Health Beliefs, Disease Severity, and Patient Adherence
A Meta-Analysis

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Background: A large body of empirical data exists on the prediction of patient adherence from subjective and objective assessments of health status and disease severity. This work can be summarized with meta-analysis.

Objectives: Retrieval and summary analysis of *r* effect sizes and moderators of the relationship between patient adherence and patients': (1) beliefs in disease threat; (2) rated health status (by physician, self, or parent); and (3) objective disease severity.

Methods: Comprehensive search of published literature (1948–2005) yielding 116 articles, with 143 separate effect sizes. Calculation of robust, generalizable random effects model statistics, and detailed examination of study diversity with moderator analyses.

Results: Adherence is significantly positively correlated with patients' beliefs in the severity of the disease to be prevented or treated ("disease threat"). Better patient adherence is associated with objectively poorer health *only* for patients experiencing disease conditions lower in seriousness (according to the Seriousness of Illness Rating Scale). Among conditions higher in seriousness, *worse* adherence is associated with objectively poorer health. Similar patterns exist when health status is rated by patients themselves, and by parents in pediatric samples.

Conclusions: Results suggest that the objective severity of patients' disease conditions, and their awareness of this severity, can predict their adherence. Patients who are most severely ill with serious diseases may be at greatest risk for nonadherence to treatment. Findings can contribute to greater provider awareness of the potential for patient nonadherence, and to better targeting of health messages and treatment advice by providers.

Key Words: patient adherence, disease severity, meta-analysis, patient compliance

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Patient adherence (also called patient compliance) is essential to the success of disease management, but close to a quarter of patients consistently fail to follow their physicians' recommendations.[1–3] Adherence rates vary considerably across disease conditions and treatment regimens, and can be quite low, even for treatments that are highly effective.[2–4] Adherence is a multifaceted process that occurs through an intricate interplay of complex human experiences.[5] For nearly 6 decades, researchers have endeavored to understand the factors that predict adherence, including the cognitive, psychological, social, environmental, contextual, and therapeutic elements of the experience of living with illness.[6]

Patients' beliefs about their disease and its treatment have been proposed to be central to adherence.[7] The Health Belief Model (HBM)[8] first conceptualized beliefs as predictors of preventive health behavior, and included perceptions of "the threat posed by illness, comprised of the likelihood of its occurrence ('perceived susceptibility') and its potential for causing physical harm and interfering with social functioning ('perceived severity')" (p. 349).[9] Perceived disease severity threat and the other HBM components have also been studied as predictors of patients' *adherence to treatment*, and it has been proposed that greater disease severity threat would be associated with better adherence.[9]

Actual disease severity (ie, patients' health status) has also been suggested as a factor in adherence to treatment.[10,11] Despite a great deal of theoretical and empirical analysis, the question of whether patients who are in better health are more, or less, adherent to treatment than those in poorer health has not yet been answered. Indeed, the process of living with severe illness, the burdens of regimen self-management, and the emotional distress, social isolation, threats to identity, and concerns about the causes, progress, and consequences of a disease can strongly influence *the lived experience of illness* and ultimately affect adherence in intricate ways.[12,13] After almost 60 years of research on patient adherence and many complex and sometimes conflicting empirical findings, consensus about how *actual disease severity* affects patient adherence remains elusive.

Meta-Analysis

Quantitative review with meta-analysis can shed light on multifaceted empirical questions such as these. Meta-analysis involves a thorough and systematic literature search, accompanied by meticulous examination of the results of primary empirical reports. The assessment of empirical find-

ings involves detailed coding of the substantive and methodological characteristics of studies, and thorough investigation of diverse studies utilizing moderator analyses.[14] Indeed, a fundamentally important requirement of meta-analytic work is that the variability among studies needs to be analyzed.[15,16]

Meta-analysis is used here as a rigorous approach to integrating statistical research findings from many individual studies. We address the role of patients' beliefs about disease severity threat, as well as the actual severity of their illness conditions (ie, their health status) as predictors of patients' adherence to prevention and treatment of a variety of acute and chronic conditions, and we analyze the variability among these conditions with detailed moderator analyses. We retrieve and compile all published empirical adherence studies offering data on the relationship of adherence to: (1) perceived disease severity threat; (2) ratings of patients' disease severity (ie, poor health) by a physician, the patient him/herself, or a parent; and (3) objective measures of disease severity (eg, T-cell count, viral load in human immunodeficiency virus [HIV] disease, and ejection fraction in heart disease). This review spans the entire history of adherence research from 1948 through 2005, assessing the direction, size, and combined significance of correlational effect sizes. We thoroughly address the variability in these effects and in the studies from which they are extracted with the examination of moderators (including sample characteristics, measurement strategies, and characteristics of diseases and treatment regimens).

