurance

The World Health Assembly considers universal coverage as an optimal strategy to provide wide access to healthcare with no increase in the financial burden of the population (WHO 2005a). In December 2012, the United Nations General Assembly unanimously adopted a resolution that emphasises health as an essential element of international development, urging governments to move towards providing all people with access to affordable, quality healthcare services, and calling for countries, civil society, and international organisations to include universal health coverage (UHC) in the international development agenda (United Nations 2012). More recently, the Sustainable Development Goals (SDG) adopted in September 2015 contains several targets related to health, but SDG 3 focuses specifically on ensuring healthy lives and promoting well-being for all. Under this goal, objective 3.8 highlights the importance to "achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all" (United Nations 2015). In this context, the issues of ensuring equitable access to affordable, quality-assured, essential medicines has become central for the global health agenda and drug insurance arises as a policy option to explore in depth (Das 2017).

Compulsory insurance can be universal or can be restricted to specific groups, such as civil workers or officially employed workers. Coverage of specific groups might protect more disadvantaged populations, for example, the disabled or the poor, thus reducing inequities, or protect more advantaged populations, such as employed workers, thus increasing inequities. If compulsory insurance focuses on vulnerable populations, it might provide protection from catastrophic payments, since vulnerable populations, such as the elderly, might be at the highest risk of being pushed into poverty (WHO 2005b).

Optional insurance might limit sharing of financial risk and provide limited protection to vulnerable populations. It is more likely to benefit people who are able to pay, such as employed workers.

In many countries, there is a mix of policies that determine who receives drug insurance. These policies might supplement each other; for example, there might be compulsory insurance for employed workers, and government-subsidised insurance for vulnerable populations.

Universal insurance, or compulsory insurance that is universal or includes a large segment of the population, might facilitate cross-subsidisation across participants and provide more financial protection due to better sharing of financial risk (WHO 2010). Universal coverage might also facilitate cost containment, by enabling unified policy actions at the national level, and improve access to essential drugs, if these are included in the basic benefit package.

See Table 2.

Who pays for drug insurance

Collection of premiums via general or earmarked taxes might facilitate universal coverage. Earmarked taxes might protect

collected premiums and ensure the availability of funds. They might also make the allocation of funds more transparent. Taxes might also be progressive, facilitating a shift of financial burden from the poor to the rich, and therefore be more equitable (Glied 2008). Payments by employers or direct payments by individuals only provide coverage for the insured population. This would not provide protection from catastrophic payments for those who were not employed or could not afford insurance and might limit access to essential drugs for those populations.

See Table 3.

Who makes decisions regarding which conditions and drugs are covered

Governments might be likely to make decisions that ensure equitable access and provide protection from catastrophic payment, although decisions might be driven by other political considerations or corruption. Due to the technical nature and complexity of coverage decisions, decision-making might be delegated, for example to health technology assessment (HTA) agencies. This might help to achieve cost containment but could potentially affect the availability of some non-essential drugs, for example, by only covering cost-effective drugs (those with a relative value that lies below a 'willingness to pay' threshold set by government or the HTA agency). Relying on private insurance companies for these kinds of decisions might reduce coverage, or shift costs to government or OOP payments in order to maximise profits. Both government bodies and insurance companies might rely on the suggestions made by HTA agencies, enabling a more collaborative approach. Although prescribers are not generally involved in decisions regarding which conditions and drugs are covered, they may be responsible for implementing these policies in clinical practice.

See Table 4.

Why it is important to do this review

We have not identified previous systematic reviews that address the effects of policies for regulating the provision of drug insurance. Several published reviews have compared not-for-profit and for-profit delivery of health services (Comondore 2009; Devereaux 2002a; Devereaux 2002b; Himmelstein 1999; Khoury 2001; Schneider 2005). These reviews have found important differences in patient outcomes, costs and the quality of care, generally favouring not-for-profit delivery of services. Reviews of the effects of social health insurance and community-based health insurance in low- and middle-income countries have found few comparative evaluations (Lagarde 2009). Several studies have evaluated the recently implemented Medicare Prescription Drug Plan (Part D) (the federal programme in the USA that subsidises the cost of prescription drugs for Medicare beneficiaries) and they have been summarised in a systematic review based on interrupted time-series and cross-sectional studies (Polinski 2010). However, this review only included a search in a single electronic database (Medline) from 2006 to 2009 in the early stages of implementation of the policy. Likewise, another review assessed the impact of Medicare Part D in a specific subgroup of the population: those on long-term care (LTC) (Pimentel 2013). However, this population subgroup (compared to those living in the community) has higher levels of functional and cognitive impairment, greater comorbidity burden, more prescription drug use and fewer financial resources, which makes its findings qualitatively different from the general population. Another systematic review by Faden 2011 revealed that drug insurance may increase access to medicines and reduce self-medication, and provided conflicting evidence about the effect on medication spending. The scope of this last review was broader, however, including studies assessing the effect of which medicines were procured or supplied, which medical services were provided, and the implementation of programmes to improve drugs prescribing and use.

Given this lack of specific evidence about the effects of policies that regulate drug insurance schemes, a systematic review of the effects of these policies is needed to inform decisions in this policy area. Many countries are in the process of reforming the way in which health systems finance pharmaceutical expenditures, and the topic has gained global concern in recent years. The Lancet Commission on Essential Medicines for UHC published its report in 2017, aiming to analyse how essential medicines policies can be harnessed to promote UHC and contribute to the global SDG agenda (Wirtz 2017). Among their recommendations, the Commission called for "governments and national health systems [to] provide adequate financing to ensure the inclusion of essential medicines in benefit packages provided by the public sector and all health insurance schemes," showing the relevance of insurance schemes that might be applied specifically on drugs. In addition, in 2016, the UN convened a High-Level Panel on Access to Medicines with the aim of addressing the incoherences between international human rights, trade, intellectual property rights, and public health objectives (United Nations Secretary General 2016). The Panel stated that there are many reasons why people do not get the healthcare they need, including — among many other factors — the unavailability of health insurance. However, some authors also commented that insurance does not protect people from the high cost of medicines nor does it guarantee access to the medicines they need even in high-income countries, as there is strong evidence that public, social and private insurance use rationing in providing expensive medicines. This shows how access and affordability of medicines is a current global health issue because of old and new challenges, even in countries with well-established systems of drug insurance.

This review is one of 13 planned or completed reviews of the effects of different types of pharmaceutical policies on rational drug use (Aaserud 2006). Pharmaceutical policies that are complementary to the regulation of the provision of drug insurance are addressed in other reviews (see Appendix 1). These include, for example, policies regarding caps and co-payments (Luiza 2015), restrictions on reimbursement for drugs that are covered (Green 2010), and policies that regulate pricing and purchasing (Acosta 2014).

OBJECTIVES

To assess the effects on drug use, drug expenditure, healthcare utilisation and healthcare outcomes of alternative policies for regulating drug insurance schemes.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised trials, non-randomised trials, interrupted time-series studies (including controlled ITS [CITS] and repeated measures [RM] studies), and controlled before-after (CBA) studies

(those studies where a comparison group is selected and outcomes are measured in both groups before and after the implementation of the policy). The possibility of making causal inferences rests on how similar both groups are before the policy and on how small the differences are at that time in relation to the main outcomes (Shadish 2002). We therefore did not include controlled before-after studies where the control group was clearly not equivalent to the intervention group prior to implementation of the policy, (because of clear differences in insurance coverage or sociodemographic characteristics such as age or gender). Likewise, we did not include studies with no control group even when they measured outcomes before and after the implementation of the policy (uncontrolled before-after studies, also known as the one group pretest/post-test design) because they generally do not permit reasonable causal inferences (Cook 1979).

Following EPOC guidance, we only included cluster-randomised trials and controlled before-after studies that included two or more sites in each comparison group (EPOC 2017b). We only included ITS studies if there was a clearly defined point in time when the intervention occurred and at least three data points before and three after implementation of the policy.

Types of participants

Healthcare consumers and providers within a large jurisdiction or system of care. Jurisdictions could be regional, national or international. We included studies within organisations, such as health maintenance organisations, if the organisation was multi-sited and served a large population.

Types of interventions

Policies that determined who can provide drug insurance, who receives it, who pays for it and who makes decisions about reimbursement. We defined policies as laws, rules, financial or administrative orders made by governments, non-government organisations or private insurers. We excluded policies at the level of a single facility and policies that did not specifically regulate the provision of drug insurance.

We included the following comparisons.

- Any restriction of who can or does provide drug insurance, including private versus public provision of drug insurance and not-for-profit versus for-profit provision of drug insurance; we included any restriction versus any other restriction or no restriction.
- Any requirement regarding who receives drug insurance, including universal coverage versus coverage for selected groups such as the employed or vulnerable groups versus any other requirement or no requirement.
- Any policy that determined who pays for drug insurance, including general tax revenues versus employer payments versus direct payment of insurance premiums versus combinations of these.
- Any policy concerning who has the authority to make decisions regarding which conditions and which drugs are covered and under which circumstances, including the government versus independent bodies to which the government has allocated authority versus the owners of private health insurance schemes versus mixed systems where some types of decisions are, for example, made by the government and others are left up to the owners of private insurance schemes, or in which some decisions are made by the federal government and others by sub-national governments.

We generally included policies that affected health insurance only if they specifically addressed drug insurance schemes, with or without addressing other healthcare benefits. We also included comparisons of policies that cut across the four categories above, for example, that regulated both who could provide and who received drug insurance.

We excluded the following policies from this review: those that determined how decisions are made about which conditions or drugs are covered; those that placed restrictions on reimbursement for drugs that were covered; and those that regulated out-of-pocket payments for drugs. These policies are the focus of other Cochrane Reviews (Aaserud 2006; Green 2010; Luiza 2015). Appendix 1 provides a full list of the types of pharmaceutical policies assessed by other Cochrane Reviews.

We only included comparisons where we considered the control group was 'equivalent' to the group affected by the policy being assessed. When a non-equivalent control group was used (such as groups with very different insurance coverage), we analysed those studies as 'uncontrolled' designs. Likewise, because the focus of the review was on assessing the impact of policies on those moving to the specific scheme, we only considered — as a post hoc decision — comparisons between those with no coverage (likely to move to the scheme) and those with generous coverage (unlikely to move to the scheme) prior to the policy implementation. This left a number of other comparisons (e.g. those with some but not generous initial coverage) out of our main analysis.

Types of outcome measures

To be included, a study had to include an objective measure from at least one of the following outcome categories.

- Drug use (including appropriate and inappropriate use, when this is reported);
- Drug expenditures (including total expenditures on drugs specifically and on healthcare generally, and catastrophic payments [i.e. OOP payments for drugs that necessitate the sacrifice of other basic needs, sale of productive assets, incurrence of debt, or result in impoverishment]);
- Healthcare utilisation (as drug insurance schemes may, through increasing the use of pharmaceutical interventions, decrease use of other non-pharmaceutical services);
- Health outcomes;
- Differences in these outcomes between vulnerable (for example low-income) and less vulnerable groups.

Search methods for identification of studies

Electronic searches

We searched PDQ-Evidence, Epistemonikos Foundation (www.pdq-evidence.org/) for related systematic reviews on 05 September 2020. We searched the following databases for primary studies:

- Cochrane Central Register of Controlled Trials (CENTRAL), 2020 Issue 9, part of *The Cochrane Library:* www.cochranelibrary.com (searched 05 September 2020);

- MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to September 04, 2020, Ovid (searched 05 September 2020);
- Embase 1974 to 2020 Week 36, Ovid (searched 05 September 2020);
- EconLit 1969 to present, ProQuest (searched 05 September 2020);
- INRUD Bibliography: www.zotero.org/groups/659457/inrud_biblio/collections/HBW4TTCK (searched 05 September 2020);
- NHS Economic Evaluation Database 2015, Issue 2, part of The Cochrane Library: www.cochranelibrary.com (searched 27 January 2017);
- PAIS International, Public Affairs Information Service 1914-current, ProQuest (searched 06 November 2014);
- Worldwide Political Science Abstracts 1975-current, ProQuest (searched 06 November 2014).

We did not search the NHS Economic Evaluation Database in 2020 as the databases has not been updated since 2015. We did not search PAIS International, and Worldwide Political Science Abstracts in 2020, as we had no access to these databases.

Search strategies are comprised of natural language and controlled vocabulary terms. We applied no limits on language or publication date. In databases where it was possible and appropriate, study design filters were used to limit to the study designs of interest. For randomised trials in MEDLINE, we used a modified version of the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision)(Lefebvre 2021) with additional terms for other relevant study designs. Limits were used in Embase to remove MEDLINE records in order to avoid duplication in downloaded results. Remaining results were deduplicated in EndNote against each other. All search strategies used are provided in Appendix 2.

Searching other resources

Trial registries

We searched the following Trial registries on 07 September 2020:

- WHO ICTRP (World Health Organization International Clinical Trials Registry Platform): www.who.int/clinical-trials-registry-platform;
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov: clinicaltrials.gov/.

Grey literature

We searched the grey literature to identify studies not indexed in the databases listed above:

- OpenGrey: www.opengrey.eu (searched 07 September 2020);
- The Grey Literature Report: www.greylit.org/ (searched 08 May 2019).

We also:

- searched the Web of Science Core Collection, Clarivate (Science Citation Index Expanded 1987-present; Social Science Citation Index 1987-present; Emerging Sources Citation Index 2015-present) for articles citing the 58 included studies (searched 15 September 2021);
- screened the reference lists of all relevant reports that we retrieved and reports from the Background section;
- Contacted authors of relevant papers, relevant organisations, and discussion lists to identify additional studies, including unpublished and ongoing studies.

Data collection and analysis

Selection of studies

Two review authors independently assessed the search results and reference lists of relevant reports. We retrieved the full text of potentially relevant references (those considered relevant by at least one author) and two review authors independently applied inclusion criteria to those studies.

We resolved disagreements at this stage by discussion and, when necessary, by including a third review author.

Data extraction and management

Two review authors independently extracted data from the included studies. We extracted the following information from the included studies using a standardised data extraction form.

- Type of study (randomised trial, interrupted time-series, controlled before-after);
- Study setting (country, key features of the healthcare system and concurrent pharmaceutical policies);
- Characteristics of the participants;
- Characteristics of the policies;
- Main outcome measures and study duration;
- The results for the main outcome measures;
- The sponsors of the study.

When a study presented results for more than one main outcome in each of the four outcome groups (drug use; drug expenditures, healthcare utilisation and health outcomes), we chose what we considered to be the most important outcome(s) in each group, either as specified by the study authors or based on discussions among ourselves. In cases where we thought additional main outcomes in the four outcome groups provided important insight, we also included them.

Assessment of risk of bias in included studies

We used the criteria suggested by the EPOC group to assess the risk of bias of included studies (EPOC 2017a). Two review authors independently assessed each study and reached consensus in the assessment. We assessed overall limitations for each main outcome within each study using the following guidelines.

- No serious limitations = low risk of bias = all criteria scored as 'met';
- Some limitations = moderate risk of bias = one or two criteria scored as 'not clear' or 'not met';
- Serious limitations = high risk of bias = more than two criteria scored as 'not clear' or 'not met'.

Measures of treatment effect

Randomised trials and controlled before-after studies

For randomised trials, non-randomised trials and CBA studies, we planned to report relative effects. For both dichotomous and continuous outcomes, we reported the relative change, adjusted for baseline differences in the outcome measures. When relative effect estimates using specific statistical approaches (e.g. difference-in-differences) were reported by authors, we used them as the primary effect estimates. Otherwise, we computed relative effect estimates as:

(absolute post-intervention difference between the intervention and control groups minus the absolute pre-intervention difference between the intervention and control groups)/post-intervention level in the control group.

Interrupted time-series, controlled interrupted time-series and repeated measure studies

For interrupted time-series and controlled interrupted time-series studies, we computed changes along two dimensions: change in level; and change in slope.

Change in level is the immediate effect of the policy and we estimated it as the difference between the fitted value for the first post-intervention data point (one month after the intervention) minus the predicted outcome one month after the intervention based on the pre-intervention slope only.

Change in slope is the change in the trend from pre- to post-intervention, reflecting the long-term effect of the intervention. Since the interpretation of change in slope can be difficult, we presented the long-term effects in the same way that we calculated and presented the immediate effects. We presented the effects after six months as the difference between the fitted value for the six-month post-intervention data point minus the predicted outcome six months after the intervention based on the pre-intervention slope only. We similarly estimated the effects after one year and annually thereafter, when available. When possible, we reported the relative change, adjusted for pre-intervention trends in the outcome measures (that is, the post-intervention level divided by the last pre-intervention point).

Given that policy changes are often announced some months prior to official implementation, we defined a transition phase as the six months from official announcement. Although this may seem arbitrary, we chose this duration for the transition phase based on our informal knowledge of the policy process in our countries (Chile, UK) and also based on the approach used in similar reviews (Acosta 2014; Rashidian 2015). When the included interrupted time-series studies stated a different transition phase, we used the study's definition. All results excluded the transition phase data.

When papers with an interrupted time-series design did not provide an appropriate analysis or reporting of results, but presented the data points in a scannable graph or in a table, we re-analysed the data using methods described in Ramsay 2003. The following segmented time series regression model was used.

$$Y(t) = B0 + B1*Preslope + B2*Postslope + B3*Intervention + e(t)$$

... where Y(t) is the outcome in month t; Preslope is a continuous variable indicating time from the start of the study up to the last point in the pre-intervention phase and coded constant thereafter; Postslope is coded 0 up to and including the first point post-intervention and coded sequentially from 1 thereafter; and Intervention is coded 0 for pre-intervention time points and 1 for post-intervention time points.

In this model, B1 estimates the slope of the pre-intervention data, B2 estimates the slope of the post-intervention data and B3 estimates the change in level of outcome as the difference between the estimated first point post-intervention and the extrapolated first point post-intervention if the pre-intervention line was continued into the post-intervention phase. The difference in slope is calculated by B2 − B1. We assumed the error term e(t) to be first order autoregressive. When possible, we calculated 95% confidence intervals (CIs).

Unit of analysis issues

We performed analysis at the same level as the allocation to avoid unit-of-analyses errors. Because we did not find any cluster studies, we did not implement the planned methods as described in the protocol (See Differences between protocol and review).

Dealing with missing data

We tried to contact study authors when important data were not available. If we were not able to obtain missing data, we reported the results that were available, provided they were not likely to be misleading — for example, if there was a unit of analysis error.

Assessment of heterogeneity

When there were sufficient numbers of comparisons for similar outcomes across studies, we planned to use graphical displays (e.g. 'box and whisker' plots) to visually explore heterogeneity of the results across studies. Likewise, we planned to use the I^2 statistic to assess the extent of variability beyond chance for each of the groups of studies assessing similar comparisons and outcomes (Higgins 2003).

Assessment of reporting biases

Provided that studies were similar enough to warrant a meta-analysis and that there was a sufficient number of estimates for each outcome (at least 10), we planned to use a funnel plot to visually explore the risk of publication bias, using the population of the included jurisdictions in each study as a proxy of the precision of the estimate, and the adjusted risk ratio (RR) or risk difference (RD) as the intervention effect. In the interpretation of the results, we planned to consider other potential causes of funnel plot asymmetry such as small-study effects (the tendency for the intervention effects estimated in smaller studies to differ from those estimated in larger studies), differences in methodological quality across studies, or true heterogeneity in intervention effects (Sterne 2011).

Data synthesis

We planned to prepare a table for each category of policies (who can provide drug insurance, who receives it, who pays for it, and who has the authority to make decisions about what is covered) including the following information: study identification, characteristics of the intervention, drug use, healthcare utilisation, health outcomes, and resource utilisation (costs). This, however, was not required as we identified studies meeting our inclusion

criteria for only two policies (with analysable data) and most of the evidence was focused on a single policy (addressing all the categories of policies). Where possible, the findings were grouped by the healthcare setting in which studies were conducted.

We planned to conduct a meta-analysis only for studies that reported similar comparisons (interventions, comparisons and outcomes that were similar enough so that an average effect across those studies would be meaningful). For randomised trials, non-randomised trials and controlled before-after studies, we planned to record the number of events (in the case of health outcomes) and the total number in each group (for RR), or mean and standard deviation (SD) in each group (for mean difference [MD], e.g. in the case of drug utilisation). We have shown all outcome effects with their associated 95% CIs, when possible. Anticipating heterogeneity across studies, we planned to use a random-effects model meta-analysis. We planned to perform data synthesis using the Cochrane statistical software Review Manager 2014.

Because of differences in the populations, comparisons and methods used by the included studies (see Included studies), we did not conduct a meta-analysis (Campbell 2020). Instead we undertook a structured synthesis following the EPOC guidance on this topic (EPOC 2017c). For each category of outcomes, we described the median and the range of (relative) effects found in the studies (more specifically, using the interquartile range (IQR or 25th and 75th percentiles) in order to leave extreme outliers outside the analysis). We did not apply any weighting to these estimates.

We only included comparisons where we considered the control group minimally 'equivalent' to the group affected by the policy being assessed. When a non-equivalent control group was used we analysed those studies as 'uncontrolled' designs.

Subgroup analysis and investigation of heterogeneity

We planned to consider the following potential effect modifiers when investigating heterogeneity: differences in the characteristics of the policies; differences in complementary policies; and differences in the settings. We planned these analyses to be exploratory. We planned no specific subgroup analyses a priori. Because there were not enough studies or comparisons available to explore heterogeneity in a reliable way, we did not conduct any subgroup analysis.

Sensitivity analysis

We planned to perform sensitivity analyses for missing data by imputing a plausible range of assumptions. We planned to discuss the potential implications of missing information. We also planned to perform sensitivity analyses if there were studies with differing risks of bias that addressed the same question by excluding studies with a high risk of bias as defined in the section Assessment of risk of bias in included studies. Because there were not enough studies, we did not conduct any sensitivity analyses.

Summary of findings and assessment of the certainty of the evidence

Two review authors independently assessed the certainty of the evidence (high, moderate, low, and very low) using the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness, and publication bias (Guyatt 2008)). We used methods and recommendations described in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2019), and the EPOC worksheets (EPOC 2017d). We resolved disagreements on certainty ratings by discussion and provided justification for decisions to down- or upgrade the ratings using footnotes in the table; we also made comments to aid readers' understanding of the review, where necessary. We used plain language statements to report these findings in the review (EPOC 2017d) (see worksheet 4 - key messages in plain language from Worksheets for preparing Summary of findings tables using GRADE).

We summarised the findings in (a) Summary of findings table(s) for the main intervention comparison(s) and included the most important outcomes (grouped in the following categories: drug use; drug expenditure; healthcare utilisation; and health outcomes) in order to draw conclusions about the certainty of the evidence within the text of the review.

RESULTS

Description of studies

We identified 58 studies that met the inclusion criteria. However in eight of them (Caetano 2006; Dranove 2017; Ettner 2011; Mott 2010; Ong 2012; Saverno 2011; Tan 2021; Tang 2019) we were not able to obtain reported data in an useful format for our quantitative analysis (see Characteristics of included studies for details). Most of the included studies (n = 54) assessed a single policy implemented in the US healthcare system: Medicare Part D (Oberlander 2007). The other four studies assessed other drug insurance schemes in Canada (British Columbia Fair Pharma Care (Caetano 2006) and Ontario expansion of public drug coverage (Tan 2021)); the US (Affordable Care Act (ACA) Medicaid expansion (Maclean 2020); and the privatisation of Medicaid Drug Benefits (Dranove 2017)); only one of these was included in the quantitative analysis (Maclean 2020). Before submitting for publication (September 2021), we additionally identified two further studies currently awaiting classification (Americo 2020; Sabety 2021).

Interventions

Medicare Part D

In 2003, the Medicare Modernization Act (MMA) created this prescription drug benefit for the elderly (although up to 15% of its recipients are under the age of 65). Its creation was motivated by the relatively large proportion of the elderly without prescription drug coverage, the growing financial burden of prescription drug spending among the elderly, and the significant and growing clinical importance of prescription drugs (Oliver 2004). The lack of coverage in this area resulted in substantial OOP spending, and the share of income spent on prescription drugs is likely to be larger for the elderly with low incomes and chronic diseases for whom prescription drugs are essential to maintaining good health. Part D's goal was, therefore, to improve beneficiaries' access to, and the affordability of, essential medications. Although the MMA started in 2003, Medicare did not cover outpatient prescription drugs until January 1, 2006, when it implemented the Part D prescription drug benefit, authorised by Congress under the MMA. Individuals on Medicare were eligible for prescription drug coverage under a Part D plan if they were signed up for benefits under Medicare Part A or Part B (or both). Beneficiaries obtained the Part D drug benefit through two types of plans administered by private insurance

companies: the beneficiaries can join a standalone Prescription Drug Plan (PDP) for drug coverage only or they can join a Part C health plan that jointly covers all hospital and medical services covered by Medicare Part A and Part B at a minimum, and typically covers additional healthcare costs not covered by Medicare Parts A and B including prescription drugs (MA-PD).

The US government was concerned about the programme's budgetary impact. The standard Part D benefit was therefore designed to include a novel cost containment feature: the 'coverage gap'. After drug spending reaches an initial threshold (USD 3750 per person in 2018) in a calendar year, beneficiaries enter the coverage gap, a period during which they are responsible for a large proportion of their drug costs (45% of the cost of brand-name drugs and 65% of the cost of generic drugs). Beneficiaries remain in the coverage gap period either until out-of-pocket drug spending reaches a catastrophic coverage spending threshold (USD 5000 per person in 2018) at which time cost-sharing is dramatically reduced, or until the benefit resets at the next calendar year. Low-income beneficiaries receive subsidies to help them pay for drugs and thus are not responsible for their drug costs during the coverage gap period.

As a policy, Medicare Part D therefore cuts across the four categories of drug insurance schemes previously mentioned (Types of interventions).

Other drug insurance schemes

British Columbia Fair Pharma Care

British Columbia (BC) Pharma Care Program was characterised by a relatively comprehensive drug coverage for social assistance recipients and seniors (with temporary co-payments for seniors), and fixed-deductible coverage for catastrophic drug cost for all others. In May 2003, the fixed-deductible catastrophic programme and the seniors' programme were combined into a new, income-based drug plan called Fair PharmaCare. Thus the change was from an age-based to an income-based drug benefits programme. As a policy, BC Fair Pharma Care was making a change mainly in who receives drug insurance.

Ontario expansion of public drug coverage

In January 2018, Ontario expanded public drug coverage through its Ontario Drug Benefit (ODB) programme to include all Ontarians less than 25 years old, through a programme called OHIP+. In that sense, this was a policy making changes in who received drug insurance.

Affordable Care Act Medicaid expansion

The Affordable Care Act (ACA) expanded Medicaid eligibility to allow enrolment of non-elderly adults with incomes through 138 per cent of the federal poverty level. Prior to the ACA, Medicaid eligibility for non-elderly adults in most states was limited to people with disabilities, pregnant women, and low-income parents. Although initially the policy was compulsory, a 2012 Supreme Court decision left Medicaid expansion optional; that is, states could decide whether to expand this programme or not. As a policy, the ACA Medicaid expansion has made changes mainly in who receives drug insurance.

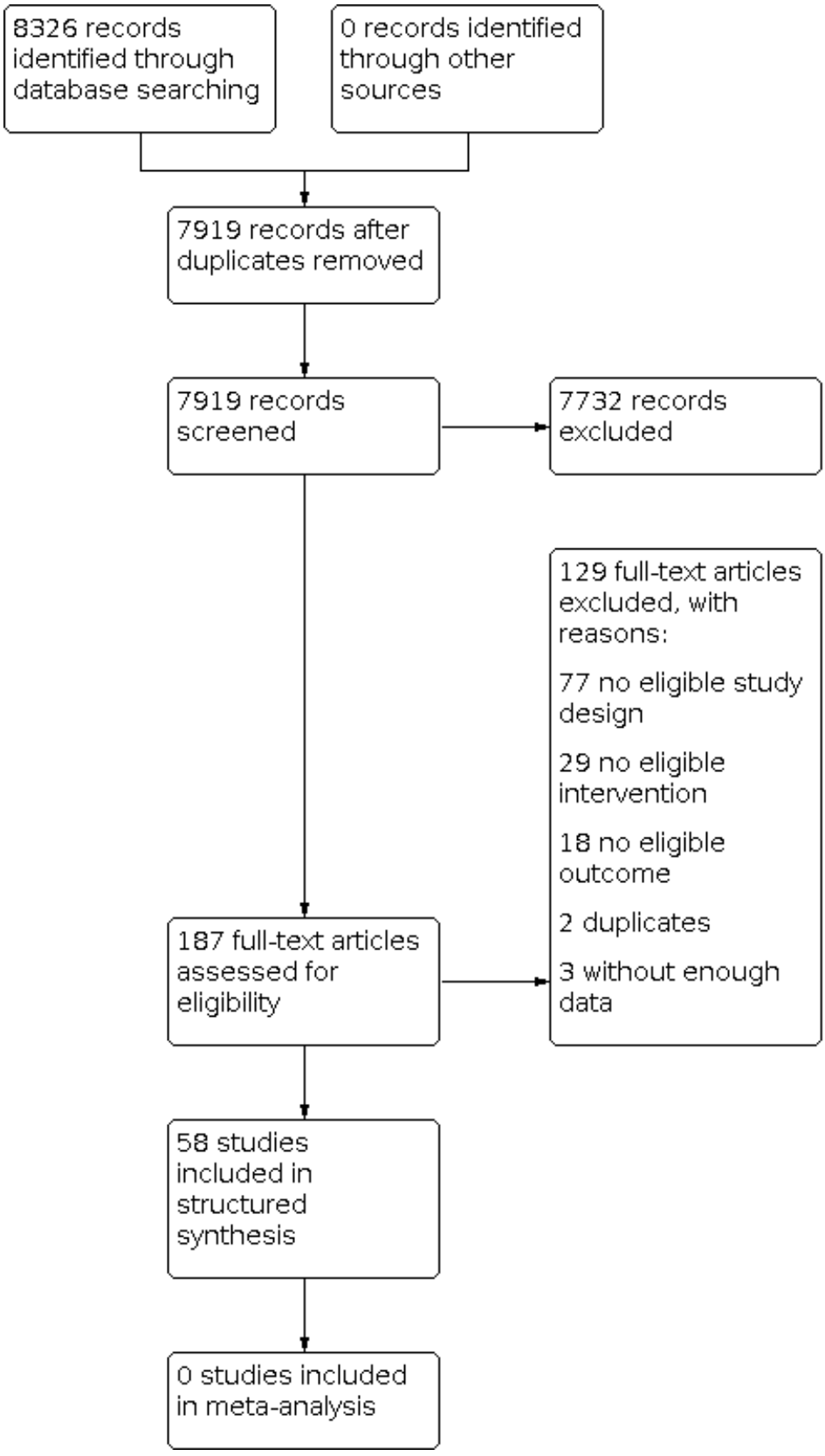
Privatisation of Medicaid Drug Benefits

The ACA previously mentioned also made two substantive changes to Medicaid drug reimbursements, making the privatisation of pharmacy benefits (by Managed Care Organizations (MCO)) more attractive than state administration of the Medicaid drug benefit. The result was a dramatic shift of drug benefits away from states to MCOs. In that sense, this (part of the) policy was making changes mainly in who can provide drug insurance.

Results of the search

The search strategy identified 8326 records; 7919 records after removing duplicates. After title/abstract screening, we excluded 7732 records, leaving 187 for full-text assessment. From these, we excluded 129 records for different reasons (Characteristics of excluded studies), and 58 studies met the inclusion criteria for this review (Characteristics of included studies) (Figure 1). In eight studies, we were not able to obtain reported data in an useful format for our quantitative analysis, leaving 50 studies for the quantitative synthesis (see Characteristics of included studies for details).

