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Running title: Adherence barriers to inhaled medicines in asthma

Adherence barriers to inhaled medicines in Japanese older patients with asthma evaluated using the "Adherence Starts with Knowledge 20" (ASK-20) questionnaire

Authors:

Jun Sasaki[1, 6], MD, sasaki_jun@med.kurume-u.ac.jp

Tomotaka Kawayama[1, 6], MD, PhD, kawayama_tomotaka@med.kurume-u.ac.jp

Makoto Yoshida[2, 6], MD, PhD, myoshida@mfukuoka2.hosp.go.jp

Koichiro Takahashi[3, 6], MD, PhD, takahak@cc.saga-u.ac.jp

Kazuhiko Fujii[4, 6], MD, PhD, k-fujii@kumamoto-u.ac.jp

Kentaro Machida[5, 6], MD, PhD, machida@m.kufm.kagoshima-u.ac.jp

Takashi Kinoshita[1, 6], MD, PhD, tkino@med.kurume-u.ac.jp

Tomoaki Hoshino[1, 6], MD, PhD, hoshino@med.kurume-u.ac.jp

Institutes and addresses:

[1]Division of Respirology, Neurology, and Rheumatology, Department of Medicine, Kurume University School of Medicine, 67 Asahi-machi, Kurume 830-0011, Japan; [2]Respiratory Medicine, National Hospital Organization Fukuoka Hospital, 4-39-1 Yakatabaru, Fukuoka 811-1351, Japan; [3]Division of Hematology, Respiratory Medicine and Oncology, Department of Internal Medicine, Faculty of Medicine, Saga University, 5-1-1 Nabeshima, Saga 849-8501, Japan; [4]Department of Respiratory Medicine, Kumamoto University Hospital, 1-1-1 Honjo, Kumamoto 860-8556, Japan; [5]Department of Pulmonary Medicine, Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima 890-8520, Japan; [6]Kyushu Asthma Seminar Investigators

Correspondence: Tomotaka Kawayama, MD, PhD

Division of Respirology, Neurology, and Rheumatology, Department of Medicine

Kurume University School of Medicine, 67 Asahi-machi, Kurume 830-0011, Japan

TEL: +81-942-31-7560

FAX: +81-942-31-7703

E-mail: kawayama_tomotaka@med.kurume-u.ac.jp

Abstract (246 words)

Objective: We investigated adherence barriers to inhaled medicines among older compared to younger adults with asthma in Japan.

Methods: Adherence barriers to inhaled medicines were evaluated in 251 Japanese older (n = 138) and younger (n = 113) adults with asthma using the self-reporting “Adherence Starts with Knowledge 20” (ASK-20) questionnaire.

Results: There were fewer older adults with poor adherence to inhaled medicines than younger adults. The ASK-20 questionnaire revealed (odds ratio [95% confidence interval]) item Q11 (“My doctor/nurse and I work together to make decisions”; 2.94 [1.31, 6.61]; $p < 0.05$) as an independent adherence barrier to inhaled medicines among older adults, whereas younger adults reported item Q3 (“My use of alcohol gets in the way of taking my medicines”; 3.91 [1.02 to 15.1]; $p < 0.05$) and item Q16 (“Taken a medicine more or less often than prescribed? “; 2.31 [1.32 to 4.06]; $p < 0.05$) as barriers. Older adults with poor adherence identified item Q1 (“I just forget to take my inhaled medicines some of the time”; 4.43 [1.77, 11.1]; $p < 0.05$) as a barrier, although the total ASK-20 scores and total barrier counts were significantly higher in older (both, $p < 0.05$) and younger (both, $p < 0.05$) adults with poor adherence than in those with good adherence.

Conclusion: Older Japanese patients had better adherence to inhaled medicines than younger patients. Barriers were different between older and younger adults. These results will help personalize education for inhaled medicines in Japanese asthmatics.

