



ORIGINAL REPORT

Policy-induced selection bias in pharmacoepidemiology: The example of coverage for Alzheimer's medications in British Columbia

Anat Fisher¹  | Greg Carney¹  | Ken Bassett^{1,2}  | K. Malcolm Maclure¹  |
Colin R. Dormuth¹ 

¹Department of Anesthesiology, Pharmacology and Therapeutics, University of British Columbia, Vancouver, British Columbia, Canada

²Department of Family Practice, University of British Columbia, Vancouver, British Columbia, Canada

Correspondence

A. Fisher, Department of Anesthesiology, Pharmacology and Therapeutics, University of British Columbia, 2176 Health Sciences Mall, Vancouver, BC V6T 1Z3, Canada.
Email: anat.fisher@ti.ubc.ca

Funding information

Ministry of Health

Abstract

Purposes: To assess the impact of a government-sponsored reimbursement policy for cholinesterase inhibitors (ChEIs) on trends in physician visits with a diagnosis of Alzheimer's disease (AD).

Methods: Longitudinal population-based study using interrupted time series methods. British Columbia outpatient claims data for individuals aged 65 and older were used to compute monthly AD visit rates and examine the impact of the ChEI reimbursement policy on the coding of AD. We examined trends in the number of patients with AD visits, the number of AD visits per patient, and visits with "competing" diagnoses (mental, neurological, and cerebrovascular disorders and accidental falls). Finally, we described demographic and clinical features of diagnosed patients.

Results: We analyzed 1.9 million AD visits. Faster growth in recorded AD visits was observed after the policy was implemented, from monthly growth of 7.5 visits per 100 000 person-months before the policy (95% confidence interval [CI], 6.1-8.9) to monthly growth of 16.5 per 100 000 person-months after the policy (95% CI, 14.8-18.3). After the implementation of the policy, we observed increased growth in the number of patients with recorded AD visits and the number of AD visits per patient, as well as a shift in diagnoses away from mental diseases and accidental falls to AD (diagnosis substitution).

Conclusions: British Columbia's reimbursement policy for ChEIs was associated with a significant acceleration in Alzheimer's visits. Evaluations of health services utilization and clinical outcomes following drug policy changes need to consider policy-induced influences on the reliability of the data used in the analysis.

KEYWORDS

Alzheimer's disease, cholinesterase inhibitors, drug reimbursement, interrupted time series analysis, pharmacoepidemiology, reimbursement policy, selection bias

This work was presented in the 33rd International Conference of Pharmacoepidemiology, August 2017, Montreal, Canada. This study was funded by the Pharmaceutical Service Division, Ministry of Health, Provincial Government of British Columbia, as part of the Alzheimer's Drug Therapy Initiative (ADTI) for the purpose of developing evidence for the use of cholinesterase inhibitor treatment in the community.

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2019 The Authors. Pharmacoepidemiology and Drug Safety Published by John Wiley & Sons Ltd.

1 | INTRODUCTION

Administrative health claims data are generated after encounters with the health care system and are collected for administrative or billing purposes.¹ These data have been used in a growing number of pharmacoepidemiology and health policy studies.^{2,3} One element of claims data is diagnosis codes. Diagnostic information is typically recorded in claims for outpatient physician visits and is frequently used to define study populations and identify study outcomes. Inaccuracies in diagnostic coding have been discussed as an important source of bias^{3,4}; however, such inaccuracies were generally assumed to be constant over the study period, in spite of evidence that this might not be the case. Multiple situations have been shown to influence the utilization of specific diagnostic codes, including a change in codes or the coding system,^{5,6} the introduction of new diagnostic criteria,^{7,8} increased awareness by physicians and the public for a specific disease,⁹ and the substitution of codes for one disease with codes for another (diagnostic shift).¹⁰⁻¹⁷

In the Canadian Province of British Columbia (BC), we identified a unique opportunity to examine the susceptibility of diagnostic coding behavior to a change in drug reimbursement policy. In October 2007, the provincial drug plan began covering the cholinesterase inhibitor medications (ChEIs: donepezil, galantamine, and rivastigmine) for patients with Alzheimer's disease (AD) as part of the Alzheimer's Drug Therapy Initiative (ADTI). The policy was implemented as part of an initiative for "coverage with evidence development,"¹⁸⁻²⁰ and its details are presented elsewhere.^{21,22} We sought to assess the effect of the ADTI reimbursement policy (aka "the policy") on health services utilization and cost in AD patients. We undertook this analysis as a preliminary measure to understand the possible influence of the policy on diagnostic information captured in the database, prior to using the database to evaluate the policy.

2 | METHODS

2.1 | Study design and data source

We conducted a longitudinal population-based study using interrupted time series analysis methods. We obtained administrative claims data from the BC Ministry of Health for the period 1 January 2001 to 31 December 2013. The anonymized data included records of fee-for-service payments to physicians and alternative providers, patient registration information and demographics, pharmacy records (PharmaNet), and hospital discharge records.

2.2 | Physician visits for AD

Our study assessed the impact of the ADTI policy on diagnostic coding for AD in outpatient visits ("Alzheimer's visits"). Alzheimer's visits were defined as a physician fee-for-service visits with an International Classification Disease, version 9 (ICD-9) code of 331, 290, 294, or 797 in any of the diagnostic fields. This definition was the only published AD

KEY POINTS

- This study assessed the effect of a new government-sponsored reimbursement policy for Alzheimer's medications in British Columbia on the rate of physician visits with a diagnosis of Alzheimer's disease.
- The new policy was associated with an increase in growth of observed Alzheimer's visits, from a monthly growth of 7.5 visits per 100 000 person-months before the policy to 16.5 per 100 000 person-months after the policy.
- This policy was also associated with faster growth in the number of patients with an Alzheimer's disease diagnosis, faster growth in the number of Alzheimer's visits per patient, and substitution of diagnosis codes from mental disorders and accidental falls to Alzheimer's disease.
- The policy implementation was associated with changes in the characteristics of diagnosed patients and could bias assessment of health services utilization and clinical outcomes associated with this policy.

definition validated on administrative data when this study was conducted,²³ and its sensitivity and specificity were 86%.^{24,25} Individuals under the age of 65 years were excluded because dementia is rare and often secondary to other diseases in that age group.^{26,27} Crude and standardized Alzheimer's visit rates were computed on a monthly basis. Crude visit rates were calculated as the numbers of Alzheimer's visits per 100 000 person-months of enrollment in the provincial medical plan. Directly standardized visit rates were computed to correct for variations in age and sex over time, using the 2007 British Columbia enrolled population as the reference population. Standardized visit rates were also corrected to a month-length of 30 days.