Figure 1. PRISMA flow diagram

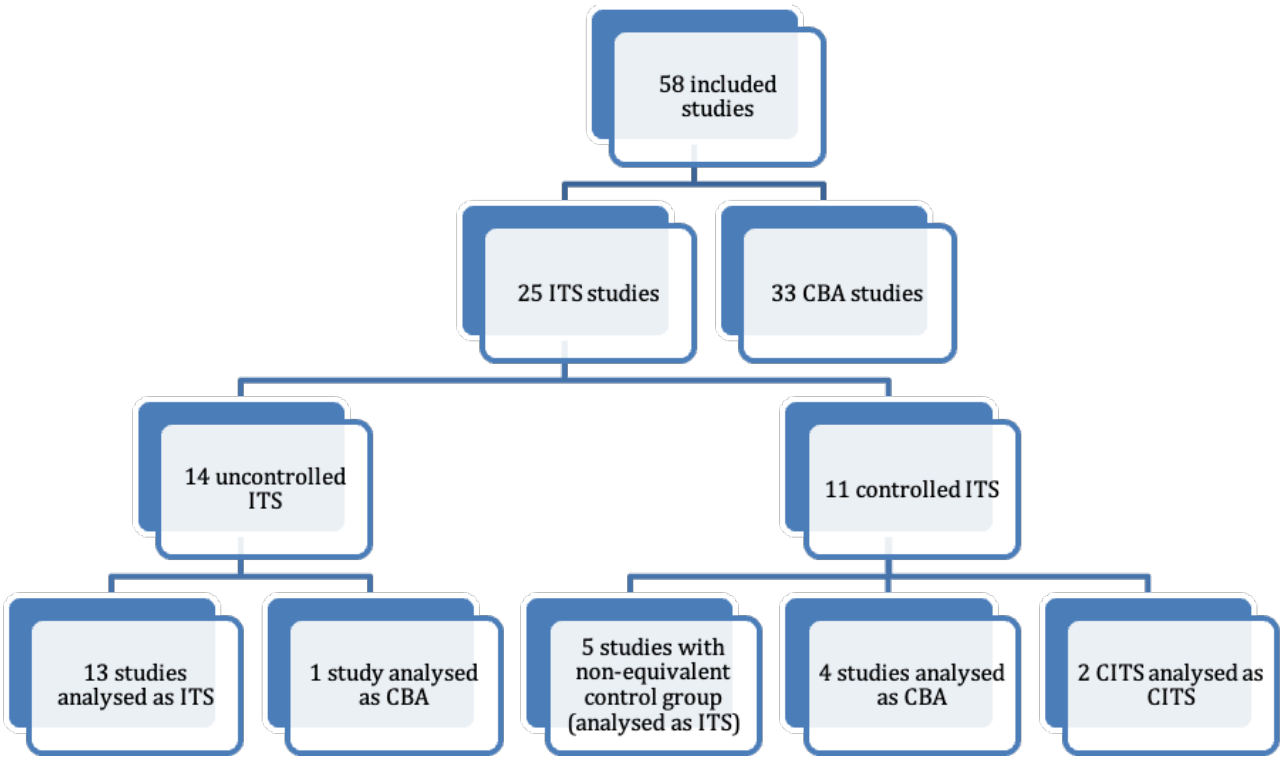


Included studies

Study design

Of the 58 studies that met the inclusion criteria, 25 used an interrupted time-series study design (Figure 2). Of these, eleven used some type of control group (Basu 2010; Briesacher 2009; Ketcham 2008; Li 2013; Lichtenberg 2007; McWilliams 2011; Saverno 2011; Zhang 2009; Zhang 2010a; Zhang 2010b; Zhang 2011); and fourteen were uncontrolled interrupted time-series studies (Adams 2014; Briesacher 2010; Briesacher 2015; Burns 2014; Caetano 2006; Chen 2008; Farley 2010; Madden 2015; Pimentel 2015; Polinski 2012; Schneeweiss 2009; Shrank 2008; Tan 2021; Yin 2008).

Figure 2. Included studies by design type



Five of the eleven controlled interrupted time-series (CITS) studies used a non-equivalent control group (see Description of studies section above) and were therefore included in the analysis as 'uncontrolled' ITS studies (Basu 2010; Briesacher 2009; Ketcham 2008; Li 2013; Lichtenberg 2007). Another four CITS studies did not provide enough detailed data for a controlled interrupted time-series analysis but presented effect estimates for a controlled before-after analysis (McWilliams 2011; Zhang 2010a; Zhang 2010b; Zhang 2011). The remaining two CITS were analysed as having an equivalent control group (Saverno 2011; Zhang 2009). Likewise, one of the 14 'uncontrolled' ITS studies (Yin 2008) only provided sufficient data for a controlled before-after effect estimate that was used as the primary analysis (Figure 2).

The other 33 included studies were controlled before-after studies. In summary, of the 58 included studies, 38 were analysed as CBA studies, 18 were analysed as ITS studies, and two were analysed as CITS studies (Figure 2).

Three out of the 18 studies analysed as interrupted time series required a full re-analysis (Briesacher 2009; Ketcham 2008; Lichtenberg 2007), whereby data points were extracted from the scanned figures and the parameters estimated. However, most of the ITS studies required some degree of additional analysis. The change in level was estimated for one study (Basu 2010), and this required extending the predicted line from the pre-intervention to the post-intervention phase as if the intervention never occurred and taking the difference between this and the line presented in the figure. For the relative change calculation, the last pre-intervention time point either had to be extracted from the figures (Basu 2010; Briesacher 2010; Briesacher 2015; Li 2013; Pimentel 2015; Schneeweiss 2009; Shrank 2008); or calculated from the results presented in the paper (intercept + baseline trend * last pre-intervention time point) (Adams 2014; Burns 2014; Chen 2008; Farley 2010; Polinski 2012). One study (Madden 2015) provided all relevant estimates and required no further analyses. For two studies, we were not able to obtain reported data in an useful format for our quantitative analysis (Caetano 2006; Tan 2021).

For the CITS studies, in one of them (Zhang 2009), all effect estimates were extracted from the study report and for the other (Saverno 2011) we were not able to obtain relative effect estimates.

We used either 100 x (effect estimate - 1)% for increase or 100 x (1 - effect estimate)% for decrease to calculate the relative effects for CBA studies that provided odds ratios or relative risks (Afendilus 2011; Chen 2018; Do 2020 (drug use: any prescription opioid); Donohue 2010; Donohue 2011; Fowler 2013; Huh 2017; Lim 2013; Nelson 2014 (health outcomes, drug use, healthcare utilisation outcomes); Park 2017 (drug use and

healthcare utilisation outcomes); Zhang 2008; Zhang 2010a; Zhang 2011). For continuous outcomes, we used a variety of methods to compute effect estimates from study reports. In twelve studies: (Asfaw 2019; Ayyagari 2015; Ayyagari 2017; Choi 2017; Engelhardt 2011 (drug use); Kaestner 2012; Kaestner 2014; Maclean 2020; McWilliams 2011; Pak 2017; Park 2017 (drug expenditure outcome); Zimmer 2015), we used the published relative effects estimates. In five studies, we divided the reported effect estimate either by the pre-intervention mean in the intervention arm (Carvalho 2019) or pre-intervention mean in the control arm (Do 2020 (number of prescriptions); Engelhardt 2011 (OOP and total prescription drug); Kircher 2014; Liu 2011). In three studies (Diebold 2018; Jung 2019; Nelson 2014 (drug expenditure outcome)), the relative effect estimate was calculated by multiplying the reported effect estimate by 100. In one study (Zhang 2010b), we extracted the data from the figure presented in the report. Finally in Belenky 2019, we used the method described above in the section Measures of treatment effect.

Comparisons

Forty-four studies included some type of comparison in the form of controlled interrupted time series (Basu 2010; Briesacher 2009; Ketcham 2008; Li 2013; Lichtenberg 2007; McWilliams 2011;Saverno 2011; Zhang 2009; Zhang 2010a; Zhang 2011; Zhang 2010b) or controlled before-and-after designs (Afendilus 2011; Asfaw 2019; Ayyagari 2015; Ayyagari 2017; Belenky 2019; Carvalho 2019; Chen 2018; Choi 2017; Diebold 2018; Do 2020; Donohue 2010; Donohue 2011; Dranove 2017; Dunn 2019; Engelhardt 2011; Ettner 2011; Fowler 2013; Huh 2017; Jung 2019; Kaestner 2012; Kaestner 2014; Kircher 2014; Lim 2013; Liu 2011; Maclean 2020; Mott 2010; Nelson 2014; Ong 2012; Pak 2017; Park 2017; Tang 2019; Zhang 2008; Zimmer 2015). Those comparisons could be categorised in two broad groups: those in which the comparator was a 'near-elderly' or 'age-ineligible' (younger) group; and those in which the comparator was a group with generous coverage before the introduction of the benefit and was therefore unlikely to be incorporated into the policy. In all the included CBA studies, we considered the comparison group equivalent, but in five out of 11 controlled ITS studies (Basu 2010; Briesacher 2009; Ketcham 2008; Li 2013; Lichtenberg 2007), we considered the comparison groups as non-equivalent and these studies were analysed as 'uncontrolled' ITS.

Participants

As in several other pharmaceutical policies' reviews (Aaserud 2006; Green 2010), the data sources in all the included studies were administrative datasets. The primary purpose of these datasets was to track transactions within the plan rather than support research projects.

Participants were beneficiaries of the US national public health insurance programmes for the elderly (Medicare) or for the poor (Medicaid) who obtained drug benefits through specific plans normally administered at the state level. For the two studies from Canada (Caetano 2006; Tan 2021), participants were described as adults (19 years of age and over) from British Columbia and the beneficiaries (especially those less than 25 years) of the Ontario Drug Benefit programme, respectively. 'Dual-eligible' beneficiaries (those beneficiaries qualifying for both Medicare and Medicaid benefits) were the focus of six studies (Adams 2014; Basu 2010; Burns 2014; Farley 2010; Saverno 2011; Shrank 2008). Five studies focused on nursing home residents (Briesacher 2009; Briesacher 2010; Jung 2019; Madden 2015; Pimentel 2015); and thirteen studies included participants with specific clinical conditions: diabetes mellitus (Adams 2014; Choi 2017; Li 2013); mental health disorders (Ayyagari 2015; Burns 2014; Chen 2008; Donohue 2011; Lim 2013); cancer (Kircher 2014), HIV (Belenky 2019; Tan 2021); dementia (Fowler 2013); and heart failure (Donohue 2010).

Drug classes

Eight drug classes were individually targeted by the studies included in the review: psychotropic drugs (Ayyagari 2015; Belenky 2019; Briesacher 2010; Burns 2014; Chen 2008; Do 2020; Donohue 2011; Lim 2013; Ong 2012; Pimentel 2015; Polinski 2012; Saverno 2011); antihypertensive drugs (Caetano 2006; Zhang 2011); lipid-lowering (LL) drugs (Adams 2014; Caetano 2006; Zhang 2009); antidiabetic medications (Li 2013; Zhang 2009); heart failure medications (Donohue 2010); medications for dementia (Fowler 2013); anti-retrovirals for HIV (Tan 2021); and antibiotics (Zhang 2010a). Four studies assessed the effect of Medicare Part D on multiple drug classes (such as statins, proton pump inhibitors, warfarin, clopidogrel and benzodiazepines) (Farley 2010; Jung 2019; Schneeweiss 2009; Shrank 2008). In the other studies, no specific drug classes were targeted for evaluation.

Outcomes

Drug use and drug expenditures were the most frequently assessed outcomes in 34 and 23 studies, respectively. Eighteen studies assessed both of them. Healthcare utilisation was measured in 12 studies and health outcomes were assessed in nine studies.

Excluded studies

We excluded 129 studies. The most common reason for exclusion (n = 77) was having a non-eligible study design. More details are described in the table Characteristics of excluded studies.

Risk of bias in included studies

For details of our assessments of risk of bias, see the Risk of bias tables for each study (Characteristics of included studies). The risk of bias graphs and the summary assessments of risk of bias for the CBA studies are presented in Figure 3 and Figure 4 and for the ITS/CITS studies in Figure 5 and Figure 6. Overall, we assessed most of the interrupted time-series studies as having some limitations (moderate risk of bias) mainly because of uncertainties about the completeness of outcome data and the risk that the intervention was not independent of other policy changes. On the other hand, we assessed all the controlled before-after studies as having serious limitations (high risk of bias) because of a high risk of baseline differences in outcomes and other characteristics between the intervention and comparison groups.

Figure 3. Risk of bias graph for CBA studies: review authors' judgements about each risk of bias item presented as percentages across all included CBA studies

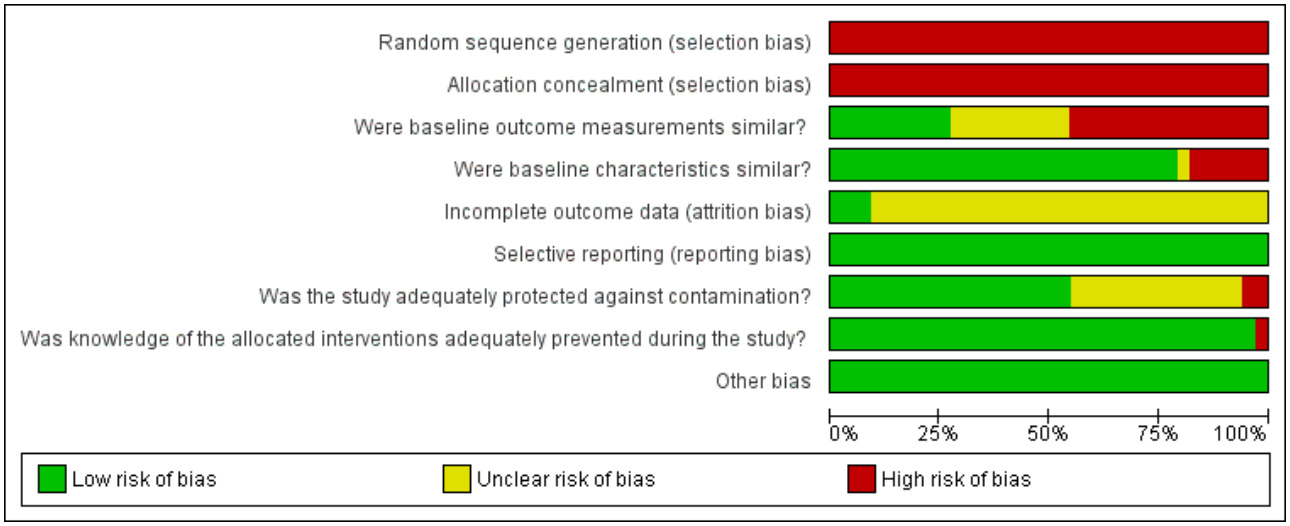


Figure 4. Risk of bias summary for CBA studies: review authors' judgements about each risk of bias item for each included CBA study

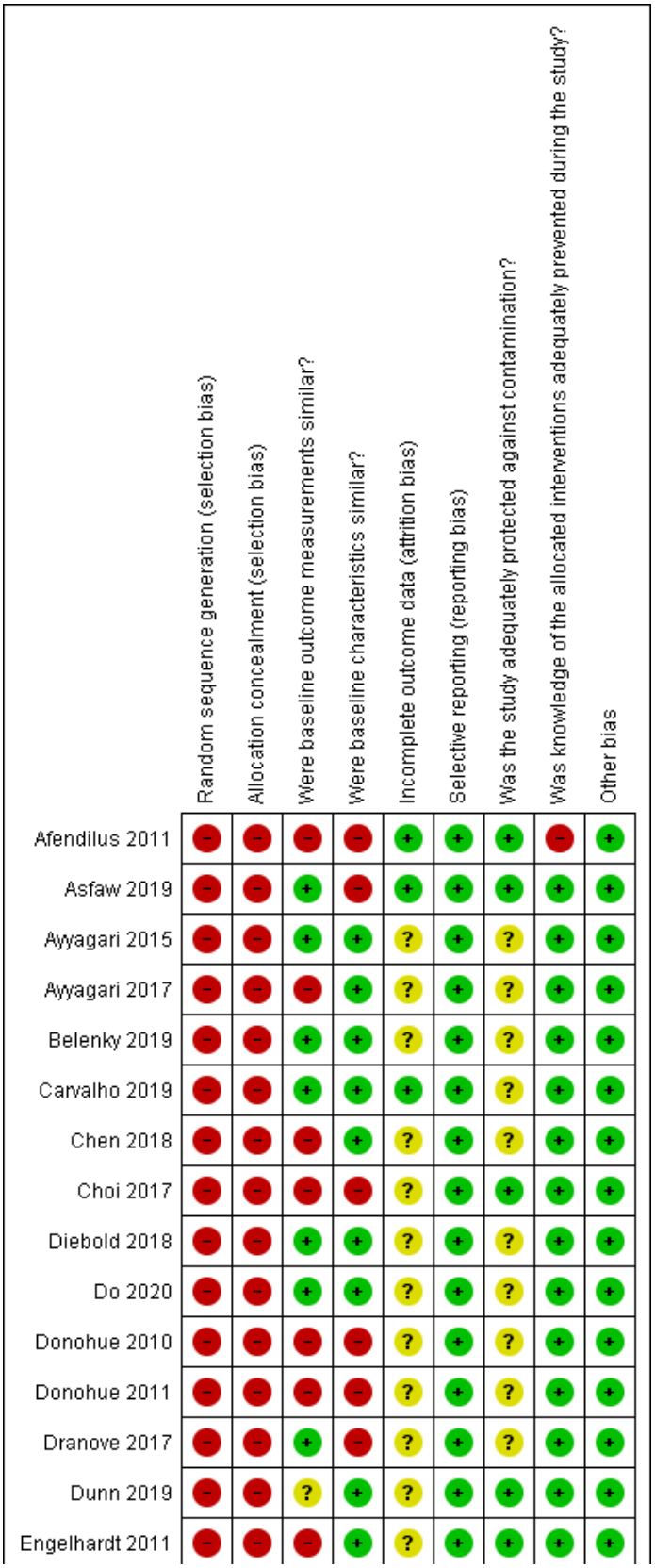


Figure 4. (Continued)

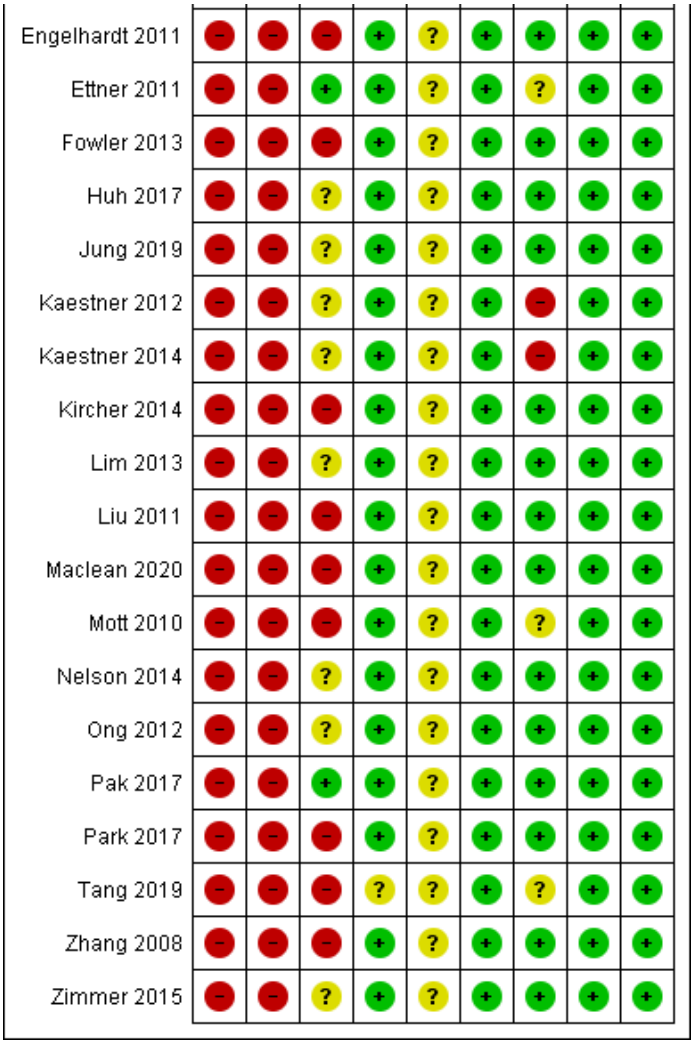


Figure 5. Risk of bias graph for ITS/CITS studies: review authors' judgements about each risk of bias item presented as percentages across all included ITS/CITS studies

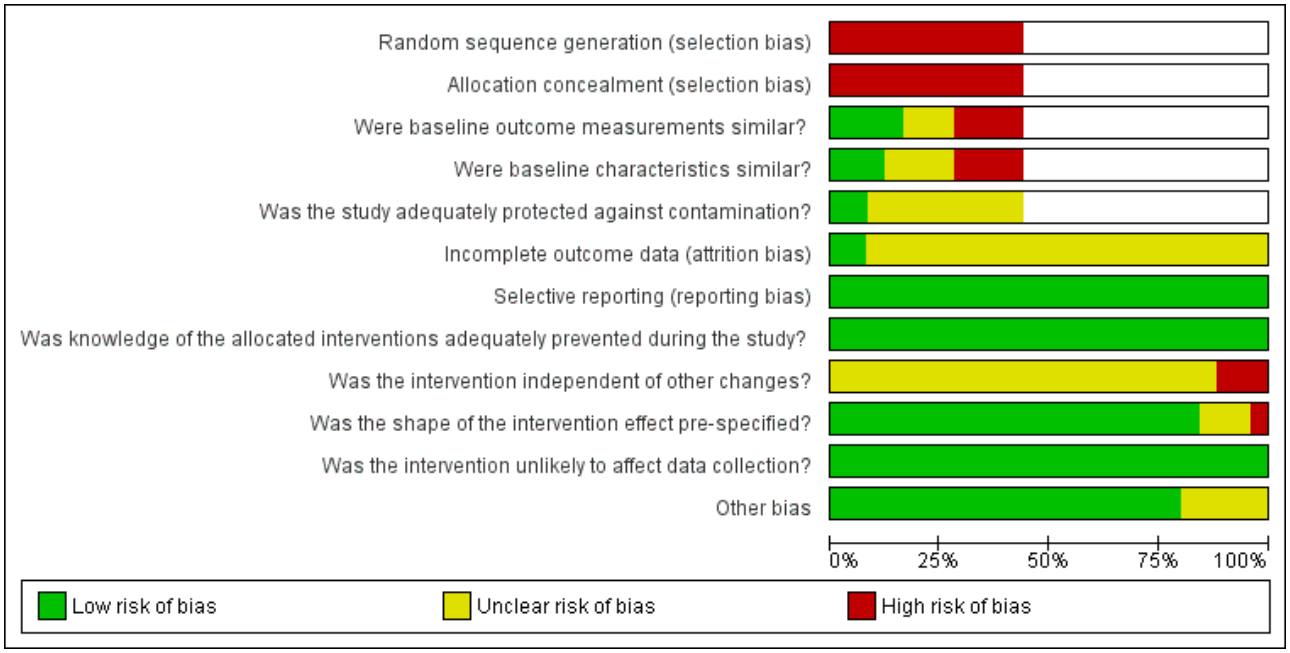


Figure 6. Risk of bias summary for ITS/CITS studies: review authors' judgements about each risk of bias item for each included ITS and CITS study

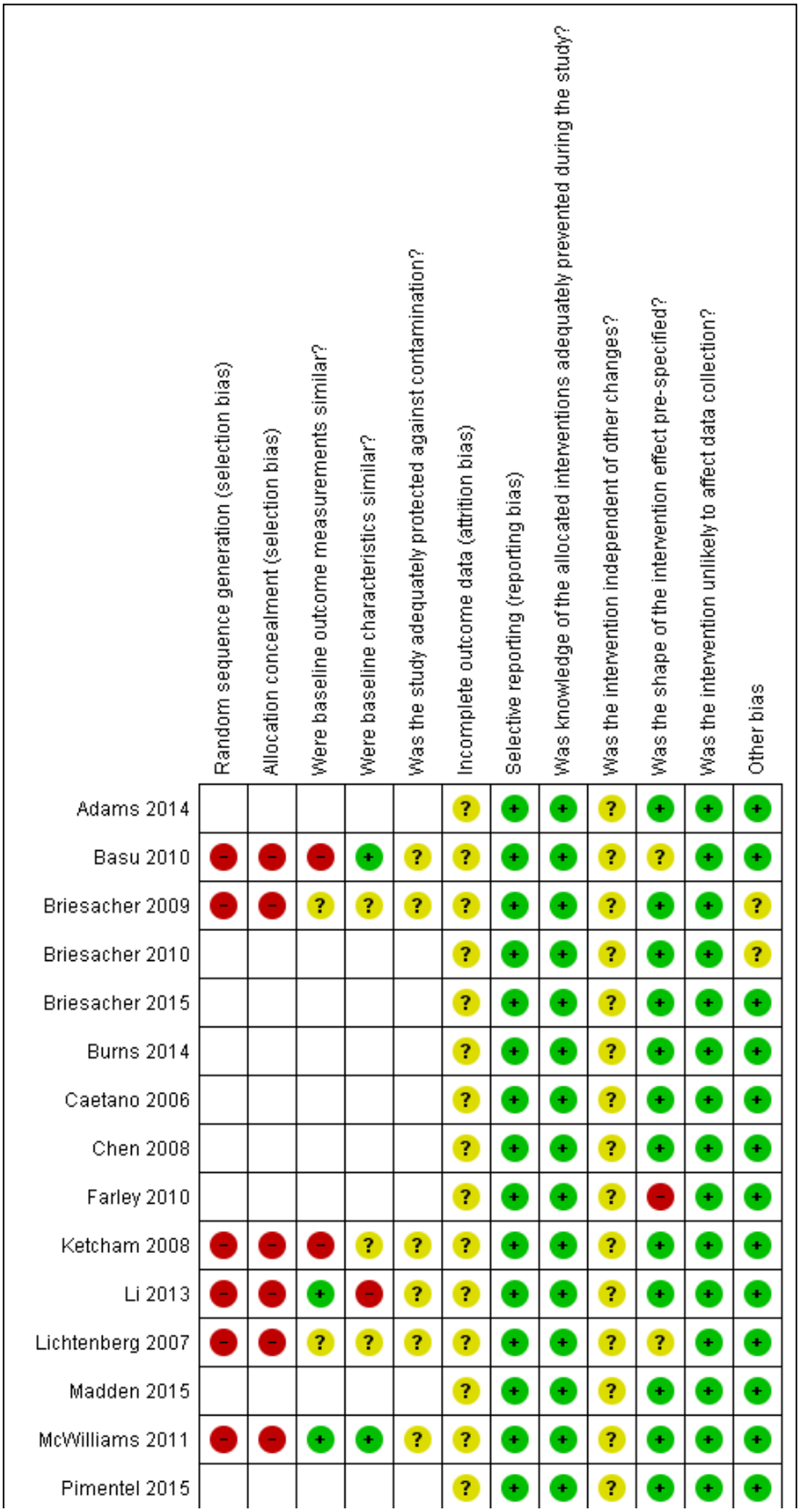
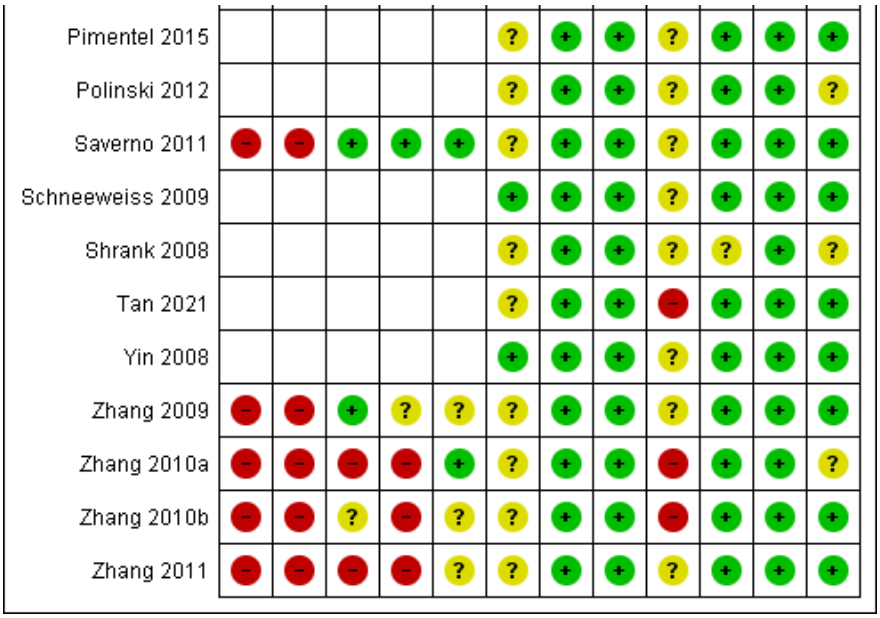


Figure 6. (Continued)



Effects of interventions

See: **Summary of findings 1** Summary of findings

We present an overall summary of the effects of drug insurance schemes (mainly focused on Medicare Part D) on drug use, drug expenditure, healthcare utilisation and health outcomes in the Summary of findings 1. Although one study included in the quantitative analysis (Maclean 2020) assessed the effect of a policy different to Medicare Part D (ACA Medicaid expansion), this provided only one effect estimate out of 116 effect estimates for drug use. Therefore, we considered that most of the evidence available in our review was for the comparison between those enrolling in drug insurance schemes as Medicare Part D and those who were not able to be enrolled. We provided detailed results from the included studies in four separate tables for drug use, drug expenditures, healthcare utilisation and health outcomes respectively (Appendix 3; Appendix 4; Appendix 5; Appendix 6).

Enrolment in a drug insurance scheme compared to no enrolment in the scheme

Drug use

Drug use was an outcome in 34 studies. We were not able to re-analyse one of these because of the way in which data were presented (as a log scale difference) (Lichtenberg 2007). Of the other 33 with analysable data, we analysed 12 as interrupted time-series studies, one as a CITS study and 20 as controlled before-after studies. We present detailed results for immediate, short- and long-term absolute and relative change for each study in Appendix 3.

Immediate post-policy implementation

Eight ITS studies (Adams 2014; Briesacher 2010; Chen 2008; Farley 2010; Pimentel 2015; Polinski 2012; Schneeweiss 2009; Shrank 2008) (32 effect estimates) reported absolute and/or relative changes in levels of drug use up to four months after the introduction of the policy. All of these studies presented effect estimates for Medicare Part D. They showed that the introduction of (or changes to) this drug insurance scheme may increase drug use immediately after the implementation of the policy (median relative effect adjusted for baseline differences: increase 3.74%; low-certainty evidence). However, the IQR showed that the policy may decrease or increase drug use (IQR −9.41% to 22.98%; low-certainty evidence). When effect estimates related to the use of benzodiazepines, a group of drugs not covered by Medicare Part D, were removed from the analysis, the studies showed similar changes in the median relative effect (increase of 7.99% (IQR 0.38% to 37.02%; 24 effect estimates; low-certainty evidence).

Six months after policy implementation

Nine ITS studies (Adams 2014; Basu 2010; Briesacher 2009; Chen 2008; Farley 2010; Ketcham 2008; Polinski 2012; Schneeweiss 2009; Shrank 2008) and one CBA study (Zhang 2008) (25 effect estimates) reported absolute and/or relative changes in levels of drug use six months after the introduction of the policy. All of these studies presented effect estimates for Medicare Part D. They showed that Medicare Part D may increase drug use six months after the implementation of the policy (median relative effect adjusted by baseline differences 8.4%, IQR -2.88% to 25.19%; low-certainty evidence). When effect estimates related to the use of benzodiazepines, a group of drugs not covered by the policy, were not included in the analysis, the studies also showed that Medicare Part D may increase drug use by a median relative effect (adjusted for baseline differences) of 11.73% (IQR 3.77% to 37.67%; 23 effect estimates; low-certainty evidence).

