Does Medication Adherence Following a Copayment Increase Differ by Disease Burden?

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Objectives. To compare changes in medication adherence between patients with high- or low-comorbidity burden after a copayment increase.

Methods. We conducted a retrospective observational study at four Veterans Affairs (VA) medical centers by comparing veterans with hypertension or diabetes required to pay copayments with propensity score-matched veterans exempt from copayments. Disease cohorts were stratified by Diagnostic Cost Group risk score: low- (< 1) and high-comorbidity (> 1) burden. Medication adherence from February 2001 to December 2003, constructed from VA pharmacy claims data based on the ReComp algorithm, were assessed using generalized estimating equations.

Results. Veterans with lower comorbidity were more responsive to a U.S.\$5 copayment increase than higher comorbidity veterans. In the lower comorbidity groups, veterans with diabetes had a greater reduction in adherence than veterans with hypertension. Adherence trends were similar for copayment-exempt and nonexempt veterans with higher comorbidity.

Conclusion. Medication copayment increases are associated with different impacts for low- and high-risk patients. High-risk patients incur greater out-of-pocket costs from continued adherence, while low-risk patients put themselves at increased risk for adverse health events due to greater nonadherence.

Key Words. Cost sharing, medication adherence, diabetes, hypertension, veterans

Increasing prescription copayments have been associated with reductions in medication adherence (Piette, Heisler, and Wagner 2004a; Piette et al. 2005; Roblin et al. 2005; Goldman, Joyce, and Zheng 2007; Doshi et al. 2009). Patients with chronic illness are likely to skip or discontinue their medications in response to copayment increases (Piette, Heisler, and Wagner 2004a; Soumerai et al. 2006; Maciejewski et al. 2010). Such cost-related nonadherence (CRN) may exacerbate chronic conditions, generate adverse health events, and increase health care utilization (Lichtenberg 1996; Mojtabai and

Olfson 2003; Sokol et al. 2005; Zeber et al. 2007; Heisler et al. 2010), and thus counteract health plan attempts to contain overall health care costs.

Much of the evidence of copayment impacts on medication adherence reflects an average effect in a population. However, responses to cost-sharing may be heterogeneous within a population, because the potential benefits and risks of medication adherence vary by patient subpopulations (Hayward et al. 2005, 2006). In particular, the patient response to a copayment increase may differ by patients' comorbidity burden and consequences of nonadherence with recommended treatment. High-risk patients may be more likely to remain adherent because they have a greater likelihood of experiencing an adverse event as a result of nonadherence. In a recent study, commercially insured patients with more severe health conditions were more likely to comply with medication regimens and avert hospitalizations and related costs (Encinosa, Bernard, and Dor 2010). If high-risk patients put a higher value in averting future adverse events than low-risk patients, then we would expect high-risk patients to be more adherent than low-risk patients in response to a medication copayment increase (Ellis and Manning 2007). On the other hand, high-risk patients with greater disease severity or greater comorbidity burden may be less likely to remain adherent than low-risk patients because high-risk patients take more medications and a copayment increase creates a greater cumulative financial burden. Assuming a fixed budget constraint, a high-risk patient would have to reduce consumption of other goods more than low-risk patients to maintain the current level of medication adherence at higher prices.

Prior studies that examined whether health status moderates the association between cost-sharing and use of health care or medications found mixed results. Prior cross-sectional studies found similar associations between cost-sharing and medication use for low-risk and high-risk patients (Jackson et al. 2004; Goldman, Joyce, and Karaca-Mandic 2006; Schneeweiss et al. 2007a, b). A study of cost-sharing and outpatient service use found that Medicare beneficiaries with worse self-reported health status were less responsive

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to cost-sharing for outpatient services than beneficiaries with better health status (Remler and Atherly 2003). A study of Medicare beneficiaries found that CRN was unchanged after the introduction of Medicare Part D for beneficiaries with worse self-reported health status or more comorbid conditions, compared with beneficiaries with better health status or fewer chronic conditions (Ellis et al. 2004; Jackson et al. 2004; Goldman, Joyce, and Karaca-Mandic 2006; Schneeweiss et al. 2007a, b; Madden et al. 2008; Yang et al. 2009). This last paper is most similar to this study in which we examine changes in medication adherence associated with a copayment increase in patients with lower and higher comorbidity burdens.

