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ORIGINAL ARTICLE

The impact of cost-sharing schemes on drug compliance in Italy: evidence based on quantile regression

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Abstract
Objectives In this article we investigate the causal effect of cost-sharing schemes on compliance with statins in a quantile regression framework.
Methods We use the health search CSD-LPD data, a longitudinal observational dataset containing computer-based patient records collected by Italian general practitioners. We exploit a series of natural experiments referring to several introductions of co-payment schemes in some of the Italian regions between 2000 and 2009. We adopt an extended difference-in-differences approach to provide quantile estimates of the impact of co-payments on compliance.
Results We find that (i) introduction of co-payments hurts residents of regions with worse quality and provision of health care; (ii) within these regions, co-payments were particularly harmful for high compliers; (iii) gender, clinical history and geographic residence are important determinants of compliance among poor compliers; (iv) compliance decreases with the potency and dosage of statins, particularly for poor compliers.
Conclusions In the presence of inefficient health-care provision, co-payments are harmful for drug compliance, and this is especially true for patients who are originally good compliers.

Keywords Compliance · Cost sharing · Co-payments · Quantile regression · Difference-in-differences · Statins · Cholesterol

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Introduction

Poor drug compliance prevents patients from obtaining complete treatment effects and may thus lead to future costly adverse events (Hockley and Gemmill 2007; Sabate 2003). Poor compliance is exacerbated in treatments of chronic asymptomatic conditions, which require long and rigorous application, but are often imperceptible in their effects (Jackevicius et al. 2002; Shrank et al. 2006). An example is of hypercholesterolemia, one of the key risk factors for cardiovascular disease. The effectiveness of cholesterol-lowering therapies such as statins is contingent on high compliance, which in practice is difficult to achieve (Deambrosis et al. 2007; Schultz et al. 2005; Gibson et al. 2006). This undertreatment of hypercholesterolemic patients results in a greater risk of cardiac events and hence a major use of expensive medical services and hospitalizations (Ellis et al. 2004; Avogaro et al. 2007).

Compliance may be utterly challenged by prescription drug cost-sharing schemes. This powerful policy tool is introduced to control drug spending, by either reducing excessive and unmotivated drug consumption or by shifting drug consumption toward cheaper generic/preferred brand drugs. The cost-effectiveness of co-payment interventions is then evaluated in terms of their capacity to control drug

expenditure in the short run (Ess et al. 2003), often neglecting their medium and long-term effects on patient health (Roy and Madhavan 2008). In fact, in the presence of inefficiencies and financial constraints, patients are likely to trade their future health for present saving and cut down too heavily on drug consumption.

The aim of this study is to investigate the impact of co-payments on compliance. Although the empirical literature suggests that on average cost-sharing reduces compliance (Choudhry et al. 2008; Gibson et al. 2006; Atella, Rosati and Rossi 2006), little is known about its distributional effects. The average impact may imply substantial effects for a few patients and negligible ones for the rest, or vice versa. We thus analyze the distributional impact of co-payments and other determinants of compliance using quantile regression (QR). In particular, we extend the standard difference-in-differences (DiD) approach, allowing for a quantile estimation of the impact of co-payment schemes (Borah et al. 2011).

We exploit a series of natural experiments based on the introduction of co-payment schemes in several regions of Italy. In 2001, Law 16 November 2001 n. 405 delegated the management of co-payments to regional authorities. Since then, several regions have introduced co-payment schemes. Each scheme imposed a flat contribution charge per prescription, independently of the drug price. The contributions were similar in magnitude across all regions.

Our empirical analysis is based on the Health Search CSD-LPD (HS) data, a rich observational dataset containing computer-based patient records collected by a sample of Italian general practitioners (GPs). The longitudinal nature of the data allows us to study not only "differences of quantiles" following co-payment introduction, but also "quantiles of differences" in compliance, accounting for the individual patient heterogeneity. Our findings show that in regions with less efficient health-care provision, co-payments cause major reductions of compliance for high compliers and hence provoke a reallocation of individuals from the upper to the lower tail of the compliance distribution. This result suggests that while low compliance is only weakly related to financial constraints, in the presence of inefficiencies high compliance is more discouraged by the introduction of additional out-of-pocket payments.

Methods

Data

The HS contains information on individual drug prescriptions [dispensing date, anatomical therapeutic chemical (ATC) code, quantity and type of active ingredient and the number of tablets], general practitioner recommended daily dose (GPRD) as well as individual socio-demographic characteristics, acute events, and co-morbidity factors. We focus on hypercholesterolemic patients with at least one statin prescription in the period from 2000 to 2009. All entries within the dataset are registered with a daily frequency, which we subsequently convert into quarterly variables.

The construction of the individual compliance rate is based on the medication possession ratio (MPR) (Gibson et al. 2006; Choudhry et al. 2008). To obtain the indicator, we first compute the number of prescribed days for patient i of statin j at date t, $D_{ijt}^{\text{pre}} = \left(N_{ijt}^{\text{pac}} N_{ijt}^{\text{pills}}\right) \Big/ \text{GPRD}_{ijt}$, where N_{ijt}^{pac} denotes the number of packets of the drug, N_{ijt}^{pills} the number of pills per packet, and GPRD_{ijt} synthesizes the individual specific GP daily dosage recommendations. GPRD_{ijt} is extremely useful for the construction of MPR_{it}, since daily dosage recommendations are very heterogeneous among Italian GPs. In fact, a compliance index based on "average dosage" or "international standards" (a frequent shortcut in the empirical literature) is likely to contain large measurement errors (Atella et al. 2006). We subsequently compute individual $\text{MPR}_{ijt} = D_{ijt}^{\text{pre}} \Big/ D_{ijt}^{\text{between}}$, where D_{ijt}^{between} is the number of days between consecutive prescription refills. Finally, we take individual quarterly averages of MPR_{ijt}. Compliance is thus obtained as a continuous index, ranging from 0 to 1, with cases taking values greater than 1 if individuals obtain overlapping prescriptions (new packet of statins is prescribed before pills from the previous packet run out). This may occur since Italian GPs do not arrange the appointments for their patients; hence individuals themselves decide whether and when to attend a visit.

