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ABSTRACT

We estimate the impact of diabetic drug adherence on hospitalizations, ER visits, and hospital costs, using insurance claims from MarketScan® employer data. However, it is often difficult to measure the impact of drug adherence on hospitalizations since both adherence and hospitalizations may be correlated with unobservable patient severity. We control for such unobservables using propensity score methods and instrumental variables for adherence such as drug coinsurance levels and direct-to-consumer-advertising. We find a significant bias due to unobservable severity in that patients with more severe health are more apt to comply with medications. Thus, the relationship between adherence and hospitalization will be underestimated if one does not control for unobservable severity. Overall, we find that increasing diabetic drug adherence from 50% to 100% reduced the hospitalization rate by 23.3% (p=0.02) from 15% to 11.5%. ER visits are reduces by 46.2% (p=.04) from 17.3% to 9.3%. While such an increase in adherence increases diabetic drug spending by $776 a year per diabetic, the annual cost savings for averted hospitalizations are $886 per diabetic, a cost offset of $110 (p=0.02), or $1.14 per $1 spent on drugs.

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1. Introduction

Patient cost-sharing in purchases of prescription drugs has been increasing dramatically. Between 2000 and 2006, copayments for generics, preferred brand drugs, and non-preferred drugs increased by 57 percent, 85 percent, and, 124 percent, respectively, in employer based plans (Kaiser Family Foundation, 2006). Similar increases in cost-sharing were observed more recently under the Medicare Part D plan introduced in 2006. For instance, in the Part D stand-alone plans, median copayments increased by 40 percent for generics, and 27 percent for preferred brand drugs, while coinsurance rates for specialty drugs increased by 10 percent in 2009 alone, despite the previous year's sharp premium increases.[1] Much of this is in response to drug price increases, which tend to have a bigger effect on the elderly. Between 2003 and 2006, prices of drugs purchased by elderly Medicare beneficiaries rose by 24.2% for drugs used more heavily by the elderly, compared to 18.8% for drugs less heavily used (Frank and Newhouse, 2008).

At the same time, many employers as well as Medicare policy-makers have begun to express concerns over the long-run effects of cost-sharing, especially in the case of prescription drugs that are used to control common chronic conditions such as hypertension, diabetes, or asthma. Specifically, excessive cost-sharing may lead to the underuse or inappropriate use of medications; thus, leading to medical complications and ultimately, higher medical costs. To address these concerns, some innovative employers have begun to experiment with value-based insurance design (VBID), whereby copayments for important preventive care drugs are reduced to zero while copayments for

[1] The average Part D premium increased sharply by 17% in 2008, followed by another 24% increase in 2009.

drugs with less value are increased.[2] Anecdotal evidence suggests that VBID has met with some success. For example, Pitney Bowes, a firm with 35,000 employees, dropped its coinsurance rate for diabetic drugs from 50% to 10%. According to the firm, this resulted in a 12 percent reduction in the overall cost of care for the median diabetic (Fuhrmans, 2004). The University of Michigan, in a 2006 pilot program, documented similar cost-offsets when it provided no-cost diabetes medications to its employees and their dependents (Chernew et al, 2007). In the broader policy arena, the Medicare Payment Advisory Commission recommended to Congress that Medicare explore the use of VBID in Part D (Medpac, 2009). In May of 2009, a U.S. Senate bill (S. 1040) entitled the "Seniors' Medication Copayment Reduction Act of 2009", was introduced to establish a Medicare Part D demonstration to test whether VBID increases adherence to prescribed drug regimens, improves outcomes, and reduces costs for fifteen conditions.

Poor adherence appears to be endemic across many medical conditions despite its potentially severe consequences. In one study, only 42 percent of glaucoma patients complied after having been told they would go blind if they did not adhere. For patients who already had gone blind in one eye, adherence rates rose only to 58 percent (Cramer, 1991). Similarly, 18 percent of renal transplant patients facing organ rejection or even death from poor adherence with immunosuppressant therapy were not taking their medication (Rovelli, 1989). Of 49 randomized control trials of interventions to improve adherence, McDonald, Garg, and Haynes (2002) found that only 17 interventions led to

[2] Economists have gone further to propose actual subsidies for preventive drugs and medical testing, for instance see Dor, 2004; Dor and Encinosa, 2004; Chernew et al 2000; Fendrick et al 2001.

improvements in treatment outcomes. Thus, there appears to be a need for further policy intervention.

While increases in patient cost-sharing have been shown to reduce adherence to prescribed drug regimens for important chronic conditions such as diabetes (Dor and Encinosa, 2004, 2009), the empirical relationship between pharmaceutical drug adherence and outcomes or costs has not yet been fully explored. While many studies show that reducing drug copayments increases drug adherence (Gibson et al, 2005), improves some outcomes (Hsu et al, 2006; Rice and Matsuoka, 2004; Goldman et al, 2007), and reduces costs (Gaynor et al, 2007; Chandra et al, 2007; Shang and Goldman, 2007; Zhang et al 2009; and Deb et al 2009); none of these recent papers have actually measured the direct effect of drug adherence on outcomes such as averted hospitalizations or their corresponding costs. Given that adherence could be improved through either direct intervention by the insurer or through optimal benefit design (Dor and Encinosa, 2004, 2009), it is important to fill the gap in that literature.