2.3 | Statistical methods

Interrupted time series analysis is considered the strongest, quasi-experimental design to evaluate the longitudinal effects of an intervention, eg, health policy, particularly when the researcher does not manage the intervention.²⁸⁻³⁰ Applying this methodology, we included the following variables in our regression model: time in months, time after the ADTI policy, and a dichotomous variable for baseline level. Time in months, from January 2001 and onwards, ie, the trend before ChEI reimbursement policy, was included to correct for a secular trend in AD diagnostic coding. Time after the new policy from November 2007 onwards was included to test for the effect of the policy on top of any preexisting trend. The model assumed a linear trend. We added a dichotomous variable denoting "before" versus "after" the

implementation of the policy. This dichotomous variable tests for a change in AD visits between the months immediately before and immediately after the policy, accounting for the prepolicy trend.³¹ In addition, we adjusted for autocorrelation and seasonality by including lag terms for up to 12 preceding months based on statistical significance (stepwise autoregression using the Yule-Walker method, SAS BACKSTEP selection option). Finally, to allow for a delayed effect of the policy, we excluded data from the first three months after the policy was launched (November 2007-January 2008). The analysis was conducted using SAS PROC AUROREG.^{28,29,32}

2.4 | Additional analyses

2.4.1 | ChEI reimbursement policy and characteristics of incident cases

We explored possible differences in the characteristics of incident Alzheimer's patients before and after the reimbursement policy implementation. Incident cases were defined based on the first of two outpatient physician claims within 18 months or first hospital discharge with Alzheimer's diagnosis between January 2001 and December 2012. We excluded patients based on an earlier Alzheimer's diagnosis, the absence of continuous enrollment within the preceding 18 months, or under 65 years old. We described the characteristics of incident cases identified each year and presented the proportions of patients with different categories for the following variables: age, gender, income, comorbidities (Romano score based on data during the year before diagnosis³³), and the specialty of the diagnosing physician.

2.4.2 | ChEI reimbursement policy and additional visits/patients' parameters

We further tested for the effect of the ChEI reimbursement policy on several monthly parameters for individuals aged 65 and older using interrupted time series analysis. Visit ratio was defined as the number of physician visits with an Alzheimer's diagnosis divided by 100 000 total physician visits. Visit density was defined as the number of physician visits with an Alzheimer's diagnosis per 100 individuals with such visits. Alzheimer's patients were the number of patients with a physician visit with an Alzheimer's diagnosis per 100 000 person-months of enrollment. Lastly, Alzheimer's administrative incidence was defined as the first physician visit or hospital discharge with Alzheimer's diagnosis in patients with at least 18 months of continuous enrollment and no ChEI prescription during this period. Incidence was calculated per 100 000 person-months of enrollment.

2.4.3 | ChEI reimbursement policy and diagnosis substitution

We considered that the ChEI reimbursement policy might have been associated with diagnosis substitution, ie, the substitution of codes

for one diagnosis by codes for another disease. Specifically, for patients with the same clinical presentation, we considered whether physicians increased the use of AD coding after the policy over other codes that had been previously used. We tested for diagnosis substitution from four "competing" disease categories that may be relevant: mental disorders (ICD-9 codes 290-319), neurological disorders (ICD-9 codes 320-359 or 430-438), cerebrovascular disorders (ICD-9 codes 430-438), and accidental falls (including orthopedic trauma, ICD-9 codes E880-E888, 800-849). In the absence of accepted methodology to identify diagnosis substitution in epidemiology studies, we a priori defined diagnosis substitution as a combination of two criteria: the first is a decrease in the coding for the "competing" diseases, and the second is an increase in the ratio of Alzheimer's visits to the "competing" diseases. The analysis included a series of two interrupted time series analyses for each "competing" disease categories. For the first criterion, we analyzed visit rates with "competing" disease diagnoses and required significantly fewer visits with "competing" diseases after the new policy, ie, smaller slope or lower baseline level after policy initiation. For the second criterion, we analyzed the visit rate ratio: the product of rates of physician visits with an Alzheimer's diagnosis divided by the rates of visits with a diagnosis of a "competing" disease. For this criterion, we required a larger slope or higher baseline level after policy initiation.

3 | RESULTS

3.1 | ChEI reimbursement policy and Alzheimer's visits

Between 2001 and 2013, 158.5 million physician visits were recorded in BC for patients aged 65 or older. About 1.9 million of these visits were coded with an AD diagnosis. The average rate of Alzheimer's visits increased from 6 160 visits per month in 2001 to 21 901 visits per month in 2013. During 13 years of follow-up, we observed a 2.5-fold increase in crude and standardized rates of Alzheimer's visits (Figure 1). The mean observed annual growth (± 1 standard deviation) in the standardized rates of visits was 6.2% (5.0%) and 8.7% (2.7%) in the periods before and following the ChEI reimbursement policy.

In the interrupted times series analysis, we observed a significant association of the ChEI reimbursement policy with trends of physician visits with an Alzheimer's diagnosis (Figure 1, Table 1). Before the policy was implemented, the monthly growth in standardized Alzheimer's visits (the slope) was +7.5 visits per 100 000 person-months (95% confidence interval [CI], 6.1-8.9). After the policy was implemented, the slope increased by 9.0 (95% CI, 6.6-11.5), to a monthly growth of +16.5 (95% CI, 14.8-18.3) without a significant change in the baseline level of visits.