Twelve months or more after policy implementation

Ten ITS studies (Adams 2014; Basu 2010; Briesacher 2009; Chen 2008; Farley 2010; Ketcham 2008; Madden 2015 Polinski 2012; Schneeweiss 2009; Shrank 2008), one CITS study (Zhang 2009) and 19 CBA studies (Asfaw 2019; Ayyagari 2015; Belenky 2019; Do 2020; Donohue 2010; Donohue 2011; Fowler 2013; Jung 2019; Kaestner 2012; Kircher 2014; Lim 2013; Liu 2011; Maclean 2020;

Nelson 2014; Park 2017; Yin 2008; Zhang 2010a; Zhang 2011; Zimmer 2015) (59 effect estimates) reported absolute and/or relative changes in levels of drug use one year or more (up to 24 months) after the introduction of the policy (Medicare Part D and ACA Medicaid expansion). All of these studies, except one (Maclean 2020), presented effect estimates for Medicare Part D. They showed that the policies may increase drug use up to 24 months after the implementation of the policy (median relative effect adjusted by baseline differences 14.73%, IQR 3.11% to 36.0%; low-certainty evidence). When the only effect estimate not related to Medicare Part D (from Maclean 2020) was removed from the analysis, there was no change in the direction or size of the effect (median relative effect adjusted by baseline differences 14.84%, IQR 4.0% to 38.0%; low-certainty evidence). Likewise, when effect estimates related to the use of benzodiazepines, a group of drugs not covered by Medicare Part D, were not included in the analysis, the studies showed that these polies may increase drug use by a median relative effect (adjusted for baseline differences) of 17.51% (IQR 4.67% to 38.46%; 56 effect estimates; low-certainty evidence).

Drug expenditure

Drug expenditures were assessed in 23 studies. We were not able to re-analyse two of the studies because the study authors did not present raw absolute data (for instance, they reported share of the out-of-pocket medication costs as a proportion of the total medication costs without presenting the total amount of medication costs) (Briesacher 2009); or because they only presented before-and-after data for drug expenditures without any data from a comparison group (Chen 2008). Of the 21 studies with analysable data, we analysed eight as interrupted time-series studies, one as a CITS study and 12 as controlled before-after studies. We presented detailed results for immediate, short- and long-term absolute and relative changes for each study in Appendix 4. Seventy-one out of the 81 effect estimates analysed in those studies were expenditures made by the patient/healthcare user only (OOP medication costs). The remaining 10 effect estimates were for total drug expenditures.

Immediate post-policy implementation

Four ITS studies (15 effect estimates) reported absolute and/or relative changes in drug expenditures up to four months after the introduction of the drug insurance policy (Farley 2010; Polinski 2012; Schneeweiss 2009; Shrank 2008). One study (one effect estimate) reported total expenditures (Farley 2010); and the other three studies (14 effect estimates) reported OOP expenditures. Overall, these studies showed that the drug insurance policy (Medicare Part D) may decrease drug expenditures immediately after the implementation of the policy (median relative effect adjusted by baseline differences −59.07%, IQR −66.33% to −26.27%; low-certainty evidence). When only effect estimates reporting OOP expenditures were included in the analysis, the effects on drug expenditure were similar to the main analysis (median relative effect adjusted by baseline differences −59.32%, IQR −66.33% to −26.27%).

Six months post-policy implementation

Seven ITS studies (19 effect estimates) reported absolute and/or relative changes in drug expenditures six months after the introduction of the drug insurance policy (Basu 2010; Farley 2010; Ketcham 2008; Lichtenberg 2007; Polinski 2012; Schneeweiss 2009; Shrank 2008). One study (one effect estimate) reported only total expenditures (Farley 2010); one study (two effect estimates) reported both total and OOP expenditures (Basu 2010); and the other five studies (16 effect estimates) reported only OOP expenditures. Overall, these studies showed that the drug insurance policy (Medicare Part D) may decrease drug expenditures six months after the implementation of the policy (median relative effect adjusted by baseline differences −46.96%, IQR −65.98% to −22.84%; low-certainty evidence). When only effect estimates reporting OOP expenditures were included in the analysis, the effects on drug expenditure were similar to the main analysis (median relative effect adjusted by baseline differences −50.22%, IQR −65.98% to −27.84%).

Twelve months or more after policy implementation

Eight ITS studies, one CITS study and 12 CBA studies (48 effect estimates) reported absolute and/or relative changes in drug expenditure one year or more (up to 36 months) after the introduction of the drug insurance policy (Medicare Part D). One study (one effect estimate) reported only total expenditures (Farley 2010); one study (two effect estimates) reported both total and OOP expenditures (Basu 2010). All the other studies (36 effect estimates) reported only OOP expenditures. Overall, these studies showed that the drug insurance policy may decrease drug expenditures up to 36 months after their implementation (median relative effect adjusted by baseline differences −43.17%, IQR −57.40% to −19.77%; low-certainty evidence). When only effect estimates reporting OOP expenditures were included in the analysis, the effects on drug expenditure were similar to the main analysis (median relative effect adjusted by baseline differences −45.87%, IQR −61.36% to −22.08%).

Health care utilisation

See Appendix 5.

Healthcare utilisation outcomes such as emergency department (ED) visits (Ayyagari 2017; Briesacher 2015; Burns 2014; Kircher 2014; Liu 2011; Nelson 2014), hospital admissions (Afendilus 2011; Belenky 2019; Briesacher 2015; Kaestner 2014; Kircher 2014; Liu 2011; Nelson 2014), or number of outpatient physician visits (Kircher 2014; Nelson 2014; Park 2017) were reported in two interrupted time-series studies, one CITS study and nine CBA studies. For this group of outcomes, we also considered studies assessing non-drug medical spending as a proxy for healthcare utilisation, including spending on a number of health services such as inpatient and skilled nursing services, physician and ancillary services (Kaestner 2014; McWilliams 2011; Zhang 2009).

Six studies (two ITS and four CBAs) reported absolute and/or relative changes in ED visits after the introduction of the drug insurance policy (Medicare Part D). Overall, these studies showed that the drug insurance policy may lead to a small increase in the number or frequency of ED visits by beneficiaries of the drug insurance scheme (median relative effect adjusted by baseline differences 9.74%, IQR 3.29% to 18.64%; low-certainty evidence).

Seven studies (one ITS and six CBAs) reported absolute and/or relative changes in hospital admissions after the introduction of the drug insurance policy (Medicare Part D). Overall, the effect of this policy on hospital admissions is uncertain because the certainty of the evidence is very low.

Three CBA studies reported absolute and/or relative changes in the number of outpatient physician visits after the introduction of the drug insurance policy (Medicare Part D). Overall, it is uncertain if the policy increases or reduces outpatient physician visits because the certainty of the evidence is very low.

Three studies (one CITS and two CBA studies) reported absolute and/or relative changes in non-drug medical spending after the introduction of the drug insurance policy (Medicare Part D). Overall, it is uncertain if the policy increases or decreases non-drug medical spending because the certainty of the evidence is very low.

Health Outcomes

See Appendix 6.

Health outcomes such as mortality, impairment in activities of daily living, self-rated health status, likelihood of engaging in physical activity, or depressive symptoms were reported in one ITS study (Briesacher 2015) and six CBA studies (Asfaw 2019; Ayyagari 2015; Belenky 2019; Chen 2008; Diebold 2018; Pak 2017). Three studies (Briesacher 2015; Huh 2017; Kaestner 2014) reported absolute and/or relative changes in mortality. Overall, it is uncertain if the policy increases or reduces mortality because the certainty of the evidence is very low. Seven studies reported absolute and/or relative changes in non-mortality health outcomes. However, because of the diversity of outcomes and the diversity of timing of outcomes assessment, it was not possible to obtain a meaningful summary effect estimate for this group of outcomes; the individual results are presented in Appendix 6. Overall, the effects include both small positive and negative impacts for these outcomes and the certainty of the evidence is very low.

DISCUSSION

Summary of main results

The introduction of a drug insurance scheme (such as Medicare Part D) may increase prescription drug use and may decrease drug expenditure (mostly OOP spending) in populations with no previous drug insurance coverage. Likewise, this type of drug insurance policy may lead to a small increase in the number or frequency of ED visits by beneficiaries of the scheme. It is uncertain whether this kind of policy increases or decreases other types of healthcare utilisation, or whether it has an effect on health outcomes, because the certainty of the evidence for these outcomes is very low. All the studies included in the quantitative analysis were conducted in the US and all but one assessed a single policy change (Medicare Part D).

Overall completeness and applicability of evidence

Almost all of the studies included in this review assessed a single policy implemented in the US healthcare system (Medicare Part D); we identified only one eligible study with analysable data assessing another intervention (Maclean 2020). However, this study only provided one effect estimate for drug use, and the median effect estimates for this outcome did not change based on whether we included this study or not. Additionally, we identified another three studies assessing other related policies in the US (Dranove 2017) and Canada (Caetano 2006; Tan 2021), but none of these reported data that we were able to incorporate into our quantitative analysis.

Our results, therefore, largely represented the effects of Medicare Part D in the US healthcare system. There are important differences in on-the-ground realities (such as the important role of the pharmaceutical industry and the high pharmaceutical expenditure in the US), in health systems arrangements (such as funding based mostly on private insurance with public funding only for the poor and the elderly), and in baseline conditions (such as the proportion of population already covered by private insurance) between US health system and other health systems (especially in low-income countries). These differences make the findings of this review less likely to be transferable to other settings, particularly low-income settings. However, considering the consistency of the findings regarding drug use and OOP expenditures across the included studies together with previous reviews (Pimentel 2013; Polinski 2010), we think that it is reasonable to expect similar effects in other countries where this type of pharmaceutical policy has not yet been implemented.

Although the body of evidence included in this review seems to be a complete representation of what has been published about the impact of Medicare Part D, we acknowledge that there is a body of literature published about other drug insurance schemes such as PHARMAC in New Zealand or British Columbia Pharmacare in Canada (Braae 1999; Daw 2012; Morgan 2012; Morgan 2015; Morgan 2017). However, the evaluation studies that we identified of these policies included components beyond the scope of this review (such as changes in user fees [caps and co-payments], stopping coverage or reimbursement [restriction on reimbursement], or reference pricing) or were assessed using methods not eligible for this review.

Although we searched in September 2021 for articles citing the 58 included studies, the last full search for studies for this review was conducted in September 2020. It is therefore possible that some recently published studies are not included in our review, limiting the completeness of the evidence presented. However, given the large number of included studies in the current version of the review, we think it is unlikely that those recent studies would change substantively the review results.

Certainty of the evidence

The certainty of the evidence was low or very low for all the primary outcomes in this review. For drug use and expenditures, the contributing studies have some methodological limitations (uncertainties about incomplete outcome data and the potential presence of other policies at the time when part D was implemented) and there were also concerns about unexplained inconsistency in the direction of effect in some of those studies. We were also uncertain whether this type of policy leads to an increase or decrease in healthcare utilisation (apart from ED visits) or health outcomes, because the studies had important methodological limitations (most of the evidence was from CBA studies with some concerns about whether baseline characteristics and baselines outcome measurements were sufficiently similar between the intervention and comparison groups) and there was serious imprecision around the estimated median effect.

Potential biases in the review process

Although we carried out a thorough search, a systematic assessment of the risk of bias of included studies and a detailed

analysis and re-analysis of data included in the studies, we have identified a number of potential biases in our review.

First, despite a sensitive search strategy, most of the studies that we identified that fulfilled our inclusion criteria assessed a single and very specific policy: Medicare Part D. We do not know if this is because of the lack of research available evaluating other policies or because we were not able to identify those studies. Therefore, a search strategy focused on locating the 'hard to find' studies (for example, those published in policy or government reports) should be carried out for future updates of this review.

Second, because of the way in which studies in this field are designed, it was not possible to ascertain if all the potential beneficiaries of Medicare Part D for which outcome data were collected were also officially enrolled in the policy. This could potentially lead to under- or over-estimation of the effect of this policy.

Third, there were a number of studies using multiple comparison groups, such as different levels of drug insurance coverage previous to the implementation of the drug insurance scheme (Donohue 2010; Donohue 2011; Zhang 2009; Zhang 2010a; Zhang 2010b; Zhang 2011). Because the focus of this review was on assessing the impact of alternative policies for regulating drug insurance schemes, we only considered comparisons between those with clearly different types of insurance coverage. In the case of studies assessing Medicare Part D, we only considered the comparisons between those with no previous coverage (likely to move to the scheme) and those with previous generous coverage (unlikely to move to the scheme) because the focus of the review was on assessing the impact of policies on those moving to the specific drug insurance scheme. Both of these issues could potentially introduce bias because of the selection of specific comparisons that could show substantially different effect estimates from other comparisons.

Agreements and disagreements with other studies or reviews

An earlier systematic review of the effects of Medicare Part D implementation in the USA found a 6% to 13% increase in drug utilisation and 13% to 18% decrease in patients' costs, based on interrupted time-series and cross-sectional studies (Polinski 2010). Although this review only searched a single electronic database (Medline) from 2006 to 2009 in the early stages of implementation of this policy, the findings are consistent with those of our review. Another systematic review by Faden 2011 revealed that drug insurance may increase access to medicines and reduce self-medication, and provided conflicting evidence about the effect on medication spending. It is, however, difficult to compare this review with our findings because its scope was broader including studies assessing the effect of which medicines were procured or supplied, which medical services were provided, and the implementation of programmes to improve drug prescribing and use.

Although a number of countries, such as Canada, the Netherlands, Switzerland and Russia, have been discussing different alternatives for implementing drug insurance schemes in their health systems, we were not able to locate any specific study or review allowing a reliable comparison of our results with results from other systems, countries, or both. This was because, in the reports describing those cases, the methods used were not clear or were based mainly on expert opinion from consultants (Daw 2012; Esmail 2015; Hong 2012; Morgan 2017; Rovere 2012a; Rovere 2012b).

AUTHORS' CONCLUSIONS

Implications for practice

The introduction of drug insurance policies such as Medicare Part D in the US health systems may increase prescription drug use and may decrease OOP payments by the beneficiaries of the scheme. However, the effects of this policy on total drug expenditure, on healthcare utilisation, and on health outcomes are uncertain. In addition, the applicability of this evidence to any setting outside the US healthcare system is probably very limited.

The increasing costs of pharmaceuticals is one of the common challenges currently faced by virtually every health system, with drug spending skewed progressively towards high-cost products (OECD 2017), which affects households, insurers and/or governments budgets. This is also being experienced by Medicare Part D in the US, with a growing share of its spending moving towards high-cost enrollees who reach the catastrophic phase of the scheme mainly because of the greater number of highly expensive biologic products and specialty drugs that have entered the market and are prescribed in the health system (MEDPAC 2018). In that sense, the challenge for decision-makers across the world is to put in place policies covering drugs that add value to the money spent, through having being proven to be beneficial for patients (effective) and, ideally, for the health system (cost-effective) (OECD 2018). Drug insurance schemes (especially those focusing on who has the authority to make decisions regarding coverage) are potentially one of those policies to address that challenge.

Any decision to create or expand existing drug insurance schemes, regardless of the country income level, needs to consider the problem of increases in pharmaceutical expenditure placing pressure on institutional (public and private) and people's budgets. Although the findings of this review do not speak directly to this issue, decision-makers and funders responsible for the regulation of drug insurance schemes need to consider how to reach a balance between providing sufficient financial protection to beneficiaries and maintaining a financially sustainable system.

Implications for research

Evidence regarding who can or do provide drug insurance, who pays for it, and who has the authority to make decisions regarding coverage remains limited. Nearly all of the studies in this review assessed a single policy implemented in the US healthcare system. Some of the implications for research from this body of evidence are:

- It is important that evaluations be conducted of this type of policy in other settings where policies regulating drug insurance schemes are being introduced, especially in low- and middle-income countries. Ideally, evaluations should be planned in advance of introducing the policy, as a routine part of the policy implementation process.
- Rigorous evaluation is also needed of different scopes of coverage — for example, coverage of vulnerable populations (e.g. low income groups) or universal coverage for the entire

population. Future research should therefore consider these areas as a priority.

- While randomised trials provide the most robust evidence, they are difficult to conduct in this field and interrupted time-series designs should be considered. These studies can be easier to conduct where robust prescription registries or databases are available in a health system or subsystem.
- The outcomes selected should be primarily relevant for both patients and the health system including, for example, access to prescribed drugs, health outcomes, inequities and costs (e.g. out-of-pocket expenditures and public spending on pharmaceuticals).
- If more studies were available, future versions of the review should attempt to analyse the effects of this type of policy by type of health condition or the type of cost (e.g. costs of orphan drugs) being covered.

ACKNOWLEDGEMENTS

The protocol for this review was based on a previous version originally prepared by Oleg V Borisenko, Irina Telegina, Dennis Ross-Degnan, Anita Katharina Wagner, and Alexandra Meagan Cameron. We would also like to thank editors and peer reviewers for their helpful comments on this review.

The Norwegian Satellite of the EPOC Group receives funding from the Norwegian Agency for Development Cooperation (Norad), via the Norwegian Institute of Public Health to support review authors in the production of their reviews.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Adams 2014

Study characteristics	
Methods	ITS
Participants	A nationally representative sample of 'dual' enrollees (Medicare and Medicaid) with diabetes in the USA
Interventions	Medicare Part D (separate ITS models for the non-elderly and elderly subgroups in both strict drug-cap states and in the comparison group of no drug-cap states)
Outcomes	Drug use: (1) the monthly proportion of patients with any use of lipid-lowering therapies (statins, niacin, bile-acid resins, fibric acid, derivatives, cholesterol absorption inhibitors) (2) the intensity of use of these medications as represented by standardised monthly doses (SMDs)
Notes	Separate 'control' groups were considered as a kind of subgroup analysis more than control groups. So the analysis was considered as an ITS (without a control group). Funding source: Supported by grants from the National Institute on Aging [R01AG032249] and the Agency for Health Care Research and Quality [R01 HS018577]

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information about missing data
Selective reporting (reporting bias)	Low risk	Outcomes presented in the Methods section were the same as those presented in the Results section.
Was the intervention independent of other changes?	Unclear risk	There was no clear description of other pharmaceutical policies occurring at the same time in the USA.
Was the shape of the intervention effect prespecified?	Low risk	"Our data indicated a period of instability during the month before and 3 months following implementation of Part D, which may reflect anticipatory policy effects, data anomalies or some combination of factors that have the potential to bias study results. Therefore, we excluded observations generated during this brief, 4-month transition period (i.e. December 2005–March 2006) from the models" (Page 698, 1st column)
Was the intervention unlikely to affect data collection?	Low risk	Data collected routinely
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	All the outcomes were objective measures. Knowledge of the intervention (the policy) was an essential part of policy implementation. Data in ITS studies come from administrative datasets, primarily claims transactions, and therefore are not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identifiable

Afendilus 2011

Study characteristics	
Methods	CBA
Participants	Individuals aged 65 and older (versus individuals aged 60–64) in states with low drug coverage in 2005 (versus those in states with high pre-Part D drug coverage)
Interventions	Medicare Part D
Outcomes	Hospitalisation rates for selected ambulatory care sensitive conditions
Notes	They used a DDD (differences-in-differences-in-differences) analytical approach what seemed adequate considering that the authors were considering not only a non-elderly comparison group but also differences among states in relation to the Part D coverage. Funding source: This study was supported by a grant from the Pharmaceutical Research and Manufacturers of America, and by funds from the Marshall J. Seidman Program in Health Economics in the Department of Health Care Policy at Harvard Medical School.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	No allocation concealment
Were baseline outcome measurements similar?	High risk	The 60-64 yo group in 2005 had lower condition specific hospitalisation rates and coverage than the 65-plus group (Table 1, page 1027).
Were baseline characteristics similar?	High risk	Regression adjusted for age and year, but not health conditions
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data reported
Selective reporting (reporting bias)	Low risk	Outcomes reported were the same in the Methods section.
Was the study adequately protected against contamination?	Low risk	They used routinely available data.
Was knowledge of the allocated interventions adequately prevented during the study?	High risk	The use of a database did not allow to prevent knowledge of the allocated interventions.
Other bias	Low risk	None identified

Asfaw 2019

Study characteristics	
Methods	CBA
Participants	Data for this study were drawn from the National Health Interview Survey (NHIS) and the Medical Expenditure Panel Survey (MEPS). Respondents aged between 60 and 64 were the control group (8923 before 2006 and 17,954 after 2006) and respondents aged between 65 and 69 were the treatment group (9045 before 2006 and 18,729 after 2006).
Interventions	Medicare Part D
Outcomes	Physical exercise, weight gain, cigarette smoking, OOP spending, prescription drug use
Notes	The study used a difference in the regression discontinuity approach (D-RD) that seemed to be equivalent to a differences study with the intervention and control groups defined by the regression discontinuity at age 65. Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-randomised allocation
Allocation concealment (selection bias)	High risk	No allocation concealment
Were baseline outcome measurements similar?	Low risk	Outcomes were similar at baseline (Table 1).
Were baseline characteristics similar?	High risk	Adjust per age and time, along with interactions, but not relevant health conditions (Tables 2-5)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	Reported outcomes were the same as those described in the Methods section.
Was the study adequately protected against contamination?	Low risk	The intervention and control group were separated by age in the database (which is the criterion used to be eligible for the intervention)
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identified

Ayyagari 2015

Study characteristics	
Methods	CBA
Participants	Data from 12,251 individuals (34,289 person-year observations) from the 2000 through 2010 waves of the Health and Retirement Study
Interventions	Medicare Part D
Outcomes	Depressive symptoms, antidepressant use, psychiatrist visits, mental health treatments, total annual OOP payments
Notes	The study used a difference in differences and an IV model (we used the DiD model as the primary analysis). The methods for the analysis of the other outcomes (apart from depressive symptoms were not explicit but they seemed to be DiD). Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	No allocation concealment
Were baseline outcome measurements similar?	Low risk	CESD scores were similar at baseline.
Were baseline characteristics similar?	Low risk	Adjusted by several demographic and socioeconomic variables, not for health variables. Several robustness checks
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing values were omitted, but no mention of their magnitude
Selective reporting (reporting bias)	Low risk	Outcomes reported were the same as in the Methods section.
Was the study adequately protected against contamination?	Unclear risk	The level of incorporation of the patients from different groups to Part D was unclear (we have assumed that the 'no coverage' group would be opting into the new policy and the 'no cap' would stay with their previous insurance benefit).
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identified

Ayyagari 2017

Study characteristics	
Methods	CBA
Participants	The study used data from the year 2000 through year 2012 of the Medical Expenditure Panel Survey (MEPS) and restricted the sample to persons between 60 and 70 years of age in each year of the survey. The final sample consisted of 20,360 persons contributing 33,956 person-year observations.
Interventions	Medicare Part D
Outcomes	Health care utilisation: ED visits (having one or more ED visits in a given year and the total number of ED visits per year)
Notes	The study used a linear DiD model. Funding source: not explicitly reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	No allocation concealment
Were baseline outcome measurements similar?	High risk	ED visits were significantly different between groups.
Were baseline characteristics similar?	Low risk	Adjusted by several demographic and socioeconomic variables, not for health variables. Several robustness checks
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing values were omitted, but no mention of their magnitude
Selective reporting (reporting bias)	Low risk	Outcomes reported were the same as in the Methods section
Was the study adequately protected against contamination?	Unclear risk	The level of incorporation of the patients from different groups to Part D was unclear (we have assumed that the 'no coverage' group would be opting into the new policy and the 'no cap' would stay with their previous insurance benefit).
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identified

Basu 2010

Study characteristics

Basu 2010 *(Continued)*

Methods	CITS
Participants	5% random sample of unique 'dual' enrollees, pharmacy customers who filled at least 1 prescription both in the 2005 and in the 2006 calendar years at any retail or mail order member of a national pharmacy chain in the USA (control group was not 'dually-eligible')
Interventions	Medicare Part D: treatment group (dual eligibles between 65 and 78 years on 1 January 2005); and control group (near-elderly patients with Medicaid coverage between 60 and 63 years on 1 January 2005)
Outcomes	Drug use: (1) total number of prescriptions per month (2) pill-day (a prescription utilisation measure similar to medication possession ratio that counts the number of days with a pill summed across all prescriptions) Drug expenditure: (3) monthly out-of-pocket costs (4) total prescription expenditures
Notes	Originally deemed as a CITS but the control group was non-equivalent. So the analysis was considered an ITS (without a control group). Funding source: Not explicitly reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	No allocation concealment
Were baseline outcome measurements similar?	High risk	'...control group had greater average annual drug utilization and expenditures...'
Were baseline characteristics similar?	Low risk	People in the intervention group '...were older and fewer preferred English as their primary language, but they were otherwise comparable to the control group of patients'.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	Outcomes presented in the Methods section were the same as those presented in the Results section.
Was the study adequately protected against contamination?	Unclear risk	Not clearly reported
Was the intervention independent of other changes?	Unclear risk	During the transition period there were various state-level and federal-level temporary measures, installed to facilitate transition (Page 137).

Basu 2010 *(Continued)*

Was the shape of the intervention effect prespecified?	Unclear risk	It was not a clear direction of effect for this specific population.
Was the intervention unlikely to affect data collection?	Low risk	Routinely collected data
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in ITS studies come from administrative datasets, primarily claims transactions, and therefore are not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identifiable

Belenky 2019

Study characteristics	
Methods	CBA
Participants	Authors used six years of data (2003 to 2008) from the Women's Interagency HIV Study (WIHS), an observational cohort investigating the treatment and prevention of HIV infection in women. Participants who 1) were living with HIV in 2003 and 2) reported Medicaid-Medicare dual eligibility or Medicaid-only enrolment in 2005, were eligible for the study. There were 125 dual eligibles (67% of all dual eligibles in 2005) and 676 Medicaid-only participants (77% of all Medicaid-only participants in 2005) who met the inclusion criteria for this study.
Interventions	Medicare Part D
Outcomes	Antidepressant use, depressive symptoms, and hospitalisation
Notes	The study used a difference-in-differences (DiD) approach on the propensity score-matched cohort to estimate the effects of Medicare Part D implementation on dual eligibles with HIV. The DiD approach consists of a linear model with an interaction term for insurance group (dual eligible or Medicaid-only) and time period (pre- or post-Medicare Part D). Funding source: This research was partially supported by a National Research Service Award Pre-Doctoral Traineeship from the Agency for Healthcare Research and Quality sponsored by the Cecil G. Sheps Center for Health Services Research, The University of North Carolina at Chapel Hill and the UNC Institute for Global Health & Infectious Diseases, Grant No. F32-HS024858.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	No allocation concealment
Were baseline outcome measurements similar?	Low risk	Propensity score match used to balance baseline outcomes

Belenky 2019 *(Continued)*

Were baseline characteristics similar?	Low risk	Propensity score match used to balance baseline characteristics
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of missing values
Selective reporting (reporting bias)	Low risk	Reported outcomes were the same as those described in the Methods section.
Was the study adequately protected against contamination?	Unclear risk	The level of incorporation of the patients from different groups to Part D was unclear (we have assumed that the 'no coverage' group would be opting into the new policy and the 'no cap' would stay with their previous insurance benefit).
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identified

Briesacher 2009

Study characteristics	
Methods	CITS
Participants	A nationwide sample of long-stay Medicare enrollees in nursing homes
Interventions	Medicare Part D: enrollees compared with no-enrollees (having third-party drug coverage or no drug coverage)
Outcomes	Drug expenditure: (1) out-of-pocket payments Drug use: (2) changes in overall prescription drug use
Notes	Originally deemed as a CITS but the control group was non-equivalent. So the analysis was considered an ITS (without a control group). Funding source: Funding for this study came from The Robert Wood Johnson Foundation.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	No allocation concealment

Briesacher 2009 *(Continued)*

Were baseline outcome measurements similar?	Unclear risk	Not explicitly reported
Were baseline characteristics similar?	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	Outcomes presented in the Methods section were the same as those presented in the Results section.
Was the study adequately protected against contamination?	Unclear risk	The enrolment in the intervention group was determined indirectly: 'Enrollment in Medicare Part D was determined from the sources of drug payments'; some risk of contamination was possible.
Was the intervention independent of other changes?	Unclear risk	There was no mention about other changes occurring at the same time.
Was the shape of the intervention effect prespecified?	Low risk	"The effect of Part D on medication use would depend on whether the program expanded coverage to individuals previously without drug benefits or merely replaced existing and possibly more-generous forms of drug coverage" (Page 1902-3).
Was the intervention unlikely to affect data collection?	Low risk	Routinely collected data
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in ITS studies come from administrative datasets, primarily claims transactions, and therefore qre not easily altered by data processors (including researchers and data analysts).
Other bias	Unclear risk	Only data from a single long-term pharmacy provider although it was large (16,000 NH from 48 states) (Page 1903).

Briesacher 2010

Study characteristics	
Methods	ITS
Participants	A nationwide sample of long-stay Medicare enrollees in nursing homes
Interventions	Medicare Part D (authors compared changes in resident outcomes before and after implementation of Medicare Part D in states with partial or no supplemental coverage for benzodiazepines with the same changes in outcome in states with complete supplemental coverage [comparator])
Outcomes	Drug use: (1) monthly proportion of residents who received benzodiazepines and each of the substitute drug categories (2) monthly average number of prescriptions dispensed Health care outcomes:

Briesacher 2010 *(Continued)*

	(3) incidence of falls (4) incidence of hip fracture (5) incidence of other types of fractures
Notes	The comparators seemed to be used in a subgroup (stratified) analysis Funding source: This study was supported by The Robert Wood Johnson Foundation. Dr Briesacher is also supported by Research Scientist Development Award K01AG031836 from the National Institute on Aging.

Risk of bias

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	Outcomes presented in the Methods section were the same as those presented in the Results section.
Was the intervention independent of other changes?	Unclear risk	There was no mention about other changes occurring at the same time.
Was the shape of the intervention effect prespecified?	Low risk	"We hypothesize that an abrupt decrease in benzodiazepine prescribing will coincide with the implementation of Medicare Part D" (Page 693).
Was the intervention unlikely to affect data collection?	Low risk	Routinely collected data
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the allocated group was not relevant. Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in ITS studies come from administrative datasets, primarily claims transactions, and therefore are not easily altered by data processors (including researchers and data analysts).
Other bias	Unclear risk	Only data from a single long-term pharmacy provider although it was large (16,000 NH from 48 states)

Briesacher 2015

Study characteristics

Methods	ITS
Participants	A nationally representative sample of Medicare beneficiaries (n = 56,293 [unweighted and unique] persons) from 2000 to 2010 who contributed 120,566 person-years to this study.
Interventions	Medicare Part D

Briesacher 2015 *(Continued)*

Outcomes	Changes in self-reported health status, limitations in activities of daily living (ADLs) (ADLs and instrumental ADLs), emergency department visits and hospital admissions (prevalence, counts, and spending), and mortality
Notes	The study used an interrupted time-series study design, generalised linear models, and survey data estimators suitable for handling probability weights and clustering within primary sampling units. Authors used a logit link for binary measures, negative binomial link for counts, and log link with γ distributions for costs. For each outcome, the model contained an intercept, an indicator of the trend before Part D, a dummy variable to capture the level change in 2006, and an indicator of the trend after Part D (2007 to 2010). They estimated models with quarterly measures for changes at 3 and 5 years after Part D to assess the stability and onset of trend changes. Funding source: this study received grant support by the National Institute on Aging (NIA) (grants R01AG028745 and R01AG022362; Dr. Soumerai [principal investigator]), a Research Scientist Award from the NIA (K01AG031836; Dr. Briesacher), and related support from the NIA and Agency for Healthcare Research and Quality (grants R01AG032249 and R01HS018577, respectively; Drs. Madden, Zhang, Ross-Degnan, and Soumerai).

Risk of bias

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	Outcomes reported were the same as in the Methods section.
Was the intervention independent of other changes?	Unclear risk	Not reported
Was the shape of the intervention effect prespecified?	Low risk	The direction of the effect was established.
Was the intervention unlikely to affect data collection?	Low risk	Data collected routinely. It was unlikely that the intervention affected data collection.
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identified

Burns 2014

Study characteristics

Methods	ITS
Participants	'Dual' eligible beneficiaries with at least 1 diagnosis of schizophrenia, bipolar I, or bipolar II disorder
Interventions	Medicare Part D

Burns 2014 *(Continued)*

Outcomes	(1) guideline-concordant pharmacotherapy for bipolar I disorder Healthcare utilisation: (2) emergency department use
Notes	Funding source: this study received the following grant support: 1K01MH092338 from the National Institute of Mental Health; 1R01-HS018577-01 from the Agency for Healthcare Research and Quality awarded to the Department of Population Medicine at Harvard Medical School and Harvard Pilgrim Health Care Institute where this study originated; a Robert Wood Johnson Foundation Investigator Award in Health Policy Research; 5R01AG032249 from the National Institute on Aging; and R01 MH084905 from the Agency for Health Care Research and Quality.