The following hypotheses are offered: (1) Based on the theoretical issues proposed by an expanded version of the HBM,[9] the combined effect across studies is expected to be a positive association between patients' adherence and their perceptions of disease severity threat. (2) Among studies that assess actual disease severity (both rated and objectively assessed), the relationship with adherence will depend upon moderators, including disease and treatment characteristics, that affect the lived experience of illness. Because of the physical and emotional challenges of adhering to complex regimens, adherence is expected to be lowest for patients who are the most severely ill with the most serious medical conditions.

METHODS

This meta-analysis summarizes results from published English language empirical journal articles providing data on the relationship of patient adherence to 3 aspects of disease severity. Table 1 presents the details of definitions, search strategies, and inclusion/exclusion criteria. Table 2 presents details of the process of article coding and effect size extraction, and the coding of moderators, including disease characteristics (eg, chronic/acute, disease seriousness),[17] measurement type/quality (eg, subjective/objective, categorical/scaled, specific/general), regimen (eg, prevention/treatment, medication/behavioral), and sample characteristics (adult/pediatric).

Appendix A presents references for the 116 included journal articles (143 independent effect sizes); Appendix B presents coding details for each reference, including the diseases, samples, regimens, and specific measurement strategies studied, as well as their effect sizes (both listed, and in stem-and-leaf graphical presentations). Both appendices are available from the first author (robin@ucr.edu) and are available on the *Medical Care* Website (www.lww-medicalcare.com).

Statistical Analyses

Precise procedures for the extraction of effect sizes appear in Table 2. The effect size "*r*" was used because it represents the *strength* (from 0 to 1.00) and *direction* (positive/negative) of association. Throughout, a *positive r* indicates that *better adherence* is associated with: (1) greater perception of disease severity threat; (2) greater disease severity (poorer health) rated by physician, self, or parent; and (3) greater objective disease severity (poorer health). A *negative r* indicates that these 3 elements are associated with *worse* adherence.

The stringent, robust, and highly generalizable random effects model was used throughout, allowing generalization of results beyond the studies sampled to population effects.[18,19] In contrast to the fixed effects model, which requires conditional inferences and is based on the total number (N) of subjects across all the studies, the random effects model requires unconditional inferences and uses each sample as one unit of analysis. The fixed effects model underlies both weighted mean analyses and tests of heterogeneity of effects, which in this work are based on extremely high N's and are almost always highly significant (and therefore not always informative). Random effects tests (unweighted means, which are equivalent to *percent risk differences*, their 95% confidence intervals, and standardized odds ratios and standardized relative risks) are based on *k* samples and are more selective.[16,19] To observe commonalities among several measures of central tendency, we present the median, the weighted mean *r* (the fixed effects test), and the unweighted mean (the random effects test) for each set of effect sizes, but we use only random effects tests for all other comparisons.

We examine variability in study effects thoroughly with random effects model tests of methodological and substantive moderators, including, as detailed in Table 2, age group, adherence measurement type/quality, regimen (preventive vs. treatment), disease type (chronic vs. acute), seriousness of the disease condition under study (above vs. below the group median on the Seriousness of Illness Rating Scale [SIRS-r]), and sample size (above vs. below the group median). Fixed effects model heterogeneity tests are presented in the table footnotes because of convention, and their limitations are also explained. We carried out a detailed analysis of moderators using random effects model *t* tests, and we present those that achieved significance in explaining effect size variation.

We calculated the "fail safe *n*" for each significant average effect size and compared it to its "tolerance level." The fail safe *n* is the number of new, unpublished, or otherwise unretrieved studies having no effect that would need to be found to reduce a significant result to nonsignificance at the 0.05 level.[18] Cohen's *d* is another common effect size estimate, and for completeness we have included it here to give an estimate of the standard deviation difference effect size (calculated according to a standard formula; see footnote of Table 3).[2,18] Medians, means, standard deviations, correla-