3.2 | Additional analysis

We examined a possible association between the ChEI reimbursement policy and the demographic and clinical characteristics of incident

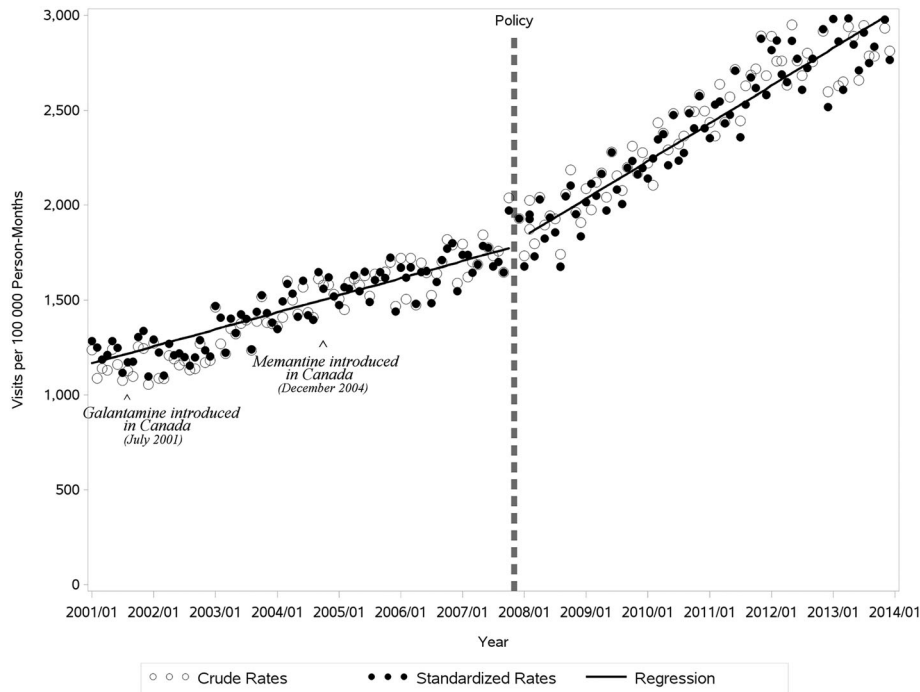


FIGURE 1 Alzheimer's visits per 100 000 patient-months age 65 and older, British Columbia. Horizontal dashed line represents the initiation of cholinesterase inhibitor (ChEi) cost coverage

TABLE 1 Results of interrupted time series regression

Outcome	Baseline Level (Intercept)	Slope Before the New Policy	Slope After the New Policy	Level Change at Policy Implementation	Slope Difference
Alzheimer's Visits [†]	1166.0 (1096.5,1236.1)	1.5 (6.1,8.9)	16.5 (14.8,18.3)	23.3 (-58.3,104.9)	9.0 (6.6,11.5)*
Visit ratio	803.9 (771.4,836.5)	3.1 (2.5,3.8)	9.2 (8.3,10.0)	22.5 (-17.9,62.9)	6.1 (4.9,7.2)*
Visit density	148.1 (145.1,151.1)	0.2 (0.1,0.2)	0.3 (0.2,0.4)	-4.5 (-8.5,-0.4)*	0.1 (0.04,0.2)*
Alzheimer's patients [†]	792.6 (746.9,838.3)	4.0 (3.1,4.9)	7.3 (6.2,8.5)	45.8 (4.0,87.6)*	3.3 (1.6,5.0)*
Alzheimer's administrative incidence [†]	241.7 (231.8,251.4)	-0.8 (-0.9,-0.6)	0.1 (-0.1,0.2)	19.5 (10.9,28.2)*	0.7 (0.6,1.1)*

Alzheimer's visits, physician visits with Alzheimer's diagnosis codes; Visit ratio, the number of physician visits with an Alzheimer's diagnosis divided by 100 000 total physician visits; Visit density, the number of physician visits with an Alzheimer's diagnosis per 100 individuals with such visit; Alzheimer's patients, the number of patients with a physician visit with an Alzheimer's diagnosis code. Alzheimer's administrative incidence is based on the first physician visit or hospital discharge with an Alzheimer's diagnosis in patients with at least 18 months of continuous enrollment and no ChEi prescription during this period. Results are presented as estimated regression parameters (95% confidence interval).

[†]Per 100 000 patient-months;

*Significant at the .05 probability level.

cases. We observed an increase in the proportion of patients with multiple comorbidities and lower income after the ChEi reimbursement policy was launched (Figure 2). Both characteristics are important confounders in health service and health outcome research.³⁴⁻³⁶

Next, we analyzed additional visits and patients' parameters. After the new reimbursement policy was implemented, we observed a significantly larger increase in three of the additional parameters studied: visit ratio (the number of physician visits with an Alzheimer's diagnosis divided by 100 000 total physician visits), visit density (the number of

physician visits with an Alzheimer's diagnosis per 100 individuals with such visits), and Alzheimer's patients (the number of patients with a physician visit with an Alzheimer's diagnosis per 100 000 person-months of enrollment) (Table 1 and Figure 3). We also compared Alzheimer's administrative incidence before and after the policy. We found that the new ChEi reimbursement policy was associated with a level increase of +19.5 (95% CI, 10.9-28.2) incident cases per month. It was also associated with a change in direction of the slope, from a decreasing trend of -0.8 (95% CI, -0.9 to -0.6) incidence cases per 100 000 person-months before the policy, to a constant trend of