In terms of regressors, we construct dummy variables for co-morbidities (hypertension, diabetes) and acute events (angina, acute myocardial infarction, stroke, transient ischemic attack and percutaneous transluminal coronary angioplasty). Since the Italian health-care plan requires that all specialist visits and drugs are prescribed by GPs, the diagnosis made by external specialists is thus always registered by GPs. Furthermore, for each individual we compute Charlson co-morbidity index (CCI). CCI predicts 10-year mortality, assigning a score of 1, 2, 3 or 6 according to the risk of dying associated with any co-morbid condition. The summed up scores are subsequently categorized in a measure taking values of zero, one, two, three and four or above.

Moreover, we account for different types and dosages of active ingredients prescribed (simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, ezetimibe simvastatin and acetyl simvastatin).

Finally, we include information on gender, age, area of residence and size of municipality where the individuals reside. We control for co-payment exemptions, granted to individuals who fulfill certain criteria in terms of their age, diseases, disabilities, income and others.

Each region which introduced co-payment imposed a flat out-of-pocket charge, known as "ticket", applied equally to all prescription drugs, irrespective of drug type, pack size, dosage or pharmaceutical form. Although regions can design individual cost-sharing schemes, in reality drug co-payments do not vary much across the Italian territory (ranging between 2 and 4 €) per prescription filled, which renders them substantially comparable. Being a fixed amount, the ticket has an intrinsic regressive structure, affecting mostly financially constrained patients. From an empirical point of view, many studies have confirmed the role of co-payments in reducing drug consumption of low-income individuals (Freemantle and Bloor 1996; Lundberg et al. 1998; Atella et al. 2006).

Our panel consists of 74,985 patients, for a total of 683,234 observations over the period 2000–2009. On average, each patient is observed for at least nine quarters. Women represent 58 % of the sample, and the mean age is 66 years. 24.5 % of patients reside in the northwest, 24.9 % in the northeast, 14.5 % at the center, and 36.1 % in the south and islands. Approximately, 21 % of the individuals suffer from hypertension, while 8 % from diabetes mellitus. Serious cardiovascular events such as acute myocardial infarction, angina pectoris or transient ischemic attack are recorded in 1.5 % of the observations, stroke in 0.5 % and, finally, percutaneous transluminal coronary angioplasty in a very modest fraction (0.06 %) of the observations. Simvastatin, rosuvastatin and atorvastatin are the most frequently prescribed active ingredients.

Determinants of compliance

First, we use a standard QR model to study the determinants of compliance. Within this specification we subsequently incorporate the conventional DiD approach to investigate the impact of cost-sharing schemes on compliance ("differences of quantiles"). Finally, we reorganize the DiD setting to exploit the longitudinal nature of the data and analyze the change in individual compliance in response to co-payments introduction ("quantiles of differences").

To study the heterogeneity in the effects of covariates across the whole distribution of compliance, we estimate the following empirical model by means of QR:

$$Y_{it} = \alpha_\theta + \beta_\theta X_{it} + \gamma_\theta \mathrm{H}_{it-1} + \delta_\theta \mathrm{AI}_{i,t-1} + u_{\theta it} \quad (1)$$

where Y_{it} is the compliance index, X_{it} is a vector of control variables including age, sex, exemption status, length of statin therapy, area of residence, population density and a time trend; H_{it-1} is a vector of lagged dummy variables for acute events and co-morbidities; $\mathrm{AI}_{i,\ t-1}$ denotes lagged dummies for active ingredients types as well as interactions between active ingredients and their mmg dosage in linear and quadratic form. Finally, $i = 1,\cdots,$ N indexes individuals, $t = 1,\cdots, T$ quarters between 2000 and 2009, $u_{\theta it}$ is the error term, while θ refers to conditional quantiles.

To render the intercept estimate more interpretable, the age of individuals was mean centered (Koenker 2005). The intercept thus refers to a 66-year-old male, resident in the south/islands, not exempted from co-payments, without co-morbidities or acute events, prescribed more than one statin type within one quarter.

The DiD quantile specification

Following Borah et al. (2011), to analyze the distributional effects of co-payments, we estimate parameters of the following DiD specification with QR:

$$Y_{ikt} = \Omega_{\theta k} + \varepsilon_{\theta k}\mathrm{CT}_{ikt} + \lambda_{\theta k}\mathrm{CR}_{ikt} + \rho_{\theta k}\mathrm{CTR}_{ikt} + u_{\theta ikt} \quad (2)$$

where Ω includes the set of covariates described in Eq. 1, while CT, CR and CTR are dummy variables which identify the causal effect of co-payments on compliance. In particular, CT_{ikt} denotes the time fixed effect, CR_{ikt} captures the time-invariant group effect accounting for systematic differences in compliance between residents of regions with and without co-payments, and CTR_{ikt} is the region-specific causal parameter of interest. Finally, $k = 1,\cdots,18$ denotes regional co-payment introductions. We refer to this specification as "difference of quantiles" model, given that we compare the distribution of compliance before and after policy changes for each quantile. In this way, we measure the impact of co-payments along the whole compliance distribution.