TABLE 1. Definitions, Search Strategies, and Inclusion/Exclusion Criteria

Population of articles	English language empirical journal articles published 1948–2005.
Defined construct: adherence	Following medical treatment recommendations as prescribed by a physician; terms include but are not restricted to: adherence, compliance, follow-up, treatment continuation, treatment discontinuation, acceptance of medical recommendations, medication omission errors, and defection from therapy, etc.
Defined construct: severity	Aspects of severity: 1. The patient's belief in the severity of the disease to be prevented or treated; belief in the severity of sequelae of failure to treat (as conceptualized in the HBM). Note that this does *not* involve the patient's belief about the severity of his/her *own* disease condition, just about the disease in general. 2. Rated severity of the patient's own disease condition (ie, health status): rated by a physician, the patient, or a parent in pediatric samples. 3. Objective parameters of disease severity of the patient's specific disease condition, including existence of comorbid disease.
Search strategies	Search strategies: 1. "Bottom-up" strategy: detailed search (by hand) of authors' adherence research database: includes all published empirical literature on patient adherence construct starting in 1948; continually updated; developed by searching PsychLit and PubMed (Core Clinical, Cancer Journals, and Abbreviated Index Medicus) databases: keywords "patient compliance," "patient adherence," and related terms as defined above. 2. "Top-down" strategy: keyword searches for published English language citations (1950–2005): PubMed (Core Clinical Journals) and Old Medline using search terms: complian* AND belief; adheren* AND belief; complian* AND sever*; adheren* AND sever*; complian* AND health status; adheren* AND health status. 3. Search for relevant references in empirical papers identified by above strategies; search of references in literature reviews on adherence in general and in specific major disease conditions.
Inclusion/exclusion criteria	Included studies that: 1. Defined and measured adherence to a prescribed treatment or preventive measure (eg, exercise, diet, medication, health-related behavior, screening, vaccination, and appointments) from a medical doctor; 2. Measured (a) beliefs about severity, (b) physician-, self-, or parent-rated disease severity, (c) parameters of severity of patients' diseases or existence of comorbid disease; and 3. A measure, or the means to calculate a measure (r, ϕ, lpoint-biserial correlation, raw data, probability level, effect size d, means and standard deviations, or statistics t, F, or χ^2) of the association between (1) and (2). Excluded (reason): 1. Samples of alcoholic, drug-abusing, homeless, or psychiatric patients/regimens/practitioners (subject of future meta-analytic treatment; beyond the scope of the present study); 2. Institutionalized patients or military personnel (potential institutional controls over adherence); 3. Studies of adherence to community-based programs, such as for screening, vaccination, exercise, weight loss, that were not medically prescribed (subject of past reviews and meta-analytic treatment; beyond the scope of the present study); 4. Studies of interventions designed to increase patient adherence (subject of past meta-analytic treatment; present research is on predictors of adherence); 5. Case studies.

TABLE 2. Details and Description of Article Coding

For each article, the following were recorded:	
1. Reference	Authors; year of publication
2. Disease studied	Prevention or treatment; acute condition or chronic disease
3. Seriousness of Illness	Revised (SIRS-r)*[17]
4. Method for assessing adherence	Self-report, collateral-report, pill count, electronic recording, medical chart, or pharmacy record
5. Measurement type/quality	Objectivity vs. subjectivity; categorical vs. scaled; measurement general or specific to disease under study
6. Regimen requiring adherence	Medication, diet, health behavior, exercise, appointment; regimen for treatment or prevention
7. Sample	Size (n) and age group: adult (age 18 and older) vs. pediatric
8. Effect size "r"	Correlation between measure of patient adherence and criterion measure; form of r extracted (Pearson, point-biserial, ϕ); or calculation of r when necessary (from statistics t, F (1 df), χ^2 (1 df), means/standard deviations, counts in tables or text; or from exact probability level ($\phi = z$ divided by the square root of n) according to recommended procedures.[18] One-tailed z's used when only probability range given: $P < 0.05$ ($z = 1.645$), $P < 0.01$ ($z = 2.326$), and $P < 0.001$ ($z = 3.09$). "Nonsignificant" results (no additional information) were assigned $z = 0.00$ (conservative). Multiple estimates of the same effect were averaged (conservative).
9. Coder agreement	Two coders assigned categories for each study (with >90% initial agreement); disagreements were negotiated before assigning a code

*SIRS-r is an ordinal level scale providing a reliable index of the relative seriousness of various disease conditions; involves expansion and restandardization of its earlier form, and ranks the seriousness of 137 different disease conditions based on ratings by 46 physicians and medical students (concordance coefficient = 0.72).

