Predictors of Self-Reported Adherence to Antihypertensive Medicines

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Title: Predictors of self-reported adherence to antihypertensive medicines: A multi-national, cross-sectional survey

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ABSTRACT [First-level Header]

Objectives:

Non-adherence to antihypertensive medicines limits their effectiveness, increases the risk of adverse health outcome and is associated with significant health care costs. The multiple causes of non-adherence differ both within and between patients and are influenced by patients' care settings. The objective of this paper is to identify determinants of patient non-adherence to antihypertensive medicines, drawing from psychosocial and economic models of behaviour.

Methods:

Hypertensive outpatients from Austria, Belgium, England, Germany, Greece, Hungary, Netherlands, Poland and Wales were recruited to a cross-sectional online survey. Non-adherence to medicines was assessed using the Morisky Medication Adherence Scale (primary outcome) and the Medication Adherence Rating Scale. Associations with adherence and non-adherence were tested for demographic, clinical, and psychosocial factors.

Results:

A total of 2595 patients completed the questionnaire. The percentage of patients classed as non-adherent ranged from 24% in the Netherlands to 70% in Hungary. Low age, low self-efficacy and respondents' perceptions of their illness and cost-related barriers were associated with non-adherence measured on the Morisky scale across several countries. In multilevel, multivariate analysis, low self-efficacy (OR 0.73, 95% CI 0.70 - 0.77) and a high number of perceived barriers to taking medicines (OR 1.70, 95% CI 1.38 - 2.09),

were the main significant determinants of non-adherence. Country differences explained 11% of the variance in non-adherence.

Conclusions:

Amongst the variables measured, patients' adherence to antihypertensive medicines is influenced primarily by their self-efficacy, illness beliefs and perceived barriers. These should be targets for interventions for improving adherence, as should an appreciation of differences among the countries in which they are being delivered.

INTRODUCTION [First-level Header]

Adherence to antihypertensive treatments is sub-optimal (1), even among patients participating in clinical studies, whose median persistence with medicines is only about one year (2). Patients who are poorly adherent (proportion of days covered ≤40%) (3) experience significantly increased risk of acute cardiovascular events, compared to those who adhere adequately (≥80%), and incur greater health care costs (4). The World Health Organisation (5) has called for further research to gain a better understanding of the determinants of non-adherence to antihypertensive medicines, and to identify common risk factors for non-adherence across different countries, in order to inform strategies for improving patient adherence.

Known determinants of non-adherence to antihypertensive treatments may broadly be categorised to factors related to the patient (6-9) and their familial and cultural context (10), condition (11), treatment (8,11), socioeconomics, and health professional / health care system (5,12). Components of sociocognitive and self-regulatory theory including attitude (13), perceived behavioural control (13-14), low self-efficacy (13,15-16), lack of perceived treatment benefits (11), perceived barriers (7-8), illness perceptions (6,10), beliefs about medicines (6,11,17-18) and lack of social support (10,19-20) are significantly associated with non-adherence. Studies based on consumer demand theory support the negative impact of the costs of medicines on adherence (21), but there is a lack of empirical evidence on alternative behavioural economic theories such as time preference. We are unaware of any study in which a range of these factors has been tested

simultaneously to assess their combined contribution to non-adherence across several countries.

The aim of this study, therefore, was to identify determinants of patient non-adherence to antihypertensive medicines, drawing from psychosocial and economic models of behaviour, from a cross-sectional survey across a number of European countries with contrasting cultures, health care systems and patient characteristics.

METHODS [First-level Header]

The research used an online, convenience cross-sectional sample of adults with hypertension recruited from 11 European countries. We tested the contribution of multiple, theory-driven determinants for association with antihypertensive treatment non-adherence, and reported our findings according to the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) statement on cross-sectional studies (22).

Procedure [Second-level Header]

Following receipt of ethical approval from all relevant committees we invited ambulatory, adult patients with hypertension to participate in an online questionnaire. Patients self-selected into this study in response to advertisements placed in community pharmacies (Austria, Belgium, England, France, Germany, Greece, Netherlands, Portugal, Poland, Wales) or hypertension clinics (Hungary). Additional strategies were

necessary to increase recruitment in some countries. These included recruiting patients via general practice surgeries (Poland, Hungary), placing advertisements in the press (England, Wales), and using online patient support groups (Poland). No incentive was offered for patients to participate. The survey was administered anonymously through SurveyMonkey®, with one entry allowed per Internet Protocol address to reduce the chance of multiple responses. Patient information sheets, consent forms and eligibility checks, were provided online.

Inclusion criteria [Second-level Header]

We included patients who consented, and who self-reported as being: aged ≥18 years, diagnosed by a doctor as having hypertension that lasted at least 3 months, currently prescribed antihypertensive medicine(s), and personally responsible for administering their medicines.

Exclusion criteria [Second-level Header]

Respondents who self-reported as being diagnosed with a "psychiatric condition" or those living in a nursing home (or similar facility) were excluded.

Potential determinants[Second-level Header]

Potential determinants of non-adherence were identified from published literature reviews (23-24). The questionnaire was developed from validated instruments, where available, and covered: participant demographics, use of medicines, self-rated health (25), and a battery of scales derived from economic (21) and sociocognitive (23-24) theories.

Affordability and cost-related behaviours were assessed by a dichotomous question asking whether respondents had to think about the money available to spend when obtaining their medicines and six related items, each measured on a 5-point Likert scale (26). Components of the European Social Survey (27) assessed household income: participants reported their main source of income, their total annual income (in bands), whether they were coping with their present income and the ease or difficulty in borrowing money when in need. We assessed participants' time preference for near, versus distant enjoyment of health benefits (28). The internationally standardised EUROPEP measure (29) assessed participants' evaluations of the health care they receive.

