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Self-reported medication nonadherence predicts cholesterol levels over time☆

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ABSTRACT

Objective: Self-report measures of medication nonadherence are frequently adapted to new clinical populations without evidence of validity. We evaluated the predictive validity of a medication nonadherence measure previously validated in patients with hypertension among patients taking cholesterol-reducing medications.
Method: This secondary analysis involves data from a randomized trial (VA HSR&D IIR 08-297) conducted at the Durham Veterans Affairs Medical Center. At baseline, 6-months, and 12-months, serum cholesterol was obtained and participants ($n = 236$) completed a 3-item measure of extent of nonadherence to cholesterol-reducing medications. Two cross-lagged panel models with covariates, in addition to growth curve analysis, were used to examine the predictive utility of self-reported nonadherence on concurrent and future cholesterol levels, while accounting for potential reverse-causation.
Results: Extent of nonadherence items produced reliable scores across time and fit a single-factor model (CFI = 0.99). Nonadherence, and changes in nonadherence, moderately predicted future cholesterol values, and changes in cholesterol values (7 of 9 longitudinal associations were significant at $p < .05$; *B's* ranged from 0.16 to 0.35). Evidence for reverse associations was weaker (3 of 9 longitudinal associations were significant at $p < .05$; *B's* ranged from 0.16 to 0.36).
Conclusion: Analyses support the predictive validity of this medication nonadherence measure over the competing reverse-causation hypothesis.

1. Introduction

Worldwide, many patients with chronic conditions struggle with medication adherence; non-adherence contributes to increased healthcare spending, poor disease control, and increased mortality [1–4]. Epidemiologic data suggest that only one-quarter of patients prescribed statins continue taking them beyond six months and that fewer than half of patients receiving these medications achieve standardized cholesterol management goals [5]. Because statins are widely prescribed and efficacious in improving cardiovascular risk, increasing adherence improves clinical outcomes [6].

In order to identify patients that might benefit from adherence-improving interventions, and to evaluate those interventions, a valid method is needed to assess nonadherence. Self-reports are convenient, inexpensive, and usable at point of care [7]. Previously, Voils and colleagues noted several problems in the self-reported medication adherence [8], and subsequently developed and validated a two-part measure assessing extent of nonadherence and reasons for nonadherence in patients with hypertension [9]. A practical extension of this instrument to a hyperlipidemia population first requires

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examination of its factor structure and concurrent validity with other measures. Additionally, however, adapting a scale to be meaningful to this population requires more thorough assessment of predictive validity due to the stable nature of cholesterol levels in response to statin or combination therapy.

Because of the chronic and stable nature of many diseases, the predictive validity of self-reported adherence measures on distal clinical outcomes is difficult to properly assess. This difficulty may contribute to the consistent trend of adherence interventions failing to show improved clinical outcomes [10]. Examining one-way longitudinal associations may offer little additional predictive validity over concurrent associations because statins do not alter cholesterol levels as quickly as some other medication-condition pairings (such as anti-hypertensives and blood pressure). If the reciprocal longitudinal relationships between medication nonadherence and cholesterol levels are tested simultaneously, this would offer a stronger test of a causal association over time [11]. In other words, a medication nonadherence-to-cholesterol link over time that is stronger or more consistent than a cholesterol-to-medication nonadherence link would support the predictive validity of the self-report measure.

Our objectives were two-fold: 1) confirm reliability and concurrent validity of this measure in a hyperlipidemia population, and 2) examine the measure's predictive validity and responsiveness to change. In doing so, we examined the longitudinal and bidirectional association between extent of nonadherence and serum cholesterol levels to strengthen the causal argument that self-reported nonadherence is a timely indicator of actual nonadherence, which affects subsequent cholesterol levels.

2. Methods

2.1. Research Study Design

This secondary analysis involves data from a recently completed randomized, controlled trial (clinicaltrials.gov identifier NCT01142908) targeting Framingham CVD risk score as its primary outcome [12]. This IRB-approved trial tested a pharmacist-delivered, telephone-administered, chronic disease self-management intervention to patients who were diagnosed with hyperlipidemia. All patients taking cholesterol-reducing medications were on a statin, although the possibility of combination therapy did not exclude participation. Patients may also have been diagnosed with hypertension and/or diabetes mellitus. Patients were recruited from three primary care clinics affiliated with the Durham Veterans Affairs Health Care System. Participants were randomized to an active educational control arm or a multicomponent, tailored, behavioral intervention arm to improve health behaviors, including cardiovascular medication adherence. Consistent with other interventions, 12-month primary outcome retention rates were 85% in the control arm, and 80% in the intervention arm. The full method and theoretical rationale of CITIES is described elsewhere [13].

