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THE EFFECT OF FINANCIAL AND EDUCATIONAL INCENTIVES ON RATIONAL PRESCRIBING. A STATE-SPACE APPROACH

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ABSTRACT

In 2005, a Dutch health insurer introduced a financial incentive directed to general practitioners to promote rational prescribing of statins and proton pump inhibitors (PPIs). Concomitantly, a regional institution that develops pharmacotherapeutic guidelines implemented two educational interventions also aiming at promoting rational statin and PPI prescribing. Utilizing a prescription database, we estimated the effect of the interventions on drug utilization and cost of statins and PPIs over time. We measured the effect of the interventions within an implementation and a control region. The implementation region included prescriptions from the province of Groningen where the educational intervention was implemented and where the health insurer is most active. The control region comprised all other provinces covered by the database. We modelled the effect of the intervention using a state-space approach. Significant differences in prescribing and cost patterns between regions were observed for statins and PPIs. These differences however were mostly related to the concurrent interventions of Proeftuin Farmacie Groningen. We found no evidence indicating a significant effect of the rational prescribing intervention on the prescription patterns of statins and PPIs. Our estimates on the economic impact of the Proeftuin Farmacie Groningen interventions indicate that educational activities as such can achieve significant cost savings. Copyright © 2014 John Wiley & Sons, Ltd.

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KEY WORDS: financial incentives; health insurers; drug prescribing; the Netherlands; state space; time series; Kalman filter

1. INTRODUCTION

Policy makers aim to control increasing pharmaceutical expenditures through various cost-containing measures. Such measures that target the consumer side rely mostly on cost sharing (Thomson and Mossialos, 2010), whereas measures directed to the health-care suppliers include financial incentives (e.g., gain-sharing, volume agreements, and pay-for-performance (P4P) incentives (Cromwell *et al*., 2011)), and educational interventions aiming to enhance more rational prescribing (RP) behavior (Boonen *et al*., 2007; Ostini *et al*., 2009; Boonen *et al*., 2010; Godman *et al*., 2010; Medves *et al*., 2010).

Pay-for-performance interventions are financial incentives, which encourage healthcare providers to achieve predefined performance targets. These interventions became popular in health care within the last decades mainly due to their attractive scope of improving the quality and/or reducing the cost of care. Although, predominantly, P4P interventions target improvements in quality of care, a number of P4P interventions aim directly at the reduction of prescribing costs (Beaulieu and Horrigan, 2005; Sheldon, 2006; Fuhrmans, 2008; Comma *et al*., 2009; Boonen *et al*., 2010; Godman *et al*., 2010; Flodgren *et al*., 2011; Godman *et al*., 2011). Estimates on the effectiveness and cost-effectiveness of such incentives are, however, inconclusive (Glasziou *et al*. 2012). A review of 32 financial incentives' studies revealed their potential effectiveness in reducing prescribing costs but found no evidence of their impact on patient outcomes (Flodgren *et al*. 2011). However, the

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review's conclusion was that overall there is limited evidence on the effect of financial incentives on altering prescribing behavior. An alternative method of reducing prescribing costs is to stimulate RP through the development of educational interventions that enhance cost-conscious behavior on the supplier's side. However, evidence on the effectiveness of these interventions is also inconclusive and varying across different types of educational interventions (Davis *et al*., 1995; Hogerzeil, 1995).

There is therefore considerable interest in the performance of such financial and educational interventions as so far their implementation has not been accompanied with enough evidence in support of their effectiveness and justifying their implementation (Cromwell *et al*., 2011). In order to contribute to this body of literature, we evaluate the effect of a financial and an educational intervention on prescribing behavior, drug utilization and treatment costs of statins and proton pump inhibitors (PPIs). To achieve that, a state-space methodology is used. State-space methods have been shown to be ideal for the analysis of intervention effectiveness through time-series data, but their use in health economics has so far been limited. All estimations are based on data extracted from a large prescription database from the northern part of the Netherlands.

2. THE INTERVENTIONS

In April 2005, Menzis, a major health insurer in the Netherlands, introduced the 'rational prescribing (RP) intervention', a target-based financial incentive aimed at enhancing RP by GPs (Sheldon, 2006). More specifically, GPs were financially rewarded for prescribing cheaper statin and PPI treatment alternatives to new patients for lowering cholesterol and reducing gastric acid, that is, the statin simvastatin and the PPI omeprazole, respectively. The rationale behind the intervention was the large share in pharmaceutical expenditures of statins and PPIs in the Netherlands, their large potential for expenditure reductions, since generics became available,[1] as well as the lack of sufficient clinical evidence on the superiority of any of the other statins or PPIs (Vakil and Fennerty, 2003; McDonagh and Carson, 2005; Weng *et al*., 2010). The financial rewards offered ranged from €0.25 per new patient for GPs who started 75% of their patients on simvastatin to €0.75 per patient for GPs who started 85% of their new statin patients on simvastatin. For the group of newly treated patients with acid-lowering therapy, the same rewards were offered for percentages of 90% and 95% of omeprazole starters, respectively. The implementation of the intervention was restricted to two provinces in the northeast of the Netherlands (Groningen and Gelderland), with a GP participation rate of 18–24% and 7–11%, respectively (iBMG, 2007). The intervention was terminated by the health insurer at the end of 2007, because the vast majority of the enrolled GPs had achieved target prescribing.

Around the same period, in an attempt to improve quality and efficiency of statin treatment for initially the diabetic and subsequently the general population, 'Proeftuin Farmacie Groningen' (PFG)[2] implemented the *hyperlipidemia* (HL) intervention. This intervention primarily aimed at the education and stimulation of GPs, pharmacists, and patients of the region of Groningen, regarding the rational use of statins and the better adherence of GPs to the PFG guidelines. In April 2004, the PFG initiated the implementation of the intervention by providing educational activities combined with a set of guidelines to health-care providers, suggesting preferred prescribing of simvastatin for patients with diabetes mellitus type 2. The HL intervention was officially announced in November 2004 and was soon expanded to non-diabetic populations. After its official announcement, the intervention was supported with additional educational activities, leaflets, and other informational materials and with wider publicity toward patients. Almost all pharmacies and the majority of GPs of Groningen participated in the HL project.

