Factors associated with medication adherence in school-aged children with asthma

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ABSTRACT   Adherence to preventive asthma treatment is poor, particularly in children, yet the factors associated with adherence in this age group are not well understood.

Adherence was monitored electronically over 6 months in school-aged children who attended a regional emergency department in New Zealand for an asthma exacerbation and were prescribed twice-daily inhaled corticosteroids. Participants completed questionnaires including assessment of family demographics, asthma responsibility and learning style. Multivariable analysis of factors associated with adherence was conducted.

101 children (mean (range) age 8.9 (6–15) years, 51% male) participated. Median (interquartile range) preventer adherence was 30% (17–48%) of prescribed. Four explanatory factors were identified: female sex (+12% adherence), Asian ethnicity (+19% adherence), living in a smaller household (−3.0% adherence per person in the household), and younger age at diagnosis (+2.7% for every younger year of diagnosis) (all p<0.02).

In school-aged children attending the emergency department for asthma, males and non-Asian ethnic groups were at high risk for poor inhaled corticosteroid adherence and may benefit most from intervention. Four factors explained a small proportion of adherence behaviour indicating the difficulty in identifying adherence barriers. Further research is recommended in other similar populations.

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Introduction

Asthma is one of the most common chronic conditions in childhood [1]. Adherence with preventive medication remains poor in this age group (≤16 years of age) [2, 3]. Poor adherence with inhaled corticosteroids is associated with morbidity [4] and mortality [5]. Interventions to improve adherence have shown benefits on adherence; however, effects are inconsistent, even when using similar strategies [6]. In order to develop effective childhood interventions it is important to investigate the unique adherence barriers children face [7], as these are different to adults [4, 7]. There are few studies in children that aim to understand these barriers, and even fewer interventional studies which aim to improve adherence in children [6, 8]. Previous research investigating adherence barriers in childhood have used inconsistent methodology, with data on adherence factors being collected from either the child, a proxy (e.g. parent) or both. Commonly used adherence measures, such as self-reported or pharmacy claims data, are subject to bias [3, 9]. Electronic monitoring provides the most objective measure of adherence monitoring [3, 8]; however, only a few studies have used electronic monitoring to provide adherence data to investigate adherence barriers [4, 10–13]. Of the studies that have used electronic monitoring, these have tended to focus on a narrow set of adherence barriers, such as psychological factors [4, 10, 12] or asthma knowledge [11], or used data collected over only a short duration [13]. MORTON et al. [3] recently reviewed the literature surrounding adherence in childhood asthma. The authors reported a paucity of studies investigating adherence barriers in children, and that future studies investigating adherence in children with asthma should use electronically monitored adherence data. Therefore, there is a need to examine a range of adherence barriers unique to children using objective adherence data.

Learning style is one adherence factor that has not been previously examined. Learning style has been linked with a patient's understanding of health information and subsequent medication taking behaviours [14] and responses to interventions [15]. Although there is no current literature examining this relationship, learning style may influence adherence. For example, individuals with an aural learning style may benefit more from an auditory intervention such as reminders, than those with alternative learning styles.

We previously conducted a randomised controlled trial investigating the effects of audio-visual reminders on medication adherence and asthma outcomes in children with asthma [16]. The present study uses the objectively measured adherence data from the randomised controlled trial to: 1) identify the adherence barriers unique to children, particularly in those at high risk of non-adherence; and 2) examine the relative importance of these factors for non-adherence, including the novel concept of learning style as a factor associated with adherence.

Material and methods

Study subjects and design

The randomised controlled trial investigated the effect of a reminder on adherence to preventer treatment and asthma outcomes, as described previously [16]. Briefly, 220 children between 6 and 15 years of age were recruited from the regional emergency department in Auckland, New Zealand. Inclusion criteria were: current diagnosis of asthma; current treatment or those started on treatment at the emergency department with a twice-daily inhaled corticosteroid; no comorbid congenital heart disease, chronic lung disease (other than asthma) or a severe chronic medical condition leading to increased morbidity; and residence inside the Auckland area.

