ORIGINAL ARTICLES

# Factors Associated with Medication Refill Adherence in Cardiovascular-related Diseases

## A Focus on Health Literacy

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***BACKGROUND:*** The factors influencing medication adherence have not been fully elucidated. Inadequate health literacy skills may impair comprehension of medical care instructions, and thereby reduce medication adherence.

***OBJECTIVES:*** To examine the relationship between health literacy and medication refill adherence among Medicare managed care enrollees with cardiovascular-related conditions.

***RESEARCH DESIGN:*** Prospective cohort study.

***SUBJECTS:*** New Medicare enrollees from 4 managed care plans who completed an in-person survey and were identified through administrative data as having coronary heart disease, hypertension, diabetes mellitus, and/or hyperlipidemia ($n$=1,549).

***MEASURES:*** Health literacy was determined using the short form of the Test of Functional Health Literacy in Adults (S-TOFHLA). Prospective administrative data were used to calculate the cumulative medication gap (CMG), a valid measure of medication refill adherence, over a 1-year period. Low adherence was defined as CMG $\geq$ 20%.

***RESULTS:*** Overall, 40% of the enrollees had low refill adherence. Bivariate analyses indicated that health literacy, race/ethnicity, education, and regimen complexity were each related to medication refill adherence ($P<.05$). In unadjusted analysis, those with inadequate health literacy skills had increased odds (odds ratio [OR]=1.37, 95% confidence interval [CI]: 1.08 to 1.74) of low refill adherence compared with those with adequate health literacy skills. However, the OR for inadequate health literacy and low refill adherence was not statistically significant in multivariate analyses (OR=1.23, 95% CI: 0.92 to 1.64).

***CONCLUSIONS:*** The present study suggests, but did not conclusively demonstrate, that low health literacy predicts poor refill adherence. Given the prevalence of both conditions, future research should continue to examine this important potential association.

*KEY WORDS:* elderly; health literacy; adherence.
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Low medication adherence is one of the most serious problems facing health care today.[1–3] Survey data demonstrate that over half of the prescription medicines dispensed in the United States are not taken as prescribed.[4] As many as 50% of prescriptions fail to produce the desired results because of improper use, and 14% to 21% of patients never even fill their original prescriptions.[1,2,4,5]

The health consequences of nonadherence can be severe, particularly for patients with cardiovascular disease or cardiovascular risk factors.[6] Nonadherence contributes to the lack of adequate blood pressure control in two-thirds of patients with hypertension.[7] Among patients with hyperlipidemia, nonadherence can lessen the degree of low-density lipoprotein cholesterol reduction.[8] Nonadherence also leads to increased cardiovascular mortality.[9]

Medication nonadherence is an especially important problem among older adults.[10–14] While persons over the age of 65 represent about 12% of the population,[15] they use approximately 30% of all prescription medications.[16,17] Older adults have an increased burden of cardiovascular disease and cardiovascular risk factors, and adherence is of crucial importance in optimizing the long-term medical management of these chronic conditions.[2] Moreover, older patients are thought to have more difficulty following prescription instructions because they commonly experience age-related changes in cognition, including worse memory for and comprehension of regimens; impaired vision; and difficulty with manual dexterity important for opening childproof drug containers.[10,18,19]

Several studies have found a relationship between knowledge of medication and medication adherence.[1,20] These studies have found that patients often have poor understanding of their medication instructions.[21–26] Furthermore, those who do not understand their drug therapy are more likely to have adherence problems.[21] Although it is the responsibility of the health care delivery system to provide appropriate information to patients about their medication therapy, an often overlooked aspect of this information exchange is patients' understanding of that information. Recently, low health literacy has emerged as a potential predictor of nonadherence.[27] Health literacy refers to the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions.[28,29] Health literacy is considered a more sensitive

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and specific index of understanding medical instructions than is the patient's education level.[30,31]

It would be expected that an adequate level of functional health literacy is essential for understanding and processing messages that generate the motivation, beliefs, and behaviors to achieve successful medication adherence.[32] It is likely that inadequate health literacy skills are related to impaired comprehension of medical care instructions, and as a consequence, reduced medication adherence.[33] The 3 published studies that have directly examined this relationship found inconsistent results. Kalichman et al.[27] noted an association between health literacy and self-reported adherence to antiretroviral agents, while Golin et al.[34] found no such association. Chew et al.[35] reported a trend toward reduced adherence with some perioperative medication instructions among patients with low health literacy skills. Each of these investigations enrolled a limited population, relied on patient self-report, and considered adherence over a relatively short time period.

Thus, additional research is needed to understand the role of health literacy in medication adherence across a broader set of chronic conditions. The current study of Medicare-managed care enrollees examines the relationship between health literacy and medication refill adherence with medications used for the prevention and control of cardiovascular disease.

