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Abstract

Title of Dissertation: Impact of Beneficiary Characteristics, Drug Plan Formulary Policies, and Environmental Factors on Medication Adherence among Low Income Beneficiaries Covered by Medicare Part D

Xian Shen, Doctor of Philosophy, 2016

Dissertation Directed by: Dr. Bruce C. Stuart, Professor, Department of Pharmaceutical Health Services Research

Research suggests that low income individuals often fail to take medications as prescribed. Various individual characteristics have been studied in relation to adherence outcomes, however, little is known regarding how drug plan formulary policies and external environmental factors may affect individuals' medication adherence.

This dissertation evaluated the independent effects of beneficiary characteristics, drug plan formulary policies, and external environmental factors on medication adherence for oral hypoglycemic agents (OHAs), statins, and renin angiotensin system (RAS) antagonists in a cohort of low-income subsidy (LIS) recipients enrolled in randomly assigned benchmark Part D plans. The data source included a random 5% sample of 2012 Medicare administrative claims and a customized dataset capturing beneficiaries' plan assignment history. Three hosts of beneficiary characteristics, including demographics, comorbidity burden, and health services utilization, were analyzed. The formulary policies of interest included non-coverage, prior authorization, and step therapy, while the environmental factors of interest were socioeconomic environment, availability of

healthcare resources, health culture, evidence-based medicine practice, and quality of primary care.

Results indicated that beneficiary characteristics, Part D plan, and external environmental factors all could significantly influence LIS recipients' medication adherence. Older age, male gender, use of multiple chronic medications were associated with higher medication adherence, whereas black race, Hispanic ethnicity, high comorbidity burden, and frequent hospitalizations and ER visits were inversely related to the adherence outcomes. Placing formulary restrictions on brand-name drugs could shift utilization toward generics and lower cost per prescription fill but had minimal impact on medication adherence among LIS recipients. Geographic variation in adherence rates was observed consistently across all three drug classes of interest. Those living in areas with low socioeconomic environment and poor quality of primary care were less likely to achieve acceptable levels of medication adherence than their counterparts.

In conclusion, low income beneficiaries' medication adherence is influenced by multiple levels of factors. Policies aimed at improving low income population's adherence for chronic medications may consider plan- and environment-oriented programs in addition to interventions targeting at individuals' behaviors.

Impact of Beneficiary Characteristics, Drug Plan Formulary Policies, and Environmental Factors on Medication Adherence among Low Income Beneficiaries Covered by Medicare Part D

by

Xian Shen

Dissertation submitted to the Faculty of the Graduate School of the University of Maryland, Baltimore in partial fulfillment of the requirements of the degree of Doctor of Philosophy
2016

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List of Abbreviations

ARBs—angiotensin II receptor blockers

CMS—Centers for Medicare and Medicaid Services

DPP4 Inhibitors—dipeptidyl peptidase-4 inhibitors

HRR—Hospital referral region

LIS—low income subsidy

MA—Medicare Advantage

OHA—oral hypoglycemic agents

PDP—stand-alone prescription drug plans

RAS— renin-angiotensin system

STN—statins

Chapter 1: Introduction

The clinical benefits of oral hypoglycemic agents (OHAs), statins, and renin-angiotensin system (RAS) antagonists in reducing patients' risk of developing diabetes complications and cardiovascular events have been well established and accepted by the medical community.[1-3] An extensive body of evidence shows that taking these chronic medications adherently is associated with improved clinical and economic outcomes.[4-6] However, research has found that individuals, especially those with low socioeconomic status, often fail to take these medications as prescribed.[7,8] Similar observations were made in a recent analysis of Medicare Part C & D performance data conducted by the Centers of Medicare and Medicaid Services (CMS). Specifically, low-income subsidy (LIS) recipients were found to be significantly less likely to achieve acceptable levels of adherence with these three classes of medications compared to non-LIS beneficiaries.[9,10] LIS recipients represent about 30% of Part D enrollees yet account for a disproportionally high amount of Medicare program spending (nearly 70% of Part D spending in 2014).[11-13] Increasing LIS recipients' adherence for chronic medications holds promise for containing total health care expenditures while improving quality of care for this high-spending population in the long run.

In order to craft effective policies to address LIS recipients' suboptimal medication adherence, the intuitive first step is to understand what factors could affect their medication-taking behaviors. Various individual characteristics, including age, race/ethnicity, co-morbidities and polypharmacy, have been studied in relation to medication adherence within both the general Medicare population and the low-income beneficiaries.[8,14-16] However, little is known regarding how prescription drug plan policies may contribute to Part D enrollees' medication adherence. [17,18] Although LIS recipients are only responsible for nominal copays for prescription drugs (full-subsidy recipients paid at most $2.60 for generics and $6.50 for brand-name drugs in 2012),[19] they are subject to the same formulary coverage policies as other Part D enrollees.

Except for the six protected classes, Part D plans are only required to include a minimum of two drugs from each therapeutic class on formulary, leaving Part D sponsors with considerable discretion in choosing which drugs to cover and how many to cover. In 2010, some plans covered all drugs from the CMS drug reference file whereas other plans included as few as 63% of those drugs.[20] Such variation in coverage occurred not only among drugs with low demand but also among widely used drugs. In 2012, five of the top 10 most commonly used brand-name drugs, including rosuvastatin, were unavailable or excluded from formulary for at least 5% of Medicare beneficiaries enrolled in stand-alone prescription drug plans (PDPs).[21] In addition, an increasing trend in use of utilization management (UM) tools among covered drugs has been seen, with the share of covered drugs with any UM restrictions doubled from 18% in 2007 to 36% in 2012.[21] Prior research showed that LIS recipients are concentrated in benchmark PDPs, which generally offer less generous benefit package than enhanced plans.[11,22] Given that formulary non-coverage and UM tools are being increasingly employed by plans, it is important to understand whether those formulary policies pose barriers for LIS recipients to access needed prescription medications.

In addition to individual and plan effects, prior studies have found considerable regional variation in medication adherence for various drug classes.[8,23-25] The question of what causes geographic variation in health services utilization has provoked controversy for years. Is it primarily due to variation in individuals' health care needs across the country? Or is it due to differences in practice patterns and other external environmental factors from region to region? Understanding sources of geographic variation in health services use is key to tailoring effective policies for improving efficiency of health care. If cost-effective treatments, such as OHAs for treating type 2 diabetes, are underutilized in parts of the country because of external environmental factors, policies targeting at those external factors could improve both efficiency and quality of care. However, if population characteristics, including differences in health status and treatment preferences drive the variation, then policies designed to reduce or eliminate such variation could discourage delivery of personalized care.[26]

Despite of the attention paid to geographic variation in health services utilization, few studies have been able to quantify the contribution of external environment to the variation independently of the role of individual characteristics.[26-29] Finkelstein et al found that 40% - 50% of geographic variation in utilization is attributable to patient demand and the remainder is due to place-specific factors. While the authors further evaluated specific factors driving patient demand, the underlying mechanisms of place-specific factors were not systematically analyzed.[27]

It is challenging to estimate independent effects of plan policies, individual characteristics, and external environmental factors on medication adherence using observational data. Factors that influence individuals' selection of prescription drug plans, such as health beliefs, life style and use of over-the-counter medications, are often unobservable and cannot be accounted for in data analysis. This work aims to address this challenge in the context of a natural experiment created by an auto-assignment process under Medicare that randomly assigns LIS recipients to benchmark Part D plans within their regions. Randomization reduces selection bias, and creates a unique research opportunity for estimating the impact of beneficiary characteristics, Part D plan policies and external environmental factors on medication adherence in low-income beneficiaries. An understanding of the roles of those multi-level factors will provide directions for future policies to improve low-income beneficiaries' adherence to chronic medications.

This work takes a two-step approach. The first step is to quantify the independent effects of enrollee, plan and region on medication adherence among LIS recipients. Following that, additional analyses are performed to further evaluate the impact of Part D plans' formulary policies and specific external environmental factors on medication adherence in this low-income population. The ***specific aims*** are:

Aim 1: To evaluate how beneficiary characteristics, benchmark Part D plan, and geographic region may independently influence medication adherence for OHAs, statins, and RAS antagonists among LIS recipients.

Aim 2: To evaluate the effects of formulary restrictions on medication adherence for OHAs, statins, and RAS antagonists among LIS recipients. Formulary restrictions of interest include formulary non-coverage, prior authorization, and step therapy.

Aim 3: To evaluate the effects of external environmental factors on medication adherence for OHAs, statins, and RAS antagonists among LIS recipients. External environmental factors of interest include socioeconomic environment, availability of health care resources, health culture, evidence-based medicine practice, and quality of primary care.

Chapter 2: Background

Overview of the Medicare Part D Program

Medicare Part D is a government-subsidized program that provides Medicare beneficiaries with optional prescription drug coverage through private plans, either PDPs or MA-PDs. Plans must provide a benefit package that is at least actuarially equivalent to the “standard benefit” mandated by law. In 2012, beneficiaries enrolled in plans offering the “standard benefit” paid an annual deductible of $310, a 25% co-insurance in the initial coverage phase, and 47.5% for brand-name drugs and 79% for generics in the coverage gap until they spent a total of $4,700 in true out-of-pocket costs (TrOOP). Once the TrOOP is reached, beneficiaries enter the catastrophic phase in which they pay 5% co-insurance, or $6.50 copay for brand-name drugs/$2.60 for generics, whichever is greater. However, most plans offer alternative benefit packages rather than the “standard benefit”.[20,30] Plans may differ from each other with respect to monthly premium, annual deductible, cost-sharing structure, formulary design, UM tools, and other plan policies.

Beneficiary premiums are determined annually through a competitive bidding process. Each year in June, CMS receives bids from plans for covering prescription drug costs for a Medicare beneficiary of average health. Based on the bids, a national average bid and a base premium (25.5% of the national average bid in 2014) are determined. Plan enrollees pay the base premium plus any difference between their plan’s bid and the national average bid. For each of the 34 PDP regions, a benchmark is also determined, calculated as enrollment-weighted average premium for basic benefit in the region. [31] Stand-alone plans that offer the basic benefit whose bids are equal to or below the benchmark in their region are called “benchmark plans”.

Low-Income Subsidy (LIS)

Medicare subsidizes beneficiary premiums by 75% overall, and provides “extra help” for those with limited income and assets. This “extra help” is also known as the low-income subsidy (LIS). Beneficiaries with full LIS pay zero monthly premium if they enroll in a benchmark plan, while those with partial LIS pay 25%, 50% or 75% of the regional benchmark amount depending on the level of their income and assets. LIS recipients also receive assistance from Medicare in the form of reduced cost sharing. Specifically, full LIS recipients pay zero annual deductible whereas partial LIS recipients pay $66. Prior to reaching the TrOOP threshold, full LIS recipients are responsible for a nominal copay for each prescription filled (<=$2.65 for generics and <=$6.60 for brand-name drugs) whereas partial LIS recipients pay 15% coinsurance. In the catastrophic phase, full LIS recipients receive prescriptions for free and partial LIS recipients pay $2.55 copays for generics and $6.35 copays for brand-name drugs.[30]

Randomization of LIS Recipients

To ensure that LIS recipients have affordable prescription drug coverage, CMS randomly assigns those who have not selected a plan to one of the benchmark plans in their region through auto-assignment or facilitated enrollment. Each year, LIS recipients who are enrolled in a plan that loses benchmark status for the next year are automatically re-assigned to a new plan unless they select a plan on their own.[22] Unlike other Part D enrollees who usually can only switch plans during the annual enrollment period between October 15th and December 7th, LIS recipients can switch to a different plan in anytime in a year. Once a LIS recipient chooses a plan, CMS will no longer re-assign that person even if his or her plan loses benchmark status.[22,30,32] In 2010, 9.8 million or 39.7% Part D enrollees received LIS.[22] It is estimated that over 80% of auto-assigned LIS recipients stay in the assigned plan throughout the year.

Chapter 3 Theoretical Framework & Causal Diagram

Theoretical Framework

The Andersen Model of Health Care Utilization provides the theoretical foundation for this dissertation (Figure 1). The model purports that health care utilization is dependent on individuals' propensity to use services (predisposing), their ability to access services (enabling), and their illness needs (need). In the context of this study, examples of predisposing factors include demographic factors such as age, gender and race, enabling factors include formulary restrictions, and need factors are beneficiaries' disease burden and comorbidities. In addition to these three hosts of factors that may influence beneficiaries' medication adherence behavior, the Model states that the health care system or external environment can also affect individuals' medication use. In this dissertation, the external environment is represented by five specific environment-level factors, including socioeconomic environment, availability of healthcare resources, health culture, evidence-based medicine practice, and quality of primary care.

Figure 1 Theoretical Framework

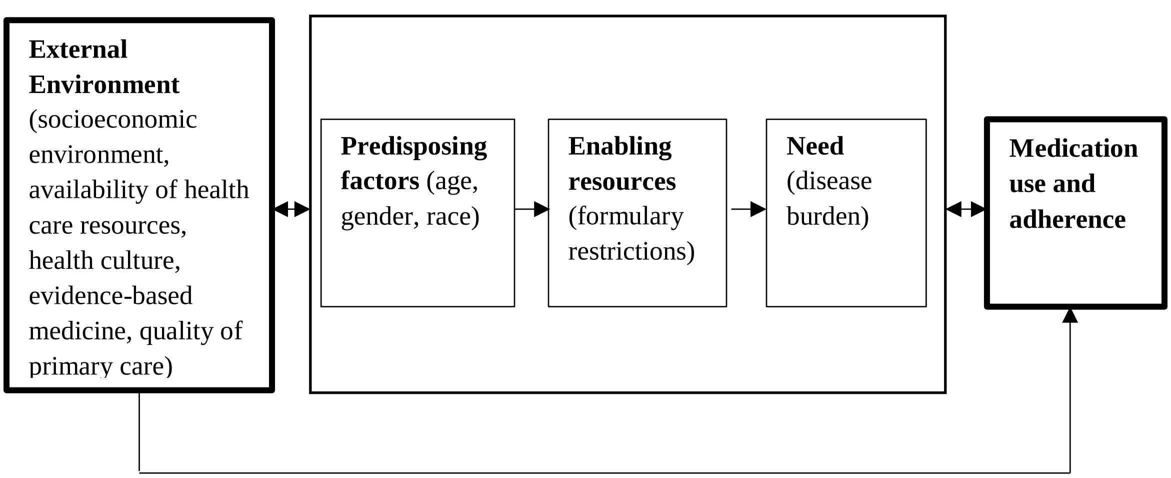


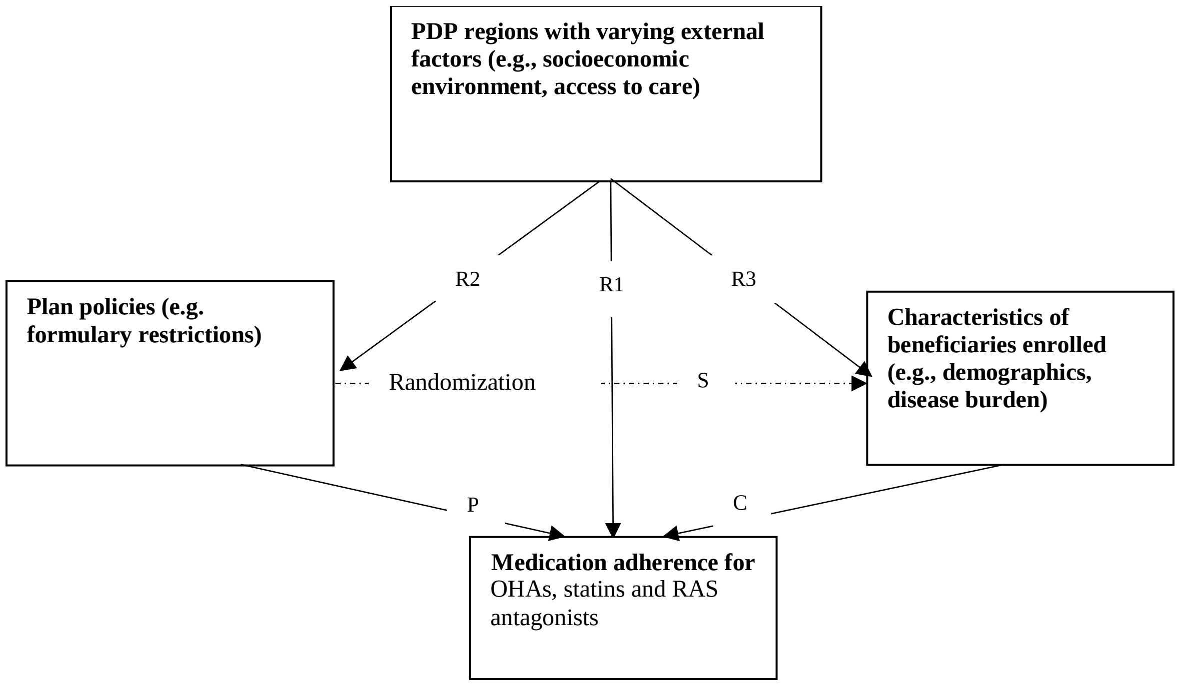
Figure 1Theoretical Framework

Causal Diagram

The directed acyclic graph (DAG) outlines the causal framework of this study (Figure 2). Part D plan policies, individual characteristics, and external environmental factors are assumed to directly affect medication adherence, as indicated by arrows P, C and R1 pointing from each domain to medication adherence. These three direct effects are what this study intends to estimate. The greatest threat to causal inference in this model is the possibility that individuals self-select into plans that best fit their needs (arrow S). As enrollee characteristics can affect medication adherence (arrow C), plan policies can affect average medication adherence of the enrollees indirectly through influencing who choose to enroll in the plan. However, the randomization eliminates the possibility of such selection behavior, hence the dashed arrow S. Finally, PDP regions may differ in factors such as socioeconomic environment, availability of health care resources, health culture, evidence-based medicine practice, and quality of primary care. Those external environmental factors may affect policies that a plan adopts, and characteristics of individuals may differ between regions (arrows R2 and R3).