Risk of bias

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	Outcomes presented in the Methods section were the same as those presented in the Results section.
Was the intervention independent of other changes?	Unclear risk	No information about other changes
Was the shape of the intervention effect prespecified?	Low risk	"It is uncertain if, or to what extent, Part D plans' utilization management policies relaxed or tightened psychiatric medication management relative to Medicaid programs".
Was the intervention unlikely to affect data collection?	Low risk	Routinely collected data
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in ITS studies come from administrative datasets, primarily claims transactions, and therefore are not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identifiable

Caetano 2006

Study characteristics

Methods	ITS
Participants	The study used a longitudinal analysis of prescription claim records for antihypertensives and statins for the adult population (19 years of age and over) of British Columbia from January 1, 1996 through December 31, 2004. Over the study period, 530,167 adults who met the inclusion criteria initiated therapy with an antihypertensive and 264,904 with a statin; a majority of both cohorts were non-seniors (65% of antihypertensive users, 58% of statin users).

Caetano 2006 *(Continued)*

Interventions	Transition from age-based to income-based pharmacare in British Columbia (BC Fair Pharma Care)
Outcomes	Drug use (monthly incidence of use), and monthly discontinuation rates for antihypertensives and statins
Notes	Two time-series analysis approaches were used. First, standard linear time-series models for each access measure and each population substratum were used. The linear model included dummy variables for monthly seasonal effects and variables to test for change in intercept and trend at the implementation of the seniors' co-payment in January 2002 and Fair PharmaCare in May 2003. Over 120 models were computed, with stepwise specification of the autoregressive component of errors. Other time-series forecasting models were specified for each access measure and for key population substrata (seniors/non-seniors by lowest/median/highest income). Models included ARIMA, seasonal exponential smoothing, log smoothing and others. Best fits were selected by SAS/ETS for each analysis. Projections and 95% confidence intervals were obtained for May 2003 through December 2004. However, authors did not provide results in a format useful for our analysis. Included but not used in the quantitative analysis Funding source: This research was supported by an operating grant from the Canadian Institutes of Health Research (CIHR) and a Research Unit Award of the Michael Smith Foundation for Health Research (MSFHR).

Risk of bias

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not explicitly reported
Selective reporting (reporting bias)	Low risk	Outcomes in the Methods section were the same as in the Results.
Was the intervention independent of other changes?	Unclear risk	The policy changed assessed (Fair Pharma Care) was one major change of a series of transformations to the British Columbia drug insurance programme since 2002.
Was the shape of the intervention effect prespecified?	Low risk	The direction of the effect was established.
Was the intervention unlikely to affect data collection?	Low risk	Routinely collected data were unlikely to affect data collection.
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identified

Carvalho 2019

Study characteristics

Methods	CBA

Carvalho 2019 *(Continued)*

Participants	The elderly (over 65 years) compared with the near-elderly (54–63 years) pre- and post-implementation of Medicare Part D
Interventions	Medicare Part D
Outcomes	Inequality in drug expenditures, mean drug expenditures
Notes	They used a DD framework and, although the primary outcome was inequality in drug expenditures, we used mean drug expenditure and its different components as the outcome in our analysis. Funding source: This work was partly supported by the Centre of Excellence in Population Ageing Research, Australian Research Council (CE170100005 awarded to Prof. Philip M Clarke) and the National Institute of Diabetes and Digestive and Kidney Diseases (Grant No. 1R01 DK090435).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	No allocation concealment
Were baseline outcome measurements similar?	Low risk	Only descriptive statistics (% of sample) for the variables and adjusted later
Were baseline characteristics similar?	Low risk	Adjusted using a standardisation process: age, gender, ethnicity, self-reported health
Incomplete outcome data (attrition bias) All outcomes	Low risk	All individuals in the sample had full information on age, income, gender and ethnicity. We excluded approximately 0.3% of individuals in each year who had missing data on self-reported health.
Selective reporting (reporting bias)	Low risk	Reported outcomes were the same as those described in the Methods section.
Was the study adequately protected against contamination?	Unclear risk	The level of incorporation of the patients from different groups to Part D was unclear (we assumed that the 'no coverage' group would be opting into the new policy and the 'no cap' would stay with their previous insurance benefit).
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identified

Chen 2008

Study characteristics

Methods	ITS

Chen 2008 *(Continued)*

Participants	Community-based seniors affiliated to Medicare and dispatching a psychotropic drug in 1 of the nation's largest retail pharmacy chain
Interventions	Medicare Part D
Outcomes	Drug use: (1) Psychotropic drug utilisation (monthly utilisation of antidepressants, antipsychotics, and benzodiazepines were measured as total number of prescriptions filled by seniors [aged 65 or older] in each month) Drug expenditures: (2) Out-of-pocket expense related to psychotropic medications (proportion of prescription expenditure paid out-of-pocket, which was calculated as prescription drug cost charged to individuals [out-of-pocket spending] divided by total pharmacy reimbursement)
Notes	Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was unclear if there were missing data from databases.
Selective reporting (reporting bias)	Low risk	Outcomes presented in the Methods section were the same as those presented in the Results section.
Was the intervention independent of other changes?	Unclear risk	No mention of any other policy
Was the shape of the intervention effect prespecified?	Low risk	"It is generally believed that Medicare Part D improves access to prescription drugs, reduces out-of-pocket payments, and will therefore increase the overall medication utilization among Medicare beneficiaries".
Was the intervention unlikely to affect data collection?	Low risk	Routinely collected data
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in ITS studies come from administrative datasets, primarily claims transactions, and therefore are not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	Although data were obtained from only a single pharmacy chain (which could be a source of selection bias), the volume of prescriptions dispensed was huge (Page 1192, 1st column).

Chen 2018

Study characteristics	
Methods	CBA

Chen 2018 *(Continued)*

Participants	The study used data from the HRS, an ongoing, longitudinal survey study of respondents' health, income, health insurance, healthcare expenditure, and demographic information among middle-aged and older adults in the United States. The study sample was the 2004–2008 HRS respondents who were aged 65 and older in 2006. There were 649 participants in the treatment group and 97 in the control group.
Interventions	Medicare Part D
Outcomes	Patient health outcomes (self-rated health, mental health status, activities of daily living (ADL) impairment)
Notes	A difference-in-differences (DiD) approach (ordered logistic regression) was used to analyse health outcomes by comparing a 2-year period before and after Part D implementation using the HRS data. Funding source: This work was supported by the Ministry of Education of the Republic of Korea and the National Research Foundation of Korea (NRF-2015S1A3A2046566).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	No allocation concealment
Were baseline outcome measurements similar?	High risk	Statistically significant differences between control and treatment group (Table 1)
Were baseline characteristics similar?	Low risk	Adjusted in regressions for several demographic, socioeconomic and health variables
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was mentioned that "58 participants were excluded because data were missing on key study variables", but it was not possible to assess its impact.
Selective reporting (reporting bias)	Low risk	Outcomes reported were the same as in the Methods section.
Was the study adequately protected against contamination?	Unclear risk	The level of incorporation of the patients from different groups to Part D was unclear (we assumed that the 'no coverage' group would be opting into the new policy and the 'no cap' would stay with their previous insurance benefit).
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identified

Choi 2017

Study characteristics

Choi 2017 *(Continued)*

Methods	CBA
Participants	Older adults with diabetes
Interventions	Medicare Part D
Outcomes	Proportion of OOP pharmacy costs to total pharmacy expenditures
Notes	A segmented regression of interrupted time-series analysis was used to assess the longitudinal effect of implementation of Medicare Part D on out-of-pocket pharmacy costs by considering pre-Part D trends. This approach compared the trend of yearly out-of-pocket prescription drug cost burden between two time periods: before (2000–2005) and after (2006–2011) the implementation of Part D. The analysis was performed for the Medicare and comparison groups separately. To estimate causal effects of Medicare Part D on the mean proportion of out-of pocket pharmacy costs, authors compared average change during the two time periods (before [2000-2005] and after [2006-2011] Part D phases) using a difference-in-difference analysis for the Medicare group with that of the comparison sample. We were not able to obtain an effect estimate from the segmented regression analysis, so we used the effect estimates derived from the DiD analysis. Funding source: This study was supported by the Columbia University School of Nursing Center for Health Policy and Sigma Theta Tau International Honor Society of Nursing Alpha Zeta Chapter.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	No allocation concealment
Were baseline outcome measurements similar?	High risk	"Compared with the Medicare group, the comparison group, on average, had ...lower out-of-pocket pharmacy spending before Medicare Part D, and lower proportion of out-of-pocket pharmacy costs during the years prior to implementation of Medicare Part D".
Were baseline characteristics similar?	High risk	"Compared with the Medicare group, the comparison group, on average, had a lower proportion of women, higher proportion of blacks or Hispanics, and lower coexisting illnesses".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not explicitly reported
Selective reporting (reporting bias)	Low risk	Outcomes reported were the same as in the Methods section.
Was the study adequately protected against contamination?	Low risk	The main comparison was between an elderly eligible group and a non-elderly (50-60 yo) non-eligible group, so the risk of contamination was low.
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identified

Diebold 2018

Study characteristics	
Methods	CBA
Participants	Newly covered medicare beneficiaries
Interventions	Medicare Part D
Outcomes	Cost-related prescription nonadherence and health outcomes (self-reported health status and HBP diagnosis)
Notes	The effect of Part D on each outcome was estimated using a difference-in-differences estimator from an ordinary least squares (OLS) regression model. Funding source: The author did not receive funding for this analysis or the paper.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	Non-randomised comparison
Were baseline outcome measurements similar?	Low risk	No apparent differences between control and treatment group, but no statistical test performed
Were baseline characteristics similar?	Low risk	Regression analyses adjusted for several demographic, socioeconomic and health variables
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of missing data
Selective reporting (reporting bias)	Low risk	Reported outcomes were the same as those described in the Methods section.
Was the study adequately protected against contamination?	Unclear risk	The level of incorporation of the patients from different groups to Part D was unclear (we assumed that the 'no coverage' group would be opting into the new policy and the 'no cap' would stay with their previous insurance benefit).
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identified

Do 2020

Study characteristics

Do 2020 *(Continued)*

Methods	CBA
Participants	Nationally representative data on community-dwelling adults aged 60–69 coming from the 2000–2015 Medical Expenditure Panel Survey (MEPS) (N = 26,545)
Interventions	Medicare Part D
Outcomes	Drug use (outpatients opioids prescription)
Notes	The association between Part D and opioid use was assessed using a difference-in-differences approach (two-part model: logistic regression and a Gamma generalised linear model with log link). Funding source: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	No allocation concealment
Were baseline outcome measurements similar?	Low risk	No significant differences at baseline
Were baseline characteristics similar?	Low risk	Regression analyses adjusted for several demographic, socioeconomic and health variables
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	In the description of the study sample, it was mentioned that "I eliminated respondents with missing information on covariate variables (N = 3143 out of 26,545 finally included). In additional analyses, missing data were imputed using multiple imputation with chained equations and 50 imputed datasets, but the interpretation of the results remained unchanged."
Selective reporting (reporting bias)	Low risk	Outcomes reported were the same as in the Methods section.
Was the study adequately protected against contamination?	Unclear risk	The level of incorporation of the patients from different groups to Part D was unclear (we assumed that the 'no coverage' group would be opting into the new policy and the 'no cap' would stay with their previous insurance benefit).
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identified

Donohue 2010

Study characteristics

Donohue 2010 *(Continued)*

Methods	CBA
Participants	The study population included beneficiaries aged ≥ 65 years who were continuously enrolled with an insurance company in Pennsylvania and alive from 2003 to 2007 with a diagnosis of heart failure.
Interventions	Medicare Part D
Outcomes	Drug use: (1) heart failure prescriptions filled annually (2) total prescriptions filled annually (3) likelihood of filling a prescription for drugs in major therapeutic classes for heart failure (4) good refill adherence (80% of days covered) for drugs in major therapeutic classes for heart failure
Notes	The main comparison analysed was between the 'no coverage' group (likely to be incorporated in Medicare Part D) and the 'no cap' group (unlikely to be incorporated in Medicare Part D because of the generosity of the coverage). Funding source: The investigators were supported by grants from the National Center for Research Resources at the National Institute of Health (05 KL2 RR024154-04) and the Veterans Administration Health Services Research and Development Service.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-randomised comparisons
Allocation concealment (selection bias)	High risk	Non-randomised comparisons
Were baseline outcome measurements similar?	High risk	Tables II, III and IV (pre-Part D figures)
Were baseline characteristics similar?	High risk	Table 1. There was a number of differences between the 'no cap' and 'no insurance' group.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was unclear if there were missing data from databases.
Selective reporting (reporting bias)	Low risk	Outcomes presented in the Methods section were the same as those presented in the Results section.
Was the study adequately protected against contamination?	Unclear risk	The level of incorporation of the patients from different groups to Part D was unclear (we assumed that the 'no coverage' group would be opting into the new policy and the 'no cap' would stay with their previous insurance benefit).
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identifiable

Donohue 2011

Study characteristics	
Methods	CBA
Participants	The study population included beneficiaries aged ≥ 65 years who were continuously enrolled with an insurance company in Pennsylvania and alive from 2003 to 2007 with a diagnosis of depression.
Interventions	Medicare Part D
Outcomes	Drug use: (1) likelihood of filling at least 1 prescription for an antidepressant (2) likelihood of filling a prescription for tricyclic antidepressants or monoamine oxidase inhibitors (3) likelihood of having 80% of days covered with an antidepressant in the first 6 months of treatment for depression
Notes	The main comparison analysed was between the 'no coverage' group (likely to be incorporated in Medicare Part D) and the 'no cap' group (unlikely to be incorporated in Medicare Part D because of the generosity of the coverage). Funding source: This publication was supported by the National Center for Research Resources, National Institutes of Health (NIH) (KL2 RR-024154-04), Agency for Healthcare Research and Quality (R01HS017695), NIH grants (R34 MH082682, R01AG027017, P30AG024827, P30MH71944, T32 AG021885, K07AG033174, R01AG034056)), the Veterans Administration Health Services Research and Development Service (IIR-06-062), the UPMC endowment in geriatric psychiatry, and John A. Hartford Foundation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-randomised comparisons
Allocation concealment (selection bias)	High risk	Non-randomised comparisons
Were baseline outcome measurements similar?	High risk	Differences showed in pre-Part D outcomes in Tables 2 and 4.
Were baseline characteristics similar?	High risk	Table 1. There were a number of differences between the 'no cap' and 'no insurance' groups.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was unclear if there were missing data from databases.
Selective reporting (reporting bias)	Low risk	Outcomes presented in the Methods section were the same as those presented in the Results section.
Was the study adequately protected against contamination?	Unclear risk	The level of incorporation of the patients from different groups to Part D was unclear (we assumed that the 'no coverage' group would be opting into the new policy and the 'no cap' would stay with their previous insurance benefit).
Was knowledge of the allocated interventions ade-	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily

Donohue 2011 *(Continued)*

quately prevented during the study?		claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identifiable

Dranove 2017

Study characteristics	
Methods	CBA
Participants	Medicaid beneficiaries in 29 states in the US (16 control states and 13 intervention states)
Interventions	Privatisation of Medicare drug benefits
Outcomes	Drug use (drug prescriptions per enrollee) and drug spending
Notes	Authors referred to the DiD analysis as the "reduced form" analysis. They also created instrumental variable estimates of what the effect of privatisation would be if all of a state's enrollees' pharmacy benefits were administered by MCOs (what they called "first stage" analysis). Authors reported no change in prescription per enrollee (Panel C) and a 22.4 per cent decrease in drug spending per enrollee (Panel B) but the estimates in the table were in log units and it was not possible to convert them to the metric used in the review with the other studies. Included but not used in the quantitative analysis Funding source: not explicitly reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	No allocation concealment
Were baseline outcome measurements similar?	Low risk	No relevant differences at baseline
Were baseline characteristics similar?	High risk	Authors performed several robustness and extensions tests, but no relevant adjustment or control variables were introduced.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was a fair amount of missing data ("I eliminated respondents with missing information on covariate variables (N = 3143 out of 26,545 finally included)"). The approach used to deal with this was not totally convincing to us ("In additional analyses, missing data were imputed using multiple imputation with chained equations and 50 imputed datasets, but the interpretation of the results remained unchanged.")
Selective reporting (reporting bias)	Low risk	Outcomes reported were the same as those in the Methods section.
Was the study adequately protected against contamination?	Unclear risk	The level of incorporation of the patients from different groups to Part D was unclear (we assumed that the 'no coverage' group would be opting into the new policy and the 'no cap' would stay with their previous insurance benefit).

Dranove 2017 *(Continued)*

Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identified

Dunn 2019

Study characteristics	
Methods	CBA
Participants	Medicare population over the age of 65
Interventions	Medicare Part D
Outcomes	Mortality (cardiovascular and non-cardiovascular)
Notes	Using the Medicare Current Beneficiary Survey (MCBS), authors estimated demographically adjusted rates of prescription drug coverage for age 65+ Medicare enrollees across counties before the implementation of Part D. They found that those areas with lower levels of coverage before the reform experienced greater drug insurance expansion as a result of Part D. This information was combined with county-level mortality data obtained from the Centers for Disease Control and Prevention (CDC) for the years 2000 to 2010. Then they examined whether those areas most impacted by the reform had a larger reduction in mortality post-reform. Authors presented two alternative strategies for measuring the impact of the reform, which both addressed the delayed mortality issue. One approach is to focus on the immediate impact of the reform just after implementation. Since this is the population that is initially affected by the reform, it is most comparable to the health of the population prior to the reform. Specifically, they focused on the mortality effects for those dying immediately following the reform from July 1, 2006, and June 30, 2007. The second approach measures the effect on mortality for the entire post-period of the sample from 2006 to 2010, but includes controls designed to remove the effects of delayed mortality. However the specific analytical approaches used were not completely clear. Funding source: not explicitly reported

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	No allocation concealment
Were baseline outcome measurements similar?	Unclear risk	No information reported
Were baseline characteristics similar?	Low risk	Regressions adjusted for county disease fixed effects, year disease fixed effects, and the unemployment rate
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported

Dunn 2019 *(Continued)*

Selective reporting (reporting bias)	Low risk	Not reported
Was the study adequately protected against contamination?	Low risk	The comparison was between counties with high and low likelihood of expanding drug coverage.
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identified

Engelhardt 2011

Study characteristics	
Methods	CBA
Participants	A Medicare eligible (65 and older) sample compared to a near-elderly (60-64 years old) sample who were not eligible.
Interventions	Medicare Part D
Outcomes	Prescription drug expenditure (OOP, public and private)
Notes	Authors used a differences-in-differences approach. Funding source: not explicitly reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	No allocation concealment
Were baseline outcome measurements similar?	High risk	Baseline differences in prescription and medical expenditure. No statistical test performed
Were baseline characteristics similar?	Low risk	Regressions adjusted for several demographic, socioeconomic and health variables
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	Outcomes reported were the same as those in the Methods section.

Engelhardt 2011 *(Continued)*

Was the study adequately protected against contamination?	Low risk	The level of incorporation of the patients from different groups to Part D was unclear, but it is reasonable to assume that the 'elderly' group would be opting into the new policy and the 'non-elderly' would not be able to opt in.
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identified

Ettner 2011

Study characteristics	
Methods	CBA
Participants	Multiple groups were compared but the reference category was that where individuals had non-capped branded drug coverage in 2005 and the standard Part D benefit (including a coverage gap) in 2006–2007.
Interventions	Medicare Part D
Outcomes	Prescription drug use (days supply) and expenditures
Notes	The analytical approach was differences-in-differences, but authors did not provide any data in text to calculate the relative effect – they only reported absolute figures. Included but not used in the quantitative analysis. Funding source: This project was funded by the Centers for Disease Control and Prevention, Cooperative Agreement U58/CCU923527-04-1: The Translating Research into Action for Diabetes (TRIAD) Study (PI: Mangione). Dr. Mangione is partially supported by the UCLA Resource Center for Minority Aging Research (NIA #P30AG021684-06).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	No allocation concealment
Were baseline outcome measurements similar?	Low risk	Authors re-estimated each model controlling for the baseline value of the outcome.
Were baseline characteristics similar?	Low risk	No relevant differences
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported

Ettner 2011 *(Continued)*

Selective reporting (reporting bias)	Low risk	Outcomes reported were the same as those in the Methods section.
Was the study adequately protected against contamination?	Unclear risk	The level of incorporation of the patients from different groups to Part D was unclear (we assumed that the group with less substantial coverage would be opting into the new policy and the group with 'non-capped' branded drug coverage would stay with their previous insurance benefit).
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identified

Farley 2010

Study characteristics	
Methods	ITS
Participants	Patients in 44 Medicaid programs in the USA
Interventions	Medicare Part D
Outcomes	Drug expenditures: (1) Medicaid prescription expenditures Drug use: (2) Medicaid drug utilisation (number of prescriptions)
Notes	Funding source: not explicitly reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No specific mention of missing data
Selective reporting (reporting bias)	Low risk	Outcomes presented in the Methods section were the same as those presented in the Results section.
Was the intervention independent of other changes?	Unclear risk	No mention about any other policy intervention occurring at the same time in the US healthcare system
Was the shape of the intervention effect prespecified?	High risk	Not specifically stated
Was the intervention unlikely to affect data collection?	Low risk	Routinely collected data

Farley 2010 *(Continued)*

Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in ITS studies come from administrative datasets, primarily claims transactions, and therefore are not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	There did not seem to be another relevant source of bias.

Fowler 2013

Study characteristics	
Methods	CBA
Participants	Community-dwelling Medicare beneficiaries in Pennsylvania aged 65 or older (n = 35,102)
Interventions	Medicare Part D
Outcomes	Use of cholinesterase inhibitors and memantine (proportion with any use and annual number of 30-day prescriptions filled)
Notes	There were four groups according to the type of drug benefit pre-Part D (no coverage, $150 cap, $350 cap, and no cap as the reference group), but the focus of our analysis should be on the comparison between the no coverage and the no cap groups. A generalised estimating equation (GEE) with a binomial distribution, logit link function, and exchangeable correlation structure was fitted to model any use of anti-dementia drugs annually, as a group and by drug class.. Funding source: This study was supported by the Agency for Healthcare Research and Quality on K12HS019461-01 and the National Institutes of Health on UL1 RR024153 and UL1TR000005.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	No allocation concealment
Were baseline outcome measurements similar?	High risk	Statistically significant differences in drug prescription between the groups compared
Were baseline characteristics similar?	Low risk	Regressions adjusted for several demographic, socioeconomic and health variables
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	Outcomes reported were the same as those in the Methods section.
Was the study adequately protected against contamination?	Low risk	The level of incorporation of the patients from different groups to Part D was unclear but we can reasonably assume that the 'no coverage' group would be

Fowler 2013 *(Continued)*

		opting into the new policy and the 'no cap' would stay with their previous insurance benefit.
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identified

Huh 2017

Study characteristics	
Methods	CBA
Participants	The primary estimation sample, which included only 64- and 66-year-old decedents, consisted of 518,514 deaths that occurred between 2001 and 2008.
Interventions	Medicare Part D
Outcomes	Mortality
Notes	Authors pursued a difference-in-differences approach that compared the change in state-level mortality rates among the young-elderly to the corresponding change among the near-elderly, before and after the implementation of Medicare Part D. Funding source: not explicitly reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	No allocation concealment
Were baseline outcome measurements similar?	Unclear risk	Not reported
Were baseline characteristics similar?	Low risk	Multiple regression adjusted by: marital status, race, educational attainment, gender, census region, and household income
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	Reported outcomes were the same as those described in the Methods section.
Was the study adequately protected against contamination?	Low risk	It is reasonable to assume that the 66-year-old group would be opting into the new policy and the 64-year-old group would not be able to opt in.

Huh 2017 *(Continued)*

Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identified

Jung 2019

Study characteristics	
Methods	CBA
Participants	Residents in long-term care facilities in Pennsylvania
Interventions	Medicare Part D
Outcomes	Generic drug use
Notes	Authors conducted DiD analyses with 3 treatment groups (eligible elderly population). These 3 analyses were conducted separately on 3 different therapeutic classes as well as on the total prescription data including more than 700 drugs. The control group was the non-elderly population (age < 65 during the study period) not enrolled in Part D. Due to difficulties with fixed-effect nonlinear models (logit or probit), such as data loss with conditional fixed effects and inconsistency with unconditional fixed effects, we used a (physician) fixed-effect linear probability model, allowing physician-level heterogeneity. Funding source: not explicitly reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	No allocation concealment
Were baseline outcome measurements similar?	Unclear risk	Not reported
Were baseline characteristics similar?	Low risk	Adjusted by patient-specific information (age, gender, number of diagnoses, monthly average number of medications)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	Outcomes reported were the same as those in the Methods section.
Was the study adequately protected against contamination?	Low risk	The level of incorporation of the patients from different groups to Part D was unclear, but it is reasonable to assume that the 'elderly' eligible group would be opting into the new policy and the 'non-elderly' would not be able to opt in.

Jung 2019 *(Continued)*

Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identified

Kaestner 2012

Study characteristics		
Methods	CBA	
Participants	A nationally representative sample of Medicare beneficiaries	
Interventions	Medicare Part D	
Outcomes	Use of prescriptions drugs, expenditure on prescription drugs, use of medical (inpatient and outpatient) medical services	
Notes	Using an instrumental variables approach, authors compared groups gaining prescription drug insurance with those with less probability of gaining insurance. Funding source: not explicitly reported	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	No allocation concealment
Were baseline outcome measurements similar?	Unclear risk	Not reported
Were baseline characteristics similar?	Low risk	Demographic and socioeconomic characteristics including age, sex, race, education, urban residence, census region of residence, income, marital status, and smoking status where similar between groups (Table 1)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	Outcomes reported were the same as those in the Methods section.
Was the study adequately protected against contamination?	High risk	Control and treatment groups were estimated using probabilities through regressions, so it is possible that individuals in the control group had been enrolled in the policy.

Kaestner 2012 *(Continued)*

Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identified

Kaestner 2014

Study characteristics	
Methods	CBA
Participants	A sample of Medicare beneficiaries
Interventions	Medicare Part D
Outcomes	Number of hospital admissions, all-cause mortality, inpatient expenditures
Notes	The primary reference is a report with 2 analytical approaches (differences-in-differences (DiD) and instrumental variables (IV)). The secondary (journal) reference is only an IV approach. We used effect estimates computed with the DiD approach. Funding source: Funding for this research was provided by the National Institute of Aging, National Institutes of Health (1R01AG042396).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	No allocation concealment
Were baseline outcome measurements similar?	Unclear risk	Not reported
Were baseline characteristics similar?	Low risk	Baseline characteristics were adjusted by a number of regressions. They included control variables such as HMO share, cell fixed effects, year fixed effects, region-by-year fixed effects, age-by-gender-by-year fixed effects.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	Reported outcomes were the same as those described in the Methods section.
Was the study adequately protected against contamination?	High risk	Authors estimated the probability of the population in different states of gaining prescription drug insurance but it was likely that some people in the control states had gained access to the intervention.

Kaestner 2014 *(Continued)*

Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identified

Ketcham 2008

Study characteristics	
Methods	CITS
Participants	A representative sample of Medicare always-age-eligible patients (compared with a group always-age-ineligible for Medicare)
Interventions	Medicare Part D
Outcomes	Drug use: (1) day's supply (2) number of patients filling prescriptions Drug expenditures: (3) patient OOP costs per day's supply
Notes	Originally deemed as a CITS but the control group was non-equivalent. It was analysed as an ITS (without a control group). Funding source: Financial support was provided from Pfizer Inc and Merck Foundation in the form of grants awarded to Cornell University to purchase the Wolters Kluwer Health data used in this study.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	No allocation concealment
Were baseline outcome measurements similar?	High risk	Not explicitly reported but data from Figure (page SP18) showed differences in day's supply and OOP from before the implementation of the intervention.
Were baseline characteristics similar?	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not documented
Selective reporting (reporting bias)	Low risk	Outcomes presented in the Methods section were the same as those presented in the Results section.

Ketcham 2008 *(Continued)*

Was the study adequately protected against contamination?	Unclear risk	Not clearly reported
Was the intervention independent of other changes?	Unclear risk	It was not explicitly mentioned by authors.
Was the shape of the intervention effect prespecified?	Low risk	For each, a direction of effect was pre-specified.
Was the intervention unlikely to affect data collection?	Low risk	Routinely collected data
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in ITS studies come from administrative datasets, primarily claims transactions, and therefore are not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	Non-equivalent comparison group but those data were not used in the analysis for this review

Kircher 2014

Study characteristics	
Methods	CBA
Participants	2147 near-elderly individuals with cancer and 5296 individuals with Medicare and cancer
Interventions	Medicare Part D
Outcomes	OOP and total costs, medication use, hospitalisations, emergency department visits, and outpatients visits
Notes	The analytical approach was DiD. Funding source: No specific funding was disclosed.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	No allocation concealment
Were baseline outcome measurements similar?	High risk	There were significant differences at baseline between groups.
Were baseline characteristics similar?	Low risk	Although there were differences, they were adjusted by sex, age, year, region, number of comorbidities, and poverty status.

Kircher 2014 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	Outcomes reported were the same as those in the methods section.
Was the study adequately protected against contamination?	Low risk	The comparison was based on age (elderly versus near-elderly) which makes contamination unlikely.
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identified

Li 2013

Study characteristics	
Methods	CITS
Participants	Diabetic patients covered by Medicare
Interventions	Medicare Part D (comparison was with diabetic patients 45 to 64 years old who were not eligible for Medicare coverage)
Outcomes	Drug expenditures: (1) annual individual out-of-pocket expenditure (OOPE) for prescription drugs (2) annual individual total OOPE for all healthcare services (3) annual total family OOPE for all healthcare services (4) percentage of persons with high family financial burden (OOPE ≥10% of income)
Notes	Originally deemed as a CITS but the control group was non-equivalent. So it was analysed as an ITS (without a control group). Funding source: one of the authors (SBS) was partially supported by the Natural Experiments for Translation in Diabetes (NEXT-D) study, RFA-DP10-002, sponsored by CDC and NIDDK.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	No allocation concealment
Were baseline outcome measurements similar?	Low risk	"Over 1996–2004 (pre-intervention period), the Medicare and comparison groups showed similar upward trends in all outcomes".

Li 2013 *(Continued)*

Were baseline characteristics similar?	High risk	There was a number of differences in the baseline characteristics of both groups: "Persons in the non-Medicare group were more likely to be married, have attained a higher educational level, have higher family income, and report better physical health status than those in the Medicare group".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not documented
Selective reporting (reporting bias)	Low risk	Outcomes presented in the Methods section were the same as those presented in the Results section,
Was the study adequately protected against contamination?	Unclear risk	Not clearly reported
Was the intervention independent of other changes?	Unclear risk	Not clearly described by authors. However, there was a mention of the introduction in 2005 of the Medicare Interim Drug Discount Card.
Was the shape of the intervention effect prespecified?	Low risk	"The policy should decrease financial burden on patients" (Page 888 (3rd paragraph)).
Was the intervention unlikely to affect data collection?	Low risk	Routinely collected objective data
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in ITS studies come from administrative datasets, primarily claims transactions, and therefore are not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	Although authors used a comparison with a non-equivalent control group, those data were not used in our analysis.

Lichtenberg 2007

Study characteristics	
Methods	CITS
Participants	A sample of elderly Medicare beneficiaries dispatching prescriptions in a pharmacy chain
Interventions	Medicare Part D (comparison group was non-elderly people < 65 years old)
Outcomes	Drug use: (1) number of prescriptions (2) number of days of therapy dispensed Drug expenditures: (3) mean amount paid by the patient (4) mean total amount paid

Lichtenberg 2007 *(Continued)*

Notes	Originally deemed as a CITS but the control group was non-equivalent. So it was analysed as an ITS (without a control group). Funding source: The authors did not receive any financial support for the preparation of this paper.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	No allocation concealment
Were baseline outcome measurements similar?	Unclear risk	Although for drug expenditures, baseline figures seemed to be similar ("From September 2004 to December 2005, the amounts paid by elderly and non-elderly patients per day of therapy were quite similar") this was not clearly reported for drug use.
Were baseline characteristics similar?	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	Outcomes presented in the Methods section were the same as those presented in the Results section.
Was the study adequately protected against contamination?	Unclear risk	Not clearly reported
Was the intervention independent of other changes?	Unclear risk	There was no mention of other concurrent changes, but it seemed that most of the elderly already had some kind of drug insurance before Part D (Page 1736).
Was the shape of the intervention effect prespecified?	Unclear risk	Not explicitly established. There was some mention of related literature but not a definitive statement about the direction of the effect.
Was the intervention unlikely to affect data collection?	Low risk	Routinely collected objective data
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in ITS studies come from administrative datasets, primarily claims transactions, and therefore are not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	Although they used a non-equivalent comparison group, our analysis only included the time-series data for elderly.