Changes in medication adherence in response to copayment changes may also differ by condition. While patients' out-of-pocket medication spending generally differs by chronic condition (Harman et al. 2004), studies have also demonstrated differential impacts of drug copayment increases across medication classes (Goldman et al. 2004; Joyce et al. 2007; Chernew et al. 2008). In this paper, we consider differences between patients with diabetes and patients with hypertension. Diabetes is physiologically more responsive to lifestyle changes in the short term and may lead patients to try and control their disease more by lifestyle than by the use of medications. Diet and exercise, which have generally been known to lower blood sugar within hours or days, are considered the cornerstone for the treatment of diabetes and are often concordantly recommended before institution of medication therapy (Vijan 2010). While diet therapy such as the DASH diet for hypertension can be successful (Obarzanek et al. 2003), it is generally very difficult for patients to transition to this very low-sodium, high-fruit and -vegetable diet (Karanja et al. 1999; Windhauser et al. 1999). Unlike diabetes, lifestyle impacts on hypertension control are subtler and generally take weeks or months to generate a detectable difference. Finally, the burden of comorbid conditions or complications may differ by primary condition. Patients with diabetes tend to have more comorbid conditions, take more medications (Maciejewski et al. 2010), and have higher health care costs (Yu et al. 2003) than patients with hypertension. Thus, a copayment increase results in a greater cumulative financial burden for patients with diabetes than for patients with hypertension.

The purpose of this study is to examine whether medication copayment increases impact patients with high-comorbidity burden and low-comorbidity burden differentially. We also examine whether differences in adherence changes between high- and low-comorbidity burden patients vary by chronic condition (diabetes or hypertension). If there is a differential impact by patient disease burden, then adherence effects and policy inferences drawn from the

population may fundamentally misrepresent patients whose response differs from the population (Hayward et al. 2005, 2006). If CRN occurs primarily among high-comorbidity patients, then it may be cost-effective to reduce copayments for these individuals following the principles of value-based insurance design (Chernew, Rosen, and Fendrick 2007; Chernew et al. 2008). Copayment policy changes might be structured differently if CRN occurs primarily among low-comorbidity patients. Identifying patients with chronic conditions who might be especially adversely impacted by copayment increases could also suggest targets for interventions to offset the adherence impacts of increased copayments.

METHODS

Veterans Affairs (VA) Copayment Increases

The VA increased medication copayments from U.S.\$2 to U.S.\$7 on February 4, 2002, for veterans required to pay copayments (Veterans Health Administration [VHA] 2001b). Two months previously (December 6, 2001), VA implemented U.S.\$15 copayments for primary care visits and increased copayments for specialty care visits from U.S.\$15 to U.S.\$50 (VHA 2001a, 2005). A veteran's obligation to pay medication (and health care) copayments is determined by priority group assignment, based on income and military service-connected disability for each diagnosed condition.¹ Veterans who are 50 percent or more disabled due to military service (i.e., priority Group 1) are exempt from all copayments. Veterans who have no military service-related disability and an income and/or net worth above the VA national income threshold (priority Groups 7 and 8) are required to pay all copayments.

Study Design and Study Samples

We used a retrospective, pre-post cohort design with a nonequivalent, co-located control group at four large tertiary VA medical centers (VAMCs) in 2000–2003, which preceded the availability of low-cost generic medications at non-VA discount and retail stores. We identified 60,017 veterans with diabetes, hypertension, or both conditions, based on diagnoses and prescribed medications in 2000. Veterans were included in the analysis if they: (1) were alive during the entire study period, (2) had a majority of their primary care visits at one of the four VAMCs, (3) had complete information on level of military service-connected disability to determine copayment exemption, (4) were not hospitalized when the copayment increase went into effect or for

more than 1 year during the study period, (5) had at least one prescription fill in a relevant drug class during the quarter before the copayment change, and (6) had at least one medication fill during the second to fourth quarters before the copayment change. We excluded from our analytic sample veterans in priority Groups 2–6, whose medication copayment benefit could not be clearly determined. We excluded subjects on nonneutral protamine hagedorn (NPH) insulin therapy that would preclude taking oral hypoglycemic agents (OHAs). We did not exclude patients on NPH because NPH insulin may be added to oral regimens in a stepped approach. The application of these criteria resulted in analytic samples of 2,426 veterans with diabetes and 7,852 veterans with hypertension.

