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RESEARCH ARTICLE

Effect of Out-of-Pocket Cost on Medication Initiation, Adherence, and Persistence among Patients with Type 2 Diabetes: The Diabetes Study of Northern California (DISTANCE)

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Objective. To estimate the effect of out-of-pocket (OOP) cost on nonadherence to classes of cardiometabolic medications among patients with diabetes.

Data Sources/Setting. Electronic health records from a large, health care delivery system for 223,730 patients with diabetes prescribed 842,899 new cardiometabolic medications during 2006–2012.

Study Design. Observational, new prescription cohort study of the effect of OOP cost on medication initiation and adherence.

Data Collection. Adherence and OOP costs were based on pharmacy dispensing records and benefits.

Principal Findings. Primary nonadherence (never dispensed) increased monotonically with OOP cost after adjusting for demographics, neighborhood socioeconomic status, Medicare, medical financial assistance, OOP maximum, deductibles, mail order pharmacy incentive and use, drug type, generic or brand, day's supply, and comorbidity index; 7 percent were never dispensed the new medication when OOP cost ≥$11, 5 percent with OOP cost of $1–$10, and 3 percent when the medication was free of charge ($p < .0001$). Higher OOP cost was also strongly associated with inadequate secondary adherence (≥20 percent of time without adequate medication). There was no clinically significant or consistent relationship between OOP costs and early nonpersistence (dispensed once, never refilled) or later stage nonpersistence (discontinued within 24 months).

Conclusions. Cost-sharing may deter clinically vulnerable patients from initiating essential medications, undermining adherence and risk factor control.

Key Words. Adherence, medical expenditures, pharmacy benefits, out-of-pocket costs

As a strategy to control expenditures and excessive use of services, insurers and health care delivery systems typically require patients to bear an out-of-pocket (OOP) cost (in the form of copayments, coinsurance, or deductibles) for prescribed medications (Goldman et al. 2007; Eaddy et al. 2012; Mann et al. 2014). While cost-sharing may reduce unnecessary utilization, it can unintentionally worsen adherence to medically necessary treatments (Mojtabai and Olfson 2003; Gibson et al. 2005; Briesacher et al. 2007; Goldman et al. 2007; Eaddy et al. 2012; Simoens and Sinnaeve 2014) and negatively impact outcomes of care (Gibson et al. 2005).

Systematic reviews have found that the association between patient OOP costs and chronic disease medication adherence varies greatly across studies (Clarke et al. 1988; Mann et al. 2014), ranging from no or mixed effects (Pilote et al. 2002) to a significant inverse relationship (Keeler and Rolph 1988; i.e., higher OOP costs are associated with poorer adherence). While the bulk of evidence suggests that patients' use of medicine is price-sensitive, adherence is also influenced by myriad noncost factors (Piette and Wagner 2006; Bosworth et al. 2011; Kirkman et al. 2015), including age, education, income (Berkowitz et al. 2014), health literacy (Bauer et al. 2013), depression (Katon et al. 2009), beliefs about clinical benefits or side effects (Piette et al. 2011), attitudes toward medications (Rosenbaum 2015), previous medication use (Solomon et al. 2009), medication type (preventive vs. symptomatic treatments; Piette et al. 2006), medication class (Gatwood et al. 2014), clinician factors (provider type, prescribing preferences, communication; Ratanawongsa et al. 2013; Riggs and Ubel 2014), and structural health system factors (e.g., mail order pharmacy; Duru et al. 2010).

Most studies of OOP cost and adherence have been based on lagged cross-sectional evaluations of select stages of medication-taking, typically secondary adherence (i.e., adherence for ongoing use of medications), or

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sometimes initiation (McCoy, Lipska et al. 2016) or discontinuation (Bright, Kaiser et al. 1983). In this paper, we describe how OOP cost impacts four distinct measures of medication initiation, adherence and persistence in 842,899 new prescriptions written for 223,730 patients with diabetes from a large, integrated health care delivery system (Kaiser Permanente Northern California). We follow participants from the point they were prescribed a new cardiometabolic medication for glucose control, dyslipidemia, or hypertension.

