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Effects of medication, treatment, and behavioral beliefs on intentions to take medication in patients with familial hypercholesterolemia

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ABSTRACT

Background and aims: Although familial hypercholesterolemia (FH) can be effectively managed using cholesterol-lowering medication, patients often fall short of complete treatment adherence. Identifying the psychological factors associated with self-regulation of FH medication is important to inform interventions to maximize adherence. The aim of the present study was to test an integrated psychological model in predicting FH patients' intentions to take medication.

Methods: FH patients attending clinics in seven countries were invited to participate in a cross-sectional survey study. Consenting patients (N = 551) completed self-report measures of generalized beliefs about medication overuse and harms, beliefs in treatment effectiveness, specific beliefs about taking medication (attitudes, subjective norms, perceived behavioral control), and intentions to take medication. Participants also completed measures of demographic variables (age, gender, education level, income, cardiovascular disease status). Data were analysed using path analysis controlling for country and demographic variables.

Results: Attitudes ($\beta = .331$, $p<0.001$), subjective norms ($\beta = .121$, $p=0.009$), and beliefs about medication overuse ($\beta = -.160$, $p<0.001$) were significant predictors of intentions to take medication. Treatment beliefs predicted intentions indirectly ($\beta = .088$, $p<0.001$) through attitudes and subjective norms. There was also an indirect effect of beliefs about medication overuse on intentions ($\beta = -.045$, $p=0.056$), but the effect was small compared with the direct effect.

Conclusions: The findings indicate the importance among FH patients of specific beliefs about taking medication and generalized beliefs about medication overuse and treatment in predicting medication intentions. When managing patients, clinicians should emphasize the efficacy of taking cholesterol-lowering drugs and the importance of treatment outcomes, and allay concerns about medication overuse.

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1. Introduction

Familial hypercholesterolemia (FH) is co-dominantly inherited form of hyperlipidemia characterized by chronically high levels of low-density lipoprotein (LDL) cholesterol and premature onset of atherosclerotic cardiovascular disease (ASCVD) [1]. ASCVD risk in patients with FH can be effectively managed through cholesterol-lowering medication [2,3]. Although medication adherence rates in FH patients are relatively high, a substantial proportion of patients fall short of full compliance or follow regimens inconsistently [4]. Non-compliance may have deleterious effects on patient health including substantive increase in ASCVD risk [5–8]. As patients with FH are typically treated as outpatients, adherence to medication regimens is largely dependent on patients' capacity to regulate their own behavior, so understanding the factors that affect treatment adherence is paramount to informing the development of effective interventions to maximize compliance [9,10].

1.1. Theories of medication adherence

Psychological theories from the 'social cognitive' tradition have been applied to guide understanding of the belief-based factors associated with taking medication and the processes involved [11–13]. Two prominent perspectives have been adopted, one focusing on individual beliefs about the effectiveness of treatment to control the illness or condition, the other focusing on beliefs in the act of performing specific treatment-related behaviors in future. The first perspective is derived from Leventhal et al.'s [14] common sense model of illness self-regulation. According to the common sense model, lay or 'common sense' beliefs about the illness motivate individuals to engage in problem-focused behaviors to manage their illness. In particular, beliefs about treatment and general beliefs about medication, such as whether medication is perceived as overused by health professionals, harmful, and has negative side effects, are proposed to be related to decisions to take medication [15–20]. For example, if an FH patient perceives his or her condition as treatable, and believes that medication is not overused or harmful, and does not have negative side effects, he or she will be more likely to be motivated to take their medication.

A second perspective is offered by Ajzen's [21] theory of planned behavior. This theory focuses on beliefs about performing the specific behavior and how they relate to intentions to perform the behavior in future. Intentions, a key construct in the theory, reflect individuals' motivation toward engaging in a target behavior in future. For example, an FH patient with strong intentions to take their medication in future is highly likely to do so. Intentions are a function of three sets of beliefs about the behavior: *attitudes*, an individual's positive or negative beliefs about whether performing the target behavior will result in desirable outcomes, *subjective norms*, beliefs about whether significant others endorse performance of the behavior in future, and *perceived behavioral control*, beliefs in general capacity to engage in the behavior in future. Intentions are proposed to mediate the effects of the three sets of beliefs on behavior [21]. Together, the two theories provide complimentary perspectives on the psychological constructs that lead individuals make decisions to engage in treatment for illnesses and conditions, and together may offer a comprehensive explanation of medication adherence in FH.[1]

[1] Further detail of the tenets of the common sense model and theory of planned behavior can be found in the original articles by Leventhal et al. [14] and Ajzen [21], respectively, and in meta-analyses of the effects of the theories in health behavior and chronic illness [22,23]. We have also provided further description and details in Supplementary Materials.