TABLE 3. Summary of Meta-Analysis Results

Measure of Severity	*k*[a]	Total N[b]	Median *r* (Range)[c]	Weighted Mean *r* (95% CI)[d]	Unweighted Mean *r* (95% CI)[c]	Fail Safe n[e]	St. OR (95% CI)[f]	St. RR[f]	Difference Between Levels of Moderator
1. Perceptions of disease severity threat[g]	27	4313	0.21 (0.00 to 0.53)	0.16 (0.13 to 0.19)*	0.22 (0.16 to 0.28)*; $d = 0.45$	1170[e]	2.45 (1.91 to 3.16)*	1.56	
Small studies	13	746	0.26 (0.00 to 0.53)	0.27 (0.19 to 0.33)*	0.28 (0.19 to 0.37)*; $d = 0.58$	233[e]	3.16 (2.16 to 4.73)*	1.78	$t(25) = 2.54$; $P = 0.018$
Large studies	14	3567	0.15 (0.00 to 0.30)	0.13 (0.10 to 0.16)*	0.16 (0.10 to 0.22)*; $d = 0.32$	342[e]	1.91 (1.49 to 2.45)*	1.38	
2. Physician-rated disease severity (poor health)[h]	5	929	0.09 (0.08 to 0.26)	0.14 (0.11 to 0.17)*	0.14 (0.03 to 0.25)[‡]; $d = 0.28$	27	1.76 (1.13 to 2.77)[‡]	1.33	
3. Self-rated disease severity (poor health)[i]	26	7601	−0.09 (−0.39 to 0.33)	−0.05 (−0.07 to −0.03)*	−0.04 (−0.12 to 0.03); $d = -0.08$	n/a	0.85 (0.62 to 1.13)	0.92	
Low SIRS-r	10	2015	0.10 (−0.24 to 0.25)	0.03 (−0.01 to 0.07)	0.03 (−0.10 to 0.16); $d = 0.06$	n/a	1.12 (0.67 to 1.91)	1.06	$t(19) = 2.19$; $P = 0.041$
High SIRS-r	11	4546	−0.12 (−0.39 to 0.05)	−0.08 (−0.11 to −0.05)*	−0.12 (−0.21 to −0.03)[†]; $d = -0.25$	123[e]	0.62 (0.43 to 0.89)[†]	0.78	
4. Parent-rated disease severity (poor health)[j]	11	1374	0.17 (−0.44 to 0.38)	0.12 (0.07 to 0.18)*	0.08 (−0.09 to 0.25); $d = 0.16$	n/a	1.38 (0.70 to 2.77)	1.17	
Low SIRS-r	7	1000	0.20 (0.00 to 0.38)	0.17 (0.11 to 0.23)*	0.20 (0.08 to 0.31)[†]; $d = 0.41$	71[e]	2.25 (1.38 to 3.60)[†]	1.50	$t(8) = 4.75$; $P = 0.001$
High SIRS-r	3	200	−0.18 (−0.44 to −0.15)	−0.23 (−0.36 to −0.09)[†]	−0.26 (−0.61 to 0.17); $d = -0.54$	n/a	0.35 (0.06 to 1.99)	0.59	
5. Objective disease severity (poor health)[k]	74	147,483	0.01 (−0.46 to 0.37)	0.01 (0.008 to 0.012)*	−0.00 (−0.04 to 0.04); $d = 0.00$	n/a	1.00 (0.85 to 1.17)	1.00	
Low SIRS-r	34	21,989	0.10 (−0.23 to 0.37)	0.07 (0.05 to 0.09)*	0.10 (0.04 to 0.15)*; $d = 0.20$	326[e]	1.49 (1.17 to 1.83)*	1.22	$t(65) = 5.58$; $P < 0.001$
High SIRS-r	33	80,616	−0.11 (−0.46 to 0.15)	−0.08 (−0.10 to −0.06)*	−0.11 (−0.16 to −0.05)*; $d = -0.22$	243[e]	0.64 (0.52 to 0.82)*	0.80	
Pediatric	11	2349	−0.19 (−0.46 to 0.31)	−0.12 (0.08 to 0.16)*	−0.14 (−0.29 to 0.02)[§]; $d = -0.28$	n/a	0.57 (0.30 to 1.08)[§]	0.75	$t(70) = 2.75$; $P = 0.008$
Adult	61	145,010	0.01 (−0.27 to 0.37)	0.02 (0.01 to 0.03)*	0.02 (−0.02 to 0.06); $d = 0.04$	n/a	1.08 (0.92 to 1.27)	1.04	
Objective measure of adherence	31	64,960	0.05 (−0.22 to 0.37)	0.02 (0.01 to 0.03)*	0.05 (−0.01 to 0.11); $d = 0.10$	n/a	1.22 (0.96 to 1.55)	1.11	$t(72) = 2.21$; $P = 0.031$
Subjective (self-rated) adherence	43	82,532	−0.03 (−0.46 to 0.28)	0.01 (0.00 to 0.02)[†]	−0.04 (−0.10 to 0.01); $d = -0.08$	n/a	0.85 (0.67 to 1.04)	0.92	

*$P < 0.001$; [†]$P < 0.01$; [‡]$P < 0.05$; [§]$P < 0.10$.