Lim 2013

Study characteristics	
Methods	CBA
Participants	A nationally representative sample of noninstitutionalised U.S. residents using antidepressants (n = 22,592) with different types of health insurance (Medicare, Medicaid, dual-eligible, private coverage)
Interventions	Medicare Part D
Outcomes	Antidepressant use
Notes	The analytical approach was DiD using logistic regression controlling for sociodemographic factors. Funding source: not explicitly reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	No allocation concealment
Were baseline outcome measurements similar?	Unclear risk	Not reported
Were baseline characteristics similar?	Low risk	Authors mentioned that "We controlled for all patient characteristics.." (page 1039).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	Outcomes reported were the same as those in the Methods section.
Was the study adequately protected against contamination?	Low risk	The comparison was between mutually exclusive groups enrolled in Medicare (intervention) or private insurance (control).
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identified

Liu 2011

Study characteristics	
Methods	CBA

Liu 2011 *(Continued)*

Participants	A sample of 1105 noninstitutionalised Medicare beneficiaries (556 elderly and 549 near-elderly)
Interventions	Medicare Part D
Outcomes	OOP costs, drug (medication) use, emergency department use, hospitalisations, and preference-based health utility
Notes	The analytical approach was a multivariate DiD model. Funding source: this study was supported by the Agency for Healthcare Research and Quality (K08 HS15699-01A1, Alexander), and the Robert Wood Johnson Physician Faculty Scholars Program (Alexander).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	No allocation concealment
Were baseline outcome measurements similar?	High risk	Significant differences between groups at baseline (Table 1)
Were baseline characteristics similar?	Low risk	Adjustments by age and education, physical functioning
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing values in any of the variables used in the analyses were excluded, but the magnitude was not clear.
Selective reporting (reporting bias)	Low risk	Outcomes reported were the same as those in the Methods section.
Was the study adequately protected against contamination?	Low risk	The comparison was based on age (65 and older versus 58-63 yo) which makes contamination unlikely.
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identified

Maclean 2020

Study characteristics

Methods	CBA
Participants	Medicaid State Drug Utilization Database (SDUD) 2011-2018, comprising the universe of outpatient prescription medications covered under the Medicaid programme

Maclean 2020 *(Continued)*

Interventions	Affordable Care Act (ACA) Medicaid expansion
Outcomes	Drug use (Medicaid-financed prescriptions filled)
Notes	Authors estimated DiD standard regression models. Funding source: Research Scholar Grant – Insurance, Grant/Award Number: 16-019-01; American Cancer Society; TUFCCC/HC Regional Comprehensive Cancer Health Disparity Partnership; National Cancer Institute, Grant/Award Number: U54 CA221704(5)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	No allocation concealment
Were baseline outcome measurements similar?	High risk	Significant differences between groups at baseline (Table 2)
Were baseline characteristics similar?	Low risk	Regressions controlled for state characteristics measured in each quarter and year (age, sex, race/ethnicity, foreign birth, education, and unemployment).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	Outcomes reported were the same as those in the Methods section.
Was the study adequately protected against contamination?	Low risk	The main comparison was between expansion and non-expansion states, so it was unlikely that people from a control state got the intervention (a decision at the state level).
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identified

Madden 2015

Study characteristics

Methods	ITS
Participants	A national sample of community-dwelling, non-elderly disabled dual enrollees with schizophrenia (n = 5554) or bipolar disorder (n = 3675)
Interventions	Medicare Part D

Madden 2015 *(Continued)*

Outcomes	Monthly rates of untreated illness, intensity of treatment, and overall prescription medication use
Notes	To evaluate post–Part D changes in drug use, authors constructed interrupted time-series regression models for each study group. The main models included an intercept, a term for baseline trend, and terms for change in level and trend after Part D. Four months of observations (from December 2005 through March 2006) were omitted as a policy phase-in period. Estimates in Table 2 (national) were analysed as a non-controlled ITS. Funding source: This work was supported by the Agency for Healthcare Research and Quality (grant R01 HS018577) and the National Institute on Aging (grants 5R01AG032249 and 5R01AG028745).

Risk of bias

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not explicitly reported
Selective reporting (reporting bias)	Low risk	Outcomes reported were the same as those in the Methods section.
Was the intervention independent of other changes?	Unclear risk	Not reported
Was the shape of the intervention effect prespecified?	Low risk	The purpose of the policy was clearly established and the point of analysis was the point of the intervention.
Was the intervention unlikely to affect data collection?	Low risk	Routinely collected data independent from the intervention
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	The intervention was at state level. Although knowledge of the intervention (the policy) is an essential part of policy implementation, data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identified

McWilliams 2011

Study characteristics

Methods	CITS
Participants	Nationally representative sample of Medicare beneficiaries (6001 elderly Medicare beneficiaries from the Health and Retirement Study)
Interventions	Medicare Part D (2538 with generous and 3463 with limited drug coverage before 2006)
Outcomes	Healthcare utilisation: (1) non-drug medical spending assessed from claims, in total and by type of service (inpatient and skilled nursing facility vs physician services)

McWilliams 2011 *(Continued)*

Notes	Although there were time-series data, it was not possible to re-analyse as a CITS and the best estimate of the effect size was from a CBA analysis. Funding source: This study was supported by grants from the Doris Duke Charitable Foundation (Clinical Scientist Development Award 2010053, Dr McWilliams), the William F. Milton Fund (Dr McWilliams), and a Robert Wood Johnson Foundation Investigator Award in Health Policy Research (Dr Huskamp).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	No allocation concealment
Were baseline outcome measurements similar?	Low risk	"...adjusted total non-drug medical spending before implementation of Part D was consistently but not significantly higher for participants with limited drug coverage than for participants with generous drug coverage (7.6% relative difference [95% CI, −2.7% to 18.9%]; P = 0.15)"
Were baseline characteristics similar?	Low risk	Although there was a number of differences between intervention and control groups (Table 1), they were adjusted for in the analysis.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	Outcomes presented in the Methods and Results sections were the same.
Was the study adequately protected against contamination?	Unclear risk	Not clearly reported
Was the intervention independent of other changes?	Unclear risk	No explicit mention of other policy changes
Was the shape of the intervention effect prespecified?	Low risk	"Part D was associated with reduced non drug medical spending for enrollees with no or limited drug coverage before 2006 but was associated with increased non drug spending for enrollees with less limited benefits before 2006" (Page 402, 1st column).
Was the intervention unlikely to affect data collection?	Low risk	Routinely collected data
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identifiable

Mott 2010

Study characteristics	
Methods	CBA
Participants	A sample of 12,785 Medicare Part D beneficiaries (11,133 intervention group and 1652 in the control group) obtaining prescriptions from a regional supermarket chain in the US
Interventions	Medicare Part D
Outcomes	Total drug spending, OOP drug spending, % spending OOP, drug use (pill days)
Notes	The analysis was DiD but it was presented separately by each pre-part D OOP drug expenditure group (highest and lowest), so we were not able to obtain effect estimates comparing both groups. Included but not used in the quantitative analysis Funding source: Dr. Carolyn T. Thorpe's work on this project was supported by the Health Innovation Program and the Community- Academic Partnerships core of the University of Wisconsin Institute for Clinical and Translational Research and grant 1UL1RR025011 from the Clinical and Translational Science Award Program of the National Center for Research Resources, National Institutes of Health.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	No allocation concealment
Were baseline outcome measurements similar?	High risk	There were significant differences at baseline (Table 1)
Were baseline characteristics similar?	Low risk	The models controlled for patient age, sex, a group dummy variable, and a study period dummy variable.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	Outcomes reported were the same as those in the Methods section.
Was the study adequately protected against contamination?	Unclear risk	"Although it is possible that a small number of individuals in this comparison *(control)* group were eligible for Medicare coverage because of disability, they were assumed to be ineligible" (Page 92).
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identified

Nelson 2014

Study characteristics	
Methods	CBA
Participants	Non-elderly Medicare beneficiaries with disabilities
Interventions	Medicare Part D
Outcomes	Expenditures and utilisation of prescription drugs, hospitalisations, physician office visits and emergency department visits
Notes	Due to the inherent differences between non-elderly individuals covered by Medicare and those not covered by Medicare, authors performed a propensity score-matching process in order to generate a more comparable sample of control subjects. They performed a one-to-one match using the nearest neighbour method, which yielded one respondent who received Medicare benefits for each respondent who did not receive Medicare benefits. The DiD estimation was employed using regression models which included three key independent variables: an indicator for Medicare coverage, an indicator for post-Medicare Part D (2006), and the interaction between the Medicare coverage and post-Medicare Part D indicator. They employed the DiD method by using a zero-inflated negative binomial regression model to estimate the number of prescriptions, ED visits, physician office visits, and hospitalisations. They used this same DiD technique to measure the impact of Medicare Part D on prescription drug, hospitalisation, physician office visit, and ED expenditures. Healthcare expenditure data are typically skewed to the right and non-normally distributed because of a small group of patients incurring high resource use. To account for this, authors fitted these data to generalised linear models (GLM) assuming gamma distributed errors and a log link function. Funding source: This work was supported in part by funding from the National Institutes of Health and the National Cancer Institute grant 1 KM1CA156723 (R.N.). B.H. was supported by a fellowship grant from Geneva University Hospitals.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	No allocation concealment
Were baseline outcome measurements similar?	Unclear risk	There was propensity score-matching for other baseline variables, but similar outcomes at baseline were not completely clear.
Were baseline characteristics similar?	Low risk	Propensity score-matching (page 66)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	Outcomes reported were the same as those in the Methods section.
Was the study adequately protected against contamination?	Low risk	The comparison was between eligible and non-eligible individuals.

Nelson 2014 *(Continued)*

Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identified

Ong 2012

Study characteristics	
Methods	CBA
Participants	Intervention participants (n = 19,339) were elderly adults from a large, national Medicare Advantage plan subject to benzodiazepine exclusion as a result of the Medicare Modernization Act (MMA). Comparison participants (n = 3488) were near-elderly individuals enrolled in a managed care plan not subject to the MMA benzodiazepine exclusion.
Interventions	Medicare Part D
Outcomes	Any psychotropic drug use and expenditures
Notes	Logistic regression models were estimated for the probability of use of psychotropic medications and specified subclasses. Two-part models were estimated for each of the non-benzodiazepine psychotropic medication expenditure and days' supply outcomes, with logistic regression used to predict use and zero-truncated negative binomial regression to predict expenditures (or days' supply) given use. Benzodiazepine expenditure and days' supply outcomes were estimated using non-zero truncated negative binomial regression models, because all individuals had been users in 2005. All regression models were adjusted for age, age squared, sex, year, and psychiatric and medical comorbidities. However, they presented before-and-after differences within each group (intervention and comparison) but not between groups. Included but not used in the quantitative analysis Funding source: This study was supported by Grants R01MH079034 and P30MH082760 from the National Institute of Mental Health.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	No allocation concealment
Were baseline outcome measurements similar?	Unclear risk	Not reported
Were baseline characteristics similar?	Low risk	Regressions controlled for a constant, sex, age, age squared, and psychiatric and medical comorbidities (Table 2)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported

Ong 2012 *(Continued)*

Selective reporting (reporting bias)	Low risk	Outcomes reported were the same as those in the Methods section.
Was the study adequately protected against contamination?	Low risk	The comparison was between elderly eligible and non-elderly non-eligible, so the risk of contamination was low.
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identified

Pak 2017

Study characteristics	
Methods	CBA
Participants	A sample drawn from six waves of the Health and Retirement Study (between 2000 and 2010) aged between 60 and 70 years at any wave during the study period (33,953 person-year observations)
Interventions	Medicare Part D
Outcomes	Cognitive functioning (episodic memory, immediate recall, delayed recall)
Notes	A difference-in-differences (DiD) framework was employed to identify the impact of Medicare Part D. Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	No allocation concealment
Were baseline outcome measurements similar?	Low risk	Reported but without statistical tests
Were baseline characteristics similar?	Low risk	Regressions controlled for several demographic, socioeconomic and health variables. In addition, robustness tests
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	Outcomes reported were the same as those in the Methods section.

Pak 2017 *(Continued)*

Was the study adequately protected against contamination?	Low risk	The comparison was between eligible and non-eligible Medicare Part D individuals, so the risk of contamination was low.
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identified

Park 2017

Study characteristics	
Methods	CBA
Participants	Using Medical Expenditure Panel Survey (MEPS) data from 2000 through 2005 (pre-Part D period) and from 2007 through 2012 (Part D era), this study identified a cohort of elderly Medicare beneficiaries (treatment group) and a near-elderly non-Medicare population (control group).
Interventions	Medicare Part D
Outcomes	Drug expenditures (OOP expenses and total expenses on prescription drugs), prescription drug use, and outpatient visits
Notes	Authors used a multivariate DiD model including 2 indicator variables, one of which indicated a treatment status (coded 0 for the control group and 1 for the treatment group) and the other indicated the post-Part D period (coded 0 for the pre-Part D period and 1 for the post-Part D period), as well as the interaction between these 2 variables. This interaction term was a variable of interest, capturing the effect of Part D on each outcome (i.e. how the change in each outcome between pre- and post-Part D periods in the treatment group differed from that in the control group). Funding source: No funding was received to conduct the study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	No allocation concealment
Were baseline outcome measurements similar?	High risk	There were differences at baseline (Table 2).
Were baseline characteristics similar?	Low risk	Adjustment by including age, gender, comorbidities, race, marital status, body mass index education, census region, poverty indicator, and self-reported health status (page 7)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported

Park 2017 *(Continued)*

Selective reporting (reporting bias)	Low risk	Outcomes reported were the same as those in the Methods section.
Was the study adequately protected against contamination?	Low risk	The comparison was between eligible elderly and non-eligible non-elderly populations, so the risk of contamination was low.
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identified

Pimentel 2015

Study characteristics	
Methods	ITS
Participants	The final sample size was 18,599 nursing home residents who were admitted to 1112 nursing homes.
Interventions	Medicare Part D
Outcomes	1) monthly proportion of nursing home residents receiving 1 prescription of interest and 2) monthly proportion of resident-therapy days covered
Notes	The analysis was a segmented Poisson regression of interrupted time-series. Funding source: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	Outcomes reported were the same as those in the Methods section.
Was the intervention independent of other changes?	Unclear risk	Not mentioned
Was the shape of the intervention effect prespecified?	Low risk	The point of analysis seemed to be the point of intervention and the direction of the effect was established (in this case, a decrease in the use of a drug not included in the policy).
Was the intervention unlikely to affect data collection?	Low risk	Routinely collected data unlikely to affect data collection
Was knowledge of the allocated interventions ade-	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily

Pimentel 2015 *(Continued)*

quately prevented during the study?		claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identified

Polinski 2012

Study characteristics	
Methods	ITS
Participants	Elderly (beneficiaries of Medicare) without prior drug insurance
Interventions	Medicare Part D
Outcomes	Drug use: (1) Antipsychotic medication (APM) utilisation Drug expenditures: (2) APM out-of-pocket costs
Notes	Funding sources: National Institute on Aging T32 AG000158 (Dr. Polinski); National Institute of Mental Health R01 5U01MH079175-02 (Dr. Schneeweiss)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	Outcomes presented in the Methods section were the same as those presented in the Results section.
Was the intervention independent of other changes?	Unclear risk	Not mention of other changes
Was the shape of the intervention effect prespecified?	Low risk	Medicare Part D's 2006 implementation was associated with both a 6% to 19% overall increase in drug utilisation and a 13% to 18% decrease in out-of-pocket costs (Introduction 1st sentence).
Was the intervention unlikely to affect data collection?	Low risk	Routinely collected objective data
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in ITS studies come from administrative datasets, primarily claims transactions, and therefore are not easily altered by data processors (including researchers and data analysts).
Other bias	Unclear risk	Because authors used retail pharmacy data, they could not capture prescription fills that took place outside a given retail pharmacy chain.

Saverno 2011

Study characteristics	
Methods	CITS
Participants	Arizona's senior dual eligible population (medical and pharmacy claims from the Medicaid programme from January 1, 2005 to December 31, 2007 were used in the analysis)
Interventions	Medicare Part D
Outcomes	Drug use (over-the-counter (OTC) medications, benzodiazepines, total prescription utilisation, generic medication utilisation) and healthcare utilisation (physician visits and hospitalisations)
Notes	A quasi-experimental time-series study design with a comparison group was used. The statistical approach was GEE using a propensity score-matching for the groups. The effect estimates were presented on a log scale and we were not able to obtain absolute or relative effect estimates. Included but not used in the quantitative analysis Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	No allocation concealment
Were baseline outcome measurements similar?	Low risk	No differences in baseline outcomes
Were baseline characteristics similar?	Low risk	No differences in baseline characteristics
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	Outcomes reported were the same as those in the Methods section.
Was the study adequately protected against contamination?	Low risk	The main comparison was between Medicaid beneficiaries between the ages of 66 and 80 (eligibles for the policy) and those between 50 and 62 (non-eligibles for the policy) which makes contamination unlikely.
Was the intervention independent of other changes?	Unclear risk	There was mention of other policy changes at the state level (Arizona) that could have influenced the outcomes assessed.
Was the shape of the intervention effect prespecified?	Low risk	Direction of effect established
Was the intervention unlikely to affect data collection?	Low risk	Routinely collected data unlikely affecting data collection

Saverno 2011 *(Continued)*

Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identified

Schneeweiss 2009

Study characteristics	
Methods	ITS
Participants	Seniors who previously lacked drug coverage
Interventions	Medicare Part D
Outcomes	Drug use: (1) use of selected essential drugs Drug expenditure (1) out-of-pocket spending of selected essential drugs (statins, clopidogrel, proton pump inhibitors and warfarin)
Notes	Funding sources: The study was funded by grants from the Robert Wood Johnson Foundation's Changes in Health Care Financing and Organization (HCFO) Initiative and from the National Institute of MentalHealth (Grant no. R01-MH079175). WilliamShrank is supported by a career development award from the NationalHeart, Lung, and Blood Institute (Grant no. K23HL090505-01).

Risk of bias

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Not reported
Selective reporting (reporting bias)	Low risk	Outcomes presented in the Methods section were the same as those presented in the Results section.
Was the intervention independent of other changes?	Unclear risk	It was not clear if the enactment of Medicare Part D was the only policy change in this area starting in 2006.
Was the shape of the intervention effect prespecified?	Low risk	Studies on the overall effect of Medicare Part D on seniors' drug use and out-of-pocket spending have suggested that the policy resulted in a 5.9% to 12.8% increase in prescription drug use and a 13.1% to 15.6% decrease in out-of-pocket spending (Page w306, 1st column).
Was the intervention unlikely to affect data collection?	Low risk	Routinely collected prescription data from pharmacy chains databases
Was knowledge of the allocated interventions ade-	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in ITS studies come from administrative datasets, primarily

Schneeweiss 2009 *(Continued)*

quately prevented during the study?		claims transactions, and therefore are not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	Although authors used only data from seniors' dispensing prescriptions in only 3 pharmacy chains, participants lived in 49 states in the USA (broad geographical representation).

Shrank 2008

Study characteristics	
Methods	ITS
Participants	A representative sample of seniors dually eligible for Medicare and Medicaid dispensing prescriptions at a large pharmacy chain operating in 34 states in the USA
Interventions	Medicare Part D
Outcomes	Drug use: (1) medication use (selected essential drugs: statins, proton pump inhibitors, warfarin, clopidogrel and benzodiazepines) (2) medication switching Drug expenditures: (3) out-of-pocket spending
Notes	Funding source: The study was funded by a grant from the Robert Wood Johnson Foundation Changes in Health Care Financing and Organization (HCFO) Initiative and from the National Institute of Mental Health (RO1-MH079175). Dr. Shrank is supported by a career development award from the National Heart, Lung, and Blood Institute (K23HL090505-01).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	Outcomes presented in the Methods section were the same as those presented in the Results section.
Was the intervention independent of other changes?	Unclear risk	This population (dual-eligibles) was exposed to a number of choices for insurance at the time of the policy change, so it was unclear if other policies could have affected the outcomes.
Was the shape of the intervention effect prespecified?	Unclear risk	"little is known about whether the changes in coverage affected the use of essential medications or patients' out-of-pocket spending" (page 2305).
Was the intervention unlikely to affect data collection?	Low risk	Routinely collected data

Shrank 2008 *(Continued)*

Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in ITS studies come from administrative datasets, primarily claims transactions, and therefore are not easily altered by data processors (including researchers and data analysts).
Other bias	Unclear risk	Not sure how representative was the population dispensing medications in this single pharmacy chain from the total of dually eligible seniors

Tan 2021

Study characteristics	
Methods	ITS
Participants	People at risk of HIV
Interventions	Ontario expansion of public drug coverage (OHIP+)
Outcomes	Drug use (number of PrEP users)
Notes	Authors fitted an interventional autoregressive integrated moving average (ARIMA) model to the monthly number of individuals receiving PrEP in Ontario. Authors selected model parameters based on the residual autocorrelation function (ACF), partial autocorrelation function (PACF), and inverse autocorrelation function (IACF) correlograms. Final model selection was confirmed using the autocorrelation plots, the Ljung-Box chi-square test for white noise, and r-square estimate of fit. They added intervention functions to the model at each intervention time point of interest. A ramp intervention function was used to test for gradual changes in trends and a step intervention function was used to test for immediate changes, based on visual inspection of the time series. Although it was possible to obtain a change in level estimate due to the quality of the graph presented in the paper, we were unable to obtain a last pre-intervention data point and therefore could not get the relative effect. Included but not used in the quantitative analysis Funding sources: This work was made possible by a grant from the Ontario HIV Treatment Network. DHST is supported by a New Investigator Award from the Canadian Institutes of Health Research and the Ontario HIV Treatment Network.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	Outcomes reported were the same as those in the Methods section.
Was the intervention independent of other changes?	High risk	There was a number of policy changes that could have affected the effectiveness of the policy.
Was the shape of the intervention effect prespecified?	Low risk	The direction of the effect was established and the point of analysis was the point of intervention.

Tan 2021 *(Continued)*

Was the intervention unlikely to affect data collection?	Low risk	Routinely collected data from pharmacy claims unlikely to affect data collection
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identified

Tang 2019

Study characteristics	
Methods	CBA
Participants	Data for this study were extracted from Medical Expenditures Panel Survey (MEPS) over a 19-year period from 1997 to 2015 (the earliest and nearest year with complete and comparable information).
Interventions	Medicare Part D
Outcomes	Expenditures for prescribed medications and office-based medical visits and the sources of payment for these goods and services
Notes	For the relevant outcome (drug expenditure) we were unable to compute effect estimates from the data presented in the paper. Included in the review but not used in the quantitative analysis Funding sources: WT acknowledges the support from Chinese National Natural Science Foundation (Grant No. 71603278) and the support from the China Scholarship Council for her postdoctoral fellowship (Grant No. 201707060001) in University of Arizona. FK acknowledges the support from the College Students Innovation Project for the R&D of Novel Drugs, National Fund for Fostering Talents of Basic Science (Grant No. J1310032/201810316074G).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	No allocation concealment
Were baseline outcome measurements similar?	High risk	Although data were not formally presented in Table 3, OOP for the different sources of insurance were different at baseline (before the intervention).
Were baseline characteristics similar?	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported

Tang 2019 *(Continued)*

Selective reporting (reporting bias)	Low risk	Outcomes reported were the same as those in the Methods section.
Was the study adequately protected against contamination?	Unclear risk	The different groups (eligible or ineligible for the policy) were derived indirectly from the sources for their drug payments.
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identified

Yin 2008

Study characteristics	
Methods	ITS
Participants	A 5% random sample of unique pharmacy customers (Medicare eligible) who filled at least 1 prescription during both the 2005 and the 2006 calendar years through the Walgreens pharmacy chain, whether at a retail store or by mail order
Interventions	Medicare Part D (the control group was people aged 60 to 63 years)
Outcomes	Drug use: (1) prescription utilisation (monthly average) Drug expenditures: (2) out-of-pocket expenditures (monthly average out-of-pocket prescription costs)
Notes	Although there were time-series data, it was not possible to re-analyse as an ITS (the control group was non-equivalent) and the best estimate of the effect size was from a CBA analysis. Funding sources: Dr. Zhang was supported in part by a grant from Merck & Co. Dr. Meltzer is supported by the Centers for Disease Control and Prevention Chicago Center of Excellence in Health Promotion Economics and the Merck Foundation through the University of Chicago Program for Pharmaceutical Policy Research. Dr. Alexander is supported by career development awards from the Agency for Healthcare Research and Quality (K08 HS15699-01A1) and the Robert Wood Johnson Physician Faculty Scholars Program.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Incomplete outcome data (attrition bias) All outcomes	Low risk	Seemed to be minimal follow-up loss
Selective reporting (reporting bias)	Low risk	Did not seem to be failing to report other relevant outcomes

Yin 2008 *(Continued)*

Was the intervention independent of other changes?	Unclear risk	In the 'Part D ineligible' group, statistically significant unadjusted changes in drug utilisation and expenditures were observed that were considered to be independent of the Part D drug benefit.
Was the shape of the intervention effect prespecified?	Low risk	In the introduction, it was mentioned that "...these reports and others point to positive effects of the Part D benefit..." and that "A 2004 projection suggested that the Medicare drug benefit would reduce average out-of-pocket expenditures..."
Was the intervention unlikely to affect data collection?	Low risk	Routinely collected data
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in ITS studies come from administrative datasets, primarily claims transactions, and therefore are not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identifiable

Zhang 2008

Study characteristics	
Methods	CBA
Participants	5% random sample of unique pharmacy customers who filled at least one prescription between January 1, 2005 and December 31, 2006 at any retail or mail-order member of the pharmacy chain
Interventions	Medicare Part D
Outcomes	Generic drug use
Notes	A differences-in-differences strategy was used (multivariate logistic regression). Funding sources: Dr. Zhang was supported in part by a grant from Merck, Dr. Yin is a Robert Wood Johnson Foundation Health Policy Scholar, and Dr. Alexander has career development awards from the Agency for Healthcare Research and Quality (K08HS15699–01A1) and the Robert Wood Johnson Physician Faculty Scholars Program.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	No allocation concealment
Were baseline outcome measurements similar?	High risk	Differences between groups at baseline (Table 2) but no statistical test presented
Were baseline characteristics similar?	Low risk	Adjusted by variables potentially affecting drug consumption (Table 1)

Zhang 2008 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	Outcomes reported were the same as those in the Methods section.
Was the study adequately protected against contamination?	Low risk	The main comparison was between a 67-79 years intervention group and a 60-63 years control group (non-eligible for enrolment into the intervention). So the risk of contamination was low.
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identified

Zhang 2009

Study characteristics	
Methods	CITS
Participants	A random sample of Medicare beneficiaries (enrolled in Medicare Advantage plans offered by a large Pennsylvania insurer)
Interventions	Medicare Part D (3 intervention groups with no or limited [quarterly caps of USD 150 or USD 350] prior coverage that obtained Part D benefits in 2006 and a comparison group with stable drug coverage from 2004 to 2007)
Outcomes	Drug use (quarterly averages of prescription per month per patient): (1) lipid-lowering medications (2) antidiabetic medications Drug expenditures: (1) expenditures for drugs (insurance payments plus co-payments) and non-drug medical care per member per month
Notes	Funding sources: this work was supported by grants from the National Center for Research Resources, a component of the National Institutes of Health (NIH); the NIH Roadmap for Medical Research (KL2-RR024154-03, to Dr. Donohue); and the Alfred P. Sloan Foundation (to Dr. Newhouse).

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	No allocation concealment

Zhang 2009 *(Continued)*

Were baseline outcome measurements similar?	Low risk	The groups compared were similar at baseline (Table 1).
Were baseline characteristics similar?	Unclear risk	Although the groups were reasonably similar at baseline, the no-cap group was younger and more likely to be male (Table 1).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The amount of missing data was not reported.
Selective reporting (reporting bias)	Low risk	Outcomes presented in the Methods section were the same as those presented in the Results section.
Was the study adequately protected against contamination?	Unclear risk	Not clearly reported
Was the intervention independent of other changes?	Unclear risk	It was unclear if other policies in the area were being implemented during those years in Pennsylvania.
Was the shape of the intervention effect prespecified?	Low risk	In the introduction, the rationale was established: better access to medications (then increase in drug expenditures) and potential saving from non-drug expenditures (because of better management of conditions) (Page 53, 1st column).
Was the intervention unlikely to affect data collection?	Low risk	Routinely collected data
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Objective outcomes and policy embedded in the health systems (not clearly labelled as intervention)
Other bias	Low risk	None identifiable

Zhang 2010a

Study characteristics	
Methods	CITS
Participants	A random sample of 36,858 members who were continuously enrolled in the Medicare Advantage plans from 1 January 2004, through 31 December 2007
Interventions	Medicare Part D (3 intervention groups with no or limited [quarterly caps of USD 150 or USD 350] prior coverage that obtained Part D benefits in 2006 and a comparison group with stable drug coverage from 2004 to 2007)
Outcomes	Drug use: (1) proportion of the population who filled at least 1 antibiotic prescription (2) likelihood of use of antibiotics

Zhang 2010a *(Continued)*

Notes	Although there were time-series data, it was not possible to re-analyse as a CITS and the best estimate of the effect size was from a CBA analysis. Funding sources: Dr Zhang was supported by a challenge grant 1RC1MH088510-01, grant 1R01HS018657-01 from the Agency for Healthcare Research and Quality (AHRQ), RAND-University of Pittsburgh Health Institute, and the University of Pittsburgh's Graduate School of Public Health Computational and Systems Models in Public Health Pilot Program. Dr Lee was supported by the National Institutes of Health National Institute of General Medical Sciences Models of Infectious Disease Agent Study (MIDAS) grant 1U54GM088491-0109, and the Pennsylvania Department of Health Center of Excellence in Prevention and Control of Antibiotic-Resistant Bacterial Infections. Dr Donohue was supported by 1R01HS017695 from the AHRQ and 1R34 MH082682 from the National Institute of Mental Health.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-randomised comparisons
Allocation concealment (selection bias)	High risk	Non-randomised comparisons
Were baseline outcome measurements similar?	High risk	Table 2, pre-Part D figures significantly different between 'no insurance' and 'no cap' group
Were baseline characteristics similar?	High risk	The comparison group was slightly more likely to be male and younger than the intervention groups.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was unclear if there were missing data from the databases.
Selective reporting (reporting bias)	Low risk	Outcomes presented in the Methods section were the same as those presented in the Results section.
Was the study adequately protected against contamination?	Low risk	It was unclear to what extent patients from different groups were included in Part D (we assumed that the 'no coverage' group would be opting into the new policy and the 'no cap' group would stay with their previous insurance benefit).
Was the intervention independent of other changes?	High risk	There was the possibility that other co-interventions were implemented at the same time as Part D (e.g. additional coverage for generic drugs for those in the no coverage group).
Was the shape of the intervention effect prespecified?	Low risk	The expected direction of the effect was established: "one might expect use of antibiotics to be somewhat less sensitive to out-of-pocket price changes because antibiotics are for short-term use and to treat specific infections that could worsen fairly rapidly without adequate antimicrobial treatment".
Was the intervention unlikely to affect data collection?	Low risk	Routinely collected data
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).

Zhang 2010a *(Continued)*

Other bias	Unclear risk	During the pre-Part D period, some patients could receive discounts from the network pharmacies (co-intervention), which could increase the use of antibiotics at that time (page 1313 [Discussion section]).

