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Original Article

Assessing usability of the “Adherence Starts with Knowledge 20” (ASK-20) questionnaire for Japanese adults with bronchial asthma receiving inhaled corticosteroids long term

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ACT, Asthma Control Test; ASK-20, Adherence Starts with Knowledge 20; CI, confidence interval; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; MARS, Medication Adherence Rating Scale; MMAS, Morisky Medication Adherence Scale; TBC, total barrier count

ABSTRACT

Background: Maintaining high treatment adherence levels is critical for effective management of chronic diseases. The Adherence Starts with Knowledge 20 (ASK-20) questionnaire is the only linguistically validated patient-reported treatment adherence tool available in Japan. We conducted additional analyses on ASK-20 data from Japanese adults with asthma.

Methods: This was a prospective, non-interventional, single-visit, multi-centre study in Japanese adults ($n = 300$) with asthma receiving long-term treatment with inhaled corticosteroids (ICS) or ICS/long-acting beta-agonists. We tested the reliability, validity and the relationship between different adherence conditions and ASK-20 score. At one centre, ICS adherence prescription rate was calculated retrospectively based on 2-year percentage ICS adherence data contained within medical records.

Results: The ASK-20 had good internal consistency reliability (Cronbach's $\alpha = 0.76$; $n = 290$). Discriminant validity was demonstrated with significant correlations between the percentage ICS adherence rates and both the mean ASK-20 total score and mean total barrier count (TBC) ($r = -0.51$ and -0.58 , $p < 0.001$; $n = 111$). The ASK-20 total score discriminated between subjects with good and poor adherence measured by patients' reported questionnaire and between those of high and low percentage ICS adherence rates. All other factors that possibly affect adherence were correlated with the mean ASK-20 total score and mean TBC in addition to the number of medicines taken every day.

Conclusions: The Japanese ASK-20 is a reliable tool for assessing possible medication adherence barriers and adherence behaviour in Japanese adults with asthma. Furthermore, our results are comparable with those obtained using the ASK-20 in the United States.

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Introduction

Maintaining high levels of treatment adherence is critical for the effective management of chronic diseases.¹ Medication compliance in asthma is lower than for other chronic illnesses² with less than 40% of patients taking their medication as prescribed.³ In a study by Breekeveldt-Postma *et al.*, persistence rates (defined as the number of days from start to time of first failure to continue renewal of the

initial treatment) after one year were low for patients using inhaled corticosteroid (ICS) treatment (10%) and fixed combination ICS (15%),⁴ which concurred with findings from an earlier pharmacy database review.⁵ As such, symptoms in patients with asthma are not well controlled⁶ and patients are more likely to have depressive symptoms and a lower quality of life.⁷ Furthermore, non-adherence contributes to an increased number of exacerbations.⁸

Patients may not take their medication as instructed for many reasons: not fully understanding the role of their asthma treatment⁹; not receiving clear guidelines on how to use their medication⁹; or having concerns about their treatment and associated side effects.¹⁰

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Understanding and measuring treatment adherence is challenging, partly because of the variety of chronic conditions.¹¹ Variation in patients' conditions and their predisposition to hide non-adherence add to the complexity of assessment.¹¹ Patients who underuse their maintenance therapies tend to over-estimate the amount they take and those who overuse tend to underestimate.¹² Therefore, effective and economical tools are needed to better evaluate and improve our understanding of the barriers to treatment adherence. This, in turn, will improve communication between doctors and their patients.

Generally, treatment adherence measures are either objective, such as pill counts or the use of electronic monitoring devices, or subjective, involving self-reporting by the patient or use of physician estimates.^{13,14} Adherence rates can change when different methods of assessments are used. For example, objectively measured adherence values (60.8%) were found to be significantly lower than those that had been self-reported (93.6%).¹⁵

Patient-reported adherence screening tools include the Morisky Medication Adherence Scale (MMAS),¹⁶ the Medication Adherence Rating Scale (MARS)¹⁷ and the Adherence Starts with Knowledge 20 (ASK-20) questionnaire.^{11,13} Currently, only the ASK-20 is available in Japan.¹⁸

The ASK-20 was developed to identify and reduce the number of barriers to treatment compliance to improve adherence. It has been validated in the United States (US) and has improved our ability to identify specific treatment adherence barriers compared with other relevant patient-reporting tools.^{11,13} Furthermore, the ASK-20 significantly reduces the number of adherence barriers (3.8–2.8, $p = 0.0021$) and improves control of asthma symptoms, defined as an Asthma Control Test (ACT) score >19 (50.0–64.6%; $p = 0.0285$).¹⁹ In the US, satisfactory validity, internal consistency and reliability have also been seen with the ASK-20.^{11,13} We performed a study to

test the ASK-20 in Japanese adults with asthma. The linguistic validation data from this study have been published.¹⁸ In this publication, we present outcomes from additional analyses of the original data to test the validity and reliability of the ASK-20 and investigate the impact of different adherence conditions.

