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Title: The role of habit in treatment adherence among adults with cystic fibrosis

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ABSTRACT

Among adults with CF, medication adherence is low and reasons for low adherence are poorly understood. Our previous exploratory study showed that stronger 'habit' (i.e. automatically experiencing an urge to use a nebuliser) was associated with higher nebuliser adherence. We performed a secondary analysis of pilot trial data (n=61) to replicate the earlier study and determine whether habit-adherence association exists in other cohorts of adults with CF. In this study, high adherers also reported stronger habit compared to low adherers. Habit may be a promising target for self-management interventions.

INTRODUCTION

Adherence to preventative inhaled treatments is associated with better health outcomes in cystic fibrosis (CF) but adherence levels are generally low.[1] Effective adherence interventions are lacking,[2] and reasons for low adherence are poorly understood. Studies of adherence determinants in CF have tended to focus on treatment burden and conscious motivational factors such as treatment beliefs.[2] However, behavioural theories such as the COM-B model (Capability, Opportunity, Motivation and Behaviour) propose a wider range of adherence predictors, including automatic processes such as habit.[3] Indeed, habit may better predict treatment adherence compared to conscious motivational factors.[4] Although commonly used to refer to frequent repetitive actions, within psychology the term 'habit' describes a non-conscious process by which situational cues (e.g. time of day) automatically prompt an impulse to perform an action (i.e. using nebuliser).[5]

Because they are automatically cued, habitual behaviours require little conscious cognitive effort to enact.[5] Habits form through consistent repetition of a specific action in a specific context, which gradually shifts the cognitive control over initiation of action from reflective to automatic processes, such that encountering the context becomes sufficient to elicit the associated action.[5] This reduces dependence on conscious attention or deliberative processes to initiate action. Habitual behaviours are thus thought to persist even if attention and conscious motivation wane.[5]

Our earlier exploratory mixed-methods study in Sheffield showed that high adherers had stronger habit than did low adherers.[6] High adherers also described automatically 'remembering' to use their nebulisers; for example, one participant experienced the urge to use his nebuliser after walking his dog every morning.[6] To determine whether the habit-adherence association exists in other cohorts of adults with CF, we performed a secondary analysis using data prospectively collected during a pilot randomised controlled trial (ACtiF pilot, ISRCTN13076797). This two-centre pilot was primarily designed to explore the use of CFHealthHub, a software platform which delivers a complex intervention to support habit formation and self-management with inhaled therapies among adults with CF.

METHODS

Participants were recruited from the Wolfson CF Centre (n=29) and the Wessex Adult CF Centre (n=32) from June-September 2016. Nebuliser habit strength was measured at the point of recruitment using the Self-Report Behavioural Automaticity Index (SRBAI).[7] The SRBAI consists of four statements (e.g. 'deciding to use my nebuliser is something I do automatically') with which participants rate agreement on a 1-5 scale, where 5 represents strongest habit. Item scores were then summed to create a scale ranging from 4 (weakest habit) to 20 (strongest habit). Adherence

data was downloaded from chipped nebulisers (eTrack®) in the 3-month period following the point of recruitment, and calculated as 'normative adherence',[8] a measure that takes into account a person's characteristics when defining the minimum required treatment regimen (see online appendix). Participants were divided into three adherence categories (<50% for low adherence, 50-79.9% for moderate adherence, ≥80% for high adherence) to mirror the analysis of our earlier Sheffield study.[6] These adherence categories were used in various other CF-related studies and were chosen based on the relationship with health outcomes.[1, 9]

Outcomes data (e.g. FEV_1) and other psychological measures were also collected as part of the pilot trial (e.g. beliefs about medicine necessity and concerns, which were combined in the Beliefs about Medicines Questionnaire – specific nebuliser adherence, BMQ,[10] a validated self-report tool that was customised for the pilot trial to identify perceived necessities and concerns for nebuliser treatment). Further details of the study variables are provided in the online appendix. Non-parametric statistical analysis methods were used, as well as multiple ordinal regression with adherence category as the dependent variable.