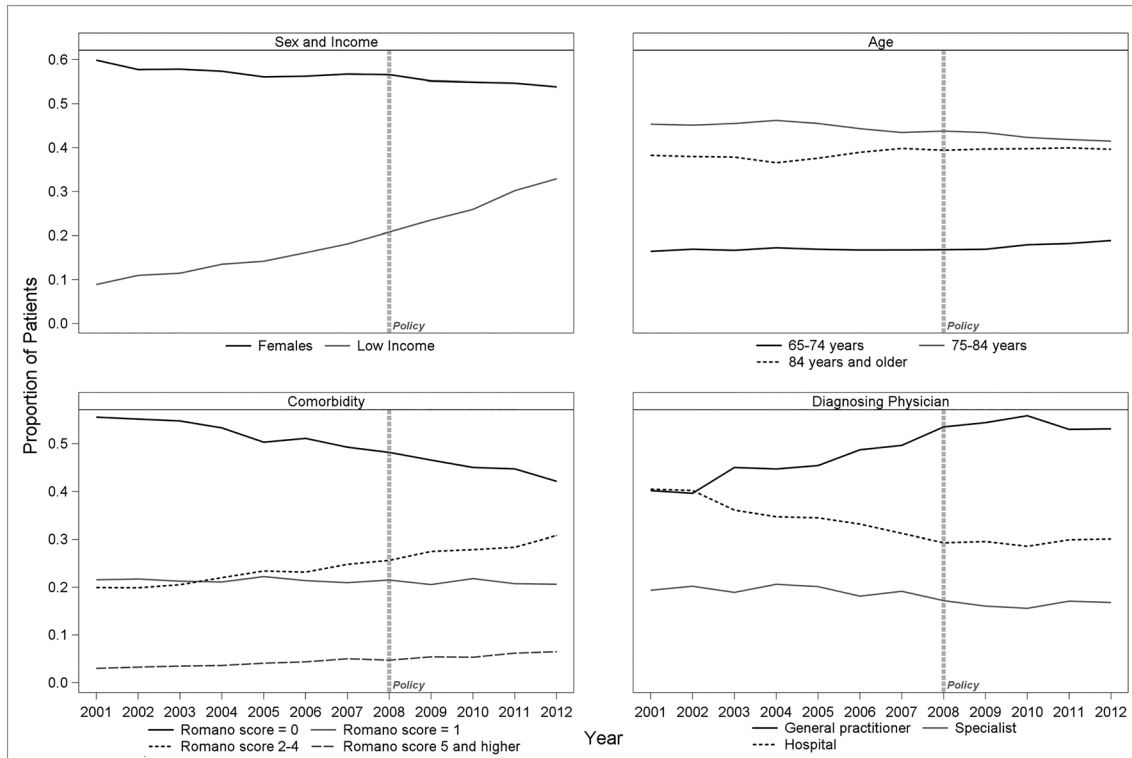


FIGURE 2 Cholinesterase inhibitor (ChEI) reimbursement policy and characteristics of incident cases. Data are presented for incidence cases of Alzheimer's disease and related dementias that were diagnosed between 2001 and 2012. In the absence of complete hospital data for the year 2013 at the time of analysis, the information for this year is not presented

+0.1 (95% CI, -0.1 to 0.2) after the reimbursement policy was implemented (Table 1 and Figure 3).

Finally, we checked whether physicians increased their use of Alzheimer's diagnosis coding over coding of other "competing" diseases after the new policy, ie, diagnosis substitution (Table 2 and Figure 4). On the basis of the two predefined criteria, we detected diagnosis substitution from mental disorders and accidental falls (Table 2). In both categories, the new policy was associated with a significant decrease in the baseline level of visits with the "competing" diseases and an increase in the baseline ratio of Alzheimer's visits to visits with "competing" diseases ratio.

4 | DISCUSSION

In this study, we tested for the effect of a new drug reimbursement policy for Alzheimer's medications in British Columbia on the frequency in which the provincial physicians recorded Alzheimer's diagnosis during visits of individuals age 65 or older. Our findings reveal a temporal selection bias in patients with presumed AD who are eligible for study in epidemiologic analysis.

When studying the effect of a new intervention, such as a new health policy, we are often interested in estimating its effect on the relevant population, eg, individuals with a specific health or morbidity status. Our analysis of the British Columbia Alzheimer's medication policy naturally focused on patients with AD and related dementias and showed that a change in drug coverage had the potential to affect

not only clinical and utilization outcomes in patients who are studied, as might be expected, but also the population of patients included in the study itself. This may cause bias when using a dynamic cohort in pharmacoepidemiological studies. A dynamic cohort in our example is a cohort to which patients continuously enter based on a first physician's visit or a hospital discharge with a diagnosis of AD. Dynamic cohort designs may be used to minimize biases caused by the duration of disease, to increase the sample size, or to deal with frequent dropping out from the study. In the current study, we showed that a drug policy can influence the number of patients entering the cohort, the reliability of the diagnosis (ie, the accuracy of the diagnosis code), and the distribution of covariates (ie, characteristics of patients entering the cohort). These effects of the policy could lead to selection bias when using a dynamic cohort design to study health care policy.

The true incidence of AD in the population, even if increasing, should have been reasonably stable and not prone to the sudden and dramatic changes that were shown in this analysis. The policy was associated with dramatically faster growth in the number of visits coded with AD even after accounting for secular trends, an increase that was composed of faster growth in the number of patients with Alzheimer's visits and visits per patient. These effects were independent of the number of all-cause visits in the province. The faster growth in the number of patients with coded AD visits was also expressed as an increase in the estimated incidence of AD. Furthermore, we described differences in comorbidities and income between incident cases identified before the policy and those identified later; both are important sources of bias in health service research.³⁴⁻³⁶

