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HIGHLIGHTING DIFFERENCES BETWEEN CONDITIONAL AND UNCONDITIONAL QUANTILE REGRESSION APPROACHES THROUGH AN APPLICATION TO ASSESS MEDICATION ADHERENCE

BIJAN J. BORAH[a,*] and **ANIRBAN BASU**[b]

[a]College of Medicine and Division of Health Care Policy and Research, Mayo Clinic, Rochester, Minnesota, USA

[b]Department of Health Services and PORPP, University of Washington, Seattle and the National Bureau of Economic Research, Cambridge, Massachusetts, USA

Abstract

The quantile regression (QR) framework provides a pragmatic approach in understanding the differential impacts of covariates along the distribution of an outcome. However, the QR framework that has pervaded the applied economics literature is based on the conditional quantile regression method. It is used to assess the impact of a covariate on a quantile of the outcome conditional on specific values of other covariates. In most cases, conditional quantile regression may generate results that are often not generalizable or interpretable in a policy or population context. In contrast, the unconditional quantile regression method provides more interpretable results as it marginalizes the effect over the distributions of other covariates in the model. In this paper, the differences between these two regression frameworks are highlighted, both conceptually and econometrically. Additionally, using real-world claims data from a large US health insurer, alternative QR frameworks are implemented to assess the differential impacts of covariates along the distribution of medication adherence among elderly patients with Alzheimer's disease.

Keywords

conditional quantile regression; unconditional quantile regression; medication adherence; medication possession ratio; Alzheimer's disease

1. INTRODUCTION

The quantile regression (QR) framework provides a pragmatic approach in understanding the differential impacts of covariates along the distribution of an outcome. For example, in line with our empirical example later, when studying determinants for medication

*Correspondence to: Division of Health Care Policy and Research, Mayo Clinic, 200 First St SW, Rochester, MN 55905, USA. borah.bijan@mayo.edu.

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adherence, the QR framework can help discover different determinants of medication adherence for different groups of patients. It explicitly accounts for the possibility that the impact of a covariate for patients who are at, say, the 25th percentile of the adherence distribution may significantly differ from the impact for patients at the 90th percentile. It naturally provides a more patient-centered approach to understanding determinants of adherence.

The most commonly used QR framework is the conditional quantile regression (CQR). It is used to assess the impact of a covariate on a quantile of the outcome conditional on specific values of other covariates. Such regressions have been widely used in statistics and econometrics literature. Examples of its use in health economics literature include modeling differential impacts of price on demand for alcohol (Manning *et al*., 1995), determinants of birth weight (Abrevaya, 2001), assessing gender differences in timeliness of thrombolytic therapy (Austin *et al*., 2005), and assessing racial and ethnic disparities along the distribution of expenditures (Cook and Manning, 2009), to name a few. As we will show in the succeeding text, the interpretation of such effects becomes limited when effects for different conditional quantiles vary. Consequently, the estimated effects do not translate to relevant policy questions that are linked to these covariates. In contrast, a recently proposed, unconditional quantile regression (UQR) approach can be used to overcome the limitations of the CQR approach.

In this paper, we attempt to highlight, both conceptually and econometrically, the differences between alternative QR frameworks – CQR and UQR. Our main findings suggest that in the presence of multiple covariates, it is often more appropriate to use the UQR framework and not the CQR that has pervaded the applied literature. We highlight some of these differences in an illustrative example of exploring determinants of medication adherence among elderly patients with Alzheimer's disease (AD).

In what follows, we start with a motivating example on medication adherence in AD patients. Then, we describe both CQRs and UQRs and present simulation results to highlight the differences between these two modeling frameworks. We then illustrate the implementation of these two frameworks to assess the determinants of medication adherence among AD patients using real-world healthcare claims data from a large US commercial health plan. We also provide references on the available software for implementing both CQR and UQR techniques. We conclude with a discussion.

2. METHODS

2.1. Motivating example – medication adherence among elderly patients with Alzheimer's disease

2.1.1. General definitions and modeling of medication adherence—Adherence to prescribed medications is often necessary for deriving the optimal benefits from any pharmacotherapeutic intervention (Myers and Midence, 1998; Encinosa *et al*., 2010). Nonadherence to medication has been found to be associated with poorer health outcomes that lead to significantly higher healthcare costs (Kane and Shaya, 2008; Sokol *et al*., 2005; The New England Healthcare Institute, 2009; Cutler and Everett, 2010; Roebuck *et al*.,

2011). Approximately one-third to one-half of patients in the USA with prescribed medications become nonadherent, and the resulting cost of nonadherence is estimated to be approximately $290bn (The New England Healthcare Institute, 2009). Understanding determinants of medication adherence is central to addressing this problem so that appropriate actions may be undertaken to improve adherence.

Medication adherence is often used interchangeably with the term *medication compliance*. Both refer to the diligence with which the patient takes medications as prescribed by her healthcare provider. There has been a proliferation in the research on medication adherence in the recent years; a simple search in PubMed with the key words 'medication adherence' generated 1674 publications in 2011, 6502 and 8466 in the previous 5 and 10 years, respectively (as of March 30, 2012). Besides assessing medication adherence or nonadherence in general, this line of research has also analyzed medication (non) adherence associated with specific disease conditions, as well as other aspects, including barriers to medication adherence and potential implications such as costs and morbidity associated with nonadherence.(ISPOR Medication Compliance and Persistence Special Interest Group (MCP), 2011)

In practice, several operational definitions of medication adherence exist depending on specific drug regimens and types of data (Cramer *et al*., 2008; Hess *et al*., 2006; Martin *et al*., 2009; Osterberg and Blaschke, 2005; Peterson *et al*., 2007; Hudson *et al*., 2007). Perhaps the most commonly used measure is medication possession ratio (MPR). The MPR is a proportion and is defined as the ratio of the number of days of medication supplied within the refill interval to the number of days in the refill interval, where refill interval refers to the gap between the first and last fill of the study medication (Peterson *et al*., 2007; Steiner and Prochazka, 1997). Determinants of medication adherence are usually explored by studying the impact of different covariates on a dichotomized MPR variable, analyzed using a binary probability model (either logit or probit). Although there is no sacrosanct rule on the cut-off value for MPR that distinguishes adherent patients from nonadherent ones, the rule of thumb in the literature has been that patients with an MPR of 80% or above are considered to be adherent (Osterberg and Blaschke, 2005; Hansen *et al*., 2009). The focus on regression coefficients in these models provides estimates for conditional effects. However, one can easily obtain unconditional effects using the method of recycled predictions (Basu and Rathouz, 2005). Moreover, the 80% cut-off in the MPR scale itself may be viewed as representing a specific quantile of the MPR distribution. To that extent, the unconditional effect of a binary covariate in a logistic regression may be viewed as the difference in the unconditional quantiles of MPR across two levels of the covariate.

An inherent limitation of dichotomizing the continuous MPR measure is that the cut-off point that separates adherent from nonadherent patients is rather arbitrary and lacks any clinical or pharmacological rationale (Steiner and Prochazka, 1997). For example, a patient with an MPR of 75% may not be significantly different from a patient with an MPR of 81% in terms of health outcomes; yet, this framework treats these two patients distinctly different as far as how medication adherence is operationalized. Moreover, although 80% adherence in terms of MPR may be considered optimal for some medications, it may be suboptimal for others. Furthermore, using an 80% cut-off mark implies that nonadherent patients with an

MPR between 0% and 79% are all lumped into one single group, despite the fact that these patients can potentially exhibit several distinct adherence subclasses. A covariate may be a determinant of adherence for some subclasses, but not all. In other words, the existing framework of exploring the determinants of adherence does not account for the possibility that covariates may have differential impacts across various parts of the adherence distribution.