RESULTS

High adherers (n=7) had lower prior-year IV use and tended to have higher $\%FEV_1$ at baseline. High adherers reported stronger habit (median 18.0, IQR 14.0-20.0) than did low adherers (n=46; median 9.0, IQR 4.8-12.0), see Table 1. Conversely, high adherers reported lower concerns (median 1.6, IQR 1.3-1.7) than did low adherers (median 2.3, IQR 1.9-2.6). In a multiple ordinal regression model with both habit and concerns scores, only habit was associated with adherence. The adjusted odds ratio indicated that 1 unit increase in habit score was associated with a 31% increase in the odds of being in the next-higher adherence category (95% CI 12-54%), see footnote of Table 1.

This two-centre pilot was not powered to determine the association between adherence and health outcomes. The absence of association between adherence and outcomes should not, therefore, be interpreted as evidence of absence.[11]

Table 1: Clinical characteristics and psychological factors among three groups of adults with CF

	Low adherence, i.e. <50% *n = 46*	**Moderate adherence**, i.e. 50-79.9% *n = 8*	**High adherence**, i.e. ≥80% *n = 7*	**P-value** [μ]
% Normative adherence, median (IQR)	15.8 (4.5 – 35.4)	65.5 (56.0 – 75.8)	91.5 (80.2 – 96.7)	
Clinical characteristics:				
Age in years, median (IQR)	27.4 (21.7 – 37.1)	23.7 (18.4 – 32.0)	26.1 (21.2 – 37.5)	0.616
Female, n (%)	22 (47.8)	5 (62.5)	1 (14.3)	0.164
Baseline %FEV_1, median (IQR)	49.5 (43.1 – 66.4)	83.5 (43.1 – 66.4)	79.7 (52.7 – 89.1)	0.068
Prior-year IV days, median (IQR)	**28 (13 – 47)**	**15 (4 – 53)**	**0 (0 – 10)**	**0.012**
IV days during trial, median (IQR)	14 (0 – 23)	15 (0 – 30)	0 (0 – 0)	0.160
Quality of life (CFQ-R), median (IQR)	50 (28 – 78)	64 (34 – 88)	67 (44 – 78)	0.306
Psychological factors:				
Anxiety (GAD) score, median (IQR)	4 (1 – 7)	1 (1 – 4)	0 (0 – 5)	0.186
Depression (PHQ-8) score, median (IQR)	6 (3 – 11)	6 (3 – 13)	4 (2 – 4)	0.389
Intention (COM-B) score, median (IQR)	7 (5 – 7)	7 (7 – 7)	7 (5 – 7)	0.256
Necessity (BMQ) score, median (IQR)	3.1 (2.7 – 3.8)	3.3 (2.8 – 3.9)	3.4 (2.7 – 4.6)	0.496
Concerns (BMQ) score,* median (IQR)	**2.3 (1.9 – 2.6)**	**1.9 (1.5 – 2.3)**	**1.6 (1.3 – 1.7)**	**0.030**
Habit (SRBAI) scores,* median (IQR)	**9.0 (4.8 – 12.0)**	**14.5 (11.3 – 18.3)**	**18.0 (14.0 – 20.0)**	**< 0.001**

[μ] All p-values were calculated using Kruskal-Wallis H test, except the p-value for gender was calculated using Fisher's exact test.

* Since concerns and habit scores were associated with adherence, both scores were included as covariates in a multiple ordinal regression model with adherence category as the dependent variable. In this model, only habit strength was independently associated with adherence:
Pseudo-R^2 of model = 0.408 (Nagelkerke); model χ^2 (2) = 22.9, p <0.001.
Adjusted odds ratio for Concerns score = 0.344 (95% CI 0.103 to 1.152, p-value 0.083)
Adjusted odds ratio for Habit score = 1.313 (95% CI 1.123 to 1.536, p-value 0.001)

DISCUSSION

We had previously found the association between stronger habit and higher nebuliser adherence in Sheffield (for our earlier study, adherence was assessed *retrospectively* in the 1-year pre-recruitment period). In this study, our earlier finding has been replicated in a larger sample of adults with CF from two other centres (note that adherence was measured *prospectively* over a 3-month post-recruitment period in this study). This suggests that habit – that is, automatically experiencing an urge to use the nebuliser in certain settings, due to learned associations between nebuliser use and cues within those settings – may be consistently associated with treatment adherence among adults with CF.