Figure 2 Directed Acyclic Graph

Figure 2 Directed Acyclic Graph



Chapter 4: Independent Effects of Beneficiary Characteristics, Part D Benchmark Plan, and Geographic Region on Medication Adherence among Low Income Subsidy Recipients

Abstract

Recent investigations reveal that receipt of low-income subsidies (LIS) for Medicare Part D coverage is associated with poorer outcomes of several quality measures in the Star Ratings program, including nonadherence to oral hypoglycemic agents (OHAs), statins, and renin angiotensin system (RAS) antagonists. We evaluated medication adherence for these three drug classes and identified contributing factors in a sample of diabetic LIS recipients who were randomly assigned to benchmark Part D plans. The overall adherence rates were 71.3% for OHAs, 69.7% for statins, and 71.9% for RAS antagonists, lower than the thresholds for two Stars in 2014. We found that benchmark plans, beneficiary characteristics, and geographic regions all can significantly affect LIS recipients' likelihoods of achieving adherence to OHAs, statins, and RAS antagonists. Policymakers may consider motivating benchmark plans to address LIS recipients' suboptimal medication adherence.

Introduction

The Centers for Medicare and Medicaid Services (CMS) recently investigated the effect of socioeconomic status on the Star Ratings of Medicare Advantage plans and stand-alone prescription drug plans (PDPs). [9,33] The findings suggest that receipt of low-income subsidies (LIS) for Medicare Part D coverage is associated with poorer outcomes of several quality measures, including nonadherence to oral hypoglycemic agents (OHAs), statins, and renin angiotensin system (RAS) antagonists.[10,34] While it is necessary to take this relationship into account in order to provide valid Star Ratings, it is also important to identify ways to improve low socioeconomic beneficiaries' medication adherence.

In this study, we aimed to understand what factors could affect LIS recipients adherence to OHAs, statins, and RAS antagonists by exploiting a natural experiment in which LIS recipients are randomly assigned to benchmark plans within PDP regions.[35,36] The power of randomization in eliminating selection bias together with data from over a dozen of benchmark plans across the country provided an unprecedented opportunity to evaluate the independent effects of prescription drug plans, beneficiary characteristics, and geographic regions on LIS recipients' medication adherence. This knowledge would in turn contribute to developing policy options for improving care and health outcomes for this vulnerable population.

Methods

To ensure that LIS recipients have affordable prescription drug coverage, CMS randomly assigns those who do not voluntarily select a Part D plan to one of the benchmark plans in their region. Each year CMS also conducts re-assignments for assignees whose plan is terminating or no longer qualified as premium-free in the following year (i.e., charging a premium above the regional benchmark threshold and not waiving de minimis amount). LIS recipients can switch to different plans of their choice any month in a year. Once a LIS recipient chooses a plan, assignment activities are stopped for that person.[35-37] We obtained a customized dataset from CMS that captured beneficiaries' histories of plan assignments, dating back to 2006. We linked this dataset to a 5% sample of 2012 Medicare research files from the Chronic Conditions Data Warehouse (CCW), which provided data on beneficiary enrollment and demographics, administrative claims, and characteristics of Part D plans.[38]

The study sample included LIS recipients with diabetes who were randomly assigned to benchmark plans and remained in their assigned plan as of January, 2012. Eligible beneficiaries must also have been continuously enrolled in Medicare Parts A, B & D and have received LIS throughout 2012. Beneficiaries who filled two or more prescriptions for insulin or stayed in inpatient facilities for ≥180 days in 2012 were excluded, so were those who elected their own Part D plan. Lastly, we grouped plans from the same sponsor with the same formulary (but operating in different regions) together and formed 17 multi-region "larger plans". To obtain stable estimates, the "larger plan" with fewer than 100 eligible study subjects were excluded from the analysis.

Medication adherence was measured based on the proportion of days covered (PDC) by any medications in the drug class. We computed PDC using the same methodology applied in the Medicare Star Ratings program.[39] Beneficiaries with a PDC ≥ 0.8 were considered adherent. We constructed variables for three categories of beneficiary characteristics, including: 1) demographics (i.e., age, gender, race/ethnicity, LIS subsidy level, and original reason for Medicare entitlement); 2) comorbidities (i.e., hypertension, hyperlipidemia, chronic heart failure, chronic kidney disease, depression, and Charlson Comorbidity Index); and 3) health services utilization (i.e., count of other chronic medications, count of physician office visits, count of hospitalizations and ER visits). We also created dummy variables to represent the benchmark plans and PDP regions.

In descriptive analysis, we calculated adherence rates (percentages of beneficiaries with a PDC ≥ 0.8) for OHAs, statins, and RAS antagonists by plan and by PDP region. We then estimated a linear probability model to evaluate the independent effects of benchmark plans, beneficiary characteristics, and PDP regions on the likelihood of achieving a PDC ≥ 0.8 for each of the three drug classes of interest. We used SAS 9.3 (Cary, NC) to perform all the statistical analyses.

This study is innovative. By exploiting the random plan assignment, we were able to identify highly comparable study groups within PDP regions (Tables A1-A3 in Appendix), which allowed us to evaluate the effects of benchmark plans on LIS recipients' medication adherence in a setting similar to a multi-site randomized controlled trial. Because the randomization virtually eliminated selection bias, any observed variation in the adherence rates between benchmark plans could be considered as true plan effects on enrollees' medication adherence. Furthermore, prior adherence research is mostly restricted to studying the influences of individual characteristics. In contrast, by exploring plan and regional effects, this study provides readers with a more in-depth understanding of factors that could affect low socioeconomic beneficiaries' medication adherence.

This study has several important limitations. Our analysis was limited to randomized LIS recipients in benchmark plans. Hence, the study findings might not be strictly generalizable to non-benchmark plans or the general Medicare population. Medication adherence is operationalized as proportion of days covered between the date of first prescription fill and end of 2012 (i.e., December 31, 2012) and computed using pharmacy claims. We recognize potential measurement errors with this operationalized definition where discontinuation resulting from clinical reasons may be misclassified as nonadherence. In addition, it was beyond the scope of this study to identify underlying causes for the observed plan and regional effects. Future studies may consider assessing the influences of specific plan characteristics and environmental factors on medication adherence.

Results

A total of 39,475 beneficiaries from 17 multi-region benchmark plans were selected for the study sample, of which the mean age was 66.3 years, half were White, 46.4% were originally eligible for Medicare due to old age, 59.7% had hyperlipidemia, and 78.2% had hypertension. About 99% of the study subjects were full LIS recipients who were exempt from monthly premiums and annual deductible and who paid at most $2.6 for generics and $6.5 for brand-name drugs in 2012. Those who received full LIS and paid no copay are beneficiaries residing in long-term care institutions or enrolled in Home and Community Based Services (HCBS) Waiver. These beneficiaries' medications are managed by health care providers and thus may have different utilization patterns than their counterparts living in community (Table 1).

A total of 21,301 study subjects (54.0%) took OHAs, 20,858 (52.8%) took statins, and 22,173 (56.2%) took RAS antagonists in 2012. The adherence rates or percentages of beneficiaries with a PDC $\geq$ 0.8 were 71.3% for OHAs, 69.7% for statins, and 71.9% for RAS antagonists. The plans' adherence rates ranged from 60.0% to 80.3% for OHAs, from 63.4% to 73.6% for statins, and from 61.7% to 81.7% for RAS antagonists (Table 2). In addition, we observed geographic variation in adherence rates for all three drug classes. The ranges were 53.9% in region 28 (AZ) to 76.1% in region 25 (IA, MN, MT, NE, ND, SD, WY) for OHAs, 51.5% in region 33 (HI) to 78.9% in region 16 (WI) for statins, and 57.3% in region 28 (AZ) to 81.7% in region 1 (NH, ME) for RAS antagonists. We also calculated an average adherence rate across the three drug classes of interest for each PDP region and plotted the average rates on a map. The northern regions appeared to have higher average adherence rates than the southern regions in 2012 (Figure 3).

Table 1 Characteristics of Study Sample (Chapter 4)

Table 1 Characteristics of Study Sample

Beneficiary Characteristics	**N (%) / Mean (SD)**
Assignment Year	
2006	3,371 (8.5%)
2007	1,317 (3.3%)
2008	4,452 (11.3%)
2009	5,102 (12.9%)
2010	7,756 (19.7%)
2011	8,917 (22.6%)
2012	8,560 (21.7%)
Age	66.34 (14.6)
Male	15,041 (38.1%)
Old Age as Original Reason for Medicare Entitlement	18,308 (46.4%)
Race	
White	21,927 (55.9%)
Black	9,570 (24.4%)
Hispanic	3,527 (9.0%)
Other Race	4,206 (10.7%)
LIS Subsidy Level	
Full LIS, No Copay	6,926 (17.6%)
Full LIS, Low Copay ($1.1/3.3)	23,298 (59.0%)
Full LIS, High Copay ($2.6/6.5)	6,926 (17.6%)
Partial LIS, 15% Coinsurance	415 (1.1%)
Chronic Heart Failure	9,683 (24.5%)
Chronic Kidney Disease	9,644 (24.4%)
Depression	10,231 (25.9%)
Hyperlipidemia	23,592 (59.8%)
Hypertension	30,857 (78.2%)
Charlson Comorbidity Index	1.53 (1.5)
Count of Physician Office Visits	9.16 (9.0)
Count of Hospitalizations	0.50 (1.2)
Count of ER Visits	1.51 (4.8)

Table 2 Medication Adherence Rates of Study Sample, Stratified by Plan, N=39,475**

Parent Organization	Plan Name	Count of Qualifying Regions*	N (%)	OHA, n1=21,301	STN, n2=20,858	RAS, n3=22,173	Average
UnitedHealth Group, Inc.	AARP MedicareRx Preferred	4	156 (0.4%)	80.3%	73.6%	81.7%	78.5%
CVS Caremark Corporation	Community CCRx Basic	30	5119 (13.0%)	74.1%	70.3%	73.1%	72.5%
CIGNA	CIGNA Medicare Rx Plan One	21	3153 (8.0%)	72.1%	71.3%	73.8%	72.4%
CVS Caremark Corporation	CVS Caremark Value	28	3871 (9.8%)	72.5%	71.1%	73.0%	72.2%
WellCare Health Plans, Inc.	WellCare Classic	22	3862 (9.8%)	72.3%	69.4%	73.8%	71.8%
CIGNA	HealthSpring Prescription Drug Plan	23	3509 (8.9%)	72.7%	71.3%	71.3%	71.8%
Coventry Health Care Inc.	First Health Part D Premier	23	3061 (7.8%)	71.6%	71.0%	72.0%	71.5%
Torchmark Corporation	United American - Select	19	814 (2.1%)	73.1%	70.2%	71.2%	71.5%
CVS Caremark Corporation	Health Net Orange Option 1	17	2407 (6.1%)	71.4%	69.9%	73.1%	71.4%
Aetna Inc.	Aetna CVS/pharmacy Prescription Drug Plan	26	1637 (4.2%)	72.2%	69.5%	71.4%	71.0%
Express Scripts Holding Company	Medco Medicare Prescription Plan - Value	16	2477 (6.3%)	70.8%	69.2%	71.2%	70.4%
Munich American Holding Corporation	Windsor Rx	10	562 (1.4%)	67.5%	68.4%	74.4%	70.1%
Humana Inc.	Humana Walmart-Preferred Rx Plan	34	4780 (12.1%)	68.9%	68.5%	71.1%	69.5%
CIGNA	BravoRx	14	1246 (3.2%)	68.1%	68.0%	67.8%	67.9%
Envision Insurance Company	EnvisionRxPlus Silver	29	2370 (6.0%)	65.9%	64.4%	66.1%	65.5%
WellPoint, Inc.	Blue MedicareRx Standard	2	105 (0.3%)	60.0%	72.2%	61.7%	64.6%
WellPoint, Inc.	MedicareRx Rewards Standard	6	346 (0.9%)	60.0%	63.4%	68.1%	63.9%

*Count of PDP regions qualified as premium-free for LIS recipients; **Aetna Medicare Rx Essentials, First United American – Select, and United American – Preferred had fewer than 100 eligible beneficiaries and thus were excluded from the analysis;

Table 2 Medication Adherence Rate of Study Sample, Stratified by Plan (Chapter 4)

Figure 3 Geographic Variation in Average Medication Adherence Rate for OHAs, Statins, and RAS Antagonists

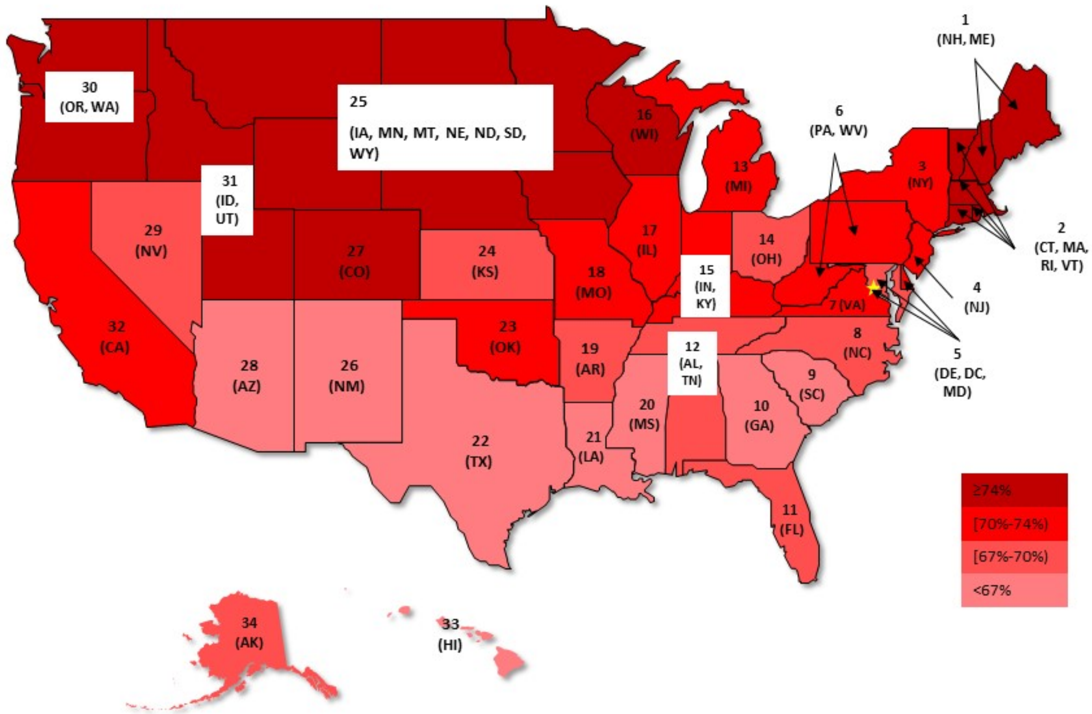


Figure 3 Geographic Variation in Average Medication Adherence Rates for OHAs, Statins, and RAS Antagonists

The estimated effects of benchmark plans, beneficiary characteristics, and PDP regions on the probability of being adherent to OHAs are presented in Figure 4.