Keywords: Biomarkers, Control/Management, Education, Quality of Life

Introduction

The World Health Organization (WHO) predicts that the proportion of people aged 65 years and older will grow from an estimated 524 million in 2010 to 1.5 billion by 2050 [1]. Japan is now considered a “super-aged” society, with older adults (age ≥65 years) already making up more than 27% of the population in 2016 [2]. Recently, mortality due to asthma has been decreasing, but in Japan, over 90% of fatal asthmatics are older adults [3]. Among older adults with uncontrolled asthma, physicians tend to under-prescribe inhaled corticosteroids (ICS) because of concern over the side effects of these medicines [4], even though regular use of ICS plays a central role in controlling the chronic airway inflammation of asthma, and can also improve quality of life and attenuate the exacerbations and mortality in patients with asthma [5]. Low rates of adherence to the regular use of controllers for asthma might contribute to this disease being poorly controlled among older patients [6], [7]. Previous reports [8], [9], [10], [11], [12] demonstrated that adherence rates to ICS use in older adults with asthma were lower than those in the total population with asthma. However, a meta-analysis did not report that age was significantly associated with adherence rates to inhaled medicines [13]. Furthermore, a previous Japanese report demonstrated that increased age was associated with better adherence scores to inhaled medicines [14]. However, efforts to address this issue, through education and interventions to improve

adherence to inhaled medicine regimes, may be more successful among older adults with asthma than among younger patients with asthma [13], [15], [16].

Adherence rates and barriers to inhaled medicines among older adults with asthma in Japan are still unclear. However, evaluating individual barriers may contribute to improvements in adherence rates for inhaled medicines, including ICS, by helping address unmet education and intervention needs. The Adherence Starts with Knowledge 20 (ASK-20) questionnaire was developed by Hahn et al for identifying barriers [17], [18] and the Japanese version of the ASK-20 questionnaire has already been validated in Japanese patients with asthma [19]. Previous studies have demonstrated good correlation between adherence and barriers in patients with asthma by using the ASK-20 questionnaire [17], [18], [19], [20]. However, the generalizability of the questionnaire remains limited, because the questionnaire has only been evaluated in English and Japanese. Building on this work, the Kyushu Asthma Seminar Investigator Group conducted a multicenter, cross-sectional, non-interventional trial to investigate adherence and barriers to inhaled medicines among older adults compared to younger adults with asthma using the ASK-20 questionnaire in Japan.

Methods

Ethical approval

The study was conducted in accordance with the Good Clinical Practice guidelines and was approved by the ethics board of each institute. The trial was registered in the University Hospital Medical Information Network (UMIN) Center (UMIN No. R000015329) on February 13, 2014. Physicians obtained written informed consent from every patient who met the inclusion criteria.

Selection of patients, and inhaled and oral medicines

Japanese adult (age ≥20 years) patients with asthma who met the inclusion criteria—regular medication with at least one inhaled medicine, including regular use of ICS, regular clinic attendance with medical records since giving consent for participation within 6 months or more before the start of the study—were enrolled at each institute. To investigate adherence in each patient, one inhaled medicine was selected as the most important among all regularly prescribed medicines by the patient's physician, without consultation with the patient (Supplementary Table 1).

Study design

After providing written consent, patients were required to complete the Japanese version of the self-reporting ASK-20 questionnaire for adherence to the selected inhaled medicines [19]. Patient characteristics—including age, sex, body mass index (BMI), smoking habits, presence of comorbid diseases, disease control levels, adherence levels to the selected inhaled medicines, and information on all regular inhaled and oral medications—were recorded. Diagnosis of asthma and asthma controlled levels were defined in accordance with the Global Initiative for Asthma (GINA) reports [5]. Comorbid diseases were defined on the basis of interview findings and information regarding all regular medicines prescribed to the study population (Supplementary Table 2). From medical records, physicians selected the best pre-bronchodilation values of forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) during stable disease status. Adherence to the selected inhaled medicines within 6 months before enrolment was assessed on the basis of questionnaire findings and prescription refill methods, and poor (< 80% of adherence) and good ($\geq$ 80% of adherence) adherence were defined by either method [21], [22], [23], [24] [25]. However, each patient was required to self-report one of the following four categories of adherence levels, namely, 100%, <100% and >80%, <80% and >50%, and <50% of adherence within 6

months, in accordance with previous studies [21] [22] [23] [24] [25] that used questionnaire methods. All data were obtained within the 6 months before enrolment.