Methods

Study design and population

This was a prospective, non-interventional, single-visit study conducted at 3 centres in Japan between 31 January and 20 November 2013. Approvals were given by the ethical review board at each institution: Juntendo University School of Medicine Research Ethics Committee (approval number: 962); The Fraternity Memorial Hospital Ethics Committee (113); and Toho University Omori Medical Center Ethics Committee (24-240). Written informed consent was obtained from each subject before they underwent any study measures and anonymity was preserved using methods approved by the ethical review boards. Japanese men and women aged 20 years or older were eligible if they had received ICS or ICS/long-acting beta-agonist (LABA) at a fixed dose for 2 years but had not received two or more ICS or ICS/LABA and had not visited other hospitals for bronchial asthma treatment.

Measures

At the consultation visit (baseline), subjects completed the following self-reporting questionnaires: ASK-20; ACT, to assess asthma symptoms; a questionnaire to assess the level of satisfaction with asthma treatment; and a questionnaire to assess treatment status in the previous 2 weeks. In addition, asthma severity

Table 1
Demographic characteristics of the Per Protocol population (n = 290) and the inhaled corticosteroid adherence sub-group (n = 111).

Item	Number of subjects n (%)	
	PP population [‡]	ICS sub-group
Age (years)	Overall	111
	Mean (standard deviation)	56.3 (13.92)
	Minimum–maximum	27–88
Age range, n (%)	20–34	6 (5.4)
	35–49	31 (27.9)
	50–64	40 (36.0)
	≥65	34 (30.6)
Gender, n (%)	Female	72 (64.9)
	Male	39 (35.1)
Severity of asthma, n (%) [†]	Mild	34 (30.6)
	Moderate	26 (23.4)
	Severe	51 (45.9)
Current medical history, n (%)	Respiratory	53 (47.7)
	COPD	4 (3.6)
	Perennial allergic rhinitis	21 (18.9)
	Seasonal allergic rhinitis	21 (18.9)
	Other respiratory	12 (10.8)
	Cardiovascular	29 (26.1)
	Gastrointestinal	23 (20.7)
	Renal	3 (2.7)
	Central nervous system	5 (4.5)
	Others	46 (41.4)
ACT total score, n (%)	≤19	28 (25.2)
	20–24	46 (41.4)
	25	37 (33.3)
Current use of ICS, n (%)	ICS/LABA	87 (78.4)
	Fluticasone propionate/salmeterol	61 (55.0)
	Budesonide/formoterol	26 (23.4)
	ICS alone	24 (21.6)

ACT, Asthma Control Test; COPD, chronic obstructive pulmonary disorder; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist.

[†] Severity was based on the evaluation criteria of the guideline, 'Asthma Prevention and Management Guideline 2012, Japan'.²⁰

[‡] Previously published data added here for comparison.¹⁸

was assessed based on current guidelines,²⁰ and current use of ICS was collected. The outcomes of these assessments have been previously summarised.¹⁸ At 1 centre, the prescription rate of ICS adherence was calculated retrospectively based on 2-year percentage ICS adherence data contained within medical records. The study design, eligible population and measures have already been reported.¹⁸

Statistical analysis

SAS statistical software version 9.2 was used for all analyses. Of the 300 subjects planned for enrolment,¹⁸ 120 were to be analysed for ICS adherence to give an estimated accuracy of 3.3%–5.7%, based on an assumption that the proportion of patients estimated to have barriers to adherence is 10–50%.

The 'per protocol' (PP) analysis set (i.e. subjects who completed the ASK-20 without significant deviation from the protocol) was used for the analyses described. The ceiling/floor effect tested whether there was any bias in scores (i.e., $\geq 50\%$ of '1' or '5' scores) regardless of adherence condition. For each survey item, the ASK-20 total score and 'with barrier' frequency, previously defined by Matza *et al.*,¹³ were analysed to compare differences between the poor adherence group (i.e., subjects who missed a dose [poor-1] and did not take medication as directed [poor-2]) and the good adherence group (i.e., subjects who didn't miss a dose [good-1] and took all medication as directed [good-2]).