# METHODS

## Study Sites and Population

This analysis is part of a larger study that examined the prevalence of low health literacy among community-dwelling Medicare enrollees in a national managed care organization.[36] Data are analyzed from the 4 sites where the baseline survey was conducted (Cleveland, OH; Houston, TX; South Florida [including Fort Lauderdale and Miami]; and Tampa, FL).

New Medicare managed care enrollees, 65 years of age and older, were eligible to participate. Individuals who indicated that they were not comfortable speaking either English or Spanish, had severe visual impairment (i.e., blind or severe vision problem that cannot be correct with glasses), or were living in a nursing home were excluded. We also excluded enrollees who missed 1 or more screening questions for severe cognitive impairment (not able to correctly identify year, month, state, year of their birth, or home address).

Eligible individuals who agreed to participate completed a 1-hour in-person orally administered questionnaire developed primarily from previously published and validated instruments. The full questionnaire included items on demographics, self-rated health status,[37] physical functioning,[37] chronic conditions, health care utilization, mental health,[37,38] cognitive impairment,[39] social support,[40] health behaviors,[41] and health literacy skills.[42] We linked 1 year of administrative data (inpatient, outpatient, and emergency room use, and pharmacy claims) to the baseline survey data for each study participant. In addition to the self-reported utilization information, we also create utilization variables (outpatient, emergency room, and inpatient visits) based on the linked administrative data.

For purposes of this analysis, we included individuals who were continuously enrolled for at least 1 year, did not spend a prolonged period in the hospital (more than 100 days during the study period), and had inpatient or outpatient claims. We selected study participants if they had any of the following 4 conditions: coronary heart disease, hypertension, diabetes mellitus, or hyperlipidemia. These cardiovascular-related conditions were selected for several reasons—they are common in the elderly, require long-term treatment with well-defined medication classes, and produce significant morbidity and mortality. Study participants were selected for this analysis if they had *both* an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis code from administrative data *and* pharmacy claims related to at least one of the 4 defined conditions (Table 1). These 2 data sources were used in combination to improve the specificity of classifying cases of cardiovascular-related disease.

## Study Variables

***Measurement of Refill Adherence.*** The primary (dependent) variable of interest was cardiovascular medication refill adherence, expressed as the cumulative medication gap (CMG).[43] Refill data were obtained from the managed care plan's Health Care Information Warehouse, which housed all outpatient medication claims processed through the retail and mail-order pharmacy networks. Among the data elements in this database are the trade and generic drug name, generic product indicator, specific therapeutic class code, drug strength, dosage form, service date, quantity dispensed, and days supply dispensed. The pharmacy claims information is very reliable and timely, generally completed within 1 to 2 months.[44] Moreover, Standard National Council for Prescription Drug Programs formats are consistently used to ensure dataset completeness and accuracy.

Pharmacy claims data were analyzed for 1 year after each study participant enrolled in the managed care plan. For each participant, refill adherence was determined separately for each medication of interest. Medications included in the adherence calculations were all the chronic, nondiscretionary medications used in the management of hypertension, diabetes mellitus, hyperlipidemia, or coronary heart disease. Nondiscretionary medications were considered to be those typically prescribed and used chronically and on a regular schedule whereas discretionary medications were considered to be typically used on an acute, intermittent, or as-needed basis. Because claims data do not provide the necessary precision to assess refill adherence for liquid, ointment, and injectable dosage forms, only oral solid, and transdermal dosage forms were included in the cardiovascular medication refill adherence calculation. However, we did include oral bile acid sequestrant powder products in the medication adherence calculation since the days supply for these products was provided. Respondents were taking between 1 and 9 medications of interest, with a mean of 2.26 and a median of 2.0 medications.

For each medication, a cumulative gap was calculated as the number of days in which the medication was not available (gap) between each prescription fill, divided by the number of days between the first and last medication fill during the study period. The CMG was expressed as a percentage.[43] For example, a medication with delayed refills resulting in 2 gaps of 40 and 50 days during a total of 360 days would have a cumulative gap of 25% (i.e., gap $=\{40+50\}/360$). Assessment of a gap involves determining, on each day of the selected interval, whether or not the patient had medication available based on the previous quantities dispensed. The method requires at