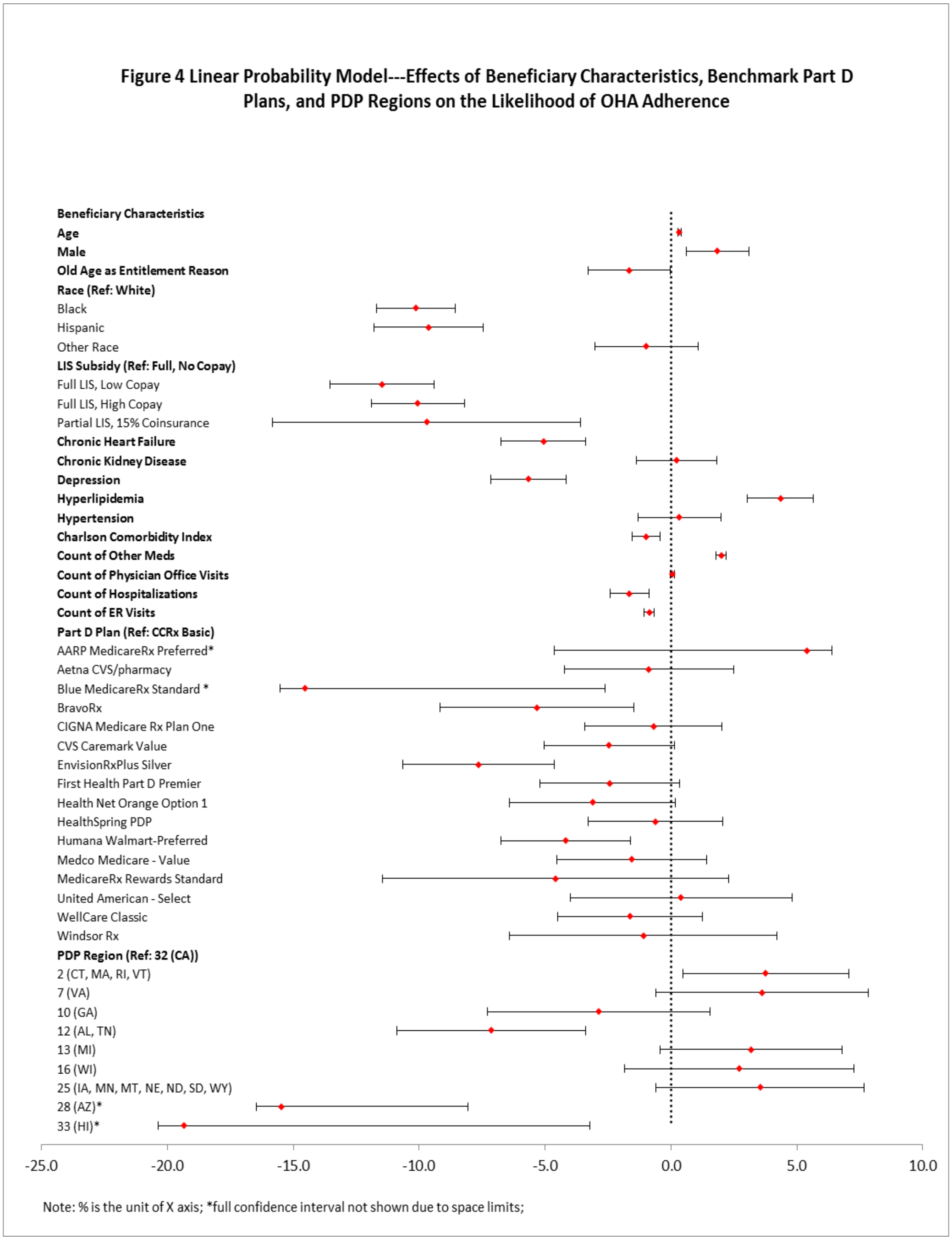


Figure 4 Linear Probability Model-- Effects of Beneficiary Characteristics, Benchmark Part D Plans, and PDP Regions on the Likelihood of OHA Adherence

Comparing to enrollees in the Community CCRx Basic Plan (highest enrollment), their counterparts from four other plans had significantly lower likelihoods of achieving a PDC of 0.8 or higher after statistical adjustment for beneficiary characteristics and PDP region. These plans were Blue MedicareRx (adjusted difference (adj diff=-14.5%, 95% Confidence Interval (CI)=[-26.5%, -2.6%])), BravoRx (adj diff= -5.3%, 95% CI=[-9.2%, -1.5%]), EnvisionRxPlus Silver (adj diff=-7.6%, 95% CI=[-10.7%, -4.6%]), and Humana Walmart-Preferred Rx (adj diff=-4.2%, 95% CI=[-6.7%, -1.6%]).

Additionally, significant regional effects were observed. Using the region with the largest number of study subjects as reference (region 32, CA), we found that beneficiaries in region 2 were 3.8% (95% CI=[0.5%, 7.0%]) more likely to be adherent to OHAs whereas those residing in regions 12 (adj diff=-7.1%, 95% CI=[-10.9%, -3.4%]), 28 (adj diff=-15.5%, 95% CI=[-22.9%, -8.1%]), and 33 (adj diff=-19.4%, 95% CI=[-35.5, -3.2%]) had lower likelihoods of being adherent. Most of the beneficiary characteristics included in the regression models were significantly associated with the study outcomes. Older age (adj diff=0.3%, 95% CI=[0.2%, 0.4%]), being male (adj diff=1.9%, 95% CI= [0.6%, 3.1%]), diagnosis for hyperlipidemia (adj diff=4.4%, 95% CI= [3.0%, 5.7%]), and taking multiple chronic medications (adj diff=2.0%, 95% CI= [1.8%, 2.2%]) were associated with higher likelihoods of being adherent to OHAs, whereas old age as original reason for Medicare entitlement (adj diff=-1.7%, 95% CI= [-3.3%, 0.0%]), Black race (adj diff=-10.1%, 95% CI=[-11.7%, -8.6%]), Hispanic ethnicity (adj diff=-9.6%, 95% CI=[-11.8%, -7.5%]), lower LIS subsidy level, diagnoses for chronic heart failure (adj diff=-5.1%, 95% CI= [-6.7%, -3.4%]) and depression (adj diff=-5.7%, 95% CI= [-7.2%, -4.2%]), higher Charlson Comorbidity Index score (adj diff=-1.0%, 95% CI= [-1.5%, -0.4%]), and higher frequencies of hospitalizations (adj diff=-1.7%, 95% CI=[-2.4%, -0.9%]) and ER visits (adj diff=-0.9%, 95% CI=[-1.1%, -0.7%]) were inversely related to OHA adherence. The regression results for statins and RAS antagonists are consistent with those for OHAs and hence are provided in the Appendix (Table A5).

Discussion

We found that the overall adherence rates of our study sample were 71.3% for OHAs, 69.7% for statins, and 71.9% for RAS antagonists, which were below the thresholds for two Stars set by CMS in 2014 (73% for OHAs and RAS antagonists and 70% for statins).[39] This is consistent with the results form CMS's investigations, highlighting substantial room for improvements. [10] The findings from the regression models suggest that benchmark plans, beneficiary characteristics, and geographic regions all can significantly affect LIS recipients' likelihoods of achieving adherence to OHAs, statins, and RAS antagonists. Beneficiary characteristics and geographic residence are difficult to modify. Policymakers may consider motivating benchmark plans to address LIS recipients' suboptimal medication adherence.

Among 8.2 million LIS recipients enrolled in PDPs in 2014, 6.4 million or 78% were enrolled in benchmark plans.[40] Such a high concentration of LIS recipients in benchmark plans can be explained by the current policies of the LIS program. First, only benchmark plans are eligible for receiving random assignments of LIS recipients. Moreover, only about 4% of LIS recipients voluntarily switch plans during a year,[11] thus a benchmark plan can retain the vast majority of its assignees for as long as it remains premium-free for LIS recipients (i.e., monthly premium below or equal to regional benchmark or waive de minimis amount). In fact, our analysis of the plan assignment data showed that approximately 4.1 million or 35% of all LIS recipients were randomly assigned by CMS and stayed in their assigned plan up to January, 2012. More importantly, we found that LIS recipients' likelihoods for achieving adherence to OHAs, statins, and RAS antagonists were significantly different between plans. For instance, those enrolled in the EnvisionRxPlus Silver Plan were consistently less likely to be adherent to OHAs (adj diff=-7.6%, 95% CI=[-10.7%, -4.6%]), statins ((adj diff=-3.7%, 95% CI=[-6.8%, -0.6%])), and RAS antagonists (adj diff=-6.0%, 95% CI=[-8.9%, -3.1%]) than their counterparts in the Community CCRx Basic Plan (Table A5 in Appendix).

The above evidence points to benchmark plans' ability to widely and significantly improve LIS recipients' medication adherence. Examples of measures that plans may adopt include: 1) waiving LIS recipients' nominal copays to eliminate cost-related nonadherence; 2) offering 90-day mail-order services to make filling prescriptions more convenient; and 3) conducting effective medication therapy management to optimize enrollees' medication use. However, whether benchmark plans have strong incentives to invest these additional resources is questionable. First, benchmark plans are PDPs and only have financial stakes in prescription drug costs. By improving enrollees' medication adherence, benchmark plans are at risk for incurring higher prescription drug costs, which they would not be able to offset by accruing savings in medical costs. Second, unlike Medicare Advantage plans, direct financial incentives such as bonus payments for achieving four or more Stars are not available for PDPs. Third, benchmark plans serve a steady pool of LIS recipients and receive an influx of new LIS assignees each year, therefore we speculate that they are relatively passive in recruiting enrollees. As a result, the marketing privileges that a 5-Star plan enjoys, including the special enrollment period and being flagged as a high-performing plan in the Medicare Plan Finder, may not be as appealing to benchmark plans as to other types of Part D plans. New incentives for benchmark plans to focus on improving LIS recipients' care and outcomes should be considered.

Conclusions

Beneficiary characteristics, benchmark plans, and geographic regions all can significantly affect LIS recipients' medication adherence for OHAs, statins, and RAS antagonists. Beneficiary characteristics and geographic residence are difficult to modify. Policymakers may consider providing benchmark plans with new incentives to improve LIS recipients' medication adherence.

Chapter 5: Impact of Formulary Restrictions on Medication Use and Costs

Abstract

Objective: To evaluate effects of formulary restrictions on utilization and costs of oral hypoglycemic agents (OHAs), statins, and renin-angiotensin system (RAS) antagonists among low-income subsidy (LIS) recipients in Medicare Part D plans. **Methods:** We analyzed a 5% sample of 2012 Medicare data from the Chronic Conditions Data Warehouse together with a customized dataset capturing beneficiaries' histories of plan assignment. Eligible study subjects were LIS recipients randomized to benchmark plans. Formulary restrictions of interest were non-coverage, prior authorization, and step therapy. Study outcomes included generic dispensing rate (GDR), mean cost per prescription fill, and medication adherence based on proportion of days covered (PDC). Random intercept regression models were performed to estimate the effects of formulary restrictions on the study outcomes by drug class. **Results:** After covariate adjustment, beneficiaries subject to formulary restrictions on brand-name pioglitazone and single-source brand-name dipeptidyl peptidase-4 inhibitors (saxagliptin, sitagliptin, and sitagliptin-metformin) had 3.0 percentage-points higher GDR, $10.8 lower cost per prescription fill but similar PDC compared to those who faced no restrictions. Restricting access to brand-name atorvastatin and single-source brand-name statins (rosuvastatin and ezetimibe-simvastatin) was associated with 14.9 percentage-points higher GDR and $29.6 lower cost per prescription fill but had no impact on PDC. Restricting use of single-source brand-name RAS antagonists (olmesartan, valsartan, and valsartan-hydrochlorothiazide) was associated with 15.0 percentage-points higher GDR, $27.2

lower cost per prescription fill, and 1.3 percentage-points lower PDC. **Conclusions:** Placing formulary restrictions on brand-name drugs shifts utilization toward generic drugs, lowers cost per prescription fill, and has minimal impact on overall adherence for OHAs, statins and RAS antagonists among LIS recipients.

Introduction

Over 30 million Medicare beneficiaries obtain prescription drug coverage through Part D each year.[41] Although the Centers for Medicare and Medicaid Services (CMS) require Part D plans to include at least two drugs from each therapeutic class on formulary, coverage of specific drugs may differ across plans. In 2010, some plans covered all drugs from the CMS drug reference file, whereas other plans included as few as 63% of those drugs.[20] Variation in coverage occurred not only to drugs with low demand or brand-name drugs with generic equivalents (i.e., multisource drugs) but also among those single-source drugs commonly used by Medicare beneficiaries. In 2012, five of the ten most frequently prescribed brand-name drugs among Medicare beneficiaries were unavailable or excluded from formulary for more than 5% of all beneficiaries enrolled in stand-alone prescription drug plans (PDPs).[21] Furthermore, use of prior authorization among covered drugs has increased from 8% in 2007 to 20% in 2012.[21]

Formulary non-coverage and utilization management tools (e.g., prior authorization, step therapy) are intended to facilitate efficient use of medications and contain prescription drug costs. Under the Medicare Part D program, a Part D plan enrollee or the enrollee's prescriber can request a coverage determination, including a request for an exception of coverage or utilization management policies. A Part D appeals process is also in place through which a Part D enrollee may appeal an unfavorable coverage determination from their plan sponsor. However, in the standard process, the adjudication timeframe is 72 hours for a coverage determination and 7 days for the first appeal. Prior research also suggests that many beneficiaries have difficulty in navigating their Part D coverage and may be unaware of the coverage determination and exception process. These issues may present challenges for beneficiaries to obtain and adhere to the medications prescribed to them. Little is known regarding the impact of non-coverage, prior authorization and step therapy (collectively referred as formulary restrictions in this paper) on medication utilization and costs, and whether those formulary restrictions may cause unintended reduction in overall medication adherence. The evidence gap is likely due to two analytic challenges. First, plans often impose formulary restrictions together or complimentarily with cost-sharing rules to control medication utilization and costs, thus it is analytically complex to isolate the effects of one from the other. Second, factors that influence beneficiaries' selection of prescription drug plans, such as health beliefs, risk preferences, and expectations for medication needs, are typically unobservable but may bias estimates of plan effects.

Our study addresses these two analytic challenges by exploiting a natural experiment in which CMS randomly assigns beneficiaries receiving low-income subsidies (LIS) to benchmark PDPs within regions. [35,36] Over 90% of all LIS recipients receive full subsidy and pay the same nominal copays for prescription drugs regardless of plan cost-sharing rules.[12,19] Hence, focusing the analysis on LIS recipients would allow us to tease out the influences of plans' cost-sharing rules and estimate the independent effects of formulary restrictions. To further ensure that LIS recipients have affordable prescription drug coverage, CMS randomly assigns those who do not voluntarily select a Part D plan to one of the benchmark PDPs in their region. Each year CMS also re-assigns LIS recipients from plans that are terminating or charging premiums above regional benchmark thresholds. [35-37] Randomization balances both observable and unobservable beneficiary characteristics between plans, thus creating a unique research opportunity for understanding how formulary restrictions work in a real world setting.

Our study focused on three classes of medications commonly used by Medicare beneficiaries: oral hypoglycemic agents (OHAs), statins, and renin angiotensin system (RAS) antagonists. Adherence outcomes for these three drug classes are included as quality measures in the Medicare Star Ratings program and assigned the highest weight in calculating overall Stars. Recent CMS investigations have revealed that receipt of LIS is associated with poorer outcomes for several Star measures, including suboptimal adherence for OHAs, statins, and RAS antagonists.[10,39] Findings from this study can also provide Part D plans with valuable insights in the extent to which lifting formulary restrictions may improve LIS recipients' medication adherence for the three drug classes.

Methods

Data Source

We analyzed a 5% sample of 2012 Medicare data from the Chronic Conditions Data Warehouse (CCW). The CCW formulary file provides detailed information regarding formulary restrictions for the drugs of interest in 2012. The CCW prescription drug event (PDE) file contains claims for prescription drugs incurred by beneficiaries during the year. The CCW files also include information on Part D plan characteristics and beneficiaries' utilization of inpatient, outpatient, and physician services. More details about the CCW data files can be found elsewhere.[42] In addition, we obtained a customized dataset from CMS that captures beneficiaries' histories of plan assignment, dating back to 2006. Through this file, we were able to identify LIS recipients who were randomly assigned to benchmark PDPs by CMS and who remained in their assigned plan as of January 1, 2012.

Study Cohorts

We constructed three non-exclusive study cohorts comprising of users of OHAs, statins, and RAS antagonists, respectively. Eligible study beneficiaries must have been continuously enrolled in Medicare Parts A, B & D, and have received LIS throughout 2012. In addition, eligible beneficiaries for a particular cohort must have at least two prescription fills for the drugs of interest in 2012. We excluded beneficiaries who made plan choices prior to 2012, but allowed those who switched plans mid-year of 2012 to remain in the data analysis according to the intention-to-treat approach commonly used in clinical trials. For technical reasons detailed below we also excluded beneficiaries enrolled in one Part D contract (Envision RxPlus Silver) from the analysis.

Measures

The three outcome measures were generic dispensing rate (GDR), mean cost per prescription fill, and medication adherence based on the proportion of days covered (PDC) by any drugs in the class. GDR was calculated as annual days of supply for generics divided by annual total days of supply for all drugs in the class. Mean cost per prescription fill was determined by dividing total drug expenditure by total number of prescription fills for all drugs in the class. PDC was computed by dividing days covered by total observation days. Days covered by overlapping prescriptions for the same drug were adjusted by rolling over the overlapping days to cover later days when lack of drug supply was identified. Similarly, days covered during inpatient stays were applied to subsequent days with no drug supply. Days in inpatient facilities were removed from both the numerator and the denominator of PDC.[19] PDC was capped at 1.

In our assessment of formulary restrictions, we only considered drugs accounting for ≥1% of overall utilization of the drug class in all LIS recipients. Among those drugs, the scope of analysis was further narrowed down to those with varying degrees of restriction across the benchmark PDPs in 2012. The rationale behind these two requirements was that the impact of formulary restriction of a specific drug cannot be detected unless the drug was prescribed in the study population and its access was restricted to different degrees across plans.