Internal consistency reliability was assessed for the ASK-20 total score and total barrier count (TBC) using Cronbach's coefficient alpha, with a value ≥ 0.70 considered acceptable.^{13,21–23} Discriminant validity was analysed by calculating the differences in the ASK-20 total score and TBC 95% confidence interval (CI) between the good and poor adherence groups. Regression analysis determined the relationship between the ASK-20 total score or TBC and factors that possibly affect adherence, including age, ACT score, number of medicines taken daily (not including immunoglobulin-E), number of missed doses in the previous 2 weeks, number of days the subject didn't take the medication as directed in the previous 2 weeks and subject satisfaction with current treatment.

Spearman's correlation confirmed any relationship between the ASK-20 total score or TBC and the prescription rate of ICS adherence ($n = 111$) where: rate = [actual amount of drug prescribed in the

previous 2 years]/[theoretical amount of drug which should have been prescribed in the same period] $\times 100$.

The 95% CI for the ASK-20 total score or TBC in the high prescription ICS adherence rate group (>75 to $\leq 125\%$) was compared with those of the low rate group (25 to $\leq 75\%$).

Results

Demographic characteristics

Demographic characteristics of the ICS adherence sub-group were similar to those of the PP population (Table 1)¹⁸ with a few exceptions: the ICS sub-group had a higher proportion of subjects with severe asthma, a lower proportion with moderate asthma, more subjects had an ACT total score between 20 and 24 than in either of the other score ranges, and the majority was taking ICS/LABA.

Descriptive ASK-20 outcomes and analysis of bias

For the ICS adherence sub-group, the mean ASK-20 total score was 38.9 (95% CI: 36.98–40.74) and mean TBC was 3.5 (2.91–3.99) which were similar to those of the PP population.¹⁸

In the PP population, our analysis of bias showed no ceiling effects, but floor effects were observed for 9 items (Q2, Q3, Q4, Q15, Q16, Q17, Q18, Q19, Q20) meaning these items were rated with the lowest possible score by over 50% of this sub-group (Table 2). The comparison between the good and poor adherence sub-groups in relation to the mean ASK-20 scores and 'with barrier frequency' for each question is presented in Table 3. Similar scores were seen in the Good-1 and Poor-1 adherence sub-groups with a difference of less than 1 unit between the groups for the majority (90%) of ASK-20 questions. However, there was a greater than 1 unit difference in mean ASK-20 score between the Poor-1 and Good-1 sub-groups for Q1 ("I just forget to take my medicines some of the time") and Q16 ("Taken a medicine more or less often than prescribed?"), with the higher score seen in the Poor-1 sub-group. In the Poor-1 sub-group, a greater than 50% 'with barrier frequency' was seen for Q1 and Q16; the highest frequency was reported for Q1 (76.5%). In the Good-1 sub-group, all questions had less than a 50% 'with barrier

Table 2

A summary of the bias analysis outcomes showing floor and ceiling effects in responses to ASK-20 questions in Japanese adults with asthma (Per Protocol population; $n = 290$).

Question	Score			
	Mean (SD)	Median	Floor n (%)	Ceiling n (%)
1 I just forget to take my medicines some of the time.	2.6 (1.42)	2.0	104 (35.9)	16 (5.5)
2 I run out of my medicine because I don't get refills on time.	1.4 (0.81)	1.0	205 (70.7)	1 (0.3)
3 My use of alcohol gets in the way of taking my medicines.	1.3 (0.74)	1.0	227 (78.3)	2 (0.7)
4 I worry about how medicine will affect my sexual health.	1.5 (0.94)	1.0	210 (72.4)	4 (1.4)
5 I sometimes forget things that are important to me.	1.9 (1.12)	2.0	141 (48.6)	7 (2.4)
6 I have felt sad, down, or blue during the past month.	2.3 (1.36)	2.0	116 (40.0)	16 (5.5)
7 I feel confident that each one of my medicines will help me.	1.9 (0.95)	2.0	104 (35.9)	11 (3.8)
8 I know if I am reaching my health goals.	2.5 (0.97)	2.0	42 (14.5)	9 (3.1)
9 I have someone who I can call with questions about my medicines.	2.7 (1.32)	2.0	51 (17.6)	45 (15.5)
10 I understand my doctor's/nurse's instructions about the medicines I take.	1.7 (0.69)	2.0	116 (40.0)	2 (0.7)
11 My doctor/nurse and I work together to make decisions.	1.8 (0.81)	2.0	117 (40.3)	4 (1.4)
12 I am able to read and understand pill bottle labels.	1.8 (0.74)	2.0	111 (38.3)	2 (0.7)
13 Taking medicines more than once a day is inconvenient.	2.5 (1.36)	2.0	100 (34.5)	23 (7.9)
14 I have to take too many medicines a day.	2.5 (1.35)	2.0	92 (31.7)	29 (10.0)
15 It is hard for me to swallow the pills I have to take.	1.7 (0.95)	1.0	155 (53.4)	4 (1.4)
16 Taken a medicine more or less often than prescribed?	2.2 (1.55)	1.0	157 (54.1)	37 (12.8)
17 Skipped or stopped taking a medicine because you didn't think it was working?	1.3 (0.79)	1.0	241 (83.1)	6 (2.1)
18 Skipped or stopped taking medicine because it made you feel bad?	1.3 (0.79)	1.0	242 (83.4)	5 (1.7)
19 Skipped, stopped, not refilled, or taken less medicine because of the cost?	1.1 (0.45)	1.0	270 (93.1)	2 (0.7)
20 Not had medicine with you when it was time to take it?	1.9 (1.30)	1.0	175 (60.3)	19 (6.6)