Measures.

2.1.1. Medication nonadherence

The self-reported medication nonadherence measure was initially developed and validated among hypertensive patients receiving care in similar facilities as the current sample [9]. Initial work indicates that the scale has produced highly reliable scores and has initial evidence of convergent, discriminant, and predictive validity. In the current analysis, self-reported nonadherence was collected verbally during phone calls at baseline, 6-months, and 12-months. Using a five-point scale (1 = none of the time, 5 = all the time), participants were asked to endorse the following three items referencing the previous 7 days: (1) I took all doses of my cholesterol medication; (2) I missed or skipped at least one dose of my cholesterol medication; and (3) I was not able to take all of my cholesterol medication. The first item was reverse-coded. Participants reporting nonadherence to *any* of the three extent items were then asked to report how much 21 reasons for nonadherence contributed to missing doses. Details of the 21 reasons for nonadherence in this hyperlipidemia population have been published elsewhere [14].

2.1.2. Serum cholesterol

Because participants' high-density cholesterol did not meaningfully change during the original trial, and due to the practical nature of total cholesterol values for CVD risk estimation, serum total cholesterol levels were obtained. These values were obtained via an in-person laboratory lipid panel at baseline, 6-months, and 12-months. Participants were requested to fast beforehand.

2.1.3. Additional measures

Upon enrollment, participants had blood drawn for serum cholesterol tests and completed a baseline survey in which they self-reported demographics, smoking status, depressive symptoms via the two-item version of the Patient Health Questionnaire (PHQ-2) [15], available support, cost paid for prescription medications, satisfaction with cholesterol levels, and desire to improve cholesterol levels. Similar procedures were performed at 6-month and 12-month follow-ups.

We included presence of a support person and depressive symptoms because they are correlated with nonadherence in the context of diabetes, renal transplant, and depression, among other health conditions [16–18]. We included cholesterol-related beliefs (satisfaction with and desire to improve) because beliefs and illness-perception have been associated with cholesterol control and related medication nonadherence [19]. We assessed self-reported prescription cost because cost may be correlated with medication nonadherence [20]. While multi-item scales may be more robust to psychometric evaluation in their own right, single-item scales such as the ones used here are the standard method of assessing constructs in these clinical settings and have been shown to correlate highly with lengthier multi-item measures of the same health-related constructs [21].

2.2. Statistical analysis

Descriptive statistics, reliability, factor structure, and individual item performance were assessed for the extent of nonadherence items. Mean responses from the three extent questions were used for all analyses, except analyses distinguishing “nonadherent” from “perfectly adherent” patients.

Using Mplus Version 6 [22], we conducted a confirmatory factor analysis (CFA) with freely estimated factor loadings and the latent factor's variance set to 1 [23]. Stata (Version 12) and R (Version 3.3.3) were used for all other analyses. Notably, the psychometric properties and associations examined in the current analysis should not be influenced by the potential for mean-level difference between control and treatment arms. The concern of validating this instrument in the context of treatment is further alleviated by the fact that the trial did not find 12-month differences in serum cholesterol or adherence between arms [12].

Longitudinal associations reported are standardized Beta weights of primary predictors in linear regression models containing gender, age, race, treatment arm and the interaction between the focal predictor (medication nonadherence or cholesterol) and treatment arm as covariates. All 2-timepoint change scores are residualized change scores to control for regression artifacts and minimize the number of predictors in each model [24]. All 3-timepoint change scores (i.e., baseline to 6-month to 12-month changes) are individual growth curves, modeling the change trajectory in covariance across all three time periods in a more flexible way than 2-timepoint change scores [25]. Both growth curves calculated evidence average *decreases* over time, but the term “growth curve” is kept to avoid confusion with the 2-timepoint residualized change scores. Missing data were multiply imputed using predictive mean-matching in the R statistical package ‘mice’ [26].