Patients were enrolled after a minimum of 4 weeks had elapsed since hospital attendance, and were followed prospectively for 6 months, with 2-monthly follow-up visits by study investigators. Patients were randomly allocated to the intervention (n=110) or control (n=110) group. All received an electronic monitoring device for use with their preventer inhaler. The intervention group had the reminder function enabled; this was disabled in the control group. Information on asthma control was collected at each visit and at the end of the study participants and their caregiver completed a series of questionnaires to assess variables associated with adherence. Verbal and written informed consent was obtained from the child's parent or caregiver, and ethics approval was received from the New Zealand Northern Y Regional Ethics Committee (NTY/08/12/116) and District Health Boards. The trial was registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12613001353785.

Adherence measurement

Inhaled corticosteroid adherence was objectively measured by an electronic monitoring device (Smart Track; Nexus 6 Ltd, Auckland, New Zealand), which recorded date, time and number of doses taken. An on-board screen displayed the date and time of the last dose. Participants were unaware of the device adherence monitoring function. This covert monitoring method followed published ethical guidelines as discussed previously by RAND and SEVICK [17], and was accordingly approved by the regional ethics committee. At the end of the study, participants and their general practitioner, or other asthma healthcare

provider, were offered access to the study results. Adherence was defined as median percentage of the daily prescribed dose taken.

Analysis of factors associated with adherence

Caregivers (parent or guardian) of participants completed self-reported questions on demographics and the primary caregiver's highest educational qualification (none (did not finish secondary school), secondary, tertiary or postgraduate). Participant ethnicity was obtained from their New Zealand National Health Index number. Deprivation was assessed using the NZDep2006 Deprivation Index (1=least deprived, 10=most deprived area) of the area the participant lived in [18]. Caregivers self-reported household size (number of people usually living in the household) and family status (single/divorced/separated/widowed/married/*de facto* (cohabitating)/extended family or whanau (Māori concept of an extended family or community of families living together)). Information on the caregivers' experience of the health system and healthcare access was collected using the following questions (scored yes/no): "Do you feel you can discuss concerns with the health professional who looks after the child's asthma?"; "Have you ever delayed or avoided picking up medications due to cost?"; "Have you ever delayed or avoided seeing the doctor due to cost?; "Is your doctor easy to access?" and "Is your local pharmacy easy to access?".

Age at diagnosis was obtained by caregiver self-report. Asthma control was measured using two validated questionnaires: the childhood Asthma Control Test (0=worst control, 27=best control) [19] completed by the child and caregiver, and the Asthma Morbidity Score [20] (17=maximal morbidity, 4=lowest morbidity) completed by the caregiver. Caregivers answered a question about side-effects (scored yes/no): "Does the child complain of, or have, any side-effects from their medications?". Caregivers gave information about the type of healthcare professional who followed up their child's asthma (in addition to the 2-monthly investigator-initiated visits), by choosing one or more of the following options: asthma nurse, specialist, general physician (family doctor), no usual care follow-up or other. Asthma responsibility was evaluated using the 10-item Asthma Responsibility Questionnaire [21] completed by the caregiver. This assesses how responsibility is shared for 10 asthma management tasks. Each item is scored from 1 (parent is completely responsible) to 5 (child is completely responsible); total score 10=maximum parent responsibility, 50=maximum child responsibility. The child's asthma knowledge was assessed using the child-reported 24-item questionnaire (0=worst knowledge, 26=best knowledge) validated for primary school-aged children [22].

Children completed the Visual Aural Read/Write Kinaesthetic (VARK) Learning Styles Inventory for Younger People [23], which identified each participant's learning style preference (visual, aural, reading/writing and kinaesthetic, or various combinations of these) based on the standard scoring system [24]. As this questionnaire was for children aged ⩾12 years, the language was modified for the reading skills of our population of 6–15 year olds. Results were categorised into two groups for analysis: those with an aural learning style preference (aural group) *versus* no aural learning style preference (non-aural group).

Statistical analysis

Descriptive statistics were used to describe the study population. All statistical tests were performed at the 0.05 level of significance (two-tailed) using SPSS Statistics (version 22; IBM, Armonk, NY, USA) or SAS (version 9.3; SAS Institute, Cary, NC, USA).