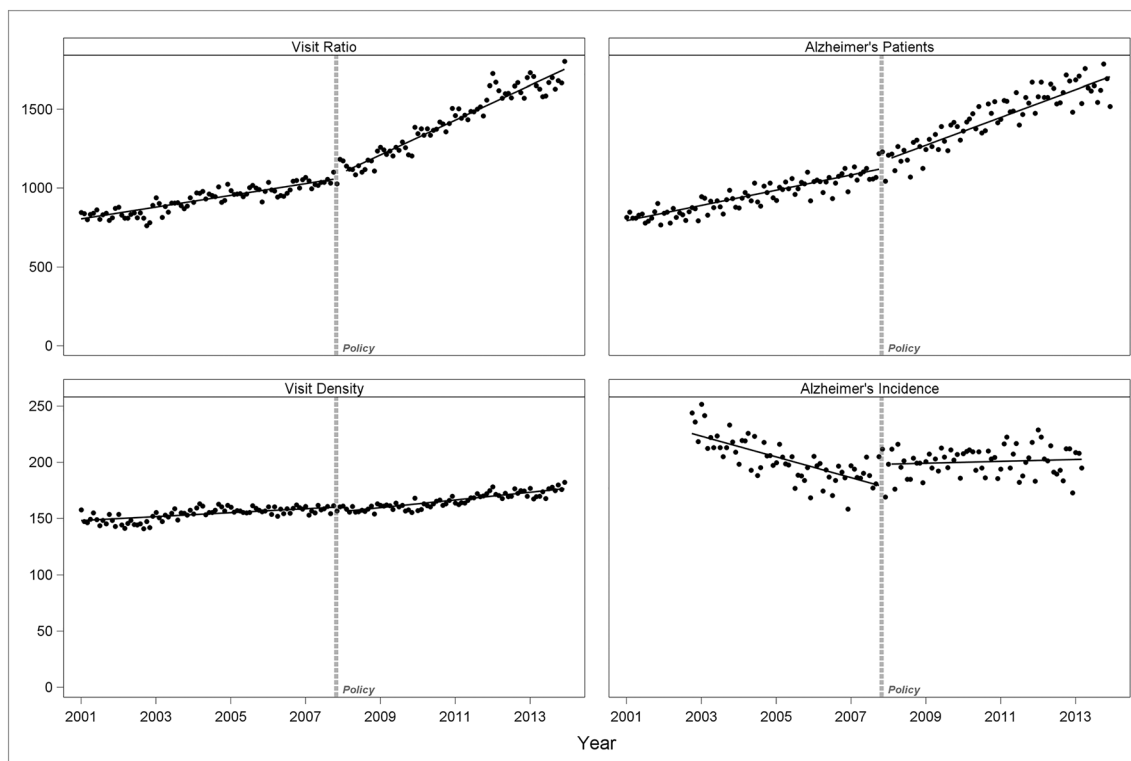


FIGURE 3 Cholinesterase inhibitor (ChEI) reimbursement policy and additional visits/patients' parameters. Visit ratio is the number of Alzheimer's visits per 100 000 all-cause physician visits for individuals aged 65 or older in the province. Visit density is the number of Alzheimer visits per 100 individuals with such visits. Patients with Alzheimer's visits is defined per 100 000 person-months of enrollment. Alzheimer's incidence is defined per 100 000 person-months of enrollment, based on first physician visit or hospital discharge with Alzheimer's diagnosis in the data, in patients with at least 18 months of continuous enrollment and no cholinesterase inhibitor (ChEI) prescription during these 18 months

Our outcomes were estimated based on administrative data, which include records that were created mainly for billing purposes. As a result, some inaccuracy is expected, and the use of specific diagnosis codes may be affected by different factors. Because we did not expect the new policy to cause a real change in the incidence trend, we suggest several possible explanations for the observed change in trends of Alzheimer's visits. First, the findings might have been caused by a time-dependent change in the accuracy of Alzheimer's diagnostic coding (reliability). While we expected a decrease in the number of visits with a different diagnosis for some AD patients (false negatives), we could not rule out an increase in the number of AD diagnoses recorded for non-AD patients (false positives). Unfortunately, we were unable to directly measure the AD coding accuracy in the BC data. Second, more patients were treated with ChEI medication when their costs were covered (data not shown). Patients on treatment were more likely to experience increased frequency of routine follow-up visits,³⁷ which were coded as AD. This explanation is supported by an increase in the frequency of visits per patient (visits density). Third, together with the reimbursement policy, the province initiated an educational program, the Dementia Education Strategy.³⁸ Physicians may have been more alert to diagnosing AD and encouraging routine visits after participating in this professional development program. Last, the administrative requirements of applying for medication reimbursement or renewing it probably promoted an increase in the use of AD

codes, which may have been associated with an increase in the frequency of visits per patient.

Our results are different from a previous BC study that examined the effect of drug coverage policy on visits.³⁹ This published study estimated no effect of drug cost sharing on trends of visits with depression. The main difference between the studies is the direction of effect on copayment; in our study, it was lower after the policy, and in the previous study, it was higher. In addition, the previous study examined a more general policy that included a few medication groups. Trends in absolute numbers of visits with AD or dementia diagnosis codes have only been studied in a single study.^{40,41} The researchers of that study estimated 18.2% annual growth in the number of physician visits with an AD diagnosis (ICD-9 codes 290, 294, and 331) between 1998 and 2009 in patients aged 40 and older in the United States. The increase in the absolute number of visits was higher than what was observed in British Columbia. However, since the results of the American study did not include rates or proportions, it is difficult to estimate the extent of growth in AD caused by population growth or aging.