Formulary restrictions of interest were non-coverage (i.e., off-formulary), prior authorization (PA), and step therapy (STEP). To identify off-formulary medications we first identified all drug products from the drug lists used by the Medicare Star Ratings program, and then cross-checked to see which plans excluded which products.[39,43] Indicators for PA and STEP were available from the CCW formulary file. We measured the degree of restriction for each drug identified at brand versus generic and dosage form level. This allowed us to examine how restricting access to brand-name version of a multi-source drug or specific dosage forms might impact the study outcomes. The degree of restriction for a drug was categorized as: (1) "none-restricted" if no strengths of that drug were subject to non-coverage, PA, or STEP; (2) "partially restricted" if at least one but not all strengths of the drug were subject to non-coverage, PA, or STEP; and (3) "all restricted" if all strengths of the drug were subject to non-coverage, PA, or STEP. Notably, we observed perfect correlations in the degree of restriction among drugs in each of the three classes. Specifically, every plan that partially restricted generic simvastatin also partially restricted ezetimibe-simvastatin. Plans either fully restricted brand-name pioglitazone, sitagliptin, and sitagliptin-metformin across the board or did not restrict any of the three drugs. Plans that fully restricted valsartan also fully restricted valsartan-hydrochlorothiazide. We constructed composite measures that grouped commonly occurring formulary restrictions and estimated the effects of each group on the study outcomes. Table 3 provides a list of drugs selected for analysis, the degrees of restrictiveness observed, and groups of formulary restrictions formed. As indicated in the table, three OHAs (sitagliptin, sitagliptin-metformin, saxagliptin), two statins (ezetimibe-simvastatin, rosuvastatin), and three RAS antagonists (olmesartan, valsartan all, valsartan-hydrochlorothiazide) were single-source drugs for which generics were unavailable in 2012.

Key covariates included a variable for count of free generic drugs, indicators for PDP regions, and a categorical variable representing state laws for generic substitution. Plan cost-sharing rules are generally not applicable to full LIS recipients as they pay flat copays for prescription drugs (at most $2.60 for generics and $6.50 for brand-name drugs in 2012).[19] However, in 2012, several plans provided free mail-order prescriptions for commonly used generics in the three drug classes of interest. The covariate, "count of generics available for free via mail order", was developed to account for the effect of this practice at plan level. Lastly, several PDP regions cover multiple states, some of which could have more forceful state laws for generic substitution than others. To represent the strictness of the state laws, we constructed a categorical variable consisting of three values, including "state law allows generic substitution", "state law mandates generic substitution but allows brand by patient request", and "state law mandates generic substitution but allows brand by provider request".

We also evaluated the impact of CMS assignment methods by comparing enrollee characteristics across the benchmark PDPs within each of the three largest PDP regions, namely New York, Texas, and California. We expected comparable enrollee characteristics between plans except for assignment year and age. This was because some plans had operated as benchmark plans for more years and thus would have received more random assignees compared to plans that achieved benchmark status in recent years. These "older" benchmark plans would also have retained an older pool of enrollees. Beneficiary age and assignment year were also included as covariates in the analysis.

Table 3 Identification of Eligible Drugs and Groups of Formulary Restrictions (Chapter 5)

Table 3 Identification of Eligible Drugs and Groups of Formulary Restrictions

	Drugs accounting for ≥1% of overall utilization	**Drugs eligible for analysis***	**Groups of formulary restrictions**
OHAs	Generic glimepiride Generic glipizide Generic glipizide XL Generic glipizide ER Generic glyburide Generig glyburide-metformin Generic metformin Generic pioglitazone Brand-name pioglitazone Sitagliptin** Sitagliptin-metformin** Saxagliptin**	Brand-name pioglitazone (r0, r2) Sitagliptin (r0, r2) Sitagliptin-metformin (r0, r2) Saxagliptin (r0, r2) Plans either fully restricted brand-name pioglitazone, sitagliptin and sitagliptin-metformin across the board or did not restrict any of the three.	None of the four restricted; Saxagliptin (r2); Brand-name pioglitazone (r2), sitagliptin (r2), sitagliptin-metformin (r2), saxagliptin (r2);
Statins	Generic atorvastatin Generic lovastatin Generic pravastatin Generic simvastatin Brand-name atorvastatin Ezetimibe-simvastatin** Rosuvastatin**	Generic simvastatin (r0, r1) Brand-name atorvastatin (r0, r2) Ezetimibe-simvastatin (r0, r1, r2) Rosuvastatin (r0, r2) Plans partially restricted generic simvastatin also partially restricted ezetimibe-simvastatin.	None of the four restricted; Brand-name atorvastatin (r2); Ezetimibe-simvastatin (r2); Generic simvastatin (r1), brand-name atorvastatin (r2), ezet simvastatin (r1); Brand-name atorvastatin (r2), ezetimibe-simvastatin (r2); Rosuvastatin (r2), ezetimibe-simvastatin (r2); Rosuvastatin (r2), brand-name atorvastatin (r2), ezetimibe-simvastatin (r2);
RAS Antagonists	Generic benazepril Generic enalapril Generic lisinopril Generic lisinopril-HCT Generic losartan Generic losartan-HCT Generic quinapril Generic ramipril Generic amlodipine-benazepril Olmesartan** Valsartan all** Valsartan-HCT **	Generic amlodipine-benazepril (r0, r2) Olmesartan (r0, r2) Valsartan (r0, r2) Valsartan-HCT (r0, r2) Plans that fully restricted valsartan also fully restricted valsartan-hydrochlorothiazide.	None of the four restricted; Generic amlodipine-benazepril (r2); Olmesartan (r2); Generic amlodipine-benazepril (r2), olmesartan (r2); Olmesartan (r2), valsartan (r2), valsartan-HCT (r2)

*r0: none restricted; r1: partially restricted; r2: all restricted; **single-source brand-name drugs in 2012; HCT: hydrochlorothiazide;

Statistical Analysis

We estimated three sets of random intercept regression models, in which dependent variables were GDR, mean cost per prescription fill, and PDC, respectively. In each regression model, we included a random effect to account for unexplained variability between plans. Formulary restrictions were modeled as fixed effects. Count of generics available for free via mail order, state law for generic substitution, PDP region, assignment year, and beneficiary age were included as covariates in the models and treated as fixed effects. We used SAS 9.3 (Cary, NC) for all statistical analyses.

Results

A total of 28,082 beneficiaries were eligible for the OHA cohort, 53,864 for the statin cohort, and 57,289 for the RAS antagonist cohort. Approximately 30% of all study subjects resided in New York, Texas, and California in 2012. As expected, enrollee characteristics were largely comparable across benchmark PDPs within each of these three regions except for assignment year and age (Tables A1-A3). Table A4 provides distributions of the three study cohorts by PDP region.

From our assessment of the benchmark PDPs' formulary designs in 2012, we found consistent patterns in formulary restrictions for OHAs, statins, RAS antagonists. For most of the drugs analyzed, plans either fully restricted its use (all strengths restricted) or applied no restrictions at all (all strengths available). Formulary restrictions were mostly placed on brand-name drugs whereas almost all generic drugs were readily available on formulary. In addition, the benchmark PDPs appeared to have three formulary approaches for handling brand-name drugs (Tables 4-6). From most restrictive to most generous, they were: 1) placing restrictions on all brand-name drugs; 2) selectively covering brand-name drugs without restrictions; and 3) covering all single-source brand-name drugs and commonly used multi-source brand-name drugs without restrictions.

The top panels in the next three tables present descriptive statistics for annual days of supply for every drug that accounted for at least 1% of overall utilization in the LIS population beginning with OHAs (Table 4), statins (Table 5), and finally RAS antagonists (Table 6). These statistics are arrayed by the groups of formulary restrictions described in Table 3. Placing formulary restrictions on a drug was associated with lower utilization of that medication. The impact was more pronounced among statins (Table 5) and RAS antagonists (Table 6) than among OHAs (Table 4).

Utilization of generic drugs was much higher among beneficiaries enrolled in plans that restricted access to brand-name drugs. Compared to those enrolled in plans that placed no formulary restrictions on the four statins under study (Table 5), beneficiaries who faced restrictions in obtaining rosuvastatin (single-source brand-name), atorvastatin (multi-source brand-name), and ezetimibe-simvastatin (single-source brand-name) not only had considerable fewer annual days of supply for the three drugs (rosuvastatin: 9.10 vs. 35.41; brand-name atorvastatin: 1.61 vs. 20.52; ezetimibe-simvastatin: 1.13 vs. 7.99), but also had higher use of generic atorvastatin (58.99 vs. 45.86), generic lovastatin (21.27 vs. 16.66), generic pravastatin (48.72 vs. 39.21), and generic simvastatin (136.30 vs. 120.77). Similarly, beneficiaries who were subject to restrictions in accessing single-source brand-name angiotensin II receptor blockers (ARBs), including olmesartan, valsartan, and valsartan- hydrochlorothiazide, had more days of supply for generic ARBs (losartan: 50.18 vs. 27.91; losartan- hydrochlorothiazide: 14.89 vs. 8.57) when compared to their counterparts who could access those drugs without requesting for plan approval (Table 6).

The bottom panels of Tables 4-6 present mean values for each of the study outcomes. The mean GDRs for the three OHA restrictiveness groups varied from 0.83 for plans with no restrictions to 0.84 for plans restricting only saxagliptin (single-source brand-name), to 0.88 for plans restricting brand-name pioglitazone and single-source brand-name dipeptidyl peptidase-4 (DPP4) inhibitors (saxagliptin, sitagliptin, and sitagliptin-metformin). For statins the mean GDR was also lowest for plans with no formulary restrictions (0.77) climbing up to 0.95 for plans placing restrictions on brand-name atorvastatin and single-source brand-name statins (rosuvastatin and ezetimibe-simvastatin). For RAS antagonists plans with no restrictions again exhibited the lowest mean GDR (0.80) with the highest mean GDR (0.95) observed among plans restricting single-source brand-name ARBs (olmesartan, valsartan, and valsartan-hydrochlorothiazide). Mean costs per prescription fill were inversely related to GDR. For OHAs, the range was $54.54 in plans with the most restrictions to $71.70 in plans with no formulary restrictions on the four OHAs under study. For statins the range was $40.49 to $73.04 and for RAS antagonists, $20.78 to $45.74. The differences in PDCs across plans by formulary restrictiveness were small. In no instance was the difference greater than 0.04.

Table 4 Descriptive Statistics for Utilization of Individual Oral Hypoglycemic Agents and Study Outcomes, Stratified by Formulary Restrictions (Chapter 5)

Table 4 Descriptive Statistics for Utilization of Individual Oral Hypoglycemic Agents and Study Outcomes, Stratified by Formulary Restriction Policies, n=28,082

	Group of Formulary Restrictions		
	Brand-name PIO all, SIT all, SIT-MET all, SAX all, n=6,777**	**SAX all, n=11,530**	**None of the four restricted, n=9,775**
Mean Annual Days of Supply (Days)			
Brand-name pioglitazone	18.56	20.25	23.80
Sitagliptin*	25.25	35.61	38.80
Sitagliptin-metformin*	5.48	8.32	9.29
Saxagliptin*	6.55	4.22	4.72
Generic pioglitazone	7.61	7.81	9.17
Generic glimepiride	30.98	31.57	33.17
Generic glipizide	40.15	35.80	35.75
Generic glipizide XL	8.55	10.81	10.47
Generic glipizide ER	14.78	16.09	12.85
Generic glyburide	25.53	24.07	24.79
Generic glyburide-metformin	9.99	8.70	11.25
Generic metformin	188.77	184.74	181.13
Study Outcomes			
Generic dispensing rate	0.88	0.84	0.83
Mean cost per prescription fill (dollars)	54.54	65.77	71.70
Proportion of days covered	0.83	0.84	0.84

*Single-source drugs in 2012; **Degree of restriction: “all” indicates all strengths restricted while “partially” indicates at least one but not all strengths restricted; PIO: brand-name pioglitazone; SIT: sitagliptin; SIT-MET: sitagliptin-metformin; SAX: saxagliptin;

Table 5 Descriptive Statistics for Utilization of Individual Statins and Study Outcomes, Stratified by Formulary Restriction Policies (Chapter 5)

Table 5 Descriptive Statistics for Utilization of Individual Statins and Study Outcomes, Stratified by Formulary Restriction Policies, n=53,864

	Group of Formulary Restrictions						
	ROS all, brand-name ATO all, EZT-SIM all, n=1,810**	**Generic SIM partially, brand-name ATO in all, EZT-SIM partially, n=7,939**	**Brand-name ATO all, EZT-SIM all, n=22,104**	**ROS all, ezetimibe-simvastatin all, n=5,124**	**EZT-SIM all, n=9,525**	**Brand-name ATO all, n=13**	**None of the four restricted, n=7,349**
Mean Annual Days of Supply (Days)							
Brand-name atorvastatin	1.61	1.10	19.43***	34.46	4.32	0.00	20.52
Ezetimibe-simvastatin*	1.13	8.32	0.71	0.33	0.42	0.00	7.99
Rosuvastatin*	9.10	37.21	36.19	3.81	33.04	62.31	35.41
Generic atorvastatin	58.99	64.04	42.40	27.44	54.23	36.92	45.86
Generic lovastatin	21.27	18.66	17.76	24.42	19.84	0.00	16.66
Generic pravastatin	48.72	35.29	35.64	36.91	41.92	34.62	39.21
Generic simvastatin	136.30	122.53	134.27	159.96	128.79	115.38	120.77
Study Outcomes							
Generic dispensing rate	0.95	0.83	0.80	0.86	0.86	0.77	0.77
Mean cost per prescription fill (dollars)	40.49	68.66	60.48	41.44	53.05	59.29	73.04
Proportion of days covered	0.81	0.83	0.83	0.83	0.82	0.80	0.83

*Single-source drugs in 2012; **Degree of restriction: "all" indicates all strengths restricted while "partially" indicates at least one but not all strengths restricted; ***Several plans rejected claims for generic atorvastatin and covered brand-name atorvastatin at generic copay during the 180 days following patent expiration.[44] This 180 days covered first four months of the study period (January-April, 2012); ATO: brand-name atorvastatin; SIM: generic simvastatin; EZT-SIM: ezetimibe-simvastatin; ROS: rosuvastatin;

Table 6 Descriptive Statistics for Utilization of Individual RAS Antagonists and Study Outcomes, Stratified by Formulary Restriction Policies (Chapter 5)

Table 6 Descriptive Statistics for Utilization of Individual Renin Angiotensin System Antagonists and Study Outcomes, Stratified by Formulary Restriction Policies, n=57,289

	Group of Formulary Restrictions				
	OLM all, VAL all, VAL-HCT all, n=1,737**	**Generic AMD-BZP all, OLM all, n=765**	**OLM all, n=28,595**	**Generic AMD-BZP all, n=4,831**	**None of the four restricted, n=21,361**
Mean Annual Days of Supply (Days)					
Generic amlodipine-benazepril	4.20	1.61	6.90	1.07	6.05
Olmesartan*	1.86	0.35	0.81	2.67	6.06
Valsartan*	1.22	24.10	24.61	27.03	28.06
Valsartan-hydrochlorothiazide*	0.55	13.87	10.42	11.40	14.25
Generic benazepril	5.38	23.15	13.36	12.49	11.35
Generic enalapril	24.71	14.65	18.18	17.53	16.25
Generic lisinopril	125.11	102.31	124.32	120.84	126.39
Generic lisinopri-hydrochlorothiazide	28.00	22.30	22.35	28.81	21.79
Generic losartan	50.18	22.24	32.44	26.15	27.91
Generic losartan-hydrochlorothiazide	14.89	8.90	10.02	11.30	8.57
Generic quinapril	2.99	6.56	3.36	4.26	3.49
Generic ramipril	11.11	5.66	6.04	8.50	6.89
Study Outcomes					
Generic dispensing rate	0.95	0.81	0.85	0.82	0.80
Mean cost per prescription fill (dollars)	20.78	41.01	38.89	43.31	45.74
Proportion of days covered	0.82	0.80	0.83	0.84	0.84

*Single-source drugs in 2012; **Degree of restriction: “all” indicates all strengths restricted while “partially” indicates at least one but not all strengths restricted; AMD-BZP: amlodipine-benazepril; OLM: olmesartan; VAL: valsartan; VAL-HCT: valsartan-hydrochlorothiazide;

These relationships persisted after covariate adjustment for assignment year, beneficiary age, count of generics available for free via mail order, PDP region, and state law for generic substitution (Table 7). For OHAs, restricting use of brand-name pioglitazone and single-source brand-name DPP4 inhibitors was associated with 3.0 percentage-points higher GDR (p<0.0001) and $10.8 lower cost per prescription fill (p=0.0001) for OHAs. Restricting access to brand-name atorvastatin and single-source brand-name statins was linked to 14.9 percentage-points higher GDR ($p<0.0001$) and $29.6 lower cost per prescription fill ($p<0.0001$) for statins. Restricting single-source brand-name statins was associated with $25.6 lower cost per prescription fill ($p=0.0158$) while restricting brand-name atorvastatin and single-source brand-name ezetimibe-simvastatin was related to a reduction of $12.4 ($p=0.0399$). Placing restrictions on single-source brand-name ARBs was related to 15.0 percentage-points higher GDR ($p<0.0001$) and $27.2 lower cost per prescription fill ($p<0.0001$) for RAS antagonists. Restricting only olmesartan was linked to 3.8 percentage-points higher GDR ($p=0.0434$) for RAS antagonists.

