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Assessing the multidimensional relationship between
Medication Beliefs and Adherence in older adults with
Hypertension using Polynomial regression

Abstract

Background: The Necessity – Concerns Framework (NCF) is a multidimensional theory describing the relationship between patients’ positive and negative evaluations of their medication which interplay to influence adherence. Most studies evaluating the NCF have failed to account for the multidimensional nature of the theory, placing the separate dimensions of medication ‘necessity beliefs’ and ‘concerns’ onto a single dimension (e.g. the BMQ-difference score model).

Purpose: to assess the multidimensional effect of patient medication beliefs (concerns and necessity-beliefs) on medication adherence using polynomial regression with response surface analysis.

Methods: Community dwelling older adults >65yrs (n=1211) presenting their own prescription for antihypertensive medication to 106 community pharmacies in the Republic of Ireland rated their concerns and necessity-beliefs to antihypertensive medications at baseline and their adherence to antihypertensive medication at 12 months via structured telephone interview.

Results: Confirmatory analysis found the difference-score model to be inaccurate; subsequent exploratory analysis identified a quadratic model to be the best fitting polynomial model. Adherence was lowest amongst those with strong medication concerns and weak necessity-beliefs, and adherence was greatest for those with weak concerns and strong necessity-beliefs (slope $\beta = -0.77$, $p < 0.001$; curvature $\beta = -0.26$, $p = 0.004$). However novel non-reciprocal effects were also observed; patients with simultaneously high concerns and necessity-beliefs had lower adherence than those with simultaneously low concerns and necessity-beliefs (slope $\beta = -0.36$, $p = 0.004$; curvature $\beta = -0.25$, $p = 0.003$). The difference-score model fails to account for potential non-reciprocal effects.

Conclusion: Results extend evidence supporting use of polynomial regression to assess the multidimensional effect of medication beliefs on adherence.

Key-words: Beliefs about Medicines Questionnaire (BMQ), Medication Adherence, Necessity-Concerns Framework, Polynomial Regression.

Introduction

Medication non-adherence is highly prevalent across chronic illnesses, estimated at approximately 34-50% (1). A meta-analysis estimated good adherence (greater than 80% by medication possession ratio) to antihypertensive medication at 59% and observed good adherence to be associated with a 19% reduced risk of cardiovascular disease and a 29% reduction in risk of all-cause mortality (2). The World Health Organisation suggests that increasing adherence may have a greater impact on the health of populations than any improvement in specific medical treatments (3). One modifiable determinant of adherence are patient beliefs of their personal need for treatment and their concerns regarding their treatment (4, 5). The Necessity-Concerns Framework (NCF) is a multidimensional theory describing this relationship between patients' positive and negative evaluations of their medication which interplay to influence adherence (6). According to the NCF, patients balance their concerns about the medication against their perceived need for the medication when deciding whether or not to take the medication, and that patients are more likely to take their medication if they have stronger beliefs in the necessity of that medication and lower medication concerns.

The Beliefs about Medicines Questionnaire Specific (BMQ-Specific), which consists of two subscales, 'necessity beliefs' and 'concerns', is a psychometric scale designed to assess the NCF (6). The necessity subscale of the BMQ assesses current and future perceived benefit of treatment, whereas the concerns subscale assesses negative emotional and cognitive representations of medication treatment (4). Numerous studies have supported the NCF, observing significant associations between concerns and necessity-beliefs, and adherence to medication across a range of chronic conditions, including asthma (7), cancer (8), cystic fibrosis (9), depression (10), HIV (11), hypercholesterolaemia (12) and hypertension (13-15). Furthermore, a meta-analysis of 94 studies showed that fewer concerns about treatment and stronger perceptions of the necessity of medication, was associated with greater adherence (16). Given the consistency of findings across

multiple illness populations, the NCF represents an important framework to underpin development of interventions aimed at improving adherence in clinical practice through modification of patient beliefs.

Despite the potential clinical utility of the NCF, Phillips et al contend that progress has been limited due to suboptimal analytical methods used to assess the relationship between concerns, necessity-beliefs, and adherence (17). Although the NCF is multidimensional with concerns and necessity-beliefs representing two separate theoretical dimensions, which have been shown to be uncorrelated and independent predictors of adherence, researchers have tended to place the separate dimensions onto a single dimension by constructing a difference score (necessity beliefs minus concerns) (4, 13, 15) or artificially categorising patients into attitude groups (7, 10, 18, 19). Phillips et al argue that difference scores or artificial categories are inappropriate as theoretically they undermine the multidimensional nature of the NCF, and statistically decrease power and increase the risk of type I and II error (17). By constructing a difference score, researchers are implying that a one point increase in necessity-beliefs has an equivalent effect on adherence as a one point decrease in concerns, which theoretically is incorrect, but also assumes statistical constraints that should be assessed.

Polynomial regression is an analytic approach that allows for the assessment of the multidimensional nature of the NCF. It is a suitable technique to test the relationships implied by difference scores (20). Applying polynomial regression to evaluate the NCF among stroke survivors, Phillips et al found support for the difference score model such that adherence was greatest when necessity-beliefs outweighed concerns. However, they also highlighted the limitations associated with a difference score model. Firstly they found the statistical constraints to be inaccurate and secondly, when applying polynomial regression they identified effects of non-reciprocal beliefs on adherence, which increased explained variance in adherence beyond the difference score.