Validated, self-report tools were used to assess personal and socio-cognitive determinants of non-adherence. Dispositional optimism was measured using the Life Orientation Test (LOT-R) on 5-point Likert scales (30). Illness representations were measured using the Brief Illness Perception Questionnaire (B-IPQ) (31) that assessed personal beliefs about illness consequence, timeline, personal control, treatment control, illness identity,

concern about illness, illness coherence and emotional representations (the causal subscale was removed due to translation issues). The Beliefs about Medicines Questionnaire (32) assessed participants' belief in the necessity of their medicines and also concerns about their medicines. Components of the Theory of Planned Behaviour (33-34) measured attitudes/behaviours towards taking medicines, subjective norms of adherence, barriers to, and facilitators of, adherence, intention to adhere and self-efficacy for adherence behaviours, each scored on a 5-point Likert scale. The BRIGHT questionnaire (35-36) was used to assess constraints/facilitators of adherence using subscales for barriers and social support.

Outcome measures [Second-level Header]

The primary outcome measure was self-reported non-adherence, based on the 4-item Morisky Medication Adherence Scale (37). This classified patients as being non-adherent according to a single 'yes' response to any of the four questions that made specific reference to "high blood pressure medicine". This validated scale is the most frequently used questionnaire measuring adherence to medication (38). An exploratory analysis was also conducted of those categorised as intentionally non-adherent based on 'yes' responses to two specific Morisky items which identify non-adherence as a result of feeling better/worse. A secondary outcome measure of adherence was provided by the Medication Adherence Rating Scale (MARS) (39), which consisted of 5 items rated on a Likert scale with a low score (on a range of 5 - 25) indicating lower levels of adherence.

Our choice of outcome measures was informed by the theoretical and empirical literature on medication adherence spanning the behavioural and medical sciences from which the study questions emerged. These two conceptually different measures provided dichotomous data on non-adherence and continuous data on adherence to patients' antihypertensive medications.

The final survey had a total of 135 items.

Translation [Second-level Header]

Measures that were not validated and available in the required language were translated into the appropriate languages using accredited translators who were native speakers of the target languages and fluent in English. Translations were checked for compatibility with the original version in a process of back translation, performed by persons who were native English speakers and fluent in each target language, to ensure that none of the original meaning was lost. For each language, a third individual acted as a reviewer and highlighted any discrepancies between the forward and back translations which were resolved by discussion with the translators. All translations were coordinated by one project partner to ensure consistency. Piloting in each country enabled identification of any semantic inconsistencies.

Sample size [Second-level Header]

Based on an expectation of 30% non-adherence (6) and a one-sided, 5% level of significance, 323 completed Morisky scores were required per country for within-country analyses.

Data analysis [Second-level Header]

Responses to the survey were coded in SPSS version 19 (IBM Corporation) and analysed in Stata version 10 (StataCorp LP). We assumed missing data to be missing at random and imputed using multiple imputations by chained equations (MICE) (40), to create 25 data sets for each country. For a single incomplete variable, multiple imputation constructs a model relating the incomplete variable to variables in the prediction model, and draws from the posterior predictive distribution of the missing data, conditional on the observed data. Using MICE, imputed values were initialised by drawing at random from observed values. Imputation of missing data was performed on variables ordered by level of 'missingness', using observed and current imputed values of all predictors. To ensure stability, this imputation step was cycled 10 times for each of the 25 imputed data sets (41). Analyses were performed on each set and imputation-specific coefficients were pooled according to Rubin's rules (42). Imputed data were used for all analyses with the exception of demographic variables where data from complete cases were used.

In the primary analysis, we calculated the percentage of patients classed as non-adherent according to Morisky score in each country. Potential associations with non-adherence were initially tested univariately using χ^2 and independent samples t-tests (associations with medicines use were adjusted for age), followed by a logistic regression with non-adherence as the dependent variable. We applied a bivariate method of selecting explanatory variables, whereby only variables found to be significant ($p<0.05$) in the univariate analysis were entered into the regression model based on a theoretical order (43-44), from determinants classified as demographic and medicines use characteristics (distal) to attitudes and behaviours (proximal). Assumptions regarding multicollinearity, singularity, normality, linearity, and homoscedasticity were tested and met. Country comparison analysis was conducted using χ^2 tests. We adopted a similar approach for the secondary outcome of MARS adherence, but with a one-way ANOVA to test differences among countries.

In order to account for variance both within-country and between-country, as a secondary analysis, 2-level multilevel regression models with respondents nested within country were specified for both Morisky (logit model) total and intentional non-adherence, and MARS adherence (linear regression model). Multilevel models with random intercepts and fixed effects were specified, initially with all variables common to all countries. Non-contributory variables were subsequently removed iteratively, determined by highest *p*-value using backwards elimination (based on $p>0.05$). We calculated the variance partition coefficient (45), to determine the attribution of country to the observed variance in non-adherence.

A complete case analysis of Morisky total non-adherence was performed to assess the sensitivity of our main findings to assumptions relating to missing data. In a *post hoc* analysis, we assessed the impact of excluding Hungary from the analysis, given that Hungary alone recruited patients from hypertension clinics.

RESULTS [First-level Header]

Participants: A total of 2630 adults from 11 countries completed the questionnaire. Target recruitment was achieved in 5 countries (Austria, England, Hungary, Poland and Wales). Study set-up and initiation was delayed in Belgium, Germany, Greece and The Netherlands leading to non-target recruitment. The analysis therefore includes these 9 countries which each recruited over 100 participants (n=2595). There was an inadequate level of available research support in France and Portugal that resulted in low response (n=11, n=33 respectively) and these were excluded from the analysis. Included participants' characteristics are presented in Table 1. The overall level of missing data by country ranged from 5% to 26%, with lowest rates seen on demographic and clinical questions (0-8%), MARS (<2%), medicine necessity and concerns (14%) and self-efficacy (14%) and highest rates seen on the income questions (22%), time preference (22%) and BRIGHT barriers (23%) (Fig. 1).