2.1.2. Medication adherence among patients with Alzheimer's disease—

Approximately 5.4 million people in the USA have AD, which is associated with $183bn in annual costs (Alzheimer's Association, 2011). All available evidence-based guidelines emphasize the importance of adherence to prescribed medication in AD patients, as nonadherence may lead to irreversible cognitive decline (DeLaGarza, 2003). However, medication nonadherence in AD patients continues to be a great concern (Small and Dubois, 2007; Harrold and Andrade, 2009). A recent review of compliance to AD treatment identified the following factors as crucial for improving medication adherence: simplifying treatment regimens, using reminder packaging, and developing more patient-friendly or caregiver-friendly modes of administration (e.g., via transdermal patch) that has been recently developed to deliver rivastigmine, a cholinesterase inhibitor (Small and Dubois, 2007). Given that cognitive disability is an important barrier to medication adherence (Pereles *et al*., 1996), other innovative ways of delivering drugs to AD patients have been suggested most of which are at experimental stages (Di Stefano *et al*., 2011; Small and Dubois, 2007).

Another recent study that used healthcare claims data from a large insurer in the USA found that age (≥86 years), daily pill burden, and lower formulary tier were associated with higher adherence with AD medications (Borah *et al*., 2010). Out-of-pocket cost of care for AD medication has also been found to be a significant barrier to medication adherence (Stefanacci, 2011).

Caregiver support, particularly family caregivers, provides a significant amount of care for AD patients over the course of the illness, which has bearing on medication adherence as well (Cummings and Cole, 2002; Hogan *et al*., 2007). In addition, collaborative care in conjunction with family care giver that is integrated within primary care, was found to improve quality of care, potentially improving the medication adherence, which resulted AD symptom management (Callahan *et al*., 2006).

The aforementioned survey of the literature on medication adherence in AD patients suggests that nonadherence to medication is an important barrier to achieving optimal therapeutic benefit in AD patients and that existing methodology has failed to assess how the effects of the covariates of interest vary across the adherence distribution. For example, instead of focusing on the effect of a covariate (e.g., tier of the drug, which is a surrogate for out-of-pocket payment) on mean adherence, a more meaningful parameter of interest is the effect on lower quantile of the adherence distribution. Both CQR and UQR can achieve this goal. However, note that conditional quantiles do not average up to their unconditional population quantiles, which is where UQR provides the additional advantage over CQR.

2.2. Conditional versus unconditional distributions

Let Y denote the outcome of interest and $F_Y(y)$ denote the population (unconditional) distribution function of Y in a target population, that is, $F_Y(y) = \Pr(Y \leq y)$. Interest lies in exploring the effect of a covariate X on Y. For the sake of simplicity, let X be a binary variable that takes values of $x = (0, 1)$. Let the potential outcomes and their distribution function under alternate values of X be denoted as Y_1 and Y_0, respectively. Therefore, $Y = X \cdot Y_1 + (1 - X) \cdot Y_0$. We assume that X is statistically independent of Y_1 and Y_0. Later, we relax this assumption to make it independent conditional on other observed covariates; that is, we will invoke the selection on observables principle on X. We do not deal with selection on unobservables in this paper and delegate those issues to future work. One can express the unconditional distribution function for Y as a weighted average of conditional distribution of Y given X, weighted by the unconditional distribution of X. The unconditional distribution of a random variable is often referred to as the marginal distribution of that variable in the statistics literature. However, because we use the term *marginal* to represent small changes in covariate values (as in marginal effect), we stick to using the term *unconditional distribution* following the work of Firpo *et al.* (2009). In our case, because X is binary,

$$F_Y(y) = \Pr(X=1) \cdot F_{Y|X}(y|X=1) + \Pr(X=0) \cdot F_{Y|X}(y|X=0). \quad (1)$$

In most cases, to understand the relationship between Y and X, one focuses on a particular feature of the distribution of Y. For example, in most regression models, the focus is on the conditional expectation of Y, $E(Y|X) = \int dF(Y|X)$. In the traditional linear model, the ordinary least squares (OLS) regression is a consistent estimator of the target parameter β_{OLS} representing the incremental effect of X on Y, that is, the difference in the conditional expectation of Y for $X = 0$ and $X = 1$: $\beta_{OLS} = E(Y|X = 1) - E(Y|X = 0)$. However, for many substantive analyses that are focused on the mean, the real interest lies in understanding how the unconditional expectation of Y will change if the unconditional distribution of X changes. Consider, for example, that we are interested in the effect of formulary tier status, a binary covariate, on the medication adherence for a particular drug treatment. An OLS regression will compare the average adherence to a drug under a lower formulary status to that under a higher formulary status for the drug. Interest may also lie on what would happen to the overall population level adherence rate if the proportion of patients facing a higher formulary status changes. This is the effect of a change in the unconditional distribution of X on the unconditional distribution of Y. Note that for continuous X (both for single-dimensional and multi-dimensional X), such questions represent interesting and rich policy questions. For example, what would happen to overall adherence rates if the population-level age-distribution changed or, in the context of racial disparities, what would adherence rates among Blacks look like if they shared other demographics and medical utilization habits of Whites? Interestingly, in the case of OLS regression, β_{OLS} is also a consistent estimator for this *marginal effect* on the unconditional distribution of Y. This is because, following (1),

$$E(Y)=p(X)\cdot E(Y|X=1)+(1-p(X))\cdot E(Y|X=0),\ \text{and}$$
$$dE(Y)/dp(X)=E(Y|X=1)-E(Y|X=0)=\beta_{\text{OLS}}. \quad (2)$$

This duality of interpretation of β_{OLS} persists even when there are other covariates (*W*) in the model, as long as the underlying data generating process (DGP) follows a linear-in-parameters additive model structure (i.e., a pure parallel location-shift DGP).

Let us consider the relationship of *X* with the quantiles of the distribution of *Y*. Let $q_Y(\tau)$ denote the τth quantile of the unconditional distribution of *Y*, $\tau = F_Y(q_Y(\tau))$. Then, following (1),

$$F_Y(q_Y(\tau))=\Pr(X=1)\cdot F_{Y|X=1}(q_Y(\tau))+\Pr(X=0)\cdot F_{Y|X=0}(q_Y(\tau)). \quad (3)$$

The effect on the unconditional quantile, $dq_\tau/dp(X)$, is obtained by implicit differentiation of (3):

$$dF_Y(q_Y(\tau))/dp(X)=(\partial F_Y(q_\tau)/\partial q_Y(\tau))\cdot(dq_Y(\tau)/dp(X)).$$
$$\text{Therefore,}\quad dq_Y(\tau)/dp(X)=[F_{Y|X=1}(q_Y(\tau))-F_{Y|X=0}(q_Y(\tau))]/f_Y(q_\tau). \quad (4)$$

Note that the definition of the effect on the unconditional quantile does not change with the set of covariates available for conditioning. That is, even in the presence of a vector of covariates *W*, the effect on the unconditional quantile is always evaluated marginally over the distribution of *W*.