In this study, we address this issue by estimating the direct impact of adherence on hospitalizations and costs in the case of diabetes. In addition, we convert our adherence measure to a dollar measure by estimating the costs of all drug prescriptions under adherence. Hence, our paper is a contribution to the drug cost-offset literature. Yet another motivation for examining the direct impact of adherence on costs (rather than indirectly through changes in cost-sharing and benefit design) is that adherence may be affected by a variety of incentives other than removal of financial barriers. Many VBID

programs currently being implemented involve much more than cost-sharing reductions. They often involve specific programs, such as the Medication Therapy Management Programs in Medicare Part D. To encourage adherence to medications, these programs offer interventions such as phone outreach, medication reviews, refill reminders, intervention letters, educational newsletters, and drug interaction screenings. Such incentives that go beyond the lowering of copayments are often needed to improve adherence.

Decreasing cost-sharing is only one factor among many that might improve adherence. This may explain why some studies find little impact in decreasing cost-sharing on cost-offsets. In this paper we will broaden the scope of prior research. Thus, we will not examine cost-sharing *per se*, rather we will examine the direct impact of drug adherence on outcomes and costs, and focus on patients diagnosed with diabetes.

Why Diabetes?

Diabetes is one of the most common chronic conditions for which prescription medications exist, with 23.6 million Americans, or 7.8 percent of the U.S. population estimated to have this diagnosis. It is the leading cause of adult blindness, kidney failure, and non-trauma amputations, and a leading cause of heart disease. 234,000 people die each year from diabetes in the U.S., making it the seventh leading cause of death. The prevalence of diabetes in the U.S. increased by more than 30% over the last ten years. Moreover, the annual costs of diabetes in medical expenditures and lost productivity climbed from $98 billion in 1997 to $174 billion in 2007. As the incidence of diabetes

reaches epidemic proportions, leading to spiraling costs, the need to undertake prevention measures is becoming even more pronounced.

There are two major forms of the disease. Type 1 diabetes occurs in about 10 percent of cases; in this manifestation of the disease, a person is unable to produce insulin, the major hormone in the body that regulates blood sugar level. Persons with Type 1 diabetes are dependent on daily insulin injections, but few oral prescription medications are available. In Type 2 diabetes mellitus, persons either produce low levels of insulin or the insulin produced is deficient in regulating blood sugars. For this variant of the disease, five types of oral prescription medications are available: Sulfonylureas (SU), Non-SU (Meglitinides), Metformin, Thiazolidinediones (TZD), and alpha-Glucosidase Inhibitors (AGI). Each of these drugs targets a separate organ site in the body to control blood sugar levels, as illustrated in Table 1. These five pharmacological methods of controlling of blood sugar can substantially delay or prevent the costly medical complications arising from diabetes (see Cohen et al, 2003), such as blindness, kidney failure, non-traumatic amputations, and heart disease.

Compliance with these medications has recently gained attention since it was found that only 55% of diabetics keep their blood sugar under control (National Healthcare Disparities Report, 2008). A person is considered compliant if he or she adheres to the anti-diabetic drug regimen prescribed by a physician (Hughes et al, 2001; Dezii, 2000). Since these anti-diabetic medications are intended to be taken permanently, measurement of compliance is relatively straightforward when tracking such individuals. In this paper,

we will examine patient compliance with all five anti-diabetic drugs in Table 1. Our main concern is that decreases in patient compliance with these drugs may cause costly, preventable hospitalizations and ER visits.

2. Data

In this analysis we use one of the largest available databases of privately insured individuals in the U.S., the MarketScan® Research Databases maintained by Thomson Reuters. These databases encompass five million individuals who are covered by employer-sponsored health insurance offered by about forty large firms. They include both active employees and annuitants (retirees). The complete database contains various files with detailed information on medical conditions, insurance coverage, and payments for persons with any insurance claims for inpatient, outpatient, and prescription drug services. For purposes of this study, five different files from the 2001-2002 MarketScan® were linked to create a single analysis file. The first file was the MarketScan® drug file, which contains the insurance drug claims for all individuals who purchased prescription drugs. The second was the Employer Benefit Plan Design (BPD) database, with information on benefit design and drug copayment structure from some of the larger employers in MarketScan®, offering a total of 50+ insurance plans with prescription drug benefits. The third was the MarketScan® Enrollment File, which contains health plan enrollment history. The fourth and fifth files, respectively, were the MarketScan® Hospital Inpatient File and the Outpatient Services File containing information on patients' medical conditions and certain demographic characteristics. Finally, the 2001

and 2002 Redbooks (Medical Economics Company, 2002) were used to obtain additional information about the particular prescription drugs for diabetes.

We focus on non-elderly adults over the age of seventeen with chronic Type 2 diabetes who require oral anti-diabetic medications on an ongoing basis, as described in Table 1, over a two year period. We include diabetics continuously enrolled during 2001-2002 with (1) at least one anti-diabetic drug claim between January 1 and April 1 in 2001, and (2) at least one anti-diabetic drug claim in 2002. Our final sample consists of 56,744 diabetics. We use any ICD-9 Type 2 diabetes diagnosis on any inpatient or outpatient claim over a two year period to identify Type 2 diabetics. Access to detailed patient information allows us to track patient compliance, as measured by the sequence of prescription refills within a defined time interval.