This study has several strengths. The Canadian health care system is based on the principles of fairness and equity, comprehensiveness, accessibility, and universality; hence, it is well suited to study the effects of new policies. We analyzed data from a population-based databases in which data were collected prospectively in a systematic manner, and examined data had been collected over a long period of

TABLE 2 ChEI reimbursement policy and diagnosis substitution—results of interrupted time series regression

Outcome	Regression Outcome	Baseline Level (Intercept)	Slope Before the New Policy	Level Change at Policy Implementation	Slope Difference	Criterion	Criterion Applied?
Visits with diagnosis of mental disorders	Visits' rate [†]	4065.0 (3894.1,4235.4)	11.4 (8.1,14.8)	-181.6 (-360.4,-2.8)*	11.4 (5.5,17.3)	Fewer visits after policy initiation	Yes, level drop
	Rates ratio (x10 ⁻³) [‡]	288.3 (275.5,301.2)	0.9 (0.6,1.1)	21.4 (7.6,35.2)*	0.4 (-0.1,0.8)	Increased rates ratio after policy initiation	Yes, level increase
Visits with diagnosis of neurologic disorders	Visits' rate [†]	2551.0 (2459.7,2641.7)	5.4 (3.6,7.2)	13.2 (-92.2,118.7)	4.2 (1.0,7.3)	Fewer visits after policy initiation	No
	Rates ratio (x10 ⁻³) [‡]	458.7 (443.3,474.2)	1.7 (1.4,2.0)	12.1 (-9.2,33.4)	1.2 (0.7,1.7)*	Increased rates ratio after policy initiation	Yes, slope increase
Visits with diagnosis of cerebrovascular disorders	Visits' rate [†]	1009.0 (960.2,1058.8)	1.6 (0.6,2.6)	44.2 (-20.2,108.6)	2.1 (0.4,3.8)	Fewer visits after policy initiation	No
	Rates ratio (x10 ⁻³) [‡]	1156.2 (1111.5,1200.9)	5.0 (4.1,5.9)	-0.4 (-67.1,66.3)	2.2 (0.6,3.7)*	Increased rates ratio after policy initiation	Yes, slope increase
Visits with diagnosis of accidental falls	Visits' rate [†]	1515.0 (1483.0,1547.9)	4.0 (3.3,4.6)	-89.0 (-135.8,42.2)*	-0.5 (-1.6,0.7)	Fewer visits after policy initiation	Yes, level drop
	Rates ratio (x10 ⁻³) [‡]	767.0 (737.8,796.2)	2.5 (1.9,3.2)	67.4 (23.3,111.6)*	4.1 (3.1,5.1)*	Increased rates ratio after policy initiation	Yes, level increase and slope increase

Abbreviation: ChEI, cholinesterase inhibitor.

[†]Visits' rate defined as visits with "competing" diseases per 100 000 person-months;

[‡]Rates ratios are the products of the rate of Alzheimer's visits divided by the rate of visit with "competing" diseases;

*Significant at the .05 probability level.

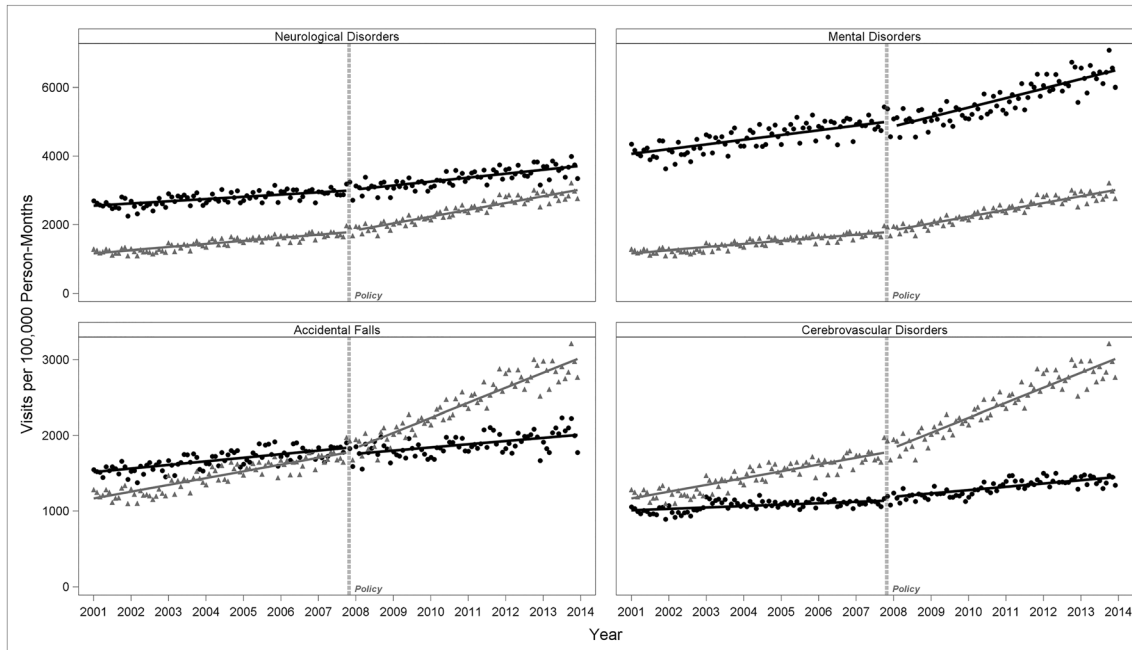


FIGURE 4 Cholinesterase inhibitor (ChEI) reimbursement policy and diagnosis substitution. Numbers are monthly visit rates, defined as the number of visits per 100 000 person-months, in individuals age 65 and older. In Black - observed monthly standardized rates (dots) and regression lines of visits with “competing” disease. In Gray - observed monthly standardized rates (triangles) and regression lines of visits with Alzheimer’s diseases

13 years. Analyses of this sort are vulnerable to bias from cointerventions. In this specific instance, there may have been other programs and incentives that could have directly influenced trends of Alzheimer’s visits during this period, such as education and guidelines for treating dementia patients^{42,43} and incentives in treating patients with chronic diseases and complex clinical presentation.^{44,45} While we were unable to validate the list of ICD codes used to identify Alzheimer’s visits, we find the validation secondary to the main purpose of the study. Regardless of the accuracy of the AD codes, we demonstrated a change in trend related to the new drug reimbursement policy.