To improve the causal inference of the predictive validity analyses,

associations across time between self-reported nonadherence and serum cholesterol were tested bi-directionally in a cross-lagged panel model design (CLPM) [11]. This allows for a more complete examination of the assumption that medication nonadherence (as measured by self-report) influences cholesterol values, rather than the possibility that longitudinal predictions still represent a concurrent relationship given that cholesterol may not change during that time-period. Because both medication nonadherence and cholesterol levels are more state-dependent [27], the CLPM offers a more parsimonious and intuitive solution over more complex models proposed to overcome autoregressive problems with more trait-like variables [28].

3. Results

3.1. Participant characteristics

The baseline survey was completed by 428 patients. Of those, 243 participants reported being prescribed a medication for dyslipidemia management. Seven participants did not respond to two or more extent of medication nonadherence items and were excluded from analysis. Thus, 236 participants reported their extent of nonadherence with cholesterol-reducing prescriptions (whether perfectly adherent or not) and make up the analytic dataset.

Of these 236 participants, 194 (82% of baseline) completed both 6-month and 12-month follow-up measures, and exhibited very similar characteristics to the 42 participants who did not report longitudinal data (all differences were nonsignificant). Absolute Standardized Differences (ASD) were also calculated to illustrate differences between the baseline only and full longitudinal samples independent of sample size (see Table 1) [29]. These similarities suggest that the data could be assumed to be missing at random (MAR). Sensitivity analyses were run on both the complete observations dataset ($N = 194$, using listwise deletion) and on multiply imputed datasets modeling a relationship between missingness, self-reported nonadherence, and cholesterol. The significance of only one longitudinal relationship was altered in each of these more extreme methods of dealing with missing data. Therefore, missing data were handled with multiple imputation assuming MAR, as described above.

3.2. Reliability, factor structure, and item performance at baseline

One-hundred and nine patients (46.2% of the $N = 236$ analytic sample) reported any degree of nonadherence at baseline. Nonadherence item distributions were not highly skewed or kurtotic (Table 2). All items had adequate item-total correlations (> 0.70) and standardized factor loadings (> 0.75). The one-factor model also provided excellent fit (SRMR = 0.01, CFI = 0.99, RMSEA = 0.01 (95% CI [0.00, 0.02]). Nonadherence items produced highly internally consistent scores (Cronbach's alpha = 0.90).

3.2.1. Concurrent validity at baseline

Serum cholesterol was positively correlated with nonadherence at baseline ($r = 0.31$, $p < .001$). Moreover, patients reporting *any* nonadherence ($n = 109$) had cholesterol laboratory values 12% higher (M = 211.40) than patients reporting adherence (M = 188.69; $n = 127$; $t = 3.97$, $p < .001$). In a hierarchical regression, even when controlling for cost, presence of a support person, satisfaction with and desire to improve cholesterol, gender, smoking status, depressive symptoms, and treatment arm, nonadherence significantly correlated with cholesterol ($\beta = 0.27$, $p < .001$; Table 3), demonstrating the robustness of this relationship. Amount paid for prescriptions ($r = -0.10$, $p = .10$), presence of a support person ($r = -0.03$, $p = .62$), desire to improve cholesterol ($r = 0.04$, $p = .51$) and satisfaction with cholesterol ($r = -0.13$, $p = .06$) were not related to nonadherence. These results support discriminant validity.

3.2.2. Predictive validity

Extent of medication nonadherence measurement remained internally consistent at 6 months ($\alpha = 0.85$), and 12 months ($\alpha = 0.75$). Overall nonadherence rates, and average responses for each item also remained similar over time (as seen in Table 2). All coefficients presented are standardized Beta weights from covariate-adjusted models. Individual timepoint associations are displayed in Fig. 1, and associations between changes across time are displayed in Fig. 2. Concurrent associations between nonadherence and cholesterol were moderate and similar at baseline ($B = 0.30$, se = 0.06, $p < .001$), 6-months ($B = 0.32$, se = 0.07, $p < .001$), and 12-months ($B = 0.36$, se = 0.07, $p < .001$).