To adjust for patient heterogeneity (case mix), we controlled for age (five categories), sex, and 27 chronic conditions developed by in the AHRQ Comorbidity Software (www.ahrq.gov/data/hcup/comorbid.htm; Elixhauser et al (1998), and updated by McDonald et al (2002)). These comorbidities were obtained from the MarketScan® Hospital Inpatient File and the Outpatient Services File. We control for the patient's number of chronic conditions. The 27 chronic conditions are congestive heart failure, arrhythmias, valvular disease, pulmonary circulation disease, peripheral vascular disease, hypertension, paralysis, other neurological disorders, chronic pulmonary disease, diabetes with chronic complications, hypothyroidism, renal failure, liver disease, peptic ulcer disease with bleeding, lymphoma, metastatic cancer, solid tumor without metastasis,

rheumatoid arthritis collagen, coagulopathy, obesity, weight loss, fluid and electrolyte disorders, chronic blood loss anemia, deficiency anemias, alcohol abuse, psychoses, and depression. In addition, we include a binary variable for insulin use, as well as a binary variable called "drug abuse," since drug abuse is a strong predictor of hospitalizations.

If the patient was not the primary insurance policy holder, but a dependent, this is recorded in the variable "Dependent". We also control for "Retiree". Next, to control for income, we used the log of the median household income of the patient's county, taken from the Area Resource File (ARF). We also include a variable "Hourly" to indicate if the worker earns an hourly wage versus a salary. County HMO penetration is included from the InterStudy data. A large HMO penetration rate is known to reduce the hospitalization rate in an area. To control for unobservable variation in health plan benefits by firm, we include 12 firm fixed effects, as well as a binary indicator "small" for firms with less than 10,000 employees.

Finally, in analyses of hospital emergency use (ER) we also control for the coinsurance rate for ER visits, since that may influence the decision to use the ER. In the hospitalization analysis, we do not use coinsurance rates since hospital coinsurance rates were too low (less than 2%) to have any effect on hospitalizations. Overall, we have 18 covariates and 12 firm fixed effects. The cost regressions do not use firm fixed effects since they were run on small samples consisting of only the patients with hospital admissions or positive ER visits.

3. Empirical Methods

The main independent variable of interest is "non-compliance," defined as the percentage of days in 2001 in which the patient did not possess a diabetic medication (i.e., 1 minus the medical possession ratio). In a series of analyses, we obtain estimates of the impact of non-compliance on patient-level outcomes measures related to probabilities of hospital utilization (admissions and emergency room visits) and to levels of hospital care conditional on positive use (hospital spending), and hospital ER visits. As explained below we use combinations of estimated parameters to calculate savings associated with improved compliance. Since reduced non-compliance is not costless (higher compliance implies higher spending on prescribed drugs) we obtain estimates of the impact of non-compliance on diabetic drug spending, and use these to calculate the costs of improved compliance. Finally, we combine all of the relevant estimates to calculate cost-offsets from compliance, using a simulation that compares partial compliance with full compliance. To allow for lagged effects, we analyze the impact of 2001 noncompliance on 2002 outcomes.

Results from regression analyses on probabilities or rates are summarized in Table 3, while results pertaining to levels are summarized in Table 4. Five regression methods were employed: Probit and IV-Probit (Table 3 only), HOLS-GMM, IV-GMM, and propensity score OLS (both Tables 3 and 4). We implement the instrumental variable models, IV-Probit and IV-GMM, because noncompliance may be correlated with unobserved patient severity. Patient severity refers to the patient's relative severity of illness, potentially biasing the estimated effects of noncompliance on the various

outcomes of interest. The IV-Probit implements the Amemiya Generalized Least Squares (AGLS) estimator based on Newey (1987). However, it maintains the same distributional assumption of the probit model (normally distributed errors), which can be viewed as somewhat restrictive. To address this we turn to the generalized method of moments (GMM), which allows for any general functional form on the error terms. In particular, we estimate the HOLS-GMM model due to Cragg (1983) that employs heteroskedastic OLS estimation using GMM. The fourth method is the IV-GMM method due to Baum, Shaffer, and Stillman, 2003, used in the Stata program ivreg2. The fifth method, which we label "propensity score OLS", uses a matched sample design (for partial compliers versus full compliers) rather than instrumental variable techniques. Finally, the last three methods are also used to estimate the log expenditure models summarized in Table 4.

To predict noncompliance, five excluded instrumental variables are used in the IV-Probit and IV-GMM models. These are the log of local and national direct-to-consumer-advertising (DTCA) spending level per 100,000 capita in 2001 for diabetic medications; the health plan's average coinsurance rate for its diabetic medications; a dummy for 90-day prescriptions, a dummy for mail order; a dummy for whether the pharmacy used by the patient was a chain store. The first instrumental variable (IV for short) is drawn from advertising data from Taylor Nelson Sofres (TNS). This DTCA includes advertising on cable TV, network TV, magazines, newspapers, radio, Sunday ads, and syndication. Of all the patients in the raw sample, 72 percent used a diabetic drug that had been advertised through some venue. Wosinska (2005) and Bradford et al (2006) have shown that DTCA is a good predictor of drug compliance. Unlike most drugs, DTCA for

diabetic drugs is mainly local. We used this cross-sectional variation in DTCA across metropolitan areas to predict compliance. Similarly, for our second excluded IV, Dor and Encinosa (2004, 2010) show that the diabetic drug coinsurance rate is a strong predictor of compliance. Our firm-region level coinsurance rate for diabetic medications took on 48 distinct values (12 firms, 4 regions), ranging from 4 to 52 percent. The remaining three IVs are exogenous drug benefit characteristics that affect compliance but are uncorrelated with severity. Descriptive statistics for these instrumental variables, as well as all other variables are included in Table 2.