Specifically, patients with ambivalent beliefs (both concerns and necessity-beliefs were high) were less adherent than those reporting indifference (both concerns and necessity-beliefs were low) (17).

These findings highlight the complexity of the relationship between patients concerns, necessity-beliefs and medication adherence which have not been assessed in previous studies. However, Margolis et al argue that these results need to be replicated in different patient populations to confirm these findings, and that a number of shortcomings identified in Phillips et al's study need to be addressed in future studies (21). Our aim thus was to use polynomial regression, an appropriate analytic technique, to assess the relationship between patient beliefs and adherence to antihypertensive medication in older adults while overcoming previous limitations; firstly assessing the longitudinal multidimensional effect of patient beliefs on adherence, thereby avoiding weaknesses associated with cross-sectional analyses and secondly assessing beliefs and adherence to a single class medication, reducing misclassification of exposure and outcome.

Methods

Study Design and Setting

We conducted a prospective cohort study, recruiting participants from 106 community pharmacies across the Republic of Ireland between March and May 2014. Community pharmacies were selected on the basis of participating in the National Pharmacy Internship Programme. Using a prevalence estimate of 51% for adherence to antihypertensive among older adults (22), a sample size of 1,300 would allow the study to determine the prevalence of adherence with a confidence interval of $\pm 3\%$, and have 95% power to detect a factor which reduces or increases adherence by 10%. Thus allowing for a 10% loss to follow-up, approximately 1,500 participants were required and each pharmacy aimed to recruit 15 patients. Consecutive participants were invited to take part if they met the following inclusion criteria: presenting to a participating pharmacy to fill their own prescription for at least one antihypertensive agent as determined by the pharmacist, aged 65 years or older, community dwelling, able to speak and understand English and no evidence of cognitive impairment. After obtaining informed consent, participants completed a structured telephone interview conducted by trained pharmacy interns and were re-contacted at 12 months to conduct a follow-up structured telephone interview. Each interview was subsequently linked to dispensing records from that pharmacy for the previous 12 months. To examine the longitudinal associations between patient beliefs and adherence, we evaluated patient concerns and necessity-beliefs at baseline, and self-reported adherence to antihypertensive medication using the 8-item Morisky Medication Adherence Scale (MMAS-8) at 12 month follow-up.

Ethical approval for this study was granted by the research ethics committee of the Royal College of Surgeons in Ireland.

Study Measures

Adherence to antihypertensive medication was measured at 12 month follow-up using the MMAS-8, which is an 8-item measure with 7 yes/no items (e.g. *“Do you sometimes forget to take your*

medication”) and one 5-point response scale (“How often do you have difficulty remembering to take all your medication”) (© 2007 Donald E. Morisky). Participants responded to these questions in relation to their antihypertensive medication. Higher scores on the MMAS-8 indicate higher adherence. The MMAS-8 has been shown to be reliable in estimating adherence to antihypertensive medications ($\alpha=0.83$) and to have predictive validity through associations with blood pressure control (23).

The concerns and necessity-beliefs subscales of the BMQ-Specific which evaluate the NCF were measured at baseline. The subscales of the BMQ-Specific consists of 5 items measuring concerns about antihypertensive medication (e.g. “Having to take medicines worries me”) and 5 items regarding patients necessity-beliefs about antihypertensive medication (e.g. “My health, at present, depends on my medicine”) (6). The response scale is a five point Likert-scale ranging from “strongly agree” to “strongly disagree”. Participants responded to these questions in relation to their antihypertensive medication. Higher scores on the necessity subscale indicate stronger beliefs in the necessity of medication while higher scores on the concerns subscale indicate greater concerns about medication.

A number of covariates known to be associated with adherence were also recorded at baseline, including demographics (e.g. age, gender, education, and state-funded healthcare status), health behaviours (smoking), comorbidities and medication history (3). The Irish health care system consists of mixed public and private funding which may influence access to medication. Eligibility for the General Medical Scheme (GMS), which provides free primary-care services and medicines at a cost of a €2.50 levy, and the Doctor Visit Card (DVC), which provides free primary-care services only, are by means testing based on income. An additional Long-term Illness (LTI) scheme exists for patients with chronic conditions such as diabetes but not hypertension which provides free primary care services and free medication. Multimorbidity was measured as a count of self-reported comorbid conditions. History of heart attack, angina and stroke, were considered important covariates, as

treatment of hypertension for secondary prevention may be associated with higher adherence (1, 24). The number of regular medicines, which may influence adherence, was determined as the count of all medication dispensed at least three times in a four month lead in period prior to the interview (25). Regimen complexity can negatively influence adherence and the number of specific antihypertensive medication and the dosing frequency (e.g. once daily, twice daily etc) were determined from pharmacy records (26-28). Higher doses may increase the frequency of adverse effects and lead to reduced adherence, thus the combined dose of the antihypertensive regimen was determined using the WHO Defined Daily Dose (WHO-DDD) system. The class of antihypertensive was determined from pharmacy records as this may affect adherence, with adherence reported to be lowest in those taking beta-blockers and diuretics and highest with angiotensin receptor blockers and angiotensin converting enzyme inhibitors (29). Repackaging of medication by pharmacists into multi-dose units (MDUs) is performed to aide management of complex medication regimes and may facilitate adherence, and was determined at baseline interview and by examining pharmacy records (30).