Whilst habit is not the only factor associated with nebuliser adherence, appreciating the importance of both non-conscious motivation (e.g. habit) and conscious motivation (e.g. treatment beliefs) could lead to more effective adherence interventions.[3, 5] The relationship between habit and adherence over time is complex and dynamic; initial repetitions of a behaviour (e.g. using a

nebuliser) will strengthen habit, which subsequently acquires the potential to direct subsequent performance.[5] While studies of the formation of adherence habits are needed to reveal the causal direction or directions of the habit-adherence relationship we observed, our results are nonetheless consistent with the suggestion that, once formed, habit may determine subsequent adherence.[5, 6] Habit-formation advice, i.e. encouraging the use of treatments in specific and unchanging contexts, so that associations may develop between those contexts and treatment adherence, is simple to deliver [5] and could be part of a comprehensive package of interventions to support adherence. Habit strength might also be usefully assessed as an intervention outcome.

It is difficult to establish the causal direction of observed relationships in this study and the small sample size is a limitation (see online appendix for more detailed discussion regarding the limitation of the study). Nonetheless, we have replicated the Sheffield findings in an independent cohort, which suggests that the habit-adherence association is not just a peculiarity specific to a single adult CF centre. Two further studies are now underway to explore habit formation in more detail using CFHealthHub in a 19-centre RCT (ISRCTN55504164) and a three-centre improvement collaborative (ISRCTN14464661). We anticipate these studies will extend our understanding of the role of habit in sustained behaviour change among adults with CF.

COMPETING INTERESTS

None declared.

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CONTRIBUTORS

HZH, BG, MJW: concept and design. HZH, SW, CM: data acquisition. HZH: drafting the manuscript. All authors involved in analysis and interpretation of data; and critically revised the manuscript and approved the final draft.

ETHICS APPROVAL

The Sheffield study was approved by the London – Westminster Research Ethics Committee (15/LO/0328). The ACtiF pilot study was approved by the London – Brent Research Ethics Committee (16/LO/0356).

DATA SHARING STATEMENT

Data for the Sheffield study are archived by Sheffield Teaching Hospitals NHS Foundation Trust, and are available upon request (Zhe Hui Hoo, clinical research fellow, z.hoo@sheffield.ac.uk) for researchers who meet the criteria for robust pre-specified data analysis plan and for access to confidential data. Data for the two-centre pilot trial are archived by the University of Sheffield, and are available upon request (Chin Maguire, trial manager, c.maguire@sheffield.ac.uk) for researchers who meet the criteria for robust pre-specified data analysis plan and for access to confidential data.

To access either dataset, a formal request will need to be submitted and considered on a case-by-case basis.

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Appendix A: Further explanation and details regarding the study variables

Demographic and health outcomes data e.g. age, gender, $\%FEV_1$, IV antibiotics use and quality of life were collected as part of the pilot trial procedure. Baseline $\%FEV_1$ collected at the time of recruitment was measured during a period of clinical stability and calculated using the Global Lung Function Initiative (GLI) equation.[1] IV antibiotic days were recorded for the 1-year period prior to recruitment, and for 6 months during the pilot trial. Quality of life at baseline was self-reported using all six relevant statements from the Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain,[2] e.g. 'Have you been coughing during the day?'; $\alpha = 0.90$. The CFQ-R scale ranged from 0 (lowest quality of life) to 100 (highest quality of life).