METHODS

Cohort Construction

We identified 260,414 patients with diabetes from the Kaiser Permanente Northern California (KPNC) Diabetes Registry who had a prescribing order ("index prescription") in the electronic health record for a glucose-, lipid- or blood pressure–lowering (cardiometabolic) therapy with a prescribing date ("index date") during January 1, 2006–June 30, 2012. Each index prescription was eligible to be in this "new prescription cohort" (Karter et al. 2009) if there was no evidence of dispensing during the 24 months prior to the index date and the patient had active membership and pharmacy benefits during that time. Adherence was based on pharmacy dispensings for each index prescription during the 24 months after the index date. To minimize the impact of missing data on medications dispensed outside the KPNC system, we excluded 36,684 patients (14 percent) who had >2 months of gap in coverage. We studied a final cohort that included 223,730 patients and their total of 842,899 new prescriptions. This study was approved by the Institutional Review Board of Kaiser Permanente.

Outcomes

We calculated four validated adherence measures (Steiner et al. 1988; Karter et al. 2009; Raebel et al. 2013; Parker et al. 2015) using pharmacy dispensing data: primary nonadherence, early-stage nonpersistence, later stage nonpersistence, and inadequate secondary adherence. Primary nonadherence: newly prescribed (index) medication not dispensed at 60 days after the index date (i.e., the date the prescription was written). Early-stage nonpersistence: index medication dispensed once but never refilled within the period defined by the days' supply in the first dispensing plus a 90-day grace

period. Later stage nonpersistence: index medication dispensed at least twice, but discontinued before 24 months (i.e., no additional dispensing within 90 days of end of days' supply of previous dispensings and before the end of the 24-month observation window). Secondary adherence was based on continuous mediation gaps (CMG), a validated, continuous measure of adherence (Steiner et al. 1988). CMG measures the percentage of time without adequate medication supply among ongoing users after the initial dispensing of oral agents. CMG accounts for stockpiled medications using a time-forward algorithm, summing the proportion of days without sufficient medication supply across refill intervals between the first and last pharmacy dispensings during the 24-month observation window. For participants taking more than one new medication, a summary measure was created using a time-weighted averaging of CMG for each therapeutic class. Because flexible insulin dosing prohibits identification of the days' supply, we excluded insulin from CMG calculations. Following convention, CMG was categorized into a binary measure of "adequate" (CMG<20 percent) versus "inadequate" secondary adherence (CMG ≥20 percent). In each of the above measures other than primary nonadherence, follow-up was censored at the end of follow-up (24 months after the index date), or if the medication was discontinued for reasons other than adherence behavior (e.g., the physician switched the patient to alternative medication or issued a stop order for the medication).

Exposures

We determined OOP cost from the amount paid at the point of dispensing (based on the KPNC electronic pharmacy records). If the medicine was prescribed, but never dispensed (i.e., primary nonadherence), we used the OOP cost that would have been charged if the prescription had been dispensed based on the patient's KPNC pharmacy benefit plan at the time of the prescription order.

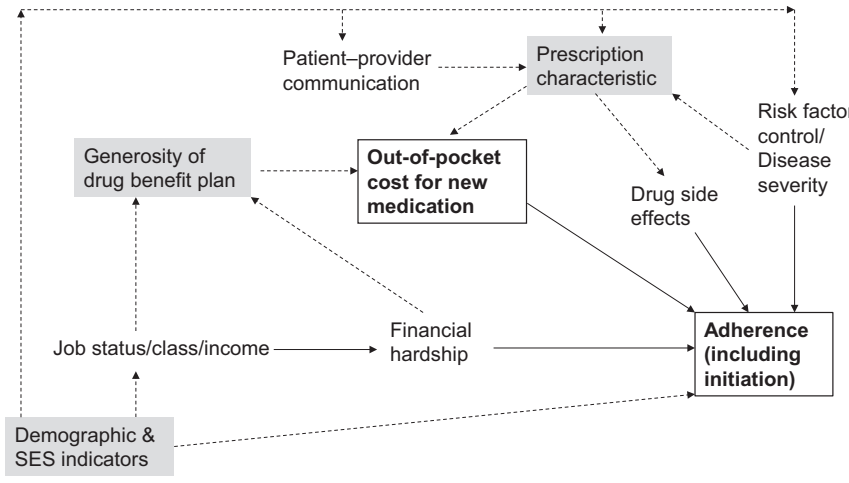
For the analysis of early nonpersistence and later stage nonpersistence, we used the OOP cost of the last dispensing. OOP cost was categorized as $0 (reference), $1–$5, $6–$10, $11–$19, and ≥$20 (i.e., quartiles of nonzero OOP cost). Given the difficulties in accounting for behavioral changes in response to OOP cost variations over time when studying longer term, secondary adherence, we restricted our analysis of inadequate secondary adherence to the subset of participants (66 percent or 147,194 of the 223,730) whose OOP cost remained constant during the follow-up window.