Zhang 2010b

Study characteristics	
Methods	CITS
Participants	A 40% random sample of 36,858 individuals continuously enrolled in Medicare Advantage plans offered by a Pennsylvania insurer between 1 January 2004, and 31 December 2007
Interventions	Medicare Part D (3 intervention groups with no or limited [quarterly caps of USD 150 or USD 350] prior coverage that obtained Part D benefits in 2006 and a comparison group with stable drug coverage from 2004 to 2007)
Outcomes	Drug expenditures: (1) out-of-pocket pharmacy spending
Notes	Although there were time-series data, it was not possible to re-analyse as a CITS and the best estimate of the effect size was from a CBA analysis. Funding sources: The National Center for Research Resources, a component of the National Institutes of Health (NIH) , NIH Roadmap for Medical Research (KL2-RR024154-01 to J.M.D.); the University of Pittsburgh's Graduate School of Public Health Computational and Systems Models in Public Health Pilot Program (Y.Z.); and the Alfred P. Sloan Foundation (J.P.N.)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	No allocation concealment
Were baseline outcome measurements similar?	Unclear risk	Not formally reported but they seemed to be similar (from Figure 1 in the study).
Were baseline characteristics similar?	High risk	There were some relevant differences at baseline "...members in the comparison group were younger and less likely to be female compared with those in the three intervention groups (P < 0.001)" "fewer members were diagnosed with the earlier three illnesses (hypertension, hyperlipidaemia and diabetes) in the no-coverage group (P < 0.001)".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	Outcomes presented in the Methods section were the same as those presented in the Results section.

Zhang 2010b *(Continued)*

Was the study adequately protected against contamination?	Unclear risk	Not clearly reported
Was the intervention independent of other changes?	High risk	There was the possibility that other co-interventions were implemented at the same time as Part D (e.g. additional coverage for generic drugs for those in the no coverage group).
Was the shape of the intervention effect prespecified?	Low risk	"A primary goal of the Medicare drug benefit (Part D), implemented in 2006, was to protect older adults from catastrophic drug spending" (first sentence in the main text of the paper).
Was the intervention unlikely to affect data collection?	Low risk	Routinely collected data
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identifiable

Zhang 2011

Study characteristics	
Methods	CITS
Participants	A 40% random sample of 36,858 individuals continuously enrolled in Medicare Advantage plans offered by a Pennsylvania insurer between January 2003 and December 2007
Interventions	Medicare Part D (3 intervention groups with no or limited [quarterly caps of USD 150 or USD 350] prior coverage that obtained Part D benefits in 2006 and a comparison group with stable drug coverage from 2004 to 2007)
Outcomes	Drug use: (1) proportion of members in each group who ever filled any antihypertensive medications as well as drugs in each subclass, including beta blockers, diuretics, ACEs, ARBs, and calcium channel blockers each year between 2004 and 2007
Notes	Although there were time-series data, it was not possible to re-analyse as a CITS and the best estimate of the effect size was from a CBA analysis. Funding sources: This publication was supported by the National Center for Research Resources, National Institutes of Health, NIH Roadmap for Medical Research (grant no. KL2-RR024154-01), and the University of Pittsburgh's Graduate School of Public Health Computational and Systems Models in Public Health Pilot Program. During the study period, Dr. Zhang was also supported by NIMH RC1MH088510 and AHRQ R01HS018657.
Risk of bias	
Bias	**Authors' judgement** **Support for judgement**

Zhang 2011 *(Continued)*

Random sequence generation (selection bias)	High risk	Non-randomised comparisons
Allocation concealment (selection bias)	High risk	Non-randomised comparisons
Were baseline outcome measurements similar?	High risk	There were important differences in the use of all the types of antihypertensive medications previous to the policy implementation between the 'no coverage' (intervention) and 'no cap' (comparison) groups (Table 2, page 191).
Were baseline characteristics similar?	High risk	The comparison group was younger, although prospective risk scores were similar across the groups. Members in the 'no coverage' group were more likely to have emergency department visits but had a fewer number of outpatient visits per year.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was unclear if there were missing data from databases.
Selective reporting (reporting bias)	Low risk	Outcomes presented in the Methods section were the same as those presented in the Results section.
Was the study adequately protected against contamination?	Unclear risk	The level of incorporation of the patients from different groups to Part D was unclear (we assumed that the no coverage group would be opting into the new policy and the no cap would stay with their previous insurance benefit).
Was the intervention independent of other changes?	Unclear risk	It was unclear if there were some other policies implemented at the time in the US (this was not explicitly mentioned).
Was the shape of the intervention effect prespecified?	Low risk	The shape and direction of the effect was at some extent established: "Medicare Part D could affect not only the overall use of antihypertensives but also the types of medications used" "Did these beneficiaries increase use of antihypertensive medications overall?"
Was the intervention unlikely to affect data collection?	Low risk	Routinely data were used, so it was unlikely that it affected data collection,
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identifiable

Zimmer 2015

Study characteristics	
Methods	CBA
Participants	Data from the Medical Expenditures Panel Survey (MEPS) including 36,141 unique seniors
Interventions	Medicare Part D

Zimmer 2015 *(Continued)*

Outcomes	Drug expenditures (total annual spending on prescription drugs, the proportion of annual drug expenses paid for out-of-pocket), and drug use (the total number of annual prescribed medicines (including refills), the total number of annual unique therapeutic classes for which medicines were prescribed, the total number of annual prescribed medicines (including refills) for seven medical conditions that typically require drug-intensive therapy)
Notes	The estimation approach compared drug demand in the years prior to Part D (2000-2004) to the three years after Part D (2006-2008) using a DiD approach with 3 different distributional shapes depending on the outcomes (γ-based GLM with log link for total annual spending, binomial-based GLM with logit link for OOP, and zero-inflated negative binomial (ZINB) for drug use outcomes). Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-randomised comparison
Allocation concealment (selection bias)	High risk	No allocation concealment
Were baseline outcome measurements similar?	Unclear risk	Some differences at baseline between groups but no statistical test provided
Were baseline characteristics similar?	Low risk	No differences in baseline characteristics
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	Outcomes reported were the same as those in the Methods section.
Was the study adequately protected against contamination?	Low risk	The comparison was between 'recently elderly' (ages 65-74) and near-elderly (ages 56-64) subjects, so the risk of contamination was low because near-elderly were not eligible for the policy.
Was knowledge of the allocated interventions adequately prevented during the study?	Low risk	Knowledge of the intervention (the policy) is an essential part of policy implementation. Data in this study came from administrative datasets, primarily claims transactions, and therefore were not easily altered by data processors (including researchers and data analysts).
Other bias	Low risk	None identified

ACE = Angiotensin-Converting Enzyme
ACA = Affordable Care Act
ACF = Autocorrelation function
ADLs = Activities of Daily Living
APM = AntiPsychotic Medication
ARB = Angiotensin receptor blockers
ARIMA = Autoregressive integrated moving average
CBA = Controlled before-after study
CDC = Centers for Disease Control and Prevention
CESD = Center for Epidemiologic Studies scale for Depression
CITS = Controlled interrupted time series study

DDD = Defined Daily Dose
DDD= Differences-in-differences-in-differences
DiD = Differences-in-differences
D-RD = Difference in the regression discontinuity
ED = Emergency Department
GEE = Generalized Estimating Equation
GLM = General Linear Model/Modeling
HBP = High Blood Pressure
HIV = Human Inmunodeficiency Virus
HMO = Health Maintenance Organization
HRS = Health and Retirement Study
IACF = Inverse autocorrelation function
ITS = Interrupted time series study
IV = Instrumental variable
MCBS = Medicare Current Beneficiary Survey
MCO = Managed Care Organization
MEPS = Medical Expenditure Panel Survey
MMA = Medicare Modernization Act
NIH = National Institutes of Health
NHIS = National Health Interview Survey
OHIP+ = Ontario expansion of public drug coverage
OLS = Ordinary least squares
OOP = Out-of-Pocket payments
OOPE = Out of Pocket expenditures
OTC = Over the Counter
PACF = Partial autocorrelation function
PrEP = Pre-exposure prophylaxis
SAS/ETS = Statistical Analysis System Econometrics and Time Series Analysis
SDUD = State Drug Utilization Database
SMD = Standardised monthly doses
WHIS = Women's Interagency HIV Study
ZINB = Zero-inflated negative binomial

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alexander 2018	Non-eligible study design (uncontrolled before-and-after)
Allin 2009	Non-eligible study design (cross-sectional)
Alpert 2016	Non-eligible intervention (intervention in the sense that this study assessed the anticipatory effect of the policy taking the announcement of the policy (2003) as the point of implementation)
Anonymous 2008	Duplicate
Assayag 2011	Non-eligible study design (retrospective matched cohort design)
Atherly 2002	Non-eligible intervention (supplemental Medicare insurance, non-drug specific)
Azagra 2010	Non-eligible study design
Baik 2012	Non-eligible intervention (caps & co-payments)
Baker 2020	Non-eligible study design
Bakk 2015	Non-eligible outcomes

Study	Reason for exclusion
Battacharya 2003	Non-eligible intervention (different types of health insurance). It assessed the relationship between health insurance (it is not possible to 'isolate' the relationship of only drug insurance) and mortality in HIV patients using modelling based on administrative data (so this was excluded because the independent variable was not drug insurance).
Bertoldi 2019	Non-eligible intervention (changes in reimbursement, reference list and reference price)
Blais 2003	Non-eligible intervention (cost-sharing policy)
Blais 2012	Non-eligible study design (matched cohort design)
Blais 2016	Non-eligible intervention (co-payment policy)
Blumberg 2015	Non-eligible outcomes
Bonakdar 2014	Non-eligible outcomes
Briesacher 2011	Non-eligible study design (ITS but with only 2 data points after the intervention)
Brill 2007	Non-eligible study design (narrative overview)
Chakravarty 2015	Non-eligible outcomes (prescription drug coverage and cost-related problems in access)
Chakravarty 2020	Non-eligible outcomes (disparities in access to prescription drugs and physicians' services as reported by patients)
Chen 2009	Non-eligible study design (uncontrolled before-and-after)
Chen 2009a	Non-eligible study design (uncontrolled before-and-after)
Chen 2011	Non-eligible study design (uncontrolled before-and-after)
Chen 2014	Non-eligible outcomes (use of a drug excluded from the policy)
Cheng 2012b	Non-eligible study design (uncontrolled before-and-after)
Cheng 2012c	Non-eligible study design (uncontrolled before-and-after)
Cheng 2012d	Non-eligible study design (uncontrolled BA with 1 point before and 2 after the intervention)
Clayton 2015	Non-eligible intervention
Cohen 2012	Non-eligible study design (a commentary of other article)
Crossley 2000	Non-eligible intervention (co-payments)
Crutchfield 2006	Non-eligible study design (a commentary)
Curtis 2004	Non-eligible study design (cross-sectional)
Dall 2013	Non-eligible study design (a simulation study with a mix of primary and secondary data)
Després 2014	Duplicate (non-eligible study design: retrospective matched cohort)
Diao 2019	Non-eligible intervention (policy regulating which drugs are reimbursed)

Study	Reason for exclusion
Dismuke 2013	Non-eligible study design (an editorial)
Domino 2010	Non-eligible study design (uncontrolled before-and-after)
Donohue 2012	Non-eligible intervention (caps & co-payments changes of Medicare Part D)
Donohue 2014	Non-eligible study design (editorial)
Dormuth 2011	Non-eligible intervention (restriction on reimbursed drug)
Doshi 2004	Non-eligible study design (a cross-sectional analysis)
Duggan 2008a	Non-eligible study design (narrative review)
Duggan 2010	Non-eligible outcomes (focused on different aspects of the drug market such as prices and using different models for estimating before-and-after differences)
Duggan 2011	Non-eligible outcomes (prices)
Duru 2010	Non-eligible intervention (coverage decisions)
Engelhardt 2016	Non-eligible study design (uncontrolled before-and-after)
Evans-Molina 2007	Non-eligible study design (only comparison after policy implementation)
Fryatt 1994	Non-eligible intervention (effect of co-payments)
Fu 2010	Non-eligible study design (CBA with only 1 intervention and 1 control site)
Gianfrancesco 1994	Non-eligible study design (uncontrolled before-and-after)
Golden 2010	Non-eligible study design (editorial)
Grootendorst 1997	Non-eligible study design (cross-sectional study)
Grootendorst 2015	Non-eligible study design (an editorial)
Hanley 2008	Non-eligible study design (uncontrolled before-and-after [2001 to 2004] design)
Hanley 2011	Non-eligible study design (see comment on Hanley 2008)
Hanlon 2013	Non-eligible study design (uncontrolled before-and-after)
Havrda 2005	Non-eligible study design (uncontrolled before-and-after)
Hoadley 2012	Non-eligible study design (cross-sectional)
Hu 2017	Non-eligible outcome (physician prescribing)
Hudson 2009	Non-eligible study design (a findings brief of a number of studies already included in the review)
Hudson 2010	Non-eligible study design (uncontrolled before-and-after)
Huh 2008	Non-eligible study design (the relationship between drug insurance (coverage) and drug use is modelled using multiple regression models (the sample is cross-sectional))

Study	Reason for exclusion
Huntington 2016	Non-eligible study design (an editorial)
Huskamp 2009	Non-eligible study design (case-control or retrospective cohort)
Huskamp 2013	Non-eligible intervention (a co-payment intervention within Medicare Part D)
Hussein 2016	Non-eligible outcomes (disparities in adherence to medications)
Joyce 2009	Non-eligible study design (non-equivalent comparison: other non-Part D plans)
Kanters 2012	Non-eligible intervention (reimbursement decisions)
Kennedy 2011	Non-eligible study design (case-control)
Ketcham 2008b	Non-eligible intervention (preferred drug lists: a kind of formularies)
Khan 2007	Non-eligible study design (uncontrolled before-and-after)
Khan 2010	Non-eligible study design (uncontrolled before-and-after)
King 2009	Non-eligible intervention (health insurance)
Lai 2014	Not enough information
Lakdawalla 2007	Non-eligible study design
Lee 2014	Non-eligible intervention (co-payments within a drug insurance scheme)
Levine 2013	Non-eligible outcomes
Li 2012	Non-eligible intervention (Medicare Part D coverage gap: co-payment intervention)
Lind 2018	Non-eligible study design (uncontrolled before-and-after)
Liu 2004	Non-eligible intervention (cost-sharing policy)
Ma 2019	Non-eligible study design (a cross-sectional study assessing the relationship of different variables (including the enrolment in a drug benefit programme) on hypertension treatment adherence)
Maclean 2019	Non-eligible intervention (Medicaid expansion (it is more than drug insurance and the effects on drugs use seem to be mediated through reducing co-payments))
Madden 2008	Non-eligible study design (uncontrolled before-and-after)
Mahmoudi 2014	Non-eligible outcome measures (disparities in relevant outcomes)
Mahmoudi 2015	Non-eligible outcome measures (disparities in relevant outcomes)
Mahmoudi 2016	Non-eligible outcomes (the dependent variable assessed was disparities in drug coverage among different racial groups (not a focus on the effect of drug coverage on drug use or expenditures))
Majercak 2013	Non-eligible study design (uncontrolled before-and-after)
Millett 2010	Non-eligible study design (uncontrolled before-and-after). The estimates were presented for each subgroup but no comparison among them

Study	Reason for exclusion
Morgan 2006	Non-eligible study design (narrative review)
Morgan 2017	Non-eligible study design (narrative review with some secondary data)
Moulton 2017	Non-eligible outcome (self-employment)
Nair 2010	Non-eligible study design (uncontrolled before-and-after)
Nattinger 2017	Non-eligible study design (a CBA comparing different socioeconomic groups before and after Part D, but no control group without the intervention)
Neuman 2007	Non-eligible study design (survey)
Neuman 2009	Non-eligible study design (narrative review)
Pacula 2015	Non-eligible outcomes (indirect effects of increasing the availability of opioids for the elderly through Medicare Part D on the use and abuse (and mortality) by the non-beneficiaries of Medicare Part D)
Patel 2006	Non-eligible study design (simulation study)
Peron 2013	Non-eligible outcome measure (appropriateness of antihypertensive prescribing)
Pezalla 2007	Without enough data available (only title available)
Pezzin 2015	Non-eligible study design (single cohort comparing different socioeconomic groups)
Polinski 2012b	Non-eligible study design (methodological approach (propensity score) to assess the coverage gap of Medicare Part D)
Powell 2017	Non-eligible study design (uncontrolled before-and-after, control group not clearly identified in the analysis)
Rubin 2000	Non-eligible study design (commentary)
Rudholm 2005	Non-eligible intervention (co-payments)
Safran 2010	Non-eligible study design (uncontrolled before-and-after)
Sarma 2007	Non-eligible study design (survey)
Semilla 2015	Non-eligible study design (micro-simulation study)
Sepulveda 2011	Non-eligible study design (uncontrolled before-and-after)
Stefanacci 2004	Non-eligible study design (commentary)
Stevenson 2014	Non-eligible study design (uncontrolled before-and-after)
Stuart 2011	Non-eligible study design (uncontrolled before-and-after)
Stuart 2013	Non-eligible intervention (change of phase within Medicare Part D that is a change in reimbursement policy)

Study	Reason for exclusion
Sun 2007	Non-eligible intervention (change of phase within Medicare Part D that is a change in reimbursement policy)
Tang 2014	Non-eligible study design (cross-sectional)
Tarrants 2010	Insufficient information
Urmie 2011	Non-eligible study design (uncontrolled before-and-after)
Vaidya 2012	Non-eligible study design (uncontrolled before-and-after study; control group not clearly identifiable in the analysis)
Wang 2012	Non-eligible study design (ITS with only 2 data points before the intervention)
Wang 2014	Non-eligible outcome measures (disparities in relevant outcomes)
Wang 2015	Non-eligible study design (an ITS study with only 2 pre-intervention measures)
Wang 2019	Non-eligible intervention (the intervention (Full Coverage of Essential Medicines) is a policy regulating the co-payment of a specific list of essential drugs)
Williams 2004	Non-eligible study design (an editorial/commentary)
Winegar 2009	Non-eligible study design (CBA with only 1 intervention and 1 control site). Non-eligible outcomes
Young 2014	Non-eligible intervention
Zeng 2013	Non-eligible intervention (it assessed the effect of a change in coverage of Part D)
Zhang 2010c	Non-eligible study design (CBA with only 1 intervention and 1 control site)
Zhang 2013	Non-eligible intervention (Medicare Part D coverage gap is a change in co-payment)
Zivin 2009	Non-eligible study design (ITS with only 3 total data points)

BA = Before-after study
CBA = Controlled before-after study
HIV = human immunodeficiency virus
ITS = Interrupted time series study

Characteristics of studies awaiting classification *[ordered by study ID]*

Americo 2020

Methods	Unclear from the abstract
Participants	Individuals aged 40 years or more with diabetes
Interventions	A large-scale subsidising program of prescription drugs
Outcomes	Mortality, hospitalisation rates
Notes	

Sabety 2021

Methods	CBA study
Participants	Elderly Medicare-eligible adults
Interventions	Prescription drug coverage under Medicare Part D
Outcomes	Opioids prescriptions, patient care-seeking for pain, pain diagnoses
Notes	Difference-in-differences design using a regression discontinuity approach

ADDITIONAL TABLES

Table 1. Ways in which different policies regarding who provides drug insurance might affect outcomes

	Universal coverage	Equitable access	Catastrophic payments	Cost containment	Availability of essential drugs
Public drug insurance	Governments might have incentives to provide universal coverage.	Governments might have incentives to provide equitable access.	Governments might have incentives to protect people from catastrophic payments.	Public drug insurance might raise public (government) expenditures.	NA*
Private for-profit drug insurance	The key incentive of for-profit insurance schemes is profit generation. For-profit schemes might not have incentives to provide universal coverage and are unlikely to provide universal coverage unless subsidised or mandated by the government.	For-profit schemes might not have incentives to provide equitable access.	For-profit schemes might not have incentives to provide protection against catastrophic payments.	For-profit schemes might be motivated to decrease their own costs. However, this might shift costs from the scheme to the insured or the government.	NA
Private not-for-profit drug insurance	Private not-for-profit drug insurance schemes are unlikely to provide universal coverage unless subsidised or mandated by the government.	Private not-for-profit drug insurance schemes might be motivated to provide access to vulnerable populations (e.g. charitable organisations).	Private not-for-profit drug insurance schemes might be motivated to provide protection against catastrophic payments.	Private not-for-profit drug insurance schemes should be as concerned with cost-containment as any other scheme.	NA

*NA = not applicable; i.e. no obvious way that the outcome might be affected

Table 2. Ways in which different policies regarding who receives drug insurance might affect outcomes

	Universal coverage	Equitable access	Catastrophic payments	Cost containment	Availability of essential drugs
Universal coverage	Provided this policy is implemented, it would ensure universal coverage. However, limited resources or implementation might result in some people not being covered.	Universal coverage might guarantee equitable access.	Universal coverage might protect against catastrophic payments, but this would depend on what is covered.	Public spending on drugs might increase. At the same time, drug costs might be reduced due to pooling funds and facilitating the implementation of other policies (e.g. purchasing policies). Effects on total healthcare spending might depend on the cost-effectiveness of drugs that are covered.	Universal coverage might guarantee access to essential drugs, but this would depend on what is covered.
Compulsory coverage	Provided this policy is implemented, it would ensure universal coverage. However, limited compliance, resources or implementation might result in some people not being covered.	Compulsory coverage might guarantee equitable access.	NA	Public spending on drugs might increase. At the same time, drug costs might be reduced due to pooling funds and facilitating the implementation of other policies (e.g. purchasing policies), although potentially less than universal coverage due to multiple pools. Effects on total healthcare spending might depend on the cost-effectiveness of drugs that are covered.	Compulsory coverage might or might not guarantee access to essential drugs.
Coverage of employed population	Limited to employed population	Vulnerable populations might not be covered.	Might or might not have maximum payments or protection against catastrophic payments.	Public spending might decrease. Employers' spending might increase.	Access to essential drugs might be provided only to the employed population.
Coverage of vulnerable populations	Limited to vulnerable populations. If coverage used to supplement private insurance (and other populations for the most part have insurance), this might lead to universal coverage.	Providing insurance to the most vulnerable populations might decrease inequities.	Catastrophic payments in vulnerable populations might be prevented.	Public spending on pharmaceuticals might increase. Effects on total healthcare spending might depend on the cost-effectiveness of drugs that are covered.	Access to essential drugs might be provided to vulnerable groups.
Optional coverage	Limited to those who can afford insurance and elect to purchase it	Vulnerable populations might be less likely to be able to afford and to purchase insurance.	Might not have maximum payments or protection against catastrophic payments and vulnerable populations might be less likely to be covered	Effects on public spending would depend on the extent to which healthcare costs are paid directly for people who need care and cannot afford OOP payments. Effects on OOP spending would depend on how many people elect to purchase coverage.	Access to essential drugs limited to those who can afford insurance

OOP = Out-of-pocket payments
NA = not applicable; i.e. no obvious way that the outcome might be affected

Table 3. Ways in which different policies regarding who pays for drug insurance might affect outcomes

	Universal coverage	Equitable access	Catastrophic payments	Cost containment	Availability of essential drugs
Payment out of general tax revenue	Might facilitate universal coverage	Might be progressive and might facilitate access for vulnerable populations	NA	Might lead to increased public spending on drugs. Effects on total healthcare spending might depend on the cost-effectiveness of drugs that are covered.	Might facilitate coverage with essential drugs
Payment out of earmarked tax	Might facilitate universal coverage. Might be progressive	Might be progressive and might facilitate access for vulnerable populations	NA	Might lead to increased public spending on drugs. Effects on total healthcare spending might depend on the cost-effectiveness of drugs that are covered. Might lead to more transparent collection and spending of funds	Might be more likely to facilitate coverage for essential drugs than payment out of general tax revenue
Payment by employers	Restricted to employed people unless there are supplementary policies to ensure coverage for other populations	Vulnerable populations might not have access.	Might not have maximum payments or protection against catastrophic payments and vulnerable populations might be less likely to be covered	Employers' spending might increase.	NA
Direct payment by individuals	Restricted to those who can afford insurance unless subsidised by the government	Vulnerable populations might not have access if not subsidised or regulated.	Might not have maximum payments or protection against catastrophic payments and vulnerable populations might be less likely to be covered	Might increase OOP spending	NA

OOP = Out-of-pocket payments
NA = not applicable; i.e. no obvious way that the outcome might be affected

Table 4. Ways in which different policies regarding who makes decisions about which conditions and drugs are covered might affect outcomes

	Universal coverage	Equitable access	Catastrophic payments	Cost containment	Availability of essential drugs
Government	NA	Government might have incentives to ensure access to all patients for cost-effective drugs.	Might protect against catastrophic payments for high-cost drugs	Might raise public expenditures on drugs due to covering expensive drugs, corruption or lobbying. Effects on total healthcare spend-	Government might have incentives to provide ac-

Table 4. Ways in which different policies regarding who makes decisions about which conditions and drugs are covered might affect outcomes *(Continued)*

				ing might depend on the cost-effectiveness of drugs that are covered.	cess to essential drugs.
Public body, authorised by government	NA	Public body might have incentives to ensure access to all patients.	Might protect against catastrophic payments for high-cost drugs	Might help ensure well-informed and cost-effective decisions	Might help ensure well-informed decisions resulting in access to effective drugs
For-profit insurance company	NA	Motivation to maximise profit might result in decisions that reduce coverage and increase inequities. Competition might mitigate this.	Motivation to maximise profit might result in decisions that reduce coverage and increase the risk of catastrophic payments. Competition might mitigate this.	Might shift costs to government or OOP expenditures. Profit and competition might motivate cost-effective decisions and management.	NA
Not-for-profit insurance company	NA	Effects on equity might vary depending on the populations that are targeted, motivation and the size of the risk pool.	Effects on catastrophic payments might vary depending on the populations that are targeted, motivation and size of the risk pool.	Effects on cost containment might vary depending on the populations that are targeted, motivation and the size of the risk pool.	Might have incentives to provide access to essential drugs

NA = not applicable; i.e. no obvious way that the outcome might be affected

APPENDICES

Appendix 1. Related reviews assessing the effects of other pharmaceutical policies

Type of pharmaceutical policy	Description
Registration and classification policies	Policies that affect decisions about the registration or licensing of drugs. Registration (licensing) is defined as mandatory approval by a government agency before a drug can be sold, offered for sale, distributed or possessed for the purposes of sales, distribution or other use. Included in this category are policies regarding the registration of new drugs, deregistration, restrictions on registered drugs, essential drug lists and changes in classification (e.g. from prescription to over-the-counter).
Patent and profit policies	Policies that regulate patents for drugs and the profits of drug manufacturers
Marketing policies (Lopes 2020)	Policies that regulate marketing by drug manufacturers, including direct-to-consumer advertising
Sales and dispensing policies (Peñaloza 2015)	Policies that regulate who can sell drugs (for example, sales by physicians, pharmacies, outside of pharmacies) and regulate ownership, location and numbers of pharmacies, policies targeted at dispensing behaviour, such as dispensing regulations, regulation of marketing by retailers, financial incentives for pharmacies and other dispensers, generic substitution by pharmacies and import/trade regulations

(Continued)

Prescribing policies (financial incentives) (Rashidian 2015)	Policies that intend to affect prescribing by means of financial incentives. Included in this category are management of drug budgets by prescribers, indicative prescribing schemes, financial incentives and disincentives for prescribers such as pay-for-performance if they specifically aim at prescribing or drug utilisation.
Prescribing policies (educational or regulatory policies targeting prescribers) (Suleman 2019)	Policies that regulate who can prescribe drugs and other policies targeted at prescribers. Included in this category are monitoring and enforcement of restrictions, generic prescribing, programmes to implement treatment guidelines, system-wide policies regarding monitoring drug safety, and legislated or mandatory continuing education or quality improvement specifically targeted at prescribing.
Policies that regulate the provision of drug insurance (this review)	Policies that determine who can provide drug insurance, who receives it, who pays for it and who makes decisions on reimbursement, e.g. decentralisation of decision-making. Included in this category are private versus public insurance, non-profit versus for-profit, and tax-based versus fee-based.
Policies that determine which drugs are reimbursed (Shafiq 2016) .	Policies that determine which drugs are eligible for third-party payment. Included in this category are 'positive lists' (formularies) that specify which drugs are eligible versus 'negative lists' that specify which drugs are not eligible, system-wide policies requiring Drugs and Therapeutic Committees, rules for determining which drugs are included or excluded (e.g. based on economic analyses), and rules for reassessment after a specified period.
Restrictions on reimbursed drugs (Green 2010)	Policies that restrict reimbursement for drugs that are covered by drug insurance. Included in this category are pre-authorisation for individual patients and general restrictions, for example, based on medical specialty, diagnostic requirements, prior use of alternative treatments. If restrictions are not followed, the reimbursements for the patients will be reduced.
Policies on price and purchasing (Acosta 2014)	Policies that determine the price that is paid for drugs. Included in this category are price control, maximum prices, price negotiations, rebates, reference pricing, index pricing, volume-based pricing, and procurement policies.
Co-payment and caps (Luiza 2015)	Policies that regulate out-of-pocket payments for drugs by patients, including increases and decreases in the amount paid directly by patients, limits on the amount paid by patients, and limits on the amount reimbursed. Included are fixed or relative co-payments (based on income or age), prescription caps, deductibles and benefits.
Patient information	System-wide requirements for drug information or patient education regarding drug use
Multi-component policies	Policies that include multiple components that cut across the above categories of policies

Appendix 2. Search strategies for electronic databases

PDQ-Evidence, Epistemonikos foundation: www.pdq-evidence.org/ (searched 05 September 2020)

Advanced search – Title/abstract – limited to Publication type: systematic reviews

(drug OR drugs OR pharmaceutical OR pharmaceuticals OR medicine OR medicines) AND (insurance OR scheme OR schemes OR plan OR plans OR benefit OR benefits OR coverage OR covered)

Cochrane Central Register of Controlled Trials (CENTRAL), 2020 Issue 9, part of *The Cochrane Library*: www.cochranelibrary.com (searched 05 September 2020)

ID	Search	Hits

(Continued)

#1	("drug insurance" or "drug scheme" or "drug schemes" or "drug plan" or "drug plans" or "drug system" or "drug systems" or "drug arrangement" or "drug arrangements"):ti	12
#2	("drug coverage" or "drugs covered" or "drug benefit" or "drug benefits"):ti	19
#3	"medicare part D":ti	17
#4	#1 or #2 or #3	43
#5	MeSH descriptor: [Insurance, Pharmaceutical Services] this term only	20
#6	MeSH descriptor: [Medicare Part D] this term only	11
#7	MeSH descriptor: [Prepaid Health Plans] this term only	6
#8	MeSH descriptor: [Insurance Coverage] this term only	65
#9	MeSH descriptor: [Drug Prescriptions] this term only	487
#10	MeSH descriptor: [Prescription Drugs] this term only	104
#11	#9 or #10	587
#12	#8 and #11	1
#13	#5 or #6 or #7 or #12	37
#14	((drug or drugs or pharmaceutical or pharmaceuticals or medicine or medicines or medication or medications) near/3 (coverage or covered))	218
#15	((drug or drugs or pharmaceutical or pharmaceuticals or medicine or medicines or medication or medications) near/3 (insurance or reimburs*))	369
#16	((drug or drugs or pharmaceutical or pharmaceuticals or medicine or medicines or medication or medications) near/3 (scheme or schemes))	189
#17	((drug or drugs or pharmaceutical or pharmaceuticals or medicine or medicines or medication or medications) near/3 (arrangement or arrangements))	16
#18	((prepay* or pre next pay* or prepaid or pre next paid or prepayment* or pre next payment*) near/3 (drug or drugs or pharmaceutical or pharmaceuticals or medicine or medicines or medication or medications))	4
#19	("drug benefit" or "drug benefits" or "drug insurance benefit" or "drug insurance benefits")	108
#20	("drug plan" or "drug plans" or "drug insurance plan" or "drug insurance plans")	46
#21	"medicare part D"	42
#22	#14 or #15 or #16 or #17 or #18 or #19 or #20 or #21	884
#23	MeSH descriptor: [Financing, Government] this term only	43
#24	MeSH descriptor: [Health Policy] this term only	193

(Continued)

#25	MeSH descriptor: [Health Care Reform] this term only	19
#26	MeSH descriptor: [Government Regulation] this term only	21
#27	MeSH descriptor: [Legislation, Drug] this term only	11
#28	MeSH descriptor: [Legislation as Topic] this term only	4
#29	(policy or policies or regulat* or deregulat* or legislat* or government* or governance or reform* or program*)	181678
#30	#23 or #24 or #25 or #26 or #27 or #28 or #29	181678
#31	(#13 or #22) and #30	383
#32	#4 or #31	403
#33	#32 in Trials	295

MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to September 04, 2020, Ovid (searched 05 September 2020)