We employ two accepted criteria for statistical identification: 'relevance' and 'validity'. To assess the relevance of our five instruments, we report the F-test of their combined effect in the first stage of the GMM estimation. To assess their validity we report the P-value of their Hansen J-statistic overidentification test. All our outcome regressions pass this validity test with the exception of the ER cost regression, where the Hansen test fails to reject the hypothesis that our model is correctly specified at the 5% level. This confirmed the IV hypothesis that drug copayments are not correlated with severity (since we averaged coinsurance rates over the firms to avoid selection effects) and similarly, DTCA is not correlated with severity. Finally, we ran separate regressions to verify that our excluded instrumental variables do not predict the second stage outcomes related to hospital care. This procedure confirmed the assumption behind the IV models, namely that drug coinsurance rates, DTCA, and benefit design characteristics (days prescribed; if mail order; retail outlet is chain pharmacy) predict drug compliance behavior but have no direct impact on whether the patient is hospitalized.

We label the last estimation method as 'propensity score OLS', specifically linear probability models in Tables 3, and ordinary least squares on levels in Table 4. Under this approach we simply pool two matched groups of patients, namely full compliers and low compliers, as an alternative to identifying compliance in the outcome regressions using IV techniques. We match patients in the 10^{th} percentile of noncompliance to patients in the 90^{th} percentile of noncompliance. In our data, these groupings corresponded exactly to those who comply less than 50% of the time versus those who comply fully, i.e., 100% of the time (ideally we would have wished to match 0% compliers to perfect compliers; in practice, however, we did not observe zero compliers in the data). That is, we match 5,721 of the 6,322 patients who comply less than 50% of the time with 5,721 patients that comply 100% of the time. The characteristics of the both the raw and matched subsamples are reported in Table 2.

To construct our matched groupings, we used the propensity score matching routine due to Leuven and Sianesi, 2003 (pscore2, Stata version 3.0.0). Accordingly, we first create the propensity score with a logit regression for the probability that the patient has a hospitalization in 2002, controlling for the 18 covariates described above in the Data Section. Next, using the nearest-neighbor method (Dehejia and Wahba, 2002; Becker and Ichino, 2002), we create the matches by balancing propensity scores across all the covariates. Three patients in the 100% compliance subsample lacked a common region of support and were excluded (Becker and Ichino, 2002). As observed in Table 2, the resulting matched subsamples have very similar characteristics for all of the covariates.

The median absolute value of the bias in the covariates between 50% compliant patients and 100% compliant patients was reduced from 19.1 to 1.8 due to the matching.[3]

Simulation results on the impact of changes from 50% compliance to 100% compliance on hospitalizations and ER visits are summarized in Table 5. Results for rates, costs conditional on positive use, and expected population costs are reported at the sample means. Expected costs were obtained using the standard two-part model (Mullahy, 1998). That is, $E(COST_{ij}) = P_{ij} \cdot (COST_{ij} \mid COST_{ij} > 0)$, where i indexes patient i, j indexes the expenditure category (admissions, ER), P is the probability of positive utilization in the expenditure category, and $(COST_{ij} \mid COST_{ij} > 0)$ is the corresponding conditional cost obtained from transforming the dependent variables in the log regressions.[4]

In addition, Table 5 compares results from naïve models (columns labeled 'Exogenous') and a reference IV estimator. For each dependent variable we define the reference IV model (columns labeled 'IV') as either the IV-GMM model or the propensity score model depending on the specification test values reported in Tables 3 and 4. This comparison indicates the direction of the bias due to unobserved patient severity. Finally, Table 5 also reports expected drug costs for 50% and 100% percent compliance. To calculate cost offsets, we compare the savings in hospital costs from this incremental

[3] The bias is the difference in the sample means between copayment and coinsurance patients as a percentage of the square root of the average of the sample variances in the copayment and coinsurance patients. See Rosenbaum and Rubin (1985).

[4] The generalized method of moments (GMM) that we use also addresses the retransformation bias issue as discussed in Manning and Mullahy (2001), where they refer to such models as generalized linear models (GLM).

increase in compliance with the corresponding increase in drug costs. Note that we do not examine physician visits in this study. Often a visit to a doctor is correlated with improved adherence, yet what the doctor says or does in the office to improve adherence is not observed. In general, instrumental variables that control for unobservable physician behavior are not available in claims data such as ours.

4. Results

Outcomes

As shown in Table 2, raw hospitalization rates among the 50% compliers and the 100% compliers were about equal. However, after controlling for the 18 covariates and 12 firm fixed effects (Table 3), all five of the regression methods indicate that noncompliance led to an increase in the likelihood of having any hospitalization; note that propensity score OLS yielded the lowest estimate for the coefficient on noncompliance at 0.036. Comparing Probit with IV-Probit, the coefficient for noncompliance increased from 0.045 to 0.058. Similarly, comparing HOLS-GMM with IV-GMM, the coefficient for noncompliance increased from 0.046 to 0.07. This suggests that without an IV correction, the effect of noncompliance on the rate hospitalization would be underestimated.

Table 2 also shows that unlike hospitalizations, the raw rate of ER visits was substantially higher among the 50% compliers compared with the 100% compliers, that is, 16.8 percent versus 10.7 percent, respectively. Nevertheless, we find here the same pattern of underestimated compliance effects associated with the 'naïve' models found in our analysis of hospitalization rates. Referring again to Table 3, comparing the Probit with

IV-Probit for ER use, the coefficient for noncompliance increased from 0.076 to 0.153. Similarly, comparing the corresponding HOLS-GMM with IV-GMM, we observe that the coefficient for noncompliance increased from 0.087 to 0.162.