Statistical Analysis Overview

Polynomial regression was used to assess the multidimensional effect of baseline medication-related concerns and necessity-beliefs on self-reported adherence at 12 month follow-up. Polynomial regression analysis consists of two-steps: firstly confirmatory polynomial regression is conducted to see if the strict difference score model is accurate (i.e. to determine whether the use of the single difference score variable to represent both concerns and necessity-beliefs is statistically appropriate in this sample) (17, 31, 32). If the difference score model is inaccurate then exploratory polynomial regression is undertaken. Polynomial models of increasing order (linear, quadratic, and cubic models) are tested for fit to the data in a hierarchical regression with the terms of each order model entered together as a step in the regression model (17, 31, 32). The polynomial terms for the BMQ-Specific are described in Table 1. We conducted exploratory polynomial regression analysis with the inclusion of control variables. The concerns and necessity-belief subscales were scale-centred by

subtracting the midpoints of their scales to reduce multi-collinearity and aide interpretation of higher order terms (20). Finally response surface methodology is employed to interpret the three dimensional joint effects of concerns and necessity-beliefs on adherence (20, 33).

Confirmatory Polynomial Regression

Confirmatory polynomial regression was conducted first, to see if the strict difference score model was accurate. The model fit of the “constrained model” (i.e., the difference score model, with the difference between concerns and necessity beliefs as the only predictor), was compared to the fit of the “unconstrained” polynomial regression model (with separate necessity beliefs and concerns variables as predictors). Relative fit was determined by evaluating four criteria: firstly the “unconstrained” model must explain significant variance in adherence; secondly, the regression coefficients for the concerns and necessity subscales must be significant and be in the expected direction; thirdly the constraints that the magnitude of the concerns and necessity coefficients are equal must be accurate; and finally higher order models should not explain significant variance beyond that of the linear terms. If all four criteria are met the use of the difference score model is supported (17, 31, 32).

If any of the four criteria to support the difference score model are not met, the constrained model is rejected and exploratory polynomial regression is conducted to find the best-fitting polynomial model.

Exploratory Polynomial Regression

In exploratory polynomial regression analysis, the increase of variance in adherence explained in each hierarchical model is calculated and tested using partial f -tests. The best-fitting model is the highest-order model to explain significant incremental variance in adherence, adjusting for covariates.

Polynomial regression results in a three-dimensional (3D) model, with the two predictors (concerns and necessity-beliefs) on the X- and Y-axis respectively, and with the outcome (adherence) on the Z-

axis. Rather than directly interpreting the estimates from the regression model, response surface methodology is used to assess the joint effect of concerns and necessity-beliefs on adherence. We can calculate the surface values of the 3D relationship, specifically along the lines of congruence and incongruence, which reveal how the outcome (adherence) is influenced when the predictors match in magnitude (are “congruent”; $X=Y$) or are opposite in magnitude (are “incongruent”; one predictor equals the negative of the other, $X=-Y$) (20, 33).

Statistical modelling was performed using Stata version 13 (StataCorp College Station, Texas, USA). Response surface analysis and graphing was performed using a Microsoft Excel template developed by Shanock et al (33).

Results

Participants

A total of 2,231 consecutive patients were invited to participate, 71.4% (N=1,592) consented and completed the baseline telephone interview (Figure 1). Twenty-eight participants were subsequently considered ineligible as they did not meet the inclusion criteria, leaving a sample of 1,564 at baseline. The mean age of participants at recruitment was 76.3 years, 46.7% were male, and 73.7% were GMS patients. Table 2 outlines baseline participant characteristics. At baseline the mean scores for the concerns and necessity-beliefs subscales were 2.17 (*SD* 0.60, n=1500) and 3.65 (*SD* 0.69, n=1503) respectively (Figure 2). At 12-months, participants were re-contacted and 1,232 (79%) agreed to the follow-up interview and complete MMAS-8 scores were available for 1,211 participants. According to the defined MMAS-8 cutoffs (34), 52.2% of participants reported high adherence (score=8), 36.3% reported medium adherence (score=6<8) and 11.5% reported low adherence (score<6). Two observations displayed signs of satisficing (responding identically for ratings on a series of multiple questionnaire items on the same response scale) and were removed.

Confirmatory Polynomial Regression

The confirmatory polynomial regression rejected the difference score model (Table 3). Firstly the unconstrained model explained significant variance in the outcome ($F(2, 1142)$, $p<0.001$); secondly the coefficients for the concerns ($\beta=-0.28$, $p<0.001$) and necessity ($\beta=0.13$, $p=0.003$) subscales were significant and in the expected direction; however, for the third criterion the unconstrained model explained significant incremental variance over the constrained model ($F(1, 1142)=4.56$, $p=0.033$). This implies the constraints imposed by the difference score model that the magnitude of the coefficients for concerns and necessity are equal but opposite in direction is inaccurate. The fourth criterion did not require testing as the third criterion was not met.