**Table 1. ICD-9 Codes and Pharmacy Codes Used to Identify Participants for the Health Literacy and Cardiovascular Disease Medication Refill Adherence Study**

| | ICD-9 Codes | Pharmacy Codes |
|---|---|---|
| Hypertension | 401 Essential hypertension | Hypotensives, vasodilators |
| | 402 Hypertensive heart disease | Hypotensives, sympatholytic |
| | 402.0 Hypertensive heart disease, malignant | Hypotensives, ganglionic blockers |
| | 402.1 Hypertensive heart disease, benign | Hypotensives, angiotensin converting enzyme blocker |
| | 402.9 Hypertensive heart disease, unspecified | Hypotensives, veratrum alkaloids |
| | 403.0 Hypertensive renal disease, malignant | Hypotensives, angiotensin receptor antagonist |
| | 403.1 Hypertensive renal disease, benign | Hypotensives, miscellaneous |
| | 403.9 Hypertensive renal disease, unspecified | Calcium channel blocking agents |
| | 404.0 Hypertensive heart and renal disease, malignant | α/β-adrenergic blocking agents |
| | 404.1 Hypertensive heart and renal disease, benign | α-adrenergic blocking agents |
| | 404.9 Hypertensive heart and renal disease, unspecified | β-adrenergic blocking agents |
| | 405.0 Secondary hypertension, malignant | Thiazide and related diuretics |
| | 405.1 Secondary hypertension, benign | Loop diuretics |
| | 405.9 Secondary hypertension, unspecified | Potassium sparing diuretics in combination |
| | | Potassium sparing diuretics |
| | | Miscellaneous diuretics |
| Coronary heart disease | 410* Acute myocardial infarction | Vasodilators, coronary |
| | 411* Other acute and subacute forms of ischemic heart disease | Platelet aggregation inhibitors |
| | 412* Old myocardial infarction | |
| | 414* Other forms of chronic ischemic heart disease | |
| Diabetes | 250* Diabetes mellitus | Oral hypoglycemic agents, sulfonylurea type |
| | Only included if oral anti-diabetic medication | Oral hypoglycemic agents, non-sulfonylurea type |
| Hyperlipidemia | 272.0 Pure hypercholesterolemia | Bile salt sequestrants |
| | 272.1 Pure hyperglyceridemia | Lipotropics |
| | 272.2 Mixed hyperlipidemia | |
| | 272.3 Hyperchylomicronemia | |
| | 272.4 Other and unspecified hyperlipidemia | |
| | 272.5 Lipoprotein deficiencies | |

**Wild card, all decimals included.*

least 2 medication fills to anchor the time period of interest. For chronic medication use, the CMG is the preferred measure of medication refill adherence compared with the commonly used medication possession ratio (MPR), as it does not allow an early medication lapse to be erased by later stockpiling, but does allow an early oversupply to carry forward and fill a later gap between refills.[43] The present calculation was further refined by correcting for days spent in the hospital (when patients do not use their outpatient medication supply), by excluding inpatient medications (which are not self-managed), and by including discharge medications (which are self-managed), if a prescription medication claim was available.

The primary outcome for each participant was a weighted average of the individual medication gaps, with weights corresponding to the time interval for each medication. Thus, an individual with a 25% gap when taking medication A for 360 days and a 50% gap when taking medication B for 100 days would have a weighted CMG of 30.4% [CMG = {(0.25)(360) + (0.50)(100)}/460]. Similar to other studies, adequate refill adherence was defined as having an overall CMG less than 20%.[43]

***Health Literacy (S-TOFHLA).*** We assessed enrollees' health literacy with the short form of the Test of Functional Health Literacy in Adults (S-TOFHLA), a valid and widely used measure which takes 12 minutes or less to administer, and is available in both English and Spanish versions.[42,45] The S-TOFHLA includes reading comprehension and numeracy sections and uses actual materials that patients might encounter in the health care setting, such as medication label instructions. The sum of the 2 sections yields the S-TOFHLA score, which ranges from 0 to 100. Scores on the S-TOFHLA are classified and interpreted as follows: Inadequate health literacy (scores 0 to 53)—individuals will often misread the simplest materials, including prescription bottles and appointment slips, and the instructions for an upper gastrointestinal tract radiograph series; Marginal health literacy (scores 54 to 66)—individuals perform better on the simplest tasks, but have difficulty comprehending the Medicaid rights and responsibilities passage; Adequate health literacy (scores 67 to 100)—individuals will successfully complete most of the tasks required to function in the health care setting, although many still have difficulty comprehending more difficult information (i.e., materials written above a 10th grade reading level).

***Explanatory Variables.*** In addition to health literacy, we included several other patient variables that have been shown to be related to refill adherence.[1]

*Sociodemographics.* We examined potential sociodemographic explanatory variables obtained from the baseline survey, including information about participants' age, race/ethnicity, gender, education, marital status, and social support.

*Regimen Complexity* was examined as a covariate to determine its influence on medication refill adherence. There is no standardized method for assessing regimen complexity, nor an accepted way to account for changes in complexity over time. We used the total number of nondiscretionary oral medications, averaged quarterly over the study year. We also tested 2 alternative approaches, representing complexity as the total number of unique discretionary plus nondiscretionary medications, or as only the number of nondiscretionary cardiovas-

cular medications (i.e., the same set of medications used for the calculation of refill adherence).