#	Searches	Results
1	(drug insurance or drug scheme? or drug plan? or drug system? or drug arrangement?).ti.	280
2	(drug coverage or drugs covered or drug benefit?).ti.	602
3	medicare part D*.ti.	649
4	or/1-3	1475
5	Insurance, Pharmaceutical Services/	4005
6	Medicare Part D/	1071
7	Prepaid Health Plans/	225
8	Insurance Coverage/	13358
9	Drug Prescriptions/	28154
10	Prescription Drugs/	6003
11	9 or 10	33693
12	8 and 11	326
13	or/5-7,12	5329

(Continued)

14	((drug? or pharmaceutical? or medicine? or medication?) adj3 (coverage or covered)).ti,ab,kf.	2768
15	((drug? or pharmaceutical? or medicine? or medication?) adj3 (insurance or reimburs*)).ti,ab,kf.	3101
16	((drug? or pharmaceutical? or medicine? or medication?) adj3 scheme?).ti,ab,kf.	1350
17	((drug? or pharmaceutical? or medicine? or medication?) adj3 arrangement?).ti,ab,kf.	157
18	((prepay* or pre pay* or prepaid or pre paid or prepayment? or pre payment?) adj3 (drug? or pharmaceutical? or medicine? or medication?)).ti,ab,kf.	52
19	(drug benefit? or drug insurance benefit?).ti,ab,kf.	1104
20	(drug plan? or drug insurance plan?).ti,ab,kf.	726
21	medicare part D*.ti,ab,kf.	1225
22	or/14-21	9143
23	13 or 22	12417
24	Financing, Government/	20895
25	Health Policy/	66560
26	Health Care Reform/	32595
27	Government Regulation/	21222
28	Legislation, Drug/	10246
29	Legislation as Topic/	15915
30	(policy or policies or regulat* or deregulat* or legislat* or government* or governance or reform* or program*).ti,ab,kf.	3065895
31	or/24-30	3146834
32	randomized controlled trial.pt.	512460
33	controlled clinical trial.pt.	93828
34	pragmatic clinical trial.pt.	1488
35	multicenter study.pt.	278505
36	non-randomized controlled trials as topic/	744
37	interrupted time series analysis/	955
38	controlled before-after studies/	542

(Continued)

39	(randomis* or randomiz* or randomly).ti,ab.	914512
40	groups.ab.	2089415
41	(trial or multicenter or multi center or multicentre or multi centre).ti.	267071
42	(intervention? or effect? or impact? or controlled or control group? or (before adj5 after) or (pre adj5 post) or ((pretest or pre test) and (posttest or post test)) or quasiexperiment* or quasi experiment* or evaluat* or time series or time point? or repeated measur*).ti,ab.	9778517
43	or/32-42	10891414
44	exp Animals/	23412783
45	Humans/	18681564
46	44 not (44 and 45)	4731219
47	review.pt.	2690462
48	meta analysis.pt.	119138
49	news.pt.	202840
50	comment.pt.	867430
51	editorial.pt.	540541
52	cochrane database of systematic reviews.jn.	14991
53	comment on.cm.	867376
54	(systematic review or literature review).ti.	166773
55	or/46-54	8725755
56	43 not 55	7721074
57	4 and 56	556
58	23 and 31 and 56	2072
59	57 or 58	2351

Embase 1974 to 2020 Week 36, Ovid (searched 05 September 2020)

#	Searches	Results
1	(drug insurance or drug scheme? or drug plan? or drug system? or drug arrangement?).ti.	375

(Continued)

2	(drug coverage or drugs covered or drug benefit?).ti.	794
3	medicare part D*.ti.	980
4	or/1-3	2076
5	health insurance/	122846
6	prescription drug/	10462
7	5 and 6	659
8	((drug? or pharmaceutical? or medicine? or medication?) adj3 (coverage or covered)).ti,ab,kw.	4661
9	((drug? or pharmaceutical? or medicine? or medication?) adj3 (insurance or reimburs*)).ti,ab,kw.	5566
10	((drug? or pharmaceutical? or medicine? or medication?) adj3 scheme?).ti,ab,kw.	2309
11	((drug? or pharmaceutical? or medicine? or medication?) adj3 arrangement?).ti,ab,kw.	248
12	((prepay* or pre pay* or prepaid or pre paid or prepayment? or pre payment?) adj3 (drug? or pharmaceutical? or medicine? or medication?)).ti,ab,kw.	38
13	(drug benefit? or drug insurance benefit?).ti,ab,kw.	1553
14	(drug plan? or drug insurance plan?).ti,ab,kw.	1249
15	medicare part D*.ti,ab,kw.	2084
16	or/8-15	15630
17	7 or 16	16139
18	"Health Policy, Economics and Management".ec.	595451
19	policy/	89114
20	health care policy/	195135
21	(policy or policies).ti,ab.	304975
22	health program/	109674
23	government regulation/	26817
24	deregulation/	8521
25	drug legislation/	14493
26	(policy or policies or regulat* or deregulat* or legislat* or government* or governance or reform* or program*).ti,ab.	3797014

(Continued)

27	or/18-26	4401225
28	17 and 27	8133
29	Randomized Controlled Trial/	618738
30	Controlled Clinical Trial/	465471
31	Quasi Experimental Study/	7199
32	Pretest Posttest Control Group Design/	494
33	Time Series Analysis/	26684
34	Experimental Design/	19223
35	Multicenter Study/	260693
36	(randomis* or randomiz* or randomly).ti,ab.	1285493
37	groups.ab.	2908565
38	(trial or multicentre or multicenter or multi centre or multi center).ti.	375078
39	(intervention? or effect? or impact? or controlled or control group? or (before adj5 after) or (pre adj5 post) or ((pretest or pre test) and (posttest or post test)) or quasiexperiment* or quasi experiment* or evaluat* or time series or time point? or repeated measur*).ti,ab.	12520222
40	or/29-39	13959442
41	exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/	27872816
42	human/ or normal human/ or human cell/	21403245
43	41 and 42	21338533
44	41 not 43	6534283
45	(systematic review or literature review).ti.	199541
46	"cochrane database of systematic reviews".jn.	14550
47	or/44-46	6746515
48	40 not 47	10793540
49	4 and 48	920
50	28 and 48	4519
51	49 or 50	4855
52	limit 51 to embase	2809

EconLit 1969 to present, ProQuest (searched 05 September 2020)

((ALL(drug OR drugs OR pharmaceutical OR pharmaceuticals OR medicine OR medicines OR medication OR medications) NEAR/3 ALL(insurance OR scheme OR schemes OR plan OR plans OR arrangement OR arrangements OR benefit OR benefits OR coverage OR covered)) OR ALL("medicare part D")) AND ALL(randomized OR randomised OR randomly OR control* OR "before and after" OR "pre and post" OR ((pretest OR "pre test") AND (posttest OR "post test")) OR quasiexperiment* OR "quasi experiment" OR "quasi experiments" OR "quasi experimental" OR evaluat* OR "time series" OR "time point" OR "time points" OR "repeated measure" OR "repeated measures" OR "repeated measurement" OR "repeated measurements" OR multicenter OR multicentre OR "multi centre" OR "multi center" OR trial OR intervention* OR effect* OR impact*)

INRUD Bibliography: www.zotero.org/groups/659457/inrud_biblio/collections/HBW4TTCK(searched 05 September 2020)

Searched in title for:

1. Drug plan
2. Drug scheme
3. Insurance
4. Coverage
5. Medicare part d

NHS Economic Evaluation Database 2015, Issue 2, part of The Cochrane Library: www.cochranelibrary.com (searched 27 January 2017)

ID	Search	Hits
#1	("drug insurance" or "drug scheme" or "drug schemes" or "drug plan" or "drug plans" or "drug system" or "drug systems" or "drug arrangement" or "drug arrangements"):ti	17
#2	("drug coverage" or "drugs covered" or "drug benefit" or "drug benefits"):ti	13
#3	"medicare part D":ti	8
#4	#1 or #2 or #3	37
#5	MeSH descriptor: [Insurance, Pharmaceutical Services] this term only	34
#6	MeSH descriptor: [Medicare Part D] this term only	14
#7	MeSH descriptor: [Prepaid Health Plans] this term only	8
#8	MeSH descriptor: [Insurance Coverage] this term only	86
#9	MeSH descriptor: [Drug Prescriptions] this term only	522
#10	MeSH descriptor: [Prescription Drugs] this term only	115
#11	#9 or #10	633
#12	#8 and #11	2
#13	#5 or #6 or #7 or #12	55

(Continued)

#14	((drug or drugs or pharmaceutical or pharmaceuticals or medicine or medicines or medication or medications) near/3 (coverage or covered))	206
#15	((drug or drugs or pharmaceutical or pharmaceuticals or medicine or medicines or medication or medications) near/3 (insurance or reimburs*))	315
#16	((drug or drugs or pharmaceutical or pharmaceuticals or medicine or medicines or medication or medications) near/3 (scheme or schemes))	129
#17	((drug or drugs or pharmaceutical or pharmaceuticals or medicine or medicines or medication or medications) near/3 (arrangement or arrangements))	10
#18	((prepay* or pre next pay* or prepaid or pre next paid or prepayment* or pre next payment*) near/3 (drug or drugs or pharmaceutical or pharmaceuticals or medicine or medicines or medication or medications))	2
#19	("drug benefit" or "drug benefits" or "drug insurance benefit" or "drug insurance benefits")	149
#20	("drug plan" or "drug plans" or "drug insurance plan" or "drug insurance plans")	52
#21	"medicare part D"	23
#22	#14 or #15 or #16 or #17 or #18 or #19 or #20 or #21	778
#23	MeSH descriptor: [Financing, Government] this term only	67
#24	MeSH descriptor: [Health Policy] this term only	374
#25	MeSH descriptor: [Health Care Reform] this term only	34
#26	MeSH descriptor: [Government Regulation] this term only	20
#27	MeSH descriptor: [Legislation, Drug] this term only	15
#28	MeSH descriptor: [Legislation as Topic] this term only	8
#29	(policy or policies or regulat* or deregulat* or legislat* or government* or governance or reform* or program*)	108868
#30	#23 or #24 or #25 or #26 or #27 or #28 or #29	108868
#31	(#13 or #22) and #30	336
#32	#4 or #31	354
#33	#32 in Economic Evaluations	93

PAIS International, Public Affairs Information Service 1914-current, ProQuest, and **Worldwide Political Science Abstracts 1975-current, ProQuest** (searched 06 November 2014)

ALL("health plan" OR "health plans" OR "drug insurance" OR "drug scheme" OR "drug schemes" OR "drug benefit scheme" OR "drug benefit schemes" OR "drug payment scheme" OR "drug payment schemes" OR "drug benefit plan" OR "drug benefit

plans" OR "drug benefit program" OR "drug benefit programs" OR "drug benefit programme" OR "drug benefit programmes" OR "pharmaceutical scheme" OR "pharmaceutical schemes" OR "pharmaceutical benefit scheme" OR "pharmaceutical benefit schemes" OR "pharmaceutical benefit plan" OR "pharmaceutical benefit plans" OR "pharmaceutical benefit program" OR "pharmaceutical benefit programs" OR "pharmaceutical benefit programme" OR "pharmaceutical benefit programmes" OR "pharmaceutical payment scheme" OR "pharmaceutical payment schemes") AND ALL(government* or state or authorit* or governance or policy or policies or regulat* or deregulat* or reregulat* or unregulat* or legislat* or law or laws or act or acts) **AND** ALL(randomised OR randomized OR randomly OR control* OR "before and after" OR "pre and post" OR ((pretest OR "pre test") AND (posttest OR "post test")) OR quasiexperiment* OR "quasi experiment" OR "quasi experiments" OR "quasi experimental" OR evaluat* OR "time series" OR "time point" OR "time points" OR "repeated measure" OR "repeated measures" OR "repeated measurement" OR "repeated measurements" OR multicentre OR multicenter OR "multi centre" OR "multi center" OR trial OR intervention* OR effect* OR impact*)

WHO ICTRP (World Health Organization International Clinical Trials Registry Platform): www.who.int/clinical-trials-registry-platform (searched 07 September 2020)

1. drug plan OR drug plans OR drug scheme OR drug schemes OR drug insurance OR drug coverage OR medicare part d (Basic search)

US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov: clinicaltrials.gov/ (searched 07 September 2020)

(Advanced search – Other terms – Limited to Interventional studies)

1. "drug plan" OR "drug plans" OR "drug scheme" OR "drug schemes" OR "drug insurance" OR "drug coverage" OR "medicare part d"

OpenGrey: www.opengrey.eu (searched 07 September 2020)

Searched for:

1. "drug plan" OR "drug plans" OR "drug scheme" OR "drug schemes" OR "drug insurance" OR "drug coverage" OR "medicare part d"

The Grey Literature Report: www.greylit.org/ (searched 08 May 2019)

Searched in title for:

1. "drug plan"
2. "drug plans"
3. "drug scheme"
4. "drug schemes"
5. "drug insurance"
6. "drug coverage"
7. "medicare part d"

Web of Science Core Collection, Clarivate (Science Citation Index Expanded 1987-present; Social Science Citation Index 1987-present; Emerging Sources Citation Index 2015-present) searched for articles citing the 58 included studies (searched 15 September 2021)

Appendix 3. The effect of drug insurance policies (such as Medicare Part-D) on drug use

Immediately after policy implementation

Study ID	Population/subgroup evaluated	Outcome/drug or drug class	Absolute change (95% CI)	Relative change
ITS studies				

(Continued)

Adams 2014	US states with strict drug caps	Proportion of patients using lipid-lowering medications (%) per month	8 (5 to 10)	35.87% (✓)
		Standardised doses per month[1] (intensity of use)	8 (3 to 12)	21.85% (✓)
Briesacher 2010	Subgroup with no supplemental coverage	Proportion of patients using benzodiazepines per month (%)	−10 (−15.96 to −4)	−37.42% (✓)
		Proportion of patients using other anxiolytics per month (%)	2 (0.5 to 3)	38.17% (✓)
		Proportion of patients using sedatives/hypnotics per month (%)	1 (0.4 to 1.6)	12.74% (✓)
		Proportion of patients using antipsychotics per month (%)	−3 (−10.5 to 4.5)	−8.81% (∅)
Chen 2008	Psychotropic drug prescriptions filled by seniors in pharmacies from a single big chain (the number of seniors who filled at least one antidepressant, antipsychotic, or benzodiazepine prescription was 1.19 billion in 2005 and 1.28 million in 2006)	Total number of antidepressant prescriptions dispensed per month	851 (−6251 to 7954)	0.29% (∅)
		Total number of antipsychotic prescriptions dispensed per month	198 (−97 to 300)	0.46% (∅)
		Total number of benzodiazepines prescriptions dispensed per month	−12339 (−16222 to −8456)	−5.16% (✓)
Farley 2010	Dual-enrollee beneficiaries	Average number of prescriptions per patient per quarter	−1.64 (−1.91 to −1.37)	−45.20% (#)
Pimentel 2015	WHO level 3 drugs - all	Rate of opioid receipt (monthly proportion of nursing home residents receiving ≥1 prescription of interest)	0.87 (0.83 to 0.89)	-13.0% (#)
	WHO level 3 drugs - fentanyl patch		0.9 (0.87 to 0.93)	-10.0% (#)
	Other WHO level 3 drugs		0.79 (0.75 to 0.84)	-21.0% (#)
	WHO level 2 drugs		1.02 (0.95 to 1.09)	2.0% (✓)
	WHO level 3 drugs - all	Rate of opioid therapy days covered (monthly proportion of resident-therapy days covered)	0.74 (0.72 to 0.77)	-26% (#)
	WHO level 3 drugs - fentanyl patch		0.78 (0.72 to 0.84)	-22% (#)
	Other WHO level 3 drugs		0.72 (0.66 to 0.78)	-28% (#)
	WHO level 2 drugs		0.97 (0.9 to 1.04)	-3.0% (∅)
Polinski 2012	Elderly using antipsychotic medication	Total days' supply of antipsychotic medication (APM) per month per 1000 patients[2]	−223 (−824 to 377)	−2.06% (∅)

(Continued)

	(APM) without prior drug insurance			
Schneeweiss 2009	62,495 elderly Medicare beneficiaries with no prior drug coverage	1000 DDD[3] of all statins dispensed per month	226.6 (48.24 to 404.96)	24.10% (✓)
		1000 DDD of generic statins dispensed per month	132.7 (−136.60 to 402.00)	1389.53% (✓)
		1000 DDD of clopidogrel dispensed per month	19.5 (0.49 to 38.61)	18.21% (✓)
		1000 DDD of all PPIs dispensed per month	63.3 (34.88 to 91.72)	39.73% (✓)
		1000 DDD of generic omeprazole dispensed per month	24 (21.06 to 26.94)	385.85% (✓)
		1000 DDD of branded omeprazole dispensed per month	1.5 (−0.26 to 3.26)	38.92% (✓)
		1000 DDD of esomeprazole dispensed per month	24.9 (12.75 to 37.05)	46.72% (✓)
		1000 DDD of warfarin dispensed per month	7.3 (−13.48 to 28.08)	5.90% (✓)
Shrank 2008	13,032 patients dually eligible for Medicaid and Medicare (dual eligibles)	Total days' supply per month of statins	8801 (−4310 to 21912)	7.95% (∅)
		Total days' supply per month of proton pump inhibitors (PPIs)	5308 (−1769 to 12385)	8.05% (∅)
		Total days' supply per month of warfarin	1653 (−798 to 4105)	7.78% (∅)
		Total days' supply per month of clopidogrel	1566 (−1352 to 4483)	5.48% (∅)
		Total days' supply per month of benzodiazepines	−2290 (−7776 to 3196)	−5.56% (∅)

Footnotes

[1] Standardised monthly dose = median number of milligrams dispensed per month across person-months with any drug use

[2] Total days' supply of APMs per month was calculated as follows: for a given patient in a given month, authors summed the days' supply for all APM prescriptions filled in that month and reported the standardised days' supply per 1000 patients.

[3] Defined Daily Dose (DDD): The assumed average maintenance dose per day for a drug used for its main indication in adults

APM = AntiPsychotic Medication
CBA = Controlled Before-and-After study
CI = Confidence Intervals
ITS = Interrupted Time-Series study
PPI = Proton Pump Inhibitors
WHO = World Health Organization

Negative figures indicate decreased drug use; positive figures indicate increased drug use.

✓: a desirable effect; ⌀: little or no effect; ?: an uncertain effect; #: an undesirable effect; #: we were unable to ascertain whether the effect was desirable or undesirable

6 to 11 months after policy implementation (short-term)

Study ID	Population/Subgroup evaluated	Outcome/drug or drug class	Absolute change (95% CI)	Relative change
ITS studies				
Adams 2014	US states with strict drug caps	Proportion of patients using lipid-lowering medications (%) per month	8.4	37.66% (✓)
		Standardised doses per month[1] (intensity of use)	7.92	21.64% (✓)
Basu 2010	10,837 unique pharmacy customers who filled at least 1 prescription both in the 2005 and in the 2006 calendar years at any retail or mail order member of a national pharmacy chain	Number of pill days per month[2]	-3.04	-3.03% (⌀)
		Number of prescriptions per month	-0.14	-4.53% (⌀)
Briesacher 2009	Only enrollees (nursing home residents)	Average number of prescriptions per patient per month	-0.64 (−1.30 to 0.013)	−6.56% (⌀)
Chen 2008	Psychotropic drug prescriptions filled by seniors in pharmacies from a single big chain (the number of seniors who filled at least one antidepressant, antipsychotic, or benzodiazepine prescription was 1.19 billion in 2005 and 1.28 million in 2006)	Total number of antidepressant prescriptions dispensed per month	10925	3.76% (✓)
		Total number of antipsychotic prescriptions dispensed per month	3600	8.39% (✓)
		Total number of benzodiazepines prescriptions dispensed per month	−9843	−4.12% (✓)
Farley 2010	Dual-enrollee beneficiaries	Average number of prescriptions per patient per quarter	−1.68	−46.42% (#)
Ketcham 2008	Medicare beneficiaries dispatching medications in a single larger pharmacy chain	Days' supply per patient per month	3.04 (0.73 to 5.34)	14.53% (✓)
Polinski 2012	Elderly using APM without prior drug insurance	Total days' supply of antipsychotic medication (APM) per month per 1000 patients[3]	683	6.30% (✓)
Schneeweiss 2009	62,495 elderly Medicare beneficiaries with no prior drug coverage	1000 DDD[4] of all statins dispensed per month	236.9	25.19% (✓)
		1000 DDD of generic statins dispensed per month	178.9	1873.30% (✓)

(Continued)

		1000 DDD of clopidogrel dispensed per month	18.4	17.18% (✓)
		1000 DDD of all PPIs dispensed per month	66.9	41.99% (✓)
		1000 DDD of generic omeprazole dispensed per month	27.1	435.69% (✓)
		1000 DDD of branded omeprazole dispensed per month	1.5	38.92% (✓)
		1000 DDD of esomeprazole dispensed per month	25.3	47.47% (✓)
		1000 DDD of warfarin dispensed per month	7.2	5.82% (✓)
Shrank 2008	13,032 patients dually eligible for Medicaid and Medicare (dual eligibles)	Total days' supply per month of statins	12992	11.73% (∅)
		Total days' supply per month of PPIs	8083	12.26% (∅)
		Total days' supply per month of warfarin	1704	8.02% (∅)
		Total days' supply per month of clopidogrel	1269	4.44% (∅)
		Total days' supply per month of benzodiazepines	−1186	−2.88% (∅)
CBA studies				
Zhang 2008	A 5% random sample of unique pharmacy customers who filled at least one prescription between January 1, 2005 and December 31, 2006 at any retail or mail-order member of the pharmacy chain	Rate of generic drug utilisation (all drugs)	1.1%	-5.0% (#)

Footnotes

[1] Standardised monthly dose = median number of milligrams dispensed per month across person-months with any drug use

[2] Pill days = the number of days with a pill, summed across all prescriptions

[3] Total days' supply of APMs per month was calculated as follows: for a given patient in a given month, authors summed the days' supply for all APM prescriptions filled in that month and report the standardised days' supply per 1000 patients.

[4] Defined Daily Dose (DDD): The assumed average maintenance dose per day for a drug used for its main indication in adults

APM = AntiPsychotic Medication
CBA = Controlled Before-and-After study
CI = Confidence Intervals
ITS = Interrupted Time-Series study

Empty cells = studies did not report data for those time periods.

Negative figures indicate decreased drug use; positive figures indicate increased drug use.

✓: a desirable effect; ⌀: little or no effect; ?: an uncertain effect; #: an undesirable effect; #: we were unable to ascertain whether the effect is desirable or undesirable

1 year or more after policy implementation (long-term)

Study ID	Population/subgroup evaluated	Outcome/drug or drug class	1 year after policy implementation		2 years or more after policy implementation	
			Absolute change (95% CI)	Relative change	Absolute change (95% CI)	Relative change
ITS studies						
Adams 2014	US states with strict drug caps	Proportion of patients using lipid-lowering medications (%) per month	9.6	43.04% (✓)	12	53.81% (✓)
		Standardised doses per month[1] (intensity of use)	7.68	20.98% (✓)	7.2	19.67% (✓)
Basu 2010	10,837 unique pharmacy customers who filled at least 1 prescription both in the 2005 and in the 2006 calendar years at any retail or mail order member of a national pharmacy chain	Number of pill days per month[2]	−7.32	−7.30% (⌀)		
		Number of prescriptions per month	−0.48	−15.26% (⌀)		
Briesacher 2009	Only enrollees (nursing home residents)	Average number of prescriptions per patient per month	−0.89 (−1.88 to 0.10)	−9.05% (⌀)		
Chen 2008	Psychotropic drug prescriptions filled by seniors in pharmacies from a single big chain (the number of seniors who filled at least one antidepressant, antipsychotic, or benzodiazepine prescription was 1.19 billion in 2005 and 1.28 million in 2006)	Total number of antidepressant prescriptions dispensed per month	20,999	7.24% (✓)		
		Total number of antipsychotic prescriptions dispensed per month	7002	16.33% (✓)		
		Total number of benzodiazepines prescriptions dispensed per month	−7347	−3.08% (✓)		
Farley 2010	Dual-enrollee beneficiaries	Average number of prescriptions per patient per quarter	−1.77	−48.84% (#)	−1.95	−53.69% (#)

(Continued)

Ketcham 2008	Medicare beneficiaries dispatching medications in a single larger pharmacy chain	Days' supply per patient per month	3.08 (−0.13 to 6.28)	14.73% (✓)	3.13 (−2.08 to 8.40)	14.97% (✓)
Madden 2015	A 5% national sample of community-dwelling, non elderly disabled dual enrollees with schizophrenia (n = 5554) or bipolar disorder (n = 3675).	Average mean of total adjusted prescription fills (total days supplied divided by 30) for schizophrenia	0.114	2.23% (✓)		
		Average mean of total adjusted prescription fills (total days supplied divided by 30) for bipolar disorder	0.322	5.72% (✓)		
Polinski 2012	Elderly using APM without prior drug insurance	Total days' supply of antipsychotic medication (APM) per month per 1000 patients[3]	1589	14.65% (✓)		
Schneeweiss 2009	62,495 elderly Medicare beneficiaries with no prior drug coverage	1000 DDD[4] of all statins dispensed per month	298.7	31.76% (✓)		
		1000 DDD of generic statins dispensed per month	456.1	4775.92% (✓)		
		1000 DDD of clopidogrel dispensed per month	11.8	11.02% (✓)		
		1000 DDD of all PPIs dispensed per month	88.5	55.55% (✓)		
		1000 DDD of generic omeprazole dispensed per month	45.7	734.73% (✓)		
		1000 DDD of branded omeprazole dispensed per month	1.5	38.92% (✓)		
		1000 DDD of esomeprazole dispensed per month	27.7	51.97% (✓)		
		1000 DDD of warfarin dispensed per month	6.6	5.34% (✓)		
Shrank 2008	13,032 patients dually eligible for Medicaid and Medicare (dual eligibles)	Total days' supply per month of statins	21,374	19.30% (∅)		
		Total days' supply per month of PPIs	13,633	20.67% (∅)		
		Total days' supply per month of warfarin	1806	8.50% (∅)		

(Continued)

		Total days' supply per month of clopidogrel	675	2.36% (⌀)	
		Total days' supply per month of benzodiazepines	1022	2.48% (⌀)	
Zhang 2009	A random sample of Medicare beneficiaries (enrolled in Medicare Advantage plans offered by a large Pennsylvania insurer)	Lipid-lowering medications (quarterly average of prescriptions per patient per month)		0.21 (0.5 to 0.27)	44% (✓)
		Antidiabetic medications (quarterly average of prescriptions per patient per month)		0.27 (0.19 to 0.35)	44% (✓)
CBA studies					
Asfaw 2019	Data for this study are drawn from the National Health Interview Survey (NHIS) and the Medical Expenditure Panel Survey (MEPS). Respondents aged between 60 and 64 years were the control group (8923 before 2006 and 17,954 after 2006) and respondents aged between 65 and 69 were the treatment group (9045 before 2006 and 18,729 after 2006)	Number of drug prescriptions		0.31 (0.11 to 0.51)	30.6% (✓)
Ayyagari 2015	Data from 12,251 individuals (34,289 person-year observations) from the 2000 through 2010 waves of the Health and Retirement Study	Antidepressant use (likelihood of having an antidepressant prescription filled during the year)		0.02 (0.00 to 0.05)	18.7% (✓)
Belenky 2019	Authors used six years of data (2003 to 2008) from the Women's Interagency HIV Study (WIHS), an observational cohort investigating the treatment and prevention of HIV infection in women.	Antidepressant use (proportion of participants taking "medication for psychological conditions or depression")		-3.6 (-3.68 to -3.52)	-10.0% (⌀)
Do 2020	Nationally representative data on community-dwelling adults aged 60–69 coming from the 2000–2015 Medical Expenditure Panel Survey (MEPS) (n = 26,545)	Number of prescriptions (number of outpatient prescription opioids consumed in a year per patient)		0.03 (-0.11 to 0.17)	10.0% (⌀)
		Use of any prescription opioid (proportion of patients who used any out-		1.08 (0.9 to 1.3)	8.0% (⌀)

(Continued)

		patient prescription opioid in a year)				
Donohue 2010	The study population included beneficiaries aged ≥ 65 years who were continuously enrolled with an insurance company in Pennsylvania and alive from 2003 to 2007 with a diagnosis of heart failure	Number of heart failure prescriptions filled annually per patient	4.8	36.0% (29 - 44%) (✓)		
		Total number of prescriptions filled annually per patient	13.7	32.0% (27 - 38%) (✓)		
Donohue 2011	The study population included beneficiaries aged ≥ 65 years who were continuously enrolled with an insurance company in Pennsylvania and alive from 2003 to 2007 with a diagnosis of depression	Likelihood (%) of filling at least 1 antidepressant prescription	)11	67.0% (40 - 99%) (✓)		
		Likelihood (%) of having 80% of days covered with an antidepressant in the first 6 months of treatment	19	117.0% (59 - 196%) (✓)		
Fowler 2013	Community-dwelling Medicare beneficiaries in Pennsylvania aged 65 or older (n = 35,102)	Proportion of beneficiaries with anti-dementia prescriptions filled annually	NR	38% (✓)		
		Proportion of beneficiaries with anti-dementia prescriptions filled annually among beneficiaries with any anti-dementia drug use pre-part D	NR	36% (✓)		
Jung 2019	Beneficiaries from a regional online pharmacy serving 24 long-term care centres in Pennsylvania	Generic drug prescription rate for atypical antipsychotics			NR	0.9% (∅)
		Generic drug prescription rate for proton pump inhibitors			NR	6.19% (∅)
		Generic drug prescription rate for statins			NR	1.48% (∅)
		Generic drug prescription rate for all drugs			NR	3.01% (∅)
Kaestner 2012	A nationally representative sample of Medicare beneficiaries	Total number of prescriptions	NR	29.3% (✓)		
Kircher 2014	2147 near-elderly individuals with cancer and 5296 individuals with Medicare and cancer	Number of new prescriptions and refills per person in one year			0.5 (-3.18 to 4.18)	1.9% (∅)

(Continued)

Lim 2013	A nationally representative sample of noninstitutionalised U.S. residents using antidepressants (n = 22,592) with different types of health insurance (Medicare, Medicaid, dual-eligible, private coverage)	Use of antidepressants (percentage of people using antidepressants)			NR	4.0% (-15% - 285) (⌀)
Liu 2011	A sample of 1105 noninstitutionalised Medicare beneficiaries (556 elderly and 549 near-elderly)	Number of prescription refills per person during a year	2.05	7.4% (⌀)		
Maclean 2020	Medicaid State Drug Utilization Database (SDUD) 2011-2018, comprising the universe of outpatient prescription medications covered under the Medicaid programme.	Medicaid-financed quarterly prescriptions per 100,000 non-elderly women			27.15 (7.12 to 47.09)	28.8% (✓)
Nelson 2014	Non-elderly Medicare beneficiaries with disabilities	Number of prescriptions (number of prescription medications filled, including refills, during the calendar year)	NR	-12.3% (⌀)		
Park 2017	A sample drawn from six waves of the Health and Retirement Study (between 2000 and 2010) aged between 60 and 70 at any wave during the study period (33,953 person-year observations)	Number of new prescription medications and refills during the calendar year per patient			0.078	3.2% (⌀)
Yin 2008	A 5% random sample of unique pharmacy customers (Medicare eligible) who filled at least 1 prescription during both the 2005 and the 2006 calendar years through the Walgreens pharmacy chain, whether at a retail store or by mail order	Pill-days (quantity of a prescription medicine sufficient for 1 day of therapy) per patient per month	3.7 (3.2 to 4.2)	5.9% (5.1% to 6.7%) (✓)		
Zhang 2010a	A random sample of 36,858 members who were continuously enrolled in the Medicare Advantage plans from 1 January 2004, through 31 December 2007	Likelihood (%) of ever filling a prescription for an antibiotic			8.3	58.0% (✓)
Zhang 2011	Medicare beneficiaries (older than 64 years) enrolled in Medicare-Advantage plans	Likelihood of use of any antihypertensive medication (likelihood (%) of ever			8.9	43.0% (✓)

(Continued)

	sold by a large insurance company in Pennsylvania with a diagnosis of hypertension and continuously enrolled between 2004 and 2007	filling a prescription for any antihypertensive medication)		
Zimmer 2015	Data from the Medical Expenditures Panel Survey (MEPS) including 36,141 unique seniors	Total number of annual prescribed medicines (including refills) per patient	4.82	20% (✓)
		The total number of annual unique therapeutic classes for which medicines were prescribed	0.12	4% (✓)

Footnotes

[1] Standardised monthly dose = median number of milligrams dispensed per month across person-months with any drug use

[2] Pill days = the number of days with a pill, summed across all prescriptions

[3] Total days' supply of APMs per month was calculated as follows: for a given patient in a given month, authors summed the days' supply for all APM prescriptions filled in that month and report the standardised days' supply per 1000 patients.