The estimated effects of formulary restrictions on overall adherence were minimal. Restricting access to brand-name pioglitazone and single-source brand-name DPP4 inhibitors was linked to 0.4 percentage-points higher PDC ($p=0.3508$), but the association was not statistically significant. Beneficiaries facing formulary restrictions of brand-name atorvastatin and single-source brand-name statins on average had 0.9 percentage-points lower PDC (p-value=0.1197) compared to those who were not subject to such restrictions. Restricting use of single-source brand-name ARBs was related to 1.3 percentage-points lower PDC ($p=0.0211$).

Stringent state laws for generic substitution (mandating generic substitution and only allowing brand-name drugs by provider request) were associated with 3.3 percentage-points higher GDR for OHAs ($p=0.0120$) and 3.0 percentage-points higher GDR for RAS antagonists (p-value=0.0091). Providing free mail-order prescriptions for one additional generic statin was associated with 1.5 percentage-points higher GDR (p-value=0.0360).

Table 7 Random Intercept Models-- Estimated Effects of Formulary Restrictions on Study Outcomes (Chapter 5)

Table 7 Random Intercept Models—Estimated Effects of Formulary Restrictions on Study Outcomes*

	GDR	**Mean $ per Rx Fill**	**PDC**
OHA Cohort, n= 28,082			
Group of formulary restrictions **(reference: none of the four restricted)**			
Brand-name PIO all, SIT all, SIT-MET all, SAX all**	**0.030 (0.005), <0.0001**	**-10.756 (2.812), 0.0001**	-0.004 (0.005), 0.3508
SAX all	-0.004 (0.004), 0.3650	1.874 (2.423), 0.4393	0.002 (0.004), 0.6668
Count of generics with zero copay via mail order	-0.001 (0.001), 0.3780	0.008 (0.534), 0.9883	0.000 (0.001), 0.5899
State law for generic substitution **(reference: allows generic substitution)**			
Mandates generic substitution, allows brand by patient request	-0.001 (0.000), 0.9320	-1.756 (2.904), 0.5455	**0.011 (0.006), 0.0429**
Mandates generic substitution, allows brand by provider request	**0.033 (0.013), 0.0120**	**-13.386 (5.111), 0.0088**	0.014 (0.010), 0.1465
Statin Cohort, n=53,864			
Group of formulary restrictions **(reference: none of the four restricted)**			
ROS all, brand-name ATO all, EZT-SIM all	**0.149 (0.029), <0.0001**	**-29.590 (6.802), <0.0001**	-0.009 (0.006), 0.1197
Generic SIM partially, brand-name ATO all, EZT-SIM partially	0.038 (0.030), 0.1997	-2.850 (7.057), 0.6863	-0.006 (0.004), 0.1353
Brand-name ATO all, EZT-SIM all	0.002 (0.026), 0.9466	**-12.401 (6.036), 0.0399**	-0.005 (0.003), 0.0921
ROS all, EZT-SIM all	0.011 (0.045), 0.8143	**-25.562 (10.589), 0.0158**	-0.006 (0.005), 0.2395
EZT-SIM all	**0.073 (0.027), 0.0068**	-18.180 (6.378), 0.6648	-0.004 (0.003), 0.2265
Brand-name ATO all	-0.107 (0.102), 0.2953	11.275 (26.018), 0.2184	-0.033 (0.059), 0.5756
Count of generics with zero copay via mail order	**0.015 (0.007), 0.0360**	-2.044 (1.661), 0.2184	0.000 (0.001), 0.6988
State law for generic substitution **(reference: allows generic substitution)**			
Mandates generic substitution, allows brand by patient request	**-0.015 (0.006), 0.0207**	0.184 (1.636), 0.9105	0.001 (0.004), 0.8935
Mandates generic substitution, allows brand by provider request	0.002 (0.011), 0.8640	-4.882 (2.832), 0.0847	-0.003 (0.007), 0.6176
RAS Antagonist Cohort, n=57,289			
Group of formulary restrictions **(reference: none of the four restricted)**			
OLM all, VAL all, VAL-HCT all	**0.150 (0.032), <0.0001**	**-27.216 (6.201), <0.0001**	**-0.013 (0.005), 0.0211**
Generic AMD-BZP all, olmesartan all	0.024 (0.027), 0.3894	-4.681 (5.431), 0.3888	-0.011 (0.008), 0.1670
OLM all	**0.038 (0.019), 0.0434**	-3.220 (3.664), 0.3795	-0.004 (0.002), 0.0907
Generic AMD-BZP all	0.008 (0.031), 0.8056	-1.185 (6.039), 0.8445	**0.008 (0.004), 0.0357**
Count of generics with zero copay via mail order	0.000 (0.003), 0.9916	-0.435 (0.572), 0.4468	0.001 (0.000), 0.0576
State law for generic substitution **(reference: allows generic substitution)**			
Mandates generic substitution, allows brand by patient request	**0.012 (0.006), 0.0500**	-2.055 (1.308), 0.1162	0.003 (0.004), 0.3995
Mandates generic substitution, allows brand by provider request	**0.030 (0.012), 0.0091**	-4.101 (2.374), 0.0841	0.002 (0.007), 0.7540

*Adjusted for assignment year, age, and PDP region; each table cell presents a beta-coefficient (standard error) followed by p-value; **Degree of restriction: "all" indicates all strengths restricted while "partial" indicates at least one but not all strengths restricted; * PIO: brand-name pioglitazone; SIT: sitagliptin; SIT-MET: sitagliptin-metformin; SAX: saxagliptin; ATO: brand-name atorvastatin; SIM: generic simvastatin; EZT-SIM: ezetimibe-simvastatin; ROS: rosuvastatin; AMD-BZP: amlodipine-benazepril; OLM: olmesartan; VAL: valsartan; VAL-HCT: valsartan-hydrochlorothiazide;

Discussion

We found that placing formulary restrictions on brand-name drugs generally shifted utilization away from brand-name agents towards inexpensive generics. The effects were consistent across the three drug classes but the magnitude of impact was smaller for OHAs than for statins or RAS antagonists. LIS recipients who faced restrictions in accessing brand-name drugs had 34.9% (38.80 vs. 25.25 days) lower annual days of supply for sitagliptin, 74.3% (34.41 vs. 9.10 days) lower days of supply for rosuvastatin, and 95.7% (28.06 vs. 1.22 days) lower days of supply for valsartan (Tables 4-6) than their counterparts who could freely access those drugs. Correspondingly, the difference in GDR between the restricted and unrestricted group was smaller for OHAs (0.88 vs. 0.83) than for statins (0.95 vs. 0.77) and RAS antagonists (0.95 vs. 0.80).

This varying magnitude of impact might be due to differences in availability of therapeutically equivalent agents. There were multiple generic statins and generic ARBs available in 2012 whereas all DPP4 inhibitors were single-source brand-name drugs. Clinical guidelines on diabetes management recommend adding a DPP4 inhibitor, sulfonylurea, or thiazolidinedione as a second oral agent for patients who cannot achieve their glycemic target with metformin monotherapy. [45] We observed that beneficiaries who faced and did not face restrictions on DPP4 inhibitors had comparable utilization of sulfonylureas and thiazolidinediones, indicating lack of substitution. Although the findings from the regression analysis suggest that restricting access to DPP4 inhibitors has minimal impact on overall OHA adherence, further work is needed to investigate concurrent adherence among patients treated with multiple OHAs as well as the clinical impact of formulary restrictions.

This study addresses the intended and unintended consequences of formulary restrictions—an understudied but important research topic given the near-ubiquity of these tools in modern formulary management.[20] The lack of literature is partially due to complexity in deciphering formulary designs, especially if a large number of drug products are involved. Most prior studies are limited to providing descriptive statistics regarding shares of restricted drugs or evaluating formulary policy changes for particular drugs.[20,46,47] Our analysis of the benchmark PDPs' formularies contributes valuable insights in identifying formulary restrictions that may materially impact medication utilization patterns.

The study estimates for the effects of formulary restrictions have high internal validity. By focusing on the randomized LIS recipients, we were able to minimize potential bias by: 1) isolating the effects of formulary restrictions from that of cost-sharing rules; and 2) removing confounding effects of virtually all beneficiary characteristics we could observe—and by extension other unobserved factors that represent critical threats to internal validity in conventional observational studies.

Additionally, LIS recipients represent about 40% of Part D enrollees yet account for over 55% of total drug spending.[11] This is a socially and economically disadvantaged population who often live with disabilities and multiple chronic conditions. They tend to have worse health outcomes yet significantly higher health care expenditures.[12] Such disparities suggest needs for improving both quality and efficiency of care for this vulnerable population.

In 2012, full LIS recipients paid at most $2.60 for generics and $6.50 for brand-name medications.[19] We found that neither availability of free generics nor generous coverage of brand-name medications seemed to meaningfully affect LIS recipients' overall adherence for OHAs, statins, and RAS antagonists. Hence, LIS recipients' suboptimal adherence might be due to behavioral or clinical causes rather than costs or access issues.[12,48] Part D plan sponsors and other health care decision makers may consider behavioral interventions to improve LIS recipients' perceived importance of medication adherence and disease management skills.

This study has a few limitations. First, the study subjects were randomized to plans rather than to varying formulary restrictions, per se. Hence, the observed effects of formulary restrictions might be confounded by other plan-level policies that also affect medication utilization patterns. We observed that several benchmark PDPs provided free mail-order prescriptions for commonly used generics, which would incentivize beneficiaries to take generics instead of brand-name drugs and use more medications overall. We also observed that Envision RxPlus Silver did not offer 90-day supply prescriptions in 2012 whereas all the other benchmark PDPs did. In general, shorter length of drug supply per prescription fill presents more opportunities for filling prescriptions late and may lead to gaps in medication usage. To eliminate these two plan-level policies as alternative explanations for the observed effects of formulary restrictions on the study outcomes, we excluded beneficiaries enrolled in the Envision RxPlus Silver plan from all analyses and included a covariate for count of free generics in the regression models. In addition, we estimated random intercept regression models to recognize variability in unobserved plan attributes.

Secondly, our randomized cohorts of LIS beneficiaries were not strictly comparable from plan to plan within PDP regions. Because Part D regional benchmark thresholds are determined annually through a competitive bidding process, plans can lose or gain benchmark status from year to year. When a plan loses benchmark status, its random assignees would be re-assigned to other plans (there is an exception when the plan premium is just above the benchmark threshold). As expected, this dynamic randomization process resulted in small differences in beneficiary assignment year and age.

Lastly, readers should use caution in generalizing findings of this study to non-LIS beneficiaries. Compared to non-LIS beneficiaries, LIS recipients tend to be younger, more socioeconomically disadvantaged, and more likely to live with disabilities and multiple chronic conditions. Unlike LIS recipients who pay nominal copays for prescription drugs, non-LIS beneficiaries are subject to their plan's cost-sharing rules which may also affect their medication utilization and costs. Nevertheless, both LIS and non-LIS beneficiaries in a given plan face the same formulary policies and appeal process for requesting coverage exceptions. Although the impact of formulary restrictions on the study endpoints may differ in magnitude, we expect the nature of the relationships to hold in non-LIS populations.

Conclusions

Placing formulary restrictions on brand-name drugs shifts drug utilization toward generics and lowers cost per prescription fill but has minimal impact on overall adherence for OHAs, statins and RAS antagonists among Medicare Part D enrollees receiving low-income subsidies.

Chapter 6: Low Income Part D Enrollees' Medication Adherence Is Influenced by External Environmental Factors

Abstract

Using publicly available data, we developed county and hospital referral region level indices for five external environmental domains, including socioeconomic environment, availability of healthcare resources, health culture, evidence-based medicine practice, and quality of primary care. We then evaluated the relationships between these five environment domains and medication adherence for oral hypoglycemic agents, statins, and RAS antagonists among a sample of Medicare Part D enrollees with diabetes receiving low-income subsidies. Although everyone in the study sample had low income by definition, those living in areas with low socioeconomic environment—representing most of the study sample—and poor quality of primary care were less likely to achieve medication adherence than their counterparts, after adjusting for individual characteristics and plan effects. This finding provides empirical evidence that supports the role of external environment in low-income beneficiaries' use of prescription medications independent of their individual characteristics. Policies aimed at improving medication adherence in poor populations may consider targeting environmental factors in addition to individuals' behaviors.

Introduction

The question of what causes geographic variation in health services utilization has provoked controversy for years. Is it primarily due to variation in individuals' health care needs across the country? Or is it due to differences in practice patterns and other external environmental factors from region to region? Understanding sources of geographic variation in health services use is key to tailoring effective policies for improving efficiency of health care. If high use and high costs are primarily driven by practice-related factors that generate excessive use of health services with little benefits to patients, then policies tailored to changing this behavior could result in substantial savings in healthcare spending. Similarly, if cost-effective treatments are underutilized in parts of the country because of external environmental factors, policies targeting at those external factors could improve efficiency and quality of care. However, if population characteristics, including differences in health status and treatment preferences drive the variation, then policies designed to reduce or eliminate such variation could discourage delivery of personalized care.[26]

Despite the attention paid to geographic variation in health services utilization, few studies have been able to quantify the contribution of external environment to the variation independently of the role of individual characteristics.[8,24,26,49] Finkelstein et al found that 40% - 50% of geographic variation in utilization is attributable to patient demand and the remainder is due to place-specific factors. While the authors further evaluated specific factors driving patient demand (i.e., demographics, health status, and habit formation as a result of past utilization of health services), the underlying mechanisms of place-specific factors were not systematically analyzed.[27]

Compared to utilization of hospital and medical services, less is known about the underlying causes of geographic variation in use of prescription medications.[49-51] While the same external environmental factors are likely to be relevant to physicians' prescribing decisions, patients have considerable discretion in use of medications, especially those indicated for chronic conditions, and the sources of this discretion are widely debated.[8,12,23,24,48,52-54]

The clinical benefits of oral hypoglycemic agents (OHAs), statins, and renin-angiotensin system (RAS) antagonists in reducing patients' risk of developing diabetes complications and cardiovascular events have been well established and accepted by the medical community.[1-3] However, numerous studies have found that individuals, especially those with low socioeconomic status, fail to take these medications as prescribed.[7,8] Similar observations were made in a recent analysis of Medicare Part C & D performance data conducted by the Centers of Medicare and Medicaid Services (CMS). Specifically, low-income subsidy (LIS) recipients enrolled in Part D were found to be significantly less likely to achieve acceptable levels of adherence with these three classes of medications compared to non-LIS beneficiaries.[9,10]

We conducted a series of analyses to understand the factors influencing LIS recipients' utilization patterns with each drug class and observed striking variation in adherence rates across geographic regions. In this study, we evaluated the influence of external environmental factors on medication adherence for OHAs, statins, and RAS antagonists in a cohort of LIS recipients diagnosed with type 2 diabetes. Our work was driven by the goal of improving policymakers' understanding of the multilevel factors that influence medication adherence in poor populations. Such an understanding is critical to crafting effective policies to improve adherence to chronic medications in this vulnerable population.

Methods

We first developed county or hospital referral region (HRR) level indices to capture five external environmental domains hypothesized to affect LIS recipients' medication-taking behaviors. The five domains were socioeconomic environment, availability of healthcare resources, health culture, evidence-based medicine practice, and quality of primary care. We then evaluated how these domains, represented by the index scores, relate to individuals' medication adherence for OHAs, statins, and RAS antagonists in a cohort of LIS recipients.

Study Sample

The study population included LIS recipients with type 2 diabetes who were enrolled in CMS-assigned benchmark prescription drug plans (PDPs) in 2012. To ensure that LIS recipients have affordable prescription drug coverage, CMS randomly assigns those who do not voluntarily select a Part D plan to one of the benchmark PDPs in their region. Each year CMS also conducts re-assignments for those whose plan is terminating or no longer qualified as premium-free in the following year. LIS recipients may switch to a different plan of their choice any month in a year.[35,36] Our analysis showed that approximately 4.1 million or 35% of all LIS recipients were enrolled in a CMS-assigned plan in the beginning of 2012. We chose to focus the analysis exclusively on randomized LIS recipients as a means of minimizing selection bias and thus strengthening the internal validity of the study.

Eligible beneficiaries were also required to have been continuously enrolled in Medicare Part A, B & D and have received LIS throughout 2012. Beneficiaries who filled two or more prescriptions for insulin or stayed in inpatient facilities for ≥180 days in 2012 were excluded from the analysis, as were those who selected their own Part D plan.