Factors associated with adherence
Unadjusted analysis

To avoid interference from the intervention, only data from the control group of the trial was used as the analytical cohort to analyse factors associated with adherence. Unadjusted analyses on 20 variables were conducted in this analytical cohort using a general linear model.

All possible subsets regression

To determine the factors associated with adherence, an all possible subsets regression was conducted. This multivariable regression technique was chosen over the traditional stepwise regression as it tests all possible subsets of potential variables. This allows models that have similar predictive value to be identified and compared, rather than selecting just one model. Binary variables with low numbers in one outcome group, *i.e.* <25% of participants in one outcome group, were not included in the multivariable regression. Participants with complete data across all remaining variables were used for the multivariable analysis. The remaining variables were included in the model and multiple subsets of variables were generated, ranging from single variable models to models using all remaining variables. By examining the five best models at each level, alternative variable combinations were assessed, including whether the addition of other variables to the model led to a masking effect. The model accounting for the greatest variance (maximum R^2), whilst still consisting of only significant (p<0.05) variables, was selected.

TABLE 1 Characteristics of 101[#] participants in the analytical cohort and unadjusted analyses of 20 factors associated with adherence

Variable	Participants	Effect size	p-value
Age years	8.9±2.7	−1.5% (95% CI−3.2–0.2%) per year	0.09
Sex			
Male	52	26 (15–43)	0.05
Female	49	40 (19–60)	
Qualification of primary caregiver			
None	8	36 (11–42)	
Secondary school	22	28 (15–53)	0.81
Tertiary	45	26 (12–47)	
Postgraduate	22	42 (21–51)	
Missing	4		
Ethnicity			
Māori	10	19 (13–44)	
European	39	26 (17–43)	
Pacific Peoples	20	28 (13–40)	**0.002**
Middle Eastern/Latin American/African	4	35 (5–68)	
Asian	19	47 (30–83)	
Other	9	31 (21–46)	
Deprivation index[¶]	6.0±2.7	+0.002% (95% CI−1.7–1.7%) per deprivation scale	0.99
People in household	4.8±1.9; 98[#]	−3.4% (95% CI−5.8–−0.1%) per person added to household	**0.005**
Family status			
Single[+]	35	26 (15–47)	0.39
Not single[§]	65	32 (18–49)	
Missing	1		
Able to discuss concerns with the healthcare professional looking after the child			
No	8	24 (6–49)	0.68
Yes	92	31 (17–48)	0.68
Missing	1		
Delayed picking up medications due to cost			
No	78	31 (16–48)	
Yes	21	26 (16–49)	0.87
Missing	2		
Delayed seeing the doctor due to cost			
No	69	31 (16–54)	
Yes	30	28 (16–46)	0.28
Missing	2		
Easy access to doctor			
No	10	37 (18–52)	0.91
Yes	90	30 (17–48)	0.91
Missing	1		
Easy access to pharmacy			
No	2	20 (7– -)	0.37
Yes	99	30 (17–48)	
Age at asthma diagnosis years	3.3±2.3	−1.7% (95% CI−3.7–0.3%) per year	0.09
Childhood Asthma Control Test	18.8±4.2; 100[#]	+0.9% (95% CI−0.2–2.0%) per 1 point on the Childhood Asthma Control Test	0.11
Asthma Morbidity Score	9.2±2.6; 100[#]	−0.3% (95% CI−2.1–1.5%) per 1 point on the Asthma Morbidity Score	0.73
Medication side-effects			
No	91	29 (17–48)	0.84
Yes	10	33 (11–46)	
Healthcare provider involved in routine follow-up asthma care			
None (no follow-up)	2	72 (60– -)	
General practitioner	74	26 (12–43)	**0.003**
Specialist	5	31 (23–61)	
Asthma nurse	15	51 (15–85)	
Multiple providers	5	46 (26–61)	