Although interesting, this setting does not allow fully understanding how patients move along the compliance distribution: for example, an increase in the number of poor compliers after a co-payment introduction could be equally due to a major reduction of compliance by high compliers and a slight decrease of compliance by low compliers. We thus innovate with respect to Borah et al. (2011) and re-specify our model in terms of "quantiles of differences". Given the longitudinal nature of our data, we study the distribution of the differences in individual compliance ($\Delta Y_{it} = Y_{it} - Y_{it-1}$), i.e., the differences in compliance of single patients between period t and $t-1$, conditional on co-payment introductions. This setting allows us to purge our data form any unobserved time-invariant patient heterogeneity, and thus obtain more accurate estimates of policy treatment effects. The new model specification takes the following form:

$$\Delta Y_{ikt} = \Omega_{\theta kt} + \varepsilon_{\theta k}\mathrm{CT}_{ikt} + \lambda_{\theta k}\mathrm{CR}_{ikt} + \rho_{\theta k}\mathrm{CTR}_{ikt} + \varphi_{\theta k}\xi(Y_{ikt-1}) + u_{\theta kit} \quad (3)$$

where Ω, CT, CR and CTR are as in Eq. 2. As changes in individual compliance may depend on the initial

compliance level, we control for $\xi(Y_{ikt-1})$, which represents a third-degree polynomial in individual lagged compliance. We refer to this model as "quantiles of differences" model.

Results

The empirical analysis, including data selection, variable construction and estimation procedures, is conducted using Stata 11 package. The commands applied are `reg` for OLS estimation and `qreg` for QR specifications, with `bootstrap`, (1,000 replications) for robust standard errors.

Determinants of compliance

Table 1 and Fig. 1 confirm that QR approach offers a broader view on the determinants of compliance with respect to OLS (Yoon and Ettner 2009; Gebregziabher et al. 2011; Borah 2011). In particular, in Fig. 1 we plot statistically significant differences between OLS and QR estimates with their corresponding confidence interval bands. The graphs show the impact of a unit change of the covariate on the compliance index, holding other variables fixed, where the horizontal line in each panel corresponds to OLS estimates.

Consistently with other studies, we find that females are significantly less compliant than males (Schultz et al. 2005; Chapman et al. 2005; Shrank et al. 2006). However, we show that this tendency is more pronounced for poor compliers. Moreover, we find that age reduces compliance in a similar way along the whole compliance distribution.

We find that compliance is lower in the northeast, northwest and center compared to the southern regions. A number of robust conclusions can be drawn from the estimates on the interactions between geographic area and town size: compliance increases with the municipality size of northwest and northeast, especially among low compliers; conversely, it diminishes with the city size in the center and in the south and islands. This interpretation is consistent with the different organization and performance of health care across Italy, where northern regions provide better quality health-care services compared to southern ones (Jappelli et al. 2007).

We also find that exemptions from co-payments are associated with higher compliance, and within all exemption categories, this association is three to four times greater for poor compliers.

Importantly, and in line with other findings (Jackevicius et al. 2002; Schultz et al. 2005; Chapman et al. 2005), we show that co-morbidities and acute events are positively associated with compliance. This relationship is more pronounced in case of acute events in poor compliers. According to Jackevicius et al. (2002), patients who have undergone adverse health conditions are more careful about their health and more compliant with treatments. The same holds true for CCI categories, despite that we do not find a monotonic pattern in their marginal effects. This can be easily explained by the fact that in our model CCI captures a sort of positive "externality" effect on compliance, resulting in the joint presence of more pathologies. In fact, when we estimate our model without controlling for single co-morbid conditions, the coefficient estimates of the CCI categories increase monotonically.

We also show that compliance increases with length of therapies up to a certain point and then decreases, in particular in case of low compliers. This result is plausibly related to apparent attainment of therapy goals or side effects, which are likely to show up in the long run (Luepker 1993). We also show that compliance is lower in patients prescribed multiple statins within one quarter. Moreover, when allowing for nonlinearities, we find an inverted U-shape relationship between compliance and statin dosage. Specifically, the relationship is steeper in case of rosuvastatin and atorvastatin (the most potent statins), while overall the relationship is stronger in magnitude and significance for poor compliers.

Finally, we find that compliance increased during the study period, especially among poor compliers. We also show that compliance presents a seasonality pattern: decreasing in the third quarter of each year (possibly due to holiday season, when patients attend less medical visits).

The effect of co-payments on compliance: "differences of quantiles" vs. "quantiles of differences"

We start this section by presenting the results based on "differences of quantiles" specification. Table 2 shows the DiD causal parameter estimates obtained by OLS and QR. Consistently with the literature (Atella et al. 2006; Gibson et al. 2006; Choudhry et al. 2008), our findings imply that co-payments reduce compliance. The only exception is the third introduction of co-payments in Abruzzo, which however came in the second quarter of 2009, a period when the region was recovering from a severe earthquake. These estimates are thus likely to capture circumstances of this particular timing. Moreover, the results point to a substantial heterogeneity across regions, as the coefficient estimates for Piedimont, Lombardia, Liguria, Lazio, Abruzzo and Sicily are greater in absolute values. QR estimates show that the negative impact of co-payments is particularly pronounced for poor and medium compliers. In case of Piedimont, Lombardia and Veneto, the effect is negative only for poor compliers, while good compliers did not seem to be hurt by the policy. The opposite heterogeneity pattern is evidenced for Campania, where co-payments induced a greater reduction of compliance for