Exploratory Polynomial Regression

As the difference score model was rejected, exploratory polynomial regression analyses was conducted. Higher order polynomial terms for the concerns and necessity-beliefs were tested for model fit in predicting adherence at 12 months, adjusting for covariates. The linear terms (R^2 change=0.031, $p<0.001$) and quadratic terms (R^2 change=0.012, $p=0.005$) predicted the outcome but the cubic terms did not (R^2 change=0.007, $p=0.128$). Thus the quadratic sets of terms were the best fitting model for predicting MMAS-8 score at 12-months. The full model including unadjusted and adjusted coefficients is detailed in table 4. Response surface analysis was performed to allow interpretation of the combined effect (quadratic terms) of concerns and necessity-beliefs on adherence, calculating the slopes along the lines of congruence and incongruence and producing a graphical representation of the 3D relationship adjusted for covariates (Figure 3). Significant reciprocal effects were observed along the line of incongruence; as medication concerns increased and medication necessity-beliefs decreased, adherence was reduced (slope $\beta = -0.77$, $p<0.001$) and adherence decreased more sharply at extreme values of concerns and necessity (curvature $\beta = -0.26$, $p=0.004$). Clinically, this is similar to the known relationship, that adherence is greatest when concerns are low and necessity-beliefs are high, however a greater decrease in adherence at more extreme values of concerns and necessity-beliefs was also observed (Figure 3). Non-reciprocal effects were also apparent which cannot be detected using the difference score model. Along the line of congruence where concerns and necessity scores simultaneously increase, adherence was also reduced (slope $\beta = -0.36$, $p=0.004$) and decreased more sharply at extreme values of concerns and necessity (curvature $\beta = -0.25$, $p=0.003$). This adds an additional clinical interpretation, that the absolute levels of concerns and necessity-beliefs are also important, as we observed those with simultaneously high concerns and necessity-beliefs have lower adherence than those with simultaneously low concerns and necessity-beliefs (Figure 3).

Other covariates associated with a lower MMAS-8 score at 12 months include male gender, an increasing number of self-reported comorbidities and having medicines repackaged into multi-dose unit containers.

The results presented are a complete case analysis, with 13.6% of missing observations due to missing data across covariates. To account for the potential biases in estimates and standard errors due to missing data, multiple imputation, with multivariate normal distribution, Markov Chain Monte Carlo procedure and 100 imputations was performed, but did not change the overall conclusions.

Discussion

Key findings

This is the first study to use a prospective design to assess the longitudinal multidimensional relationship between patient medication beliefs (concerns and necessity-beliefs) and adherence to a single medication class using polynomial regression. Confirmatory polynomial regression analysis found that the constraints implied by the difference score are inaccurate and polynomial regression should be used to assess the multidimensional relationship between concerns, necessity-beliefs, and adherence. Exploratory polynomial analysis found a quadratic model to be the best fitting model to assess the multidimensional relationship and identified novel effects of non-reciprocal patient medication beliefs on adherence to antihypertensive medication. Specifically, “ambivalent” patients who have simultaneously high beliefs in the necessity of their antihypertensive medication but also hold strong concerns about these medications had lower adherence than “indifferent” patients who had simultaneously low concern and necessity-beliefs.

The study in the context of other studies

Similar to previous studies assessing the relationship of medication beliefs with adherence to antihypertensive medication, we found lower concerns and higher necessity-beliefs to be associated with better adherence. However these studies either used the difference score model (13, 15), BMQ-categorisation (19), or non-polynomial regression methods such as logistic regression or χ^2 -tests (14, 15, 35, 36). The use of the difference score and BMQ-categorisations methods do not appropriately assess the NCF, the theoretical underpinning of the BMQ and also present statistical issues that may increase both type I and II error, thus undermining findings obtained using these methods (17). Our confirmatory polynomial analysis found the difference score model to be inaccurate. Similarly, using logistic regression analyses, by dichotomising the adherence outcome results in loss of statistical power and often arbitrary cut-points are chosen to dichotomise adherence with no justifying rationale, raising issues of the face validity of the adherence measure (37, 38). In addition we also observed novel effects of non-reciprocal concerns and necessity-beliefs

on adherence to antihypertensive medication which cannot be observed using other analytical methods. In contrast to the recommendations of a recent systematic-review to use the BMQ-difference score (39), we recommend researchers use polynomial regression to assess the relationship between beliefs about medicines and adherence by keeping concerns and necessity-beliefs as separate variables, and measuring adherence on a continuous scale. To interpret our findings in a clinical setting, clinicians should note the absolute levels of beliefs in addition to determining whether concerns outweigh necessity-beliefs. Patients with high concerns and necessity-beliefs may have lower adherence than those with low concerns and necessity-beliefs.

The previous study utilising polynomial regression assessed the cross-sectional multidimensional relationship between medication beliefs and adherence in a population of stroke survivors (17). We have utilised a prospective design to assess the longitudinal relationship between medication beliefs and adherence to antihypertensive medications, overcoming potential response bias associated with concurrent assessments of medication beliefs and adherence (i.e. earlier responses to one questionnaire may influence subsequent responses to the other questionnaire). Additionally, we used the original items and responses from the BMQ, which will allow improved comparability with other studies, and we assessed beliefs and adherence to a specific class of medication reducing potential misclassification of exposure and outcome (e.g. responding to belief questions about a statin, and responding subsequently to adherence questions about an antihypertensive). The confirmatory polynomial analysis in the stroke cohort concluded similarly that the difference score model was inaccurate and in exploratory polynomial regression found a linear model to be the best fitting model. In contrast, we found a quadratic model to be the best fitting model. This may reflect slight differences in the longer-term relationship between beliefs and adherence, or potential differences in the study population (older hypertensive adults versus stroke survivors). Non-linear relationships may also arise because the distance between each step on the likert response scale may not infer the same meaning to the respondent. The interpretation of linear and quadratic models however is similar – the quadratic model characterises additional curvature effects with

sharper decreases in adherence at extreme values of the necessity beliefs and concerns subscales. For clinical settings, a quadratic model means that the effects on adherence will be greater at extreme levels of necessity beliefs or concerns.