A similar pattern is found in the conditional levels regressions summarized in Table 4. Thus, comparing HOLS-GMM with IV-GMM for the log of hospital days, the coefficient for noncompliance increased from 0.131 to 0.565. Comparing HOLS-GMM with IV-GMM for conditional hospital spending, the coefficient for noncompliance increases from 0.024 (p=0.7) to 0.53 (p=0.086). Note that an exception occurs in the ER spending models, where the noncompliance coefficient declines in the IV-GMM and the instrumental variables do not satisfy the overidentification test. We will therefore refer to the propensity score OLS model for purposes of simulation in this particular case.

Additional interpretation of the IV and non-IV comparisons can be offered by noting that, by definition, very severely ill patients are more apt to require hospital services, but patient severity may be unobservable. Not controlling for unobservable severity gives rise to two possible biases:

(1) Very severely ill patients have difficulties complying with their medications. This implies an overestimation of the effect of noncompliance on hospitalization when not controlling for unobservable severity.

(2) Very severely ill patients are more apt to comply. This implies an underestimation of the effect of noncompliance on hospitalization when not controlling for unobservable severity

Given that both the non-IV models tended to underestimate the compliance effects relative to the IV methods as previously described, we can conclude that the latter (2) bias dominates.[5] This inference is consistent with another one of our findings that pertains to an observable dimension of severity that is available in our data; the number of chronic conditions. A greater proportion of the 100% compliant patients have chronic conditions compared to the 50% compliant patients (see Table 2). A similar result not shown in the tables is that the mean number of chronic conditions was significantly higher for the 100% compliant patients than for the 50% compliant patients, that is 1.5 days versus 1.4 ($p<0.01$), respectively.

The magnitude of this bias can be gauged in the top panel of Table 5, where we simulate the marginal effects of compliance on the probabilistic outcomes. Under HOLS-GMM (in the "exogenous" columns of Table 5), not controlling for unobservable severity, moving from 50% compliance to 100% compliance reduces the probability of hospitalization from 14.2% to 11.9%, a 2.3 percentage point drop ($p<0.01$). However, under IV-GMM (in the "IV" columns of Table 5), moving from 50% compliance to 100% compliance reduces the probability of hospitalization from 15 percent to 11.5 percent, a 3.5 percentage point decline ($p=0.02$). The bias associated with unadjusted severity appears to be even higher in the case of ER visits. By moving from 50% to 100% compliance, the

[5] Our IV results could also traditionally be interpreted as an attenuation in OLS due to measurement error in noncompliance. However, we do not suspect there is much measurement error in noncompliance due to missing drug claims since our data has been taken only from the health plans in MarketScan® with complete drug claims data. One other potential source of measurement error in noncompliance would be due to patients splitting pills (e.g., a patient ordering an extra strength 30 day prescription to split into a 60 day prescription). However, there are only four categories of drugs recommended for pill splitting: ace inhibitors, Angiotensin Receptor Blockers (ARBs), antidepressants, and lipid-lowering medications (see United Healthcare. 2007. Tablet Splitter, http://www.halftablet.com/faq.html). Diabetic medications are not to be split. Thus, we do not believe that the IV is solely correcting for measurement error, but is controlling for unobservable patient severity.

percentage decline in the probability of ER visits is 4.3 percentage points ($p<0.01$) under the exogenous model (14.9% to 10.6%) versus 8 percentage points under IV-GMM (17.3% to 9.3%) ($p=.04$).

Analogous findings apply to the conditional levels regressions. In particular, the decline in hospital costs is substantially greater under IV- GMM (middle panel of Table 5). Thus, using the regression coefficients obtained earlier from Table 4, increasing compliance from 50% to 100% reduces hospital costs by $3,262 ($p<0.01$) from $13,977 to $10,715 for a hospitalized patient using the IV-GMM model, compared with virtually no change in these costs when the HOLS-GMM is used. Similar findings apply to side regressions we ran on the number of hospital days, conditional on hospital use. Results for the days regressions are not shown in Table 5. Under HOLS-GMM, moving from 50% compliance to 100% compliance reduced the number of hospital days from 5.4 to 5.0 days, a drop of 7 percent. Under IV-GMM, moving from 50% compliance to 100% compliance reduced the number of hospital days from 7.4 to 5.6 days, a more dramatic decline of 24 percent. Overall, these findings indicate that failing to correct for unobservable severity leads to a substantial negative bias in measuring the impact of compliance.

Drug Expenditures and Cost Offsets

In our next set of results, we compare the incremental change in *expected* hospital costs associated with an increase from 50% to 100% compliance to the corresponding change in drug costs (bottom panel of Table 5). Note that expected hospital costs where

estimated from the previously described two-part model. However, this procedure was not needed for calculating expected drug expenditures since all patients in our sample incurred positive drug expenditures (hence the conditional is equal to the expected in this case). Given our discussion above, we base this analysis on the estimates obtained from the IV estimators as summarized in Table 5, rather than the naïve models. Accordingly, increasing compliance from 50% to 100% reduces expected hospital costs for all patients in our sample from $2,097 per patient to $1,232 per patient. This implies expected annual savings of $865 ($2,097 - $1,232) in hospital costs per diabetes patient, with a 95% confidence interval of ($596 , $1,176).[6]