There were significant differences between country samples on all demographic and clinical characteristics assessed. Self-rated health was more often rated as poor or fair in

Poland (48.6%) and Hungary (47.6%) than in Belgium (16.1%), England (19.5%) and Wales (19.8%). Fewer respondents from Hungary, Greece and Poland had received higher education than in other countries. Respondents from Greece tended to be older and more predominantly female, and together with Hungary and Austria, had the greatest number of co-morbidities and were more likely to be taking medicines more frequently than 3 times per day.

Insert Table 1 and Figure 1

Prevalence of non-adherence [Second-level Header]

Based on Morisky scores, non-adherence was least prevalent in the Netherlands, and most prevalent in Hungary (Table 2). Intentional non-adherence was highest in Greece. Polish respondents had significantly lower levels of adherence, as measured by MARS, than respondents from other countries.

Insert Table 2

Associations with Morisky non-adherence and MARS adherence [Second-level Header]

Among demographic factors, only age showed associations across several countries with younger age associated with Morisky non-adherence in Austria, Belgium, Netherlands

and Wales (Table 3), and older age associated with MARS adherence in the Netherlands (Table 4). Unemployment was associated with non-adherence in England and Hungary only. None of the medicines-related factors showed associations with non-adherence in more than one country. The perceived ease or difficulty in borrowing money was associated with non-adherence in England and Germany and having available strategies to cope with the costs of medicines were significantly associated with MARS-rated adherence in Belgium, England, Greece and Hungary.

No significant associations were evident for optimism but in contrast, beliefs about the illness did play a significant role. B-IPQ factors of low perceived illness consequences, low concern about illness, and low beliefs in personal control over illness were significantly associated with non-adherence on the Morisky scale in Austria, Greece Poland and Wales (Table 3); and high belief in treatment control, high illness coherence, high belief in personal control significant in Austria, Greece and Hungary based on MARS assessment of adherence (Table 4). Illness identity, perceived illness timeline and emotional representations were not significant, neither were beliefs about medicines, in terms of their necessity or concerns about taking them (BMQ).

The socio-cognitive variables, drawn mainly from the theory of planned behaviour (TPB), did not emerge consistently in the inter-country analysis. Perceived barriers to adherence (whether changes to daily routine makes taking medicines more difficult) were related only to non-adherence in Greece, although a high number of barriers assessed by the BRIGHT (35-36) were associated with non-adherence in Austria and Poland.

Intention to adhere was associated with adherence in Hungary and Wales. Low self-efficacy, however, emerged significant in relation to non-adherence in all countries except the Netherlands, and high self-efficacy explained adherence in all countries except Poland. Social support factors emerged significant only in Hungary but in a counter-intuitive direction, in relation to low perceived environmental support and greater adherence.

The variables examined in this study explained between 13.4% and 65.2% of the variability in MARS adherence (Table 4).

Insert Tables 3 and 4

Multilevel model [Second-level Header]

The multilevel logit model for Morisky non-adherence identified males, being of younger age, being employed, low number of medicines, high dosing frequency, high normative beliefs, low self-efficacy, high perceived barriers, low personal control, low concern about illness and difficulty in borrowing money as being significantly associated with non-adherence (Table 5). Associations were consistent in the model specified with Morisky *intentional* non-adherence. Multilevel linear regression found older age, a lower level of education, a greater number of medicines, less frequent dosing, having low

perceived barriers, low perceptions of illness consequences, beliefs in treatment control, and high self-efficacy were connected to higher adherence as measured by MARS. Based on the Morisky scale, 11% and 7% of explained variances in total and intentional non-adherence were attributable to differences among countries; and 23% of the variance in adherence based on MARS was attributable to differences among countries.

Sensitivity analysis [Second-level Header]

The analysis of complete cases resulted in less precise estimators, as expected, altering the significance of some variables and hence their inclusion in the final model. Self-efficacy and perceived barriers (BRIGHT), however, remained significant as in the primary analysis.

When Hungary was excluded from the multilevel model (due to the aforementioned difference in recruitment method), we observed a reduction in between-country variance in Morisky non-adherence (from 11% to 4%). Other factors emerged as being significant, including education, number of medical conditions, attitudes and intention to adhere; though self-efficacy and barriers remained significant.

DISCUSSION [First-level Header]

Self-reported non-adherence to antihypertensive medicines is prevalent, even among the sampled population who were in receipt of a current prescription for antihypertensive treatment. Prevalence differs significantly across countries but while a proportion of this variance is explained by country-level effects and demographic characteristics, our principal finding is that potentially modifiable factors of low perceived self-efficacy and, to a lesser extent, low personal control beliefs, and high perceived barriers are consistently associated with non-adherence. Perceived barriers to adherence included forgetfulness or interruption of daily routine, practical difficulties, and feeling overwhelmed by circumstances or complexity of regimen. Our finding of common associations with non-adherence across different countries supports the importance of these factors, particularly given the significant differences that exist in cultural, medical practices and health care systems that contribute to a small proportion of the variance in non-adherence.

Adherence is generally explained by the converse of the above but additionally, cost-related behaviour (i.e. strategies to cope with the cost of prescriptions) and intention also emerged as significant in several countries. The multilevel analysis of all countries show that whilst many factors act in the opposite direction depending on whether we are addressing non-adherence or adherence, some uniquely explain non-adherence e.g. employment status, low normative beliefs, low personal control, low illness concern, and low borrowing potential; and others uniquely explain adherence e.g. lower education, low perceived illness consequences, (both these are counter-intuitive) and beliefs in treatment control. The multilevel analyses also suggest that where possible, a reduction in dose

frequency and number of prescribed medicines might achieve improvements in adherence.