Concomitantly, PFG's multidisciplinary guidelines may also have significantly influenced the prescribing behavior for PPIs. In particular, these guidelines represent a set of prescribing recommendations, developed

[1]The generic version of omeprazole was introduced in April 2002 and that of simvastatin in May 2003, also initiating the availability of cheaper versions of the branded drugs (Pechlivanoglou, 2011).

[2]The institution Proeftuin Farmacie Groningen is a collaboration between health-care professionals in the northern Netherlands that primarily develops regional, pharmacotherapeutic guidelines. The main financial supporter of PFG until January 2012 had been the health insurer Menzis.

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by a panel of specialists, GPs and pharmacists, designed to assist the GP in prescribing effectively and rationally. In the multidisciplinary guidelines, advice is not limited on the effectiveness of treatment with a particular drug, but it refers also to its costs in comparison with the other drugs in the same group. By the end of 2003, a new version of the multidisciplinary guidelines had been distributed to the GPs, where omeprazole was indicated as the most rational option for starting PPI treatment given its costs and effectiveness.

Throughout the article, we broadly differentiate between two interventions; that is, (i) the RP intervention by Menzis concerning financial incentives for both simvastatin and omeprazole from the beginning of the initiative in 2005 and (ii) the PFG initiatives concerning education and guidelines on the RP of statin (HL intervention) and PPI (PFG guidelines) treatment.

3. DESCRIPTION OF THE DATA

All data were retrieved exclusively from InterAction database (IADB.n.l), a prescription database that comprises the full populations of the main cities and some regional centers in the northern and eastern parts of the Netherlands. The adherent population of IADB.nl is approximately 500,000 patients. The database was lastly updated to include prescription data up to the end of 2007. IADB.nl offers data that include patient level (such as date of birth, gender, and registered physician), prescription level (such as date of delivery, prescribing physician, geographical region, and health insurer), and drug level information (ATC, HPK, Z-index codes, etc.). Prescriptions were classified according to the region of the prescription's origin. Two regions were identified, one implementation region, where the RP and PFG interventions were primarily implemented, and one control region. The implementation region data included all prescriptions from the province of Groningen, whereas the control region data comprised all prescriptions from the rest of the provinces. The proportion of starters with simvastatin and omeprazole, the simvastatin and omeprazole utilization and the costs of average statin and PPI treatment per defined daily dose (DDD), was calculated using the prescription data on a monthly frequency and was subsequently analyzed using state-space time-series methods as described in the succeeding texts.

4. METHODS

Time-series data that may capture the impact of interventions are often analyzed through the difference-in-difference (DID) time-series method. This method estimates the impact of an intervention by comparing the difference of an outcome of interest in an implementation and a control region before and after the date the intervention was launched. Although this is an intuitively attractive method to estimate the impact of an intervention, it relies on a number of assumptions that often limit the accuracy or the efficiency of the estimates. Firstly, the DID method relies on the assumption that, conditional on a number of covariates, the trend between the implementation and the control region only differs because of the intervention of interest (Angrist and Pischke, 2008). This assumption is often likely to fail potentially causing bias on the estimates of the DID model. Moreover, the underlying assumption is difficult to be tested. Secondly, the DID method makes the implicit assumption of no serial correlation, which in a time-series setting is frequently present. The presence of serial correlation can result in an underestimation of the standard errors of the intervention coefficients (Bertrand *et al*., 2004). Although methods exist on incorporating serial correlation in a DID model (Greene, 2002), they are cumbersome and rarely used in practice (Bertrand *et al*., 2004).

In this study, an alternative and potentially more adequate approach is followed where a 'state-space' method is used (Durbin and Koopman, 2001; Commandeur and Koopman, 2007) in order to assess the effects of the two interventions on physician prescribing behavior. In particular, state-space methods have been shown to be ideal for the analysis of interventions when control groups are present with potentially differing trends prior to the interventions (Durbin and Koopman, 2001). In a state-space approach, the issue of serial correlation

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can also be straightforwardly incorporated (Koopman, 1997). In the succeeding texts, we first discuss the general state-space approach and then present the model that we specified for our empirical analyses.

4.1. State-space approach

A state-space model consists of two equations, an observation equation and a system or state equation. Let y_t be a q-dimensional vector having as elements the values of the outcome variables at time t (with $t = 1,\ldots, T$). The observation equation can then be described as

$$\underset{q\times 1}{y_t} = \underset{q\times p}{F_t}\ \underset{p\times 1}{\theta_t} + \underset{q\times 1}{u_t},$$

where F_t is a matrix containing p regressors that possibly affect y_t and θ_t is a p-dimensional vector containing the corresponding p parameters to be estimated. The values of θ_t are not directly observed but are determined in the system and describe the 'state' of the system. Therefore, θ_t is denoted as the state vector. The error term u_t is assumed to be serially independent and normally distributed with zero mean and variance-covariance matrix U_t. The numbers below the formula indicate the dimensions of the vectors and matrices involved.

One of the advantages of a state-space model is that the parameters (or states) θ_t are allowed to vary over time, as indicated by the index t, thereby accommodating longitudinal changes in the model's functional form. This is especially useful in applications where θ_t contains level and trend parameters, which are possibly affected by interventions. The evolution of the parameter vector over time is described in the state equation:

$$\underset{p\times 1}{\theta_t} = \underset{p\times p}{G_t}\ \underset{p\times 1}{\theta_{t-1}} + \underset{p\times r}{R_t}\ \underset{r\times 1}{w_t},$$

where G_t is the matrix, which describes the evolution of the state vector over time, and R_t is an indicator matrix, governing which states are time varying. The error term w_t is assumed to be serially independent and normally distributed with mean zero and variance W_t. Estimates for the states θ_t can be obtained through the use of the Kalman filter (Koopman, 1997).