1.2. A comprehensive theory of medication adherence

Recent research has integrated beliefs relating to illness and treatment from the common sense model and beliefs relating to performing specific behaviors from theory of planned behavior to arrive at a comprehensive explanation of health behavior adherence including medication adherence [9,24–26]. Research has demonstrated that beliefs relating to the behavior from the theory of planned behavior, rather than those relating to the illness itself and its treatment, tend to have the largest and most consistent effects on behavior. For example, research has shown that attitudes and subjective norms are the most pervasive predictors of intentions to engage in behaviors aimed at managing chronic conditions such as taking medication and screening attendance [9,25]. However, previous research has not tested the simultaneous effects of medication and treatment beliefs alongside beliefs about the behavior on intentions to take medication. Furthermore, integrated models may mask the processes by which medication and treatment beliefs relate to intentions and behavior. In particular, generalized beliefs about medication and treatment may be mediated by the specific beliefs, consistent with theory predictions [27–29]. The mediation effect suggests that generalized factors serve as sources of information in the formation of beliefs toward the behavior. For example, generalized beliefs about the effectiveness of medication to treat FH may assist patients in forming specific beliefs and intentions with respect to taking cholesterol lowering medication. This is an important process because it outlines how beliefs regarding illness management behaviors, such as medication adherence, are formed.

1.3. Aims and hypotheses

Our study had two objectives: (1) to examine relationships between FH patients' intentions to take cholesterol-lowering medication, their general beliefs about medication and treatment for FH, and their beliefs about taking the medication itself; (2) to test how patients' beliefs about taking medication serve to explain, or *mediate*, relations between their medication and treatment beliefs and their intentions to take medication. We realized these objectives by testing a novel process model in which generalized beliefs about medication harm and overuse, treatment effectiveness, and side effects of FH medication were proposed to predict FH patients' intentions to take cholesterol-lowering medication in future. Specific beliefs about taking medication were expected to mediate relations between the generalized beliefs and medication intentions, consistent with previous research combining the common sense model and the theory of planned behavior [9,24–26]. The model was tested in a large sample of FH patients prescribed cholesterol-lowering medication from clinics in seven countries [30].

Our proposed model is presented in Fig. 1. We predict that FH patients' intentions to take their medication in future will be related to their attitudes, subjective norms, and perceived behavioral control. Generalized beliefs about medication harms and overuse, treatment control, and perceived side effects are proposed as distal beliefs that predict intentions mediated by attitudes, subjective norms, and perceived behavioral control. We therefore propose indirect effects of each of the distal medication and treatment beliefs through the beliefs about taking medication. Direct effects of the distal beliefs about medication and treatment on intention are, therefore, expected to be zero. Finally, we predict that both sets of beliefs will mediate effects of past medication adherence on intentions to take medication in future, consistent with research examining effects of past behavior in social cognitive models [29]. We expect our process model to provide detail on the

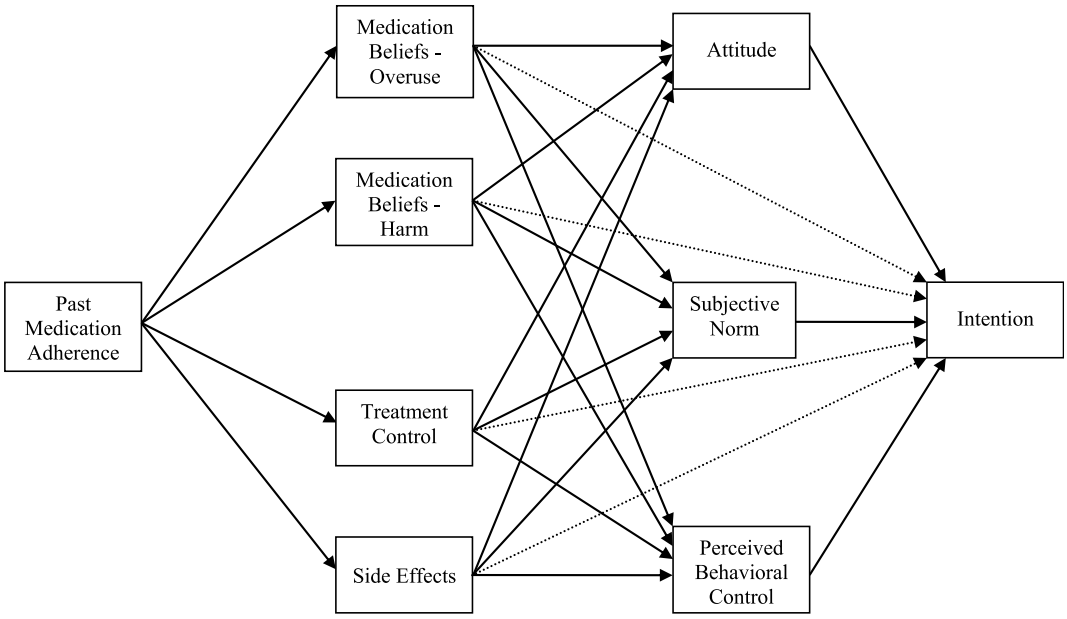

Fig. 1. Hypothesized model of proposed relationships between study constructs familial hypercholesterolemia patients' intentions to take prescribed cholesterol-lowering medication is the dependent variables and attitudes, subjective norms, perceived behavioral control, medication beliefs, treatment control, perceived side effects, and past medication adherence are independent variables.
Direct effects of past medication adherence on attitude, subjective norm, perceived behavioral control, and intentions not shown for clarity.

effects of beliefs about medication and treatment, and beliefs about medication behavior, from two theoretical perspectives relate to intentions to take cholesterol-lowering medication in FH patients. We also expect effects to be universal across national groups and, therefore, estimate whether proposed effects hold when controlling for national group membership.