The literature on adherence to medicines contains many analyses that have tested the significance of clinical, treatment and demographic characteristics as predictors of non-adherence, assuming that behaviour is a function of these characteristics alone. This approach has significant limitations. Our analysis is rooted in behavioural theories to reflect the notion that individual beliefs and social influences are potentially more relevant determinants of intentional and non-intentional non-adherence (and of adherence) than relatively fixed attributes of the person or their clinical situation. Previous studies have shown that, based on socio-cognitive and self-regulation theories, personal and perceived control (6,10,13,15-16), perceived benefits of treatment (7,11) and perceived barriers – such as forgetfulness and experienced or anticipated side effects (7,8) are significant predictors of non-adherence in patients taking antihypertensive medicines. Associations between higher levels of self-efficacy and adherence in patients with hypertension have been noted previously (13,46).

The novelty and key strength of our study is that a range of theoretically informed factors derived from behavioural theories in health psychology and economics were tested concurrently across several European countries. Our analysis also considered the distinction between intentional and unintentional non-adherence. Associations with intentional non-adherence were fewer, and although several overlapped with those associated with overall non-adherence i.e. age, self-efficacy and perceived barriers, other

factors included the number of medical conditions, concerns about medicines, perceived illness identity and behavioural intention. The act of deliberately choosing to avoid taking medicines, therefore, warrants interventions which more explicitly target illness and treatment and behavioural beliefs.

There are several caveats to our analysis, however, which may limit the strength of the interpretations. First, only five of the intended eleven countries reached target recruitment. We pragmatically included all 9 countries which recruited an appreciable number of patients, however this reduced the precision of the estimates of non-adherence in each country and limited the strength of inferences. Second, our analyses might be confounded by differences in methods of recruitment. While all countries–except Hungary–recruited via community pharmacies, the exclusion of Hungary from the secondary analysis resulted in more variables being significant. The main findings of the primary (per country) analysis, however, remained unchanged. Third, as responses were elicited via self-administered questionnaires, we had no means of confirming hypertension diagnosis, nor other responses, or mitigate any self-presentation bias which would reduce the external validity of our findings. Fourth, we were unable to assess the impact of non-response bias (47) as those who failed to complete the outcome measures–which were at the beginning of the questionnaire–were not allowed to progress through the remainder of the survey. The length of the survey represents a fifth limitation, which may have impacted on completion rates. The variables ultimately emerging as being associated with non-adherence and adherence (i.e. TPB barriers and self-efficacy), however, had relatively low levels of missingness and we improved precision by

performing multiple imputation. While multiple imputation addresses problems in complete case analyses related to loss of efficiency and bias due to differences between observed and unobserved data, it is no substitute for a complete dataset and requires an important but unverifiable assumption that data are missing at random. Moreover, only subscale totals rather than every individual item were imputed for health psychology measures. This may introduce bias as data from respondents who completed some, but not all, of the items in a subscale were discarded. Sixth, whilst employing validated scales wherever possible, full testing of the BRIGHT measure did not exist at the time of the study. Finally, self-reported measures of adherence are prone to bias (38), and may not distinguish between failure to initiate dosing, incorrect implementation of the dosing regimen and treatment discontinuation (48). In mitigation, however, we employed two measures of adherence, and both had a significant association with self-efficacy.

Notwithstanding these limitations, the findings can inform the development of non-adherence reducing (or adherence-enhancing) interventions. Most importantly, the common variables identified within our study are amenable to change through improved communication with health care professionals or brief cognitive-behavioural intervention. Reviews of adherence-improving interventions (49-50) offer support for self-efficacy enhancement, with modest effects reported in trials of supportive and individually tailored telephone calls, information on self-management, checks on understanding and concerns regarding medicines and empowerment. Our analysis suggests that a theoretically informed, controlled trial of cognitive-behavioural interventions, focused at increasing self-efficacy and related control beliefs and reducing perceived barriers to

adherence behaviours is warranted. Given the broad spectrum of potential barriers and the observation of independent, country-level differences, which may be related to cultural, health service or other factors, interventions which are tailored specifically to the population in which they are being delivered are the most likely to be effective.

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Table 1. Demographic data and cross country comparison

Explanatory variable	Country (number respondents)									χ^2 p-value
	Austria (323)	**Belgium (180)**	**England (323)**	**Germany (274)**	**Greece (289)**	**Hungary (323)**	**Netherlands (237)**	**Poland (323)**	**Wales (323)**	
Age - mean (95% CI)	60.2 (58.8, 61.5)	57.3 (55.6, 59.1)	59.6 (58.5, 60.7)	56.8 (55.4, 58.2)	63.9 (62.6, 65.2)	58.2 (56.8, 59.7)	58.3 (57.0, 59.5)	54.5 (53.2, 55.8)	61.1 (59.9, 62.2)	16.62 p < 0.001 df = 8
Sex (female, %)	145 (44.9%)	64 (35.6%)	141 (43.7%)	154 (56.2%)	173 (59.9%)	179 (55.4%)	115 (48.5%)	171 (52.9%)	119 (36.8%)	64.54 p < 0.001 df = 8
Education Secondary only*	120 (37.2%)	6 (3.3%)	110 (34.1%)	51 (18.6%)	148 (51.2%)	253 (78.3%)	7 (3.0%)	167 (51.7%)	98 (30.3%)	64.54 p < 0.001 df = 8
Higher education	194 (60.1%)	174 (96.7%)	211 (65.3%)	222 (81.0%)	135 (46.7%)	68 (21.1%)	229 (96.6%)	155 (48.0%)	224 (69.3%)	
Marital status Married	209 (64.7%)	134 (74.4%)	241 (74.6%)	184 (67.2%)	187 (64.7%)	234 (72.4%)	186 (78.5%)	246 (76.2%)	258 (79.9%)	36.11 p < 0.001 df = 8
Student / in employment	119 (36.8%)	98 (54.4%)	166 (51.4%)	150 (54.7%)	119 (41.2%)	124 (38.4%)	151 (63.7%)	169 (52.3%)	143 (44.3%)	70.47 p < 0.001 df = 8
Health status Poor	23 (7.1%)	4 (2.2%)	10 (3.1%)	6 (2.2%)	0 (0%)	26 (8.0%)	5 (2.1%)	24 (7.4%)	13 (4.0%)	322.59 p < 0.001 df = 24
Fair	96 (29.7%)	25 (13.9%)	53 (16.4%)	84 (30.7%)	93 (32.2%)	128 (39.6%)	49 (20.7%)	133 (41.2%)	51 (15.8%)	
Good	128 (39.6%)	77 (42.8%)	123 (38.1%)	140 (51.1%)	140 (48.4%)	132 (40.9%)	112 (47.3%)	138 (42.7%)	116 (35.9%)	
Very good	74 (22.9%)	72 (40.0%)	137 (42.4%)	44 (16.1%)	55 (19.0%)	36 (11.1%)	69 (29.1%)	28 (8.6%)	142 (44.0%)	
Mean number of medical conditions (95% CI)	2.84 (2.59, 3.08)	2.29 (2.10, 2.47)	2.28 (2.15, 2.42)	2.13 (1.97, 2.30)	2.85 (2.64, 3.06)	2.85 (2.68, 3.02)	2.08 (1.93, 2.24)	2.15 (2.02, 2.27)	2.42 (2.26, 2.57)	13.16 p < 0.001 df = 8
Mean number of medicines (95% CI)	4.43 (4.06, 4.79)	3.54 (3.19, 3.90)	3.84 (3.58, 4.10)	3.42 (3.14, 3.70)	4.37 (3.99, 4.75)	5.17 (4.80, 5.53)	3.44 (3.09, 3.79)	4.12 (3.83, 4.42)	3.80 (3.54, 4.06)	12.01 p < 0.001 df = 8
Mean units of	5.51	3.78	4.93	3.92	5.06	7.44	4.31	3.20	4.97	22.41