It turns out that in the absence of any other covariates with potential effects on outcomes, the conditional and the unconditional treatment effects of a binary *X* are also identical for any quantile of *Y*. Similarly, even in the presence of other covariates (*W*), under a pure parallel location-shift DGP, as assumed in an OLS regression model, where the conditional effect is independent of values of other covariates, the conditional and unconditional effects on the quantiles converge.

However, when the DGP allows for the conditional effects to be heterogeneous and vary over values of other covariates, the definition of the unconditional quantile effect deviates from the definition of the effects on the conditional quantiles as the later vary with the set of conditioning variables available. Under such DGPs, discrepancies exist even in the interpretation of effects on the conditional versus the unconditional mean of *Y*. For example, when the conditional mean is expressed in nonlinear (either in *Ws* or in parameters) formulations, such as OLS regression with interaction terms or the broad class of generalized linear models including logit and probit models (Ai and Norton, 2003; Manning *et al*., 2005), the effect on the unconditional distribution of *Y* must be recovered using methods of recycled predictions once the coefficients, which represent conditional effects, are estimated (Basu and Rathouz, 2005). Such effects were termed as unconditional average partial effects by Wooldridge (2004).

Similarly, in the case of QR, the unconditional effect can be recovered using a weighted average of conditional effects as shown in Firpo *et al*. (2009). However, such calculations are usually fairly complicated because it needs to understand how each of the conditional quantiles maps onto the unconditional quantile of *Y*.

To better understand the difference between conditional and unconditional effects, we set up a simulation study under different DGPs. But first, we explain the conditional and unconditional quantile estimators.

2.2.1. Conditional quantile regression—The terminology 'quantile regression', as used in the statistics and econometrics literature, commonly refers to the CQR, introduced by Koenker and Bassett (1978). Specifically, conditional on the vector of observed covariates, $Z = \{X, W\}$, let $Q_\tau(Y|Z) = Z'\beta_\tau^{\mathrm{CQR}}$ be the conditional quantile operator such that $Q_\tau(Y|Z) = \inf_q\{q : F_{Y|Z}(q|Z) \geq \tau\}$, where inf{} is the *infimum* operator that represents the maximum lower bound of all values of q in the set defined by $F_{Y|Z}(q|Z) \geq \tau$. The conditional quantile operator can be expressed as any function of Z: $Q_\tau(Y|Z) = \xi(Z'\beta_\tau)$. Typically, a linear function, $Z'\beta_\tau$, is specified for $\xi(Z'\beta_\tau)$.

Analogous to the OLS regression of Y on Z, where βs are estimated as a solution to the problem of minimizing sum of square residuals, the β_τs associated with the τth conditional quantile function may be estimated by minimizing a sum of *asymmetrically* weighted absolute residuals (Koenker, 2005; Koenker and Bassett, 1978):

$$\min_{\beta_\tau \in R^p} \sum_{i=1}^{n} \rho_\tau(y_i - z_i'\beta_\tau), \quad (5)$$

where $\rho_\tau(.)$ is titled absolute value function defined as $\rho_\tau(u) = u \cdot (\tau - I(u < 0))$ for any $\tau \in (0,1)$. The estimated coefficients ($\hat{\beta_\tau}$s) may be interpreted as marginal or partial effects (depending on whether the corresponding covariate is continuous or binary) on conditional quantile of interest (Koenker and Hallock, 2001). A coefficient on a binary covariate X from a CQR is given by

$$\beta_\tau^{\mathrm{CQR}} = F^1_{Y|X=1,W=\tilde{\omega}}(\tau) - F^{-1}_{Y|X=0,W=\tilde{\omega}}(\tau) \quad (6)$$

where w $\bar{}$represents a vector of the sample means for W.

Whether $\beta_\tau^{\mathrm{CQR}}$ is a consistent estimator will depend on the underlying DGP. If the DGP is a pure parallel location-shift DGP for every covariate, then $\beta_\tau^{\mathrm{CQR}}$ is a consistent estimator for the effect of X on both the conditional and unconditional quantile of Y.

Under nonparallel location-shift DGPs, where the conditional effect of X varies over levels of W, $\beta_\tau^{\mathrm{CQR}}$ may be a consistent estimator for the conditional effect of X evaluated at the mean values of W, but it is not a consistent estimator of the unconditional effect of X as defined in (4). This is mainly because $F^{-1}_{Y|X=1,W=\overline{w}}(\tau) = q_{Y|X=1,W=\overline{w}}(\tau) \neq q_Y(\tau)$. That is, the (say) 95th percentile of the unconditional distribution of Y may not be the same as the 95th

percentile on the conditional distribution of *Y*|*X* (Firpo *et al*., 2009). Most modern statistical software including SAS, STATA, and R provides standardized routines to estimate CQR. The CQR implementation in our example was conducted using the STATA routine 'qreg' (StataCorp, 2009).

2.2.2. Unconditional quantile regression—There are two ways to obtain a covariate effect on the unconditional quantile. The first approach is to use the coefficient estimates from the CQR to recover (4). As Firpo *et al* show, this may be intuitively appealing but often practically intractable (2009). Specifically, they show that the partial effect of a covariate on an unconditional quantile of *Y* can be written as a weighted average (over the distribution of *X*) of the partial effect on a *specific conditional quantile* of *Y* that corresponds to the unconditional quantile that is of interest. For example, the 90th percentile of adherence conditional on high-tier status of a drug may only represent the 75th percentile of the overall adherence distribution. Therefore, if one can map all of the unconditional quantiles of *Y* to the corresponding conditional quantiles under different conditioning arguments, then such weighted approach can be easily implemented. However, it is evident that such a task can be quite arduous, requires nonparametric techniques, and is often intractable given the data at hand. An alternative to the aforementioned approach was proposed by Machado and Mata, who took a change in the unconditional distribution over time and decomposed that change into components that are attributable to changes in the marginal distribution of different *X*s (2005). However, their methods capture the total effect of a change in the marginal distribution of *X* over all unconditional quantiles of *Y* but not just one specific quantile.

A second approach, proposed recently by Firpo *et al*., circumvents the aforementioned problem of intractability and overcomes the limitation of the CQR model (2009). They suggest a UQR model based on the concepts of influence function (IF) and recentered influence function (RIF), as used in the robust statistics literature (Hampel *et al*., 1986). An IF is an analytical tool that can be used to assess the effect (or 'influence') of removing/adding an observation on the value of a statistic, $\nu(F)$, *without having to recalculate that statistic* and is defined as

$$\mathrm{IF}(y;\nu(F))=\lim_{\varepsilon\to 0}\frac{[\nu((1-\varepsilon)\cdot F+\varepsilon\cdot\delta_y)-\nu(F)]}{\varepsilon},0\le\varepsilon\le 1, \quad (7)$$

where *F* represents the cumulative distribution function for *Y* and δ_y is a distribution that only puts mass at the value *y*.