The simplest form of a state-space model is the local level model (Commandeur & Koopman, 2007), which is achieved by setting $\theta_t = \mu_t$, $U_t = \sigma_w^2$, $W_t = \sigma_w^2$, and $F_t = G_t = R_t = 1$. This model resembles in structure the classical linear regression model $y_t = \mu + w_t$ the only difference being that the intercept μ is allowed to vary over time.

The state-space modeling method provides a general and flexible structure, making it widely applicable (Durbin and Koopman, 2001). For example, the linear regression models, as well as the Box–Jenkins and autoregressive integrated moving average (ARIMA) time-series models, are special cases of this modeling approach. In contrast to ARIMA models, state-space models can handle non-stationarity issues in a very straightforward way. Particularly, the application of the exact initialization procedure, where the parameters are separated into stationary and nonstationary ones, facilitates the application of the Kalman filter for any nonstationary model (Koopman, 1997). Hence, state-space models do not rely on unit root testing procedures thereby avoiding their known weaknesses, as highlighted by Maddala and Kim (1998, p. 45). Specifically, as Mandala and Kim comment unit root tests 'are useless in practice and should not be used.' (See also Osinga *et al.*, 2010 for a discussion on the advantages of avoiding unit root tests). Secondly, state-space methods accommodate the possibility that a time series contains periods in which the system is stationary, as well as periods where the system is nonstationary. This very aspect makes state-space modeling a very suitable approach for our situation, where we want to study the effect of multiple interventions (Zivot and Andrews, 1992). Thirdly, multivariate analysis in state-space models is applied much easier compared with conventional time-series methods, such as in ARIMA models (Durbin and Koopman, 2001). Fourthly, state-space models are capable of dealing with missing observations on the studied variable easier than standard ARIMA models by for example skipping the Kalman filter updating equation at the time points of missing observations (Harvey, 1989). A fifth advantage of the Kalman filter method comes from its Markovian nature, because large models can be estimated without disproportionate increase in computational times. For the same reason, updating of the parameter estimates

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after the addition of a new time point in the time series can be performed in a computationally efficient way (Stathopoulos and Karlaftis, 2003). Finally, specification of explanatory variables in the observation and/or state equations allows controlling for external parameters that might have an impact on the studied variables of the state-space model. Durbin and Koopman (2001) offer a thorough presentation of the advantages of the state-space methodology, in comparison with more conventional approaches in the analysis of time-series data.

4.2. Model specification

Given that the interventions of interest primarily targeted new users with the goal to enhance the overall use of the preferred drugs and subsequent lowering of the treatment costs, we focused our analysis on the frequency of prescriptions to starters, the market share of simvastatin and omeprazole and the average monthly cost per DDD of statin and PPI treatment.

In the succeeding texts, we introduce different variables that capture the effect of the interventions and other events on the variable of interest. We distinguish between pulse, level and trend variables. Pulse variables capture instantaneous effects of specific events; they are equal to one at the time point of the event and zero for all other time points. Level variables capture permanent or temporary effects of an event on the level of the time series. Permanent level variables are zero for the period before the event takes place and take the value of one thereafter. Temporary level variables are set to one for the period in which the event takes place and to zero for all other time points. Finally, trend variables capture the effect of an intervention on the trend of the time series. Similarly to the level variables, trend variables capture either temporary or permanent effects.

Let FSt_t^S, MS_t^S, and Ctr_t^S be the vectors capturing the frequency of simvastatin starters, simvastatin market share among statins and the monthly average cost of statins, measured as the average statin cost per DDD, in both implementation (superscript I) and control regions (superscript C) at time t for $t = 1,\ldots, T$. We specify the measurement equations for statins as

$$FSt_t^S = \begin{pmatrix} FSt_t^{I,S} \\ FSt_t^{C,S} \end{pmatrix} = \beta_{0t} + \beta_1 d_t + \beta_2 HL1lev_t + \beta_3 HL1tr_t + \beta_4 HL2NOV_t + \beta_5 HL2lev_t + \beta_6 HL2tr_t + \beta_7 RPlev_t + \beta_8 RPtr_t + \beta_9 EXPSlev_t + \beta_{10} EXPStr_t + \beta_{11} COV_t + v_t \quad , \tag{1}$$

$$MS_t^S = \begin{pmatrix} MS_t^{I,S} \\ MS_t^{C,S} \end{pmatrix} = \gamma_{0t} + \gamma_1 d_t + \gamma_2 HL1lev_t + \gamma_3 HL1tr_t + \gamma_4 HL2NOV_t + \gamma_5 HL2lev_t + \gamma_6 HL2tr + \gamma_7 RPlev_t + \gamma_8 RPtr_t + \gamma_9 EXPSlev_t + \gamma_{10} EXPStr_t + \gamma_{11} COV_t + z_t \quad , \tag{2}$$

$$Ctr_t^S = \begin{pmatrix} Ctr_t^{I,S} \\ Ctr_t^{C,S} \end{pmatrix} = \xi_{0t} + \xi_1 d_t + \xi_2 HL1lev_t + \xi_3 HL1tr_t + \xi_4 HL2NOV_t + \xi_5 HL2lev_t + \xi_6 HL2tr_t + \xi_7 RPlev_t + \xi_8 RPtr_t + \xi_9 EXPSlev_t + \xi_{10} EXPStr_t + \xi_{11} COV_t + e_t \quad , \tag{3}$$

where d_t is a trend variable capturing the overall trend of the independent variable. The variables $HL1lev_t$ and $HL1tr_t$ capture the level and trend effects of the initiation of the HL intervention between April 2004 (initiation of HL intervention) and November 2004 (official announcement of HL intervention). The variables $HL2lev_t$ and $HL2tr_t$ capture the level and trend effects of the official announcement (November 2004) of the HL intervention. The pulse variable $HL2NOV_t$ was added to capture the instantaneous effect of the official announcement of the HL intervention (November 2004). The level and trend effects of the RP intervention (April 2005) are captured in the model through the variables $RPlev_t$ and $RPtr_t$. All these variables have zero value for the control region, because the intervention was active only in the implementation region.