*Health Status.* We included several self-reported measures to assess various aspects of health status, including: general health status, presence of a chronic condition, physical and mental health, cognitive impairment, health system utilization (i.e., self-reported doctor visits, hospitalizations, nursing home stays), and health behaviors (i.e., smoking, alcohol consumption, exercise, influenza and pneumoccocal vaccination, mammogram). Each of these measures was examined separately.

## Analysis

We first examined if the study inclusion criteria resulted in a representative study population by comparing the health literacy skills, age, and education of the final sample with the excluded population with respect to health literacy skills, age, and education ($\chi^2$ test). Second, we examined the distribution of the participants' refill adherence, using the weighted average gap method described above. Third, we examined the frequency of key variables of interest (e.g., health literacy, sociodemographic factors, medication complexity, health status), and whether any of these variables were significantly associated with medication refill adherence (bivariate analysis, $\chi^2$ test). Finally, we developed unadjusted and adjusted logistic regression models to determine the relationship between health literacy and low medication refill adherence (defined as CMG $\geq$ 20%). The adjusted models controlled for age, gender, and any significant ($P<.05$) explanatory variables from bivariate analyses. All variables in the multivariate analysis were included together.

All analyses were conducted using SAS, Version 8.2 (SAS Institute Inc., Cary, NC). This study was approved by the Institutional Review Board of the managed care organization.

## RESULTS

The study population includes all respondents to our initial health literacy baseline survey ($n$=3,260). Respondents were excluded during the 1-year study period if they: disenrolled within 1 year ($n$=206); had no inpatient or outpatient claims ($n$=170); did not have any pharmacy data ($n$=252); or were hospitalized more than 100 days ($n$=3). Furthermore, to identify respondents with a cardiovascular-related condition, we excluded those who did not have an ICD-9-CM code ($n$=769) or pharmacy code ($n$=228) related to any of the 4 conditions of interest (Table 1) and finally we excluded 83 individuals who had less than 2 prescription medication fills for at least 1 study medication, which would have not allowed an adherence calculation. These criteria resulted in 1,549 respondents in the final sample for analysis. There were no significant differences between the final study sample and the excluded population based on age, race, health literacy skills, and education characteristics.

Overall, 40% of the patients in our study had low refill adherence to their medications as defined by a CMG of 20% or more (Table 2). In bivariate analysis, there was a significant inverse relationship between health literacy level and medication refill adherence. Among those with low refill adherence, 27.3% had inadequate health literacy compared with 21.9% of those with adequate refill adherence ($P$=.035). Race/ethnicity, education, and regimen complexity were also significantly related to refill adherence ($P<.05$), and the effect of cognitive health was marginally significant ($P$=.07). Age, gender, marital status, social support, health status measures (self-reported health status, chronic conditions, physical and mental health, depression, functional health, self-reported, and administrative calculated utilization), and health behaviors (smoking, drinking, exercise, influenza and pneumoccocal vaccination, and mammogram) were not significantly related to refill adherence.

The unadjusted model indicated that health literacy was significantly associated with medication refill adherence; those with inadequate health literacy skills had 1.37 times (95% confidence interval [CI] 1.08 to 1.74) the odds of low refill adherence compared with those with adequate health literacy (Table 3). However, the ORs for health literacy and refill compliance was not statistically significant after adjusting for age,