Data Source

Individual-level data were drawn from a random 5% sample of Medicare beneficiaries in 2012 from the Chronic Conditions Data Warehouse (CCW).[42] The CCW files were linked to a customized dataset from CMS to ascertain beneficiaries' histories of plan assignments dating back to 2006. Variables included in the county/HRR-level indices for the five environmental domains of interest were taken from publicly available data; specifically, County Health Rankings & Roadmaps for county-level data on socioeconomic environment and health culture [55], the Area Health Resource Files for county-level estimates regarding availability of health care professionals [56], and the Dartmouth Atlas of Health Care data for information related to evidence-based medicine practice and quality of primary care at the HRR level. [57]

Measures

Medication adherence was determined based on proportion of days covered (PDC) by any medications in the drug class for OHAs, statins, and RAS antagonists, respectively. PDC was operationalized using the same methodology applied in the Medicare Star Ratings program for adherence measures.[39] Beneficiaries with a PDC ≥ 0.8 were considered adherent.[58]

The main independent variables were the five indices of environmental domains measured either at the county or HRR level depending on availability of data. Our choice of these five domains was based on existing literature. Prior research suggests that socioeconomic environment [59,60] and availability of healthcare resources [61,62] play a role in individuals' health services utilization. Building upon the work of Finkelstein et al. on the impact of clinical practice styles [26,27], we hypothesized that medication adherence would be higher in areas with greater adoption of evidence-based medicine practice. Lastly, adherence to OHAs, statins, and RAS antagonists can be perceived as a form of primary care in the sense that being adherent with these medications can help prevent diabetes complications and cardiovascular events. To explore this hypothesis, we included two constructs pertinent to primary care in the analysis, namely quality of primary care and health culture.

For the purpose of this study, we grouped plans from the same Part D sponsor and contract together into 17 "plans" and created a set of dummy variables for them. The plan-level variables were analyzed as fixed effects. In addition, we constructed three groups of covariates for beneficiary characteristics, including: 1) beneficiary demographics (age, gender, race/ethnicity, LIS subsidy level, and original reason for Medicare entitlement); 2) beneficiary comorbidities (hypertension, hyperlipidemia, chronic heart failure, chronic kidney disease, depression, and Charlson Comorbidity Index); and 3) beneficiary health services utilization (count of physician office visits, count of hospitalizations and emergency room (ER) visits).

Statistical analysis

The development of an index value for each environmental domain involved six steps: 1) selecting items that fit the underlying construct of the index; 2) reverse coding certain items so that higher values consistently represented more desirable outcomes across all items; 3) performing a principal component analysis of candidate items to obtain item loadings to the underlying construct; 4) dropping items that had a loading <0.3;[63] 5) estimating Cronbach's alpha to evaluate whether the remaining items were related to the same underlying construct and belonged together (i.e., examining internal consistency); and 6) dropping those items that degraded internal consistency.[64] Table 8 presents the data sources, geographic units, and specific items that were considered and ultimately selected for creating each index.

After an index was developed, index scores were assigned to geographic units (counties or HRRs), which were then categorized into quartile groups based on their designated index score. For example, counties whose index score for socioeconomic environment fell in the top 25 percentile of all counties were assigned to the highest or 1st quartile. Correspondingly, the same quartile designation was assigned to all study subjects who were residents of the county/HRR. We arrayed the quartile ranking for LIS recipients along the five environmental domains and by mean medication adherence rates for the three drug classes of interest. In addition, we estimated three linear probability models to evaluate the associations between the geographic unit level indices and adherence for the three medication classes while controlling for the plan- and beneficiary-level covariates. Although binary outcomes (adherent versus non-adherent) are often analyzed using logit or probit models in biomedical research, we opted for linear probability models because the interpretation of the modeling results is more appealing in a policy context. In contrast to odds ratios and relative risks which measure relative differences, the beta coefficients from a linear model estimate absolute differences, which are more meaningful in understanding the expected effect of a particular policy or program. In the instance of medication adherence, a beta coefficient estimate for a particular policy from a linear probability model can be directly interpreted as the expected change in adherence rate if the policy were to be implemented.

Limitations

This study has several important limitations. The development of indices for the five environmental domains was limited by the data available to us. There are undoubtedly other factors that may be important to medication use such as travel distance to a pharmacy and access to medication counseling, among others. The choice of geographic unit was also restricted by what was available. Socioeconomic environment may vary considerably from one part of a county to another, and thus assigning county-level measures to all individuals may have resulted in misclassification bias. Future research should consider measuring environment factors at more granular level (e.g., 5-digit Zip code level). In addition, like any other measures, construct validity of the index measures could not be readily evaluated. We selected candidate items for each index based on whether they conceptually fit the underlying construct, but admittedly, those decisions were subjective. Lastly, the scope of the study is limited to examining secondary non-adherence as unfilled prescriptions (primary nonadherence) are not captured in administrative claims.

Results

The specifications for the five environmental domains indices are presented in Table 8. The Cronbach's alpha of the selected items for evidence-based medicine domain was 0.67, slightly below the rule of thumb threshold of 0.7. The other four indices had a Cronbach's alpha above 0.8, indicating high internal consistency.

A total of 39,417 eligible beneficiaries were included in the study cohort (Table 9). The mean age was 66.3 years, 38.1% were males, 46.4% aged into Medicare, 55.6% were white, and over 98% received full LIS and paid only nominal copays for prescription medications. Coexisting conditions were common among the beneficiaries: 24.6% had chronic heart failure, 24.4% had chronic kidney disease, 25.9% had depression, 59.8% had hyperlipidemia, and 78.2% had hypertension. The mean Charlson Comorbidity Index count was 1.5. On average, the study subjects had 9.2 physician office visits, 0.5 hospitalizations, and 1.5 ER visits in 2012.

We identified 21,276 users of OHAs, 20,838 users of statins, and 22,143 users of RAS antagonists. Approximately half of the study cohort resided in counties in the lowest quartile (4th quartile) of socioeconomic environment domain, 63.1% in counties in the highest quartile (1st quartile) of availability of healthcare resources index, and 52.4% in counties in the highest quartile of health culture index. A total of 19.7% and 32.8% of the study cohort lived in HRRs in the lowest quartile of evidence-based medicine practice index and quality of primary care index, respectively (Table 9).

Table 8 Data Source and Items of County/HRR-Level Indexes (Chapter 6)

Table 8. Data Source and Items of County/HRR-Level Indexes

Index	Index Items	Loading	Cronbach's Alpha without the Item	Selected	Cronbach's Alpha of Selected Items
Socioeconomic Environment (CHR)	1. Percentage of population ages 16 and older unemployed but seeking work*	0.67	0.83	Yes	0.85
	2. Number of membership associations per 10,000 population	0.28	-	No	
	3. Percentage of children under age 18 in poverty*	0.91	0.80	Yes	
	4. Ratio of household income at the 80th percentile to income at the 20th percentile*	0.69	0.83	Yes	
	5. Percentage of children that live in a household headed by single parent*	0.81	0.81	Yes	
	6. Number of reported violent crime offenses per 100,000 population*	0.53	0.85	Yes	
	7. Number of deaths due to injury per 100,000 population*	0.34	0.86	Yes	
	8. Median household income	0.74	0.82	Yes	
	9. Percentage of households with at least 1 of 4 housing problems: overcrowding, high housing costs, or lack of kitchen or plumbing facilities	0.52	0.85	Yes	
	10. USDA index of factors that contribute to a healthy food environment	0.79	0.81	Yes	
Availability of Healthcare Resources (AHRF)	1. Number of doctors per 1000 population	0.95	0.83	Yes	0.87
	2. Number of primary care doctors per 1000 population	0.80	0.85	Yes	
	3. Number of specialists per 1000 population	0.92	0.83	Yes	
	4. Number of surgeons per 1000 population	0.92	0.83	Yes	
	5. Number of dentists per 1000 population	0.67	0.86	Yes	
	6. Number of physician assistants per 1000 population	0.55	0.87	Yes	
	7. Number of nurse practitioners per 1000 population	0.66	0.86	Yes	
	8. Number of physical therapists per 1000 population	0.36	0.88	Yes	
	9. Number of pharmacists per 1000 population	0.36	0.88	Yes	
Health Culture (CHR)	1. Percentage of adults aged 20 and over reporting no leisure-time physical activity*	0.86	0.68	Yes	0.84
	2. Percentage of population with adequate access to locations for physical activity	0.70	0.70	Yes	
	3. Number of newly diagnosed chlamydia cases per 100,000 population*	0.44	0.74	Yes	
	4. Teen birth rate per 1,000 female population, ages 15-19*	0.79	0.68	Yes	
	5. Percentage of adults that report a BMI of 30 or more*	0.81	0.67	Yes	
	6. Percentage of adults who are current smokers*	0.67	0.70	Yes	
	7. Percentage of adults reporting binge or heavy drinking*	-0.44	0.85	No	
	8. Percentage of driving deaths with alcohol involvement*	0.04	-	No	
	9. Number motor vehicle crash deaths per 1,000 deaths*	0.74	0.69	Yes	

Table 8. Data Source and Items of County/HRR-Level Indexes, CONTINUED

Index	Index Items	Loading	Cronbach's Alpha without the Item	Selected	Cronbach's Alpha of Selected Items
Evidence-Based Medicine Practice (DA)	1. Percent of patients filling beta-blocker prescription in the first 6 months following heart attack	0.47	0.65	Yes	0.67
	2. Percent of patients filling statin prescription in the first 6 months following heart attack	0.77	0.51	Yes	
	3. Percent of diabetic patients age 65-75 filling ACE-I or ARB prescription	0.41	0.67	No	
	4. Percent of diabetic patients age 65-75 filling statin prescription	0.77	0.50	Yes	
	5. Percent of beneficiaries filling at least one prescription for a high-risk medication*	0.74	0.55	Yes	
Quality of Primary Care (DA)	1. Average annual percent of Medicare enrollees having at least one ambulatory visit to a primary care clinician	0.38	0.78	No	0.84
	2. Average annual percent of diabetic Medicare enrollees age 65-75 having hemoglobin A1c test	0.87	0.63	Yes	
	3. Average annual percent of diabetic Medicare enrollees age 65-75 having eye examination	0.81	0.65	Yes	
	4. Average annual percent of diabetic Medicare enrollees age 65-75 having blood lipids (LDL-C) test	0.68	0.71	Yes	
	5. Average percent of female Medicare enrollees age 67-69 having at least one mammogram over a two-year period	0.88	0.62	Yes	
	6. Discharges for ambulatory care sensitive conditions per 1,000 Medicare enrollees*	0.32	0.79	No	

*reversed coded;

Table 9 Characteristics of Study Sample (Chapter 6)

Table 9. Characteristics of Study Sample (N=39,417)

	N (%) / Mean (Std Dev)
Individual Characteristics	
Age (years)	66.3 (14.6)
Male	15,023 (38.1%)
Old Age as Original Reason for Medicare Entitlement	18,279 (46.4%)
Race	
White	21,903 (55.6%)
Black	9,555 (24.2%)
Hispanic	3,525 (8.9%)
Other Race	4,189 (10.6%)
LIS Subsidy Level	
Full LIS, No Copay	6,909 (17.5%)
Full LIS, Low Copay ($1.1/3.3)	23,273 (59.0%)
Full LIS, High Copay ($2.6/6.5)	8,820 (22.4%)
Partial LIS, 15% Coinsurance	415 (1.1%)
Chronic Heart Failure	9,676 (24.6%)
Chronic Kidney Disease	9,635 (24.4%)
Depression	10,217 (25.9%)
Hyperlipidemia	23,567 (59.8%)
Hypertension	30,822 (78.2%)
Charlson Comorbidity Index	1.5 (1.5)
Count of Physician Office Visits	9.2 (9.0)
Count of Hospitalizations	0.5 (1.2)
Count of Emergency Room Visits	1.5 (4.8)
Geographic Factors	
Socioeconomic Environment	
1st quartile	6,004 (15.2%)
2nd quartile	7,179 (18.2%)
3rd quartile	8,861 (22.5%)
4th quartile (poorest)	16,852 (42.8%)
Availability of Healthcare Resources	
1st quartile	24,852 (63.1%)
2nd quartile	7,757 (19.7%)
3rd quartile	3,840 (9.7%)
4th quartile (poorest)	2,146 (5.4%)
Health Culture	
1st quartile	20,647 (52.4%)
2nd quartile	7,874 (20.0%)
3rd quartile	5,904 (15.0%)
4th quartile (poorest)	4,057 (10.3%)
Evidence-Based Medicine Practice	
1st quartile	10,616 (26.9%)
2nd quartile	9,255 (23.5%)
3rd quartile	11,791 (29.9%)
4th quartile (poorest)	7,755 (19.7%)
Quality of Primary Care Index	
1st quartile	7,825 (19.9%)
2nd quartile	10,071 (25.6%)
3rd quartile	8,581 (21.8%)
4th quartile (poorest)	12,940 (32.8%)

Table 10 Adherence Rate Stratified by Quartile of Index Scores (Chapter 6)

Table 10. Adherence Rate Stratified by Quartile of Index Scores

Geographic Factors	OHA (n=21,276)	STN (n=20,838)	RAS (n=22,143)
Socioeconomic Environment			
1st Quartile	76.5%	75.1%	77.0%
2nd Quartile	74.3%	71.8%	73.7%
3rd Quartile	70.5%	69.5%	70.5%
4th Quartile (poorest)	68.7%	67.0%	70.1%
Availability of Healthcare Resources			
1st Quartile	72.3%	70.2%	72.4%
2nd Quartile	69.9%	68.9%	71.2%
3rd Quartile	70.0%	68.6%	70.7%
4th Quartile (poorest)	70.4%	69.9%	71.8%
Health Culture			
1st Quartile	73.4%	70.9%	73.2%
2nd Quartile	70.6%	69.2%	71.5%
3rd Quartile	68.7%	68.0%	69.2%
4th Quartile (poorest)	67.7%	66.8%	69.4%
Evidence-Based Medicine Practice			
1st Quartile	75.7%	73.3%	75.1%
2nd Quartile	71.0%	68.9%	71.5%
3rd Quartile	70.5%	69.2%	71.5%
4th Quartile (poorest)	67.2%	66.1%	68.8%
Quality of Primary Care Index			
1st Quartile	73.6%	73.5%	74.9%
2nd Quartile	73.8%	70.7%	73.0%
3rd Quartile	69.4%	68.6%	69.4%
4th Quartile (poorest)	69.3%	67.1%	71.0%
Overall	71.3%	69.7%	71.9%

The overall adherence rates were 71.3%, 69.7%, and 71.9% for OHAs, statins, and RAS antagonists, respectively. Across the three drug classes, adherence rates were consistently lower among those residing in counties in the lowest quartile than in the highest quartile of the socioeconomic environment index (Table 10). Specifically, the adherence rates were 68.7% in the lowest quartile for OHAs vs. 76.5% in the highest quartile, 67.0% vs. 75.1% for statins, and 70.1% vs. 77.0% for RAS antagonists, respectively. Similar patterns were observed for the indices for health culture (67.7% vs. 73.4% for OHAs, 66.8% vs. 70.9% for statins, and 69.4% vs. 73.2% for RAS antagonists), evidence-based medicine (67.2% vs. 75.7% for OHAs, 66.1% vs. 73.3% for statins, and 68.8% vs. 75.1% for RAS antagonists), and quality of primary care

(69.3% vs. 73.6% for OHAs, 67.1% vs. 73.5% for statins, and 71.0% vs. 74.9% for RAS antagonists), whereas adherence rates appeared to be comparable across quartiles of the availability of healthcare resource index (range: 69.9%-72.3% for OHAs, 68.6%-70.2% for statins, 70.7%-72.4% for RAS antagonists).

After adjusting for the differences in Part D plan assignment and beneficiary characteristics, the likelihood of achieving medication adherence remained lower among beneficiaries residing in counties with low socioeconomic environment and HRRs with low quality of primary care than their counterparts (Table 11). Compared to beneficiaries residing in counties in the highest quartile of the socioeconomic environment domain, those in the lowest quartile were -3.5% (95% confidence interval (CI) = [-5.5%, -1.5%]) less likely to achieve a PDC≥0.8 for OHAs, -3.9% (95% CI= [-6.0%, -1.8%]) for statins, and -3.8% (95% CI= [-5.7%, -1.8%]) for RAS antagonists. Compared to beneficiaries living in HRRs in the 1st quartile of the quality of primary care domain, those in other quartiles were less likely to reach a PDC of 0.8 for statins: -4.2% (95% CI=[-6.3%, -2.1%]) for 4th quartile; -3.2% (95% CI=[-5.4%, -1.1%]) for 3rd quartile; and -2.7% (95% CI=[-4.6%, -0.8%]) for 2nd quartile. Those living in the 4th quartile and 3rd quartile also had -2.3% (95% CI=[-4.3%, -0.3%]) and -3.2% (95% CI=[-5.2%, -1.1%]) lower likelihoods of having a PDC≥0.8 for RAS antagonists than their counterparts residing in the highest quartile HRRs for quality of primary care. The other environmental factors, including availability of healthcare resource, health culture, and evidence-based medicine, were no longer predictive of beneficiaries' likelihood of reaching a PDC of 0.8, after controlling for differences in plan- and beneficiary-level covariates.