To reduce significant covariate imbalance between copayment-exempt and nonexempt veterans, we conducted one-to-one nearest-neighbor propensity score matching with replacement via logistic regression (Rubin and Thomas 2000; Sales et al. 2005; Baser 2006; Jones and Richmond 2006). We used logistic regression to model the probability that a veteran was exempt from copayments and to generate predicted probabilities, which served as the propensity scores for matching exempt and nonexempt veterans in the study cohort. After generating propensity scores and matching, we excluded copayment-exempt veterans ($n = 288$ with diabetes and $n = 762$ with hypertension) whose propensity score did not match to those of our nonexempt veteran sample (see appendix SA2 in Maciejewski et al. 2010 for more propensity score modeling details). Our final diabetes matched sample included 1,069 copaying and 1,069 copayment-exempt veterans (2,138 in total). Our final hypertension matched sample included 3,545 copaying veterans and 3,545 copayment-exempt veterans (7,090 in total).

Next, we stratified each disease cohort by comorbidity burden, based on the Diagnostic Cost Group (DCG) Hierarchical Cost Categories version 6.0 score, which was originally developed to predict Medicare payments using inpatient diagnoses and later expanded to include all outpatient diagnoses (Ash et al. 2000). DCGs have been shown to reliably predict veterans' total costs (Maciejewski et al. 2005; Maciejewski, Liu, and Fihn 2009) and risk of hospitalization or death (Fan et al. 2006). A DCG score < 1 indicates that a veteran has a below-average comorbidity burden, and a DCG score > 1 indicates above-average comorbidity burden. For this analysis, veterans with a DCG score < 1 were defined as "low burden" and those with a DCG score > 1 were considered "high burden." The unit of analysis was the person-month, with each veteran having up to 43 repeated measures (June 2000–December 2003).

Data Sources

We used four datasets for this study, including VA Pharmacy Benefits Management data to generate the medication adherence outcome (Sales et al. 2005), VA inpatient and outpatient care files to generate demographic characteristics, and Benefit Identification and Record Locator System death record data to determine which veterans died during the study period (see Maciejewski et al. 2010 for more details).

Medication Adherence Outcome and Covariates

We calculated monthly medication adherence to OHAs and antihypertensive medications using the ReCOMP algorithm, a modification of a widely used method that has been validated and correlated with a variety of clinical outcomes (Steiner et al. 1988; Steiner and Prochazka 1997; Bryson et al. 2007). This electronic pharmacy-based refill adherence algorithm estimates the proportion of days covered for a given measurement interval using the dispense date and number of days supplied with each fill, while accounting for medication gaps and overstocking. Subjects were considered adherent if they had medications available for at least 80 percent of each month and this binary adherence measure was the outcome of interest (Rudd 1994; Insull 1997; Benner et al. 2002; Andrade et al. 2006). All medications within a class are treated as the same for purposes of adherence. Compared with other more formulaic adherence measures, the underlying assumption behind ReCOMP's algorithmic measurement—that patients take medication as prescribed and the absence of future refills constitutes nonadherence—has been demonstrated to work well for medication nonadherence and within the VA health system (Bryson et al. 2007).

There were three explanatory variables of interest: (1) an indicator of whether a veteran was required to pay copayments; (2) time indicators for a 12-month preperiod before the copayment increase (February 2001–January 2002), a 12-month “proximal” postperiod just after the copayment increase (February 2002–January 2003), and the subsequent 11-month longer-term postperiod (February 2003–December 2003); and (3) an interaction of the copayment exemption and time indicators to enable a difference-in-difference analysis. The postperiod was subdivided to examine whether adherence differed in the short and longer term.

All multivariate models adjusted for age, gender, race, marital status, hospitalization in prior or current months, presence of a depression diagnosis at baseline, presence of comorbid diabetes or hypertension, the numbers of

diabetes, antihypertensive, and all other medications that the patient was prescribed during the preperiod, and VA site fixed effects. Sensitivity analysis that adjusted for clustering by site did not alter our results, so we report findings that do not cluster by site.

To adjust for the impact of the December 2001 outpatient visit copayment increases, our analysis controlled for the number of primary care, specialty care, and mental health visits 90–180 days before the current month. Because it is possible that the increase in health care copayments would decrease outpatient visits and decrease prescription renewals, we used lagged visit counts to control for these cross-price effects (Goldman, Joyce, and Karaca-Mandic 2006). To test the effectiveness of this adjustment, we conducted two sensitivity analyses: (1) replaced lagged visits with contemporaneous visits and (2) excluded outpatient visit covariates altogether. Results were consistent across all three specifications, so we present the lagged visits model to be consistent with prior work (Maciejewski et al. 2010).