Three additional variables *w*ere included to correct for possible market shocks. A level and a trend variable ($EXPSlev_t$ and $EXPStr_t$, respectively) were included in order to capture any effects of the introduction of generic simvastatin (May 2003). The level variable COV_t corrects for the Covenant agreement, made in February 2004, between pharmacies, health insurers, generic producers and the government aiming at the reduction of retail drug prices for generics. These variables were defined in a similar way in both implementation and control region, as

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it was assumed that both regions could have been affected by these market shocks. Finally, v_t, z_t, and e_t are serially independent normally distributed errors with variance-covariance matrix V_t, Z_t, and E_t, respectively.

Similarly we introduce FSt_t^P, MS_t^P, and Ctr_t^P as the vectors capturing the frequency of omeprazole starters, omeprazole market share, and cost of treatment of PPIs in both implementation (superscript *I*) and control regions (superscript *C*) at time t for $t = 1,\ldots, T$. We specify the corresponding measurement equations as

$$FSt_t^P = \begin{pmatrix} FSt_t^{I,P} \\ FSt_t^{C,P} \end{pmatrix} = \beta_{0t} + \beta_1 d_t + \beta_2 MGlev_t + \beta_3 MGtr_t + \beta_4 RPlev_t + \beta_5 RPtr_t + \beta_6 EXPOlev_t + \beta_7 EXPOtr_t + \beta_8 COV_t + v_t \quad (4)$$

$$MS_t^P = \begin{pmatrix} MSt_t^{I,P} \\ MSt_t^{C,P} \end{pmatrix} = \gamma_{0t} + \gamma_1 d_t + \gamma_2 MGlev_t + \gamma_3 MGtr_t + \gamma_4 RPlev_t + \gamma_5 RPtr_t + \gamma_6 EXPOlev_t + \gamma_7 EXPOtr_t + \gamma_8 COV_t + z_t \quad (5)$$

$$Ctr_t^P = \begin{pmatrix} Ctr_t^{I,P} \\ Ctr_t^{C,P} \end{pmatrix} = \xi_{0t} + \xi_1 d_t + \xi_2 MGlev_t + \xi_3 MGtr_t + \xi_4 RPlev_t + \xi_5 RPtr_t + \xi_6 EXPOlev_t + \xi_7 EXPOtr_t + \xi_8 COV_t + e_t \quad (6)$$

where, in addition to the variables defined earlier, we let $MGlev_t$ and $MGtr_t$ capture the effect of the introduction of the multidisciplinary guidelines (January 2004) on the level and trend of the variables of interest in the implementation region whereas $EXPOlev_t$ and $EXPOtr_t$ are the level and trend variables that capture the effect of the introduction of generic omeprazole (April 2002) in both regions.

Because we are primarily interested in the impact of the RP and PFG interventions, but simultaneously in the most parsimonious models possible, we utilized the Akaike information criterion (AIC) to reduce the number of parameters to be estimated (Akaike, 1973; Durbin and Koopman, 2001). Thus, the final model for each of the 1–6 models consisted of a number of key variables and a number of control variables that were selected according to their impact on the model's AIC. As key variables, we selected those that are related to the RP and PFG interventions ($HL1lev_t$, $HL1tr_t$, $HL2NOV_t$, $HL2lev_t$, $HL2tr_t$, $RPlev_t$, and $RPtr_t$, for the statin models; and $MGlev_t$, $MGtr_t$, $RPlev_t$, and $RPtr_t$ for the PPI models); the other variables were selected on the basis of their impact on AIC.

The evolution of the parameters over time in all six models is specified in the state equations:

$$\beta_t = G_{Ft}\beta_{t-1} + R_{Ft}w_{Ft},$$
$$\gamma_t = G_{Mt}\gamma_{t-1} + R_{Mt}w_{Mt},$$
$$\xi_t = G_{Ct}\xi_{t-1} + R_{Ct}w_{Ct},$$

where β_t, γ_t, and ξ_t are state vectors consisting of the parameters estimated in equations 1 and 4, 2 and 5, and 3 and 6, respectively; G_{Ft}, G_{Mt}, and G_{Ct} are identity evolution matrices; and R_{Ft}, R_{Mt}, and R_{Ct} are indicator matrices, which ensure that only the intercepts β_0, γ_0, and ξ_0 vary over time. Finally, w_{Ft}, w_{Mt}, and w_{Ct} are normally distributed serially independent error terms with mean zero and variances W_{Ft}, W_{Mt}, and W_{Ct} for the three models, respectively. We assume that w_{Ft}, w_{Mt}, and w_{Ct} are mutually uncorrelated.

In order to verify that the underlying assumptions for the estimation procedure were satisfied, we performed a number of diagnostic tests on all models. We assessed the independence, heteroscedasticity, and normality of the residuals based on the procedures described in Durbin and Koopman (2001). On the basis of the standardized transformed prediction errors $\hat{u}_t$, we calculated the Box–Ljung Q statistic, the H statistic, and the Jarque–Bera N statistic in order to test for independence, heteroscedasticity, and normality, respectively (Durbin and Koopman, 2001; Commandeur and Koopman, 2007). We additionally estimated the auxiliary observation and state residuals, $\hat{\varepsilon}_t^s$ and $\hat{\eta}_t^s$ (Commandeur and Koopman, 2007), to detect potential outliers and structural breaks that the model did not accommodate. The statistical procedures described earlier were performed using the freely available software *R* version 2.13.2 (R Development Core Team, 2010) and the R package KFAS (Kalman Filter and Smoother for Exponential Family State Space Models) (Helske 2011).

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4.3. Economic impact of the interventions

To approximate the potential savings of the interventions of Menzis and the PFG, we followed the same state-space modeling approach as aforementioned, but now we applied it to the difference of the cost per DDD of treatment between the implementation and the control regions. Through that approach, we distinguished the effect of the interventions from events that affected the treatment cost on a national scale. Subsequently, we calculated the effect of the interventions on this cost difference by predicting the cost difference in the absence of the interventions and subtracting it from the observed cost difference. Finally, in order to calculate the total cost savings, we multiplied the effect of the intervention on the cost difference with the total volume in DDDs that was prescribed in the implementation region. We followed this procedure for both statins and PPIs.