5 | CONCLUSIONS

The observed increase in the number of physician visits with an AD diagnosis after the implementation of a government-sponsored reimbursement policy for ChEI could present a challenge when studying other aspects of the new drug coverage policy. Policy-induced influences on the selection of a study population could bias assessment of health services utilization and clinical outcomes in before-after designs even when they include historical or concurrent control groups. We encourage researchers to critically evaluate the accuracy of diagnostic coding and trends and consider describing the effect of the policy on the cohort studied as part of the policy effect.

ETHICS STATEMENT

The study protocol was approved by the Clinical Research Ethics Board of the University of British Columbia (H09-01696) and the Human Research Ethics Board of the University of Victoria (08-164).

ACKNOWLEDGEMENTS

This study was funded by the Pharmaceutical Service Division, Ministry of Health, Provincial Government of British Columbia as part of the Alzheimer’s Drug Therapy Initiative (ADTI), for the purpose of developing evidence for the use of cholinesterase inhibitor treatment in the community. All inferences, opinions, and conclusions drawn in this publication are those of the ADTI researchers and do not reflect the opinions or policies of the British Columbia Ministry of Health. This work was presented in the 33rd International Conference of Pharmacoepidemiology, August 2017, Montreal, Canada. We thank Ms Im Sujin for assistance with processing and presenting the results.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Anat Fisher <https://orcid.org/0000-0001-9730-5107>

Greg Carney <https://orcid.org/0000-0002-7438-5172>

Ken Bassett <https://orcid.org/0000-0001-9414-562X>

K. Malcolm Maclure <https://orcid.org/0000-0002-3655-6495>

Colin R. Dormuth <https://orcid.org/0000-0001-8577-8783>

REFERENCES

1. Cadarette SM, Wong L. An introduction to health care administrative data. *Can J Hosp Pharm.* 2015;68(3):232-237.
2. Sinha S, Peach G, Poloniecki JD, Thompson MM, Holt PJ. Studies using English administrative data (Hospital Episode Statistics) to assess health-care outcomes—systematic review and recommendations for reporting. *Eur J Pub Health.* 2013;23(1):86-92.

3. Van Walraven C, Bennett C, Forster AJ. Administrative database research infrequently used validated diagnostic or procedural codes. *J Clin Epidemiol*. 2011;64(10):1054-1059.
4. Jonsson Funk M, Landi SN. Misclassification in administrative claims data: quantifying the impact on treatment effect estimates. *Curr Epidemiol Rep*. 2014;1(4):175-185.
5. Knight L, Halech R, Martin C, Mortimer L. Impact of changes in diabetes coding on Queensland hospital principal diagnosis morbidity data. Queensland, Australia: Queensland Government. *Queensland Health*. 2011;9:1-7. Available from: http://www.health.qld.gov.au/hsu/tech_report/techreport_9.pdf Accessed April 10, 2019
6. Link J, Glazer C, Torres F, Chin K. International Classification of Diseases coding changes lead to profound declines in reported idiopathic pulmonary arterial hypertension mortality and hospitalizations: implications for database studies. *Chest*. 2011;139(3):497-504.
7. Muniz J, Cordido F, Rodriguez IL, Beiras AC. Effect of the application of the new diagnostic criteria of diabetes mellitus in the prevalence estimates and diagnostic level in the general population. *Eur J Pub Health*. 1999;9(2):149-151.
8. Cordido F, Muniz J, Rodriguez IL, Beiras AC. New diagnostic criteria for diabetes and mortality in older adults. *Lancet*. 1999;353(9146):69-70.
9. Benson L, Baer HJ, Kaelber DC. Trends in the diagnosis of overweight and obesity in children and adolescents: 1999-2007. *Pediatrics*. 2009;123(1):e153-e158.
10. Fransoo RR, Martens PJ, Need to Know Team. The rising prevalence of asthma: true increase, diagnostic exchange or diagnostic accuracy? *Health Policy*. 2013;8(4):27-34.
11. Lundback B, Ronmark E, Jonsson E, Larsson K, Sandstrom T. Incidence of physician-diagnosed asthma in adults—a real incidence or a result of increased awareness? Report from The Obstructive Lung Disease in Northern Sweden Studies. *Respir Med*. 2001;95(8):685-692.
12. Tinkelman DG, Price DB, Nurdyke RJ, Halbert RJ. Misdiagnosis of COPD and asthma in primary care patients 40 years of age and over. *J Asthma*. 2006;43(1):75-80.
13. Byard RW. Changing infant death rates: diagnostic shift, success story, or both? *Forensic Sci Med Pathol*. 2013;9:1-2.
14. Moore BM, Fernbach KL, Finkelstein MJ, Carolan PL. Impact of changes in infant death classification on the diagnosis of sudden infant death syndrome. *Clin Pediatr (Phila)*. 2008;47(8):770-776.
15. Shapiro-Mendoza CK, Tomashek KM, Anderson RN, Wingo J. Recent national trends in sudden, unexpected infant deaths: More evidence supporting a change in classification or reporting. *Am J Epidemiol*. 2006;163(8):762-769.
16. Malloy MH, MacDorman M. Changes in the classification of sudden unexpected infant deaths: United States, 1992-2001. *Pediatrics*. 2005;115(5):1247-1253.
17. Schnitzer PG, Covington TM, Dykstra HK. Sudden unexpected infant deaths: sleep environment and circumstances. *Am J Public Health*. 2012;102(6):1204-1212.
18. Miller FG, Pearson SD. Coverage with evidence development: ethical issues and policy implications. *Med Care*. 2008;46(7):746-751.
19. Tunis SR, Pearson SD. Coverage options for promising technologies: Medicare's "coverage with evidence development". *Health Aff (Millwood)*. 2006;25(5):1218-1230.
20. Chong E, Lun E, Chappell N. The Alzheimer's Drug Therapy Initiative (ADTI): drug coverage with evidence development in British Columbia. 2017 CADTH Symposium. Ottawa, Ontario, Canada: 2017 CADTH Symposium. Available from: <https://www.cadth.ca/real-world-evidence-pharmaceuticals>. Accessed April 11, 2019.
21. Chappell NL, Beattie BL, Hsiung JYR, Dormuth C, Maclure M. *Alzheimer's Drug Therapy Initiative (ADTI): research report*. Victoria, British Columbia, Canada: The Government of British Columbia; 2015:1-138. Available from: <https://www2.gov.bc.ca/assets/gov/health/health-drug-coverage/pharmacare/adtiresearchstudiesuvic.pdf>. Accessed April 10, 2019.
22. Fisher A, Carney G, Basset K, Chappell NL. Cholinesterase Inhibitor utilization: the impact of provincial drug policy on discontinuation. *Value Health*. 2016;19(5):688-696.
23. Wilkinson T, Ly A, Schnier C, et al. Identifying dementia cases with routinely collected health data: a systematic review. *Alzheimers Dement*. 2018;14(8):1038-1051.
24. Taylor DH Jr, Fillenbaum GG, Ezell ME. The accuracy of Medicare claims data in identifying Alzheimer's disease. *J Clin Epidemiol*. 2002;55:929-937.
25. Taylor DH Jr, Ostbye T, Langa KM, Weir D, Plassman BL. The accuracy of Medicare claims as an epidemiological tool: the case of dementia revisited. *J Alzheimers Dis*. 2009;17:807-815.
26. Harvey RJ, Skelton-Robinson M, Rossor MN. The prevalence and causes of dementia in people under the age of 65 years. *J Neurol Neurosurg Psychiatry*. 2003;74(9):1206-1209.
27. McMurtry A, Clark DG, Christine D, Mendez MF. Early-onset dementia: frequency and causes compared to late-onset dementia. *Dement Geriatr Cogn Disord*. 2006;21(2):59-64.
28. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther*. 2002;27(4):299-309.
29. Penfold RB, Zhang F. Use of interrupted time series analysis in evaluating health care quality improvements. *Acad Pediatr*. 2013;13(6):S38-S44.
30. Lopez Bernal J, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. *Int J Epidemiol*. 2016;46:348-355.
31. Kontopantelis E, Doran T, Springate DA, Buchan I, Reeves D. Regression based quasi-experimental approach when randomisation is not an option: interrupted time series analysis. *BMJ*. 2015;350(jun09 5):h2750.
32. Lagarde M. How to do (or not to do) ... Assessing the impact of a policy change with routine longitudinal data. *Health Policy Plan*. 2012;27(1):76-83.
33. Romano PS, Roos LL, Jollis JG. Adapting a clinical comorbidity index for use with ICD-9-CM administrative data: different perspectives. *J Clin Epidemiol*. 1993;46(10):1075-1079; discussion 1081-1090.
34. Schneeweiss S, Maclure M. Use of comorbidity scores for control of confounding in studies using administrative databases. *Int J Epidemiol*. 2000;29(5):891-898.
35. Schneeweiss S, Seeger JD, Maclure M, Wang PS, Avorn J, Glynn RJ. Performance of comorbidity scores to control for confounding in epidemiologic studies using claims data. *Am J Epidemiol*. 2001;154(9):854-864.
36. Blakely T, Kawachi I, Atkinson J, Fawcett J. Income and mortality: the shape of the association and confounding New Zealand Census-Mortality Study, 1981-1999. *Int J Epidemiol*. 2004;33(4):874-883.
37. Hu T, Dattani ND, Cox KA, et al. Effect of comorbidities and medications on frequency of primary care visits among older patients. *Can Fam Physician*. 2017;63(1):45-50.
38. Lynn B, Keesey A, Wu C, Hatry A. *Continuing Professional Development. Final report: dementia education strategy for BC physicians 2010-2012*. Vancouver, British Columbia, Canada: University of British Columbia; 2013:1-53. Available from: <http://www.health.gov.bc.ca.ezproxy>.