Analysis

Bivariate statistics (*t*-tests, chi-square test) and standardized differences were estimated to compare patient characteristics, baseline adherence, and adherence in the last month of the study period between matched and nonmatched veterans, and between matched exempt and nonexempt veterans in the diabetes and hypertension cohorts (Austin 2009).

We estimated generalized estimating equations (GEEs) assuming a binomial distribution, logit link and independent working covariance structure with person-month as the unit of analysis in adjusted analyses of the binary medication adherence outcome. GEE models were conducted on each disease cohort and stratified by low- versus high-comorbidity burden, controlling for several covariates that were not balanced in the propensity matching process. To estimate first differences, we obtained predictions from these GEE models for the proportion of copayment-exempt and nonexempt veterans in each cohort who were adherent in the preperiod, the immediate postperiod and the longer term postperiod. Confidence intervals for these proportions were estimated through 1,000 bootstrap iterations. All analyses used *Stata* version 11.0 (Statacorp 2010). This study was approved by the Institutional Review Boards of the Durham and Seattle VA Medical Centers.

RESULTS

Descriptive Statistics

In both the diabetes cohort and the hypertension cohort, nearly all veteran characteristics were statistically different between propensity-matched and unmatched groups (Appendix SA2). Propensity matching eliminated imbalance in several covariates between copayment-exempt and nonexempt veterans for the diabetes and hypertension cohorts, but site imbalances remained (Tables 1 and 2). In both disease cohorts, low-burden veterans required to pay copayments were older than copayment-exempt veterans ($p < .001$). High-burden nonexempt veterans were more often nonwhite, compared with copayment-exempt veterans (standardized differences > 10). Low-burden diabetic and hypertensive nonexempt veterans had fewer lagged primary and specialty care visits, but more lagged mental health utilization than veterans exempt from copayments ($p < .01$ – $.001$). Among diabetic veterans, high-burden and nonexempt patients took more diabetes medications than copayment-exempt veterans.

Unadjusted Differences in Medication Adherence by Low-Risk and High-Risk Veterans

Among low-burden veterans with diabetes, unadjusted adherence at baseline was similar between veterans required to pay copayments and copayment-exempt veterans, but adherence in the last month of the study postperiod was significantly lower among veterans required to pay copayments (60.1 percent versus 67.6 percent, $p < .01$; Table 1). For high-burden veterans with diabetes, veterans required to pay copayments had lower unadjusted adherence at baseline (66.7 percent versus 79.8 percent, $p < .01$) and in the last month of the study period (57.6 percent versus 72.2 percent, $p < .001$) than copayment-exempt veterans.

For low-burden veterans with hypertension, veterans required to pay copayments had higher unadjusted adherence at baseline (56.9 percent versus 53.1 percent, $p < .01$) but similar adherence in the last month of the study period (58.1 percent versus 58.4 percent) compared with copayment-exempt veterans. Unadjusted adherence among high-burden veterans with hypertension was similar at baseline and in the last month of the study period for copayment-exempt veterans and veterans required to pay copayments (Table 2).

Table 1: Descriptive Statistics of Diabetic Veterans, by Disease Risk Cohort and Copayment Status