Continued

TABLE 1 Continued			
Variable	Participants	Effect size	p-value
Asthma Responsibility Questionnaire	23.7±8.1	−0.2% (95% CI−0.7–0.4%) per 1 point of Asthma Responsibility Questionnaire	0.53
Asthma Knowledge Test	19.1±2.7	+0.7% (95% CI−1.0–2.4%) per 1 point of Asthma Knowledge Test	0.42
Learning styles			
Aural	64	29 (17–48)	0.76
Non-aural	30	30 (14–49)	
Missing	7		

Data are presented as mean±SD, n or median (interquartile range), unless otherwise stated. Bold data indicates statistical significance. [#]: data do not total 101 for some parameters due to missing data from participants who did not completed the relevant questionnaire(s). Median (interquartile range) adherence for the total sample (n=101) was 30% (17–48%); [¶]: based on the NZDep2006 deprivation index (1=least deprived, 10=most deprived). This is an indicator of socioeconomic deprivation of the area where the individual resides. Scores are derived from census data on income, home ownership, employment, qualifications, family structure, housing, access to transport and communications; [+]: single parent/divorced/separated /widowed/single; [§]: *de facto*/extended whanau/married.

Data were then analysed using an alternative model as a sensitivity analysis by performing the all subsets regression with the variables that had missing data removed (rather than removal of participants with missing data).

Effect of aural learning styles
Analysis of the effect of aural learning styles on adherence was conducted using a general linear model. Data from both the intervention and control groups were used as participants with an aural learning style may not only be more responsive to an auditory adherence intervention, but may also be more responsive to adherence advice from health providers, which is often delivered verbally.

Results
Of the 110 participants forming the analytical cohort, nine did not complete the questionnaires, leaving 101 for analysis. Overall adherence was low (median (interquartile range) adherence 30% (17–48%)). Table 1 shows the characteristics of the analytical cohort (n=101) and describes the unadjusted analyses of factors associated with adherence.

Unadjusted analyses of factors associated with adherence
Only three out of 20 variables examined were significantly associated with adherence to preventive treatment (table 1). These were ethnicity (Asian ethnicity most adherent), living with a lower number of people in the household, and type of healthcare provider involved in asthma follow-up (those with no asthma follow-up by their own healthcare provider had better adherence, though the outcome group only had two participants). Younger age, female sex and a younger age at diagnosis were of borderline significance.

Multivariable analysis of factors associated with adherence
The following variables, which had very low numbers in one outcome group compared to the other, were not included in the analysis: whether or not the caregiver could discuss concerns with their asthma healthcare provider; whether or not the caregiver had ever delayed picking up medicines due to cost; whether or not the caregiver had easy access to the doctor or pharmacy; presence or absence of medication adverse effects in the child; and lack of follow-up for the child's asthma by their own healthcare provider. After removal of these variables, 87 of the 101 participants in the analytical cohort had complete data across all variables and were included in the multivariable analysis.

The all subsets regression selected a subset of four factors that together explained 30% of the variance in objective adherence (R^2=0.33; adjusted R^2=0.30) (table 2). The addition of all the other predictor variables only accounted for an additional 14% in variance (R^2=0.47; adjusted R^2=0.29) and included variables that were not statistically significant. The multivariable analysis found those of Asian ethnicity, female sex, living with a lower number of people in the household and having a younger age at diagnosis were more likely to adhere to treatment. Lack of asthma follow-up by their own healthcare provider was also significant, but as there were only two participants who did not have follow-up this was not included in the model (median adherence 72%) (table 1). These two participants had high adherence. There was no

TABLE 2 Multivariable regression analysis with objective adherence as independent variable[#]		
Variable	**Effect size**	**p-value**
Sex	12±4%	0.005
Asian ethnicity	19±5%	<0.001
People in the household	−3.0±1.0% per person	0.01
Age at asthma diagnosis years	−2.7±0.9% per year	0.004
Data are presented as change±SE. [#]: n=87.		

indication that any variables were masked by the presence of other variables. The sensitivity analysis produced very similar results confirming the results of the all subsets regression described above.

Effect of aural learning styles

There was no relationship between aural learning style and adherence in either the control (analytical cohort for this study) or in the intervention (reminder) group (aural 29% *versus* non-aural 30% (p=0.76) and aural 85% *versus* non-aural 88% (p=0.34), respectively).