An RIF is obtained by adding the statistic to its IF:

$$\mathrm{RIF}(y;\nu)=\nu(F)+\mathrm{IF}(y;\nu) \quad (8)$$

One convenient feature of RIF is that its expectation is equal to that of $\nu(F)$. For example, when the statistic of interest is the mean, the IF is simply the residual evaluated at the particular value of *Y*, and the RIF is the value of *Y* itself:

$$\mathrm{IF}(y;\mu)=\underset{\varepsilon\to 0}{\mathrm{Lim}}\frac{[(1-\varepsilon)\cdot\mu+\varepsilon\cdot y-\mu]}{\varepsilon}=y-\mu,\ \text{and}\ \mathrm{RIF}(y;\mu)=\mu+(y-\mu)=y. \quad (9)$$

Consequently, regression of the RIF for the mean on *X* would yield the same coefficients as the regression coefficients of the standard OLS regression.

When the statistic of interest is a specific quantile τ of the outcome distribution,

$$\mathrm{IF}(y;q_\tau)=(\tau-I\{Y\le q_\tau\})/f_Y(q_\tau), \quad (10)$$

where q_τ refers to the τth quantile of the unconditional distribution of *Y*, $f_Y(q_\tau)$ is the probability density function of *Y* evaluated at q_τ, and $I\{Y\le q_\tau\}$ is an indicator variable to denote whether an outcome value is less than q_τ or not. By definition,

$$\mathrm{RIF}(y;q_\tau)=q_\tau+\mathrm{IF}(y;q_\tau). \quad (11)$$

Firpo *et al*. (2009) have shown that when the conditional expectation of RIF($y;q_\tau$) is modeled as a function of explanatory variables, that is, $E[\mathrm{RIF}(Y;\tau)|Z=z]=m_\tau(z)$, an RIF regression can be viewed as a UQR. This is because, as $E_Z E[RIF(Y;\tau)|z]=q_\tau$ by the definition of RIF, $E_Z(dm_\tau(z)/dZ)$ can be shown to be the marginal effect of a small location shift in the distribution of covariates on the τth unconditional quantile of *Y*, keeping everything else constant.

The implementation of the UQR, as illustrated in the article by Firpo *et al*, is straightforward and similar to the OLS regression implementation (2009). For a specific quantile τ, the first step is to estimate the RIF of the τth quantile of *Y* following (10) and (11). q_τ is estimated using the sample estimate of the unconditional τth quantile. Similarly, the density $f_Y(q_\tau)$at that point q_τ is estimated using kernel (or other) methods. The second step is to run OLS regression of the RIF(y, q_τ) on the observed covariates, *Z*.

Firpo *et al*. also outline the steps to compute the unconditional quantile partial effect that measures the effect of an explanatory covariate on the outcome of interest at the specific quantile (2009). In the RIF-OLS regression implementation adopted in this paper, which assumes that the outcome quantiles are linear function of the observed covariates, the unconditional quantile partial effects are nothing but estimated coefficients (Firpo *et al*., 2007). The UQR may be implemented by the STATA routines -rifreg- or -ivqte-, available at the websites, http://faculty.arts.ubc.ca/nfortin/datahead.html and http://www.econ.brown.edu/fac/Blaise_Melly/code_ivqte.html, respectively (accessed on March 30, 2012). For a binary *Z* variable, the STATA command -rifreg- estimates the effect of an epsilon change in the probability distribution of *Z* on a specific quantile. In contrast, the command -ivqte- estimates the full effect when *Z* is changed from 0 to 1. We use -ivqte- for our following simulations.

2.3. Simulations to illustrate conditional versus unconditional effects

To illustrate the variations in coefficient estimates generated under the CQR and the UQR framework, we employ a simple simulation exercise under different DGPs.

Specifically, we generate three covariates, $X \sim I(\text{Uniform}() > 0.5)$ and $W = (W_1, W_2)$, where $W_1 \sim$ Uniform (−1, 1) and $W_2 \sim$ Normal(0, 1) such that $E(W_1) = E(W_2) = 0$. Our theoretical interest lies on the effects of X on outcome Y in the overall target population from which Y is generated. However, we compare the estimated effect of X on Y which may vary under alternative DGPs when certain conditionings are implemented

DGP 1: (No covariates DGP)

$$Y = 1 + 2 * X + \varepsilon, \varepsilon \sim \text{Normal}(0, 1)$$

DGP 2: (Parallel location shift)

$$Y = 1 + 2 * X + 1 * W_1 + 1 * W_2 + \varepsilon, \varepsilon \sim \text{Normal}(0, 1)$$

DGP 3: (Interactive shift type I)

$$Y = 1 + 2 * X + 1 * W_1 + 1 * W_2 + 2 * X * W_1 + \varepsilon, \varepsilon \sim \text{Normal}(0, 1)$$

DGP 4: (Interactive shift type II)

$$Y = 1 + 2 * X + 1 * W_1 + 1 * W_2 + 2 * X * W_1 + 2 * X * W_2 + \varepsilon, \varepsilon \sim \text{Normal}(0, 1)$$

We draw a sample of 10,000 observations under each DGP. We estimate the effects of X on the 10th percentile of Y using both the CQR and UQR regression frameworks for each sample and under each DGP and average the results over 500 samples. Under each of the CQR and UQR frameworks, we consider adjusting for either W_1 or W_2, or both. The documentation including the STATA code for this simulation exercise is provided in APPENDIX A.

Table I presents the results from these regressions. Note that, by construction, each of the CQR or UQR provides a consistent estimator of the specific target parameter that the corresponding CQR or the UQR model seeks to estimate. Although the UQR target parameter represents the effect on outcomes in the overall target population, CQR target parameters represent effects on outcomes in specific parts of the target population defined by the conditioning implemented by CQR. Therefore, even in the absence of omitted variables, the CQR may be a biased estimator of the target parameter of a UQR model.

In the absence of additional covariates in the DGP (DGP 1), the effect of X is the same on every unconditional quantile of Y. Therefore, all the CQRs and the UQRs are able to estimate this constant effect. Even in the presence of covariates, when the DGP follows a parallel shift in the distribution of Y in response to X (DGP 2), the effect of X is deemed constant across all unconditional and conditional quantiles of Y. Again, both the CQR and

UQR are able to estimate this constant effect. However, this luxury of constant covariate effect across conditional quantiles of Y changes disappears in DGPs 3 and 4. In interactive shift type I (DGP 3) where the effect of X on a conditional quantile of Y conditioned on a level of W_1 varies, the CQR produces different results depending on whether W_1 or W_2 or both are included in the model. The UQR, on the other hand, estimates the effect on the unconditional quantile, which is different from any of the conditional quantile effects but does not vary depending on the covariates included in the model. Similar results follow in DGP 4.

Overall, the simulations confirm three main differences between CQR and UQR regressions:

1. Estimated effects of a covariate on a specific quantile of outcome are the same under CQR and UQR regression framework only if no other covariates influence the DGPs, or effect of the covariates is constant across levels of other covariate that influence DGPs.
2. When the effect of a covariate on a specific quantile of outcome vary over levels of other covariates (interactive shift DGPs 3 and 4), the CQR regression produces estimates of the effect on the conditional quantile, conditioned on the mean value of all other covariates, which differs from the effect on the unconditional quantile.
3. In the presence of interactive shift DGPs (such as DGPs 3 and 4), inclusion of alternate sets of covariates would alter the estimates from the CQR model, whereas it would not affect estimates from the UQR model, as long as all covariates are exogenous in nature.

We do not study a DGP where W's are correlated. In that case, as anticipated, the UQR and CQR estimates should deviate further.