**Table 2. Selected Characteristics of Respondents by Cumulative Medication Gap (CMG)**

| Characteristic | Low adherence CMG $\geq$ 20% *N* (%) | Adequate adherence CMG $<$ 20% *N* (%) | Total *N* (%) |
|---|---|---|---|
| Total | 620 (40.0) | 929 (60.0) | 1,549 (100) |
| Health literacy ($P$=.035) | | | |
| Adequate | 376 (60.6) | 619 (66.6) | 995 (64.2) |
| Marginal | 75 (12.1) | 107 (11.5) | 182 (11.8) |
| Inadequate | 169 (27.3) | 203 (21.9) | 372 (24.0) |
| Sociodemographic | | | |
| Age (y)[NS] | | | |
| 65 to 69 | 220 (35.4) | 315 (33.9) | 535 (34.5) |
| 70 to 74 | 171 (27.6) | 263 (28.3) | 434 (28.0) |
| 75 to 79 | 121 (19.5) | 184 (19.8) | 305 (19.7) |
| 80 to 84 | 75 (12.1) | 113 (12.2) | 188 (12.1) |
| $>$85 | 33 (5.3) | 54 (5.8) | 87 (5.6) |
| Race/Ethnicity ($P$=.0003) | | | |
| White | 440 (71.0) | 744 (80.1) | 1,184 (76.7) |
| Black | 95 (15.3) | 88 (9.5) | 183 (11.9) |
| Hispanic | 72 (11.6) | 87 (9.4) | 159 (10.3) |
| Other | 11 (1.8) | 8 (1.0) | 19 (1.2) |
| Gender [NS] | | | |
| Male | 259 (41.8) | 391 (42.1) | 650 (42.0) |
| Female | 361 (58.2) | 538 (57.9) | 899 (58.0) |
| Education ($P$=.03) | | | |
| Grade school or less | 126 (20.3) | 145 (15.6) | 271 (17.5) |
| Some high school | 115 (18.5) | 186 (20.0) | 301 (19.5) |
| High school | 213 (34.4) | 299 (32.2) | 512 (33.1) |
| More than high school | 165 (26.6) | 296 (31.9) | 461 (29.8) |
| Marital status [NS] | | | |
| Married | 345 (55.6) | 503 (54.1) | 848 (54.8) |
| Separated/divorced | 69 (11.1) | 83 (8.9) | 152 (9.8) |
| Widowed | 194 (31.3) | 328 (35.3) | 522 (33.7) |
| Never married | 12 (1.9) | 13 (1.4) | 25 (1.6) |
| Regimen complexity * ($P$=.01) | | | |
| $\leq$3 | 326 (52.6) | 426 (45.9) | 752 (48.5) |
| $>$3 | 294 (47.4) | 503 (54.1) | 797 (51.5) |
| Cognitive health[†,‡] ($P$=.07) | | | |
| Severe dementia | 10 (1.6) | 15 (1.6) | 25 (1.6) |
| Mild dementia | 157 (25.3) | 189 (20.3) | 346 (22.4) |
| Normal | 450 (72.6) | 722 (77.7) | 1,172 (76.0) |

[NS]*P-value not significant.*

[*]*Cutpoint was selected based on median value.*

[†]*Cutpoints were selected based on the validated instrument and scoring.*[39]

[‡]*Although we asked screening (eligibility) questions to exclude people with obvious severe cognitive difficulties, some respondents may have had more problems when more rigorous testing was done (i.e., cognitive health screening questions).*

**Table 3. Unadjusted and Adjusted Models of the Relationship Between Health Literacy and Medication Refill Adherence, Health Literacy and Cardiovascular Disease Medication Refill Adherence Study, *n*=1,549**

| Characteristic | Unadjusted OR (95% CI) | Model 1 OR (95% CI) | Model 2 OR (95% CI) |
|---|---|---|---|
| Health literacy | | | |
| Adequate | Reference | Reference | Reference |
| Marginal | 1.15 (0.84 to 1.59) | 1.15 (0.82 to 1.61) | 1.15 (0.82 to 1.62) |
| Inadequate | 1.37 (1.08 to 1.74) | 1.21 (0.91 to 1.62) | 1.23 (0.92 to 1.64) |
| Age (y) | | | |
| 65 to 69 | Reference | Reference | Reference |
| 70 to 74 | 0.93 (0.72 to 1.21) | 0.91 (0.70 to 1.19) | 0.91 (0.70 to 1.19) |
| 75 to 79 | 0.94 (0.71 to 1.25) | 0.91 (0.68 to 1.23) | 0.91 (0.67 to 1.22) |
| 80 to 84 | 0.95 (0.68 to 1.33) | 0.96 (0.67 to 1.36) | 0.96 (0.67 to 1.36) |
| >85 | 0.88 (0.55 to 1.39) | 0.86 (0.53 to 1.40) | 0.86 (0.53 to 1.40) |
| Race | | | |
| White | Reference | Reference | Reference |
| Black | 1.83 (1.34 to 2.50) | 1.73 (1.24 to 2.42) | 1.74 (1.25 to 2.43) |
| Hispanic | 1.40 (1.00 to 1.95) | 1.32 (0.91 to 1.90) | 1.32 (0.91 to 1.91) |
| Other | 2.33 (0.93 to 5.82) | 2.32 (0.92 to 5.84) | 2.27 (0.90 to 5.72) |
| Gender | | | |
| Male | 0.99 (0.80 to 1.21) | 1.02 (0.83 to 1.27) | 1.04 (0.84 to 1.28) |
| Female | Reference | Reference | Reference |
| Education | | | |
| Grade school | 1.56 (1.15 to 2.12) | 1.20 (0.84 to 1.72) | 1.21 (0.85 to 1.74) |
| Some high school | 1.11 (0.82 to 1.50) | 0.99 (0.72 to 1.35) | 1.01 (0.74 to 1.39) |
| High school graduate | 1.28 (0.99 to 1.66) | 1.27 (0.98 to 1.66) | 1.28 (0.98 to 1.66) |
| More than high school | Reference | Reference | Reference |
| Regimen complexity | | | |
| ≤3 | Reference | | Reference |
| >3 | −0.27 (0.10 to 6.72) | | 0.77 (0.73 to 0.95) |

*Model 1—includes demographics (age, race, gender, education).*
*Model 2—includes demographics plus complexity measure (number of medications).*
*CI, confidence interval; OR, odds ratio.*

race, gender, education, and regimen complexity (OR=1.23, 95% CI: 0.92 to 1.64). Only black race and regimen complexity remained independent predictors of refill adherence in the adjusted models. For example, blacks had 1.74 times the odds of having low refill adherence compared with white enrollees (95% CI: 1.25 to 2.43); and those taking more medications had a lower odds of having low refill adherence compared with those taking less medications (OR=0.77, 95% CI: 0.73 to 0.95).