3.2.2.1. Sensitivity to change. Regarding mean-level changes over time, nonadherence exhibited considerable variability over 6-month and 12-month periods. Baseline to 6-month nonadherence was moderately correlated ($B = 0.47$, se = 0.06, $p < .001$), as were 6-month to 12-month nonadherence ($B = 0.36$, se = 0.07, $p < .001$) and baseline to 12-month nonadherence ($B = 0.34$, se = 0.07, $p < .001$). Cholesterol also exhibited considerable variability over 6-month and 12-month periods. Baseline to 6-month cholesterol was moderately correlated ($B = 0.54$, se = 0.06, $p < .001$), as were 6-month to 12-month cholesterol ($B = 0.51$, se = 0.06, $p < .001$) and baseline to 12-month cholesterol ($B = 0.46$, se = 0.06, $p < .001$). In 12-month growth curves, nonadherence exhibited a modest but significant average decrease over 12 months ($B = -0.09$, se = 0.03, $p = .003$). Similarly, cholesterol exhibited a modest but significant average decrease over 12 months ($B = -0.11$, se = 0.03, $p < .001$). See Fig. 1.

Baseline to 6-month nonadherence change was moderately associated with baseline to 6-month cholesterol change ($B = 0.35$, se = 0.07, $p < .001$). Similarly, 6-month to 12-month nonadherence change was moderately associated with 6-month to 12-month cholesterol change ($B = 0.37$, se = 0.07, $p < .001$). Baseline to 12-month nonadherence growth curves were moderately associated with baseline to 12-month cholesterol growth curves ($B = 0.37$, se = 0.07, $p < .001$). See Fig. 2.

3.2.2.2. Predictive validity of individual timepoint measurements. Nonadherence predicted cholesterol, but cholesterol did not predict nonadherence (Fig. 1). Baseline nonadherence modestly predicted cholesterol at 6-months ($B = 0.16$, se = 0.07, $p = .02$), and 6-month nonadherence modestly predicted cholesterol at 12-months ($B = 0.20$, se = 0.08, $p = .01$). Baseline nonadherence did not significantly predict 12-month cholesterol ($B = 0.09$, se = 0.07, $p = .19$). Conversely, baseline cholesterol did not predict 6-month nonadherence ($B = 0.10$, se = 0.07, $p = .15$), 6-month cholesterol did not predict 12-month nonadherence ($B = 0.10$, se = 0.08, $p = .18$), and baseline cholesterol did not predict 12-month nonadherence ($B = 0.13$, se = 0.07, $p = .06$).

3.2.2.3. Predictive validity of changes over time. Given that the nonadherence measure is sensitive to self-reported changes over time, and these changes continue to yield reliable scores, the validity of those changes needed to be examined. Changes in nonadherence predicted four of five cholesterol associations, whereas changes in cholesterol only predicted two of five nonadherence associations (Fig. 2). Baseline to 6-month changes in nonadherence moderately predicted 6-month cholesterol values ($B = 0.27$, se = 0.07, $p < .001$), modestly predicted 12-month cholesterol values ($B = 0.16$, se = 0.07, $p = .03$), and modestly predicted baseline to 12-month cholesterol growth curves ($B = 0.21$, se = 0.07, $p = .01$), but did not predict 6-month to 12-month cholesterol change ($B = 0.01$, se = 0.08, $p = .89$). Conversely, baseline to 6-month changes in cholesterol moderately predicted 6-month nonadherence ($B = 0.29$, se = 0.07, $p < .001$), but did not predict 12-month nonadherence ($B = 0.001$, se = 0.07, $p = .99$), 6-month to 12-month nonadherence change ($B = -0.10$, se = 0.07,

Table 1
Sample characteristics of participants at baseline and follow-up (n = 236).