SD, standard deviation. We used the Japanese version of ASK-20 in this study.

Table 3

The association between adherence and 'with barrier frequency' with the mean ASK-20 scores for each question in the ASK-20 (Per Protocol population; n = 290).

Question	Subjects with adherence barrier n (%)	Subjects without a missed dose		Subjects who missed a dose		Subjects who took medication as directed		Those who did not take medication as directed	
		Good-1 [†] (n = 205)		Poor-1 [†] (n = 85)		Good-2 [‡] (n = 197)		Poor-2 [‡] (n = 93)	
		Mean score	With barrier n (%)	Mean score	With barrier n (%)	Mean score	With barrier n (%)	Mean score	With barrier n (%)
1	119 (41.0)	2.1	54 (26.3)	3.6	65 (76.5)	2.1	47 (23.9)	3.6	72 (77.4)
2	24 (8.3)	1.3	10 (4.9)	1.7	14 (16.5)	1.4	12 (6.1)	1.6	12 (12.9)
3	23 (7.9)	1.2	8 (3.9)	1.6	15 (17.6)	1.2	7 (3.6)	1.6	16 (17.2)
4	17 (5.9)	1.4	8 (3.9)	1.8	9 (10.6)	1.4	9 (4.6)	1.7	8 (8.6)
5	39 (13.4)	1.8	25 (12.2)	2.2	14 (16.5)	1.9	26 (13.2)	2.0	13 (14.0)
6	16 (5.5)	2.3	8 (3.9)	2.4	8 (9.4)	2.2	10 (5.1)	2.6	6 (6.5)
7	44 (15.2)	1.9	28 (13.7)	2.0	16 (18.8)	1.9	25 (12.7)	2.0	19 (20.4)
8	135 (46.6)	2.4	91 (44.4)	2.6	44 (51.8)	2.5	89 (45.2)	2.5	46 (49.5)
9	83 (28.6)	2.7	56 (27.3)	2.8	27 (31.8)	2.7	53 (26.9)	2.8	30 (32.3)
10	23 (7.9)	1.7	21 (10.2)	1.7	2 (2.4)	1.7	19 (9.6)	1.7	4 (4.3)
11	34 (11.7)	1.7	21 (10.2)	1.8	13 (15.3)	1.7	23 (11.7)	1.8	11 (11.8)
12	33 (11.4)	1.7	21 (10.2)	1.8	12 (14.1)	1.7	20 (10.2)	1.8	13 (14.0)
13	86 (29.7)	2.3	45 (22.0)	3.1	41 (48.2)	2.2	39 (19.8)	3.2	47 (50.5)
14	77 (26.6)	2.4	53 (25.9)	2.6	24 (28.3)	2.5	52 (26.4)	2.6	25 (26.9)
15	18 (6.2)	1.7	13 (6.3)	1.8	5 (5.9)	1.7	13 (6.6)	1.8	5 (5.4)
16	103 (35.5)	1.8	48 (23.4)	3.3	55 (64.7)	1.7	41 (20.8)	3.4	62 (66.7)
17	16 (5.5)	1.2	6 (2.9)	1.5	10 (11.8)	1.1	3 (1.5)	1.7	13 (14.0)
18	19 (6.6)	1.2	11 (5.4)	1.4	8 (9.4)	1.2	10 (5.1)	1.5	9 (9.7)
19	6 (2.1)	1.1	2 (1.0)	1.2	4 (4.7)	1.0	1 (0.5)	1.2	5 (5.4)
20	49 (16.9)	1.6	20 (9.8)	2.5	29 (34.1)	1.6	16 (8.1)	2.5	33 (35.5)

[†] 'Good-1' was defined as the good adherence group that responded 'No' to the question, 'Have you missed doses of any of your medicines in the last 2 weeks?'; Poor-1 was defined as the poor adherence group who responded 'Yes' to the same question. Questions were from the treatment adherence questionnaire.