Table 1 Determinants of individual compliance with statin treatment-estimation results from Ordinary Least Squares (OLS) and Quantile Regression (QR) method

	OLS	QR 0.10	QR 0.25	QR 0.50	QR 0.75	QR 0.90
Female	−0.031***	−0.038***	−0.040***	−0.037***	−0.021***	−0.012***
Age	0.001***	0.001***	0.001***	0.001***	0.001***	0.001***
Northwest	−0.017***	0.028***	−0.005	−0.041***	−0.040***	−0.015***
Northeast	−0.020***	0.023***	−0.009*	−0.048***	−0.033***	−0.012***
Center	−0.024***	−0.003	−0.016***	−0.041***	−0.031***	−0.017***
Residents × Northwest	0.002***	0.002***	0.002***	0.002***	0.001***	0.001*
Residents × Northeast	0.004***	0.005***	0.004***	0.003***	0.003***	0.003***
Residents × Center	−0.001	0.003	−0.002	−0.001*	−0.001*	−0.001
Residents × South/Islands	−0.003***	−0.002***	−0.003***	−0.003***	−0.003***	−0.001***
Time	0.006***	0.006***	0.007***	0.007***	0.005***	0.002***
Seasonality	−0.011***	0.004***	−0.010***	−0.020***	−0.018***	−0.011***
Co-pay exemption—income	0.029***	0.033***	0.038***	0.035***	0.021***	0.013***
Co-pay exemption—income and age	0.020***	0.027***	0.027***	0.018***	0.014***	0.006**
Co-pay exemption—pathology	0.033***	0.047***	0.043***	0.034***	0.021***	0.012***
Co-pay exemption—disability	0.027***	0.031***	0.035***	0.031***	0.020***	0.013***
Co-pay exemption—other	0.001	0.015***	0.002	−0.003	−0.005	−0.001
Diabetes	0.006***	0.006*	0.008***	0.008***	0.001	0.001
Hypertension	0.002*	0.003	0.001	0.001	0.002*	0.003**
Transient Ischemic Attack	0.021***	0.031***	0.026***	0.020***	0.013***	0.007*
Percutaneous transluminal coronary angioplasty	0.035***	0.067***	0.065***	0.028***	0.016**	0.008
Acute Myocardial Infarction	0.035***	0.040***	0.048***	0.043***	0.017***	0.009***
Stroke	0.031***	0.055***	0.058***	0.025***	0.014*	0.011*
Angina	0.028***	0.037***	0.043***	0.030***	0.016***	0.009***
Charlson index 1	0.023***	0.025***	0.029***	0.027***	0.018***	0.012***
Charlson index 2	0.016***	0.018***	0.023***	0.019***	0.012***	0.008***
Charlson index 3	0.023***	0.024***	0.030***	0.027***	0.019***	0.013***
Charlson index 4 and more	0.017***	0.016**	0.020***	0.022***	0.018***	0.012***
Length of therapy (quarters)	0.0029***	0.0068***	0.0044***	0.0027***	0.0008***	0.0001
Length of therapy (quarters) sq.	−0.0001***	−0.0002***	−0.0001***	−0.0001***	−0.0001*	0.0001
Simvastatin	0.175***	0.184***	0.242***	0.249***	0.156***	0.086***
Lovastatin	0.042***	0.105***	0.138***	0.098***	−0.042***	−0.089***
Pravastatin	0.149***	0.167***	0.214***	0.218***	0.125***	0.047***
Fluvastatin	0.184***	0.164***	0.221***	0.270***	0.190***	0.087***
Atorvastatin	0.181***	0.194***	0.254***	0.269***	0.148***	0.052***
Rosuvastatin	0.113***	0.157***	0.176***	0.161***	0.085***	0.003
Simva–Ezetimibe	0.222***	0.241***	0.314***	0.316***	0.183***	0.068***
Simva–Acetyl	0.126*	0.124	0.140	0.175	0.178*	0.115*
mg Simvastatin	0.014***	0.015***	0.018***	0.017***	0.013***	0.007***
mg Lovastatin	−0.002**	0.006***	0.006***	0.001	−0.010***	−0.013***
mg Pravastatin	0.007***	0.011***	0.013***	0.010***	0.003***	−0.004***
mg Fluvastatin	0.004***	0.007***	0.008***	0.007***	0.001***	−0.002***
mg Atorvastatin	0.017***	0.022***	0.027***	0.023***	0.011***	0.000
mg Rosuvastatin	0.024***	0.026***	0.035***	0.035***	0.017***	0.008***
mg Simva–Ezetimbe	0.009***	0.012***	0.015***	0.012***	0.005***	0.001*
mg Simva–Acetyl	0.015*	0.002	0.025***	0.023*	0.015	0.004
mg Mix of statins	0.001***	0.000	0.002***	0.002***	0.001***	0.001*
mg sq. Simvastatin	−0.001***	−0.001***	−0.001***	−0.001***	−0.001***	−0.001***