Similar results were obtained using the 2 alternate measures of regimen complexity (data not shown). Moreover, in addition to looking at refill compliance for all 4 disease groups combined, we also ran separate subgroup analyses for each of the disease groups (hypertension, coronary heart disease, diabetes, and hyperlipidemia) and did not find any significant associations between medication refill adherence and our variables of interest. It is likely that these results were not significant because of the much smaller sample size of each of the disease groups.

## DISCUSSION

To the best of our knowledge, this is the first published study to examine the relationship between health literacy and refill adherence in a community-dwelling elderly population. Overall, 40% of the patients in our study had low refill adherence to their medications for cardiovascular-related conditions. This rate of nonadherence is consistent with, if not slightly higher than, what has been shown in other studies.[46,47] Health literacy showed a moderate effect on refill adherence in unadjusted analyses, but the CI overlapped with the null when controlling for other factors. The present findings therefore do not support an association between health literacy and refill adherence.

Nonetheless, these results do not rule out a relationship between health literacy and other aspects of medication adherence. Previous research has demonstrated that patients with inadequate health literacy have lower self-reported adherence, experience greater difficulty reading and understanding instructions on medication labels, and are more likely to cite confusion about the regimen as a reason for nonadherence.[27] Perhaps an individual's health literacy skills are more important in correctly taking their medication or in their decision to initially get a prescription filled, rather than having a prescription refilled.

The protective effect of medication complexity (measured by total number of medications) is consistent with other studies that found better adherence with an increased number of medications.[48,49] It may be that those who are taking more medications are more focused around the management of their health. Another possible reason may be that perhaps more resources are available for managing more complex regimens. Clearly more research is needed to understand this relationship between adherence and medication complexity.

The independent relationship between adherence and race is interesting in light of this patient population having similar access to care through a single managed care plan. Previous research has more directly examined the potential association between race and adherence, showing in some cases that African-American patients have lower adherence, even after adjustment for income, co-pay, insurance, or other measures of socioeconomic status.[50,51] However, others have not found an independent association between African-

American race and adherence.[1,52,53] It is clear that more work is needed in this area, with attention to other factors that may mediate this relationship, such as beliefs about medicines, participatory decision-making preferences, and geographic location.[54–56]

Strengths of our study include its prospective nature, 1-year timeframe, large sample size, and availability of extensive patient information to assess and control for confounding. In this managed care population, all of the enrollees had pharmacy coverage and thus were most likely to have their prescriptions filled and recorded through the pharmacy system. Thus, the use of objective claims information from this relatively closed system helped ensure a complete and accurate assessment of refill behavior. Finally, the CMG method used in this study is the preferred methodologic approach to the assessment of refill adherence.[43] We took additional steps to refine the accuracy of this measure, weighting it across the medication regimen and accounting for periods of hospitalization during the study year.

At least 2 limitations deserve mention. First, there is no clear gold standard for the assessment of adherence, and the caveats associated with the use of refill adherence as the dependent measure in this study should be acknowledged.[1] These include the inability to capture information concerning the accuracy of dose timing, assess the clinical importance of treatment gaps, account for stockpiling of medications prior to the study timeframe, clinically confirm medication or dosing changes, and assess the legitimacy of alterations in medication administration due to side effects, physician instructions, or pill splitting. Despite these limitations, refill behavior remains a common and accepted approach to the assessment of adherence, due to its objective nature and relative ease of data collection from administrative sources.[1] Another limitation with our study is that some potential explanatory variables that have previously been shown to be related to medication refill adherence were not available in our dataset, such as self-efficacy, understanding of the regimen, and provider and health care system factors.