[4] Defined Daily Dose (DDD): the assumed average maintenance dose per day for a drug used for its main indication in adults

APM = AntiPsychotic Medication
CBA = Controlled Before-and-After study
CI = Confidence Intervals
HIV = Human Inmunodeficiency Virus
ITS = Interrupted Time-Series study
MEPS = Medical Expenditure Panel Survey
NHIS = National Health Interview Survey
NR = Not Reported
SDUD = State Drug Utilization Database
WIHS = Women's Interagency HIV Study

Empty cells = studies did not report data for those time periods.

Negative figures indicate decreased drug use; positive figures indicate increased drug use,

✓: a desirable effect; ⌀: little or no effect; ?: an uncertain effect; #: an undesirable effect; #: we were unable to ascertain whether the effect is desirable or undesirable

Appendix 4. The effects of drug insurance policies (such as Medicare Part-D) on drug expenditure

Immediately after policy implementation

Study ID	**Population/subgroup evaluated**	**Outcome/ drug or drug class**	Immediate	
			Absolute change (95% CI)	**Relative change**
ITS studies				

(Continued)

Farley 2010	Dual-enrollee beneficiaries	Average spending (2007 USD) per member per quarter	−123.95 (−141.98 to −106.32)	−45.35% (✓)
Polinski 2012	Elderly using APM without prior drug insurance	Total OOP costs for APM per 30 days' supply (USD)	−31 (−36 to −25)	−26.27% (✓)
Schneeweiss 2009	62,495 elderly Medicare beneficiaries with no prior drug coverage	Monthly OOP spending per thirty DDD[1] of all statins (USD) per month	−26.9 (−32.39 to −21.41)	−59.07% (✓)
		Monthly OOP spending per thirty DDD of generic statins (USD) per month	−32.4 (−47.1 to −17.7)	−67.06% v
		Monthly OOP spending per thirty DDD of clopidogrel (USD) per month	−80.4 (−95.49 to −65.31)	−66.33% (✓)
		Monthly OOP spending per thirty DDD of all PPIs (USD) per month	−71.9 (−81.11 to −62.69)	−65.88% (✓)
		Monthly OOP spending per thirty DDD of generic omeprazole (USD) per month	−60.2 (−71.96 to −48.44)	−85.63% (✓)
		Monthly OOP spending per thirty DDD of branded omeprazole (USD) per month	−47.7 (−72.79 to −22.61)	−61.76% (✓)
		Monthly OOP spending per thirty DDD of esomeprazole (USD) per month	−69 (−85.46 to −52.54)	−71.10% (✓)
		Monthly OOP spending per thirty DDD of warfarin (USD) per month	−15.5 (−18.24 to −12.76)	−42.32% (✓)
Shrank 2008	13,032 patients dually eligible for Medicaid and Medicare (dual eligibles)	Co-pays per 30-day supply of statins (USD)	−0.49 (−0.83 to −0.15)	−21.79% (✓)
		Co-pays per 30-day supply of PPIs (USD)	−0.57 (−1.17 to 0.03)	−22.84% (✓)
		Co-pays per 30-day supply of warfarin (USD)	−0.84 (−1.17 to −0.51)	−59.57% (✓)
		Co-pays per 30-day supply of clopidogrel (USD)	−1.34 (−2.14 to −0.54)	−46.45% (✓)
		Co-pays per 30-day supply of benzodiazepines (USD)	2.47 (1.96 to 2.99)	93.28% (✓)

Footnotes

[1] Defined Daily Dose (DDD): The assumed average maintenance dose per day for a drug used for its main indication in adults

APM = AntiPsychotic Medication
DDD = Defined Daily Dose
ITS = Interrupted Time-Series
OOP = Out-Of-Pocket
PPI = Proton Pump Inhibitors
USD = United States Dollars

Negative figures indicate a decrease in drug expenditures; positive figures indicate an increase in drug expenditures.

✓: a desirable effect; ⌀: little or no effect; ?: an uncertain effect; #: an undesirable effect; #: we were unable to ascertain whether the effect is desirable or undesirable

6 to 11 months after policy implementation (short-term)

Study ID	Population/subgroup evaluated	Outcome/ drug or drug class	Absolute change (95% CI)	Relative change
ITS studies				
Basu 2010	5% random sample of unique 'dual' enrollee pharmacy customers who filled at least 1 prescription both in the 2005 and in the 2006 calendar years at any retail or mail order member of a national pharmacy chain in the USA (control group was not 'dually-eligible')	Monthly OOP costs (USD) per person	−8.10	−44.63% (✓)
		Monthly total prescription expenditures (USD) per person	−9.57	−5.03% (✓)
Farley 2010	Dual-enrollee beneficiaries	Average spending (2007 USD) per member per quarter	−128.36	−46.96% (✓)
Ketcham 2008	Medicare beneficiaries dispatching medications in a single larger pharmacy chain	Average OOP cost (USD) per days' supply	−0.13 (−0.17 to −0.09)	−19.26% (✓)
Lichtenberg 2007	Medicare beneficiaries dispatching medications in a single larger pharmacy chain	Amount paid for prescription drugs (USD) by the patient per day of therapy	−0.13 (−0.15 to −0.10)	−18.67% (✓)
Polinski 2012	Elderly using APM without prior drug insurance	Total OOP costs for APM per 30 days' supply (USD)	−43	−36.44% (✓)
Schneeweiss 2009	62,495 elderly Medicare beneficiaries with no prior drug coverage	Monthly OOP spending per thirty DDD[1] of all statins (USD) per month	−27.2	−59.73% (✓)
		Monthly OOP spending per thirty DDD of generic statins (USD) per month	−32.8	−67.89% (✓)
		Monthly OOP spending per thirty DDD of clopidogrel (USD) per month	−80.2	−66.16% (✓)
		Monthly OOP spending per thirty DDD of all PPIs (USD) per month	−72	−65.98% (✓)
		Monthly OOP spending per thirty DDD of generic omeprazole (USD) per month	−59.2	−84.21% (✓)
		Monthly OOP spending per thirty DDD of branded omeprazole (USD) per month	−47.4	−61.37% (✓)

(Continued)

		Monthly OOP spending per thirty DDD of esomeprazole (USD) per month	−69.1	−71.20% (✓)
		Monthly OOP spending per thirty DDD of warfarin (USD) per month	−15.7	−42.69% (✓)
Shrank 2008	13,032 patients dually eligible for Medicaid and Medicare (dual eligibles)	Co-pays per 30-day supply of statins (USD)	−0.61	−27.12% (✓)
		Co-pays per 30-day supply of PPIs (USD)	−0.57	−22.84% (✓)
		Co-pays per 30-day supply of warfarin (USD)	−0.93	−65.96% (✓)
		Co-pays per 30-day supply of clopidogrel (USD)	−1.61	−55.81% (✓)
		Copays per 30-day supply of benzodiazepines (USD)[1]	2.47	93.28% (✓)

Footnotes

[1] Defined Daily Dose (DDD): The assumed average maintenance dose per day for a drug used for its main indication in adults

APM = Anti-Psychotic Medication
DDD = Daily Defined Doses
ITS = Interrupted Time-Series
OOP = Out-Of-Pocket
PPI = Proton Pump Inhibitors
USD = United States Dollars

Negative figures indicate a decrease in drug expenditures; positive figures indicate an increase in drug expenditures.

✓: a desirable effect; ⌀: little or no effect; ?: an uncertain effect; #: an undesirable effect; #: we were unable to ascertain whether the effect is desirable or undesirable

1 year or more after policy implementation (long-term)

Study ID	Population/subgroup evaluated	Outcome/ drug or drug class	1 year after policy implementation		2 years or more after policy implementation	
			Absolute change (95% CI)	Relative change	Absolute change (95% CI)	Relative change
ITS studies						
Basu 2010	5% random sample of unique 'dual' enrollees pharmacy customers who filled at least 1 prescription both in the 2005 and in the 2006 calendar years at any	Monthly OOP costs (USD) per person	−10.38	−57.18% (✓)		
		Monthly total prescription expenditures (USD) per person	−20.84	−10.98% (✓)		

(Continued)

	retail or mail order member of a national pharmacy chain in the USA (control group was not 'dually-eligible')					
Farley 2010	Dual-enrollee beneficiaries	Average spending (2007 USD) per member per quarter	−137.18	−50.19% (✓)	−154.82	−56.64% (✓)
Ketcham 2008	Medicare beneficiaries dispatching medications in a single larger pharmacy chain	Average OOP cost (USD) per days' supply	−0.14 (−0.19 to −0.08)	−20.29% (✓)	−0.15 (−0.24 to −0.06)	−22.06% (✓)
Li 2013	Persons with self-reported diabetes who had Medicare coverage	Annual per capita OOP expenditure for all outpatient prescription drugs (USD)	−680 (−1084 to −275)	−39.38% (✓)	−995 (−1587 to −402)	−57.63% (✓) (-70.25% at 36 months)
		Annual per capita total OOP expenditure for all healthcare services (USD)	−579 (−923 to −234)	−25.19% (✓)	−1048 (−1672 to −423)	−45.60% (✓) (-46.78% at 36 months)
		Annual family OOP expenditure on all healthcare services for persons with diabetes and their families (USD)	−860 (−1372 to −347)	−25.08% (✓)	−1421 (−2267 to −574)	−41.45% (✓) (-46.78 at 36 months)
Lichtenberg 2007	Medicare beneficiaries dispatching medications in a single larger pharmacy chain	Amount paid for prescription drugs (USD) by the patient per day of therapy	−0.14 (−0.17 to −0.10)	−20.15% (✓)		
Polinski 2012	Elderly using APM without prior drug insurance	Total OOP costs for APM per 30 days' supply (USD)	−55	−46.61% (✓)		
Schneeweiss 2009	62,495 elderly Medicare beneficiaries with no prior drug coverage	Monthly OOP spending per thirty DDD[1] of all statins (USD)	−29	−63.68% (✓)		
		Monthly OOP spending per thirty DDD of generic statins (USD)	−35.2	−72.86% (✓)		
		Monthly OOP spending per thirty DDD of clopidogrel (USD)	−79	−65.17% (✓)		
		Monthly OOP spending per thirty DDD of all PPIs (USD)	−72.6	−66.53% (✓)		
		Monthly OOP spending per thirty DDD of generic omeprazole (USD)	−53.2	−75.67% (✓)		

(Continued)

		Monthly OOP spending per thirty DDD of branded omeprazole (USD)	−45.6	−59.04% (✓)		
		Monthly OOP spending per thirty DDD of esomeprazole (USD)	−69.7	−71.82% (✓)		
		Monthly OOP spending per thirty DDD of warfarin (USD)	−16.9	−46.14% (✓)		
Shrank 2008	13,032 patients dually eligible for Medicaid and Medicare (dual eligibles)	Co-pays per 30-day supply of statins (USD)	−0.85	−37.80% (✓)		
		Co-pays per 30-day supply of PPIs (USD)	−0.57	−22.84% (✓)		
		Co-pays per 30-day supply of warfarin (USD)	−1.11	−78.72% (✓)		
		Co-pays per 30-day supply of clopidogrel (USD)	−2.15	−74.52% (✓)		
		Co-pays per 30-day supply of benzodiazepines (USD)[1]	2.47	93.28% (✓)		
Zhang 2009	A random sample of Medicare beneficiaries (enrolled in Medicare Advantage plans offered by a large Pennsylvania insurer)	Total monthly drug spending per person per month (USD) (insurance payments plus co-payments)			41 (33-50)	74% (#)
CBA studies						
Ayyagari 2015	Data from 12,251 individuals (34,289 person-year observations) from the 2000 through 2010 waves of the Health and Retirement Study.	OOP (USD annually spent by beneficiary)			-112.90 (-172.56 to -53.26)	-22.1% (✓)
Carvalho 2019	The elderly (over 65 years) compared with the near-elderly (54–63 years) pre- and post-implementation of Medicare Part D	Total mean drug expenditure per person per year (2012 USD)			77.1 (75.49 to 78.71)	3.6% (#)
		OOP drug expenditure per person per year (2012 USD)			-285.7 (-270.92 to -300.48)	-26.2% (✓)
Choi 2017	Older adults with diabetes	Mean proportion (%) of OOP pharmacy costs			NR (in text)	-19.4% (✓)

(Continued)

Engelhardt 2011	A Medicare eligible (65 and older) sample compared to a near-elderly (60-64 years old) sample who are not eligible	OOP drug expenditure per person per year (USD)	-293 (-368.15 to -217.85)	-55% (✓)		
		Total prescription drug expenditure per person per year (USD)	213 (20.33 to 407.07)	3.9% (#)		
Kaestner 2012	A nationally representative sample of Medicare beneficiaries	Total drug expenditure	NR	42.9% (#)		
Kircher 2014	2147 near-elderly individuals with cancer and 5296 individuals with Medicare and cancer	OOP cost for prescription drugs per person per year (USD)			-356 (-655.94 to -56.06)	-49.4% (✓)
Liu 2011	A sample of 1105 noninstitutionalised Medicare beneficiaries (556 elderly and 549 near-elderly)	OOP drug expenditure per patient per year (USD)	-229.05 (-344.46 to -113.64)	-52.7% (✓)		
Nelson 2014	Non-elderly Medicare beneficiaries with disabilities	Total prescription expenditures	NR	-5.3% (⊘)		
		OOP drug expenditure	NR	-79.4% (✓)		
Park 2017	Using Medical Expenditure Panel Survey (MEPS) data from 2000 through 2005 (pre-Part D period) and from 2007 through 2012 (Part D era), this study identified a cohort of elderly Medicare beneficiaries (treatment group) and a near-elderly non-Medicare population (control group).	Annual average OOP expenditures for prescription medications (USD)			-349	-21.8% (✓)
Yin 2008	A 5% random sample of unique pharmacy customers (Medicare eligible) who filled at least 1 prescription during both the 2005 and the 2006 calendar years through the Walgreens pharmacy chain, whether at a retail store or by mail order	Average monthly OOP expenditures per customer (USD)	7.3	-13.1% (✓)		
Zhang 2010b	A 40% random sample of 36,858 individuals continuously enrolled in Medicare Advantage plans offered by a Pennsylvania insurer between 1 January 2004, and 31 December 2007	Mean of annual out-of-pocket drug spending per patient (USD)			−59	−12.99 (✓) (adjusted by authors −13.4%)
		Proportion (%) of drug spending paid by OOP			−47	−156% (✓) (adjusted

(Continued)

				by authors −44.9%)
Zimmer 2015	Data from the Medical Expenditures Panel Survey (MEPS) including 36,141 unique seniors	Total annual spending on prescription drugs (2008 USD) per person	272	15.0% (#)
		Proportion (%) of annual drug expenses paid for OOP		- 20.0% (✓)

Footnotes

[1] Defined Daily Dose (DDD): The assumed average maintenance dose per day for a drug used for its main indication in adults

APM = Anti-Psychotic Medication
CBA = Controlled Before-and-After study
DDD = Daily Defined Doses
ITS = Interrupted Time-Series
MEPS = Medical Expenditure Panel Survey
NR = Not Reported
OOP = Out-Of-Pocket
PPI = Proton Pump Inhibitors
USD = United States Dollars

Negative figures indicate a decrease in drug expenditures; positive figures indicate an increase in drug expenditures.

✓: a desirable effect; ∅: little or no effect; ?: an uncertain effect; #: an undesirable effect; #: we were unable to ascertain whether the effect is desirable or undesirable

Appendix 5. The effects of drug insurance policies (such as Medicare Part-D) on healthcare utilisation

Emergency department visits

Study ID[1]	Population/subgroup evaluated	Outcome/drug or drug class	Absolute change (95% CI)	Relative change
ITS studies				
Burns 2014	1431 dual-beneficiaries with bipolar I disorder	Proportion of population with any ED visits per month (immediately after policy implementation)	1.1	9.40% (∅)
		Mean number of ED visits per patient per month (immediately after policy implementation)	0.03	19.04% (#)
Briesacher 2015	Community-dwelling Medicare population with cardiovascular disease	Proportion of patients having any ED visits (immediately after policy implementation)	0.25%	3.45% (∅)
		Mean number of ED visits per 100 persons (immediately after policy implementation)	0.08	0.5% (∅)
CBA studies				

(Continued)

Ayyagari 2017	5% random sample of unique 'dual' enrollee pharmacy customers who filled at least 1 prescription both in the 2005 and in the 2006 calendar years at any retail or mail order member of a national pharmacy chain in the USA (control group was not 'dually-eligible')	ED visits (number of ED visits per year) (3 or more years after policy implementation)	-0.011 (-0.03 to 0.01)	-5.7% (∅)
Kircher 2014	2147 near-elderly individuals with cancer and 5296 individuals with Medicare and cancer	Number of annual emergency department visits per patient (2 years after policy implementation)	0.06 (-0.56 to 0.68)	-17.1% (∅)
Liu 2011	A sample of 1105 noninstitutionalised Medicare beneficiaries (556 elderly and 549 near-elderly)	Annual emergency department visit per patient (1 year after policy implementation)	0.05 (-0.01 to 0.12)	51.4% (∅)
Nelson 2014	Non-elderly Medicare beneficiaries with disabilities	Change in the number of ED visits per person per year (1 year after policy implementation)	NR	29.2% (∅)

Footnotes

CBA = Controlled Before-and-After study
ED = Emergency Department
ITS = Interrupted Time-Series study
NR = Not Reported

[1] None of the data from the studies included in this table required re-analysis.

Negative figures indicate a decrease in utilisation; positive figures indicate an increase in utilisation.

✓: a desirable effect; ∅: little or no effect; ?: an uncertain effect; #: an undesirable effect; #: we were unable to ascertain whether the effect is desirable or undesirable

Hospital admissions

Study ID[1]	Population/subgroup evaluated	Outcome/drug or drug class	Absolute change (95% CI)	Relative change
ITS studies				
Briesacher 2015	Community-dwelling Medicare population with cardiovascular disease	Proportion (%) of patients having any inpatient hospital visits (5 years after policy implementation)	-0.99 (0.93 to 1.06)	-0.9% (∅)
		Mean number of inpatient hospital visits per 100 persons per year (5 years after policy implementation)	-0.99 (0.91 to 1.07)	-0.7% (∅)
CBA studies				

(Continued)

Afendilus 2011	Individuals aged 65 and older (versus individuals aged 60–64) in states with low drug coverage in 2005 (versus those in states with high pre-Part D drug coverage)	Hospitalisation rate per 10,000 for any condition (1 year after policy implementation)	-20.5	-4.4% (✓)
Belenky 2019	Authors used six years of data (2003 to 2008) from the Women's Interagency HIV Study (WIHS), an observational cohort investigating the treatment and prevention of HIV infection in women. Participants who 1) were living with HIV in 2003 and 2) reported Medicaid-Medicare dual eligibility or Medicaid-only enrolment in 2005, were eligible for the study. There were 125 dual eligibles (67% of all dual eligibles in 2005) and 676 Medicaid-only participants (77% of all Medicaid-only participants in 2005) who met the inclusion criteria for this study.	Hospitalisation (proportion of participants with any hospitalisation in the last six months) (2 years after policy implementation)	0.8 (0.74 to 0.86)	3.4% (⌀)
Kaestner 2014	A sample of Medicare beneficiaries	Number of hospital admissions per 1000 beneficiaries (2 years after policy implementation)	-19.8 (-34.70 to -4.90)	-7.7% (✓)
Kircher 2014	2147 near-elderly individuals with cancer and 5296 individuals with Medicare and cancer	Number of discharge hospitalisations per patient per year (2 years after policy implementation)	-0.05 (-0.29 to 0.19)	-14.3% (⌀)
Liu 2011	A sample of 1105 noninstitutionalised Medicare beneficiaries (556 elderly and 549 near-elderly)	Average annual number of hospitalisations per patient for any condition (1 year after policy implementation)	0.03 (-0.02 to 0.07)	32.2% (⌀)
Nelson 2014	Non-elderly Medicare beneficiaries with disabilities	Average annual number of hospitalisations per patient (1 year after policy implementation)	NR	-37.2% (⌀)

Footnotes

CBA = Controlled Before-and-After study
HIV = Human Inmunodeficiency Virus
ITS = Interrupted Time-Series study
NR = Not Reported
WIHS = Women's Interagency HIV Study

[1] None of the data from the studies included in this table required re-analysis.

Negative figures indicate a decrease in hospitalisations in the intervention group; positive figures indicate an increase in hospitalisations in the intervention group.

✓: a desirable effect; ⌀: little or no effect; ?: an uncertain effect; #: an undesirable effect; #: we were unable to ascertain whether the effect is desirable or undesirable

Outpatient visits

Study ID[1]	Population/ Subgroup evaluated	Outcome/drug or drug class	Absolute change (95% CI)	Relative change
CBA studies				
Kircher 2014	2147 near-elderly individuals with cancer and 5296 individuals with Medicare and cancer	Annual number of outpatient visits per person (2 years after policy implementation)	-1.55 (-3.1 to 0)	-109.9% (✓)
Nelson 2014	Non-elderly Medicare beneficiaries with disabilities	Annual number of physician office visits per person (1 year after policy implementation)	NR	-16.8% (⌀)
Park 2017	Using Medical Expenditure Panel Survey (MEPS) data from 2000 through 2005 (pre-Part D period) and from 2007 through 2012 (Part D era), this study identified a cohort of elderly Medicare beneficiaries (treatment group) and a near-elderly non-Medicare population (control group).	Annual number of outpatient visits per person (3 or more years after policy implementation)	-0.116	-28.6% (⌀)

Footnotes

CBA = Controlled Before-and-After study
ITS = Interrupted Time-Series study
MEPS = Medical Expenditure Panel Survey
NR = Not reported

[1] None of the data from the studies included in this table required re-analysis.

Negative figures indicate a decrease in outpatient visits in the intervention group; positive figures indicate an increase in outpatient visits in the intervention group.

Non-drug medical spending[1]

Study ID[2]	Population/subgroup evaluated	Outcome/drug or drug class	Absolute change (95% CI)	Relative change
ITS studies				
Zhang 2009	A random sample of Medicare beneficiaries (enrolled in Medicare Advantage plans offered by a large Pennsylvania insurer)	Average monthly non drug medical spending per month (USD)[2]	-33 (-29 to -37)	-5.33% (✓)
CBA studies				

(Continued)

Kaestner 2014	A sample of Medicare beneficiaries	Average annual inpatient expenditures per person (USD)	-694 (-1352.56 to -35.44)	-11.4% (✓)
McWilliams 2011	11,179 elderly participants on the Health Retirement Study	Quarterly total nondrug medical spending per participant (2008 USD)[2]	−306 (−586 to −51)	−10.6% (−18.5% to −2.0%) (✓)

Footnotes

CBA = Controlled Before-and-After study
ITS = Interrupted Time-Series
USD = United States Dollars

[1] Nondrug medical spending was considered a 'proxy' of healthcare utilisation (this spending was probably done in different types of healthcare services).

[2] None of the data from the studies included in this table required re-analysis.

Negative figures indicate a decrease in utilisation; positive figures indicate an increase in utilisation.

Appendix 6. The effects of drug insurance policies (such as Medicare Part-D) on health outcomes

Mortality

Study ID	Population/ Subgroup evaluated	Outcome/drug or drug class	Absolute change (95% CI)	Relative change
ITS studies				
Briesacher 2015	A nationally representative sample of Medicare beneficiaries (n = 56,293 [unweighted and unique]) from 2000 to 2010. The total sample was 56,293 unique persons who contributed 120,566 person-years to this study.	Mortality (proportion of the sample who had died at 4 years after policy implementation)	NR	-0.2% (∅)
CBA studies				
Huh 2017	The primary estimation sample, which includes only deaths between 64- and 66-year-olds, consisted of 518,514 deaths that occurred between 2001 and 2008	Annual mortality for any cause in the 3 years following policy implementation	-0.036%	-2.2% (✓)
Kaestner 2014	A sample of Medicare beneficiaries	Mortality from any cause (3 or more years after policy implementation)	-0.015%	-0.5% (∅)

Footnotes

NR: not reported

Negative figures indicate a decrease in mortality for the intervention group; positive figures indicate an increase in mortality in the intervention group.

✓: a desirable effect; ⌀: little or no effect; ?: an uncertain effect; #: an undesirable effect; #: we were unable to ascertain whether the effect is desirable or undesirable

Non-mortality outcomes

Study ID	Population/subgroup evaluated	Outcome/drug or drug class	Absolute change (95% CI)	Relative change
ITS studies				
Briesacher 2015 (5 years after policy implementation)	A nationally representative sample of Medicare beneficiaries (n = 56,293 [unweighted and unique]) from 2000 to 2010. The total sample was 56,293 unique persons who contributed 120,566 person-years to this study.	Proportion of the sample with perceived fair or poor health	-2%	-8.4% (⌀)
		Proportion of the sample with perceived ADL limitations	1.6%	4.9% (⌀)
		Proportion of the sample with perceived IADL limitations	0.1%	-0.5% (⌀)
CBA studies				
Asfaw 2019 (2 or more years after policy implementation)	Data for this study are drawn from the National Health Interview Survey (NHIS) and the Medical Expenditure Panel Survey (MEPS). Respondents aged between 60 and 64 were the control group (8923 before 2006 and 17,954 after 2006) and respondents aged between 65 and 69 were the treatment group (9045 before 2006 and 18,729 after 2006)	Proportion of respondents engaged in moderate exercise (moderately paced walking, bicycling, slow swimming or dancing, and simple gardening)	-12.23%	-6.36% (#)
		Proportion of respondents engaged in vigorous exercise (fast walking, fast bicycling, jogging, strenuous swimming or sport play, vigorous aerobic dance, or strenuous gardening)	NR	-0.36% (⌀)
		Proportion of respondents engaged in muscle strength activities (weight-lifting, resistance training, push-ups, and sit-ups)	NR	1.6% (⌀)
		Likelihood of being overweight (25 ≤BMI < 30)	-13.64%	-5.73% (#)
		Likelihood of being obese (BMI ≥ 30)	NR	-5.46% (⌀)
Ayyagari 2015 (2 or more years after policy implementation)	Data from 12,251 individuals (34,289 person-year observations) from the 2000 through 2010 waves of the Health and Retirement Study	Number of depressive symptoms (CESD score)	-0.20 (-0.30 to -0.1)	-14.8% (✓)

(Continued)

Belenky 2019 (2 or more years after policy implementation)	Authors used six years of data (2003 to 2008) from the Women's Interagency HIV Study (WIHS), an observational cohort investigating the treatment and prevention of HIV infection in women. Participants who 1) were living with HIV in 2003 and 2) reported Medicaid-Medicare dual eligibility or Medicaid-only enrolment in 2005, were eligible for the study. There were 125 dual eligibles (67% of all dual eligibles in 2005) and 676 Medicaid-only participants (77% of all Medicaid-only participants in 2005) who met the inclusion criteria for this study.	Depressive symptoms (proportion of patients with CESD > 16)	-1 (-1.08 to -0.92)	2.2% (⌀)
Chen 2018 (2 or more years after policy implementation)	The study used data from the HRS, an ongoing, longitudinal survey study of respondents' health, income, health insurance, healthcare expenditure, and demographic information among middle-aged and older adults in the United States. The study sample was the 2004–2008 HRS respondents who were aged 65 and older in 2006. There were 649 participants in the treatment group and 97 in the control group.	Self-rated health (likelihood of having worse health status)	NR	-52% (7 - 75%) (✓)
		Depressive symptoms (likelihood of having a worse mental health status as measured by the CESD)	NR	-22% (-54% - 61%) (⌀)
		Activities of daily living impairment (likelihood of having ADL impairment)	NR	-45% (-88% - 84%) (⌀)
Diebold 2018 (2 or more years after policy implementation)	Newly covered Medicare beneficiaries	Good health (self-reported health status)	0.03 (-0.01 to 0.07)	2.8% (✓)
		Likelihood of being diagnosed with high blood pressure	-0.03 (-0.06 to -0.01)	-3.0% (✓)
		Likelihood of having high blood pressure under control	-0.07 (-0.52 to 0.34)	-6.6% (⌀)
Pak 2017 (2 or more years after policy implementation)	A sample drawn from six waves of the Health and Retirement Study (between 2000 and 2010) aged between 60 and 70 at any wave during the study period (33,953 person-year observations)	Improvement in episodic memory	0.17 (0.03 to 0.33)	1.7% (✓)

Footnotes

ADL: Activities of Daily Living (e.g. bathing without help)
CBA = Controlled Before-and-After
CESD: Center for Epidemiologic Studies scale for Depression
HIV = Human Inmunodeficiency Virus
HRS = Health and Retirement Study
IADL: Instrumental Activities of Daily Living (e.g. shopping without help)
ITS = Interrupted Time Series study
MEPS = Medical Expenditure Panel Survey
NHIS = National Health Interview Survey

NR: Not Reported
WIHS = Women's Interagency HIV Study

Negative figures indicate a decrease in the specific outcome for the intervention group compared with the control group; positive figures indicate an increase in the specific outcome for the intervention group compared with the control group.

✓: a desirable effect; ⌀: little or no effect; ?: an uncertain effect; #: an undesirable effect; #: we were unable to ascertain whether the effect is desirable or undesirable

HISTORY

Protocol first published: Issue 5, 2015

CONTRIBUTIONS OF AUTHORS

Tomas Pantoja and Blanca Peñaloza prepared the protocol based on a previous version, as mentioned above. Camilo Cid provided content expertise. Cristian A Herrera provided methodological expertise. Jemma Hudson and Craig Ramsay provided statistical expertise.

DECLARATIONS OF INTEREST

Tomas Pantoja: no conflict of interest declared
Blanca Peñaloza: no conflict of interest declared
Camilo Cid: no conflict of interest declared
Cristian A Herrera: no conflict of interest declared

Tomas Pantoja and Cristian A Herrera are editors with Cochrane Effective Practice & Organisation of Care but had no role in the editorial process for this review.

SOURCES OF SUPPORT

Internal sources

- Department of Family Medicine, Pontificia Universidad Catolica de Chile, Chile

  This is the host institution of the corresponding author and it has provided time for developing and finishing the review.

External sources

- Alliance for Health Policy & Systems Research, Systematic Review Centres, Switzerland

  The review team received a grant for working in the first stages of this review.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Because no cluster-allocated studies were found, we did not implement the following methods, described in the protocol, at the review stage.

- Unit of analysis issues: when there was a unit of analysis error in the reported analysis for a study and there was insufficient information to re-analyse the data, we tried to contact the authors to obtain the necessary data. If these data were not available, we did not report CIs or P values for which there was a unit of analysis error.

Because the focus of the review was on assessing the impact of policies on those moving to the specific scheme, we only considered comparisons between those with no coverage (likely to move to the scheme) and those with generous coverage (unlikely to move to the scheme) prior to the policy implementation. This left a number of other comparisons (e.g. with those with some but not generous initial coverage) out of our main analysis.

We initially planned to report risk ratios (adjusted for baseline differences in the outcomes measures) for dichotomous outcomes, but in order to make the report of effect estimates more consistent, we used the relative change between intervention and control groups adjusted by baseline differences for both dichotomous and continuous outcomes. Likewise, in the protocol we planned to calculate those relative changes for each study using

(the absolute post-intervention difference between the intervention and control groups minus the absolute pre-intervention difference between the intervention and control groups)/the post-intervention level in the control group.

However, considering that most of the CBA studies computed effect estimates using specific reliable statistical approaches (e.g. difference-in-differences), we used those estimates as the primary effect estimates when they were available.

Maryam Bigdeli provided content expertise and advice to the review. Due to changes in her employment, she was not able to continue as a review author.