Table 1 continued

	OLS	QR 0.10	QR 0.25	QR 0.50	QR 0.75	QR 0.90
mg sq. Lovastatin	0.001***	−0.001	0.001	0.001***	0.001***	0.001***
mg sq. Pravastatin	−0.001**	−0.001***	−0.001***	−0.001***	0.001***	0.001***
mg sq. Fluvastatin	−0.001***	−0.001***	−0.001***	−0.001***	0.001***	0.001***
mg sq. Atorvastatin	−0.001***	−0.001***	−0.001***	−0.001***	−0.001***	0.001***
mg sq. Rosuvastatin	−0.001***	−0.001***	−0.001***	−0.001***	−0.001***	−0.001***
mg sq. Simva–Ezetimbe	−0.001***	−0.001***	−0.001***	−0.001***	−0.001***	−0.001
mg sq. Simva–Acetyl	−0.001	0.001	−0.001	−0.001	−0.001	−0.001
mg sq. Mix of statins	−0.001***	−0.001	−0.001***	−0.001***	−0.001***	−0.001
Constant	0.327***	−0.179***	−0.069***	0.218***	0.661***	0.989***
R2	0.10					
N	683,234					

Health search CSD–LPD data, Italy, 2000–2009. Estimation obtained in `Stata` with commands `reg` and `sqreg`, with option bootstrap with 1,000 replications, (*** $p < 0.01$, ** $p < 0.05$, * $p < 0.1$)

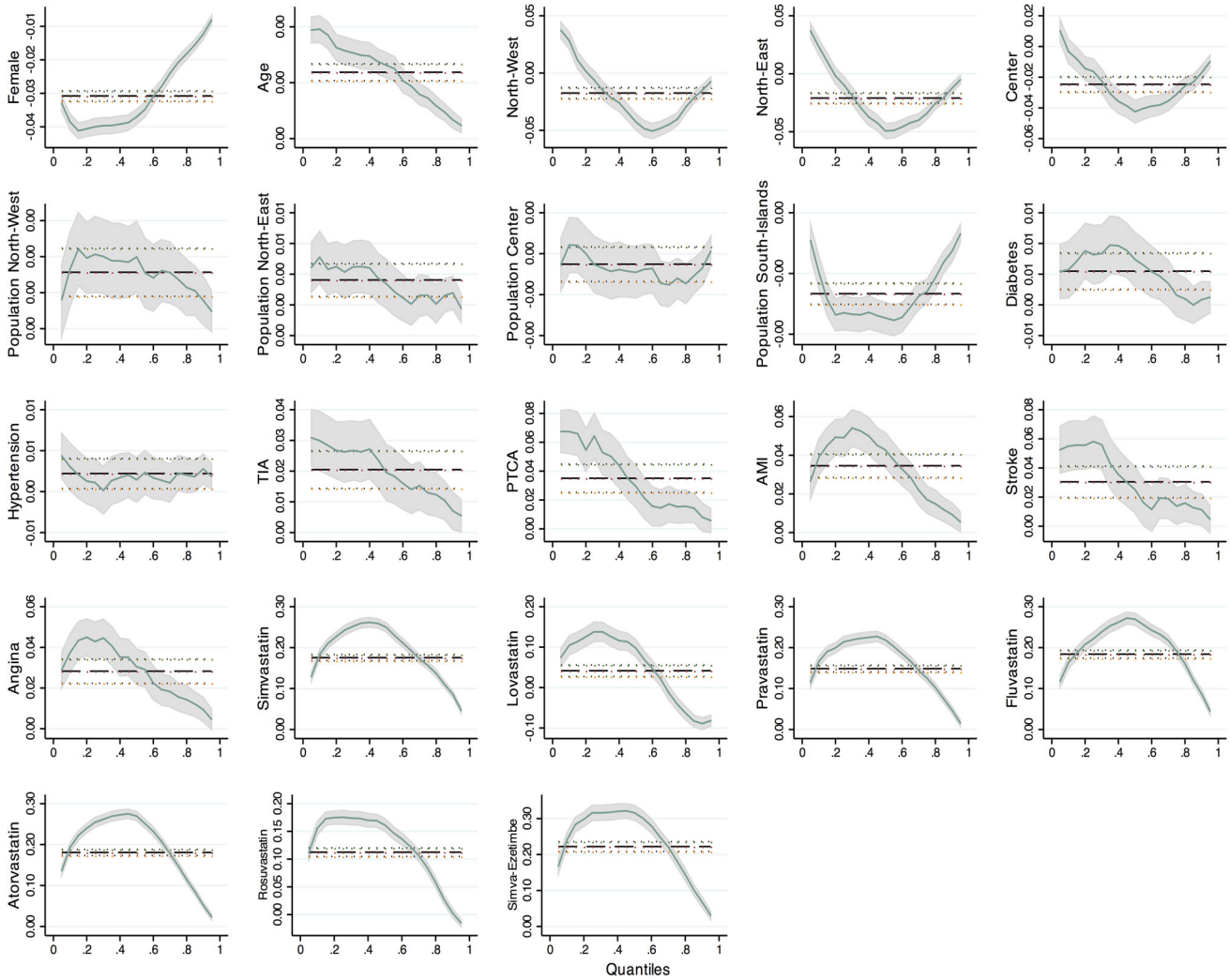

Fig. 1 Impact on compliance with statin treatment of each covariate—Quantile Regression and Ordinary Least Squares estimates. Each panel presents Quantile Regression point estimates with confidence interval bands and Ordinary Least Squares point estimates with confidence interval bands (*horizontal lines*). Health search CSD-LPD data, Italy, 2000–2009. Figure obtained in `Stata` with command `grqreg`

high compliers. Overall, these results are in line with Borah et al. (2011), who found that the QR DiD model provided heterogeneous insights along the distribution of outcomes.

Although interesting, this approach does not disentangle the patients responsible for the backward shift of the left tail of compliance distribution. In fact, as mentioned before, compliance reduction evidenced in low quantiles after co-payment introductions could be equally driven by high/medium compliers who reduce substantially their compliance or by low compliers who become slightly less compliant.