[a]No. independent samples.

[b]Total N across all samples.

[c]For each sample, a *positive r* demonstrates that *better adherence* is associated with (1) greater perception of disease severity threat; (2) greater disease severity (poorer health) rated by physician, self, or parent, and (3) greater objective disease severity (poorer health). A *negative r* indicates that these 3 elements are associated with *worse* adherence. The unweighted mean *r*, as a percent, is also the standardized percent risk difference (eg, for perceptions of disease severity threat, there is a 22% difference in risk of nonadherence between patients who believe, and those who do not believe, that their disease is serious ($r = 0.22$, CI 0.16–0.28). Cohen's *d* is presented here as another, and for some, more familiar effect size (*r* is converted to *d* with this formula: $d = 2r/\sqrt{(1 - r^2)}$.[18]

[d]Analysis is weighted by n − 3 and is a fixed effects analysis. Weighted mean analysis is generalizable only to the studies here, and based on the large total N across studies is significant in all but 1 case.

[e]The fail-safe N exceeds the level of "tolerance for future null results" above which the "file drawer problem" is unlikely to be a bias (pp. 508–511).[18] Note that the fail-safe N is only applicable to significant findings.

[f]Standardized OR (odds ratio) and standardized RR (relative risk) are based on the binomial effect size display from the unweighted mean effects in the random effects model.

[g]Perception of disease severity threat: random effects moderator analyses: sample sizes ranged from 30 to 972 with a median of 109. After median split, small studies had ≤101 subjects, larger studies had ≥109 subjects. Fixed effects (limited generalizability analyses based on total subject N across studies): perception of disease threat homogeneity test: χ^2 (26) = 61.62, $P < 0.001$. Note that the χ^2 test of homogeneity is a fixed effects test and it is highly dependent upon the sample size of each study; analysis of moderators of variation in effects is essential.

[h]Physician-rated disease severity: random effects moderator analyses: no significant moderators. Of 5 samples, 2 were general ambulatory care and 1 was dermatologic care, with no SIRS-r. The 2 SIRS-r scores were 85 and 89 (mean = 87); therefore no high-SIRS-r diseases are represented in this analysis. Fixed effects (limited generalizability analyses based on total subject N across studies): physician-rated severity homogeneity test: χ^2 (4) = 5.53, ns.

[i]Self-rated disease severity: random effects moderator analyses low SIRS-r: <106; high SIRS-r: ≥106; fixed effects (limited generalizability analyses based on total subject N across studies): self-rated disease severity homogeneity test: χ^2 (25) = 143.04, $P < 0.001$.

[j]Parent-rated disease severity: random effects moderator analyses low SIRS-r: ≤85; high SIRS-r: ≥113; fixed effects (limited generalizability analyses based on total subject N across studies): Parent-rated disease severity homogeneity test: χ^2 (10) = 48.01, $P < 0.001$.

[k]Objective disease severity (poor health): random effects moderator analyses low SIRS-r 109 and below; high SIRS-r 110 and above. The intercorrelations of these 3 significant moderators are low and nonsignificant. Fixed effects (limited generalizability analyses based on total subject N across studies): Objective measures of disease severity homogeneity test: χ^2 (73) = 370.61, $P < 0.001$.

n/a indicates not applicable.

tions, and *t* tests were calculated using Statistical Package for the Social Sciences (SPSS) 11.5, and all meta-analysis components were hand-calculated with a 5-function TI-503 calculator following recommended methods.[16]

RESULTS

The results of this meta-analysis are summarized in Table 3, where statistics are presented for 5 disease severity concepts in relation to adherence: (1) Perceptions of Disease Severity Threat; (2) Physician Rated Disease Severity (poor health); (3) Self-Rated Disease Severity (poor health); (4) Parent-Rated Disease Severity (poor health of their children); and (5) Objective Disease Severity (poor health). For each concept, the following statistics are presented: the number of independent samples (*k*); the total number of subjects across all of the samples (N); minimum, maximum, and median *r*; fixed effects weighted (by *n*) mean *r* (95% confidence interval [CI]); random effects model unweighted mean *r* (95% CI) (also the risk difference as a percentage); *d* effect size; fail safe *n*, standardized odds ratio (95% CI); and standardized relative risk. All moderators that achieved significance in the random effects model are presented. Additional statistical explanations are included in the footnotes.