Adherence data were downloaded from chipped nebulisers (eTrack®) in the 3-month period following the point of recruitment; and calculated as was calculated as 'normative adherence'. 'Normative adherence takes into account a person's characteristics when defining the minimum required treatment regimen.[3] Calculation of 'normative adherence' involves adjusting the denominator based on the clinical characteristics of a person with CF, adjusting the numerator by capping daily maximum nebuliser use at 100% (also accounting for doses taken after midnight) and adjusting the numerator by accounting for dose spacing of inhaled antibiotics. For example, a person with chronic *Pseudomonas aeruginosa* infection should take at least a nebulised mucolytic and an antibiotic. Thus the denominator for a person with chronic *Pseudomonas aeruginosa* infection will be at least 3 (1x dornase alfa, 2x antibiotic). If a person with chronic *Pseudomonas aeruginosa* infection only agreed to use nebulised dornase alfa once daily (which is 1 nebuliser/day), even if they take every does of their dornase alfa, the 'normative adherence' is only 33%. This is because in the calculation of 'normative adherence', the denominator is at least 3 nebulisers/day for a person with chronic *Pseudomonas aeruginosa* infection. The detailed methods and worked examples of calculating 'normative adherence' are provided in the paper by Hoo et al.[3] 'Normative adherence' is a continuous scale that ranged from 0 (lowest possible adherence level) to 100 (highest possible adherence level, due to capping of daily adherence levels at 100%), with higher adherence being more desirable.

Severity of anxiety at baseline was self-reported using all seven statements from the General Anxiety Disorder 7-item anxiety scale (GAD),[4] e.g. 'Feeling nervous, anxious or on edge'; $\alpha = 0.83$. The GAD scale ranged from 0 (lowest anxiety severity) to 21 (most severe anxiety).

Severity of depressive disorder at baseline was self-reported using all eight statements from the Patient Health Questionnaire depression scale (PHQ-8),[5] e.g. 'Little interest or pleasure in doing things'; $\alpha = 0.84$. The PHQ-8 scale ranged from 0 (lowest depressive disorder severity) to 24 (most severe depressive disorder)

Intention at baseline was self-reported using a statement adapted from the Capability Opportunity Motivation Behaviour (COM-B) Self Evaluation Questionnaire.[6] The statement used was "I want to do all my prescribed nebuliser treatments in the next two weeks" with which participants rate agreement on a scale of 1-7, where 7 represents strongest intention.

Necessity at baseline was self-reported using all seven 'necessity statements' from the Beliefs about Medicines Questionnaire – specific (nebuliser adherence) (BMQ), e.g. 'My life would be impossible

without this nebuliser treatment'; α = 0.84. The necessity BMQ ranged from 1 (lowest perceived necessity) to 5 (highest perceived necessity). BMQ is a validated self-report tool [7] that was customised for the pilot trial to identify perceived necessities and concerns for nebuliser treatment.

Concerns at baseline was self-reported using all 14 'concern statements' from the Beliefs about Medicines Questionnaire – specific (nebuliser adherence) (BMQ), e.g. 'I sometimes worry about becoming too dependent on this nebuliser'; α = 0.84. The concern BMQ ranged from 1 (lowest perceived concern) to 5 (highest perceived concern). BMQ is a validated self-report tool [7] that was customised for the pilot trial to identify perceived necessities and concerns for nebuliser treatment. Necessity and concerns are components of conscious motivation.

Habit strength at baseline was self-reported using all four statements from the Self-Report Behavioural Automaticity Index (SRBAI),[8] e.g. 'deciding to use my nebuliser is something I do automatically'; α = 0.93. Each statement begins with 'Deciding to use my nebuliser …' to capture habitual instigation. Habit strength ranged from 4 (weakest habit) to 20 (strongest habit). Habit is a component of unconscious motivation.

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Appendix B: Further discussion regarding the strengths and limitations of this study

One of the strengths of this study is that medication adherence was objectively measured using an intelligent nebuliser device (eTrack®) that provides time-stamped data on how every dose of nebulised medication is being used. We chose to analyse the adherence data over a 3-month post recruitment period because baseline objective adherence data (i.e. prior to adherence intervention) was unavailable, sampling adherence over shorter periods is an unreliable measure of stable behaviour [1] and adherence were similar in both arms of the pilot for the first three months (median 38.5%, IQR 8.7 – 71.8% for intervention; median 37.9%, IQR 5.5 – 54.6% for usual care). Sampling adherence over a 6-month post recruitment period would be complicated by the divergence in adherence at month 4–6 (median 33.7%, IQR 7.2 – 75.0% for intervention; median 21.2%, IQR 7.0 – 55.9% for usual care).