Table 11 Adjusted Effects of External Environmental Factors on Medication Adherence Rates (Chapter 6)

Table 11 Adjusted Effects of Environmental Factors on Medication Adherence Rates

	OHA				STN				RAS			
	Beta	**95% CI**		**p value**	**Beta**	**95% CI**		**p value**	**Beta**	**95% CI**		**p value**
Socioeconomic Environment Index												
1st Quartile	-	-	-	-	-	-	-	-	-	-	-	-
2nd Quartile	0.002	-0.019	0.023	0.864	-0.013	-0.035	0.009	0.235	-0.015	-0.036	0.007	0.175
3rd Quartile	**-0.028**	**-0.050**	**-0.007**	**0.009**	**-0.028**	**-0.050**	**-0.006**	**0.012**	**-0.044**	**-0.065**	**-0.023**	**<0.001**
4th Quartile	**-0.035**	**-0.055**	**-0.015**	**0.001**	**-0.039**	**-0.060**	**-0.018**	**<0.001**	**-0.038**	**-0.057**	**-0.018**	**<0.001**
Availability of Healthcare Resources Index												
1st Quartile	-	-	-	-	-	-	-	-	-	-	-	-
2nd Quartile	-0.016	-0.032	0.001	0.066	-0.004	-0.022	0.013	0.643	-0.011	-0.027	0.006	0.209
3rd Quartile	-0.003	-0.026	0.020	0.793	-0.010	-0.034	0.015	0.452	-0.013	-0.036	0.010	0.267
4th Quartile	0.012	-0.021	0.046	0.468	0.013	-0.023	0.048	0.481	-0.001	-0.035	0.032	0.936
Health Culture Index												
1st Quartile	-	-	-	-	-	-	-	-	-	-	-	-
2nd Quartile	-0.006	-0.023	0.012	0.535	0.004	-0.015	0.022	0.711	0.013	-0.004	0.031	0.143
3rd Quartile	-0.018	-0.039	0.004	0.104	-0.007	-0.029	0.016	0.549	-0.005	-0.026	0.017	0.670
4th Quartile	-0.014	-0.043	0.015	0.344	-0.012	-0.043	0.019	0.445	-0.005	-0.033	0.024	0.754
Evidence-Based Medicine Index												
1st Quartile	-	-	-	-	-	-	-	-	-	-	-	-
2nd Quartile	**-0.021**	**-0.040**	**-0.002**	**0.027**	-0.016	-0.035	0.003	0.106	-0.001	-0.020	0.017	0.883
3rd Quartile	-0.018	-0.037	0.001	0.067	-0.006	-0.026	0.014	0.547	-0.003	-0.022	0.016	0.738
4th Quartile	-0.020	-0.043	0.005	0.112	-0.013	-0.038	0.012	0.299	-0.009	-0.032	0.015	0.483
Quality of primary care Index												
1st Quartile	-	-	-	-	-	-	-	-	-	-	-	-
2nd Quartile	0.012	-0.007	0.031	0.209	**-0.027**	**-0.046**	**-0.008**	**0.005**	-0.015	-0.034	0.003	0.108
3rd Quartile	-0.001	-0.022	0.019	0.903	**-0.032**	**-0.054**	**-0.011**	**0.003**	**-0.032**	**-0.052**	**-0.011**	**0.002**
4th Quartile	-0.010	-0.030	0.010	0.337	**-0.042**	**-0.063**	**-0.021**	**<0.001**	**-0.023**	**-0.043**	**-0.003**	**0.024**

Discussion

An extensive body of prior research has examined the associations between medication adherence and various individual characteristics, but few studies have focused on the LIS population. LIS recipients represent about 30% of Part D enrollees yet account for a disproportionally high amount of Medicare program spending (nearly 70% of Part D spending in 2014).[11-13] All three medication classes evaluated in this study are recommended for most patients with type 2 diabetes as they provide long-term benefits in preventing or delaying complications and cardiovascular events.[1-3] Hence, ensuring LIS recipients' adherence to these medications provides promise for containing total health care expenditures of this high-spending population in the long run.

However, among the LIS recipients included in the analysis, the overall adherence rates were only 71.3% for OHAs, 69.7% for statins, and 71.9% for RAS antagonists, lower than the thresholds CMS set for two Stars in 2014 (73% for OHAs and RAS antagonists and 70% for statins).[39] But more importantly, adherence rates were consistently lower among LIS recipients residing in geographic areas that rank low in socioeconomic environment, health culture, evidence-based medicine practice, and quality of primary care. Those living in counties in the highest quartile of socioeconomic environment had adherence rates of 76.1% for OHAs, 75.1% for statins, and 77.0% for RAS antagonists, which were on par with Medicare population average rates in 2014.[39]

The relationships between LIS recipients' medication adherence and socioeconomic environment and quality of primary care persisted across the three medication classes even after adjusting for Part D plan effect and over a dozen covariates for beneficiary characteristics. This finding provides empirical support for the role of external environment in individuals' use of health services as described in Andersen's Behavioral Model of Health Services Use.[65] It illustrates that external environment itself can affect an individual's medication adherence separately from that person's own individual characteristics. This finding also has policy implications for designing effective programs to address LIS recipients' suboptimal medication adherence.

Currently, challenges exist in improving Medicare beneficiaries' medication adherence for chronic medications with extended time to benefit. The medication therapy management (MTM) program under Part D is intended to optimize beneficiaries' therapeutic outcomes through improved medication use and adherence. Unfortunately, the participation rate has been lower than expected since its initial launch in 2006 and questions have been raised regarding its effectiveness.[66,67] CMS recently announced a Part D Enhanced MTM model that will test whether providing Part D sponsors with additional payment incentives and regulatory flexibilities will enable enhancements to the Part D MTM program, leading to improvement in beneficiaries' medication and health outcomes.[68]

Earlier this year, the Medicare Payment Advisory Commission (MedPAC) proposed that Congress reduce or eliminate copays for generics and biosimilars for LIS recipients with the intention of encouraging use of lower cost drugs.[13] If implemented, this policy may have a spillover effect in increasing LIS recipients' medication adherence. However, the magnitude of the spillover effect would depend on the extent to which the current copays for generics (<=$2.95 for full subsidy recipients) pose access barriers to obtaining needed medications for LIS recipients.

Both the Part D Enhanced MTM program and MedPAC's proposal for reducing generic copays for LIS recipients are policy measures planned to be implemented uniformly across the country with the aim of modifying beneficiaries' behaviors. However, as evident from the findings of this study, the average adherence rates among LIS recipients residing in neighborhoods that rank high on socioeconomic environment and quality of primary care are comparable with the national average, while their counterparts who also have low income but live in poor areas with low quality of primary care are significantly less likely to achieve medication adherence. From a return to investment perspective, policy makers may consider more tailored interventions that specifically address the challenges and barriers faced by poor populations in selective low socioeconomic and quality of primary care areas. In addition to interventions aimed at modifying individuals' behaviors, eliminating nonadherence in low-income populations may also require changes in the surrounding external environment, such as improving social and economic wellbeing, increasing supply of health care resources, cultivating a health culture, and promoting practice of evidence-based medicine and primary care. These aspects of external environment are interrelated with one another, hence the payoff for improving one of those aspects is expected to be multiplicative.

Several strengths of this study are worth mentioning. Firstly, the study is methodologically innovative. Despite of thorough documentation of geographic variation in health services utilization in the literature, few studies have been able to explain the variation in utilization beyond differences in population characteristics between geographies.[26,49] Using publicly available data, we created geographic unit level indices that enabled us to explore the role of five environmental-level domains on adherence outcomes of a socioeconomically disadvantaged population. This opens up new venues for future research in further understanding sources of geographic variation in health services use, which could in turn provide directions in tailoring effective policies for improving efficiency of health care.

Secondly, it is well known that a small percent of the population accounts for the vast majority of the total health care expenditure in the United States.[69] Our work focused on LIS recipients, the highest spending demography in the Medicare program, among whom the needs for improving quality of care and reducing health care spending are the greatest. Our study showed that external factors such as socioeconomic environment and quality of primary care also affect LIS recipients' medication adherence in addition to their own characteristics. This finding indicates that multilevel factors are responsible for poor individuals' nonadherence for chronic medications. This insight is informative for designing future policies and interventions to improve quality and efficiency of care for this vulnerable population.

Chapter 7: Summary

This dissertation provides a comprehensive assessment of the respective impact of beneficiary characteristics, drug plan formulary policies, and external environmental factors on medication adherence in a low-income population. LIS recipients represent about 30% of Part D enrollees yet account for a disproportionally high amount of Medicare spending.[11-13] The adherence outcomes for OHAs, statins, and RAS antagonists are included as quality measures in the Medicare Star Ratings program. Adherence to these three classes of medications is recommended as they provide long-term benefits in preventing or delaying complications and cardiovascular events.[1-3] Improving LIS recipients' adherence to these medications holds promise for containing total health care expenditures of this high-spending population while improving quality of care in the long run.

Results from aim 1 indicated that the overall adherence rates were only 71.3% for OHAs, 69.7% for statins, and 71.9% for RAS antagonists among LIS recipients with diabetes in 2012. In the assessment of the overall impact of beneficiary characteristics, benchmark Part D plan, and PDP region, I found that all three domains can significantly influence LIS recipients' medication adherence. The observed relationships between beneficiary characteristics and medication adherence is consistent with the literature. Specifically, older age, male gender, use of multiple chronic medications were associated with higher medication adherence whereas Black race/Hispanic ethnicity, high comorbidity burden, and frequent hospitalizations and ER visits were inversely related to the adherence outcomes. These relationships represent the variation in utilization driven by differences in individuals' healthcare needs, and may be inappropriate to modify.

In contrast, the variation in medication adherence attributable to prescription drug plan policies or external environmental factors presents opportunities for improving quality and efficiency of care for poor populations. Community CCRx Basic Plan had significantly higher adherence rates than BravoRx and EnvisionRx Plus Silver Plan across all three drug classes of interest. Since the random plan assignment virtually removed selection bias, the estimated differences in adherence rates should represent unbiased plan effects. Results from aim 2 suggested that formulary restrictions on brand-name drugs only effectively shifted utilization towards generic drugs but had negligible impact on LIS recipients' overall adherence for OHAs, statins, and RAS antagonists. This dissertation did not examine other aspects of prescription drug plan policies (e.g., disease management program, quality of customer service, pharmacy network) due to data limitations. Further research is needed to understand the sources for the between-plan differences in adherence rates observed in aim 1. Knowledge may be drawn from plans with high adherence rates and disseminated to improve the experience of the Part D program for low-income beneficiaries and their adherence outcomes.

In addition, material geographic variation in adherence rates was observed where the northern regions appeared to have higher adherence rates than the southern regions. In aim 3, county and hospital referral region level indices for five external environmental domains were developed and assessed in relation to LIS recipients' medication adherence. Approximately half of the study cohort resided in counties in the lowest quartile of socioeconomic environment index in 2012. Even though everyone in the study sample had low income by definition (qualifying criterion for LIS), those living in areas with low socioeconomic environment and poor quality of primary care were less likely to achieve acceptable levels of medication adherence for OHAs, statins and RAS antagonists than their counterparts. This finding illustrates that external environment can affect individuals’ medication-taking behaviors, and calls for innovative programs to deliver tailored interventions that address the specific barriers faced by low-income individuals living in low socioeconomic areas.

As evident from the findings of this dissertation, medication adherence among low-income populations is affected by multiple sources of factors. The results from the attempts to understand plan- and environmental effects are encouraging. Continued research is needed to further understand the roles that prescription drug plan and external environment play in low income individuals’ utilization of medications. Such an understanding will inform future policies to improve medication adherence and health outcomes for low income populations.

Appendix

Table A1 Beneficiary Characteristics by Plan in PDP Region 3 (New York), n=3,553

Beneficiary Characteristics	BravoRx	CIGNA Medicare Rx Plan One	CVS Caremark Value	Community CCRx Basic	EnvisionRxPlus Silver	Medco Rx Plan Value	WellCare Classic	p-value
Age	68.9	68.5	69.9	70.1	68.9	67.9	65.9	**0.0049**
Male	199 (37.8%)	212 (36.2%)	140 (35.9%)	271 (33.6%)	99 (43.6%)	206 (38.6%)	49 (32.0%)	0.1888
Race								0.8496
White	262 (50.2%)	314 (54.1%)	214 (55.3%)	441 (55.2%)	114 (50.7%)	270 (51.2%)	77 (51.0%)	
Black	113 (21.7%)	124 (21.4%)	78 (20.2%)	169 (21.2%)	53 (23.6%)	111 (21.1%)	38 (25.2%)	
Hispanic	67 (12.8%)	59 (10.2%)	38 (9.8%)	75 (9.4%)	28 (12.4%)	59 (11.2%)	15 (9.9%)	
Other	80 (15.3%)	83 (14.3%)	57 (14.7%)	114 (14.3%)	30 (13.3%)	87 (16.5%)	21 (13.9%)	
LIS Subsidy Level								0.776
Full LIS/Zero copay	106 (20.2%)	123 (21.0%)	81 (20.1%)	176 (21.8%)	41 (18.1%)	123 (23.0%)	33 (21.6%)	
Full LIS/Low copay ($1.1/$3.3)	371 (70.5%)	408 (69.6%)	266 (68.2%)	573 (71.1%)	172 (75.8%)	367 (68.7%)	105 (68.6%)	
Full LIS/High copay ($2.6/$6.5) or Partial LIS/15% coinsurance	49 (9.3%)	55 (9.4%)	43 (14.1%)	57 (7.1%)	14 (6.2%)	44 (8.2%)	15 (9.8%)	
Old Age as Original Reason for Entitlement	296 (56.3%)	321 (54.8%)	228 (58.5%)	464 (57.6%)	134 (59.0%)	295 (55.2%)	82 (53.6%)	0.7535
Chronic Heart Failure	151 (28.7%)	158 (27.0%)	113 (29.0%)	227 (28.2%)	74 (32.6%)	147 (27.5%)	36 (23.5%)	0.7026
Chronic Kidney Disease	120 (22.8%)	109 (18.6%)	71 (18.2%)	190 (23.6%)	50 (22.0%)	120 (22.5%)	31 (20.3%)	0.3600
Depression	109 (20.7%)	137 (23.4%)	92 (23.6%)	198 (24.6%)	47 (20.7%)	130 (24.3%)	42 (27.5%)	0.5727
Hyperlipidemia	332 (63.1%)	393 (67.1%)	278 (71.3%)	527 (65.4%)	155 (68.3%)	350 (65.5%)	92 (60.1%)	0.1386
Hypertension	407 (77.4%)	450 (76.8%)	315 (80.8%)	620 (76.9%)	170 (74.9%)	429 (80.3%)	105 (68.6%)	0.0656
CCI	1.3	1.3	1.2	1.3	1.4	1.3	1.3	0.5337
# of Doctor Visits	12.1	11.4	12.9	12.5	11.0	11.9	10.8	0.2050
# of Hospitalizations	0.5	0.5	0.4	0.5	0.6	0.4	0.5	0.4048
# of ER Visits	1.1	0.8	1.1	0.9	1.1	0.8	0.7	0.5295

Table A2 Beneficiary Characteristics by Plan in PDP Region 22 (Texas), n=2,789

Beneficiary Characteristics	**Aetna CVS/pharmacy Rx Drug Plan**	**BravoRx**	**CIGNA Medicare Rx Plan One**	**Community CCRx Basic**	**EnvisionRx Plus Silver**	**First Health Part D Premier**	**HealthSpring Rx Drug Plan**	**WellCare Classic**	**p-value**
Age	70.4	65.1	66.6	67.8	67.3	66.6	66.5	67.6	**<0.0001**
Male	141 (36.1%)	93 (35.1%)	89 (36.0%)	125 (33.1%)	103 (38.3%)	151 (40.6%)	141 (39.1%)	126 (36.0%)	0.6111
Race									0.9568
White	217 (55.5%)	142 (54.0%)	130 (53.1%)	212 (56.2%)	128 (47.9%)	190 (51.1%)	194 (53.9%)	178 (51.6%)	
Black	64 (16.4%)	42 (16.0%)	43 (17.6%)	61 (16.2%)	55 (20.6%)	78 (21.0%)	71 (19.7%)	66 (19.1%)	
Hispanic	87 (22.3%)	63 (24.0%)	59 (24.1%)	84 (22.3%)	68 (25.5%)	80 (21.5%)	71 (19.7%)	74 (21.5%)	
Other	23 (5.9%)	16 (6.1%)	13 (5.3%)	20 (5.3%)	16 (6.0%)	24 (6.5%)	24 (6.7%)	27 (7.8%)	
LIS Subsidy Level									**0.0054**
Full LIS/Zero copay	57 (14.6%)	31 (11.7%)	31 (12.6%)	47 (12.4%)	40 (14.9%)	48 (12.9%)	53 (14.7%)	39 (11.1%)	
Full LIS/Low copay ($1.1/$3.3)	226 (57.8%)	137 (51.7%)	113 (45.8%)	209 (55.3%)	143 (53.2%)	183 (49.2%)	183 (50.7%)	191 (54.6%)	
Full LIS/High copay ($2.6/$6.5) or Partial LIS/15% coinsurance	108 (27.6%)	97 (36.6%)	103 (41.7%)	122 (32.3%)	86 (32.0%)	141 (37.9%)	125 (34.6%)	120 (34.3%)	
Old Age as Original Reason for Entitlement	234 (59.9%)	139 (52.5%)	131 (53.0%)	207 (54.8%)	150 (55.8%)	206 (55.4%)	205 (56.8%)	185 (52.9%)	0.7358
Chronic Heart Failure	114 (29.2%)	57 (21.5%)	67 (27.1%)	103 (27.3%)	78 (29.0%)	95 (25.5%)	106 (29.4%)	105 (30.0%)	0.3735
Chronic Kidney Disease	114 (29.2%)	69 (26.0%)	65 (26.3%)	115 (30.4%)	81 (30.1%)	90 (24.2%)	79 (21.9%)	80 (22.9%)	0.1226
Depression	97 (24.8%)	72 (27.2%)	67 (27.1%)	97 (25.7%)	72 (26.8%)	91 (24.5%)	100 (27.7%)	83 (23.7%)	0.7381
Hyperlipidemia	249 (63.7%)	165 (62.3%)	155 (62.8%)	242 (64.0%)	168 (62.5%)	223 (60.0%)	238 (65.9%)	229 (65.4%)	0.7080
Hypertension	332 (84.9%)	207 (78.1%)	207 (83.8%)	313 (82.8%)	221 (82.2%)	306 (82.3%)	293 (81.2%)	284 (81.1%)	0.3402
CCI	1.5	1.5	1.5	1.5	1.5	1.5	1.4	1.5	0.9285
# of Doctor Visits	9.9	9.1	9.2	9.6	9.1	9.1	9.0	9.1	0.7635
# of Hospitalizations	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.9992
# of ER Visits	1.4	1.6	1.5	1.3	1.3	1.7	1.3	1.3	0.6298