medicines per day (95% CI)	(4.95, 6.07)	(3.33, 4.23)	(4.45, 5.40)	(3.56, 4.27)	(4.57, 5.54)	(6.90, 7.98)	(3.45, 5.16)	(2.89, 3.51)	(4.45, 5.49)	p < 0.001 df = 8
Most frequently dosed medicine										
Once daily	114 (35.3%)	123 (68.3%)	224 (9.3%)	100 (36.5%)	51 (17.6%)	54 (16.7%)	157 (66.2%)	131 (40.6%)	241 (74.6%)	557.56 p < 0.001 df = 16
Twice daily	110 (34.1%)	35 (19.4%)	63 (19.5%)	129 (47.1%)	112 (38.8%)	155 (48.0%)	56 (23.6%)	143 (44.3%)	47 (14.6%)	
≥ Thrice daily	96 (29.7%)	19 (10.6%)	26 (8.0%)	44 (16.1%)	123 (42.6%)	113 (35.0%)	22 (9.3%)	48 (14.9%)	35 (10.8%)	

Data are counts (%), unless otherwise indicated.

* Secondary education meaning to secondary (high) school level

Table 2. Prevalence of self-reported total non-adherence and intentional non-adherence across European countries based on Morisky responses, and adherence based on MARS

	Morisky		MARS
	Respondents self-reporting as being non-adherent (as a percentage of all respondents) (95% Confidence Interval)	Respondents self-reporting as being intentionally non-adherent (as a percentage of non-adherers) (95% Confidence Interval)	Mean score (95% Confidence Interval)*
The Netherlands	24.1 (18.6, 29.5)	21.1 (10.5, 31.6)	23.86 (23.64, 24.16)
Germany	33.2 (27.6, 38.8)	35.2 (25.4, 45.0)	23.47 (23.28, 23.75)
Austria	33.7 (28.6, 38.9)	51.4 (42.0, 60.8)	23.25 (23.03, 23.56)
Wales	38.1 (32.8, 43.4)	25.2 (17.5, 32.9)	23.46 (23.30, 23.77)
Belgium	38.9 (31.8, 46.0)	17.1 (8.3, 26.0)	23.59 (23.50, 23.99)
England	41.5 (36.1, 46.9)	23.9 (16.7, 31.1)	23.41 (23.17, 23.65)
Greece	50.2 (44.4, 55.9)	57.2 (49.2, 65.3)	22.08 (21.71, 22.48)
Poland	57.6 (52.2, 63.0)	44.6 (37.5, 51.8)	18.19 (17.77, 19.01)
Hungary	70.3 (65.3, 75.3)	18.1 (13.1, 23.1)	22.88 (22.74, 23.26)
Cross country comparison	χ^2: 191.52 df: 8 p = 0.000 Tests cross country difference in self-reported non-adherence	χ^2: 108.87 df: 8 p = 0.000 Tests cross country difference in self-reported intentional non-adherence, as a proportion of all self-reported non-adherence	ANOVA F-test: 106.08 – 115.49† (Complete case F: 103.24) p = 0.000

*95% CI of mean based on imputed data
†Range of imputation specific statistics

Table 3: Summary of the logistic regression model using the Morisky non-adherence as the dependent variable. Figures are reported as odds ratio (95% confidence interval) and exact p-values.