Sample characteristics	Longitudinal (n = 194)	Baseline only (n = 42)	χ^2	p-value	ASD
Active Treatment Arm, n(%)	96 (49.5%)	23 (54.8%)	0.20	0.65	0.11
Age at baseline, mean(SD)	61.69 (8.13)	61.79 (8.19)	−0.33[a]	0.74	0.06
Male, n(%)	170 (87.6%)	36 (85.7%)	0.01	0.93	0.06
Race			2.53	0.47	.33[b]
White	88 (45.4%)	24 (57.1%)			
Black	97 (50.0%)	17 (40.5%)			
Other minority race	9 (4.6%)	1 (2.4%)			
Smoking Status	53 (27.3%)	13 (31.0%)	0.23	0.77	0.09
PHQ-2 Elevated Score	46 (23.7%)	12 (28.6%)	0.22	0.64	0.11
Education			1.85	0.76	.27[b]
Grade school/junior high	3 (1.5%)	1 (2.4%)			
Some high school	4 (2.1%)	0 (0.0%)			
High school equivalent or graduate	54 (27.8%)	9 (21.4%)			
Some college or technical school	89 (45.9%)	21 (50.0%)			
College graduate	44 (22.7%)	11 (26.2%)			
Marital status			4.77	0.31	.47[b]
Married or living with partner	110 (56.7%)	20 (47.6%)			
Single, never married	9 (4.6%)	3 (7.1%)			
Separated or divorced	66 (34.0%)	19 (45.2%)			
Widowed	9 (4.6%)	0 (0.0%)			
Employment status			5.65	0.46	.48[b]
Employed full or part time	54 (27.8%)	8 (19.0%)			
Disabled and unable to work	61 (31.4%)	14 (33.3%)			
Retired and not working	79 (40.7%)	20 (47.6%)			
Cholesterol information					
Serum Cholesterol Levels	198.43 (36.2)	202.67 (47.3)	−0.65[a]	0.52	0.10
Doctor said you have high cholesterol	184 (94.8%)	41 (97.6%)	< 0.01	0.99	0.00
Blood relative has high cholesterol	101(52.1%)	24 (57.1%)	0.03	0.86	0.10
How many years ago you learned you had high cholesterol, mean(SD)	10.61 (11.29)	10.19 (8.45)	0.21[a]	0.83	0.04
Out-of-Pocket Medication Costs			2.05	0.36	.10[b]
$0–50 per month	152 (78.4%)	33 (78.6%)			
$51–100 per month	33 (17.0%)	5 (11.9%)			
More than $100 per month	9 (4.6%)	4 (9.5%)			
Someone who can help with tasks – Yes	174 (89.7%)	36 (85.7%)	0.32	0.57	0.14
Satisfaction with cholesterol control[†]	4.47 (2.96)	4.23 (2.93)	0.45[a]	0.65	0.08
Desire to improve cholesterol[†]	9.36 (1.46)	9.08 (1.40)	1.12[a]	0.27	0.20
Reported *any* nonadherence to cholesterol-reducing medications, n(%)	89 (45.9%)	20 (47.6%)	< 0.01	0.97	0.00
Medication Nonadherence-by-Serum Cholesterol Level Relationship	r = 0.31	r = 0.32	−0.12	0.91	0.02

Note: Due to rounding some totals exceed 100%. Missing responses: doctor told you that you have high cholesterol (n = 3), blood relative has high cholesterol (n = 88), how many years ago you learned you had high cholesterol (n = 14), someone who could help you (n = 1), satisfaction with cholesterol (n = 20), and how much would you like to improve your cholesterol (n = 10). [†]Response scale: 1–10. [a]Values represent t-test statistics for continuous variables. ASM = Absolute Standardized Difference. [b] Based off highest between-category ASD calculation.

p = .16), or baseline to 12-month nonadherence growth curves (B = −0.003, se = 0.07, p = .97). Six-month to 12-month changes in nonadherence moderately predicted 12-month cholesterol (B = 0.29, se = 0.07, p < .001), and similarly, 6-month to 12-month changes in cholesterol moderately predicted 12-month nonadherence (B = 0.36, se = 0.07, p < .001).

Baseline to 12-month nonadherence growth curves moderately predicted 12-month cholesterol (B = 0.35, se = 0.06, p < .001). Similarly, baseline to 12-month cholesterol growth curves moderately predicted 12-month nonadherence (B = 0.32, se = 0.07, p < .001).

4. Discussion

Our analysis demonstrates that the self-reported extent of

Table 2
Characteristics of extent of medication nonadherence items (n = 236).

Item	n	Mean (SD)	Skewness	Kurtosis	Item-total correlation	Standardized factor loading
1. I took all doses of my cholesterol medication.	236	T1: 1.79 (1.27) T2: 1.64 (1.13) T3: 1.63 (1.22)	1.42	3.74	0.80	0.87
2. I missed or skipped at least one dose of my cholesterol medication.	236	T1: 1.97 (1.28) T2: 1.70 (1.06) T3: 1.68 (1.16)	1.08	2.97	0.85	0.95
3. I was not able to take all of my cholesterol medication.	236	T1: 1.72 (1.20) T2: 1.37 (0.85) T3: 1.41 (0.98)	1.59	4.45	0.73	0.77
Average of extent items	236	T1: 1.83 (1.14) T2: 1.57 (1.17) T3: 1.58 (1.15)	1.23	3.63	NA	NA

Note: T1 = Baseline. T2 = 6-month follow-up. T3 = 12-month follow-up. Items scored on a 5-point scale: 1 = none of the time, 5 = all of the time. Item 1 is reverse coded. Cronbach's alpha = 0.90. SRMR = 0.01, CFI = 0.99, RMSEA = 0.01 (95% CI: 0.00, 0.02).