Interventions should be informed from appropriate application of theoretical frameworks (40, 41), and interventions developed to improve adherence through modification of patient beliefs may have been misinformed due to inappropriate application of theory. For example O'Carroll et al developed a complex intervention to improve adherence in stroke survivors which aimed "to correct misperceptions and provide evidence so that participants' medication necessity beliefs come to outweigh their medication concerns beliefs" (42). This intervention was grounded in the NCF framework, specifically the BMQ-difference model (43), and reported no significant effects for two of the three primary adherence measures. These results may be an artefact of relying on the difference score in designing the intervention, although a significant decrease in concerns was observed (44). Researchers developing interventions utilising the NCF to modify medication beliefs to improve adherence need to be aware of the multidimensional effect of beliefs and consider non-reciprocal effects.

Limitations

Our study is limited by the self-report measure of adherence used, which may be subject to recall bias and social desirability bias resulting in overestimation of adherence (45). The Medication Possession Ratio (MPR), an objective measure of adherence, has been shown to be associated with clinical outcomes such as blood pressure control (46-48), however was considered an unsuitable measure in our study. Specifically our cohort are largely publically insured under the General Medical Scheme (GMS) and obtain medication at a low cost of €2.50, largely removing the cost barrier associated with non-adherence except for the most socioeconomically disadvantaged. Additionally it was common dispensing practice to record all medication from GMS prescriptions to the dispensing record on the same day, regardless of whether the patient obtains all medication on that particular day, or collects some or all medication at a later time-point. Finally approximately

11% of participants have medication repackaged into multi-dose unit containers and are subject to pharmacy workflow procedures to manage these tasks. These unique limitations overinflate adherence objective measures including the MPR. However the MMAS-8 is suitable for use in clinical practice and was developed specifically for hypertension and has demonstrated predictive validity with blood pressure control (23, 49, 50). Additionally, meta-analyses have found consistent findings of a relationship between beliefs and adherence, for both self-report or objective adherence measures (16).

The generalizability of the findings may be limited; our cohort consisted of hypertensive adults over 65 years from an Irish community setting; it is possible that relationships between medication beliefs and adherence may differ between condition, age-group, and healthcare setting. It may also be possible that the non-reciprocal effects observed in our cohort, which are similar to that observed in stroke survivors, may differ in other conditions, i.e. ambivalent patients may have higher adherence than indifferent patients. As with all observational studies the possibility for residual confounding exists. Further replication and extension of this method in hypertensive and other disease populations is required.

In conclusion, our study extends the evidence supporting the use of polynomial regression to evaluate the multidimensional nature of the NCF. Methods such as the BMQ-difference score are both theoretically and statistically inaccurate. Indeed polynomial regression with response surface analysis could be considered when the interest of the research is the effect on a continuous outcome of the difference between two continuous variables measured on a commensurate scale (31). Researchers should apply polynomial regression when assessing the NCF and efforts to modify medication beliefs to improve adherence should consider non-reciprocal effects when designing interventions. Finally clinicians addressing poor patient adherence should consider the absolute levels of concerns and necessity-beliefs in addition to determining whether one is greater than the other.

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Figure legends

Figure 1 Flowchart of patient recruitment and follow-up

Figure 2A Frequency and distribution of mean BMQ-Specific Necessity scores and Figure 2B frequency and distribution of mean BMQ-Specific Concerns scores. Each subscale consisted of 5 items with 5 response options ranging from strongly disagree to strongly agree which were scored from 1-5. The sum of scores for each item in the subscales was used to calculate an overall mean score for the two subscales.

Figure 3 The observed three-dimensional relationship between concerns, necessity and adherence, where x = concerns, y =necessity and z =adherence. Along the line of congruence we observe non-reciprocal effects where $x=y$. If we follow the line from the left corner of the graph from $x=-2$ and $y=-2$ to the right corner of the graph where $x=2$ and $y=2$ we observe the non-reciprocal effect. Using response surface analysis we estimate the slope of the line is -0.36 ($p=0.004$) and the curvature is -0.25 ($p=0.003$). The negative slope indicates that adherence decreases as both concerns and necessity beliefs increase. The significant curvature indicates that the relationship is non-linear and the negative value indicates that it is a concave surface (downward curving), meaning that the effect on adherence will be sharper at extreme values of $x=y$. Along the line of incongruence we observe the reciprocal effects where $x=-y$. If we follow the graph from the top corner where $x= -2$ and $y= 2$ to the bottom corner, where $x= 2$ and $y= -2$ we observe a decrease in adherence. We estimate the slope to be -0.77 ($p<0.001$) and the curvature to be -0.26 ($p=0.004$). The significant negative slope indicates that adherence decreases when concerns increase and necessity decreases. A significant negative curvature here indicates that the surface is concave and that adherence decreases more sharply at extreme values of $x=-y$ (i.e. as the difference between concerns and necessity increases). Permission to use the MMAS scales is required. Reproduction and distribution of the MMAS is protected by US copyright laws. A license agreement to use the scale is available from: Donald E. Morisky, ScD, ScM, MSPH, Professor, Department of Community Health Sciences, UCLA School of Public Health, 650 Charles E. Young Drive South, Los Angeles, CA 90095-1772, dmorisky@gmail.com.