<i>Disease Risk Cohort Copayment Status</i>	<i>Low Burden (DCG < 1)</i>			<i>High Burden (DCG > 1)</i>		
	<i>Exempt</i>	<i>Nonexempt</i>	<i>d_i</i>	<i>Exempt</i>	<i>Nonexempt</i>	<i>d_i</i>
<i>N</i>	846	814		223	255	
Hypertension (%)	65.1	63.4	− 3.6	70.4	72.2	3.9
Depression (%)	0.7	1.4	6.4	6.7	3.9	− 12.5
Age	65.5 (9.5)***	67.4 (9.4)	20.2	67.0 (9.4)	66.6 (9.4)	− 3.8
Married (%)	76.7	76.5	− 0.1	76.2	76.9	1.5
Male (%)	98.9	99.2	2.1	98.7	98.0	− 4.8
White (%)	53.2	54.0	1.5	69.5	63.2	− 13.5
Nonwhite (%)	7.9	7.1	− 3.0	11.2	13.3	6.5
Unknown race (%)	38.9	38.9	0.1	19.3	23.5	10.4
Education: college graduate (%)	28.5**	30.5	4.4	26.6	27.8	2.7
Education: <high school (%)	17.7	16.9	− 2.3	18.8	19.0	0.6
Per-capita income	2.2 (0.7)***	2.3 (0.8)	17.6	2.1 (0.6)	2.2 (0.8)	15.4
Hospitalized in month (%)	0.4	0.1	− 4.8	4.0	2.4	− 9.6
Hospitalized in prior month (%)	0	0	0	2.2	0.4	− 16.3
Prior DxCG risk score	0.3 (0.3)***	0.3 (0.3)	− 24.0	1.9 (1.7)	2.0 (1.7)	7.7
Prior diabetes drugs	1.5 (0.6)	1.5 (0.7)	1.9	1.4 (0.6)	1.5 (0.7)	7.0
Prior all other drugs	5.5 (2.8)***	4.9 (3.0)	− 20.3	8.3 (4.2)	7.6 (4.5)	− 16.0
Prior primary care visits	0.7 (0.9)**	0.6 (0.7)	− 19.4	0.9 (1.4)	0.7 (1.0)	− 15.3
Prior specialty care visits	1.2 (1.5)***	0.8 (1.7)	− 20.0	2.7 (2.5)	2.5 (3.3)	− 8.6
Prior mental health visits	0.2 (1.0)***	0.05 (0.5)	− 21.0	0.6 (1.7)	0.5 (4.5)	− 2.7
Study site A (%)	15.6	12.4	− 9.2	15.7	11.0	− 13.9
Study site B (%)	21.5***	53.4	69.9	23.8***	45.9	47.7
Study site C (%)	39.4***	21.6	− 39.3	45.3*	34.5	− 22.2
Study site D (%)	23.5***	12.5	− 28.9	15.2*	8.6	− 20.5
Adherent at baseline (%)	68.7	65.5	− 6.8	79.8**	66.7	− 30.0
Adherent at study end (%)	67.6**	60.1	− 15.7	72.2***	57.6	− 30.9

Note. Mean (SD) unless otherwise noted; standardized difference between exempt and nonexempt matched cohorts is denoted by d_i (Austin 2009).

* $p < .05$;

** $p < .01$;

*** $p < .001$.

Adjusted Changes in Medication Adherence by Low-Risk and High-Risk Veterans

After covariate adjustment, adherence to OHAs by low-burden veterans with diabetes diverged over time, with a greater change from baseline in the longer-term postperiod (first difference − 9.5 percent, $p < .01$ in February–December 2003) than in the more immediate postperiod (first difference − 4.9 percent,

Table 2: Descriptive Statistics of Hypertensive Veterans, by Disease Risk Cohort and Copayment Status

Disease Risk Cohort Copayment Status	Low Burden (DCG < 1)			High Burden (DCG > 1)		
	Exempt	Nonexempt	d_i	Exempt	Nonexempt	d_i
<i>N</i>	3,077	2,962		468	583	
Diabetes (%)	27.2*	24.7	-5.5	49.8	46.3	-7.0
Depression (%)	1.1	1.5	2.8	6.0*	3.4	-12.1
Age	67.3 (9.7)***	68.5 (9.3)	13.0	67.0 (10.1)***	68.0 (9.7)	9.2
Married (%)	74.4	75.0	1.4	70.5	67.4	-6.7
Male (%)	97.5	97.6	0.3	98.5	98.1	-3.0
White (%)	49.8	49.4	-0.6	76.7	66.9	-21.9
Nonwhite (%)	7.3	6.8	-2.3	11.8	14.6	8.4
Unknown race (%)	42.9	43.8	1.8	11.5**	18.5	19.6
Education: college graduate (%)	30.6	30.7	0.3	28.7	28.9	0.4
Education: <high school (%)	16.5	16.8	0.9	17.7	18.3	1.5
Per-capita income	2.3 (0.8)*	2.4 (0.8)	5.9	2.2 (0.7)	2.2 (0.8)	6.4
Hospitalized in month (%)	0.1	0.3	5.0	6.0	4.6	-6.0
Hospitalized in prior month (%)	0	0.03	2.6	2.8	1.9	-5.9
Prior DxCG risk score	0.2 (0.2)	0.2 (0.3)	-0.2	2.1 (1.8)	2.2 (1.8)	0.8
Prior hypertension drugs	2.3 (1.2)	2.3 (1.2)	-3.6	2.8 (1.4)	2.9 (1.5)	4.2
Prior all other drugs	3.4 (2.5)***	3.2 (2.5)	-10.5	6.7 (3.8)	6.3 (4.1)	-9.9
Prior primary care visits	0.6 (0.8)***	0.5 (0.7)	-18.4	0.9 (1.2)	0.8 (1.2)	-8.8
Prior specialty care visits	1.0 (1.6)***	0.6 (1.4)	-25.5	3.5 (5.0)**	2.7 (4.8)	-18.7
Prior mental health visits	0.1 (0.6)**	0.04 (0.4)	-10.2	0.7 (3.1)	0.6 (4.9)	-2.1
Study site A (%)	14.5	12.9	-4.7	11.5	13.0	4.6
Study site B (%)	43.7***	51.3	15.1	34.6**	43.9	19.1
Study site C (%)	27.1***	23.3	-8.9	33.8*	27.3	-14.1
Study site D (%)	14.6*	12.6	-6.0	20.1	15.8	-11.2
Adherent at baseline (%)	53.1**	56.9	7.6	46.2	43.6	-5.2
Adherent at study end (%)	58.1	58.4	0.6	47.4	43.6	-7.8