To address this question, in Table 3 we present the estimation results of "quantiles of differences" specification. These estimates, which are conditional on the initial level of compliance before the policy change, are substantially different in terms of magnitude and statistical significance from the results presented in Table 2. Estimates of co-payments cease to be significant for almost all quantiles in case of Bolzano, Veneto, Liguria, as well as the second and third introduction of co-payments in Abruzzo, while for Lombardia the effect becomes positive and is barely significant. This result suggests that once we account for the individual heterogeneity of patients in these regions, co-payments do not play any regressive role in their compliance. On the other hand, we find that the negative effect of co-payments is stronger for patients who belong to the left tail of the distribution of compliance differences in case of Lazio, Campania, Apulia, Sicily and Sardegna, regions with significantly inferior health-care provision. In fact, low quantiles consist of patients with negative ΔY_{it}, and hence greater reductions in compliance. This finding implies that decrease in compliance resulting from co-payments is likely to be driven by high compliers switching to low compliance levels.

For a further assessment of this result, we re-run our estimates separately for "high" and "low" compliers, according to their compliance before the policy change (with the cutoff point equal to 0.65). This alternative approach should improve the ability of the model to account for the individual response heterogeneity to co-payment introductions.

Table 4 confirms the results presented in Table 3. For Lazio, Campania, Apulia, Sicilia and Sardinia the coefficient estimates are greater in magnitude for "high" than for "low" compliers. Moreover, QR coefficients suggest that among both, "high" and "low" compliers of these regions, the effect of the policy was stronger for patients belonging to the left tail of compliance differences distribution. In case of Piedimont and Veneto, the negative effect of co-payments evidenced in Table 2 for low quantiles is confirmed to be driven by "low" compliers. Moreover, the lack of statistically significant negative results for Lombardia, Bolzano, Liguria, Abruzzo and Calabria in Table 3 is also evidenced in Table 4.

In terms of geographical heterogeneity, the results are very insightful and their interpretation is consistent with

Table 2 Impact of regional co-payment introductions on individual compliance with statin treatment—Ordinary Least Squares (OLS) and Quantile Regression (QR) results

	OLS	QR 0.10	QR 0.25	QR 0.50	QR 0.75	QR 0.90
Co-pay Piedmont	−0.012***	−0.041***	−0.034***	−0.001	0.015***	0.011***
Co-pay Lombardia	−0.018***	−0.040***	−0.033***	−0.015***	0.006	0.007*
Co-pay Bolzano	−0.026***	−0.019	−0.028**	−0.030***	−0.018**	−0.016**
Co-pay Veneto	0.010*	−0.032***	−0.009	0.027***	0.047***	0.033***
Co-pay Liguria	−0.033***	−0.072***	−0.062***	−0.027***	−0.004	−0.001
Co-pay Lazio I	0.004	−0.020***	−0.018***	0.014	0.020	0.017
Co-pay Lazio II	−0.004	−0.055**	−0.006	−0.011	0.026	0.019
Co-pay Abruzzo I	−0.011***	−0.015***	−0.019***	−0.011*	−0.001	0.002
Co-pay Abruzzo II	−0.049***	−0.040***	−0.061***	−0.062***	−0.035***	−0.015***
Co-pay Abruzzo III	0.031***	0.079***	0.051***	0.022*	0.002	−0.004
Co-pay Campania	−0.017***	0.014*	−0.002	−0.037***	−0.036***	−0.022***
Co-pay Apulia	−0.020***	−0.014***	−0.025***	−0.028***	−0.018***	−0.007**
Co-pay Calabria I	−0.008*	−0.009	−0.006	−0.010*	−0.005	−0.003
Co-pay Calabria II	−0.039***	−0.038***	−0.045***	−0.051***	−0.034***	−0.017*
Co-pay Sicily I	−0.027***	−0.034**	−0.044***	−0.037***	−0.008	−0.010
Co-pay Sicily II	−0.047***	−0.103***	−0.091***	−0.040*	−0.002	−0.009
Co-pay Sicily III	−0.086***	−0.149***	−0.141***	−0.088***	−0.027	−0.024
Co-pay Sardinia	−0.015	−0.067***	−0.026	0.008	0.031*	0.016

Health search CSD–LPD data, Italy, 2000-2009. Estimation obtained in `Stata` with commands `reg` and `sqreg`, with option `bootstrap` with 1,000 replications, (*** $p < 0.01$, ** $p < 0.05$, * $p < 0.1$)

Table 3 Impact of regional co-payment introductions on differences in individual compliance with statin treatment between two consecutive periods—Ordinary Least Squares (OLS) and Quantile Regression (QR) results