Tables

Table 1 Polynomial terms for the BMQ-Specific

Polynomial Terms	
<hr/>	
Linear Terms	x, y
Quadratic Terms	x^2, xy, y^2
Cubic Terms	$x^3, 2x^2y, 2xy^2, y^3$

The polynomial terms used in for exploratory polynomial regression where x =BMQ-concerns scores, and y =BMQ-necessity scores

Table 2 Participant demographics at baseline

Demographics	
Age, years: mean (<i>SD</i>)	76.3 (6.29)
Male: % (n)	46.7% (n=730)
Education attainment: % (n)	
Primary	28.3% (n=440)
Secondary	40.8% (n=638)
Third-level	25.8% (n=404)
Health Cover: % (n)	
GMS	73.7% (n=1152)
GP Visit Card	1.2% (n=18)
Drug Payment Scheme	16.4% (n=257)
Long-Term Illness	2.2% (n=34)
None	4.7% (n=74)
Medical History	
Current Smoker: % (n)	8.3% (n=129)
Heart Attack: % (n)	13.1% (n=205)
Angina: % (n)	12.8% (n=200)
Stroke: % (n)	3.3% (n=52)
No. of comorbidities : median (IQR)	2 (1, 3)
Medication History	
No. of regular medicines: median (IQR)	6 (3, 8)
Medication repackaged in MDU: % (n)	10.5% (n=165)
No. of AHT medication: median (IQR)	2 (1, 3)
AHT Dosing Frequency: median (IQR)	1 (1, 1)
AHT Defined Daily Dose (WHO DDD): mean (<i>SD</i>)	2.59 (2.23)
Angiotensin acting agents: % (n)	73.9% (n=1156)
Alpha-blockers: % (n)	6.1% (n=96)
Beta-blockers: % (n)	46.9% (n=734)
Calcium Channel Blockers: % (n)	42.5% (n=665)
Diuretics: % (n)	29.2% (n=457)

SD= standard deviation, IQR= interquartile range, GMS= General Medical Services, GP=General Practitioner, MDU=Multiple Dose Units, AHT=antihypertensive.

Table 3 Confirmatory Polynomial Regression (n=1145).

Model 1	β	95% CI	<i>p</i> -value	<i>R</i> ²
BMQ-Specific Score Difference	0.196	0.128-0.264	<0.001	0.0276
Model 2				
BMQ-Specific Concerns	-0.280	-0.382 to -0.178	<0.001	0.0314
BMQ-Specific Necessity	0.135	0.047 to 0.223	0.003	

To support the difference score (Model 1), we find the polynomial model (Model 2) is overall significant ($R^2=0.0314$, $p<0.001$); the coefficients for Concerns and Necessity beliefs are in the expected direction and are significant; however the coefficients are of differing magnitude and the polynomial model significantly improves the prediction of the outcome (increase in R^2 -squared 0.0038, $F(1, 1142) = 4.56$, $p=0.033$). Thus the constraints implied by the score difference model, that a one point increase in necessity beliefs has an equivalent effect on adherence as a one point decrease in concerns, are inaccurate.

Table 4 Exploratory Polynomial Regression: unadjusted and adjusted regression coefficients for baseline predictors of the MMAS-8 score at 12 months follow-up.

	<i>Unadjusted (n=1211)</i>			<i>Adjusted (n=1046)</i>		
	β	95% CI	<i>p</i>	β	95% CI	<i>p</i>
BMQ Specific Concerns	-0.55	-0.79 to -0.33	<0.001	-0.56	-0.80 to -0.33	<0.001
BMQ Specific Necessity	0.24	0.05 to 0.44	0.016	0.21	0.01 to 0.41	0.046
BMQ Concerns Squared term	-0.17	-0.29 to -0.05	0.006	-0.21	-0.34 to -0.09	0.001
Interaction term	0.02	-0.05 to 0.10	0.549	0.01	-0.07 to 0.08	0.877
BMQ Necessity Squared term	-0.06	-0.15 to 0.03	0.217	-0.05	-0.14 to 0.05	0.340
Age	0.01	0.00 to 0.02	0.033	0.01	-0.01 to 0.01	0.582
Male Gender	-0.17	-0.28 to -0.05	0.004	-0.21	-0.34 to -0.08	0.001
<i>Education</i>						
Primary	Ref.			Ref.		
Secondary	0.01	-0.13 to 0.15	0.877	-0.01	-0.14 to 0.15	0.963
Third-Level	0.04	-0.12 to 0.19	0.643	0.08	-0.09 to 0.25	0.352
<i>Health Cover</i>						
GMS	Ref.			Ref.		
GP Visit Card	-0.15	-0.75 to 0.44	0.613	-0.18	-0.78 to 0.41	0.542
Drug Payment Scheme	0.04	-0.11 to 0.20	0.541	0.04	-0.13 to 0.21	0.625
Long-term Illness	-0.33	-0.72 to 0.06	0.093	-0.17	-0.58 to 0.25	0.428
None	0.04	-0.26 to 0.34	0.803	0.14	-0.18 to 0.45	0.393
Current Smoker	-0.20	-0.42 to 0.02	0.074	-0.12	-0.35 to 0.11	0.309
Heart Attack	-0.17	-0.34 to 0.01	0.053	-0.10	-0.30 to 0.10	0.310
Angina	-0.09	-0.26 to 0.09	0.321	0.07	-0.13 to 0.27	0.505
Stroke	-0.14	-0.46 to 0.18	0.397	-0.02	-0.35 to 0.33	0.933
No. of comorbidities	-0.04	-0.08 to -0.002	0.038	-0.07	-0.12 to -0.02	0.006
No. of regular medication	0.02	0.00 to 0.03	0.062	0.04	0.02 to 0.06	<0.001
Medication repackaged in MDU	-0.27	-0.47 to -0.08	0.006	-0.29	-0.51 to -0.07	0.010
AHT Dosing Frequency	0.05	-0.13 to 0.23	0.863	0.03	-0.16 to 0.22	0.740
AHT Defined Daily Dose	0.00	-0.03-0.02	0.784	0.02	-0.02 to 0.06	0.322
Angiotensin Agents	0.02	-0.12 to 0.16	0.796	-0.04	-0.20 to 0.12	0.603
Alpha-Blockers	-0.03	-0.27 to 0.21	0.798	-0.15	-0.41 to 0.12	0.272
Beta-Blockers	0.03	-0.09 to 0.14	0.664	-0.02	-0.12 to 0.15	0.810
Calcium Channel Blockers	0.01	-0.11 to 0.13	0.863	-0.02	-0.16 to 0.12	0.778
Diuretics	0.08	-0.05 to 0.21	0.245	0.01	-0.15 to 0.14	0.956