Note. Mean (SD) unless otherwise noted; standardized difference between exempt and non-exempt matched cohorts is denoted by d_i (Austin 2009).

* $p < .05$;

** $p < .01$;

*** $p < .001$.

$p < .05$ in February 2002–January 2003). Among high-burden veterans with diabetes, there were no significant changes in adjusted medication adherence in the postperiod (Figure 1).²

In the hypertension cohort, low-burden veterans’ adherence to anti-hypertensive medications was similar to the preperiod in the immediate postperiod (February 2002–January 2003) but significantly different in the longer-term postperiod (first difference -3.7 percent, $p = .05$). Among high-burden veterans with hypertension, there were no significant changes in adjusted adherence in the postperiod (Figure 2).

DISCUSSION

In this study, we found that medication copayment increases have different adverse impacts for low-burden and high-burden patients, which imply that population-average effects may be misleading. Previous research found that,

Figure 1: Adjusted Medication Adherence Trends for the Diabetes Cohort

Note. See Appendix SA3 for Full Model Estimates.

Figure 2: Adjusted Medication Adherence Trends for the Hypertension Cohort

Note. See Appendix SA4 for Full Model Estimates.

similar to the general population, veterans’ medication adherence generally declined following an increase in drug copayments, and reductions in adherence were greater in the diabetes cohort than the hypertension cohort (Maciejewski et al. 2010). Based on the stratified analysis presented here, this population-averaged effect was concentrated in the majority of the sample that had a lower comorbidity burden (defined by DCG score < 1). A U.S.\$5 copayment increase had a negative impact on medication adherence among patients with a lower comorbidity burden and little impact on adherence for high-comorbidity patients (DCG > 1) in the 23 months following the copayment increase. The increased medication payments generated greater cumulative financial outlays for patients with high-comorbidity burden. It is possible that there were other important impacts of this increased copayment, such as long-term medication adherence, reductions in other health care services, or discontinuation of medications for other comorbid conditions.

Although meta-analysis on the relationship between disease severity and patient adherence yielded mixed findings in the literature (DiMatteo, Haskard, and Williams 2007), in the context of cost-related adherence changes, our findings are consistent with prior research that found patients at greater risk of an adverse event less responsive to copayment changes than patients at lower risk (Remler and Atherly 2003; Madden et al. 2008; Encinosa, Bernard, and Dor 2010). The price insensitivity and better medication adherence we observed among high-comorbidity patients after a copayment increase may be due to an (unobserved) greater physical manifestation of disease, symptomatic conditions, or cognizance of the need to continue therapy to avert future adverse events (DiMatteo, Haskard, and Williams 2007; Elliott et al. 2007; Nolte et al. 2009). These explanations could not be tested with our study data, but should be examined in future research with comprehensive survey and health risk assessment data.