[‡] 'Good-2' was defined as the good adherence group that responded 'No' to the question, were there any days that you did not take your medicine exactly as directed in the last 2 weeks?; Poor-2 was defined as the poor adherence group who responded 'Yes' to the same question. Questions were from the treatment adherence questionnaire.

frequency'. A similar outcome was seen when comparing the Good-2 and Poor-2 sub-groups.

Three questions (Q1, Q16 and Q13, "Taking medicines more than once a day is inconvenient") showed differences of more than 1 unit between the Good-2 and Poor-2 sub-groups; mean scores were either the same in each sub-group, or the higher values were reported in the Poor-2 group. In the Poor-2 sub-group, a greater than 50% 'with barrier frequency' was seen for Q1 and Q16 with the highest frequency reported for Q1 (77.4%), while in the Good-2 sub-group, all questions had lower than a 50% 'with barrier frequency'.

Internal consistency reliability

For the PP population, the ASK-20 demonstrated acceptable internal consistency reliability, with a Cronbach's alpha of 0.76. The TBC appeared less reliable, with a Cronbach's alpha of 0.65.

Discriminant validity

In the PP population, the mean ASK-20 total score and mean TBC discriminated between the good and poor adherence sub-groups

since both were higher in the Poor-1 and Poor-2 groups, and there was no overlap of CI (Table 4). In the regression analysis, all other factors that might affect adherence were correlated with the mean ASK-20 total score and TBC in addition to the 'number of medicines taken every day' (Table 5). Statistically significant correlations ($p < 0.0001$) were seen between the mean percentage prescription rate of ICS adherence and both the mean ASK-20 total score ($r = -0.51$) and mean TBC ($r = -0.58$) showing that the ASK-20 total score and the TBC decrease when the percentage prescription rate of ICS adherence increases.

For the ICS adherence sub-group, the mean ASK-20 total score and mean TBC discriminated between groups with high and low percentage prescription rates of ICS adherence: higher mean ASK-20 total scores and mean TBC were obtained from those subjects in the group with a low percentage rate of ICS adherence (Fig. 1).

Discussion

In this study we tested the validity and reliability of the Japanese version of the ASK-20 using similar statistical models to those used in studies conducted in the US.^{11,13}

Table 4

Summary of the validity outcomes in which dichotomous responses in criteria by ASK-20 total score and total barrier count were analysed (Per Protocol population; n = 290).

Validity criteria	Group [†]	ASK-20 total score		ASK-20 TBC [‡]	
		Mean (SD)	95% CI	Mean (SD)	95% CI
Missed dose(s) of any of your medicines in the last 2 weeks	Good-1 (n = 205)	35.7 (8.12)	34.59–36.82	2.7 (2.16)	2.38–2.98
	Poor-1 (n = 85)	43.5 (8.85)	41.55–45.37	4.9 (2.64)	4.31–5.45
Did not take your medicine exactly as directed	Good-2 (n = 197)	35.3 (7.87)	34.23–36.45	2.6 (2.12)	2.32–2.91
	Poor-2 (n = 93)	43.6 (8.85)	41.75–45.39	4.8 (2.63)	4.29–5.37

CI, confidence interval; SD, standard deviation; TBC, total barrier count.

[†] 'Good-1' was defined as the good adherence group that responded 'No' to the question, 'Have you missed doses of any of your medicines in the last 2 weeks?'; Poor-1 was defined as the poor adherence group who responded 'Yes' to the same question; 'Good-2' was defined as the good adherence group that responded 'No' to the question, were there any days that you did not take your medicine exactly as directed in the last 2 weeks?; Poor-2 was defined as the poor adherence group who responded 'Yes' to the same question. Questions were from the treatment adherence questionnaire.