Statistical analysis

Patient characteristics were expressed as number (percentage) of patients or mean ± standard deviation (SD). Total ASK-20 scores and total barrier counts (TBCs) for adherence to the selected inhaled medicines were calculated in accordance with the methods described in previous studies [17], [18], [19], [20]. To investigate adherence rates and barriers among older patients, the adherence parameters were compared between older (age ≥ 65 years) and younger (age ≥20 years and <65 years) adults after evaluating each age group. The cutoff of 65 years in Japan as developed country was based on a WHO report [1]. In addition, the patients were divided into four groups — those with poor and good adherence to the selected inhaled medicines in older and younger adults, respectively. The proportions of patients with poor adherence, and the median values (lower and higher percentiles) of total ASK-20 scores and TBCs of inhaled medicines were compared between older and younger adults. Comparative analysis between two groups was performed by using the two-tailed unpaired t-test or non-parametric Wilcoxon test, and the chi-squared test or Fisher's exact test with an expected frequency of <5.0 in cells >20%. Total ASK-20

scores and TBCs among age groups were compared by using the non-parametric Wilcoxon test with Steel-Dwass correction. To identify the barriers to inhaled medicines, the odds ratio (95% confidence interval [CI] and p value) was analyzed by the chi-square or Fisher's exact test in univariate and multivariate logistic regression analyses. Differences at $p < 0.05$ were considered statistically significant. Statistical analyses were performed using the software package JMP version 9.0 (SAS Institute Japan Inc., Tokyo, Japan).

Results

Two hundred and eighty-three patients provided written consent, and 251 patients (older [n = 138] and younger [n = 113] adults; mean age 63.2 years [range 26 to 90 years]) were finally analyzed in the study (Figure 1). Among age groups, an age group between 75 years and 84 years was the smallest population of patients with poor adherence to inhaled medicines (p = 0.328) and the proportions were like an inverted J-character curve from 25 years to 85 or more years (Figure 2A). The age group of 85 or more years had a greater, but not significantly so, population with poor adherence to inhaled medicines than the age group between 75 and 84 years (p = 0.594) (Figure 2A). The population of patients with poor adherence to inhaled medicines was 24.3% of total study population. In terms of poor adherence, the population with older adults was smaller, but not significantly so, than the younger adults (p = 0.107) (Figure 2B).

Table 1 presents a comparison of characteristics between older and younger adults. Older adults had significantly less proportions of current smokers and regular/part-time workers, and lower pulmonary functions, and had a higher proportion of patients with regular use of mucolytic agents than younger adults. In regular treatment, the number of oral

medicines in older adults was significantly higher than that in younger ones, although there was no difference in the number of inhaled medicines between the two groups.

As shown in Figure 3, the median of total ASK-20 scores, but not of TBCs ($p>0.05$), for older adults was significantly less than that for younger adults ($p = 0.037$). Figure 4 presents the comparison between the proportion of older and younger adults with barriers to inhaled medicines identified for each ASK-20 item. A significantly higher proportion of older adults reported the ASK-20 item Q10 (“I understand my doctor’s/nurse’s instructions about the medicines I take”) and item Q11 (“My doctor/nurse and I work together to make decisions”), whereas a higher proportion of younger adults reported item Q3 (“My use of alcohol gets in the way of taking my medicines”) and item Q16 (“Taken a medicine more or less often than prescribed? “) as barriers to inhaled medicines. Multivariate analyses found that the item Q11 (odds ratio, 2.94 [95% CI, 1.31 to 6.61]; $p = 0.009$) was an independent barrier among older adults, whereas the items Q3 (3.91 [1.02 to 15.1]; $p = 0.048$] and Q16 (2.31 [1.32 to 4.06]; $p = 0.004$) were independent barriers among younger adults (full analyses in Supplementary Table 3).

Figure 5 presents the results of the comparison of total ASK-20 scores and TBCs between patients with poor and good adherence to selected inhaled medicines in older and younger adults. Both older and younger adult groups with poor adherence had significantly

higher total ASK-20 scores and TBCs than those with good adherence. Multivariate analyses found that older adults patients with poor adherence had item Q1 (“I just forget to take my medicines some of the time”; odds ratio, 4.43 [95% CI, 1.77 to 11.1]; p = 0.001) as an independent barrier, whereas younger adults with poor adherence had items Q1 (6.88 [1.94 to 24.4]; p = 0.003], Q4 (“I worry about how medicine will affect my sexual health”; 7.43 [1.15 to 46.6]; p = 0.035), and Q20 (“Not had medicine with you when it was time to take it?”; 4.14 [1.08 to 15.9]; p = 0.038) as independent barriers to inhaled medicines.