2. Materials and methods

2.1. Design and participants

The current study adopted a cross-sectional survey design and was part of the "Ten Countries Study" [30]. Participants were consecutive patients with a positive diagnosis for FH from a genetic test, or with probable FH identified through a blood test, attending FH clinics in seven countries: Royal Perth Hospital, Australia; Heart Institute (InCor), University of São Paulo Medical School Hospital, Brazil; Beijing Anzhen Hospital, China; Prince of Wales Hospital, Hong Kong; Universiti Teknologi MARA Faculty of Medicine Clinical Training Centre, Malaysia; National Taiwan University Hospital, Taiwan; and UK NHS Trusts in Manchester, Bristol, Coventry and Warwickshire, and Bath. Ethical clearance was obtained from the research ethics committee of each participating clinic prior. Patients were offered the opportunity to participate by referral from clinic staff between January 2015 and July 2017. Eligible patients were provided with information regarding the study and required to complete a written informed consent form prior to participation. Participants completed a questionnaire containing self-report measures of psychological variables relating to their FH and their treatment in a private waiting room.

2.2. Measures

Psychological constructs were measured using scaled self-report measures adopted from previous research and standardized guidelines [18,31,32]. Participants were presented a brief introductory passage: "This section of the survey asks you your opinions about the medication prescribed to you by your physician to manage your FH over the next three months. You need to be aware of the exact prescription of your medication. Please indicate the extent to which you agree with the statements by placing a 'tick' in the appropriate circle. There are no right or wrong answers. We are interested in your personal views." Participants were then presented with the study measures. Full measures are presented in Appendix B (supplementary materials).

2.2.1. Theory of planned behavior constructs

Measures of intentions, attitudes, subjective norms, and perceived behavioral control with respect to taking medication were adapted from standardized guidelines [31].

2.2.2. Treatment beliefs

Treatment beliefs were measured using the treatment control scale from the revised illness perceptions questionnaire (IPQ-R) [32].

2.2.3. Beliefs about medication

Medication beliefs were measured using the beliefs that medication is overused and beliefs that medication is harmful subscales from the beliefs about medicines questionnaire (BMQ) [18].

A brief side effects for FH questionnaire was developed by adapting items from previous research regarding beliefs about side effects [33,34].

2.2.4. Past medication adherence

Past medication adherence was assessed using a single item with responses provided on a binary scale.[2] Lower scores on this

[2] The only exception was the Australian sample in which medication adherence was measured using an item ("In the course of the past 3 months, how often have you taken your medication?") with scale endpoints 1 ("*never*") and 6 ("*everyday*"). To maintain equivalence across measures, the scale was reverse-scored and standardized.

Table 1
Sample characteristics for the full sample and each national sample.

National group	Age	Gender[a]	Income[a]	Education[a]	ASCVD[a]	Health literacy[a]
	M (SD)					
Full sample ($N = 551$)	51.88 (14.14)	51.36	45.01	59.17	32.1	12.35 (2.72)
		48.64	54.99	40.83	67.9	
Australia ($n = 60$)	52.98 (14.64)	45.0	40.0	30.0	26.7	12.73 (2.78)
		55.0	60.0	70.0	73.3	
Brazil ($n = 86$)	50.19 (15.25)	41.9	15.1	61.6	33.7	12.14 (3.08)
		58.1	84.9	38.4	66.3	
China ($n = 61$)	45.61 (13.53)	49.2	85.2	45.9	63.9	11.36 (2.75)
		50.8	14.8	44.1	36.1	
Hong Kong ($n = 80$)	50.79 (14.19)	45.0	31.2	55.0	11.2	12.10 (2.32)
		55.0	66.8	45.0	88.8	
Malaysia ($n = 100$)	51.04 (11.16)	63.8	55.1	73.9	53.6	12.71 (3.08)
		36.2	44.9	26.1	46.4	
Taiwan ($n = 115$)	58.44 (12.71)	64.3	73.0	93.0	23.5	11.97 (2.42)
		35.7	27.0	7.0	76.5	
UK ($n = 80$)	49.33 (14.24)	45.0	15.0	31.2	25.0	13.51 (2.24)
		55.0	85.0	68.8	75.0	

ASCVD = cardiovascular disease.
[a] All values are percentages with the exception of age and health literacy, which are reported as means and standard deviations. Values presented on the upper line are for males, lower income, lower education, and received a diagnosis of ASCVD. Values presented on the lower line are for females, higher income, higher education, and has not been diagnosed with ASCVD.

scale represented better adherence.