Next, to examine whether these savings create cost offsets, we need to estimate the increase in drug costs associated with the increase in compliance. To select the appropriate model for these calculations, we followed the same general approach described above for the outcome regressions, with some changes. First, we based our assessment of the bias due to unobservable severity from the comparison of HOLS – GMM with the propensity score OLS rather than IV-GMM. Note that all our instrumental variables (drug coinsurance, DTCA, 90-day prescriptions, mail order, and the use of a pharmacy chain) directly predict drug spending as well as noncompliance; therefore, they cannot be used as instrumental variables in the model in which drug spending is the outcome. In Table 4, comparing the log of drug spending regressions in the HOLS-GMM and the propensity score models, we observe that the magnitude of the coefficient for

[6] In contrast, if one does not control for unobservable severity, this expected annual savings of $865 in hospital costs per diabetes patient declines to $290 (=$1,687 - $1,397 from naïve "exogenous" columns of the bottom panel of Table 5, where $1,687=.142*$11,880 and 1,397=.119*$11,738). Thus, using the naïve HOLS-GMM model results in an underestimation of the hospital cost savings arising under improved compliance.

noncompliance increases from -2.147 ($p<0.01$) to -2.422 ($p<0.01$), an 11 percent increase. Thus, not controlling for unobservable severity leads to an underestimation of the magnitude of drug savings due to increased noncompliance. The C-statistic from the HOLS-GMM drug regression confirms that noncompliance is indeed endogenous with respect to drug costs (this C-statistic is based on the unrestricted and restricted Anderson-Rubin over-identification statistics and the test is a likelihood-ratio test. See Hayashi (2002)).

Second, given the results above, in Table 5 we define the propensity score OLS as the reference IV model for estimating drug costs. Next, we repeat our simulation of costs at 50% compliance and 100% compliance as with hospitalization outcomes; (again, we do not use the two part model for this variable since all patients in the data have positive expenditures on prescription drugs). From this we predict that increasing compliance from 50% to 100% increases diabetic drug costs from $329 to $1,105, an additional $766 per diabetic patient, with a 95% confidence interval of ($646 , $886). The analogous change when no attempt is made to control for patient severity is made under HOLS-GMM (see the 'Exogenous' column in Table 5) is somewhat smaller, at $548 per diabetic, from $284 to $832. Combining results for the models that control for unobservable severity, we find that an increase in compliance from the 50% level to the 100% level yields an estimated cost offset of $89 ($p=0.02$) ($89=$865-$776), or 12 percent. Put differently, for every dollar spent on drug expenditures to increase compliance with diabetic drug prescriptions, payers incur savings of 0.12 dollars in hospital care, a net gain of 12 percent.

These cost offsets are further increased by ER cost savings arising under better compliance. Here too, we take the propensity score OLS as the reference model for our final calculation in lieu of the IV-GMM. Note that while our instrumental variables for ER spending in Table 4 satisfy the threshold for the F-tests, they fall short of the threshold for the Hansen overidentification test ($p>0.10$), leading us to reject the hypothesis that the instruments are uncorrelated with unobservable severity (at $p<0.01$). Thus, comparing HOLS-GMM with the propensity score estimates for the log of ER spending per visit, we find a decrease in the coefficient for noncompliance, from 0.153 ($p=0.019$) to 0.099 ($p=0.24$). Thus, while controlling for unobservable severity increases the probability of an ER visit, it decreases the costs of ER visits once the patient makes an ER visit. Overall, by using the two-part model for expected ER cost (Table 5), we can estimate that increasing compliance from 50% to 100% reduces these costs from \$49 (=.173*\$283) to \$28 (=.093*\$297) for a diabetic. This yields an additional expected savings of \$21 per diabetes patient annually ($p<0.05$).

Combining hospital and ER cost savings results in an overall cost savings of \$886 and an estimated cost offset of \$110 ($p=0.02$) with a 95% confidence interval of (\$8, \$212). This is an estimated cost offset of 1.14 dollars for each additional dollar spent on diabetes drugs. Finally, it should be noted that repeating the full set of calculations described above using the parameter estimates of the Exogenous models rather than the IV models would have resulted in overall dollar loss of 45% rather than a gain of 14% from the same incremental increase in compliance. Again, this indicates that failure to control for

unobservable patient severity can lead to a large downward bias in estimating cost offsets associated with patient adherence with prescribed medications. In this study we used various estimation techniques to address that issue. Our adjusted estimates are relevant for evaluating the potential returns from insurer-based or employer-based programs designed to improve patient adherence.

5. Conclusion

Our research is one of the first demonstrations of a direct effect between medication adherence and hospitalizations after controlling for unobservable patient heterogeneity. Most other studies on the cost-offsets of prescription drugs have examined the impact of cost-sharing or prescription drug spending on inpatient and outpatient care rather than the pattern of use as would be reflected in adherence measures. Generally, such studies do not account for gaps in drug utilization or irregular use. Hence, our paper fills an important gap in the literature. We focus particularly on the privately insured non-elderly.