5. RESULTS

We extracted 1,105,598 statin and 1,147,577 PPI prescriptions from approximately 58,700 and 111,850 patients, respectively, for the period between January 1st 2000 and December 31st 2007.We estimated the effect of the RP and the HL interventions on the utilization and cost of statins in both study regions.

Figure 1a displays the proportion of the statin population starting treatment with simvastatin FSt_t^S; Figure 1b, the market share of simvastatin MS_t^S; and Figure 1c, the cost per DDD of statin treatment Ctr_t^S. A significant

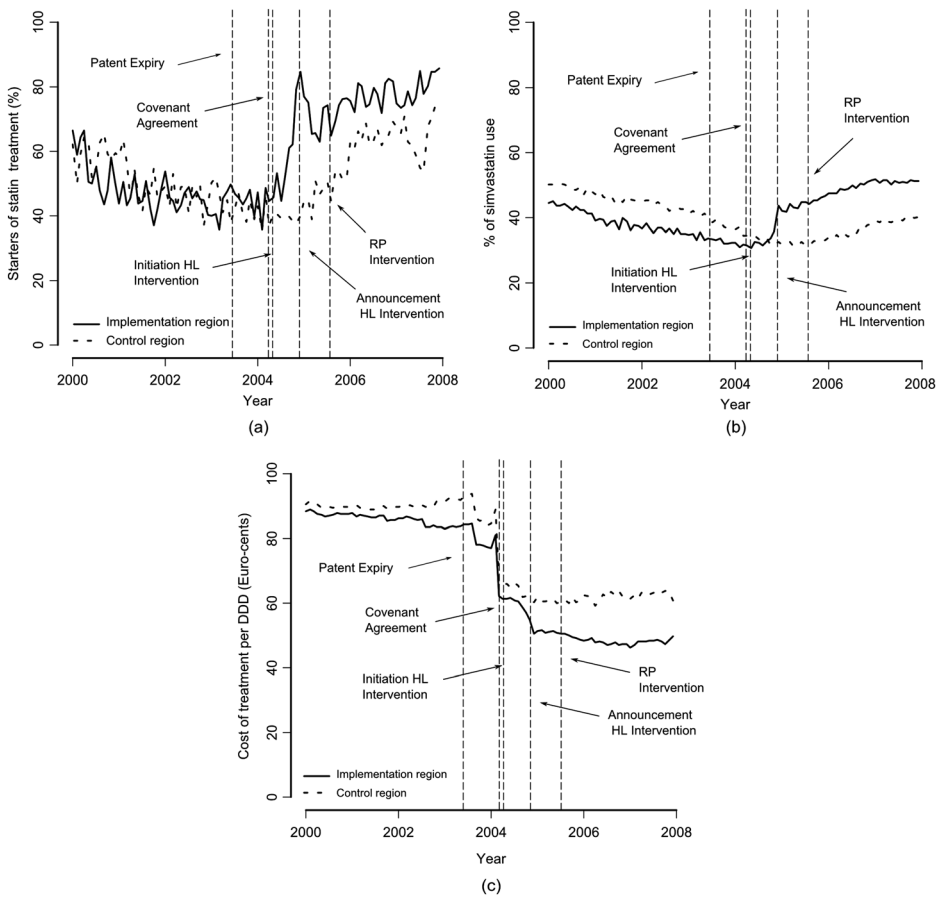

Figure 1. Frequency of starters of simvastatin (a), simvastatin market share (b), and cost per defined daily dose (DDD) of statin treatment (c) from January 2000 to December 2007. HL, hyperlipidemia; RP, rational prescribing

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divergence can be noticed in the prescribing patterns and statin treatment costs between the control and implementation regions, after the HL intervention. Regarding the initiation of simvastatin treatment and simvastatin's market share in the implementation region, we observe a change around the date of the initiation of the HL intervention by the PFG (April 2004), whereas the cost of statin treatment in the implementation region seems to be smaller throughout the whole study period. No significant effect of the RP intervention can be visually identified in either region. A considerable reduction in simvastatin starters is observed around the second trimester of 2007, in the control region. This is the effect of a Dutch TV program (Tros RADAR), broadcasted in March 2007, which broadly exposed the various side effects that can accompany statin use (Bos, 2007).

In Figure 2, we present the proportion of PPI users starting with omeprazole FS_t^P (Figure 2a), the total market share for omeprazole MS_t^P (Figure 2b), and the cost per DDD of PPI treatment Ctr_t^P (Figure 2c) between January 2000 and December 2007, for both regions. We notice an increase in the market share of omeprazole in the implementation region around the beginning of 2004, the time point when the multidisciplinary guidelines were issued by PFG. The market share of omeprazole in the implementation region started diverging from that in the control region after 2002, when generic omeprazole was introduced. A similar pattern can be observed for the proportion of PPI users starting with omeprazole although the increasing trend in the implementation can be observed already from the first trimester of 2003. The cost per DDD of PPI treatment follows a similar pattern