2.2.5. Demographic variables

Participants also provided their age, gender, ASCVD status (patients diagnosed with ASCVD *vs.* those without an ASCVD diagnosis), annual household income stratified by seven income levels relative to national averages, and highest level of formal education in categories relevant to the national group. Binary income and highest education level variables were computed for subsequent analyses. Our process model focuses on generalized processes that likely affect decisions to take medication, so we expected model effects to be consistent across participants independent of any idiosyncratic differences due to extraneous variables. As a consequence, our analysis tested these processes in the model across the entire sample, controlling for effects of national group and other demographic variables [27,35].

2.3. Data analysis

We tested for differences in study demographic variables and psychological constructs between patients included in the final sample for analysis and those excluded due to incomplete behavioral and demographic data or eligibility because they were not currently taking prescribed medication for their FH. Differences in demographic variables were tested using chi-square and *t*-tests. Differences in psychological constructs was tested using a MANOVA with psychological constructs as multiple dependent variables and inclusion status as a dichotomous independent variable. Statistically significant differences were followed up using univariate ANOVAs. Reliability of scales was estimated using alpha (α) [36] or omega (ω) [37] coefficients, depending on the number of items in the scale.

Hypothesized relations among constructs in our proposed model was tested using path analysis. Missing data were imputed using full-information maximum likelihood method. To minimize the number of free parameters in our model, we controlled model variables (intentions, attitudes, subjective norms, perceived behavioral control, BMQ-overuse, BMQ-harm, treatment control, side effect beliefs, past medication use) for demographic variables (gender, age, income, education, ASCVD status, health literacy, national group membership) by computing unstandardized residual scores using multiple linear regression. Each model construct was regressed on the set of demographic variables to produce an unstandardized residual score for the construct. The scores were used in the subsequent path analysis to test the model.

We adopted Hayes' [38] regression-based analytic approach to estimate our path analytic model with bootstrapped standard errors with 1000 replications. Goodness of fit of the models was evaluated using multiple criteria including the goodness-of-fit chi-square, the comparative fit index (CFI), the root mean square error of approximation (RMSEA), and the standardized root mean square residual (SRMSR). The chi-square should return a non-significant result, although in complex models it is usually sensitive to sample size, so values for the CFI should exceed .95, and values for the RMSEA and SRMSR should approach or be below .05 and .08, respectively [39]. The model was implemented using the lavaan package in R [40] [3].

3. Results

3.1. Participants

Of the eligible FH patients initially invited to participate in the study ($N = 1145$), 762 consented and responded to the questionnaire, a response rate of 66.55%. Of these, 629 reported receiving cholesterol-lowering medication and were eligible for inclusion in the analysis. In addition, patients that reported incomplete data ($n = 78$) were excluded leaving 551 complete cases for analysis. Patients included in the analysis were more likely to have been diagnosed with ASCVD than those excluded from the analysis ($\chi^2 = 5.021$, $p = 0.025$). There were no differences in age, gender, income, and education level across patients included in the analysis and those excluded. A MANOVA testing differences in psychological constructs between patients included in the analysis and those excluded revealed a statistically significant main effect, Wilks' $\Lambda = 0.88$, $F\,(10,597) = 8.00$, $p < 0.001$, $\eta^2 = .118$. Univariate follow-up ANOVAs revealed that included patients scored significantly higher on medication adherence ($F\,(1,606) = 62.39$, $p < 0.001$,

[3] Data files and analysis scripts and supplemental materials are available online from the Open Science Framework project for this article: https://osf.io/mquwh/.

$\eta^2 = 0.093$), intentions (F (1,606) = 4.96, p = 0.026, $\eta^2 = 0.001$), attitudes (F (1,606) = 3.90, p = 0.049, $\eta^2 = 0.006$), and perceived behavioral control (F (1,606) = 5.35, p = 0.021, $\eta^2 = 0.009$), although effect sizes for all significant effects were small with the exception of medication adherence. Sample characteristics are presented in Table 1. Reliability and correlation coefficients for study constructs are presented in Table 2.

3.2. Model test

The proposed integrated process model exhibited acceptable fit statistics (χ^2 (3) = 10.040, p = 0.018, CFI = 0.990, RMSEA = 0.065, SRMSR = 0.018). Parameter estimates and confidence intervals for the direct and indirect effects of relations among constructs in the proposed model are presented in Fig. 2 and Table 3. We found significant, positive direct effects of attitudes and subjective norms on intentions to take medication, as predicted, but no effect for perceived behavioral control, which was contrary to hypotheses. Beliefs that medication is overused was also a significant, negative predictor of intentions, which was not consistent with our predictions because we expected the effect to be mediated by theory of planned behavior constructs. Beliefs about medication overuse was also a statistically significant, negative predictor, and treatment control a statistically significant positive predictor, of attitudes, as predicted. Beliefs that medication has harmful effects was a negative predictor of attitudes, but the coefficient fell short of conventional levels of statistical significance by a trivial margin ($p < 0.051$). Treatment control was a significant, positive predictor, and beliefs in side effects a significant, negative predictor, of subjective norms, supporting our hypotheses. Treatment control was also a significant, positive predictor of perceived behavioral control, as predicted. Importantly, there was a significant, positive indirect effect treatment control on intention mediated by attitudes, and a significant, positive total indirect effect. There was also a positive indirect effect of treatment control on intention mediated by subjective norms, and a negative indirect effect of beliefs in medication overuse on intentions mediated by attitudes, but both effects fell short of conventional levels of statistical significance by a trivial margin ($ps < 0.058$). The sum of indirect effects of beliefs that medication is overused on intentions fell short of statistical significance by a trivial margin ($p < 0.056$), and the total effect was statistically significant. The proportion mediation statistic (P_M), an expression of the proportion of the total effect of a variable on an outcome accounted for by the indirect effect, indicated that the indirect effect of beliefs about medication overuse accounted for a relatively small proportion of the total effect ($P_M = 0.218$), so the majority of the effect of this variable was accounted for by the direct effect. Finally, we found a significant negative total effect of past medication adherence on medication intentions.