Discussion

To our knowledge, this is the first report comparing adherence ratios and adherence barriers between older and younger Japanese adults with asthma. Poor adherence to inhaled medicines is affected by barriers to taking these medicines [19], [26]. In our study, adherence barriers to inhaled medicines were investigated among older and younger adults with poor adherence to medicines. Total ASK-20 scores and TBC with poor adherence were significantly higher than those with good adherence in both older and younger adults. A comparison between patients with poor and good adherence revealed that older adults reported taking medicines at fixed times (item Q1) as an independent barrier, although younger adults had three independent barriers; first, taking medicines at fixed times (item Q1); second, being concerned about the effects of medicines on their sexual health (item Q4); and third, not having their medicines on hand at the appropriate times (item Q20). The relatively simpler barriers for older adults may be associated with certain treatment beliefs among this population, which may have a strong influence on adherence in older asthmatics [15].

Older adults had less, but not significantly so, age sub-groups with poor adherence to inhaled medicines than younger adults. Total ASK-20 scores, but not TBCs, for older adults were significantly lower than those for younger adults. A correlation between age groups with poor adherence and aging was like an inverted J-character curve with the bottom in the age groups between 75 and 84 years. An age group of 85 years and over might be an important target for reeducation for adherence, although the difference compared with the next older group, between 75 and 84 years, did not reach statistical significance due to the small sample size. The results of better adherence with aging confirmed a previous Japanese report [14]. In addition, despite having more comorbid diseases and total daily medications, older adults had better adherence than younger adults. These results were different from previous reports in Western populations that showed that adherence levels were lower with older adults with more comorbid diseases and total daily medications than with individuals of other age groups [8], [9], [10], [11], [12], [27], [28]. Our study found that over 70% of the enrolled patients were associated with good adherence to inhaled medicines and had good persistent attendance at clinics. In other Asian patients with asthma, a previous study reported embarrassment or annoyance regarding using or carrying medicines to be a barrier to inhaled medicines [26]. The better adherence among older adults may be unique to Japanese populations.

Our analyses of each item found that about one-third of the patients reported that taking medicines on a fixed regimen (item Q16) or at specific times (item Q1), and reaching their health goals (item Q8) as barriers to inhaled medicines in both older and younger adults. The analyses also found different barriers between older and younger adults. Older adults reported that making decisions with doctors or nurses (item Q11), understanding the instructions of their medicines (item 10), and asking someone about their medicines (item Q9) as barriers more often than younger adults. Communication and partnerships between patients and physicians are an important part of achieving effective disease control [29], [30], [31], [32]. Better patient-physician communication may lead to better treatment compliance [29]. The patient-physician partnership is a contributory factor in the improvement of asthma treatment [30]. However, a previous report demonstrated that only 22% of asthmatics reported having had a good discussion with their doctor or nurse, and only 9% felt that they were given plenty of information at the time of diagnosis [31]. Another study reported that an examination of doctor-patient communications indicated that 5 to 10% of patients with asthma could not accurately recall what a caregiver had advised during their consultation [32]. Among our older patients with good adherence, better adherence may further improve communication and the partnerships with their physicians. In contrast, younger adults

identified taking medicines more or less often than prescribed and the use of alcohol as barriers.

This study has some limitations. First, adherence levels were limited, because they were obtained indirectly by questionnaire and through different refill methods [21], [22], [23], [24] [25]. Second, inhalation techniques were not assessed in the study, although it is well-known that older patients are more likely to make mistakes regarding techniques when compared with younger patients [33], [34], [35]. Third, health literacy and cognitive status were not accessed [8], [9]. Previous studies found that older asthmatics with limited health literacy and cognitive impairment were associated with poorer adherence to controller medications [33], [36], [37]. Our study found that there was no difference in the disease control levels and comorbidities associated with health literacy such as psychogenic and cerebrovascular diseases between older and younger adults. Further studies are necessary to address these limitations.

Conclusion

We comparatively analyzed adherence barriers to inhaled medicines among older and younger patients with asthma by using the ASK-20 questionnaire. There were differences in the underlying factors for adherence barriers between older and younger patients with

asthma. Older patients with even good adherence may need more communication and stronger partnerships with physicians to improve adherence. In addition, we found different barriers between older and younger patients with poor adherence to inhaled medicines. We believe that our results will contribute to personalized education for adherence to inhaled medicines among Japanese patients with asthma.