GMS=General Medical Services, GP=General Practitioner, MDU=Multiple Dose Units, AHT=antihypertensive.

The unadjusted coefficients for the BMQ-Specific Concerns and Necessity subscale polynomial terms are representative of the five quadratic terms entered jointly to a null model. Missing data (participants): BMQ (66); Age (9); Education (60); Health Cover (22); Smoker (6); Medical History (3); Drug History (18). The adjusted model is a complete case analysis, which resulted in 13.6% of missing observations. To account for the potential biases in estimates and standard errors due to missing data, multiple imputation, with multivariate normal distribution, Markov Chain Monte Carlo procedure and 100 imputations was performed, but did not change the overall conclusions. This data has been presented as supplementary information. Permission to use the MMAS scales is required. Reproduction and distribution of the MMAS is protected by US copyright laws. A license agreement to use the scale is available from: Donald E. Morisky, ScD, ScM, MSPH, Professor, Department of Community Health Sciences, UCLA School of Public Health, 650 Charles E. Young Drive South, Los Angeles, CA 90095-1772, dmorisky@gmail.com.

Figures

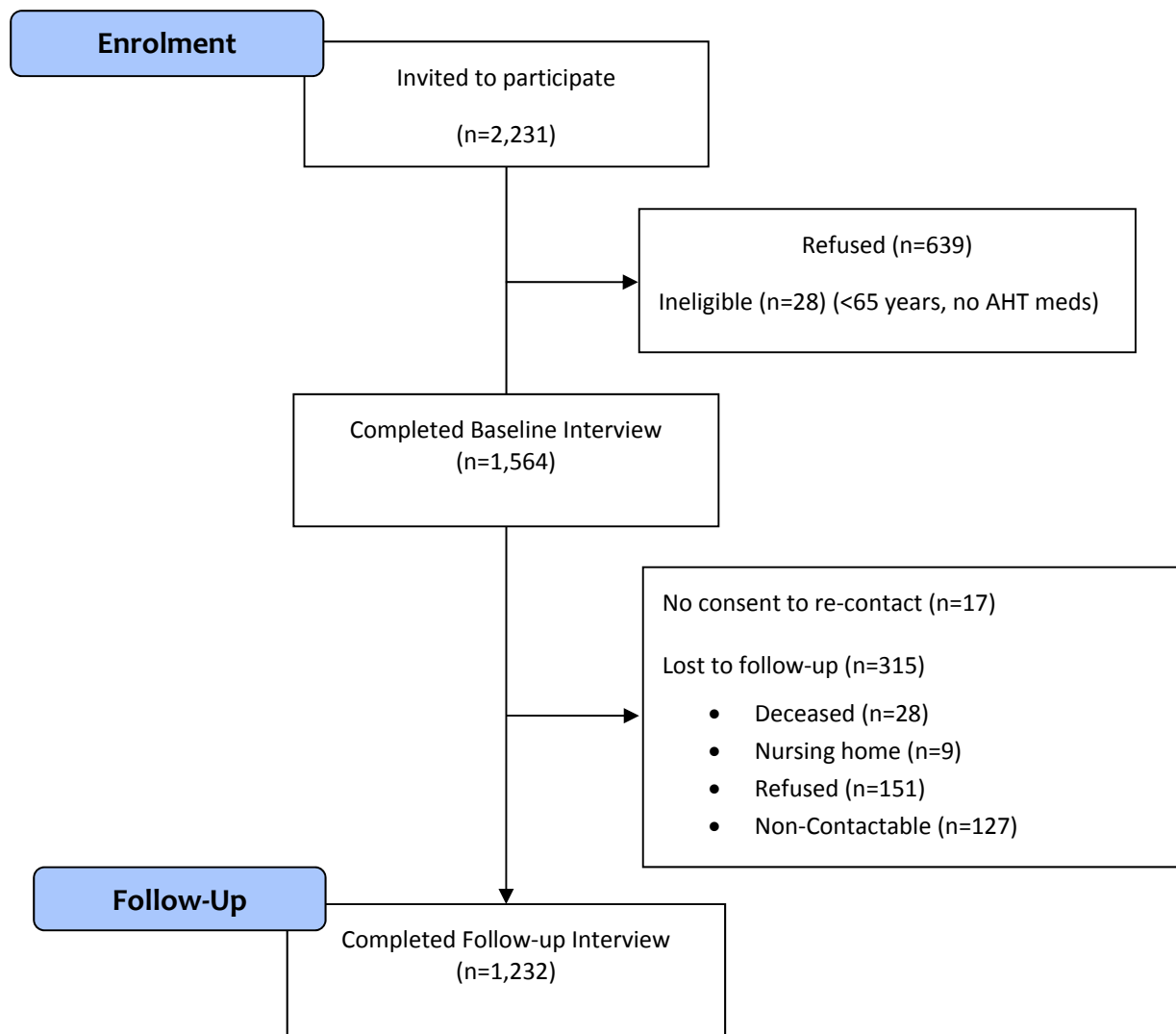


Figure 1

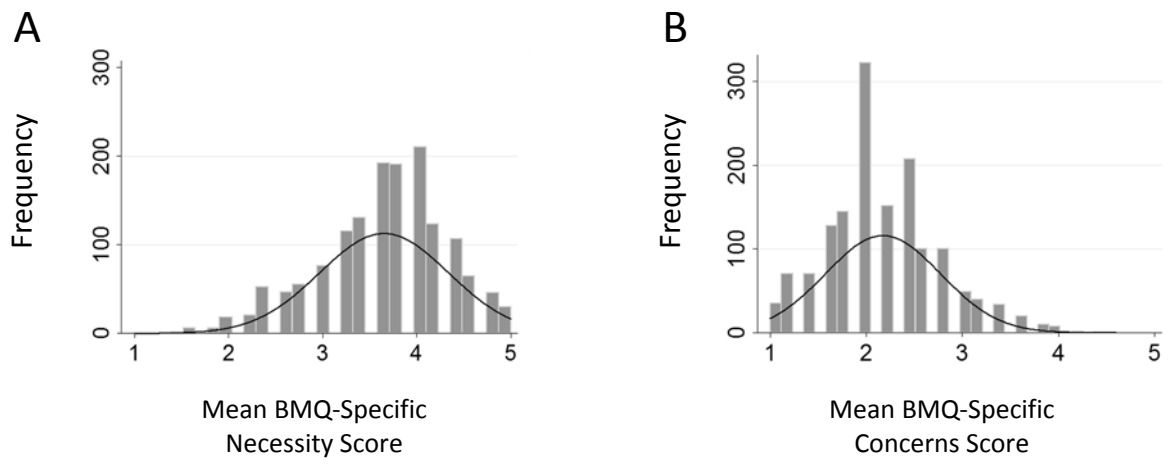


Figure 2

Three-dimensional relationship between patient medication beliefs and adherence

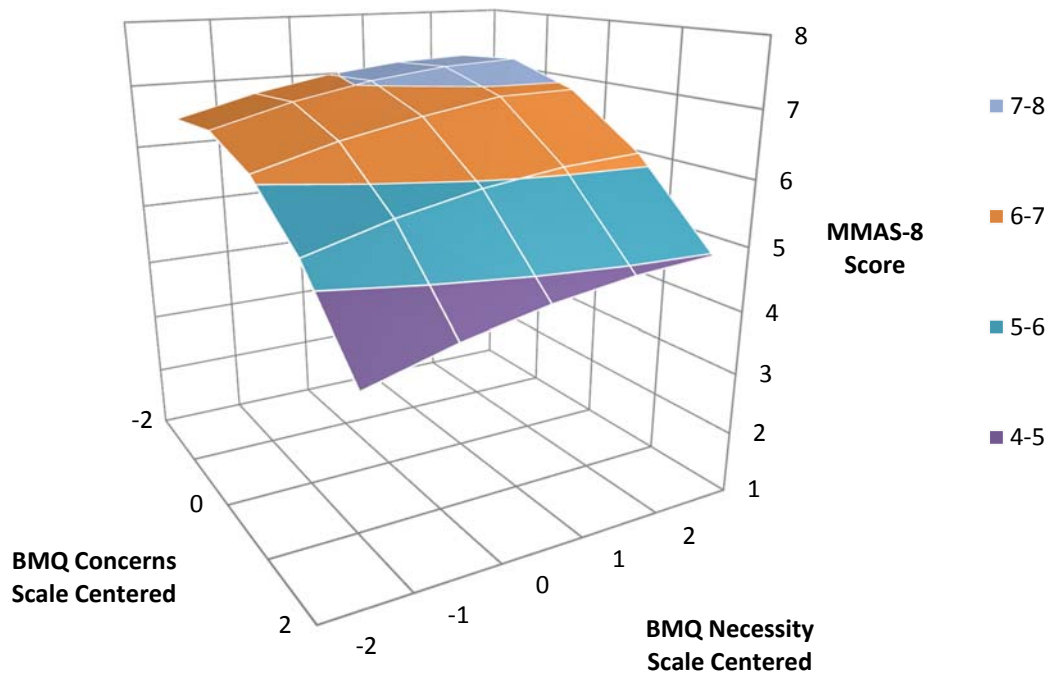


Figure 3