4. Discussion

We aimed to examine the effects of beliefs about medication and treatment, and beliefs about taking medication itself, on intentions to take cholesterol-lowering medication in the future in a sample of FH patients from seven countries. Given that successful treatment and associated adaptive outcomes including effective management of the illness is highly dependent on patients taking medication as prescribed [1], identifying the personal factors that determine effective self-regulation of medication in this context is important [10]. Our findings indicated that specific beliefs about taking medication, attitudes and subjective norms, and generalized beliefs about medication overuse were related to intentions to take medication. Treatment beliefs also predicted intentions via attitudes and subjective norms, suggesting that patients take

Table 2
Reliability estimates and correlations for generalized beliefs about medication and treatment, specific beliefs about taking medication, and intentions to take medication in the proposed model.

Construct	Reliab.	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. Gender	–	–													
2. Age	–	−0.048	–												
3. Education	–	0.093*	−0.226***	–											
4. Income	–	−0.029	−0.208***	0.197***	–										
5. Health literacy	–	−0.003	−0.116**	0.139***	0.226***	–									
6. CVD	–	0.167***	−0.077	0.019	0.156***	.081*	–								
7. Treatment control	0.46[a]	−0.050	0.053	−0.055	−0.130**	−0.125**	−0.027	–							
8. Intention	–	−0.117**	0.130**	−0.298***	−0.280***	−0.095*	0.091*	0.166***	–						
9. Attitude	0.91[b]	−0.090*	0.174***	−0.286***	−0.297***	−0.096*	0.063	0.262***	0.779***	–					
10. Subjective norms	0.62[b]	−0.012	0.139***	−0.266***	−0.289***	−0.097*	0.086*	0.219***	0.637***	0.682***	–				
11. PBC	0.42[b]	−0.052	0.121**	−0.329***	−0.347***	−0.233***	−0.044	0.152***	0.606***	0.585***	0.608***	–			
12. Past medication use	–	0.069	0.066	0.211***	0.040	0.066	0.058	0.020	−0.248***	−0.196***	−0.169***	−0.329***	–		
13. BMQ - Harm	0.79[a]	0.099*	−0.037	0.145***	0.211***	0.151***	0.032	−0.032	−0.321***	−0.386***	−0.277***	−0.336***	0.378***	–	
14. BMQ - Overuse	0.80[a]	0.100*	−0.084*	0.275***	0.294***	0.217***	0.050	−0.086*	−0.494***	−0.479***	−0.417***	−0.474***	0.469***	0.744***	–
15. Side effect beliefs	0.89[a]	0.075	−0.070	0.171***	0.188***	0.087*	0.089*	−0.131***	−0.242***	−0.301***	−0.278***	−0.279***	0.219***	0.402***	0.432***

Reliab. = Reliability coefficient; PBC = Perceived behavioral control; BMQ = Beliefs about medication questionnaire.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.
[a] Omega (ω) reliability coefficient.
[b] Alpha (α) reliability coefficient.