[‡] The mean score and 95% CI have been previously reported.¹⁸

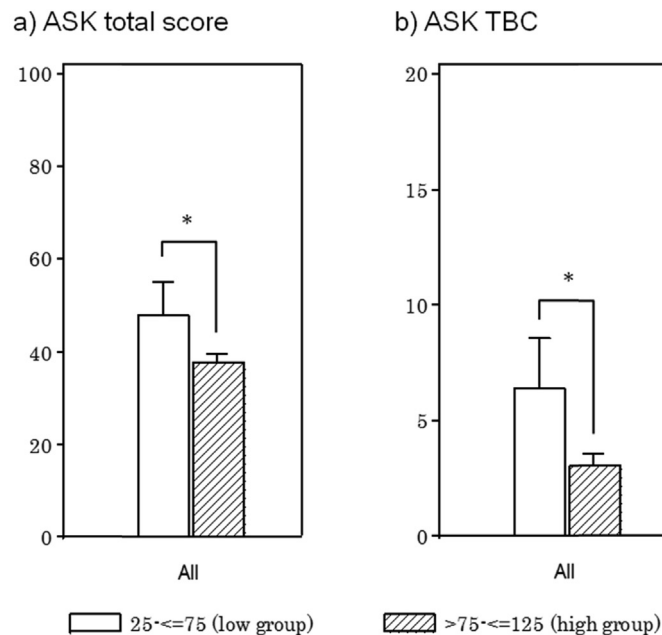
Table 5

Association between possible influencing factors such as age, Asthma Control Test score, number of different medicines taken per day; missed dose frequency, dose not taken as directed and treatment satisfaction on the mean ASK-20 total scores and mean total barrier counts (Per Protocol population; n = 290).

Factor	Mean ASK-20 total score		Mean TBC	
	Regression coefficient	p-Value	Regression coefficient	p-Value
Age	−0.1526	<0.0001**	−0.0298	0.0011*
ACT score	−0.2627	0.0141*	−0.0918	0.0020*
Number of different medicines taken every day	−0.1903	0.2570	0.0222	0.6351
Number of times missed doses of medication (past 2 weeks)	0.8622	<0.0001**	0.2396	<0.0001**
Number of days did NOT take medication exactly as directed (past 2 weeks)	1.0372	<0.0001**	0.2691	<0.0001**
How satisfied are you with your current medicines?	4.3010	<0.0001**	0.8985	0.0006**

* $p < 0.05$; ** $p < 0.01$.

ACT, Asthma Control Test; TBC, total barrier count.



	ICS prescription rate (n=111)			
	Low group n=13	High group n=98	Low group n=13	High group n=98
	Total score (a)	Total score (b)	TBC (a)	TBC (b)
Mean	47.8	37.7	6.4	3.1
95% CI	40.62 - 55.08	35.83 - 39.49	4.23 - 8.54	2.56 - 3.57
Difference of mean values (95% CI) (b)-(a)	-10.2 (-15.73 - -4.64)		-3.3 (-4.88 - -1.77)	

Fig. 1. Plots showing the relationship between **a)** mean ASK-20 total score or **b)** mean total barrier count with prescription rate of inhaled corticosteroid adherence (left: 25 to ≤75%, right: >75 to ≤125% in each error bar set) (inhaled corticosteroid adherence sub-group; n = 111) ASK, adherence starts with knowledge; CI, confidence interval; ICS, inhaled corticosteroid; TBC, total barrier count.

There were no ceiling effects, but 9 items from ASK-20 showed floor effects of which 4 questions (Q3 'My use of alcohol gets in the way of taking my medicines'; Q17 'Skipped or stopped taking a medicine because you didn't think it was working'; Q18 'Skipped or stopped taking a medicine because it made you feel bad'; and Q19 'Skipped, stopped, not refilled, or taken less medicine because of the cost') matched those that had shown floor effects in the US.¹³ These findings suggest that these 4 items are not as

challenging as the other items to patients taking medicines long term.

The subjects in our study were under specialist care for their asthma and were, therefore, more likely to be a high adherence population compared to those not receiving this care. However, our results are similar to those obtained from a global validation study and, therefore, they still demonstrate that this Japanese questionnaire may be reliable.

Acceptable internal consistency reliability was achieved with the mean ASK-20 total score but not the mean TBC, which is consistent with published data in a US population.¹³ Although this suggests that the ASK-20 scoring is more reliable than TBC, we agree with Matza *et al.* that while the ASK-20 score is recommended for use under research conditions, the TBC remains helpful in clinical settings for improving communication between physicians and patients.¹³

The 95% CI for the mean ASK-20 total score and mean TBC successfully discriminated between the poor adherence sub-groups i.e., those who had missed a dose or had not taken the dose exactly as directed and good adherence patients i.e., those who had taken all the medication as directed.