Perceptions of Disease Severity Threat

Across 27 studies, the relationship between respondents' adherence and their perception of disease severity threat is strongly positive and significant ($P < 0.001$) with both fixed and random effects tests; greater perceived disease severity threat is associated with better adherence. All except two ($r = 0.00$) effects are positive. Based on the random effects model unweighted mean, there is a 22% higher risk of nonadherence ($r = 0.22$, CI 0.16 to 0.28) among individuals who do not believe that the medical condition in question is a threat because of its severity. The fail-safe *n* is well above the tolerance level of 145 and indicates that over 1170 studies with null effects would need to exist to render this finding nonsignificant. Nonadherence is more than 1.5 times greater (standardized relative risk) among individuals who do not perceive a disease severity threat, and the odds (standardized odds ratio) of adhering are almost 2.5 times higher if patients believe the disease to be prevented or treated is severe and a potential threat. Careful analysis of the variation in these effects, testing all moderators with the random effects model, produced one significant moderator: sample size. In smaller studies with 101 subjects or less (below the median sample size), the average effect is significantly larger than in samples with more subjects ($r = 0.28$ vs. $r = 0.16$). There is no consistent variation because of regimen (prevention or treatment), sample, disease, or measurement type/quality.

Physician-Rated Disease Severity

Across 5 studies, patients rated poorer in health by their physicians are more adherent to treatment (standardized risk difference 14%; $r = 0.14$, CI 0.03 to 0.25). No moderators are significant. The disease conditions/settings in these 5 studies include 2 with a variety of conditions in ambulatory primary medical care, 1 with a variety of conditions in a dermatology clinic, 1 of patients with asthma, and 1 of patients with rheumatoid arthritis (both conditions low; 85 and 89, respectively on the SIRS-r).

Self-Rated Disease Severity

In 26 studies, there is a near-zero average association of adherence with patients' self-rated disease severity (poor health). Because of the large total N, the fixed effects weighted mean is significant, but the more robust random effects unweighted mean is nonsignificant. The variability of these effects (as seen in the median and range) necessitates a detailed analysis of moderators. Only one is significant: the seriousness of the disease condition assessed by the SIRS-r. In studies of less serious conditions (SIRS-r scores below the median), there is a nonsignificant near-zero relationship ($r = 0.03$) between adherence and self-rated disease severity. In samples of more serious diseases (above the SIRS-r median), patients with greater self-rated disease severity (poorer health) are significantly *less adherent* than healthier patients ($r = -0.12$, CI -0.21 to -0.03).

Parent-Rated Disease Severity

A similar pattern arises with parents' ratings of the disease severity (poor health) of their children. The unweighted mean *r* is not significant (although the fixed effects weighted mean *r* is), and one moderator is significant. In the samples of less serious diseases (which include pharyngitis, otitis media, and asthma), children judged by their parents to be in poorer health have significantly better adherence. In more serious diseases (including end stage renal disease [ESRD], and diabetes), the reverse pattern occurs. Children judged by their parents to be in poorer health have significantly *worse* adherence. Although this effect does reach significance in the fixed effects model, it does not in the random effects model (where $k = 3$). Nonetheless, the standardized risk difference of 26% ($r = -0.26$, CI -0.61 to 0.17) is worthy of note.

Objective Disease Severity

This research also investigates *objective assessments* of disease severity (poor health). These assessments are, for the most part, physiological (eg, T-cell counts, viral load in HIV, forced expiratory volume in 1 second [FEV1] in chronic obstructive pulmonary disease [COPD], ejection fraction in heart failure, and erythrocyte sedimentation rate in rheumatoid arthritis). They also include focused, disease-specific measures (eg, medical record documented comorbid medical conditions, visual acuity in cataracts, and seizure frequency in epilepsy). Across 74 studies, there is a zero average unweighted mean correlation between objective disease severity and patient adherence. (The weighted mean *r* is 0.01 and significant with N = 147,483.) Variability in these effects compels a detailed analysis of substantive and methodological moderators, and 3 independent moderators (ie, uncorrelated with each other) are significant in accounting for study variability.