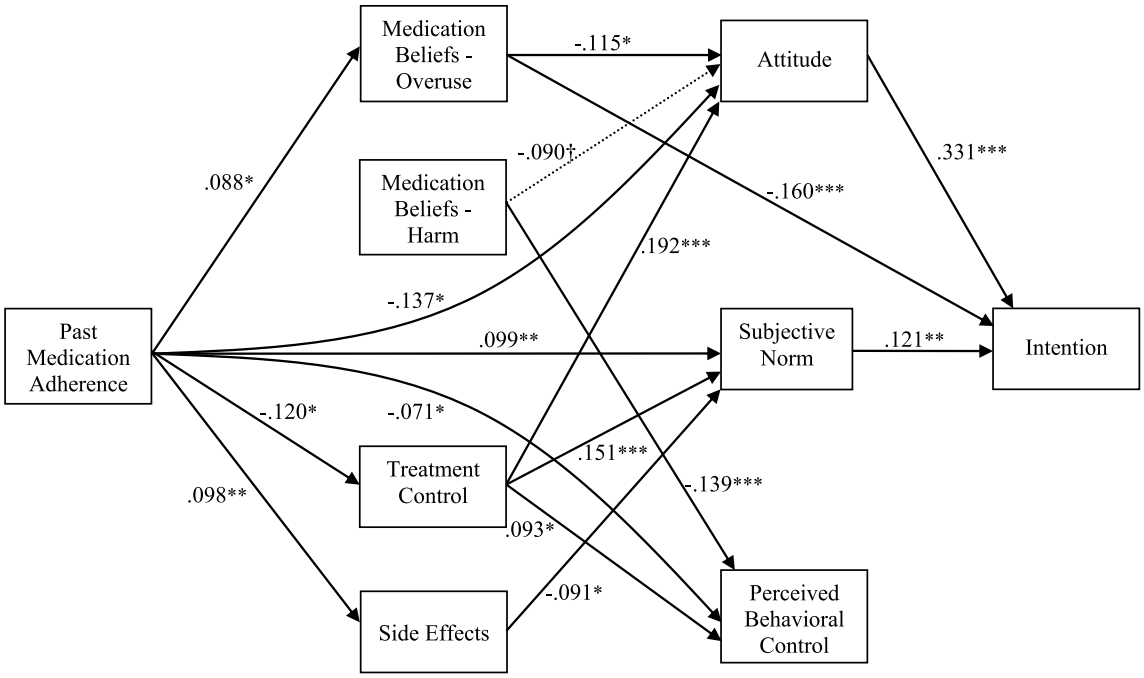

Fig. 2. Final path model presenting statistically significant effects of beliefs on familial hypercholesterolemia patients' intentions to take prescribed cholesterol-lowering medication.
Solid lines represent statistically significant effects, broken lines represent effects falling short of the conventional level of statistical significance by a trivial margin* $p < 0$ .05, **$p < 0.01$, ***$p < 0.001$, †$p < 0.058$.

treatment beliefs into account when forming their attitudes and subjective norms. Our results applied after controlling for demographic variables and national group.

Current findings provide important information on the independent belief-based predictors of intentions to take cholesterol-lowering medication in FH patients, and the processes involved. Unsurprisingly, the attitude and subjective norms constructs from the theory of planned behavior, reflecting positive and negative beliefs about taking medication and social influence, respectively, had the most pervasive influences on FH patients' intentions to take medication in future. This is consistent with previous research demonstrating the importance of these factors in determining future intentions to engage in specific behaviors aimed at managing chronic illness [23]. Our findings are also consistent with research integrating the common sense model and the theory of planned behavior, indicating that the beliefs relevant to the behavior have the most pervasive influence [9,24–26]. Our findings extend this research by demonstrating that generalized beliefs in treatment effectiveness predicted intentions to take FH medication, but did so only via the mediation of beliefs about taking medication from the theory of planned behavior. This mediation effect suggests that generalized beliefs relating to treating FH are a distal influence on medication intentions because they serve as a source of information for the more proximal, behavior-specific constructs. This may also explain why previous research including both sets of beliefs have found zero or non-significant effects of treatment beliefs on intentions. It points to the imperative of examining mediating effects when including these sets of beliefs.

Perceived behavioral control had no effect on intentions, contrary to our hypotheses and in contrast to previous research in other health contexts [23]. However, it is consistent with previous research examining specific beliefs about medication in FH patients [9]. Some have argued that failure to find one of the key predictions in the theory is grounds for falsification of the theory predictions, at least in the population and for the behavior of interest [41]. In this context, it may be that the strong correlations and substantive shared variable between attitudes, intentions, and perceived behavioral control may have attenuated effects of perceived behavioral control. Current findings indicate that researchers should direct their attention to generalized beliefs about treatment control rather than specific control beliefs.

We predicted that generalized beliefs that medication is overused and harmful, and beliefs about side effects, would predict intentions to take FH medication mediated by specific beliefs about taking medication. In contrast, our findings revealed that the indirect effect of beliefs about medication overuse on intentions was modest relative to the much larger direct effect. Furthermore, beliefs that medication is harmful and side effects had no unique effects on intentions, even though there were significant correlations between these factors and intentions. These findings suggest that generalized beliefs that medications are overused are an important correlate of intentions to take medication, independent of specific beliefs about the behavior. This has important implications for social cognitive theories like the theory of planned behavior, which focus on a relatively narrow set of beliefs relating to the act of taking medication, and neglect influential generalized beliefs regarding the medication itself. Thus prompting individuals to report their beliefs about taking medication, likely fails to account for generalized beliefs about medication, such as beliefs that medications tend to be overused by medical practitioners, and fail to identify important additional beliefs that ultimately determine intentions to take medication. While side effects and harms have been found to be significant correlates of medication adherence in other research [18,20,42], they were not related to intentions to take medication in the current sample. A possible reason for this is that although perceived side effects and harms may be important considerations for cholesterol-lowering drugs in FH patients, beliefs relating to taking the medication itself, and beliefs about

Table 3
Summary of relationships between FH patients' generalized beliefs about medication and treatment, specific beliefs about taking medication, and intentions to take medication in the proposed model.