Table 1. Characteristics between older and younger adults

Characteristics	Total (n = 251)	Older (n = 138)	Younger (n = 113)	p value
Age, years	63.2 ± 14.1	73.4 ± 5.9	50.7 ± 10.6	<0.0001*
Female, n (%)	158 (63.0)	82 (59.4)	76 (67.3)	0.2
Body mass index, kg/m^2	24.0 ± 4.6	23.7 ± 4.3	24.3 ± 4.9	0.4
Smoking habit, Cu/Ex/Non, n (%)	29/60/162 (11.5/23.9/64.3)	6/38/94 (4.4/27.5/68.1)	23/22/68 (20.4/19.5/60.2)	0.0003*
Smoke index, pack-year	9.8 ± 20.2	11.5 ± 23.1	7.6 ± 15.6	0.1
Occupation, Regular/Part-time/Student/Non, n (%)	99/11/1/140 (39.3/4.4/0.4/55.8)	33/2/0/103 (23.9/1.5/0/74.6)	66/9/1/37 (58.4/8.0/0.9/32.7)	<0.0001*
Any comorbid diseases, n (%)	215 (85.7)	123 (89.1)	92 (81.4)	0.1
No. of comorbid diseases per patient	2.8 ± 2.1	3.1 ± 2.3	2.4 ± 1.8	0.0050*
Not well attention to detail in personality, n (%)	37 (14.7)	15 (10.9)	22 (19.5)	0.1
Poor concordance rates between visit and reserved date to clinic (<100%)	65 (25.9)	30 (21.7)	35 (31.0)	0.1
Poor controlled diseases, n (%)	72 (28.7)	35 (25.4)	24 (21.2)	0.5
Lung function tests				
FVC, L	2.7 ± 0.8	2.4 ± 0.8	3.1 ± 0.8	<0.0001*
% predicted FVC, %	94.2 ± 17.9	92.1 ± 19.1	96.9 ± 16.0	0.0329*
FEV_1, L	1.9 ± 0.7	1.6 ± 0.6	2.3 ± 0.7	<0.0001*
%FEV_1 predicted, %	80.1 ± 20.7	76.5 ± 21.3	84.4 ± 19.1	0.0025*
FEV_1/FVC ratio	68.7 ± 12.7	65.3 ± 12.2	72.9 ± 11.9	<0.0001*
Regular use of medicines for asthma	251 (100)			
ICS	251 (100)	138 (100)	113 (100)	1.0
LABA	209 (83.3)	119 (86.2)	90 (79.7)	0.2
LAMA	17 (6.8)	11 (8.0)	6 (5.3)	0.5
CysLTRA	165 (65.7)	92 (66.7)	73 (64.6)	0.8
slow release theophylline	57 (22.7)	29 (21.0)	28 (24.8)	0.5
oral prednisolone	36 (14.3)	23 (16.7)	13 (11.5)	0.3
macrolides	15 (6.0)	10 (7.3)	5 (4.4)	0.4
mucolytic agents	53 (21.1)	37 (26.8)	16 (14.2)	0.0192*
No. of regular inhaled devices, n (range)	1.1 ± 0.4 (1 to 3)	1.2 ± 0.4 (1 to 3)	1.1 ± 0.4 (1 to 3)	0.4
No. of regular oral medicines, n (range)	4.5 ± 3.2 (0 to 18)	5.2 ± 3.3 (1 to 15)	3.7 ± 2.9 (0 to 18)	0.0003*

Notes: Data are presented as numbers (percentages) of patients and mean ± standard deviation.

* $p < 0.05$ between older and younger adults

Abbreviations: Cu/Ex/Non, current/ex/non-smoker; CysLTRA, cysteinyl leukotriene receptor antagonist; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; ICS, inhaled corticosteroid; LABA, long-acting β_2 agonist; LAMA, long-acting muscarinic antagonist.