Table 3
Hierarchical regression analysis showing incremental concurrent criterion validity of extent of nonadherence with serum cholesterol (n = 236).

	β	*t*	p	R^2(p)	ΔR^2(p)
Step 1				0.06*(0.005)	
Intercept	0.03	0.45	0.65		
Amount paid for prescription medications	−0.14*	−2.18	0.03		
Help with tasks if needed	−0.05	−0.66	0.51		
Satisfaction with cholesterol levels	−0.18*	−2.64	0.01		
Desire to improve cholesterol levels	0.03	0.46	0.65		
Gender - female	−0.13	−2.00	0.047*		
Smoking status – smoker	−0.09	−1.37	0.17		
Elevated depressive symptoms	−0.01	−0.18	0.86		
Treatment Arm	−0.01	−0.22	0.82		
Step 2				0.12*(< 0.001)	0.06*(< 0.001)
Intercept	0.02	0.36	0.72		
Amount paid for prescription medications	−0.10	−1.63	0.10		
Help with tasks if needed	−0.03	−0.49	0.62		
Satisfaction with cholesterol levels	−0.13	−1.90	0.06		
Desire to improve cholesterol levels	0.04	0.66	0.51		
Gender - female	−0.16*	−2.42	0.02		
Smoking status – smoker	−0.11	−1.61	0.11		
Elevated depressive symptoms	−0.05	−0.69	0.49		
Treatment Arm	−0.01	−0.21	0.84		
Average extent of medication nonadherence	0.27*	4.02	< 0.001		

Note: *p-value below level for significance. Because 'amount paid for prescription medications' is an ordinal variable, the reported correlations are Spearman correlations. For other variables, we report Pearson correlations.

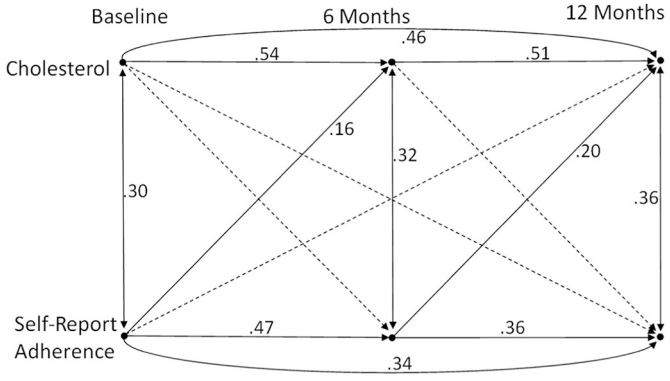

Fig. 1. Predictive Validity of Individual Timepoint Nonadherence and Cholesterol Values. All solid lines with numbers are significant Beta weights from linear regressions, controlling for age, gender, race, and treatment arm. Dotted lines represent nonsignificant associations. Double-sided arrows represent concurrent associations. Single-sided directional arrows represent predictive relationships over time.

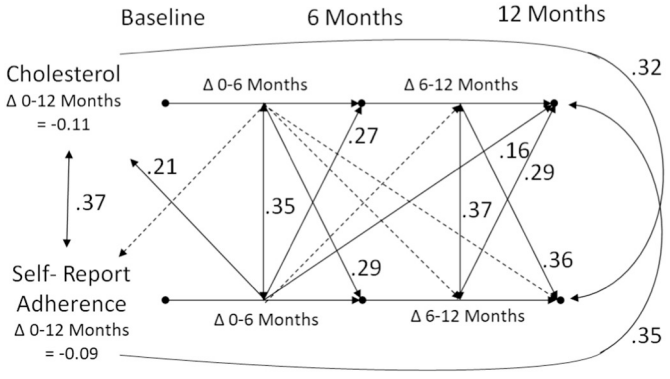

Fig. 2. Predictive Validity of Changes in Nonadherence and Cholesterol Values. All solid lines with numbers are significant Beta weights from linear regressions, controlling for age, gender, race, and treatment arm. Dotted lines represent nonsignificant associations. Double-sided arrows represent concurrent associations. Single-sided directional arrows represent predictive relationships over time. Δ represents change over time.