This discrimination and the moderate to high correlation of the mean ASK-20 total score and mean TBC with most of the factors affecting medication adherence concurred with US results,¹¹ although it should be noted that age and ACT score were not examined in either the US or Japanese populations. Significant correlation with percentage ICS adherence was seen with the mean ASK-20 total score and mean TBC – both discriminated between the high and low ICS prescription rate groups. Therefore, the ASK-20 may help to discriminate between different ICS adherence rates.

Study limitations

One of our study centers was a large university hospital in the metropolitan area of Tokyo. This is perhaps not an ideal environment in which to monitor subjects because non-specialist physicians examine patients with a variety of conditions within a limited timeframe. Greater monitoring may have been achieved in primary care institutions.

An additional limitation was the influence of Tokyo's subsidisation policy for self-funding patients with bronchial asthma, which may have underestimated scores for the cost-related item, Q19. Also, our use of a specialised respiratory centre may have reduced the effect of treatment adherence barriers compared to if a non-specialist centre had been used.¹⁸

Furthermore, ASK-20 is not the questionnaire only for asthma patients,¹³ therefore this includes questions unrelated to asthma. On the other hand, there are no questions about inhalation technique or education. These might be limitations in using ASK-20 to detect asthma specific adherence barriers.

Finally, only subjects who had taken ICS at a fixed dose for at least 2 years were enrolled, so a considerable number of poor adherence subjects might have been excluded thus creating a bias towards fewer adherence barriers as seen in our study.

Future development of the ASK-20 in Japan

Our study represents one step in the ongoing development and validation of the ASK-20 in Japanese adults and future research is needed to further validate this instrument. In the future, when other relevant questionnaires have been translated and validated for use in Japanese patients, studies comparing the ASK-20 with the MMAS and MARS would test the validity of the Japanese ASK-20. This has already been achieved in the US where a strong correlation was reported between the ASK-20 total score and the following questionnaires: MMAS ($r = -0.61, p < 0.001$); Short Form Survey (SF)-12 (mental health composite score) ($r = -0.40, p < 0.001$); SF-12 (physical composite score) ($r = -0.19, p < 0.05$); and mini asthma quality of life questionnaire ($r = -0.32, p = 0.05$).¹³

ASK-20 is not an asthma specific questionnaire for asthma patients. Therefore we will try continuously to understand the issue of

adherence and consider effective intervention program with a view to develop a new asthma specific questionnaire.

In conclusion, our results confirm that the Japanese ASK-20 is a reliable tool for assessing possible medication adherence barriers and adherence behaviour in Japanese adults with asthma. Furthermore, our results are comparable with those obtained using the ASK-20 in the United States.

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Conflicts of interest

RA received research funds and lecture fees from GlaxoSmithKline, AstraZeneca, Kyorin Pharmaceutical, Ono Pharmaceutical, Astellas Pharma, Taiho Pharmaceutical, Boehringer Ingelheim, and Novartis Pharma. YT received research funds and lecture fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Kyorin Pharmaceutical, Novartis Pharma, MSD, ASKA Pharmaceutical, Sumitomo Dainippon Pharma, Astellas Pharma, and Taisho Toyama Pharmaceutical. SS received lecture fees from GSK. IM and AKo are employees of GlaxoSmithKline. KT received research funds and lecture fees from GlaxoSmithKline, AstraZeneca, Kyorin Pharmaceutical, Ono Pharmaceutical, Astellas Pharma, and EBMs. AKi has no conflict of interest.

Authors' contributions

RA and IM developed the design and concept of the study. Statistician, AKo, contributed to protocol development. RA, YT, SS and AKi collected the data; AKo is accountable for the data analysis performed by The Institute of Japanese Union of Scientists & Engineers (JUSE). All authors were involved in interpretation of the data and draughting and critically reviewing the manuscript.