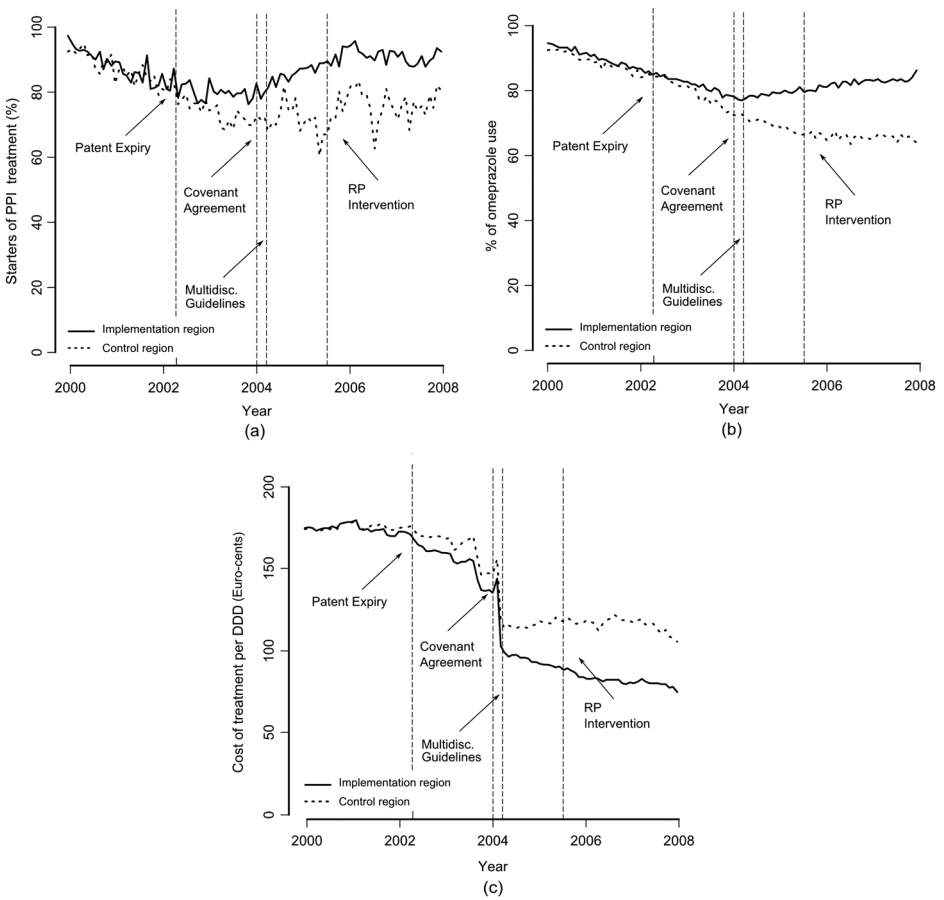

Figure 2. Frequency of starters of omeprazole (a), omeprazole market share (b), and cost per defined daily dose (DDD) of proton pump inhibitors (PPI) treatment (c) from January 2000 to December 2007. RP, rational prescribing

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to that of statins in Figure 1c where the costs in both regions are mostly influenced by national shocks such as the Covenant agreement.

Table I presents the estimates of the state-space models for FSt_t^S, MS_t^S, and Ctr_t^S. We observe a positive trend effect from the initiation of the HL intervention and a subsequent level increase of the simvastatin starters, after the official announcement of the HL project (November 2004), in the implementation region. For the market share of simvastatin, the effect of the HL intervention in the implementation region is more apparent both on the trend and on the level of the time series. Regarding the cost of statin treatment, we notice the highly significant effect of the Covenant agreement for both regions, as well as the reflection of the increased use of the cheaper simvastatin in the implementation region after the announcement of the HL intervention. None of the level or trend variables of the RP intervention captured a significant effect in the implementation region for all statin time series studied. Nevertheless, we observe an increase in the market share of simvastatin in the control region after the date of the RP intervention. This increase however coincides with an increase in simvastatin use on a national level and can, at least partially, be attributed to other national initiatives that took place from the end of 2005 onwards (Ohlsson *et al*., 2011). According to the AIC, the contributions of the generic introduction variables were not substantial and were therefore excluded from the final model. No heteroscedasticity or serial correlation was observed for any of the time series; however, the normality assumption of the standardized residuals was violated slightly for the time

Table I. Parameter estimates and standard errors of the state-space models on the proportion of simvastatin starters, simvastatin market share and cost per defined daily dose of statin treatment. Standard errors presented in brackets. Bold estimates indicate significance in a significance level $\alpha = 0.05$

	Proportion of starters		Market share		Cost of treatment	
Explanatory variables	Implementation region	Control region	Implementation region	Control region	Implementation region	Control region
Overall trend	−0.338	−0.317	**−0.267**	**−0.304**	−0.153	−0.05
	(0.326)	(0.351)	**(0.05)**	**(0.041)**	(0.141)	(0.158)
Covenant agreement						
Level					**−18.662**	**−21.989**
					(1.043)	**(1.338)**
Post initiation of HL intervention						
Level	−6.42	−3.26	−0.884	−0.337	0.239	0.126
	(4.952)	(4.986)	(0.857)	(0.707)	(1.105)	(1.423)
Trend	**4.526**	0.278	**0.815**	−0.106	−0.761	−0.657
	(1.106)	(1.151)	**(0.186)**	(0.155)	(0.4)	(0.458)
Post announcement of HL intervention						
Pulse	10.808	−2.075	**2.193**	0.556	−1.059	−1.682
	(5.842)	(5.747)	**(1.048)**	(0.859)	(1.117)	(1.441)
Level	**31.22**	1.843	**11.76**	−1.154	**−9.021**	−3.872
	(9.035)	(9.453)	**(1.556)**	(1.298)	**(3.423)**	(3.928)
Trend	−0.008	1.406	**0.752**	0.267	−0.01	−0.189
	(1.244)	(1.292)	**(0.21)**	(0.174)	(0.428)	(0.493)
RP intervention						
Level	−3.03	−2.27	−0.113	−0.252	0.045	0.834
	(4.671)	(4.708)	(0.806)	(0.665)	(1.049)	(1.321)
Trend	0.932	−0.203	−0.25	0.338	0.124	0.274
	(1.279)	(1.33)	(0.215)	(0.179)	(0.446)	(0.512)
Diagnostic tests (*P*-values)						
Nu	0.482	0.667	0.230	0.554	**<0.001**	**<0.001**
Nε	0.952	0.116	**0.005**	0.274	0.721	0.837
Nη	0.546	0.822	0.358	0.750	**<0.001**	0.446
Q	0.524	0.975	0.065	0.279	0.393	0.937
$H_{n/3}$	0.139	0.362	0.279	0.315	0.947	0.999

DDD, defined daily dose; HL, hyperlipidemia; RP, rational prescribing; N, Jarque–Bera normality test; Q, Box–Ljung test; H, heteroscedasticity test.