Discussion

This study investigated factors associated with adherence in children presenting to a regional emergency department with an asthma exacerbation. Electronically monitored adherence was poor with median adherence being 30%, a rate similar to other studies in children at high risk of non-adherence [25–27] but lower than the average reported adherence from studies using electronic monitoring and when compared to other developed Western countries [3, 8]. We examined a number of factors that have previously been associated with adherence, such as ethnicity [13, 28] and asthma knowledge [10], as well as factors not previously investigated, such as learning style. Of the variables examined in this study, only a few were significantly associated with adherence.

Ethnicity had a strong association with adherence, with Asian participants having the highest overall adherence (47%). The reason for this is unclear. There is little literature available on adherence for ethnic groups in New Zealand beyond Māori, Pacific and European populations. Education studies in Australia show that Asian students are more compliant with orders from teachers than other ethnic groups [29] due to respect and perceived dominance of the teacher [30]. The healthcare provider–patient relationship may be associated with a similar respectful or submissive response, which may enhance adherence. Māori children had the poorest adherence (median adherence 19%), followed closely by New Zealand European (26%) and Pacific peoples (28%). From studies in mild-to-moderate asthmatics, Māori and Pacific children show poorer asthma control than other ethnic groups [31] due to under treatment and poor adherence with preventive treatment [31, 32]. Therefore, the ethnic differences in our study were unexpected, as although adherence rates for New Zealand Europeans were higher than Māori children, they were lower than that of other minority ethnic groups. The participants in our study attended the emergency department for asthma and therefore represent those with the poorest asthma control and adherence [27]. This suggests that the effect of ethnicity may be different in those with poorly controlled asthma and at high risk of non-adherence, but more research is needed to confirm this. We note that the adherence rate in our population of high-risk children was particularly low when compared to populations recruited from outpatient clinics [12, 33–37], and more similar to those recruited from tertiary centres or hospitals [38]. Indeed, in adults, KRISHNAN *et al.* [39] reported a drop in inhaled corticosteroid use to ∼50% within a week of hospital discharge after an asthma exacerbation. This highlights the potential vulnerability of patients presenting to tertiary care settings and the importance of considering the contribution of this as a potential marker of poor adherence. The high-risk nature of a population presenting to the emergency department with asthma may override the usual effects of other adherence determinants, such as ethnicity, as seen in our study.

Female sex was significantly associated with better adherence in our study. The relationship between sex and adherence is inconsistent in the literature, with many studies showing no association [9, 40, 41]. Only one study has reported an association between female sex and higher adherence in adult asthma [42]. In other chronic conditions, female sex has been linked with poorer adherence in adolescents [43]. Mental health and coping strategies may mediate the relationship between sex and adherence [43], but we did not measure psychological factors.

No clear relationship was found between socioeconomic status, determined by NZDep scores, and adherence. Some studies have reported a lack of correlation between adherence and general socioeconomic status, family income or qualifications of the primary caregiver [35, 44], although others report low

adherence rates in those with poor socioeconomic status [3]. Compared to studies that report higher overall adherence, the population in our study did incline towards higher deprivation scores (mean deprivation 6 out of 10). We found a significant relationship between household size and adherence, a factor seldom studied in asthma. KYNGÄS [45] found that adherence improved with increasing number of siblings and similarly LIEU et al. [46] reported better adherence in larger families. Our study found the opposite effect, with larger household size associated with poorer adherence. It is possible that larger families present more competing demands, thus limiting the time available to manage a child's asthma [47] and increasing forgetfulness, a key reason for non-adherence in childhood asthma [48]. This negative effect of family size on adherence may be more pronounced in our study as over half of the participants were aged <8 years of age. Previous studies have demonstrated that younger children have the majority of their medications managed by their parents [4, 47, 49], which may contribute to poorer adherence with increased household size. This is also supported by the negative relationship seen between asthma responsibility scores and adherence, where adherence decreased with increasing child responsibility for their own asthma management, though the relationship did not reach statistical significance.