References

- Chrystyn H, Small M, Milligan G, Higgins V, Garcia Gil E, Estruch J. Impact of patients' satisfaction with their inhalers on treatment compliance and health status in COPD. *Respir Med* 2014;**108**:358–65.
- Thier SL, Yu-Isenberg KS, Leas BF, Cantrell CR, DeBussey S, Goldfarb NI, et al. In chronic disease, nationwide data show poor adherence by patients to medication and by physicians to guidelines. A widespread approach that incorporates various stakeholders may be necessary to change adherence behavior. *Manag Care* 2008;**17**:48–52. 55–47.
- Tamura G, Ohta K. Adherence to treatment by patients with asthma or COPD: comparison between inhaled drugs and transdermal patch. *Respir Med* 2007;**101**:1895–902.
- Breekveldt-Postma NS, Koerselman J, Erkens JA, van der Molen T, Lammers J-WJ, Herings RMC, for the CAMERA Study Group. Treatment with inhaled corticosteroids in asthma is too often discontinued. *Pharmacoepidemiol Drug Saf* 2008;**17**:411–22.
- Bender BG, Pedan A, Varasteh LT. Adherence and persistence with fluticasone propionate/salmeterol combination therapy. *J Allergy Clin Immunol* 2006;**118**:899–904.
- Iwanaga T, Kumar M, Goren A, Mukai I, Hattoir T. Cross sectional patient-reported survey on asthma control and associated burdens in Japanese patients with asthma in 2013. *Ther Res* 2015;**36**:235–46.
- Krauskopf KA, Sofianou A, Goel MS, Wolf MS, Wilson EAH, Martynenki ME, et al. Depressive symptoms, low adherence, and poor asthma outcomes in the elderly. *J Asthma* 2013;**50**:260–6.
- Williams LK, Peterson EL, Wells K, Ahmedani BK, Kumar R, Burchard EG, et al. Quantifying the proportion of severe asthma exacerbations attributable to inhaled corticosteroid non-adherence. *J Allergy Clin Immunol* 2011;**128**:1185–91.
- World Health Organization. *Adherence to Long-Term Therapies: Evidence for Action WHO/MNC/03.01*. 2003.
- Boulet L-P. Perception of the role and potential side effects of inhaled corticosteroids among asthmatic patients. *Chest* 1998;**113**:587–92.
- Hahn SR, Park J, Skinner EP, Yu-Isenberg KS, Weaver MB, Crawford B, et al. Development of the ASK-20 adherence barrier survey. *Curr Med Res Opin* 2008;**24**:2127–38.
- Patel M, Perrin K, Pritchard A, Williams M, Wijesinghe M, Weatherall M, et al. Accuracy of patient self-report as a measure of inhaled asthma medication use. *Respirology* 2013;**18**:546–52.

13. Matza LS, Yu-Isenberg KS, Coyne KS, Park J, Wakefield J, Skinner EP, et al. Further testing of the reliability and validity of the ASK-20 adherence barrier questionnaire in a medical center outpatient population. *Curr Med Res Opin* 2008;**24**:3197–206.
14. LaFleur J, Oderda GM. Methods to measure patient compliance with medication regimens. *J Pain Palliat Care Pharmacother* 2004;**18**:81–7.
15. Krishnan JA, Bender BG, Warmboldt FS, Szefer SJ, Adkinson NF, Zeiger RS, et al. Adherence to inhaled corticosteroids: an ancillary study of the Childhood Asthma Management Program clinical trial. *J Allergy Clin Immunol* 2012;**129**:112–8.
16. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care* 1986;**24**:67–74.
17. Thompson K, Kulkarni J, Sergejew AA. Reliability and validity of a new Medication Adherence Rating Scale (MARS) for the psychoses. *Schizophr Res* 2000;**42**:241–7.
18. Atsuta R, To Y, Sakamoto S, Mukai I, Kobayashi A, Kinoshita A, et al. [Assessing barriers to medication adherence using the Adherence Starts with Knowledge 20 questionnaire for Japanese adult patients with bronchial asthma receiving inhaled corticosteroid-containing medications]. *[Ther Res]* 2015;**36**:341–53 (in Japanese).
19. Park J, Jackson J, Skinner E, Ranghell K, Saiers J, Cherney B. Impact of an adherence intervention program on medication adherence barriers, asthma control, and productivity/daily activities in patients with asthma. *J Asthma* 2010;**47**:1072–7.
20. Japanese Society of Allergology. *[Asthma Prevention and Management Guideline 2012]*. Tokyo: Kyowa Kikaku; 2012 (in Japanese).
21. Aronson N, Alonso J, Burnam A, Lohr KN, Patrick DL, Perrin E, et al. Assessing health status and quality-of-life instruments: attributes and review criteria. *Qual Life Res* 2002;**11**:193–205.
22. Nunnally JC. *Psychometric Theory*. 2nd ed. New York: McGraw-Hill; 1978.
23. Leidy NK, Revicki DA, Genesté B. Recommendations for evaluating the validity of quality of life claims for labeling and promotion. *Value Health* 1999;**2**:113–27.