	OLS	QR 0.10	QR 0.25	QR 0.50	QR 0.75	QR 0.90
Co-pay Piedmont	−0.0174	−0.0467*	−0.0414**	−0.0063	0.0008	0.0161
Co-pay Lombardia	0.0038	−0.0160	0.0003	0.0155*	0.0206**	0.0068
Co-pay Bolzano	−0.0351	−0.0088	−0.0133	−0.0221	−0.0283	−0.0479
Co-pay Veneto	−0.0172	−0.0160	−0.0223	−0.0109	−0.0131	−0.0065
Co-pay Liguria	0.0015	−0.0211	−0.0182	0.0207	0.0037	−0.0059
Co-pay Lazio I	−0.0551***	−0.0921***	−0.0967***	−0.0525***	−0.0379**	−0.0031
Co-pay Lazio II	−0.0792***	−0.1046**	−0.0882***	−0.0890***	−0.0635***	−0.0491**
Co-pay Abruzzo I	−0.0036	−0.0578**	−0.0498***	−0.0034	0.0075	0.0317
Co-pay Abruzzo II	−0.0249	−0.0138	−0.0145	−0.0142	−0.0194	0.0166
Co-pay Abruzzo III	0.0263	0.0421	0.0688	0.0284	0.0257	0.0045
Co-pay Campania	−0.0073	−0.0487**	−0.0169	0.0084	0.0144	0.0039
Co-pay Apulia	−0.0411***	−0.0883***	−0.0442***	−0.0286*	−0.0352***	−0.0331*
Co-pay Calabria I	−0.0069	−0.0603*	−0.0427	0.0042	0.0084	0.0233
Co-pay Calabria II	−0.0003	−0.0223*	−0.0182	−0.0010	0.0041	0.0175
Co-pay Sicily I	−0.0013	−0.0576***	−0.0025	0.0126	0.0071	0.0159
Co-pay Sicily II	−0.0241	−0.0473**	−0.0455**	−0.0127	−0.0051	−0.0015
Co-pay Sicily III	−0.0230*	−0.0721***	−0.0385**	−0.0154	0.0132	0.0020
Co-pay Sardinia	−0.0694***	−0.0863**	−0.0686*	−0.0605***	−0.0611***	−0.0486*

Health search CSD–LPD data, Italy, 2000–2009. Estimation obtained in `Stata` with commands `reg` and `sqreg`, with option `bootstrap` with 1,000 replications, (*** $p < 0.01$, ** $p < 0.05$, * $p < 0.1$)

the differences existing in the quality of health-care provision across Italy. In fact, we expect that the effect of co-payments on drug compliance is stronger in regions characterized by low-quality and inefficient health-care services. This is what Table 4 shows, as the coefficient estimates are stronger and statistically significant for the residents of Lazio, Campania, Apulia, Sicily and Sardinia, regions with poor health-care management, organization and financing (Atella and Kopinska 2012). The example of Lazio, one of the most inefficient areas, shows a clear coherence of the estimates with the Italian health services reality.

Finally, Fig. 2 presents graphically the geographical differences of the impact of co-payments on compliance. The lines plot average regional differences in individual compliance, measured before and after co-payment introductions, against compliance before the policy, conditional on age, sex, exemption status, treatment length and type of statin therapy. For comparison, on the same figure we superimpose the plot for Italy, with the relative confidence interval. Moreover, we group patients into non-compliers, low compliers and compliers, where 0.3 and 0.65 are the cutoff points. The figure should be interpreted according to the slope of single plots within distinct compliance thresholds and the intercept point, with the red horizontal cutoff line denoting differences in compliance equal to zero: the steeper the plot, the larger are the distributional differences induced by co-payment introductions, whereas the lower the initial compliance at which plots intercepts the "0" difference horizontal line, the greater is the portion of patients who reduce their compliance in response to policy changes.

The figure shows that patients belonging to the group of compliers have on average reduced their compliance after co-payment introductions. The reduction is substantial and, importantly, it is more pronounced for high compliers. The figure suggests also that non-compliers and low compliers have, on average, increased their compliance, although the increase is marginal and represents only a minor change, which does not allow them to cross the 0.65 compliance cutoff level. Moreover, the figure shows substantial differences between regions, where again Lazio remains one of the most remarkable evidence of the negative impact of co-payments for high compliant patients.

Discussion

Based on a large sample of Italian hypercholesterolemic patients, in this paper we investigate the determinants of compliance and the impact of co-payments on compliance using QR. Overall, we point to a number of conclusions: (i) co-payment introductions reduce compliance in regions where performance of health-care services is lower than the

Table 4 Impact of regional co-payment introductions on differences in individual compliance with statin treatment between two consecutive periods for subsamples of high (H $\geq$ 0.65) and low (L $<$ 0.65) compliers—Ordinary Least Squares (OLS) and Quantile Regression (QR) results