Our study is also one of the first to find inpatient cost-offsets in the non-elderly private sector. Most other papers in the literature focus on the elderly Medicare population. Hsu et al (2006) found a cap on drug benefits in Medicare reduced drug use and costs, and increased inpatient and outpatient use. However, the added costs did not outweigh the drug costs savings. Similarly, Stuart et al (2007) found no cost offset in Medicare 1999-2000 MCBS survey data. Shang and Goldman (2007) used a longer panel with 1992-2000 MCBS data and found a $1 increase in prescription drug spending was associated with a $2.06 reduction in Medicare spending. In a California Medicare sample, Chandra,

Gruber, and McKnight (2007) generally found no net cost-savings (a 20 cent offset per one dollar drop in drug and doctor payments), but found net cost-savings for very ill patients with four or more chronic conditions (a 1.77 dollar offset per one dollar drop in drug and doctor payments). Zhang et al (2009) found similar results among the elderly, with cost offsets ranging from 0.8 to 1.7 for those with modest or no drug coverage prior to enrolling in Medicare Part D. However, they also found that those with more generous coverage before Part D actually had cost increases (a $2.30 dollar increase in medical spending per dollar increase in drugs). It is important to note that most of this literature offers estimates of cost-offsets for comparisons of patients without any drug coverage and patients with such coverage. By contrast, our study pertains only to patients who had drug coverage, and everyone in our sample incurred some positive level of prescription drug usage. As a result, we were not able to examine uninsured diabetics who did not have access to any antidiabetic medications during the year. Thus, our cost-offset of 1.14 dollars may be a conservative estimate.

Although measurement issues required us to limit our analysis to hospital-related outcomes without office-related outcomes, we were able to obtain a rich set of results that yield important implications for optimal benefit design. First, we have shown a direct effect between medication adherence and either averted hospitalizations or visits to the hospital emergency room. After controlling for unobservable severity, we can conclude that patients with higher (unobservable) severity are more apt to comply with their medications; conversely, patients with relatively lower severity are less likely to comply. We speculate that non-compliance among less severe patients may be due to the relative

absence of easily recognizable symptoms during early stages of the disease. This suggests that health plans and employers might benefit (in terms of cost-offsets) from targeting younger, healthier diabetes patients in particular, with campaigns aimed at improving medication adherence. Similarly, patients in this group stand to reap the greatest benefit from adherence as a prevention strategy.

Our estimated cost-offset of 1.14 dollars in averted hospital costs per dollar of additional drug spending is higher than that found in most of the recent research on the non-elderly. For instance, in another study of the non-elderly, Gaynor, Li, and Vogt (2007) found no net cost-savings. They found that the drug cost-savings from increasing copayments had no impact on inpatient hospital costs. However, they also found a 35 cent cost-offset for outpatient services (a dollar drop in drug spending increased outpatient spending by 35 cents). One limitation of our study, as well as prior related papers, is the lack of appropriate instrumental variables to address the endogeneity of adherence with respect to outpatient (office) utilization, stemming from the direct influence of prescribing physicians on the behavior of their patients. Future research should examine this issue by linking physician office data with patient data.

One limitation of study is that the data are not nationally representative. The MarketScan® databases have disproportionately more workers in the southern United States and fewer workers in the West. Another limitation of our study is that we did not include any potential indirect costs of interventions required to move patients from 50%

compliance to 100% compliance. Future research should examine the costs of such outreach programs and interventions.

By focusing on drug expenditures as a function of levels of adherence, our research findings shed light on the potential success of value-based insurance design (VBID), in which drug benefit packages are designed specifically to reward better adherence. While VBID should avert hospitalizations and lead to better outcomes it is not clear that the relatively modest cost-offsets reported in the literature (in our case $1.14 cost-offsets over a one year period from averted hospitalizations per dollar increase in drug spending.) will be large enough to justify the costs of implementing VBID programs without further policy intervention. There may be sufficiently large net-cost savings even if some outpatient office visits are in fact averted in ways not identified in prior research.

One approach to ensure the viability of VBID is to combine it with value-based purchasing of drugs. Under value-based purchasing, a shift towards generic medications in PBM formularies will aid in creating cost offsets, which could be passed on to consumers or used to cross-subsidize VBID programs. Negotiating discounts would be particularly efficacious if drug manufacturers and pharmacy benefit managers (PBMs) already set certain drug prices just high enough to partly capture inpatient cost-offsets. We further note the need for future research to examine longer term benefits of adherence, using extended follow-up periods, where additional gains may occur.

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Table 1: Pharmacological Treatment of Type 2 Diabetes Mellitus[a]	
Major Metabolic Defect	Drug Therapy
Defective Insulin Secretion	*Secretagogue Therapy*
Pancreatic Beta Cells (decreased insulin secretion)	Sulfonylureas (SU) Non-SU Secretagogues (Meglitinides)
Insulin Resistance	*Insulin Sensitizer Therapy*
Skeletal Muscle (decreased glucose uptake)	Thiazolidinediones (TZD)
Liver (increased glucose production)	Biguanides (Metformin) TZD
Adipose Tissue (increased lipolysis)	TZD
Carbohydrate Absorption	Drug Therapy
Small Intestines	*Alpha-Glucosidase Inhibitors (AGI)*