Statistical Analysis

We specified modified Poisson and least-squares regression models to estimate unadjusted (crude) associations between OOP cost and the binary medication adherence outcome (i.e., adequate vs. inadequate adherence), defining participants with $0 OOP cost as the reference group. We used these models to calculate the adjusted predicted probabilities (PP), risk ratio (RR; Zou 2004), and risk difference (RD; Cheung 2007). We used a hierarchical model structure to adjust the variance for the within-person clustering because some participants had multiple new prescriptions. Confidence intervals were calculated using robust standard errors.

We constructed a causal directed acyclic graph (DAG) based on our interpretation of a review of the literature and hypothesized effect of OOP cost on medication adherence (see Figure 1; Greenland et al. 1999). DAGs graphically illustrate assumptions regarding the causal relationships (depicted as arrows) between measured or unmeasured variables (nodes) linking OOP cost to adherence, and we provide guidance for adjustment of standard regression models (Greenland et al. 1999) and avoiding drawing incorrect causal inferences. We also hypothesized that the strength of the cost-related medication underuse (based on the OOP cost–adherence

Figure 1: Directed Acyclic Graph (DAG) Graphically Illustrating Assumptions Regarding the Causal Relationships (Depicted as Arrows) between Measured or Unmeasured Variables (Nodes) That Ultimately Link OOP Cost to Adherence



relationship) may be modified by demographics, socioeconomic status, total number of medications used, total OOP cost for all medications combined, or type of index medication. We therefore specified additional models with interaction terms to test whether the main effect relationship differed by these potential effect modifiers. All statistical analyses were performed using *SAS* software, version 9.3 (SAS Institute Inc., Cary, NC, USA).

Covariate Measurement

We specified multivariate models adjusting for demographics (age, sex, race/ethnicity) and socioeconomic status (SES), generosity of pharmacy benefit plan, and index prescription characteristics, which we obtained from KPNC administrative data. SES was categorized by the neighborhood deprivation index (Messer et al. 2006), a validated characterization of neighborhood-level deprivation based on a linkage of a participant's residence address to SES indicators from the 2010 American Community Survey. Adjustment for plan generosity was based on whether OOP cost was based on a fixed copayment or coinsurance, the amount of any pharmacy deductible, whether there was a financial incentive (discount) to use mail order dispensing, out-of-pocket limits, and enrollment in a medical financial assistance plan or enrollment in Medicare Advantage Part D. Index prescription characteristics included the index medication's indication (antihypertensive, lipid-lowering, or glucose-lowering), therapeutic class, days' supply dispensed, brand versus generic, and inclusion in the KPNC pharmacy formulary. We also categorized dispensings as picked up from the pharmacy or via mail order. We characterized risk factor control and disease severity by including covariates for diabetes duration (time since diabetes diagnosis), Charlson comorbidity score (Charlson et al. 1994), and a validated (Katon et al. 2012) indicator for depression based on use of antidepressants or an outpatient diagnosis of depression. Total number of medications used and quartile of total annual OOP cost for chronically used medications ("prebaseline annual OOP cost") were extrapolated from the dispensings during the 6 months prior to the index date.

RESULTS

Our cohort included 223,730 adult patients with diabetes who were prescribed any new cardiometabolic therapy during a 7.5-year observation window (January 1, 2006, to June 30, 2012); 70, 67, and 70 percent of patients

were prescribed one or more new glucose-, lipid-, or blood pressure-lowering medications, respectively (Table 1) for a total of 842,899 new prescriptions. Thirty-three percent of the participants were Medicare members, 41 percent had a mail order pharmacy incentive, and 97 percent had some limit on total prebaseline annual OOP expenses. At the beginning of this study (2006), few had a deductible (0.5 percent) or received medical financial assistance (0.3 percent). The mean number of all unique medications dispensed during the 6 months prior to the index date was 4.7; the mean and median total prebaseline annual OOP expenses for those medications was $215.40 and $127.32, respectively.

There was more than a doubling (RR = 2.04) in the risk of primary nonadherence among patients whose OOP cost was ≥$20 per dispensing relative to those whose OOP cost was $0 (7 versus 3 percent predicted probability; $p < .0001$; Figure 2 and Table S1 in Appendix SA2). Higher OOP costs were also associated with early nonpersistence (i.e., never refilling); the effect was statistically significant, but not substantive; 20 percent never refilled among those paying $6 or more, compared to 19 percent among those paying $1–$5 and 18 percent among those paying $0. There was no consistent or substantive difference in later stage nonpersistence (i.e., discontinuing medication after the first refill) across categories of OOP cost.