Consistent with prior studies (Goldman et al. 2004; Harman et al. 2004; Joyce et al. 2007; Chernew et al. 2008), we also found a differential effect of copayment changes on medication adherence by disease class. Veterans with diabetes and a lower comorbidity burden exhibited greater medication non-adherence after a copayment increase than veterans with hypertension and a lower comorbidity burden. This may have been due to low-burden patients with diabetes taking more medications than low-burden patients with hypertension (exempt: 5.5 versus 3.4; nonexempt: 4.9 versus 3.2), so the copayment increase represented a larger cumulative financial burden to veterans with a lower comorbidity burdened with diabetes than they were willing to bear. The differential responses we observed may also be due to the availability of substitutable, less expensive drugs and nonpharmaceutical therapies to treat patients with diabetes, as was similarly detected in other natural experiments of copayment introduction and myocardial infarction patients' use of statin and β -blocker therapies (Schneeweiss et al. 2007a, b).

Our results should be interpreted in view of the nearly simultaneous increase in outpatient visit copayments, which we attempted to adjust via lagged visits and contemporaneous visits in sensitivity analyses. The consistency of results with and without adjustment for outpatient visits (Appendix SA5) may be interpreted in one of two ways: (1) we effectively accounted for outpatient visits and our results are unbiased or (2) we did not effectively adjust for the cointervention effects and our results are biased. It is not possible to identify which of these interpretations is definitive, but the results would be biased away from zero if the results are biased. Increases in medication copayments have been associated with modestly higher rates of health care

utilization (Soumerai et al. 1987; Tamblyn et al. 2001) as well as modest cost offsets in inpatient and outpatient care (Gaynor, Li, and Vogt 2007; Chandra, Gruber, and McKnight 2010) that likely increase prescribing and adherence, and suggest that our findings are modestly biased toward zero. This impact biasing toward zero is offset by the adherence reduction likely induced by fewer outpatient visits in response to increased outpatient visit copayments (Cherkin, Grothaus, and Wagner 1989; Wong et al. 2001; Trivedi, Moloo, and Mor 2010). If we did not effectively adjust for the visit copayment increase, decreased visits from higher visit copayments lead to adherence reductions and the adherence reduction from higher visit copayments is greater than the adherence increase from cost offsets, then our results are biased away from zero.

Our study has several limitations. First, we were unable to track veterans' use of non-VA primary care and medications. It is possible that veterans with Medicaid or private insurance who became nonadherent to VA-acquired medications obtained them elsewhere. The omission of non-VA medications is likely to be minimal because VA copayments remained lower than prevailing rates at the time of the study. Second, we stratified patients by comorbidity burden using the DCG score but were unable to stratify by disease severity because we lacked severity-related proxies in administrative data. Prior studies have shown that patients with more complex regimens have lower adherence rate than patients on monotherapy (Dailey, Kim, and Lian 2001; Donnan, MacDonald, and Morris 2002; Melikian et al. 2002; Rubin 2005). Future research should examine whether adherence differences are found using alternative methods for risk stratification and compare adherence responses on the basis of validated disease severity measures. Finally, the generalizability of our results is somewhat limited because our analysis observed medication consumption from four large VAMCs. However, we chose to conduct this study in geographically dispersed VAMCs to reduce small area variation biases. The longitudinal natural experiment enabled us to control for fixed person-specific effects and time trends to minimize unobserved confounding, while propensity score matching and covariate adjustment reduced the likelihood of observed or unobserved confounding; these results appear to be robust.

This study contributes to the extensive literature on copayment impacts on medication adherence by assessing whether effects varied by comorbidity burden and chronic disease type. The availability of the electronic medical record and extensive administrative data in the VA facilitated a rigorous study design, improving upon prior evaluations of formulary and cost-sharing that

did not contrast pre–post changes (Joyce et al. 2002; Goldman et al. 2004; Piette et al. 2004b; Schultz et al. 2005) or lacked colocated control groups (Tamblyn et al. 2001; Joyce et al. 2002; Goldman et al. 2004; Schultz et al. 2005; Taira et al. 2006), which limited their internal validity (Lu et al. 2008). Specifically, we employed a study design that assessed differential adherence changes before and after a copayment increase, included a colocated control groups of patients exempt from copayments, and minimized bias from non-equivalent control groups with propensity score matching.