Explanatory variable[†]	**Country**								
	Austria	**Belgium**	**England**	**Germany**	**Greece**	**Hungary**	**Netherlands**	**Poland**	**Wales**
Demographics									
Age	0.96 (0.93, 0.99) p = 0.012	0.97 (0.95, 1.00) p = 0.047	0.98 (0.94, 1.03) p = 0.431	0.97 (0.94, 1.01) p = 0.012			0.94 (0.91, 0.98) p = 0.001	0.98 (0.94, 1.00) p = 0.088	0.97 (0.93, 1.00) p = 0.037
Employment	1.32 (0.56, 3.13) p = 0.521		3.14 (1.34, 7.34) p = 0.008	1.25 (0.49, 3.19) p = 0.646		2.93 (1.58, 5.42) p = 0.001		1.12 (0.55, 2.27) p = 0.762	0.82 (0.37, 1.82) p = 0.618
Socio-demographics / Clinical factors									
Number of tablets	0.97 (0.88, 1.07) p = 0.502				0.88 (0.78, 0.98) p = 0.025				
Dosing frequency Once daily				0.08 (0.03, 0.26) p < 0.001					
Twice daily				0.24 (0.09, 0.62) p = 0.004					
Income source	0.72 (0.31, 1.67) p = 0.445		0.99 (0.36, 2.73) p = 0.977	3.83 (1.31, 11.18) p = 0.014					1.08 (0.45, 2.58) p = 0.864
Borrowing income: Difficult			6.26 (1.14, 34.46) p = 0.035		3.01 (0.81, 11.12) p = 0.098	1.30 (0.64, 2.62) p = 0.469			
Neither difficult or easy			5.28 (0.93, 30.17) p = 0.061		1.82 (0.43, 7.72) p = 0.418	3.36 (1.34, 8.43) p = 0.010			
Easy			5.47 (1.00, 29.77) p = 0.050		3.08 (0.65, 14.59) p = 0.157	0.59 (0.24, 1.47) p = 0.261			
Number of items prescribed	1.06 (0.95, 1.19)		0.86 (0.76, 0.97)	0.84 (0.70, 1.00)					

	p = 0.313		p = 0.017	p = 0.051					
Illness perceptions									
Illness consequences	0.89 (0.81, 0.99) p = 0.029								
Personal control	0.94 (0.84, 1.04) p = 0.230		0.94 (0.83, 1.07) p = 0.333		0.79 (0.66, 0.95) p = 0.013	0.93 (0.82, 1.06) p = 0.289			0.88 (0.79, 0.99) 0.031
Concern about illness								0.79 (0.68, 0.92) p = 0.002	
Theory of planned behaviour									
Barrier					1.28 (1.03, 1.60) p = 0.028		1.26 (0.97, 1.63) p = 0.078		0.93 (0.72, 1.22) p = 0.610
Self efficacy	0.79 (0.70, 0.90) p < 0.001	0.82 (0.69, 0.96) p = 0.016	0.62 (0.52, 0.74) p < 0.001	0.53 (0.43, 0.67) p < 0.001	0.82 (0.71, 0.95) p = 0.006	0.84 (0.73, 0.96) p = 0.013	0.81 (0.68, 1.04) p = 0.111	0.70 (0.60, 0.82) p < 0.001	0.66 (0.56, 0.79) p < 0.001
BRIGHT									
Barriers	1.04 (1.00, 1.08) p = 0.035		1.04 (0.98, 1.10) p = 0.155		1.05 (1.00, 1.10) p = 0.061	1.05 (1.00, 1.10) p = 0.051		1.06 (1.00, 1.11) p = 0.034	1.05 (0.99, 1.11) p = 0.107
Constant‡	133.99 (6.92, 2593.41) p = 0.001	33.32 (4.06, 273.37) p = 0.001	11.78 (0.17, 833.40) p = 0.256	649.33 (28.07, 15018.96) p < 0.001	8.10 (0.36, 183.93) p = 0.189	4.13 (0.49, 35.10) p = 0.194	33.71 (1.92, 591.49) p = 0.016	320.84 (9.36, 10993.92) p = 0.001	124.91 (1.44, 10848.02) p = 0.034
Other predictors in model where p>0.05§	2, 18, 19, 22, 24	20	6, 7, 8, 9, 15, 16, 17, 19, 20, 25		1, 9, 10, 13, 15, 17, 19, 20, 25	9, 10, 17, 23, 26	11, 12	10, 13, 14, 15, 16, 22, 25	3, 4, 5, 15, 17, 20, 21, 23, 25
Final Model χ^2 and p value+	64.94, 78.87 p < 0.001	14.36, 27.28 p < 0.001	104.25, 145.31 p < 0.001	89.41, 123.04 p < 0.001	76.51, 89.42 p < 0.001	64.02, 81.23 p < 0.001	25.74, 47.98 p < 0.001	76.56, 120.57 p < 0.001	75.19, 94.15 p < 0.001

†Only Odds ratios for predictors with p<0.05 for at least one country are presented.

‡Constant reported for all values of p

§Number of medical conditions (1), Number of different medicines (2), Income deciles 1-4 (3), Income deciles 5-7 (4), Income deciles 8-10 (5), Perception of income: Living comfortably (6), Perception of income: Coping (7), Perception of income: Finding it difficult (8), Affordability problem (9), Cost coping strategies (10), Time preference: long (11), Time preference: short (12), Prescriber of medicines (13), Gender of prescriber (14), Satisfaction with practitioner (15), Satisfaction with practice (16), Optimism (17), Timeline (18), Treatment control (19), Illness coherence (20), Emotional representations (21), Necessity of medicines (22), Concern about medicine (23), Attitude (24), Intention (25), Social Support (26)

[+]As χ^2 cannot be pooled, we report the range of imputation specific χ^2. The degrees of freedom per imputation is given by (number of variables -1). Imputation-specific, p-values were $p < 0.001$ in all cases, with the exception of 3 imputations in Belgium (which were p=0.001, 0.001, 0.002).