2.4. Empirical example – medication adherence in patients with Alzheimer's Disease (AD) revisited

We compare the advantages of QRs over the use of dichotomized MPR (using a cut-off point of 80%) measure and illustrate the difference between the CQR and UQR methods using a case study to evaluate risk factors for medication adherence among patients with AD.

2.4.1. Data—The retrospective data for this real-world example come from a large managed care health insurer in the USA with nationwide coverage. As of 2006, the plan had approximately 14 million enrollees with both medical and pharmacy benefits. For the purpose of this study, enrollment information as well as medical and pharmacy claims data for commercial and Medicare Advantage health plan members were used. The database was accessed in accordance with the Health Insurance Portability and Accountability Act to maintain required privacy. Because only de-identified data for patients were used, a full Institutional Review Board review was not required for this study.

Subjects included had at least two medical claims with AD or related dementia (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] code 290.xx, 294.1x, 331.0, 331.82, 331.83) in either primary or secondary diagnosis

position during January 1, 2006, through December 31, 2007. An index date was assigned to each study subject based on the first prescription fill date for an oral AD therapy (i.e., rivastigmine, donepezil, galantamine, or memantine), so that there was no use of the AD therapy 6 months prior to the index date (baseline period). All patients were followed for a period of 1 year following their index dates (follow-up period). Patients had to have at least one additional fill of the index oral AD medication during the follow-up period and be continuously enrolled during the entire study period (i.e., during the baseline and follow-up period). Patients on combination AD therapy were not included in the study.

The outcome variable, MPR, was operationalized following standard definition as follows (Peterson *et al*., 2007):

$$MPR = \frac{Sum\ of\ number\ of\ days\ supplied\ for\ all\ but\ the\ last\ prescription\ fill}{Number\ of\ days\ between\ the\ first\ and\ the\ last\ prescription\ fill} \times 100 \ldots \ldots \ldots \quad (12)$$

Patient demographic variables (age, gender, and geographic location) were captured from enrollment data. The formulary status of AD medication (whether Tier 2 or Tier 1) was also determined from the pharmacy benefit. Note that the copayment amounts in these two tiers were not available in the data. Patients' baseline utilizations were assessed during the baseline period. The baseline Charlson–Quan comorbidity score was calculated based on baseline comorbid conditions (Charlson *et al*., 1987; Quan *et al*., 2005). Baseline costs (pharmacy, medical, and total, which is the sum of pharmacy plus medical costs) included both health-plan-paid and patient-paid amounts for any medical and pharmacy claims during the baseline. We also controlled for the average daily pill burden, a measure that tracked the number of pills that the patient consumed each of the 365-day follow-up period. Other confounders that were controlled for were baseline utilization measures including office visits, outpatient visits, emergency room (ER) visits, and inpatient visits, as well as the logarithm of baseline total health care costs.

We highlight the implications of alternative estimating approaches by focusing on the effect of four covariates. Although in a more substantive analysis, one must account for the endogeneity of some or all of these variables, we only discuss the likely associations for illustration.

1. Tier 2 versus Tier 1: Tier 2 status of the AD drugs received by patients may be associated with lower adherence via two ways. Patients receiving Tier 2 drugs may have more severe disease progression as they may not have responded to Tier 1 drugs with lower out-of-pocket costs. Hence, compared with patients receiving Tier 1 drugs, those receiving Tier 2 drugs may be less adherent, as they are more likely to be treatment-resistant patients or are more likely to forget to take their medications. Furthermore, the higher out-of-pocket costs for Tier 2 drugs may make patients less adherent.
2. Daily pill burden: pill burden is naturally expected to reduce adherence, although it may not have a significant effect on those who are already substantially nonadherent to medications.

3. Baseline office visits: higher number of office visits at baseline may be a proxy for severity of illness or may also be a proxy for a higher level of commitment on the patients' part. In the former case, the effect would be negative, as in the severity argument under Tier2 versus Tier1. In the latter case, a higher number of visits would lead to increased adherence, but this effect would be muted among those who already have high adherence.

4. Baseline emergency visit count: This factor is most likely a proxy for disease severity and would lead to decreased adherence.

Descriptive statistics for the study variables are provided in terms of means and standard deviations for continuous variables and the frequencies and percentages for categorical variables. Unless otherwise specified, a *p*-value of 0.05 or less was considered to be statistically significant. The standard errors for the coefficients in CQR and UQR were obtained through 500 bootstrap replications. The analytic data for the study were created using SAS, and the descriptive and multivariate analyses were conducted using STATA (StataCorp, 2009; SAS Institute Inc, 2003).

3. RESULTS

The final sample comprised 3091 subjects. Table II provides the descriptive statistics for the covariates in the study sample. The mean age of the study patients was 80 (SD = 8.25), and approximately 36% of the subjects were male. Approximately 35% of the subjects had health insurance with pharmacy benefit from the commercial plan, whereas the rest were from the Medicare Advantage plan.

The average MPR, the outcome variable, was 82 (SD = 22). The unconditional MPR distribution is skewed to the left with a spike at 1 (Figure 1). Approximately 28% of the subjects had perfect medication adherence. Consequently, CQR and UQR regression can only assess the effect of covariates up to the 70th percentile. The effect of covariates at the highest quantile (about 70th percentile in our data) would represent the effects for those patients who are almost perfectly adherent. Each QR was carried out at 7 quantiles: 0.1, 0.2, …, 0.7.

For τth percentile CQR regression, the intercept represents the τth percentile of the conditional distribution of adherence, with all variables being evaluated at zero. The coefficient on a covariate represents the marginal (for continuous covariate) or partial effect (for binary covariate) on the conditional quantile of the outcome distribution, conditioned on the mean values of other covariates. The covariate effects under the UQR framework represent the effect of changing that covariate value by one unit keeping the full distribution of all other covariates the same.

As previously mentioned, we will describe covariate effects under the logistic regression, CQR and UQR frameworks only for the four covariates. Interpretation of the other covariate effects will follow similarly.

3.1. Effects of formulary tier status

Under the logistic regression model, where adherence is defined as MPR ≥80%, patients on Tier 2 medication were significantly less likely to be adherent (odds ratio = 0.62, $p < 0.05$) compared with patients on Tier 1 AD medication (Table III). The accompanying marginal (unconditional) effect shows that the probability of adherence declined by 10 percentage points if patients were on Tier 2 medications.

However, an 80% MPR represents about the 35th percentile of either the conditional or unconditional quantile of MPR distribution (as indicated by the intercept terms in Tables IV and V). Both the CQR and UQR results show that the effect of Tier 2 shifts the 40th conditional and unconditional percentile value significantly. Both frameworks suggest that the effect is nonsignificant for the highest quantile, that is, patients with high adherence levels (~99% MPR). But the bigger effects of Tier 2 status are concentrated among patients who have much lower adherence. The CQR framework suggests that significantly larger effects of Tier 2 status prevail for 10th, 20th, and 30th conditional quantiles of MPR (Table IV). However, the UQR suggests that that effect is nonsignificant at the 10th unconditional quantile, that is, among patients with very low MPR (~20%). Tier 2 status may not have a big effect (Table V).