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Table II. Parameter estimates and standard errors of the state-space models on the proportion of omeprazole starters, omeprazole market share, and cost per defined daily dose of proton pump inhibitor treatment. Standard errors presented in brackets. Bold estimates indicate significance in a significance level $\alpha = 0.05$

	Proportion of starters		Market share		Cost of treatment	
Explanatory variables	Implementation region	Control region	Implementation region	Control region	Implementation region	Control region
Overall trend	**−0.314**	**−0.462**	**−0.345**	**−0.317**	−0.796	0.001
	(0.126)	**(0.222)**	**(0.015)**	**(0.051)**	(0.285)	(0.348)
Covenant agreement						
Level					**−40.113**	**−37.147**
					(2.054)	**(2.753)**
Generic introduction (4–2002)						
Level						
Trend				**−0.232**		
				(0.081)		
Multidisciplinary guidelines						
Level	−0.778	0.369	−0.842	−0.097	**9.601**	**9.237**
	(1.908)	(3.097)	(0.404)	(0.671)	**(2.052)**	**(2.737)**
Trend	**0.903**	0.17	**0.512**	**0.189**	−0.132	0.486
	(0.263)	(0.455)	**(0.038)**	**(0.092)**	(0.569)	(0.698)
RP intervention						
Level	0.575	**6.514**	0.099	0.180	1.463	2.749
	(1.893)	**(3.07)**	(0.406)	(0.655)	(2.028)	(2.679)
Trend	−0.522	−0.507	−0.034	**0.299**	0.417	−0.48
	(0.287)	(0.497)	(0.041)	**(0.087)**	(0.618)	(0.757)
Diagnostic tests (*P*-values)						
Nu	**0.037**	**<0.001**	**0.035**	0.626	0.347	**<0.001**
Nε	**0.015**	0.063	0.550	0.856	**0.001**	**0.002**
Nη	0.819	**0.030**	0.208	0.977	0.124	0.054
Q	0.267	0.897	0.292	0.692	0.711	**0.021**
$H_{n/3}$	0.051	0.987	0.986	0.927	0.981	0.678

DDD, defined daily dose; RP, rational prescribing; N, Jarque–Bera normality test; Q, Box–Ljung test; H, heteroscedasticity test.

series capturing the cost per DDD of statin treatment. No significant outliers or structural breaks were observed through the auxiliary residuals.[3]

In Table II, we notice that the effect of the multidisciplinary guidelines on the trend of omeprazole utilization in the implementation region is evident, but the same region was not significantly affected by the RP intervention. Again, we observe a positive effect on the trend of omeprazole's market share from the RP intervention, in the control region. Similar to the cost of statins, the cost of PPI treatment was significantly affected by the Covenant agreement, but there is no evidence for a significant effect of the RP intervention on the cost of PPI treatment in any region. The significant effect of the multidisciplinary guidelines on the level of cost of PPI treatment is possibly caused by yet another earlier measure to control prices, known as the 'De Geus' measure (Griens *et al.*, 2008). Diagnostic checking of the estimated models provided no evidence of serial correlation and heteroscedasticity. However, some deviations from normality were observed. No important outliers or structural breaks were observed through the auxiliary residuals.

As far as the economic impact is concerned, we observed a significant financial benefit resulting only from the influence of the PFG interventions in prescribing behavior (Figure 3). For statins, we estimated that the HL intervention reduced the cost of treatment with €0.038/DDD, on average, which resulted in a total estimated cost savings of €1.57m in a 3.5-year period. Regarding the PPIs, the absolute difference in the treatment cost

[3]There was one outlier observed for the proportion of the statin population starting treatment with simvastatin in the control region around the period of the Tros RADAR TV program. However, inclusion of a pulse variable capturing the effect of this TV program did not significantly improve the model, based on the AIC, and was therefore excluded.

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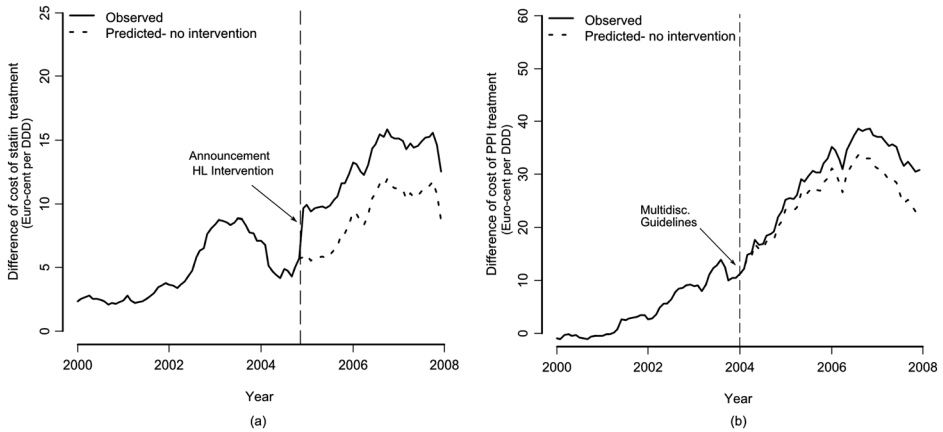

Figure 3. Difference of cost per defined daily dose (DDD) between the implementation and the control region with or without the Proeftuin Farmacie Groningen interventions for statin (a) and proton pump inhibitors (PPI) (b) treatment from January 2000 to December 2007

was similar to that of statins (average €0.039/DDD), but because the DDD volume of PPI prescriptions was smaller to that of statins, this resulted in the total savings of approximately €0.79m, in the 4 years since the recommendation for omeprazole in the multidisciplinary guidelines was introduced.

6. DISCUSSION

In this study, we analyzed the longitudinal effect of a financial incentive offered by an insurer in the Netherlands, aiming at the stimulation of GPs' RP of statins and PPIs, while taking into account the effect of concomitant, regional interventions by PFG, an institution that develops pharmacotherapeutic guidelines. We applied a novel, for health economics, state-space model to identify the effect of these interventions on the prescribing patterns of statins and PPIs. Our analysis did not identify any significant effects from the RP intervention in the implementation region for both drug classes. Yet, the introduction of the HL intervention and the multidisciplinary guidelines by the PFG was found to be strongly related to increases in the proportions of starters of simvastatin and omeprazole. We can conclude that the identified prescribing patterns of statins and PPIs mainly originated from the interventions of the PFG, whereas the RP intervention was not found to be associated with any changes in prescribing behavior.