First, a median split (across the 67 studies for which SIRS-r could be assessed) shows a significant difference in *r* effect sizes between conditions assessed as low versus high in seriousness. Among less serious diseases (eg, hypertension,

arthritis, and cataracts), patients in objectively poorer health are *more likely* to be adherent than patients in better health. In more serious conditions (eg, cancer, HIV, ESRD, and heart failure), however, patients who are more severely ill (in poorer health) are significantly *less likely* to be adherent. Those in poorer health have an 11% greater risk of nonadherence than those in better health ($r = -0.11$, CI -0.16 to -0.05).

Second, age group moderates the effects of objective disease severity and patient adherence. Among 11 pediatric samples, there is a negative association between objective disease severity and adherence (unweighted means analysis trend: $P < 0.10$), whereas for adult samples the association is near-zero. The difference between these means is significant [$t(70) = 2.75$, $P = 0.008$]. Thus, in pediatric samples, there is a 14% higher risk of nonadherence among individuals with objectively poorer health (unweighted mean $r = -0.14$, CI -0.29 to 0.02; $P = 0.097$).

The third significant moderator is objective versus subjective assessment of adherence [$t(72) = 2.21$, $P = 0.031$], although for both types of adherence measurement the weighted mean r is significantly different from zero, but the random effects model unweighted mean is not.

DISCUSSION

The meta-analytic work described here summarizes the results of a comprehensive literature search for empirical studies on the relationship between several aspects of disease severity and patient adherence to treatment. Past meta-analytic research has pointed to a possible influence of disease conditions on adherence.[2] The present research quantifies and examines in detail the seriousness of various disease conditions and patients' health status within those conditions, allowing a better understanding of factors that may influence patient adherence. The present meta-analysis has included a broad range of subjects, disease conditions, and treatment regimens. Measurement type/quality also varied across studies. Meta-analytic methods allow the combining of results from these studies, offering stable estimates of effects and (with the random effects model) the opportunity to generalize findings to related populations. Meta-analysis also *requires* the analysis of the variability in these effects, and the identification of moderators that explain patterns in this variation.

One goal of this research has been to assess the effect size and significance of the relationship between patients' adherence and their perceptions of disease severity threat, as proposed in a broadened conceptualization of the HBM.[9] Across 27 studies, the average correlation is substantial and comparable in effect size (from meta-analysis) to 2 major predictors of adherence: depression and social support.[20,21] Perceptions of disease severity threat involve the assessment that a disease to be prevented or treated is serious. This finding suggests the importance of attention to health education, persuasive messages, and the enhancement of patients' health literacy in promoting adherence. It also points to the importance of the effective management in clinical practice of communication barriers such as language, culture, ethnicity, and social class in helping to enhance patient adherence.[22–26] Knowing that patients' awareness of disease severity can affect their adherence may offer health professionals more effective options for intervention. Health messages should be developed to increase adherence in the context of patient-centered and trusting therapeutic relationships in which patients are helped to recognize when their health threats are severe and health-promoting behaviors can reduce their risks and improve their well-being.[27–30]

The second goal of this study has been to assess the relationship between patients' adherence and the severity of their own disease conditions, whether their poor health status was rated or measured objectively. The question addressed was simple: Are patients in worse health more adherent than patients in better health? This meta-analysis found that the answer is "yes," but only when patients' disease conditions are relatively low in seriousness (as measured by the SIRS-r). When patients have quite serious conditions (including HIV, ESRD, cancer, and heart disease), those who are *in worse health* are *less likely* to be adherent, whether their health is assessed objectively or is rated by their parents or themselves. In interpreting this result, it is suggested that when patients are severely ill with quite serious diseases, many physical, psychological and practical limitations, and personal illness models (regarding the causes, consequences, controllability, and trajectory of illness) can significantly disrupt patients' efforts at adherence.[31] Appendix B presents a number of individual studies included in this meta-analysis that make precisely this point. Establishing medication and treatment routines central to the management of complex regimens, and attempting to live normal gratifying lives despite the demands of serious disease, can be very difficult when health status becomes increasingly poor.[32] Patients may have doubts about the efficacy of their treatments, particularly if some have failed them,[33] and their expectations for and interactions with their providers may be reduced in quality as they grow more severely ill.[34,35] For patients in poor health with serious disease conditions, adherence may even seem futile, and patients may become depressed, pessimistic, socially withdrawn, and hopeless (or even ambivalent) about surviving.[36,37]