The heterogeneous effects observed in this VA sample and prior Medicare samples (Remler and Atherly 2003; Madden et al. 2008) suggest the same may be found in other insurance populations. This is the first study to examine the variation of this association in the context of a copayment increase. As medication copayments continue to increase, future research should examine whether this variation is found in commercial, Medicaid and Medicare populations using medications to treat chronic conditions. In light of the Institute of Medicine's recommendation that comparative effectiveness research (CER) studies conduct subgroup analyses (Institute of Medicine 2009), and our findings highlight the importance of comparing treatment effects by health status in future CER analyses. Equally important, studies should at the very least acknowledge simultaneous benefit changes that commonly occur along with medication copayment changes (e.g., visit copayments) in order to better understand the larger set of policy changes co-occurring with the single benefit change under examination. When possible, studies with rigorous study designs, data, and comparators should model multiple benefit changes in simultaneous equation systems. Recent studies that modeled the indirect effects of medication copayment changes on health care utilization and direct impact of medication copayment changes on medication use (Gaynor, Li, and Vogt 2007; Chandra, Gruber, and McKnight 2010) represent important steps in this direction.

These results have important clinical and policy implications. Increased cost-sharing incent more patients with low-comorbidity burden to reduce their adherence and exacerbates the financial burden of patients with high-comorbidity burden if they remain adherent. Nonadherence by low-comorbidity patients and eventual nonadherence by high-comorbidity patients may lead to adverse events that require more intensive and expensive health care services, subverting health system goals of short-term cost reductions to the detriment of long-term interests of the health system and patients (Gaynor, Li, and Vogt 2007; Chandra, Gruber, and McKnight 2010). Thus, the differential impact of copayment increases on adherence by

comorbidity burden and chronic condition suggests that alternative copayment policy models are greatly needed.

A recent copayment policy innovation, referred to as value-based insurance design (VBID), proposes to align patient and health system interests by setting copayments according to their clinical value, not their acquisition cost to the insurer (Fendrick et al. 2001; Chernew, Rosen, and Fendrick 2007). Current VBID proposals suggest reducing or eliminating copayments for cost-effective or cost saving medications, or for medications used by patients with a higher comorbidity burden. In principle, these proposals seem reasonable and well targeted, but VBID evaluations to date have shown modest (2–5 percent) impacts on adherence at 1 year (Chernew et al. 2008; Maciejewski et al. 2011).

Current VBID approaches that reduce copayments for all patients may only improve adherence for patients with low comorbidity, if our results hold in respect to a copayment decrease. This may be socially desirable because of the potential long-term health and economic benefits that would accrue to patients with low-comorbidity burden. However, these differential responses to a copayment reduction may not satisfy the business case for many insurers who would like to realize a positive return on investment (ROI) in the short term. Creation of VBID programs that reduce medications used by patients with a higher comorbidity burden might increase the possibility of a positive ROI in a shorter timeframe, but such a copayment structure might have little effect and would create perverse incentives for patients to become sicker in order to receive copayment relief. VBID and other copayment policy innovations are needed to reverse a long-standing trend of increasing copayments, and it is vitally important for future research to assess the heterogeneity in policy impacts to ensure that medication copayments are structured in the best interest of patients and payors.

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NOTES

1. Veterans were exempt from medication copayments if: (1) their annual income was <U.S.\$9,556 if single and U.S.\$12,516 if married, (2) they had ≥ 50 percent disability or unemployability that was service connected, or (3) their diabetes or hypertension were not service-connected disabilities but they exceeded the U.S.\$840 copayment cap in a given year.
2. Statistical significance in Figures 1–2 refer to estimates of difference-in-differences from the point estimates associated with the 95 percent confidence intervals for each time period. Confidence intervals may overlap within a given time period (e.g., preperiod, short-term postperiod, or longer-term postperiod) yet generate significant difference-in-differences because the bootstrapped standard errors include a covariance term (related to correlation of differences of exempt and nonexempt veterans) that is nonzero.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article:

Appendix SA1: Author Matrix.

Appendix SA2: Descriptive Statistics of the Sampled Veterans, by Inclusion in Propensity-Matched Sample.

Appendix SA3: Generalized Estimating Equation Regression of Adherence on Propensity-Matched Diabetes Sample, by Disease Burden Cohort.

Appendix SA4: Generalized Estimating Equation Regression of Adherence on Propensity-Matched Hypertension Sample, by Disease Burden Cohort.

Appendix SA5: Results of Sensitivity Analyses Adjusting for Co-Occurring Outpatient Visit Copayment Increase on Medication Adherence, by Disease and Disease Burden Cohort.

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