Table 4: Summary of the final regression model (all variables) using the MARS adherence dependent variable (β-coefficient, 95% confidence intervals)

Explanatory variable*	**Country**								
	Austria	**Belgium**	**England**	**Germany**	**Greece**	**Hungary**	**Netherlands**	**Poland**	**Wales**
Demographics									
Age	0.01 (-0.02, 0.03) p = 0.606	0.00 (-0.02, 0.03) p = 0.922	0.02 (-0.01, 0.05) p = 0.109	0.02 (-0.01, 0.04) p = 0.153			0.03 (0.00, 0.06) p = 0.026		0.00 (-0.02, 0.03) p = 0.976
Sex				0.39 (-0.10, 0.88) p = 0.119					0.49 (0.00, 0.98) p = 0.050
Socio-demographic / Clinical factors									
Cost coping strategies	-0.10 (-0.22, 0.01) p = 0.076	-0.17 (-0.30, -0.06) p = 0.004	-0.12 (-0.21, -0.02) p = 0.020	-0.06 (-0.16, 0.05) p = 0.319	-0.35 (-0.42, -0.28) p < 0.001	-0.21 (-0.28, -0.15) p < 0.001		-0.12 (-0.25, 0.02) p = 0.094	
Time preference									
Short					7.12 (2.14, 12.09) p = 0.005				
Illness perceptions									
Personal control			0.01 (-0.10, 0.11) p = 0.931		-0.11 (-0.26, 0.04) p = 0.144	0.17 (0.04, 0.30) p = 0.011	0.11 (-0.02, 0.24) p = 0.102	0.05 (-0.24, 0.33) p = 0.735	0.05 (-0.05, 0.15) p = 0.348
Treatment control	0.26 (0.13, 0.39) p < 0.001		0.13 (-0.02, 0.28) p = 0.095	-0.02 (-0.17, 0.13) p = 0.794	0.08 (-0.08, 0.24) p = 0.299	-0.09 (-0.25, 0.07) p = 0.284		0.11 (-0.27, 0.50) p = 0.558	0.07 (-0.08, 0.20) p = 0.366
Illness coherence			-0.07 (-0.20, 0.06) p = 0.274		0.17 (0.02, 0.32) p = 0.032	0.08 (-0.06, 0.21) p = 0.257			-0.01 (-0.13, 0.10) p = 0.814

Theory of planned behaviour									
Intention	-0.09 (-0.25, 0.07) p = 0.286		0.06 (-0.17, 0.28) p = 0.623		0.15 (-0.03, 0.33) p = 0.112	0.32 (0.09, 0.55) p = 0.007		-0.01 (-0.53, 0.51) p = 0.971	0.33 (0.04, 0.62) p = 0.028
Self efficacy	0.28 (0.16, 0.40) p < 0.001	0.19 (0.02, 0.36) p = 0.027	0.30 (0.17, 0.42) p < 0.001	0.32 (0.19, 0.46) p < 0.001	0.39 (0.26, 0.52) p < 0.001	0.15 0.03, 0.26 p = 0.016	0.25 (0.09, 0.41) p = 0.002	0.29 (-0.03, 0.61) p = 0.072	0.37 (0.22, 0.51) p < 0.001
BRIGHT									
Barriers	-0.04 (-0.07, 0.00) p = 0.062	-0.01 (-0.05, 0.03) p = 0.698	-0.04 (-0.09, 0.01) p = 0.081	-0.00 (-0.03, 0.03) p = 0.893	-0.05 (-0.09,0.01) p = 0.010	-0.07 (-0.11, -0.03) p = 0.101		-0.08 (-0.17, 0.00) p = 0.057	-0.06 (-0.11, 0.00) p = 0.060
Social Support	-0.02 (-0.09, 0.04) p = 0.520		0.00 (-0.04, 0.05) p = 0.920			-0.05 (-0.10, -0.01) p = 0.024			0.03 (-0.02, 0.07) p = 0.270
Constant	18.97 (15.83, 22.10) p < 0.001	21.72 (19.04, 24.40) p < 0.001	17.83 (13.96, 21.69) p < 0.001	20.15 (17.35, 22.96) p < 0.001	19.06 (16.32, 21.80) p < 0.001	19.76 16.70, 22.82) p < 0.001	19.48 (17.29, 21.68) p < 0.001	13.74 (8.97, 18.51) p < 0.001	19.37 (15.86, 22.88) p < 0.001
Other predictors in model where p>0.05[†]	2, 6, 11, 13, 14, 20, 22, 23	11, 14, 20	3, 8, 9, 10, 11, 13, 14, 15, 16, 17, 18, 19, 20, 22, 24	13, 14, 16, 17, 19, 20, 22	3, 5, 7, 8, 10, 11, 12, 14, 15, 17, 19, 24	1, 7, 10, 13, 14, 15, 16, 17, 19, 20, 22, 23, 24	24	13, 21, 23	3, 4, 5, 8, 11, 13, 14, 15, 16, 17, 19, 20, 23, 24
Adjusted R^2	0.2831	0.2005	0.3809	0.2223	0.6521	0.4589	0.1335	0.1482	0.3570

[*]Only coefficients for predictors with p<0.05 for at least one country are presented.

[†]Marital status (1), Employment (2), Dosage frequency (3), Number of medicines (4), Number of medical conditions (5), Income source (6), Total income (7), Income perception (8), Borrowing (9), Affordability problem (10), Health status (11), Time preference: long (12), Satisfaction with practitioner (13), Satisfaction with practice (14), Optimism (15), Illness consequences (16), Identity (17), Concern about illness (18), Emotional representations (19), Concern about medicine (20), Necessity of medicine (21), Attitude (22), Normative beliefs (23), Barriers-TPB (24)