The predictive probability of inadequate secondary adherence (CMG >20 percent) over the 24 months following a new prescription was also associated with OOP cost. Inadequate secondary adherence (CMG ≥20 percent) was 32 percent as for $0; 35 percent for $1–$5; 36 percent for $6–$10; 38 percent for $11–$19; and 39 percent for ≥$20. After adjustment, there was ~6 percent greater risk of inadequate secondary adherence for those paying $20 or more for their medications relative to no cost. In a sensitivity analysis, we further evaluated models that adjusted for Charlson comorbidity index even though it was not indicated by our DAG analysis; the results were essentially unchanged.

The strength of the observed associations differed in a statistically significant manner (i.e., effect modification) across several demographic (age, sex, race/ethnicity), socioeconomic (living in an economically deprived neighborhood), and medication burden-related factors (number of and total OOP cost for ongoing medications). However, only select relationships differed in a clinically substantive way. Similar to previous reports, younger patients tended to have poorer adherence. The relationship between OOP cost and primary nonadherence was markedly stronger ($p < .0001$ for interaction) among younger patients and attenuated among older patients (Figure 3). These age

Table 1: Baseline Characteristics for the 223,730 Diabetes Subjects[†]

Characteristic	*N (%) or Mean (SD)*
Type of index therapy	
Glucose-lowering medications	157,724 (70)
Lipid-lowering medication	150,278 (67)
Blood pressure-lowering medications	157,382 (70)
Sex	
Women	105,403 (47)
Men	118,327 (53)
Age	
≤40 years	25,272 (15)
41–50 years	40,976 (25)
51–60 years	49,781 (30)
≥61 years	49,696 (30)
Mean age (SD)	58.1 (13.3)
Race/ethnicity	
Non-Hispanic white	101,835 (48)
African American	22,392 (11)
Latino	34,242 (16)
Native American	1,503 (1)
Pacific Islander	1,925 (1)
Asian	39,463 (19)
Other	106 (0)
Mixed race/ethnicity	10,866 (5)
Standardized neighborhood deprivation index	
1st Quartile—Least deprived	46,108 (21)
2nd Quartile	61,683 (28)
3rd Quartile	64,304 (29)
4th Quartile—Most deprived	47,873 (22)
Mean Charlson score (SD)	2.1 (1.6)
Mean time since diabetes diagnosis (years; SD)	7.0 (8.3)
Depression	38,429 (17)
Medicare	74,754 (33)
Prescription drug plan characteristics include the following	
Mail order incentive	92,504 (41)
Out of pocket maximum	216246 (97)
Benefit deductible	1,054 (0.5)
Medical financial assistance	586 (0.3)
Total medication utilization and average annual out-of-pocket cost	4.7 (3.3)
Total number of prescription drugs prior to baseline, Mean (SD)	$215.40 ($302.16),
Average annual prebaseline OOP medication expenses for prescription drugs, Mean (SD), Median, [IQR]	$127.32 [$40.00, $280.00]

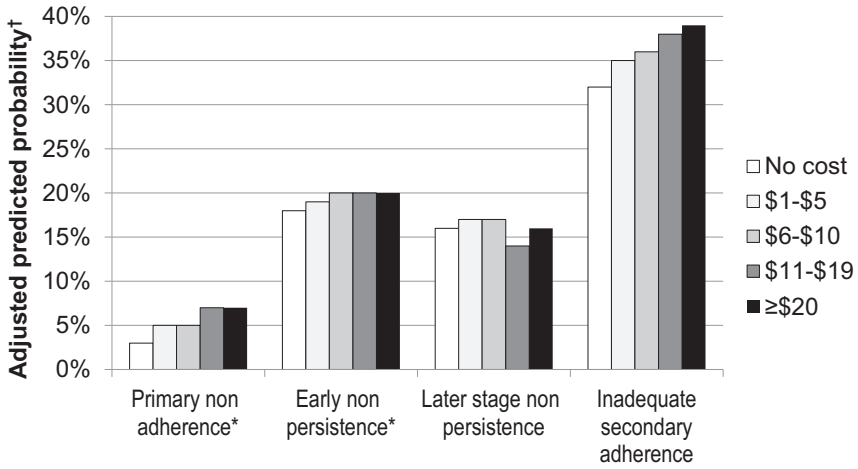
continued

Table 1. *Continued*

Characteristic	*N (%) or Mean (SD)*
Medication copayment or coinsurance for the index prescription	
Free of charge	14,963 (7)
$1–$5	57,358 (26)
$6–$10	69,961 (31)
$11–$19	32,092 (14)
$20 or more	49,356 (22)

[†]Missing data for race/ethnicity (n = 11,398), duration of diabetes (n = 58,005), and neighborhood deprivation index (n = 3,762).