	OLS	QR 0.10	QR 0.25	QR 0.50	QR 0.75	QR 0.90
Co-pay Piedmont						
L	−0.0056	−0.0341	−0.0586***	−0.0279	−0.0084	0.0429
H	−0.0060	−0.0271	−0.0130	0.0052	−0.0033	0.0169
Co-pay Lombardia						
L	0.0072	−0.0190	0.0131	0.0180*	0.0260**	0.0038
H	−0.0098	−0.0077	−0.0114	−0.0031	−0.0262	−0.0200
Co-pay Bolzano						
L	−0.0291	0.0191	−0.0293	−0.0207	0.0011	0.0061
H	−0.0380	−0.0529	−0.0507	−0.0574	−0.0236	−0.0288
Co-pay Veneto						
L	−0.0368*	0.0039	−0.0292*	−0.0271*	−0.0846***	−0.0199
H	−0.0100	−0.0249	−0.0251	−0.0019	0.0011	−0.0061
Co-pay Liguria						
L	−0.0390	−0.0646	−0.0125	−0.0043	0.0168	0.0113
H	0.0228	0.0589	0.0169	0.0435	0.0104	0.0210
Co-pay Lazio I						
L	−0.0357	−0.0411	−0.0373**	−0.0243	−0.0256	0.0012
H	−0.0437	−0.1058***	−0.0791	−0.0425	−0.0529	−0.0220
Co-pay Lazio II						
L	−0.0379	−0.0169	−0.0200	−0.0454	−0.0556	−0.0147
H	−0.0881***	−0.0764*	−0.1113***	−0.1311***	−0.0688***	−0.0362*
Co-pay Abruzzo I						
L	0.0210	−0.0115	−0.0171	−0.0114	0.1073	0.0996
H	0.0071	0.0098	−0.0139	0.0110	−0.0025	0.0008
Co-pay Abruzzo II						
L	−0.0318	0.0086	−0.0446	−0.0456	−0.0343	−0.0916
H	−0.0193	−0.0356	−0.0349	−0.0142	−0.0090	0.0376
Co-pay Abruzzo III						
L	0.0102	0.0015	−0.0223	0.0178	0.0089	0.1271
H	0.0333	0.0331	0.0780	0.0150	0.0222	−0.0214
Co-pay Campania						
L	−0.0068	−0.0440*	−0.0043*	0.0112	0.0084	−0.0074
H	−0.0131	−0.0763*	−0.0615	0.0112	0.0231	0.0071
Co-pay Apulia						
L	−0.0372*	−0.0509	−0.0774	−0.0034*	−0.0527	−0.0159
H	−0.0641*	−0.1268***	−0.0855**	−0.0709	0.0656	−0.0404
Co-pay Calabria I						
L	−0.0134	−0.0512	−0.0307	−0.0314	0.0383	0.0369
H	−0.0151	−0.0336	−0.0259	−0.0174	−0.0068	0.0255
Co-pay Calabria II						
L	−0.0484	−0.0348	−0.0232	−0.0460	−0.0633	0.0412
H	0.0103	0.0134	0.0064	−0.0042	−0.0194	−0.0073
Co-pay Sicily I						
L	−0.0145	−0.0338	0.0005	−0.0021	−0.0607	−0.1124
H	0.0123	−0.0083	0.0309	0.0226	0.0140	0.0181
Co-pay Sicily II						
L	−0.0372	−0.0529*	−0.0435***	−0.0521	−0.0309	−0.0493
H	−0.0261	−0.0881*	−0.0674	−0.0169	−0.0209	0.0068

Table 4 continued

	OLS	QR 0.10	QR 0.25	QR 0.50	QR 0.75	QR 0.90
Co-pay Sicily III						
L	−0.0137	−0.0625***	−0.0325	−0.0049	−0.0238	0.0276
H	−0.0451	−0.0873**	−0.0788	−0.0469	−0.0438*	0.0079
Co-pay Sardinia						
L	−0.0527***	−0.0738*	−0.0720	−0.0518	−0.0519	−0.2047
H	−0.1069***	−0.1398***	−0.0544***	−0.0604	−0.0785**	−0.0288

Health search CSD-LPD data, Italy, 2000–2009. Estimation obtained in `Stata` with commands `reg` and `sqreg`, with option `bootstrap` with 1,000 replications, (*** $p < 0.01$, ** $p < 0.05$, * $p < 0.1$)

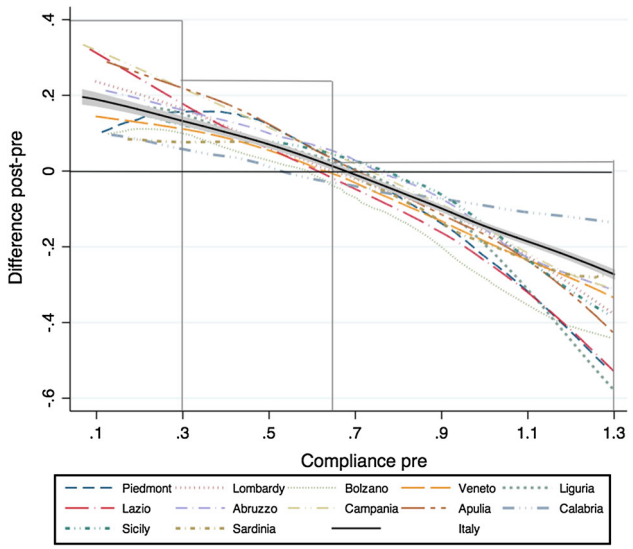

Fig. 2 Individual compliance with statins pre and post co-payment introduction, averages by Italian regions. Non-compliers <0.3, low-compliers ≥0.3 and <0.65, compliers ≥0.65, Health Search CSD–LPD data, Italy, 2000-2009. Figure obtained in Stata with command `twoway`

national average; (ii) the reduction is mainly driven by high compliers moving toward the lower tail of the compliance distribution; (iii) determinants such as gender, acute events or geographic residence affect compliance of low compliers more than high compliers; (iv) compliance decreases with the potency and dosage of statins, particularly for low compliers.

These results are important for health policy. By offering a better understanding of determinants of compliance, they allow to identify patients "at-risk" of under-treatment. Importantly, we show that in the presence of inefficient health-care services, co-payments end up hurting mainly high compliers. On the other hand, this finding suggests that poor compliance is primarily determined by behavioral characteristics, less related to financial aspects. Unfortunately, we cannot test this hypothesis with the data at hand. The HS does not provide information on income of patients; hence we cannot verify if high compliers reducing compliance after co-payment introductions are also financially constrained. Although the existing literature supports this hypothesis (Freemantle and Bloor 1996; Lundberg et al. 1998; Atella et al. 2006), certainly more research in this direction would be desirable.

From a medical perspective our findings have negative implications: reduction of compliance by low compliers does not result in tangible health outcomes, but the same is not true for high compliers. In case of inefficient health-care provision, co-payments may thus lead to outcomes that are far from their original objectives.

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