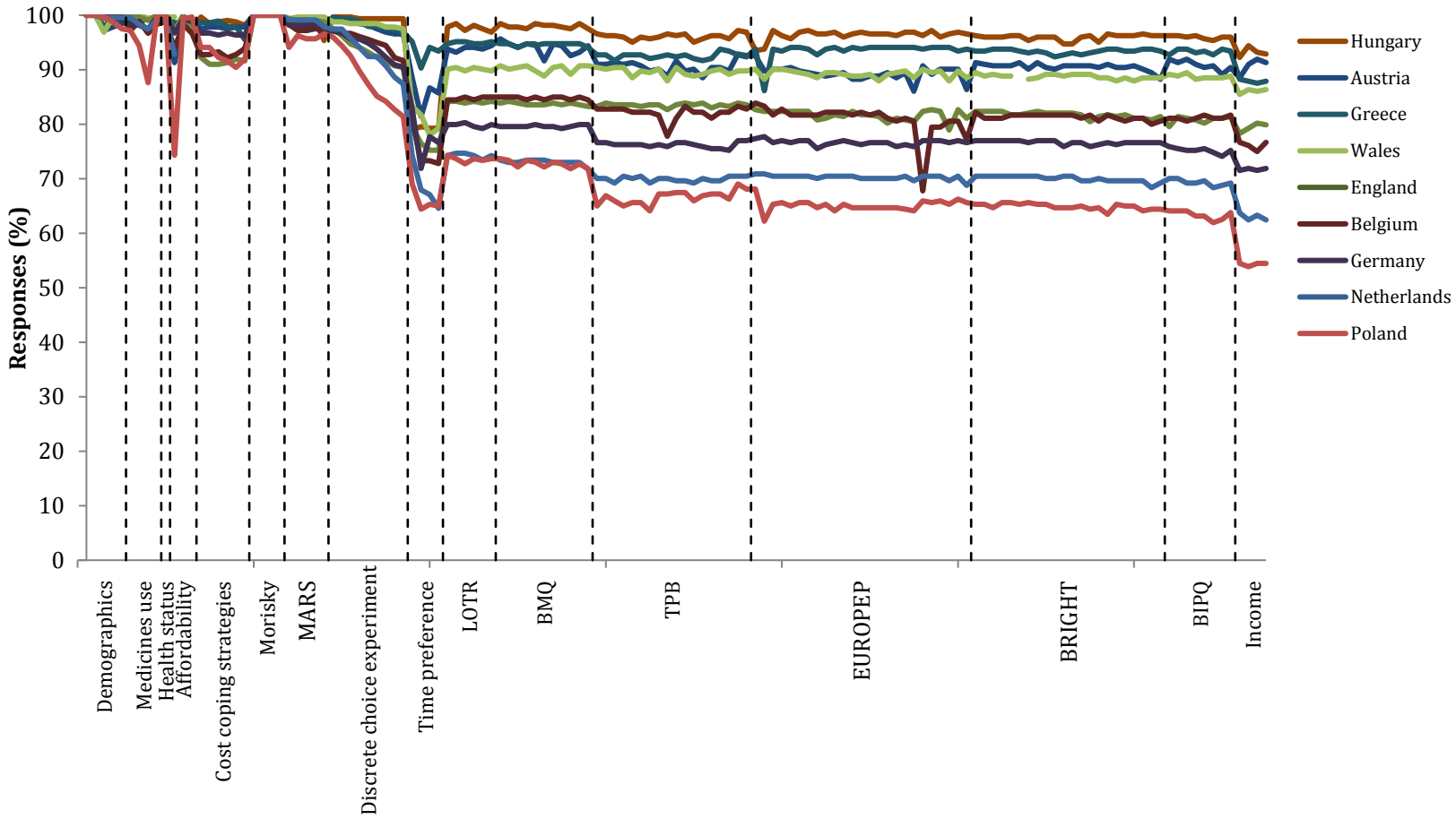
Table 5: Summary of multilevel regression models for Morisky and MARS as outcome measures.

	Morisky		MARS	
Explanatory variable	Odds Ratio	95% Confidence Interval	β-coefficient	95% Confidence Interval
Sex	1.22*	1.01, 1.47		
Age	0.98‡	0.97, 0.99	0.01*	0.00, 0.02
Employment	0.74*	0.59, 0.94		
Education			-0.34**	-0.60, -0.09
Number of medicines	0.89‡	0.86, 0.93	0.06*	0.01, 0.10
Dosing frequency	1.30†	1.12, 1.52	-0.24†	-0.42, -0.06
Normative beliefs	1.05*	1.01, 1.09		
Self-efficacy	0.73‡	0.70, 0.77	0.36‡	0.30, 0.42
Barriers (BRIGHT)	1.70‡	1.38, 2.09	-0.83‡	-1.10, -0.57
Illness consequences			-0.06*	-0.10, -0.01
Personal control	0.94†	0.90, 0.97		
Treatment control			0.11†	0.04, 0.19
Concern about illness	0.94†	0.91, 0.98		
Borrowing money	0.85†	0.78, 0.94		
Constant	34.59‡	13.5, 88.5	19.45‡	18.1, 20.8
Random effects parameters	Variance	95% Confidence Interval	Variance	95% Confidence Interval
Between country variance (σ_u^2)	0.40	0.15, 1.07	2.14	0.79, 5.80
Within country variance (σ_e^2)			7.09	6.63, 7.57
% variance attributable to differences between countries	10.82	4.35, 24.49	23.20	10.63, 43.40

*p<0.05, †p<0.01, ‡p<0.001
For the logit model $\sigma_e^2 = \pi^2/3$
Variance partition coefficient, VPC = $\sigma_u^2/(\sigma_u^2 + \sigma_e^2)$

Full model specification: age, sex, education, marital status, employment, number of medical conditions, number of different medicines, number of tablets, dosing frequency, number of items prescribed, health status, affordability problem, optimism, necessities, concerns about medicine, attitudes, normative beliefs, barrier (theory of planned behaviour), facilitators, intention, self-efficacy, prescriber of medicines, gender of prescriber, satisfaction with practitioner, satisfaction with practice, barriers (averaged as one less collected in Wales), social support, illness consequences, illness timeline, personal control, treatment control, illness symptomaticity, concern about illness, illness coherence, emotional representations, income source, income perception, ease of borrowing, total income.

Figure 1. Percentage of complete responses according to country and item of the questionnaire.



Abbreviations: MARS Medication Adherence Rating Scale; LOTQ Life Orientation Test; BMQ Beliefs about Medicines Questionnaire; TPB Theory of Planned Behaviour; EUROPEP European Task Force on Patient Evaluations of General Practice; BRIGHT Building Research Initiative Group Illness Management and Adherence in Transplantation; BIPQ Brief Illness Perception Questionnaire