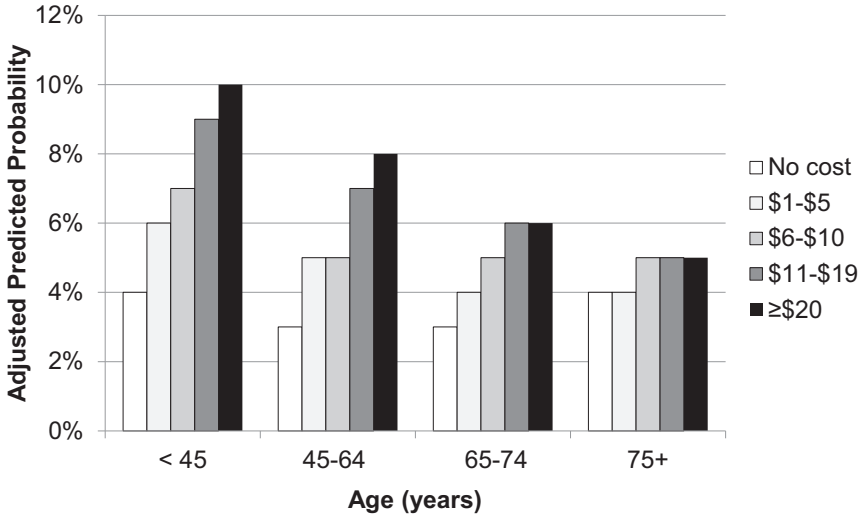
Figure 2: Relationship between Out-Of-Pocket Cost for the Index Therapy and Adjusted Predicted Probability of Primary Nonadherence, Early Nonpersistence, Later Stage Nonpersistence, and Inadequate Secondary Adherence



Notes. *Primary nonadherence and early nonpersistence models include insulin. Later stage nonpersistence and inadequate secondary adherence models are based on oral agents only. Inadequate secondary adherence is based on continuous medication gaps (CMG)>20 percent. [†]Models were adjusted for the following categorical covariates: Demographics (age, race/ethnicity, sex, neighborhood deprivation index), drug plan characteristics (mail order incentive, Medicare Part D, medical financial assistance, out-of-pocket maximum, deductible indicator, coinsurance vs. copay indicator), prescription characteristics (drug indication –diabetes, lipid- or blood pressure-lowering), generic versus brand, formulary versus nonformulary, days' supply dispensed, and use of mail order pharmacy. Predicted probabilities were calculated for a population whose marginal covariate distributions were aligned with the overall sample.

patterns were also significant ($p < .002$ for age × OOP cost interaction) for CMG<20 percent (not shown), but were not observed for later stage nonpersistence. There was also a strong relationship between OOP cost and primary

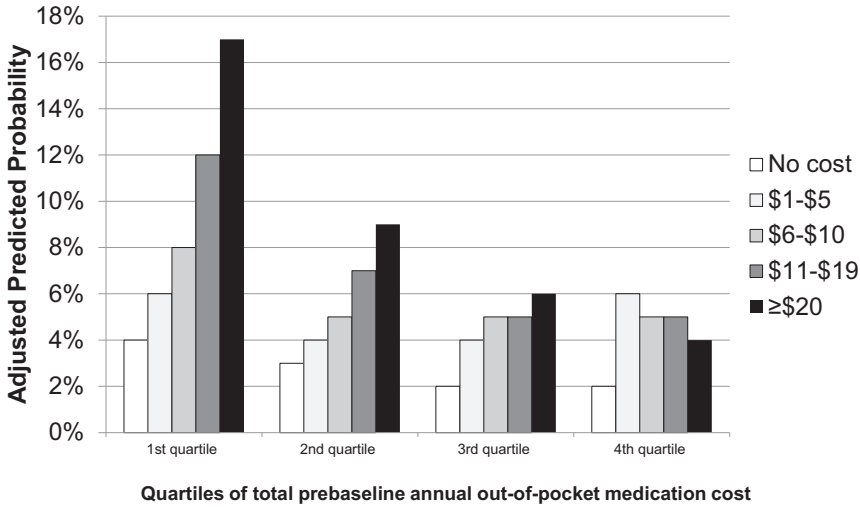
Figure 3: Relationship between Out-of-Pocket Cost and Adjusted Predicted Probability of Primary Nonadherence by Age Class*