Table A3 Beneficiary Characteristics by Plan in PDP Region 32 (California), n=6,774

Beneficiary Characteristics	CVS Caremark Value	EnvisionRxPlus Silver	Health Net Orange Option 1	Humana Walmart-Preferred Rx Plan	WellCare Classic	p-value
Age	70.0	70.0	71.0	69.6	70.8	**0.0084**
Male	225 (42.9%)	244 (40.5%)	664 (43.5%)	642 (43.5%)	1,045 (41.8%)	0.2790
Race						0.2237
White	230 (44.1%)	275 (46.1%)	805 (48.4%)	652 (44.8%)	1,107 (44.5%)	
Black	40 (7.7%)	49 (8.2%)	157 (9.4%)	148 (10.2%)	257 (10.3%)	
Hispanic	112 (21.5%)	131 (21.9%)	302 (18.1%)	295 (20.3%)	510 (20.5%)	
Other	140 (26.8%)	142 (23.8%)	401 (24.1%)	362 (24.9%)	614 (24.7%)	
LIS Subsidy Level						0.3098
Full LIS/Zero copay	35 (6.7%)	57 (9.5%)	143 (8.6%)	140 (9.5%)	221 (8.8%)	
Full LIS/Low copay ($1.1/$3.3)	462 (88.0%)	509 (84.4%)	1,450 (86.9%)	1,278 (86.5%)	2,168 (86.7%)	
Full LIS/High copay ($2.6/$6.5) or Partial LIS/15% coinsurance	28 (5.3%)	37 (6.1%)	76 (4.6%)	59 (4.0%)	111 (4.4%)	
Old Age as Original Reason for Entitlement	341 (65.0%)	357 (59.2%)	997 (59.7%)	884 (59.9%)	1,511 (60.4%)	0.2485
Chronic Heart Failure	107 (20.4%)	159 (26.4%)	418 (25.0%)	339 (23.0%)	625 (25.0%)	0.0778
Chronic Kidney Disease	127 (24.2%)	169 (28.0%)	436 (26.1%)	366 (24.8%)	666 (26.6%)	0.4254
Depression	114 (21.7%)	122 (20.2%)	246 (20.7%)	261 (17.7%)	479 (19.2%)	0.1478
Hyperlipidemia	315 (60.0%)	348 (57.7%)	1,012 (60.6%)	900 (60.9%)	1,512 (60.5%)	0.7237
Hypertension	408 (77.7%)	469 (77.8%)	1,314 (78.7%)	1,147 (77.7%)	1,957 (78.3%)	0.9550
CCI	1.2	1.3	1.3	1.3	1.3	0.5946
# of Doctor visits	9.6	9.0	10.2	10.2	10.1	0.0667
# of Hospitalizations	0.4	0.4	0.4	0.4	0.4	0.7017
# of ER Visits	0.8	1.1	1.0	1.0	1.0	0.3520

Table A4 Distribution of Study Subjects by PDP Region

PDP Region	Region Name	OHA Cohort, n=28,082		Statin Cohort, n=53,864		RAS Antagonist Cohort, n=57,289	
		#	%	#	%	#	%
1	**Northern New England (New Hampshire[1] and Maine[3])**	89	0.32	223	0.41	192	0.34
2	**Central New England (Connecticut[1], Massachusetts[3], Rhode Island[2], and Vermont[2])**	1482	5.28	3218	5.97	2865	5.00
3	**New York[3]**	2251	8.02	4504	8.36	4421	7.72
4	**New Jersey[2]**	543	1.93	1055	1.96	1095	1.91
5	**Mid-Atlantic (Delaware[1], District of Columbia[1] and Maryland[1])**	589	2.1	1154	2.14	1271	2.22
6	**Pennsylvania[1], West Virginia[2]**	1100	3.92	2239	4.16	2196	3.83
7	**Virginia[1]**	661	2.35	1420	2.64	1473	2.57
8	**North Carolina[1]**	1322	4.71	2641	4.90	2869	5.01
9	**South Carolina[1]**	528	1.88	1176	2.18	1311	2.29
10	**Georgia[1]**	687	2.45	1372	2.55	1649	2.88
11	**Florida[2]**	500	1.78	1055	1.96	1159	2.02
12	**Alabama[1], Tennessee[2]**	1192	4.24	2236	4.15	2604	4.55
13	**Michigan[1]**	1245	4.43	2607	4.84	2593	4.53
14	**Ohio[1]**	1054	3.75	1992	3.70	2011	3.51
15	**Indiana[1], Kentucky[2]**	1267	4.51	2578	4.79	2726	4.76
16	**Wisconsin[1]**	595	2.12	1220	2.26	1165	2.03
17	**Illinois[1]**	1389	4.95	2418	4.49	2570	4.49
18	**Missouri[1]**	343	1.22	672	1.25	746	1.30
19	**Arkansas[1]**	293	1.04	496	0.92	657	1.15
20	**Mississippi[1]**	796	2.83	1346	2.50	1702	2.97
21	**Louisiana[1]**	600	2.14	1078	2.00	1334	2.33
22	**Texas[1]**	1849	6.58	3147	5.84	3551	6.20
23	**Oklahoma[1]**	337	1.20	591	1.10	716	1.25
24	**Kansas[1]**	250	0.89	443	0.82	484	0.84
25	**Upper Midwest and Northern Plains (Iowa[1], Minnesota[2], Montana[1], Nebraska[1], North Dakota[1], South Dakota[1] and Wyoming[1])**	835	2.97	1840	3.42	1759	3.07
26	**New Mexico[1]**	167	0.59	232	0.43	288	0.50
27	**Colorado[1]**	180	0.64	301	0.56	348	0.61
28	**Arizona[1]**	204	0.73	270	0.50	372	0.65
29	**Nevada[2]**	149	0.53	241	0.45	294	0.51
30	**Oregon[1], Washington[2]**	776	2.76	1537	2.85	1556	2.72
31	**Idaho[1], Utah[1]**	168	0.60	288	0.53	315	0.55
32	**California[1]**	4548	16.2	8078	15.00	8756	15.28
33	**Hawaii[2]**	40	0.14	77	0.14	85	0.15
34	**Alaska[1]**	53	0.19	119	0.22	156	0.27

State generic substitution law: 1-Allows for generic substitution by pharmacists if "brand only" not indicated by physician; 2-Mandates generic substitution by pharmacists if "brand only" not indicated by physician and allows for brand if requested by patient; 3- Mandates generic substitution by pharmacists if "brand only" not indicated by physician and only allows for brand if requested by prescriber;

Table A5 Effects of Beneficiary Characteristics, Benchmark Part D Plans, and PDP Regions on the Likelihoods of Adherence to OHAs, Statins, and RAS Antagonists

	OHAs				Statins				RAS Antagonists			
	Estimate	95% CI		p-value	Estimate	95% CI		p-value	Estimate	95% CI		p-value
Age	**0.003**	**0.003**	**0.004**	**<.0001**	**0.003**	**0.002**	**0.004**	**<.0001**	**0.004**	**0.003**	**0.004**	**<.0001**
Male	**0.019**	**0.006**	**0.031**	**0.004**	**0.029**	**0.016**	**0.042**	**<.0001**	-0.002	-0.015	0.010	0.724
Old Age as Original Reason for Entitlement	**-0.017**	**-0.033**	**0.000**	**0.048**	-0.012	-0.029	0.005	0.175	-0.009	-0.025	0.007	0.285
Race (Ref: White)												
Black	**-0.101**	**-0.117**	**-0.086**	**<.0001**	**-0.105**	**-0.121**	**-0.088**	**<.0001**	**-0.074**	**-0.089**	**-0.059**	**<.0001**
Hispanic	**-0.096**	**-0.118**	**-0.075**	**<.0001**	**-0.138**	**-0.161**	**-0.114**	**<.0001**	**-0.088**	**-0.109**	**-0.066**	**<.0001**
Other Race	-0.010	-0.030	0.011	0.358	**-0.022**	**-0.043**	**-0.001**	**0.043**	-0.014	-0.035	0.006	0.162
LIS Subsidy Level (Ref: Full LIS, No Copay)												
Full LIS, Low Copay	**-0.115**	**-0.136**	**-0.094**	**<.0001**	**-0.113**	**-0.135**	**-0.092**	**<.0001**	**-0.085**	**-0.106**	**-0.065**	**<.0001**
Full LIS, High Copay	**-0.101**	**-0.119**	**-0.082**	**<.0001**	**-0.103**	**-0.121**	**-0.085**	**<.0001**	**-0.082**	**-0.100**	**-0.065**	**<.0001**
Partial LIS, 15% Coinsurance	**-0.097**	**-0.158**	**-0.036**	**0.002**	**-0.088**	**-0.154**	**-0.022**	**0.009**	-0.039	-0.097	0.019	0.187
Chronic Heart Failure	**-0.051**	**-0.067**	**-0.034**	**<.0001**	-0.016	-0.032	0.001	0.059	**-0.039**	**-0.054**	**-0.024**	**<.0001**
Chronic Kidney Disease	0.002	-0.014	0.018	0.786	0.014	-0.002	0.029	0.089	**-0.029**	**-0.044**	**-0.015**	**<.0001**
Depression	**-0.057**	**-0.072**	**-0.042**	**<.0001**	**-0.025**	**-0.040**	**-0.009**	**0.002**	**-0.047**	**-0.061**	**-0.032**	**<.0001**
Hyperlipidemia	**0.044**	**0.030**	**0.057**	**<.0001**	**0.016**	**0.001**	**0.032**	**0.041**	**0.030**	**0.017**	**0.043**	**<.0001**
Hypertension	0.003	-0.013	0.020	0.681	0.004	-0.014	0.022	0.660	0.018	-0.002	0.038	0.074
Charlson Comorbidity Index	**-0.010**	**-0.015**	**-0.004**	**0.001**	**-0.011**	**-0.016**	**-0.005**	**<.0001**	**-0.012**	**-0.017**	**-0.007**	**<.0001**
Count of Other Chronic Medications	**0.020**	**0.018**	**0.022**	**<.0001**	**0.017**	**0.015**	**0.019**	**<.0001**	**0.018**	**0.017**	**0.020**	**<.0001**
Count of Physician Office Visits	0.001	0.000	0.001	0.173	0.000	-0.001	0.001	0.694	0.000	-0.001	0.000	0.395
Count of Hospitalizations	**-0.017**	**-0.024**	**-0.009**	**<.0001**	**-0.012**	**-0.018**	**-0.005**	**0.001**	**-0.021**	**-0.027**	**-0.015**	**<.0001**
Count of ER Visits	**-0.009**	**-0.011**	**-0.007**	**<.0001**	**-0.007**	**-0.009**	**-0.005**	**<.0001**	**-0.007**	**-0.008**	**-0.005**	**<.0001**

Table A5 Effects of Beneficiary Characteristics, Benchmark Part D Plans, and PDP Regions on the Likelihoods of Adherence to OHAs, Statins, and RAS Antagonists, CONTINUED

	OHAs				Statins				RAS Antagonists			
	Estimate	95% CI		p-value	Estimate	95% CI		p-value	Estimate	95% CI		p-value
Benchmark Part D Plan (Ref: Community CCRx Basic)												
AARP MedicareRx Preferred	0.054	-0.046	0.154	0.291	0.049	-0.049	0.148	0.326	0.088	-0.006	0.182	0.067
Aetna CVS/pharmacy Prescription Drug Plan	-0.009	-0.042	0.025	0.615	0.002	-0.032	0.037	0.893	0.000	-0.032	0.033	0.984
Blue MedicareRx Standard	**-0.145**	**-0.265**	**-0.026**	**0.017**	0.028	-0.096	0.152	0.660	-0.095	-0.210	0.019	0.102
BravoRx	**-0.053**	**-0.092**	**-0.015**	**0.007**	-0.013	-0.053	0.027	0.520	**-0.047**	**-0.085**	**-0.009**	**0.015**
CIGNA Medicare Rx Plan One	-0.007	-0.034	0.020	0.619	0.017	-0.011	0.045	0.233	0.007	-0.019	0.034	0.595
CVS Caremark Value	-0.025	-0.050	0.001	0.063	0.006	-0.021	0.033	0.668	-0.011	-0.037	0.014	0.395
EnvisionRxPlus Silver	**-0.076**	**-0.107**	**-0.046**	**<.0001**	**-0.037**	**-0.068**	**-0.006**	**0.018**	**-0.060**	**-0.089**	**-0.031**	**<.0001**
First Health Part D Premier	-0.024	-0.052	0.004	0.087	-0.001	-0.030	0.028	0.924	-0.015	-0.042	0.013	0.301
Health Net Orange Option 1	-0.031	-0.064	0.002	0.064	0.009	-0.026	0.043	0.625	-0.012	-0.045	0.020	0.466
HealthSpring Prescription Drug Plan	-0.006	-0.033	0.021	0.652	0.013	-0.015	0.041	0.361	-0.016	-0.042	0.011	0.244
Humana Walmart-Preferred Rx Plan	**-0.042**	**-0.067**	**-0.016**	**0.002**	0.004	-0.023	0.031	0.764	-0.022	-0.048	0.003	0.084
Medco Medicare Prescription Plan - Value	-0.016	-0.045	0.014	0.309	0.003	-0.028	0.034	0.834	-0.011	-0.041	0.018	0.450
MedicareRx Rewards Standard	-0.046	-0.115	0.023	0.191	-0.004	-0.078	0.071	0.922	0.011	-0.055	0.078	0.740
United American - Select	0.004	-0.040	0.048	0.860	0.022	-0.024	0.068	0.343	-0.007	-0.050	0.036	0.748
WellCare Classic	-0.016	-0.045	0.013	0.270	0.011	-0.019	0.041	0.481	0.009	-0.019	0.038	0.515
Windsor Rx	-0.011	-0.064	0.042	0.689	0.000	-0.056	0.057	0.993	0.036	-0.018	0.089	0.192
PDP Region (Ref: Region 32 (CA))*												
Region 2 (CT, MA, RI, VT)	**0.038**	**0.005**	**0.070**	**0.025**	**0.050**	**0.017**	**0.084**	**0.003**	**0.038**	**0.005**	**0.071**	**0.025**
Region 7 (VA)	0.036	-0.006	0.079	0.091	0.022	-0.022	0.066	0.331	**0.044**	**0.003**	**0.085**	**0.037**
Region 10 (GA)	-0.029	-0.073	0.015	0.202	-0.020	-0.067	0.027	0.406	**-0.070**	**-0.113**	**-0.026**	**0.002**
Region 12 (AL, TN)	**-0.071**	**-0.109**	**-0.034**	**0.001**	-0.005	-0.045	0.035	0.801	-0.005	-0.042	0.032	0.799
Region 13 (MI)	0.032	-0.004	0.068	0.085	**0.048**	**0.012**	**0.084**	**0.010**	**0.039**	**0.005**	**0.074**	**0.026**
Region 16 (WI)	0.027	-0.019	0.073	0.244	**0.074**	**0.026**	**0.123**	**0.002**	0.035	-0.013	0.082	0.150
Region 25 (IA, MN, MT, NE, ND, SD, WY)	0.035	-0.006	0.077	0.093	**0.071**	**0.026**	**0.115**	**0.002**	-0.005	-0.048	0.038	0.817
Region 28 (AZ)	**-0.155**	**-0.229**	**-0.081**	**<.0001**	**-0.157**	**-0.241**	**-0.072**	**0.001**	**-0.127**	**-0.201**	**-0.054**	**0.001**
Region 33 (HI)	**-0.194**	**-0.355**	**-0.032**	**0.019**	**-0.201**	**-0.358**	**-0.043**	**0.012**	-0.109	-0.262	0.044	0.163

*Only regions with statistically significant estimates are shown;

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