3.2. Effects of daily pill burden

The general effects are very similar to Tier 2 status. Greater daily pill burden was associated with a significantly less likelihood of being adherent (odds ratio = 0.59, $P < 0.05$), and the marginal effect on the probability of being adherent was −10 percentage points (Table III). Under CQR, all seven conditional quantile effects of daily pill burden considered in the study were significant, with the effects being more pronounced in the lower tail of the MPR distribution and then tapering off monotonically as one moves through the upper percentiles (Table IV). Results are similar under UQR, except that the effect is nonsignificant at the 10th unconditional quantile (i.e., among patients with MPR ~49%, daily pill burden may not have a big effect) (Table V).

3.3. Effects of baseline office visit count

Baseline office visit count was not found to be a significant predictor of adherence in the logistic framework (Table III). The conditional quantile effects were significant at only 20th percentile of the MPR distribution (Table IV). In general, the unconditional effects of office visit count on the percentiles considered were negative and were found statistically significant for five of the seven percentiles (Table V). Note, however, that both conditional and unconditional effects that were statistically significant were small in magnitude (varying between −0.10 and −0.42), perhaps due to the opposing forces that increase in office visits signify.

3.4. Effects of baseline emergency room visit count

Baseline ER visit count was not significantly associated with the probability of being adherent (Table III). The conditional quantile effect of the same was significant only for the 10th and 60th percentiles (−3.99 and −0.55, $p < 0.05$) but not for the remaining five

percentiles. Unconditional quantile effects, on the other hand, were significant only in the upper tail of the adherence (MPR) distribution (at 50th, 60th, and 70th percentiles). This underscores that the conditional and unconditional effects for the same quantile may differ substantially depending on the application/data on hand.

Figure 2 presents the conditional and unconditional effects, along with their 95% confidence intervals, for the four covariates used to illustrate the differences between CQR and UQR estimate of covariate effects. The two panels on the first row of Figure 2 reinforce the previous discussion on the heterogeneity of effects of Tier 2 status for medication and daily pill burden across different parts of the adherence (MPR) distribution. Furthermore, the approximate overlap of the two curves representing conditional and unconditional effects as well as their 95% confidence bands indicate that, except for the lower quantiles, the two sets of effects did not differ substantially in this specific application. For this application, this was expected, given that the intercepts across the CQR and UQR regressions revealed that the percentiles of the conditional and unconditional adherence distributions were fairly similar (Tables IV and V). However, these similarities were only divulged after running the UQR regression. Furthermore, subtle differences between the effects of covariates on conditional versus unconditional quantiles, especially at lower percentiles, were revealed.

4. DISCUSSION OF RESULTS – WHAT DID WE LEARN FROM ALTERNATIVE ESTIMATORS?

Our results illustrate that the traditional way of modeling MPR as a binary outcome based on an arbitrary cut-off point will not provide a full picture of the heterogeneous impacts of the determinants across different parts of the adherence distribution (Hansen *et al*., 2009). As seen from Table III, the standard approach did identify four covariates (age, south, Tier 2, and daily pill burden) as statistically significant determinants of probability of being adherent, as defined by MPR equal to or above 80%. However, note that the CQR and UQR frameworks go further in the sense that they identified how these determinants have heterogeneous impacts across different parts of the medication adherence distribution. For example, both CQR and UQR unequivocally showed that medication adherence was significantly lower in the south than in the west and that the impact was higher in the lower tail of the adherence (MPR) distribution (Tables IV and V). Similarly, Tier 2, which indicates higher copayment, appeared to have significantly higher impact in the lower tail of the adherence distribution. Clearly, the policy maker in charge of improving medication adherence will find the QR results more useful to indentify subgroups of patients for intervention than the logistic regression results that merely identify the determinants of probability of being adherent. Furthermore, note that QR results also identified additional determinants (baseline office visits and ER visits) that impacted medication adherence only on some selected quantiles, which were not revealed in the traditional logistic regression framework.

In addition, because the effects of covariates such as Tier 2 and pill burden are shown to be stronger at the lower quantiles than at the upper quantiles, both CQR and UQR frameworks reveal a change in the dispersion of the conditional or unconditional distribution of

outcomes with the covariate levels, a phenomenon that is completely masked by traditional methods.

The advantage of UQR over CQR may also be apparent by considering a hypothetical policy situation in which the policy maker decides to intervene on all those patients with an MPR of 70% or less. Under the CQR, this threshold may fall within different quantiles depending upon observed characteristics of the subjects (Firpo *et al*., 2007). This problem is obviated under the UQR framework.

Previous studies have considered the impact of different definitions of MPR on medication adherence (Hudson *et al*., 2007; Martin *et al*., 2009). Our study, however, employed a widely used continuous MPR measure and provided a novel way of assessing the impact of observed determinants. Naturally, the CQR and UQR techniques can be extended to other continuous measures of MPR.

In our specific application, standard errors for many of the covariates are rather high, implying that covariates included in the current model may not be enough to explain the overall variation in medication adherence. Given that caregiver support is an important component of care delivery for AD patients, the fact that the database used for this study does not have any information on caregiver support is an important limitation. Note that this is a drawback of the claims database that is deficient of important clinical variables but not of the CQR or UQR methods. Our application used healthcare claims data that often lack important clinical and socioeconomic information on the subjects. Thus, all the standard limitations of observational studies using claims data, including the possibility of selection bias, apply to this study as well, and therefore interpretation of the study results must take into account these potential limitations (Schneeweiss and Avorn, 2005; Motheral *et al*., 2003).

5. CONCLUSION

Despite the widespread use of the CQR framework in the applied literature, we have shown how this framework may generate results that are often not generalizable or interpretable in a policy or population context. In contrast, the UQR provides more interpretable results, as it marginalizes the effect over the distributions of other covariates in the model. We have highlighted the conditions under which results from CQR and UQR would vary. However, it is important to note that unlike the interpretation of a conditional effect, the unconditional effect produced in a UQR framework must be interpreted in the context of a target population to which the estimates pertain. Therefore, defining the target population is an important step toward interpreting results from UQR. The use of CQR and UQR is illustrated in an empirical study of exploring determinants of medication adherence among patients with AD. To the best of our knowledge, this is the first attempt in the literature to model medication adherence in QR framework. This study demonstrates that, compared with the standard approach of modeling medication adherence through logistic modeling, the CQR and UQR methods provide additional insights on the potential heterogeneous impacts of the determinants on medication adherence, with important differences observed between the results of CQR and UQR methods.

We hope that the UQR framework would gain more popularity in applied research, especially given the ease of interpretation of its results and the ease of implementing these methods in standard statistical software packages.