medication nonadherence measure performs well in patients with hyperlipidemia. The study also provides empirical support that self-reported nonadherence can predict future cholesterol levels, and is sensitive to changes in self-reported adherence that predict future cholesterol levels. The CLPM specifically provides evidence that this observed longitudinal relationship is unlikely to arise from a simpler concurrent relationship in very stable phenomena over time, or a reverse-causal relationship where monitoring of cholesterol values inherent in treatment could influence future adherence rates. The impact of monitoring, reflected in lab values predicting future nonadherence, has been observed in other diseases in which medications have a more immediate effect, such as hypertension and diabetes [30,31]. Nonetheless, we observed that self-reported nonadherence predicted subsequent cholesterol levels *better* than cholesterol levels predicted subsequent self-reported nonadherence: Seven of nine associations over time were significant where self-reported nonadherence occurred first, whereas only three of nine associations over time were significant where cholesterol values occurred first.

Replicating previous research [9,27], the three extent of nonadherence items exhibited high internal consistency across multiple timepoints, suggesting coherence among the items without directly duplicating each other. The endorsement of *any* of these items demonstrated concurrent validity with serum cholesterol above and beyond other factors influencing cholesterol, such as presence of a support person, desire to improve cholesterol, satisfaction with cholesterol, overall cost of medications, and gender. This study provides the first evidence, to our knowledge, of sensitivity to change with this specific self-reported measure of medication adherence: changes in self-reported medication nonadherence predicted changes in cholesterol levels.

Taken together, this evidence demonstrates that the extent of medication nonadherence questions function similarly well in patients with hyperlipidemia as they do in patients with hypertension. The need for self-reported nonadherence measures that have been validated in multiple disease populations is high, and this study adds support for the assertion that the measurement of effect indicators of nonadherence (*extent of* items) can be meaningfully separated from the measurement of causal indicators of nonadherence (*reasons for* items) [8]. In addition, this study is the first to examine sensitivity of changes in this specific self-reported nonadherence across longer periods of time.

Given the measure's sensitivity to valid changes in nonadherence (as

opposed to instability related to error variance across time), this self-report measure of medication adherence may be especially appropriate for clinical trials research. There is much room for improvement in treatment, as statins are widely prescribed and yet fewer than half of patients receiving these medications achieve cholesterol management goals. These goals are not met due to variable adherence rates [5,6], and a large array of barriers to proper adherence (at least 147) [14,32]. Continued advancement in measurement can help increase the sensitivity of trials, leading to more refined and thoughtful interventions targeting the mechanisms behind nonadherence [33,34].

Our analysis had several limitations. First, cholesterol may be more strongly related to nonadherence measured over longer time periods than that captured by seven-day recall. Still, there is some evidence that shorter-term, fixed-day recall measures generally perform better at predicting functional outcomes than longer-term questionnaires [35]. Second, our study lacked electronic adherence monitoring data, which would have provided a more objective measure of concurrent validity. Despite this, we identified that self-reported nonadherence was associated with serum cholesterol concurrently and over time, which would be the most important outcome of any instrument assessing nonadherence – and the outcome that most adherence trials fail to support [10]. Third, the potential for polypharmacy (either combination therapy for cholesterol or contra-indicated medications that could reduce the effect of statins) is present. While this possibility is somewhat unlikely, we hold that any presence of polypharmacy would only strengthen the representativeness and generalizability of the current results in a clinical setting. Finally, this study represents secondary analyses of data from a trial whose aim was to evaluate whether an intervention would improve medication adherence and clinical outcomes of blood pressure and cholesterol. Patients enrolled in the trial may not represent broader patient populations in that they had to meet eligibility criteria, which included having uncontrolled blood pressure and/or cholesterol. Nevertheless, nonadherence rates were commensurate with national averages [36]. Moreover, the psychometric performance of the measure, including its ability to produce reliable and valid scores, would not be undermined by differences in treatment arms.

In sum, our analysis extends previous research 1) by providing evidence that the extent of nonadherence items produce reliable scores in a new population—patients taking cholesterol-lowering medications—and 2) by providing evidence of predictive validity, including sensitivity to change. Utilization of this measure can help move the field beyond one-size-fits-all interventions, and more robust causal models can provide more stringent tests of predictive validity of self-reports, maximizing their value.

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Competing interest statement

All authors declare no competing interests to report.

Conflict of interest

All authors declare no conflicts of interest regarding this work.

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