Effect[a]	B	SE	95%CI		β
			LB	UB	
Direct effects					
Attitude → Intention	0.389	0.055	0.298	0.528	0.331***
SN → Intention	0.153	0.059	0.055	0.304	0.121**
PBC → Intention	0.084	0.050	-0.032	0.189	0.063
Medication beliefs-Harm → Intention	0.097	0.055	-0.049	0.187	0.076
Medication beliefs-Overuse → Intention	-0.218	0.058	-0.325	-0.067	-0.160***
Treatment control → Intention	-0.013	0.061	-0.140	0.124	-0.011
Side effects → Intention	-0.002	0.032	-0.064	0.061	-0.003
Past medication adherence → Intention	-0.241	0.167	-0.497	0.246	-0.084
Medication beliefs-Harm → Attitude	-0.098	0.050	-0.229	-0.020	-0.090[b]
Medication beliefs-Overuse → Attitude	-0.133	0.062	-0.271	-0.003	-0.115*
Side effects → Attitude	-0.022	0.033	-0.062	0.064	-0.032
Treatment control → Attitude	0.202	0.049	0.078	0.280	0.192***
Past medication adherence → Attitude	-0.335	0.141	-0.628	0.022	-0.137*
Medication beliefs-Harm → SN	0.014	0.051	-0.123	0.084	0.013
Medication beliefs-Overuse → SN	-0.091	0.065	-0.195	0.082	-0.084
Side effects → SN	-0.058	0.029	-0.113	0.003	-0.091*
Treatment control → SN	0.147	0.041	0.067	0.238	0.151***
Past medication adherence → SN	-0.226	0.082	-0.415	-0.043	-0.099**
Medication beliefs-Harm → PBC	-0.134	0.050	-0.225	-0.014	-0.139**
Medication beliefs-Overuse → PBC	0.046	0.054	-0.075	0.160	0.044
Side effects → PBC	-0.023	0.030	-0.065	0.055	-0.037
Treatment control → PBC	0.087	0.038	-0.016	0.145	0.093*
Past medication adherence → PBC	-0.153	0.075	-0.377	-0.044	-0.071*
Past medication adherence → Medication beliefs-Harm	0.110	0.096	-0.166	0.251	0.049
Past medication adherence → Medication beliefs-Overuse	0.185	0.074	0.015	0.353	0.088*
Past medication adherence → Side effects	0.347	0.105	0.097	0.611	0.098**
Past medication adherence → Treatment control	-0.277	0.129	-0.437	0.097	-0.120*
Indirect effects					
Medication beliefs-Harm → Attitude → Intention	-0.038	0.023	-0.101	-0.008	-0.030
Medication beliefs-Harm → SN → Intention	0.002	0.010	-0.023	0.015	0.002
Medication beliefs-Harm → PBC → Intention	-0.011	0.007	-0.024	0.005	-0.009
Medication beliefs-Overuse → Attitude → Intention	-0.052	0.027	-0.114	-0.001	-0.038[b]
Medication beliefs-Overuse → SN → Intention	-0.014	0.011	-0.032	0.017	-0.010
Medication beliefs-Overuse → PBC → Intention	0.004	0.005	-0.008	0.016	0.003
Treatment control → Attitude → Intention	0.078	0.023	0.031	0.128	0.063**
Treatment control → SN → Intention	0.023	0.012	0.006	0.056	0.018[b]
Treatment control → PBC → Intention	0.007	0.005	-0.003	0.017	0.006
Side effects → Attitude → Intention	-0.009	0.014	-0.027	0.027	-0.011
Side effects → SN → Intention	-0.009	0.006	-0.022	0.001	-0.011
Side effects → PBC → Intention	-0.002	0.003	-0.006	0.006	-0.002
Sums of indirect effects					
Medication beliefs-Harm → Intention	-0.047	0.027	-0.122	-0.008	-0.037
Medication beliefs-Overuse → Intention	-0.062	0.032	-0.133	0.004	-0.045[b]
Treatment control → Intention	0.108	0.026	0.053	0.162	0.088***
Side effects → Intention	-0.019	0.017	-0.044	0.024	-0.024
Total effects					
Medication beliefs-Harm → Intention	0.050	0.062	-0.122	0.131	0.039
Medication beliefs-Overuse → Intention	-0.280	0.064	-0.392	-0.120	-0.206***
Treatment control → Intention	0.095	0.064	-0.034	0.228	0.077
Side effects → Intention	-0.022	0.035	-0.083	0.057	-0.027
Past medication adherence → Intention	-0.472	0.233	-0.875	0.157	-0.165*

B = Unstandardized parameter estimate; 95% CI = 95% confidence intervals of unstandardized parameter estimate using bootstrapped standard errors (replications, n = 1000); LB = Lower bound of 95% CI; UB = Upper bound of 95% CI; β = Standardized parameter estimate.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
[a] Effects are parameter estimates and variability statistics from path analytic model.
[b] Effect falls marginally short of conventional criterion for statistical significance ($p < 0.058$).

medication overuse, have stronger effects and explain more variance in intention.