Notes. *p-Value for the age class × OOP cost interaction was <.002; models were adjusted for demographics (age, race/ethnicity, sex, neighborhood deprivation index), drug plan generosity (Medicare Part D, medical financial assistance, out of pocket maximum, deductible indicator, coinsurance versus copay indicator, mail order incentive), prescription characteristics (drug class (glucose-lowering, lipid-lowering, antihypertensive medication), generic versus brand, formulary versus nonformulary, days' supply dispensed.

nonadherence (Figure 4) among patients with lower total prebaseline annual OOP expenses for chronically used medications ($p < .0001$ for quartile of total baseline medication expenditures × OOP cost interaction). For example, among patients who had the lowest (i.e., first quartile) total prebaseline annual OOP medication expenses, there was more than a fourfold greater (17 vs. 4 percent) rate of primary nonadherence for patients with OOP cost ≥$20 compared with those who received that new medication at no cost. In comparison, among patients who had the highest (i.e., fourth quartile) total prebaseline annual OOP medication expenses, there was only a doubling (4 vs. 2 percent) of the rate of primary nonadherence for patients with OOP cost ≥$20 compared to those who received that new medication at no cost. Thus, we observed strong price sensitivity to OOP cost for a new prescription among those with the lower total prebaseline annual OOP medication expenses for chronically used medications. There was a similar but weaker relationship between OOP cost and early nonpersistence (data not shown). Consistent

Figure 4: Relationship between Out-of-Pocket Cost and Adjusted Predicted Probability of Primary Nonadherence by Quartile of Annual Prebaseline Medication Expense for Chronically Used Medications*



Notes. **p*-Value for the quartile of total annual baseline medication expenditures × OOP cost interaction was <.0001; models were adjusted for demographics (age, race/ethnicity, sex, neighborhood deprivation index), drug plan generosity (Medicare Part D, medical financial assistance, out-of-pocket maximum, deductible indicator, coinsurance vs. copay indicator, mail order incentive), prescription characteristics (drug class [glucose-lowering, lipid-lowering, antihypertensive medication]), generic versus brand, formulary versus nonformulary, days' supply dispensed.

with previous research, we observed poorer adherence among minorities, but the OOP cost–adherence patterns, while often statistically significantly different, did not differ substantively across racial/ethnic groups. Similarly, while sometimes statistically significant, the OOP cost–adherence patterns did not differ substantively by sex or neighborhood deprivation (data not shown). We also observed a stronger relationship between OOP cost and primary nonadherence for newly prescribed lipid-lowering medications compared to antihyperglycemic or antihypertensive medications ($p < .0001$ for drug type × OOP cost interaction; see Figure S1 in Appendix SA2).

Conclusion

The current understanding of the effect of cost-sharing on medication adherence has largely been based on studies of adherence of ongoing

users; ours is the first to detail a long-term history of adherence starting at the time a prescription is ordered by the physician (Solomon et al. 2009). The novel finding of this study was the strong, inverse association between OOP cost and primary adherence to a newly prescribed cardiometabolic therapy. OOP cost ≥$20 approximately doubled the risk of primary nonadherence compared to those with $0 OOP cost. Consistent with the literature, we found that OOP cost had a graded association with secondary adherence among ongoing users of cardiometabolic therapies. OOP cost modestly increased the likelihood of early nonpersistence, but less substantively impacted later stage nonpersistence. The association of OOP cost and primary adherence also varied by age; younger patients were more sensitive to OOP cost. There was also greater price sensitivity among those newly prescribed lipid-lowering medications and those with the lowest total prebaseline OOP annual expense for their chronically used medications.

We do not have data to establish why OOP cost had a strong impact on initiation. However, the behavioral economic theory of loss aversion (Kahneman and Tverksy 1992) suggests that the initial OOP cost for a new prescription could be perceived as a loss. However, once the patient chooses to pay the OOP cost for the first dispensing, the same OOP cost for subsequent dispensings would not invoke as large a sense of loss as the initial fill given the new reference point. Future studies could examine these specific hypotheses.