Limitations of This Research

The present findings are correlational, necessitating caution in drawing causal inferences. The temporal ordering of measurements does support some causal interpretation: both perceptions of disease severity threat and patients' health status were assessed *before* adherence was measured. Thus, it could be argued that the causal arrow points *from* perceptions and baseline health status *to* adherence, and not the reverse. These severity–adherence relationships might be the result of one or more "third variables" that are causally linked to both adherence and disease severity. Such variables, which would need to be measured within study, include patients' socioeconomic vulnerability, ethnicity, depression, social isolation, and age, among others.[1,38,39] Additional possibilities include aspects of measurement type/quality, although many of these have been examined as moderators in the present research, and in only one case is there a moder-

ating effect of measurement: the objectivity (vs. subjectivity) of adherence assessment.

There are other limitations to be acknowledged as well. First, the search may have missed some relevant studies, although the combined strategies (top-down, bottom-up, and cross-referencing) allowed a thorough search of the literature; multiple cross-checks of the methods eventually yielded no new references. Second, this meta-analysis excluded adherence to mental health care, which should be the subject of future meta-analytic work. Third, studies may have had a greater likelihood of publication if they had significant findings, although here the fail-safe *n* corrects for this potential. It was, of course, not possible to correct for potential biases of researchers to conduct studies for which certain severity–adherence effects might be expected. Such a bias might exist for focused studies of the HBM construct. Studies providing effect sizes for rated and objective disease severity measures, however, usually offered these effects incidentally in the context of other research issues and, therefore, were less subject to such bias. Fourth, this work was limited to the compilation and assessment of within-study linear relationships that are, by far, the most common statistical approach in adherence prediction research. We used moderator analyses to identify and assess nonlinear relationships *across* studies, however, and some of these were quite informative. Finally, in the fixed effects model (weighted mean) analyses, some small effects were significant because of their large total sample size. Random effects tests (eg, unweighted mean), on the other hand, were based on the number of samples and offered much more limited significance. It should be noted that in the random effects model, numerically small effects (eg, 0.11) can still be quite important,[19] and may be larger than many in medical research, such as aspirin and the prevention of heart attacks ($r = 0.03$), propanolol and the prevention of death ($r = 0.04$), indinavir and the prevention of serious AIDS complications ($r = 0.09$), and numerous others.[14,40]

Future Research

Future research should quantify and assess the reasons why those in worse health with more severe conditions face greater challenges to adherence, and whether patients' expectations for the benefits of adhering decrease when their health status declines. Future studies should examine multiple correlates of adherence, and assess nonlinear relationships within studies, using a standard set of correlates (eg, demographics, disease-related variables, and regimen characteristics) allowing direct comparisons across studies and combining these effects with meta-analysis.[41] Future work should also assess in more detailed and complex ways the additive and interactive effects of disease severity on adherence and treatment outcomes.

Clinical Implications

There is growing theoretical and empirical evidence that many aspects of the physician–patient relationship, including the content and quality of communication, can affect patients' health outcomes by influencing their adherence.[42] The present research suggests that patients' personal models of illness, and their suffering in the face of serious disease, should be addressed effectively in physician–patient communication lest they compromise the process of care. Effective relationships with physicians can help patients to cope with the complexities of serious illness, manage identity and self-image, and come to terms with the meaning of illness and treatment in their lives.[43,44] The present findings show how disease severity, and patient's awareness and understanding of it, can lead to better targeting of health messages and provider advice for patients. Patients' perceptions and beliefs should be fully understood in efforts to foster their adherence,[7,10,11,45] and in the context of social and cultural sensitivity, physicians should assure that their patients fully understand the severity of their disease conditions and the necessity of carefully adhering to treatment.[23] The present findings also suggest that when patients struggle with serious conditions, distressed states, such as anxiety and depression, may contribute to difficulty in processing and acting upon clinical directives.[46] When patients have very serious illnesses, those who are in the poorest health should be recognized as having the greatest risk for nonadherence to treatment. Further, when children are suffering from serious diseases and parental management of adherence is crucial, parents' perceptions should be monitored closely because of potential implications for adherence to their children's care.[47–49] The findings of this research are likely to become increasingly relevant as the population ages and poor health status, in the context of serious comorbid conditions, combines with psychological distress, challenges to coping, and complex treatment regimens to threaten levels of adherence essential to achieving effective health outcomes.[39,50]

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