Even with these limitations, the prevalence of low refill adherence and the potential association with health literacy observed in this study strongly suggest the need for additional research to better define the relationship, particularly by examining other aspects of medication adherence. A better understanding of the motivational and behavioral factors that influence medication adherence will assist the development of effective strategies to improve patient adherence.[57]

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## REFERENCES

1. **Osterberg L, Blaschke T.** Adherence to medication. N Engl J Med. 2005;353:487–97.
2. **Haynes RB, Yao X, Degani A, Kripalani S, Garg A, McDonald HP.** Interventions to enhance medication adherence. Cochrane Database of Systematic Reviews, 2005.
3. **Sabate E.** Adherence to long-term therapies; Evidence for action. Geneva: World Health Organization, 2003. Available at: http://www.who.int/chronic_conditions/adherencereport/en/. Accessed July 2005.
4. **The Boston Consulting Group.** The hidden epidemic: finding a cure for unfilled prescriptions and missed doses; 2003. Available at: http://www.bcg.com/media_center/media_press_releases.jsp?id=1057. Accessed April 2006.
5. **Stephenson J.** Nonadherence may cause half of antihypertensive drug "failures". JAMA. 1999;282:313–4.
6. **McDermott MM, Schmitt B, Wallner E.** Impact of medication nonadherence on coronary disease outcomes: a critical review. Arch Intern Med. 1997;157:1921–9.
7. **Chobanian AV, Bakris GL, Black HR, et al.** The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. JAMA. 2003;289:2560–72.
8. **Insull W.** The problem of compliance to cholesterol altering therapy. J Intern Med. 1997;241:317–25.
9. **The Coronary Drug Project Research Group.** Influence of adherence to treatment and response of cholesterol on mortality in the coronary drug project. N Engl J Med. 1980;303:1038–41.
10. **Stewart RB, Caranasos GJ.** Medication compliance in the elderly. Med Clin of North Am. 1989;73:1551–63.
11. **Col N, Fanale Je, Kronholm P.** The role of medication noncompliance and adverse drug reactions in hospitalizations of the elderly. Arch Intern Med. 1990;150:841–5.
12. **Ryan AA.** Medication compliance and older people: a review of the literature. Int J Nurs Stud. 1999;36:153–62.
13. **Murray MD, Callahan CM.** Improving medication use for older adults: an integrated research agenda. Ann Intern Med. 2003;139(part 2):425–9.
14. **MacLaughlin EJ, Raehl CL, Treadway AK, Sterling TL, Zoller DP, Bond CA.** Assessing medication adherence in the elderly. Which tools to use in clinical practice? Drugs Aging. 2005;22:231–55.
15. Census PHC-T-9 Population by Age, Sex, Race and Hispanic or Latino Origin for the United States: 2000. Available at: http://www.census.gov/population/cen2000/phc-t9/tab01.pdf. Accessed December 2005.
16. **Baum C, Kennedy DL, Forbes MB, Jones JK.** Drug use in the United States in 1981. JAMA. 1984;251:1293–7.
17. **Lamy PP.** Prescribing for the Elderly. Littleton: PSG Publishing; 1980.
18. **Morrow D, Leirer V, Sheikh J.** Adherence and medication instructions: review and recommendations. J Am Geriatr Soc. 1988;36:1147–60.
19. **Gray SL, Mahoney JE, Blough DK.** Medication adherence in elderly patients receiving home health services following hospital discharge. Ann Pharmacother. 2001;35:539–45.
20. **Esposito L.** The effects of medication education on adherence to medication regimens in an elderly population. J Adv Nurs. 1995;21:935–43.
21. **Hanchak NA, Patel MB, Berlin JA, Strom BL.** Patient misunderstanding of dosing instructions. J Gen Intern Med. 1996;11:325–8.
22. **Morrell RW, Park DC, Poon LW.** Quality of instructions on prescriptions drug labels: effects on memory and comprehension in young and old adults. Gerontologist. 1989;29:345–54.
23. **Chung MK, Bartfield JM.** Knowledge of prescription medications among elderly emergency department patients. Ann Emerg Med. 2002;39:605–8.
24. **Persell SD, Heiman HL, Weingart SN, et al.** Understanding of drug indications by ambulatory care patients. Am J Health Syst Pharm. 2004;61:2523–7.
25. **Rosenow EC III.** Patients' understanding of and compliance with medications: the sixth vital sign? Mayo Clin Proc. 2005;80:983–7.
26. **Raynor DK, Silletto M.** Patient noncomprehension of labeled instructions. Pharm J. 1982;229:648–9.
27. **Kalichman SC, Ramachandran B, Catz S.** Adherence to combination antiretroviral therapies in HIV patients of low health literacy. J Gen Intern Med. 1999;14:267–73.
28. **Institute of Medicine.** Health Literacy: A Prescription to End Confusion. Washington, DC: National Academy Press; 2004.
29. **Ratzan S, Parker R.** Introduction. Current bibliographies in Medicine 2000–1: Health literacy January 1990 through October 1999. Bethesda, MD: National Library of Medicine (February 2000). Available at: http://www.nlm.nih.gov/pubs/cbm/hliteracy.html.
30. **Davis T, Crouch M, Wills G, Miller S, Adebhou D.** The gap between patient reading comprehension and the readability of patient education materials. J Fam Pract. 1990;31:533–8.
31. **Weiss BD.** Health Literacy: A Manual for Clinicians. AMA Foundation; 2003.
32. **Green J, Hibbard J.** How much do health literacy and patient activation contribute to older adults' ability to manage their health? Available at:

http://www.aarp.org/research/health/healthliteracy/2005_05_literacy.html. Accessed December 2005.
33. **Pignone M, DeWalt DA, Sheridan S, Berkman N, Lohr KN.** Interventions to improve health outcomes for patients with low literacy. A systematic review. J Gen Intern Med. 2005;20:185–92.
34. **Golin CE, Liu H, Hays RD, et al.** A prospective study of predictors of adherence to combination antiretroviral medications. J Gen Intern Med. 2002;17:756–65.
35. **Chew LD, Bradley KA, Flum DR, Cornia PB, Koepsell TD.** The impact of low health literacy on surgical practice. Am J Surg. 2004;188:250–3.
36. **Gazmararian JA, Baker DW, Williams MV, et al.** Health literacy among Medicare enrollees in a managed care organization. JAMA. 1999;281:545–51.
37. **Ware JE, Kosinski M, Keller SD.** SF-36 Physical and Mental Health Summary Scales: A User's Manual. Boston, MA: The Health Institute; 1994.
38. **Yesavage JA, Brink TL, Rose TL.** Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res. 1999;17:37–49.
39. **Folstein MF, Folstein SE, McHugh PR.** "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189–98.
40. **Sherbourne CD, Stewart AL.** The MOS social support survey. Soc Sci Med. 1991;32:705–14.
41. **Remington PL, Smith MY, Williamson DF, Anda RF, Gentry EM, Hogelin GC.** Design, characteristics, and usefulness of state-based behavioral risk factor surveillance: 1981–87. Pub Health Rep. 1988;103:366–75.
42. **Baker DW, Williams MW, Parker RM, Gazmararian JA.** Development of a brief test to measure functional health literacy. Patient Educ Couns. 1999;38:33–42.
43. **Steiner JF, Prochazka AV.** The assessment of refill compliance using pharmacy records: methods, validity, and applications. J Clin Epidemiol. 1997;50:105–16.
44. **Parker RM, Baker DW, Williams MV, Nurss JR.** The test of functional health literacy in adults: a new instrument for measuring patients' literacy skills. J Gen Intern Med. 1995;10:537–41.
45. National Council for Prescription Drug Program, Basic Guide to Standards. February 2006.
46. **Vermeire E, Hearnshaw H, Van Royen P, Denekens J.** Patient adherence to treatment: three decades of research. A comprehensive review. J Clin Pharm Ther. 2003;26:331–42.
47. **Haynes RB, Taylor DW, Sackett DL,** eds**.** Compliance in Health Care. Baltimore: Johns Hopkins; 1979.
48. **Grant RW, O'Leary KM, Weilburg JB, Singer DE, Meigs JB.** Impact of concurrent medication use on statin adherence and refill persistence. Arch Intern Med. 2004;164:2343–8.
49. **Shalansky SJ, Levy AR.** Effect of number of medications on cardiovascular therapy adherence. Ann Pharmacother. 2002;36:1532–9.
50. **Kaplan RC, Bhalodkar NC, Brown EJ, White J, Brown DL.** Race, ethnicity, and sociocultural characteristics predict noncompliance with lipid-lowering medications. Prev Med. 2004;39:1249–55.
51. **Schectman JM, Bovbjerg VE, Voss JD.** Predictors of medication-refill adherence in an indigent rural population. Med Care. 2002;40:1294–300.
52. **Weng FL, Israni AK, Joffe MM, et al.** Race and electronically measured adherence to immunosuppressive medications after deceased donor renal transplantation. J Am Soc Nephrol. 2005;16:1839–48.
53. **Raji MA, Kuo YF, Salazar JA, Satish S, Goodwin JS.** Ethnic differences in antihypertensive medication use in the elderly. Ann Pharmacother. 2004;38:209–14.
54. **Li X, Margolick JB, Conover CS, et al.** Interruption and discontinuation of highly active antiretroviral therapy in the multicenter AIDS cohort study. JIDS. 2005;38:320–8.
55. **Dominick KL, Golightly YM, Bosworth HB.** Racial differences in analgesic/anti-inflammatory medication adherence among patients with osteoarthritis. Ethnic Disease. 2005;15:116–22.
56. **Klein D, Turvey C, Wallace R.** Elders who delay medication because of cost: health insurance, demographic, health, and financial correlates. Gerontologist. 2004;44:779–87.
57. **Haynes RB, McKibbon KA, Kanani R.** Systematic review of randomized trials of interventions to assist patients to follow prescriptions for medications. Lancet. 1996;348:383–6.