A previous study described initiation of secondary prevention medications among those with newly diagnosed hypertension, hypercholesterolemia, or diabetes. Similar to the findings in this present study, they also reported that patients without experience with prescription medications were more price-sensitive and less willing to initiate prescription drug therapy (Solomon et al. 2009). The additional cost of the one newly prescribed medication could be a dramatic change for a patient with little or no previous experience of OOP medication expense compared to those already incurring OOP expense for several, preexisting medications. Similarly, among those with no prior history of taking prescription medications, there may be apprehension about the idea of taking regular, daily medications, and the potential hurdle posed by the OOP cost could be amplified. Price sensitivity was also greater for newly prescribed lipid-lowering agents than for antihyperglycemic or antihypertensive medications. Previous research has shown that the perceived importance of a therapy modifies the impact of OOP cost (Piette et al. 2011). Participants may consider lipid-lowering medications less essential, and thus be more price-

sensitive. Price sensitivity has been shown to differ across conditions (Collier et al. 1987; Gatwood et al. 2014). Others have found that patients diagnosed with a chronic illness were less responsive to change in OOP cost than those without chronic conditions (Goldman et al. 2007).

Out-of-pocket cost had almost no impact on persistence in this study. This is consistent with theories of cognitive dissonance which posit that past behaviors predict future behaviors (i.e., habit formation) because people form favorable opinions about their own past habits, which promote similar intentions for future behavior (Ouellette and Wood 1998).

Several study limitations should be considered. The study cohort only included patients with diabetes who were prescribed new cardiometabolic medications. As price sensitivity has been shown to be somewhat reduced in chronically ill patients (Collier et al. 1987), our findings may underestimate sensitivity to OOP costs for patients without chronic conditions and may not apply to other types of medications. Although our cohort is large and ethnically diverse, all participants were insured and received uniform access to integrated care at KPNC; therefore, results may not be generalizable to settings serving uninsured populations with more limited health care access. Kaiser Permanente is a more cautious user of expensive, brand drugs than other types of care delivery systems (e.g., fee-for-service), and, thus, patients are less often exposed to very high OOP expenditures for their medications compared to other health delivery systems. The total prebaseline annual OOP expenditure for all medications incurred by the patients with diabetes in this study was quite modest, with an average of ~$215. However, these OOP expenditures ranged widely, from a minimum of $0 (full coverage) to a maximum of $14,404 annually. OOP expenditures also varied by coverage type. Medicare patients with Part D coverage had a prebaseline average of $312 (maximum of $8,944) for OOP medication expenditures, while commercially covered patients with diabetes had an average of $166 (maximum of $14,404). In 2002, the national, average annual OOP for prescription drug expenditures for diabetes was $680 (Institute for Health Care Research and Policy 2002). Another study reported annual OOP expenditures for prescription medications during the 2007–2012 period averaged $623 for Medicare patients and $524 for patients aged 55–64 who were not yet Medicare eligible (Park and Jung 2017). Thus, the average OOP medication expenditures at Kaiser Permanente were substantively lower than national averages. However, the range of expenditures incurred within our sample was wide enough to support evaluation of the relationship between out-of-pocket expenditures and

adherence. That relationship is likely generalizable even though the distribution of OOP expenditures at Kaiser Permanente is dissimilar to other settings.

While we used an accepted approach for causal modeling (Hernan et al. 2002), the validity of the interpretation of the impact of OOP cost on adherence is limited by the validity of our DAG assumptions. As this is an observational study of a nonrandomized exposure, we cannot rule out residual confounding or selection effects; for example, we lacked information on patients' beliefs regarding the importance of taking their medications or their concerns about medication side effects or harmfulness of medications.

We cannot entirely rule out some pharmacy utilization at non-Kaiser pharmacies, which is not captured in our databases. Because the benefits are not honored at non-Kaiser pharmacies (i.e., a "closed pharmacy system"), Kaiser members with pharmacy benefits have a financial incentive to use only Kaiser pharmacies. We evaluated survey responses from 20,188 Kaiser diabetic patients involved in the Diabetes Study of Northern California (DISTANCE; Moffet et al. 2009) regarding their out-of-plan pharmacy utilization in the previous 12 months. Of the 96 percent who had a pharmacy benefit, non-Kaiser pharmacies were used less than a single time (0.4 times) during the previous year (Karter et al. 2009). Because we excluded the ~4 percent lacking prescription benefits, the underascertainment of pharmacy utilization in this present study should be minimal.