Due to the cross-sectional nature of the analysis, the directionality of the association between habit and adherence cannot be established. The relationship between adherence and habit over time is complex; initial adherence episodes (undertaken in consistent settings) cause habit to form, and as habit forms, it acquires the potential to direct subsequent adherence.[2] While the habit scores analysed were collected at baseline, prior to the delivery of any intervention during the pilot trial, we did not have detailed data on participants' adherence (or intervention) histories. It is possible that some of the participants to have been "successfully intervened upon" in the past, and so may have achieved higher adherence prior to entering the study, and maintained these throughout the study. Assuming stability of adherence and habit over time, high adherence prior to entering the study may have caused higher habit scores at baseline, which then subsequently predicted (in a statistical sense) higher adherence over the following three months.

The habit measure used in this study is the Self-Report Behavioural Automaticity Index (SRBAI),[3] which is an automaticity subscale of the Self-Report Habit Index (SRHI).[4] Unlike SRHI, SRBAI does not enquire about behaviour frequency.[3] That means it is perhaps less likely for SRBAI scores to be just acting as a proxy measure for behaviour frequency. Although changing adherence could potentially change habit (since habit is strengthened through consistent repetition of a specific action in a specific context, i.e. content-dependent repetition),[2] it is important to note that habit is not synonymous with behaviour (e.g. adherence). It is possible that someone using his or her nebuliser frequently to have weak habit if he or she does not use the nebuliser in a consistent setting, and instead rely on consciously remembering to use the nebuliser. It is also, in theory, possible to strengthen habit without directly increasing the frequency of nebuliser use, by instead encouraging more consistent performance.[5] For example, adults with CF might be encouraged to identify cues that they encounter reliably and regularly in everyday routines, in the presence of which they should use their nebuliser.[6] Such habit-based advice would therefore focus on harnessing potential contextual cues, not increasing the frequency of nebuliser use per se.

Although habit was found to be the only independent factor that is associated with nebuliser adherence in this study, this is not to say that other factors are irrelevant. Due to modest sample size, the pilot trial could only detect differences if the effect size is sufficiently large.[7] For example, a 1 unit decrease in concerns score (concerns score could vary from 1, lowest perceived concern to 5, highest perceived concern) was associated with a 65% increase in the odds of being in the next-higher adherence category (e.g. from <50% to 50–79.9%, or 50– 79.9% to ≥80%) but the pilot trial was not sufficiently powered to detect that effect with a conventional α level of 0.05.

It is likely that both reflective (e.g. treatment beliefs) and automatic (e.g. habit) processes are associated with adherence levels, which would be detected with larger sample sizes. Nonetheless, we have replicated the Sheffield findings in an independent cohort. Replication of results reduces the uncertainty of evidence, hence these exploratory studies provide tentative evidence for the role of habit in the health behaviour of using nebuliser among adults with CF. The modest sample size for both studies is a limitation, but studies with larger sample sizes could still find that habit is more strongly associated with nebuliser adherence compared to other factors.

There is only one previous study examining the association between respiratory medication adherence and habit strength. The study among 139 asthma patients also found that medication adherence was most strongly associated with habit strength compared to other psychological factors such as self-efficacy and attitude.[8] In other long-term conditions, habit has been shown to better predict medication adherence compared to conscious motivational factors.[9] A recent meta-analysis of 771 medication adherence intervention studies identified habit as a promising target for intervention.[10] Therefore, further studies of habit as an adherence determinant and the investigation of habit-formation as a potential intervention to support adherence should be seen as a priority within cystic fibrosis and other areas of respiratory medicine.

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