The relationship between age at diagnosis and adherence is unclear; the few studies investigating this relationship have not found any association [40, 41]. Our study found age at diagnosis was a significant factor, with a reduction in adherence of 3% per increasing year of age at diagnosis. There was a corresponding nonsignificant trend between age of the child and adherence, with adherence being worse in older children, similar to previous findings [2, 4, 44, 45, 50]. This may, in part, explain the association between age of diagnosis and adherence. The association between increased age and worsened adherence might also explain the overall low adherence seen in this population. Most previous studies that have reported higher adherence have included much younger age range, from as young as 15 months [3]. Disease duration may play a role as those with a younger age of onset have more opportunity for habit formation for medication adherence [51]. Conditioning may lead children or their parents to believe that asthma is a long-term condition requiring long-term preventive treatment and, as a result, lead to better adherence. Indeed, adherence is higher in those that believe asthma is a long-lasting condition [42].

This is the first study investigating the impact of learning style on adherence. A link between the two is plausible given that learning style is associated with behaviour [14, 15], but no association was found in either the group receiving the auditory intervention or control. This may be due to the difficulties in characterising learning styles in children as younger children tend to have multimodal learning styles rather than a single learning modality [23]. The lack of a validated tool for assessing learning style in the younger age groups in our study may have also limited the accuracy of determining the child's learning style. Although a relationship between learning styles and adherence was not found, there is a possibility that interventions tailored to an individual's learning style may be more successful. The literature supports interventions that are personalised to an individual [3, 8]; future research should investigate the usefulness of incorporating learning style into the intervention tailoring process.

Of the factors that were investigated, only four were found to be significantly associated with adherence. However, these factors still only explained 30% of the variance seen in adherence. Although a wide range of adherence determinants were examined, we did not investigate the effect of illness perceptions [52–57] or medication beliefs [12, 50, 58–62], which are thought to be more powerful determinants of adherence [57] than sociodemographic and clinical factors in adults. In children, the review by DROTAR and BONNER [63] of studies investigating the factors associated with adherence in children reports that parental and, to a lesser extent, child beliefs demonstrate significant relationships with adherence. Medication beliefs and illness perceptions were not measured in our study but future research should include them in order to develop a clearer understanding of the extent to which these may explain adherence behaviour in children with poorly controlled asthma and to investigate how these may interact with the adherence determinants identified in our study.

The generalisability of our study results may be limited by data collection in a single centre and country. Nevertheless, our study population were representative of the total population presenting to the emergency department with asthma, as described previously [16], and included a wide range of ethnic and socioeconomic groups. Due to missing data we excluded 14 participants from the multivariable analysis, which could have led to selection bias. However, bias as a result of this exclusion is unlikely as our sensitivity analysis, where variables with missing data were excluded rather than participants, showed similar results. Questionnaires were administered in the presence of research personnel, which may have affected the reliability of the data collected. A small number of participants chose not to complete some questions, but the numbers with missing data were low and unlikely to affect our results. The application of these findings to the design of adherence interventions may be limited, as the adherence determinants identified were largely non-modifiable. Nevertheless, our findings add important information to the literature on factors that contribute to poor adherence in children, particularly in those with poorly controlled asthma. As the factors identified from our study are easily quantifiable, they may be used to

help prioritise those at greatest need for intervention. Our work sets a platform for further research into how potentially modifiable adherence determinants, such as medication beliefs, may be related to non-modifiable factors such as ethnicity or duration/experience in managing asthma, and how these non-modifiable factors may serve as proxies for identifying those who are most at risk of poor adherence.

In summary, female sex, Asian ethnicity, smaller household size and younger age at diagnosis were strongly associated with better preventive medication adherence in children with poorly controlled asthma presenting to a regional emergency department. These factors explained only 30% of the variation in adherence, highlighting the difficulty of identifying adherence barriers in this age group. There was no association between adherence and learning styles. Further research in other emergency department populations is needed. Given the combination of poor adherence and high risk for life-threatening asthma in children presenting to the emergency department, there is an urgent need to identify the specific adherence barriers and develop effective interventions for this population of children.

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