While the rates of primary nonadherence reported in this study are similar to those from a study in another closed pharmacy system (e.g., pharmacy benefit restricted to members of an integrated health care delivery system rather than the general public) in the United States (Clarke and Snyder 1990), a study from Sweden (Ekedahl and Mansson 2004), and an earlier assessment in the Kaiser population (Karter et al. 2009), they are lower than a report from health care delivery relying on an open pharmacy system of retail pharmacies open to the general public (Fischer et al. 2010). The variation in primary adherence estimates across studies may be attributable to differences in cost-sharing across populations. However, assessing adherence in health care systems relying on open pharmacies requires linkage of multiple sources of data (e-prescribing, transactions, and pharmacy claims) and is more vulnerable to misinterpreting missing pharmacy dispensing data as nonadherence (Engler et al. 1989; Karter et al. 2010). The vast majority of KPNC membership with benefits uses health plan pharmacies given their competitive generic pricing. Members are charged the lesser

of the member price or their copayment, and in the case of cheap generics like metformin, the member price is comparable to what patients would pay at large retail pharmacies such as Walmart. Kaiser Permanente does not permit the use of free samples at any of their facilities, further avoiding underascertainment of medication use.

Improving adherence for essential preventive medications is critical to population management for chronic conditions, and thus it has public health and policy implications. CMS's Medicare Star ratings incentivize health plans to achieve adequate levels of adherence among their members. Health plans with high levels of adherence to medications used in an ongoing way among their diabetes and congestive heart failure patients have been shown to have lower average health care expenditures and hospitalizations for complications, suggesting the utility of promoting secondary adherence as a performance measure (Seabury et al. 2015). Our findings suggest that there may be a tradeoff between OOP cost and the likelihood that a health care delivery system achieves high ratings. However, the initiation phase of adherence may have similar or stronger health economic implications as secondary adherence, and the value of extending the Medicare Star performance measures to include the early stages of adherence has been suggested (Schmittdiel et al. 2014).

In the United States, annual premiums for employer-sponsored family coverage increased 3 percent in 2014 (to $16,834), continuing a trend in modest increases, while OOP cost for medications (and deductibles) remained stable (Claxton et al. 2014). Another national study reported a decrease in OOP costs in the past decade, along with narrowed insurance and income-related disparities for patients with diabetes (Li et al. 2014). Nonetheless, approximately a quarter of patients with diabetes still face a high OOP cost burden because of their need for increasingly complex polypharmacy (Li et al. 2014). Newer quality improvement efforts are targeting poor adherence by subsidizing OOP cost. For example, value-based insurance designs (VBIDs) provide the most essential, preventive medications (e.g., antihypertensives) at a reduced or no cost, and they have demonstrated health economic and public health benefits (Clarke et al. 1979; Gibson et al. 2011; Tang et al. 2014). A study evaluated the impact on adherence to diabetes medications when patients switched from a tiered copayment design to a value-based insurance design (VBID) resulting in generic oral agents and insulin dropping from $15 to $0, and brand medications dropping from $30 to $10–$15 (Clarke et al. 1979). Although electronic prescribing data were not available to

determine the impact of OOP cost on primary adherence explicitly, VBID stimulated an increased rate of drug initiation based on dispensing. Our findings suggest that, in addition to improving secondary adherence, greater initiation of newly prescribed medications may extend the VBID impact of subsidizing or reducing OOP cost as a way of improving adherence.

Cost-sharing, which deters clinically vulnerable patients from initiating essential medications, is a growing public health concern. This was particularly apparent for younger patients, who may have the most to gain from good adherence given its potential to minimize a long future of risk factor exposure. Qualitative research is needed to understand whether the differing role of financial barriers across stages of adherence is attributable to selective exclusion of patients not willing to pay or due to a growing acceptance of OOP costs and appreciation for the clinical importance of adherence to essential medications. Cost-sharing is a blunt instrument with intended (e.g., reducing unnecessary health care expenditures) and unintended consequences (e.g., delayed treatment initiation or poorer adherence), and it should be updated with more sophisticated insurance benefit designs that take into account patients' complex responses to cost-sharing (Solomon et al. 2009). VBID and benefit designs with initial cost-free dispensing of essential medications should be tested as a way of avoiding the initial price sensitivity and getting patients started on essential medications. Finally, it has been reported that only a minority of patients with chronic disease discuss OOP costs with their providers (Piette et al. 2004; Rodriguez-Gutierrez et al. 2016). Our findings underscore the importance of providers initiating a discussion with their patients about potential cost barriers for medications, particularly when prescribing a new medication (Piette et al. 2004).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the supporting information tab for this article:

Appendix SA1: Author Matrix.

Appendix SA2:

Table S1. Relative Risk (RR), Risk Difference (RD) and Predicted Probability (PP) Based on Poisson and Least-Squares Regression Models of Out-of-Pocket Cost and Stages of Adherence and Persistence.

Figure S1. Relationship between Out-of-Pocket Cost and Predicted Probability of Primary Non-Adherence by Drug Type.