This lack of association is not entirely surprising because both the HL intervention and the multidisciplinary guidelines had already significantly affected the GPs' behavior regarding treatment initiation with simvastatin and omeprazole, accordingly. Hence, the additional incentive of Menzis by means of the RP intervention might have not been relevant in further increasing these proportions of starters. Furthermore, because of potential intolerability to certain drug types or because of other clinical or patient reasons, it may be expected that a ceiling for the number of starters on one specific drug exists. It is interesting to note that the average proportion of starters for both groups was approximately equal or larger than the thresholds for the GPs within the RP intervention. Therefore, many GPs were already eligible for the financial bonus even without any changes in prescribing. Finally, the absence of an effect on drug utilization from the treatment cost reductions due to the 'covenant agreement' is not surprising because prescribers in the Netherlands are generally inelastic to price fluctuations and price has a little impact on prescribing behavior (Leeflang and Wieringa, 2010).

The absence of a positive effect for the RP intervention is consistent with previous findings on the effect of financial incentives. Particularly, a behavior-independent financial incentive given to Dutch GPs with the aim of closer adherence to the national guidelines had small and only temporary effects on prescribing behavior (Martens *et al*., 2007). Additionally, a similar finding was recently observed for the effect of the Quality and

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Outcomes Framework, a P4P incentive introduced in UK (Serumanga *et al*., 2011). Conversely, Sturm *et al.* (2007) identified, through a literature review, reductions in prescribing costs in a number of studies on financial incentives. These controversies in the findings illustrate that the success of financial incentives is highly dependent on the effect modifiers at the setting in which they are applied (Glasziou *et al*., 2012).

The positive impact of the educational interventions of PFG on statin and PPI prescribing is in line with what was identified earlier in the literature for the same interventions (iBMG 2007); although in our study, this effect was more pronounced than in the Institute of Health Policy & Management (iBMG) study. Another difference with the iBMG study is the explicit incorporation of the effect of the RP intervention on the analysis, because in our study, a non-intervention region has been used as control. Additionally, the econometric approach followed in our study offered the opportunity to test the impact of the interventions on drug utilization and costs using hypothesis testing and not in a purely descriptive way.

Similar educational interventions as the PFG one were not always deemed equally successful. A significant number of controlled interventions in education activities offered to prescribers were modestly, if at all, effective on altering their prescribing behavior (Headrick *et al*., 1992; Hogerzeil, 1995; Grimshaw *et al*., 2004; Keller *et al*., 2011). Within the Netherlands, an intervention aiming at the dissemination of clinical multidisciplinary guidelines found a significant effect on altering prescribing behavior for statin dugs, thereby increasing statin utilization (Martens *et al*., 2006). However they did not find a change in prescribing behavior for any other drug classes studied. Although the result regarding statin prescribing supports our finding, lack of an observed effect in the other drug classes reduces the potential of an extrapolation of our study's finding to other drug classes.

The state-space methodology used in this study has so far not been extensively used in the field of health economics. The flexibility of the state-space analysis, as well as the possibility it offers to structurally analyze the problem, gives advantages over other time-series approaches such as the ARIMA or the Box–Jenkins analysis. The recursive estimation procedure of the state-space model does not require stationarity, because any type of time-varying effects can be accommodated by its structure. In addition, the joint specification of equations for the two regions accommodates shocks to the system, such as national market shake-ups, that might have simultaneously affected both markets. Durbin and Koopman (2001) offer a thorough presentation of the state-space methodology's advantages, in comparison with traditional approaches in the analysis of time-series data. Finally, another advantage is that the implementation of state-space methodology is now becoming available in standard statistical software thereby facilitating its implementation.

As every model, our approach suffers from a number of limitations. An important drawback is the proximity of concomitant, possibly related interventions in our models, which are sometimes difficult to disentangle, both on a technical and on a theoretical level. However, we have tried to reduce the number of interventions modeled by removing uninformative effect variables, through the use of the AIC, and applied even more parsimonious models with similar results (data not shown, available on request at the 1st author).

Next to the regional interventions mentioned in this paper, a number of national interventions took place concomitantly, which might have influenced our estimates. In particular, the significant increase in the relative level of simvastatin starters after the RP intervention in the control group can mainly be present because, next to the regional interventions, other national initiatives took place from the end of 2005 onwards. A large influence must have been the recommendation of the national guideline for cardiovascular risk management in 2006 for the initiation of statin treatment with simvastatin. The effect of this guideline, as well as the same increase in simvastatin as the one noted in our results, has been recently illustrated in the paper of Ohlsson *et al.* (2011) but also earlier in iBMG (2007). Additionally, other local initiatives from other health insurers and local guidelines could have been influential for that increase of simvastatin and omeprazole use.

As already mentioned, the uptake of the RP intervention in the implementation region was limited ($<24\%$). This implies that our inability to observe an effect of the RP intervention might be, at least partially, due to the low uptake and not to its lack of influence. Ideally, analyzing the subsample of GPs in the implementation region that had been contracted by Menzis would give more information regarding the effectiveness of the intervention to influence prescribing behavior on the individual GP. Unfortunately, the database used

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did not include such information. However, the low uptake itself can be seen as a reflection of the ineffectiveness of the intervention.

In the estimation of the expected savings of the interventions, we assumed that the control region can serve as a proxy for the cost of treatment had the interventions not occurred. This might be a very general assumption, although the mean, annual costs per DDD of statin and PPI treatment for the control region, during the period 2000–2008, are indeed comparable with the national ones (www.gipdatabank.nl).

7. CONCLUSION

In summary, we have found that the prescribing behavior of GPs and, consequently, the costs of treatment with statins and PPIs differed over time, both within and between the two regions. On the basis of the results of our state-space models, it can be concluded that the differences have been more likely caused by the concurrent interventions of PFG rather than the RP prescribing intervention of Menzis. Our estimates on the economic impact of the PFG intervention indicate that such educational activities can achieve significant cost savings for the healthcare payer, as long as they do not exceed the intervention cost.

CONFLICT OF INTEREST

The authors have no conflict of interest.

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