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APPENDIX A: STATA CODES FOR GENERATING SIMULATION RESULTS

```
clear
set obs 1
gen simul = .
save qte1, replace
qui forv i = 1(1)500{
clear
set obs 10000
gen u = uniform()
gen x = (u > 0.5)
gen w1 = -1 + 2*uniform()
gen w2 = invnormal(uniform())
summ w1
replace w1 = w1-r(mean)
summ w2
replace w2 = w2-r(mean)
/* The following needs to be run one by one for each of the DGPs separately
*/
gen y = 1+ 2*x + 0*w1 +0*w2 + 0*x*w1 + 0*x*w2 + invnorm(uniform()) /*[DGP
1]*/
*gen y = 1+ 2*x + 1*w1 +1*w2 + 0*x*w1 + 0*x*w2 + invnorm(uniform()) /*[DGP
2]*/
*gen y = 1+ 2*x + 1*w1 +1*w2 + 2*x*w1 + 0*x*w2 + invnorm(uniform()) /*[DGP
```

```
3]*/
*gen y = 1+ 2*x + 1*w1 +1*w2 + 2*x*w1 + 2*x*w2 + invnorm(uniform()) /*[DGP
4]*/
/* Conditional Quantile Regression: Using -ivqte- command */
ivqte y w1 (x), quantiles(0.10)
gen cqte1 = _b[x]
ivqte y w2 (x), quantiles(0.10)
gen cqte2 = _b[x]
ivqte y w1 w2 (x), quantiles(0.10)
gen cqte12 = _b[x]
/* Conditional Quantile Regression: Using -qreg- command */
qreg y x w1, q(10)
gen c1qte1 = _b[x]
qreg y x w2, q(10)
gen c1qte2 = _b[x]
qreg y x w1 w2, q(10)
gen c1qte12 = _b[x]
/* Unconditional Quantile Regression: Using -ivqte- command */
ivqte y (x), continuous(w1) quantiles(0.10)
gen uqte1 = _b[Quantile_1]
ivqte y (x), continuous(w2) quantiles(0.10)
gen uqte2 = _b[Quantile_1]
ivqte y (x), continuous(w1 w2) quantiles(0.10)
gen uqte12 = _b[Quantile_1]
/* Unconditional Quantile Regression: Using recentered influence function
(RIF) estimated manually */
egen pct10 = pctile(y), p(10) by(x)
kdensity y, at(pct10) generate(newvar_d1) kernel(gaussian) nograph
gen rif = pct10 + (.10 - (y =pct10))/newvar_d1
reg rif x w1
gen mqte1 = _b[x]
reg rif x w2
gen mqte2 = _b[x]
reg rif x w1 w2
gen mqte12 = _b[x]
gen simul = ‘i’
keep if _n==1
keep cqte* c1qte* uqte* mqte* simul
append using qte1
save qte1, replace
noi di’i’
}
use qte1, replace
sum, sep(3)
```

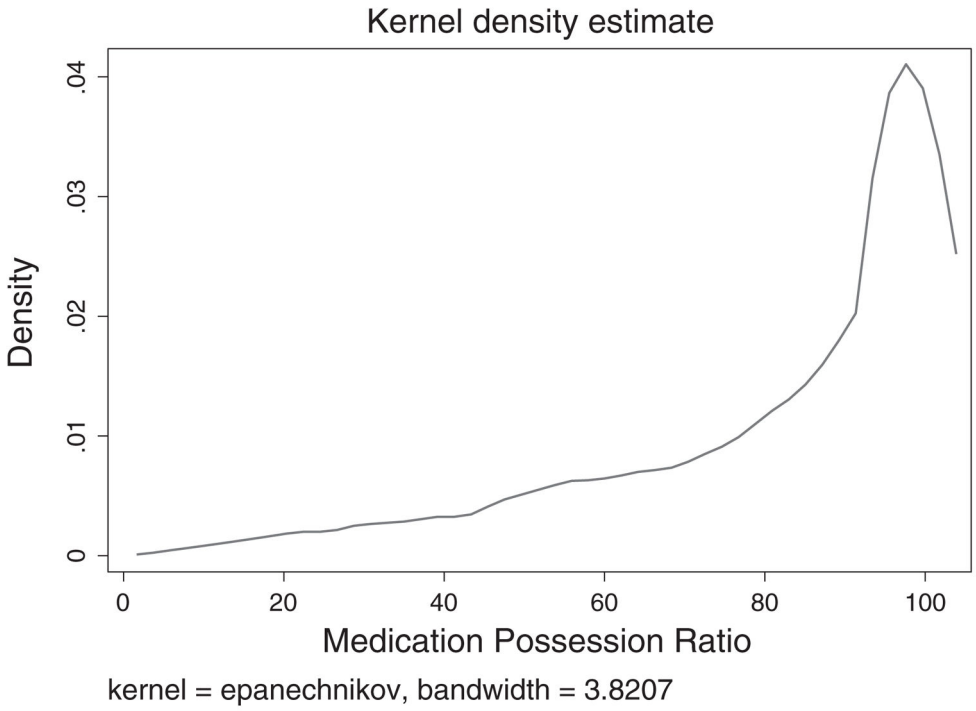

Figure 1.
Unconditional distribution of medication possession ratio

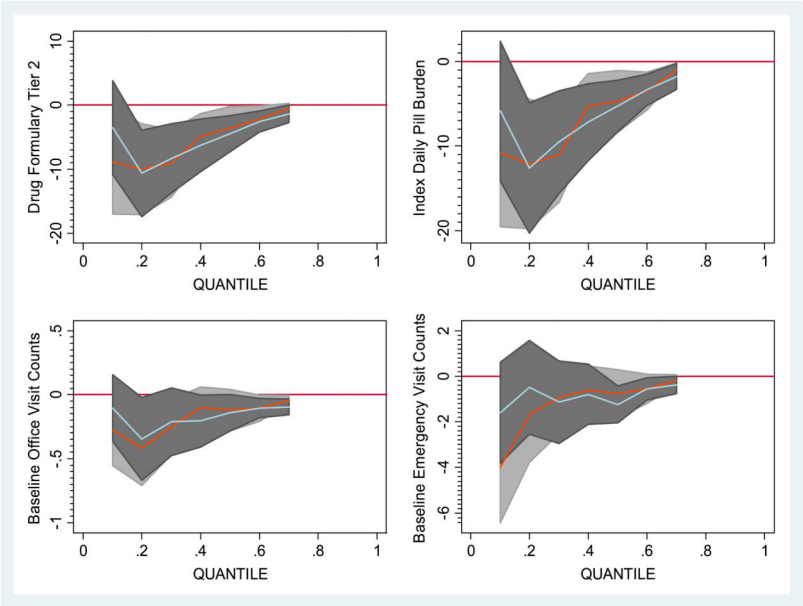

Figure 2.

The plot of the conditional and unconditional quantile regressions for medication possession ratio (adherence)

Note: The red line traces the conditional quantile regression (CQR) point estimates, while the blue line traces the unconditional quantile regression (UQR) point estimates. The light shade is the 95% confidence bands for the CQR estimates, and the darker shade represents the 95% confidence bands for the UQR estimates. The straight line at 0 helps assess the differences of the quantile effects from zero.

Table I

Simulation results – average (SD) coefficient estimates of X on the conditional versus unconditional 10th percentile of Y

	DGP 1	DGP 2	DGP 3	DGP 4
CQR				
$Y \sim X, W_1$	2.00 (0.03)	2.00 (0.05)	2.00 (0.06)	−0.31 (0.08)
$Y \sim X, W_2$	2.00 (0.03)	2.00 (0.04)	0.84 (0.05)	0.73 (0.07)
$Y \sim X, W_1, W_2$	2.00 (0.03)	2.00 (0.03)	2.00 (0.05)	2.00 (0.10)
UQR				
$Y \sim X, W_1$	2.00 (0.03)	2.00 (0.05)	1.03 (0.06)	−0.67 (0.09)
$Y \sim X, W_2$	2.00 (0.03)	2.00 (0.05)	1.03 (0.06)	−0.67 (0.08)
$Y \sim X, W_1, W_2$	2.00 (0.03)	2.00 (0.05)	1.03 (0.06)	−0.67 (0.08)

DGP, data generating process.