- library.ubc.ca/pharmacare/pdf/adti-ubc-cpd-final-report-for-distribution.pdf. Accessed April 15, 2019.
39. Wang PS, Patrick AR, Dormuth C, et al. Impact of drug cost sharing on service use and adverse clinical outcomes in elderly receiving antidepressants. *J Ment Health Policy Econ*. 2010;13(1):37-44.
40. Chen YJ, Sankaranarayanan J, Murman DL. PMH66 12-year trend analysis on the characteristics, primary payer, and prescribed medications of physician-office visits for patients with dementia in the United States. *Value Health*. 2011;14(7):A298-A299.
41. Sankaranarayanan J, Chen Y, Murman DL. PMH61 National estimates and characteristics of ambulatory care visits for dementia care in the United States, 1998-2007. *Value Health*. 2011;14(3):A197.
42. British Columbia Ministry of Health. The provincial dementia action plan for British Columbia. Available from: <http://www.health.gov.bc.ca/library/publications/year/2012/dementia-action-plan.pdf>. Accessed.
43. Antifeau E, Cook H, Drance E, et al. *Best practice guideline for accommodating and managing behavioural and psychological symptoms of dementia in residential care, a person-centered interdisciplinary approach*. British Columbia, Canada: Ministry of Health; 2012; 2019:1-16. Available from: <http://www.health.gov.bc.ca/library/publications/year/2012/bpsd-guideline.pdf>. Accessed April 15, 2019.
44. General Practice Services Committee. Complex care planning and management. Available from: <http://www.gpsc.bc.ca/family-practice-incentive/complex-care-initiative>. Accessed April 15, 2019.
45. Lavergne MR, Law MR, Peterson S, et al. A population-based analysis of incentive payments to primary care physicians for the care of patients with complex disease. *CMAJ*. 2016;188(15):E375-E383.

How to cite this article: Fisher A, Carney G, Bassett K, Maclure KM, Dormuth CR. Policy-induced selection bias in pharmacoepidemiology: The example of coverage for Alzheimer's medications in British Columbia. *Pharmacoepidemiol Drug Saf*. 2019;28:1067-1076. <https://doi.org/10.1002/pds.4804>