Although the current research focuses on FH, our findings may have ramifications for other cardiovascular diseases where cholesterol-lowering medication is an essential component of disease management. The factors identified in the current model are derived from generalized theories of illness beliefs and intentional behavior, so findings may reflect processes that may operate across multiple illness contexts, as indicated by meta-analyses of research applying these theories in chronic illness [23]. However, the current model has not been previously tested, so statements on generalizability to other cardiovascular disease and other disease contexts should be considered speculative pending empirical verification. We advocate future replications of our model in multiple disease contexts.

4.1. Strengths and limitations

The current research has numerous strengths including testing a model based on the integration of two prominent theoretical

perspectives on medication use, adoption of appropriate measures and analytic procedures, and recruiting a large sample of FH patients from multiple clinics and national groups. However, some limitations of the current research should be noted. An important limitation was the lack of a prospective measure of medication adherence. This precluded drawing conclusions on the effectiveness of the sets of beliefs on taking medication in future. This can be inferred from the theory given that intentions are proposed as the most proximal predictor of behavior, and the consistent relations between intentions and behavior in health behavior research on chronic illness including medication adherence. However, the relationship between intentions and behavior is seldom perfect, indicating a substantial shortfall in individuals converting their intentions into action, known as the intention-behavior 'gap'. While means exist to augment intentions to strengthen the relationship and 'close the gap' [43], the current research is not informative on the strength of the relationship between medication intentions and behavior. In addition, in the absence of a behavioral measure means we cannot test whether generalized beliefs relating to medication overuse and harms direct prediction medication adherence. Direct effects of traits and other generalized factors may be indicative of more spontaneous, non-conscious pathways to behavior that affect behavior independent of the reasoned processes reflected by intentions [44]. It may, therefore, be possible that more generalized beliefs about medication may directly predict medication adherence in FH patients, and serve to influence behavior beyond the awareness of the patient. We look to future research to test these effects.

Other limitations include the exclusive reliance on self-report measures and samples of FH patients that was not randomly selected. Use of self-report measures has the potential to introduce common-method variance when estimating effects, and verification against objective measures, particularly of behavioral and demographic measures, may be appropriate to validate the pattern of effects. Furthermore, although we controlled for demographic factors, it would be remiss to make definitive population-level generalizations regarding the reported patterns of effects based on the current sample alone. We look to future research that replicates current findings in randomly-recruited, stratified samples that closely represent population demographics.

4.2. Conclusion

The current study provided preliminary evidence for the effects of beliefs about medication and treatment, and behavioral beliefs about taking medication, on intentions to take medication in future among FH patients from seven countries. The findings may point to potential candidate factors that should be targeted in messages promoting FH patients' intentions to take medication in future and actual medication adherence. Such interventions may aim to provide messages aimed at highlighting adaptive outcomes of taking medication, downplaying negative effects, dispelling beliefs surrounding medication overuse in an FH context, emphasizing the importance significant others' support for taking prescribed medication, and promoting general treatment beliefs in the effectiveness of medication in managing FH. Such messages could be communicated by clinic staff when patients' visit the clinic. For example, the occasion when newly diagnosed FH patients are first prescribed cholesterol-lowering medication may be an opportunity to provide information on medication concerns and effectiveness to pre-empt the formation of negative beliefs. For example, clinic nurses could engage initiate a brief discussion with new patients to discuss their general beliefs about medication and any concerns they have, suggest that side effects can be well managed by selecting in the appropriate type of medication, and discuss strategies on when and how to take the medication, and how to recruit significant others to help them. Clinics could also develop clear-language leaflets to support the brief in-clinic discussions, which patients can also take home. The discussions could also be administered to existing patients during routine follow-up visits to the clinic. Future research may seek to test the efficacy behavioral interventions that include messages targeting the beliefs identified in the current study on patients' intentions to take their medication, and on their actual medication adherence.

Conflicts of interest

RDS has received honoraria and consulting fees from Amgen, AstraZeneca, Biolab, Merck, Kowa, Sanofi/Regeneron, Novo-Nordisk and Pfizer. RDS has also received research grants from Amgen, Sanofi/Regeneron and Akcea. HS has received research grants from Alexion, Pfizer, Amgen and MSD, and honoraria from Sanofi, Pfizer, Takeda, AMGEN and MSD. BT has received research funding from Amgen, AstraZeneca, Merck Serono, Merck Sharp and Dohme, Novartis, Pfizer and Roche, and he has acted as consultant, advisor or speaker for Amgen, AstraZeneca, Merck Serono, Merck Sharp, and Dohme and Sanofi. GW has received research grants and lecturing fees from Amgen, Sanofi and Regeneron. All other authors declare no conflict of interest.

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Author contributions

MSH and GFW contributed to the conception and design of the research, and drafted the manuscript. SJH and JP contributed to the acquisition of data. SJH, MH, SK, JL, HMN, JP, RDS, HS, TCS, and BT contributed to data interpretation and critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.atherosclerosis.2018.06.010.

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