These simulation results are based on STATA's -ivqte- command for both conditional quantile regression (CQR) and unconditional quantile regression (UQR). The STATA Code provided in the APPENDIX 1 also demonstrates how CQR estimates may be obtained by the standard STATA command -qreg- and UQR estimates may be obtained by first estimating the recentered influence function (RIF) and then regressing on the covariates of interest as outlined in the work of Firpo *et al*. (2009).

The numbers are rounded to two decimal places.

Table II

Descriptive statistics (N = 3091)

Variable	Mean	SD
Age as of the index year	79.81	8.25
Baseline Charlson–Quan comorbidity score	1.84	1.8
Daily pill burden	1.24	0.43
Baseline office visits count	6.13	6.5
Baseline outpatient visits count	2.62	4.08
Baseline emergency room visits count	0.61	1.1
Baseline inpatient visits count	0.38	0.71
Baseline pharmacy cost ($)	966.28	1407.50
Baseline medical cost ($)	7848.52	16819.55
Baseline total cost ($)	8814.81	17007.25
Baseline logged total costs	7.99	1.71
Medication possession ratio	82.31	21.75
	n	%
Male	1100	35.59
Northeast	509	16.47
Midwest	1211	39.18
South	1082	35
West	289	9.35
Insurance type (commercial)	1070	34.62
Drug formulary Tier 2	2121	68.62
	Quantiles #	Value
MPR quantiles	0.1	49.34
	0.2	65.22
	0.3	77.25
	0.4	85.47
	0.5	91.56
	0.6	95.93
	0.7	99.34
	0.8	100
	0.9	100

Table III

Logistic regression for adherence (whether MPR ≥80%)

Variables	Odds ratio	95% CI	Average marginal effect (dy/dx)	95% CI for marginal effects
Age	**1.01**	(1.00, 1.02)	**0.002**	(0.000, 0.004)
Male	0.92	(0.79, 1.09)	−0.017	(−0.052, 0.018)
Northeast (ref: west)	0.89	(0.64, 1.25)	−0.024	(−0.097, 0.048)
Midwest (ref: west)	0.88	(0.64, 1.19)	−0.029	(−0.096, 0.038)
South (ref: west)	**0.70**	(0.52, 0.95)	−0.076	(−0.141, −0.011)
Whether commercial (ref: Medicare Advantage)	1.19	(0.99, 1.42)	0.037	(−0.002, 0.076)
Baseline comorbid score	1.04	(0.99, 1.10)	0.008	(−0.003, 0.020)
Tier 2	**0.62**	(0.46, 0.83)	**−0.103**	(−0.166, −0.040)
Daily pill burden	**0.59**	(0.43, 0.81)	**−0.113**	(−0.180, −0.046)
Baseline office visit count	0.99	(0.98, 1.00)	−0.002	(−0.005, 0.000)
Baseline outpatient visit count	1.00	(0.98, 1.02)	0.000	(−0.005, 0.004)
Baseline ER visit count	0.96	(0.88, 1.04)	−0.010	(−0.028, 0.009
Baseline inpatient visit count	1.05	(0.90, 1.23)	0.011	(−0.023, 0.045)
Log of total costs	**1.12**	(1.05, 1.19)	**0.024**	(0.011, 0.037)

MPR, medication possession ratio; ER, emergency room.

Boldfaced estimates indicate statistical significance (p-value ≤0.05).

Table IV

Conditional quantile regression results for MPR (adherence)

	Q10	Q20	Q30	Q40	Q50	Q60	Q70
Age	0.24	**0.28**	**0.29**	**0.24**	0.11	**0.07**	0.03
Male	−0.92	0.45	1.13	0.15	−1.19	−0.87	−0.44
Northeast (ref: west)	−2.67	−2.79	−1.97	−1.68	−1.86	−0.98	−0.56
Midwest (ref: west)	−4.49	−2.60	−3.84	−2.74	−1.49	−1.15	−0.44
South (ref: west)	−8.46	**−8.72**	**−7.87**	−5.48	**−3.75**	**−2.60**	**−1.28**
Whether commercial (ref: Medicare Advantage)	−1.32	**3.96**	2.16	1.94	1.52	0.81	0.34
Baseline comorbid score	1.38	1.25	0.70	0.18	0.25	0.15	0.07
Tier 2	−8.87	**−10.01**	**−9.07**	**−4.83**	**−3.62**	**−2.18**	−0.49
Daily pill burden	**−10.82**	**−12.12**	**−11.03**	**−5.26**	**−4.74**	**−3.49**	**−1.04**
Baseline office visit count	−0.28	**−0.42**	−0.25	−0.10	−0.12	−0.11	−0.04
Baseline outpatient visit count	−0.17	−0.25	−0.20	−0.08	0.04	0.02	−0.01
Baseline ER visit count	**−3.99**	−1.69	−0.94	−0.61	−0.76	**−0.55**	−0.17
Baseline inpatient visit count	0.60	−0.36	−0.29	0.93	0.11	0.07	−0.14
Log of total costs	**4.43**	**3.43**	**2.63**	**1.81**	**1.70**	**1.15**	**0.48**
Constant	**49.57**	**64.72**	**77.13**	**85.11**	**91.37**	**95.24**	**98.62**

MPR, medication possession ratio; ER, emergency room.

Boldfaced estimates indicate statistical significance (p-value ≤0.05).

Table V

Unconditional quantile regression results for MPR (adherence)

	Q10	Q20	Q30	Q40	Q50	Q60	Q70
Age	0.23	**0.28**	0.17	**0.20**	**0.14**	**0.08**	**0.06**
Male	−0.61	−0.42	−0.66	−0.28	−0.78	**−1.08**	−0.62
Northeast (ref: west)	−4.77	−4.33	−0.44	−2.63	−1.69	−0.66	−1.10
Midwest (ref: west)	−3.96	−2.37	−1.60	−3.51	−2.39	−1.06	−1.08
South (ref: west)	**−8.25**	**−9.35**	**−6.05**	**−6.25**	**−4.47**	**−2.18**	**−2.35**
Whether commercial (ref: Medicare Advantage)	0.00	4.69	2.71	2.30	0.95	0.66	0.43
Baseline comorbid score	0.66	0.93	0.61	0.52	0.33	0.11	0.13
Tier 2	−3.54	**−10.66**	**−8.31**	**−6.30**	**−4.44**	**−2.57**	−1.37
Daily pill burden	−5.88	**−12.59**	**−9.53**	**−7.16**	**−5.26**	**−3.36**	**−1.78**
Baseline office visit count	−0.10	**−0.34**	−0.21	**−0.20**	**−0.14**	**−0.10**	**−0.10**
Baseline outpatient visit count	0.07	0.01	−0.01	−0.03	0.00	−0.01	0.00
Baseline ER visit count	−1.59	−0.48	−1.14	−0.80	**−1.23**	**−0.55**	**−0.38**
Baseline inpatient visit count	−0.76	−0.94	0.09	0.17	1.02	0.52	0.26
Log of total costs	**3.42**	**3.35**	**2.67**	**2.11**	**1.44**	**0.88**	**0.76**
Constant	**49.35**	**65.27**	**77.26**	**85.59**	**91.57**	**95.94**	**99.34**

MPR, medication possession ratio; ER, emergency room.

Boldfaced estimates indicate statistical significance (p-value ≤0.05).