[a] *Source: Inzucchi (2002).*

Table 2: Descriptive Statistics

Variables	Raw Sample	Raw Subsamples		Matched Subsamples	
	All Patients	50% Compliance	100% Compliance	50% Compliance	100% Compliance
2001 Instrumental Variables					
Direct-to-consumer advertising (spending per 100,000 capita)	$158 (390)	177 (413)	134*** (343)	177 (413)	120 *** (333)
Firm's average coinsurance rate for diabetic drugs	.292 (.103)	.314 (.099)	.272*** (.095)	.314 (.098)	.293*** (.125)
90 day prescriptions	.236	.058	.539***	.058	.424***
Mail order	.127	.032	.299***	.032	.247***
Chain pharmacy	.642	.748	.495***	.748	.550***
2002 Outcomes					
Patient's noncompliance rate	.176	.675	0	.675	0
ER visit rate	.121	.168	.107***	.168	.108***
Hospitalization rate (non-maternity)	.127	.134	.137	.134	.110***
Hospital days	.938 (4.967)	.978 (4.470)	1.003 (4.897)	.979 (4.471)	.638***(3.254)
ER spending	$72 (414)	98 (450.49)	75*** (426)	97 (450)	52*** (260)
ER spending for ER visits	$601 (1,055)	585 (966)	701** (1,127)	584 (967)	485** (653)
Hospital expenditures	$2,802 (15,495)	2,801 (13,297)	3,079 (18,518)	2,803 (13,300)	2,420 (13,490)
Hospital expenditures on hospital admissions	$21,658 (38,053)	20,019 (30,327)	22,491 (45,516)	20,019 (30,327)	21,834 (35,375)
Drug expenditures	$898 (938)	379 (518)	1,422*** (975)	379 (518)	1,462*** (935)
Patient Characteristics					
Insulin use	.170	.106	.264***	.106	.102
Age	53.98 (7.516)	49.782 (9.295)	55.749*** (6.026)	49.786 (9.296)	51.052 (7.618)
Male	.534	.533	.430***	.533	.521
Drug Abuse	.002	.002	.002	.002	.002
Hourly wage worker	.256	.297	.311*	.297	.313
Dependent	.310	.316	.347***	.317	.308
County HMO penetration rate	.215 (.160)	.197 (.163)	.239*** (.154)	.197 (.163)	.201 (.161)
County median household income	$42,551 (11,211)	40,590 (10,933)	44,031*** (11,088)	40,601 (10,925)	40,856 (10,693)
Small Firm Size	.027	.024	.029*	.024	.021
Retiree	.385	.255	.510***	.255	.244
ER coinsurance rate	.094 (.057)	.087 (.058)	.109*** (.056)	.087 (.058)	.087 (.057)
Number of Chronic conditions					
1	.692	.707	.673***	.707	.721
2	.199	.191	.208**	.191	.184
3	.069	.062	.073**	.062	.058
4	.025	.027	.031	.027	.025
5+	.016	.013	.016	.013	.012
N:	56,744	6,322	5,724	5,721	5,721

Notes: Means reported. Standard deviations are in parentheses. The subsamples consist of the patients that either always complied, or complied less than 50% of the time. Matching of subsamples was done by propensity score matching.*** Significant at 99%.** Significant at 95%.* Significant at 90%

Table 3: The Estimated Impact of Non-Compliance on Hospital Use

	Any Hospitalization	Any ER Visit
PROBIT	.045 ***	.076 ***
	(.007)	(.006)
IV-PROBIT	.058 *	.153 ***
	(.032)	(.038)
HOLS-GMM	.046 ***	.087 ***
	(.007)	(.007)
IV-GMM	.070 **	.162 ***
	(.033)	(.035)
Propensity Score OLS	.036 ***	.075 ***
	(.009)	(.009)
Over-identification test (Hansen J-stat P-value)	.190	.460
First stage F-Statistic	699.18	703.26

Notes: Standard errors are in parentheses.
**** Significant at 99%.** Significant at 95%.* Significant at 90%*

Table 4: The Estimated Impact of Non-Compliance on Drug, Hospital, and ER Spending

	Log (Diabetic Drug Spending)	Log (Hospital Days | Hospital Admission)	Log (Hospital Spending | Hospital Admission)	Log (ER Spending | ER Visit)
HOLS-GMM	-2.147***	.131 ***	.024	.153**
	(.023)	(.044)	(.062)	(.065)
IV-GMM	--	.565 ***	.532*	-.336
		(.209)	(.310)	(.424)
Propensity score OLS	-2.422***	.194 ***	.047	.099
	(.028)	(.060)	(.083)	(.085)
Over-identification test (Hansen J-stat P-value)	--	.209	.46	.00
First stage F-Statistic	--	150.15	77.43	83.60

Notes: Standard errors are in parentheses.
**** Significant at 99%.** Significant at 95%.* Significant at 90%*

Table 5: Simulation of 2002 Outcomes Due to 2001 Diabetic Drug Compliance[a]

Variable	50% Compliance		100% Compliance	
	Exogenous[b]	IV	Exogenous[b]	IV
Distribution				
Any Hospitalization	14.2% (0.8)	15.0% (1.3)	11.9% (0.7)	11.5% (0.9)
Any ER Visit	14.9% (0.7)	17.3% (1.6)	10.6% (0.7)	9.3% (1.6)
Drug Sending> 0	100.0%	100.0%	100.0%	100.0%
Conditional costs[c]				
Hospital Costs	$11,880 (606)	$13,977 (1,446)	$11,738 (574)	$10,715 (798)
ER Costs	$302 (20)	$283 (36)	$280 (18)	$297 (36)
Drug Costs	$284 (6)	$329 (16)	$832 (18)	$1,105 (54)
Expected costs[d]				
Hospital Costs	$1,687 (127)	$2,097 (281)	$1,397 (112)	$1,232 (136)
ER Costs	$43 (4)	$49 (8)	$30 (3)	$28 (7)
Drug Costs	$284 (6)	$329 (16)	$832 (18)	$1,105 (54)

Notes:

a. Standard errors are in parentheses.
b. All "Exogenous" predictions are based on the HOLS-GMM estimates of Tables 3 and 4. The IV predictions are based on the IV-GMM estimates of Tables 3 and 4, except for the drug and ER conditional and expected costs, which are based on the propensity score OLS regressions.
c. Conditional costs are conditional upon positive use.
d. Expected costs are conditional costs multiplied by the probability of use in the top panel.