Table 2 Characteristics in selected inhaled medicines by physicians between older and younger adults

Selected inhaled medicines	Total (n = 251)	Older (n = 138)	Younger (n = 113)	p value
Compounds, n (%)				
ICS monotherapy	49 (19.5)	25 (18.1)	24 (21.2)	0.6
ICS/LABA combination therapy	202 (80.5)	113 (81.9)	89 (78.8)	0.6
Devices, n (%)				
Dry powder inhalers	217 (86.5)	117 (84.8)	100 (88.5)	0.5
Pressured-Metered dose inhalers	34 (13.6)	21 (15.2)	13 (11.5)	0.5
Regimens, n (%)				
No. of administration per day				
2 times	233 (92.8)	133 (92.4)	100 (88.5)	0.0247*
1 time	18 (7.2)	5 (3.6)	13 (11.5)	0.0247*
Dose per one administration				
4 puffs	4 (1.6)	0 (0)	4 (3.5)	0.0399*
3 puffs	6 (2.4)	4 (2.9)	2 (1.8)	0.7
2 puffs	60 (23.9)	35 (25.4)	25 (22.1)	0.7
1 puff	181 (72.1)	99 (71.7)	82 (72.6)	1.0

Notes: Data are presented as numbers (percentages) of patients. Full data are shown in supplementary Table 1. * $p < 0.05$ between older and younger adults.

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting β_2 agonist.

Table 3 Odds ratios of each item on independent barriers to inhaled medicines in patients with poor adherence when compared to those with good adherence to inhaled medicines

item		Older		Younger	
		Odds (95% CI)	p value	Odds (95% CI)	p value
Q1.	I just forget to take my medicines some of the time	4.43 (1.77, 11.1)	0.0014*	6.88 (1.94, 24.4)	0.0028*
Q4.	I worry about how medicine will affect my sexual health	–		7.34 (1.15, 46.6)	0.0346*
Q20.	Not had medicine with you when it was time to take it?	–		4.14 (1.08, 15.9)	0.0384*

Notes: Data are expressed as odds ratios (95% CI) and p values. Full analyses were shown in supplementary Tables 4A and 4B.

Abbreviations: CI, confidence interval

Figure Legends

Figure 1. Study design

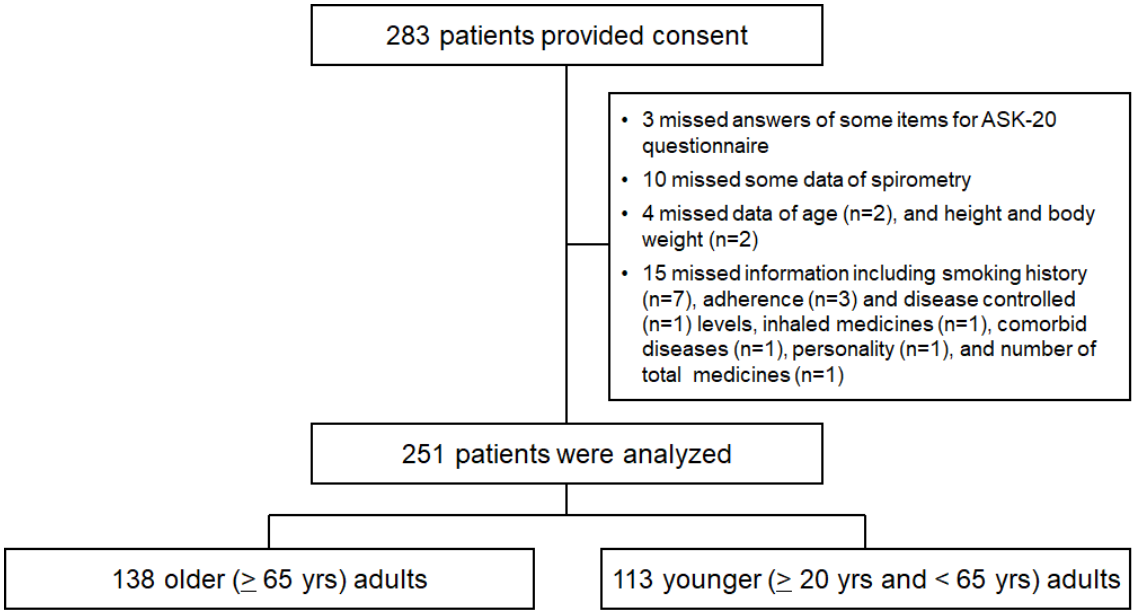
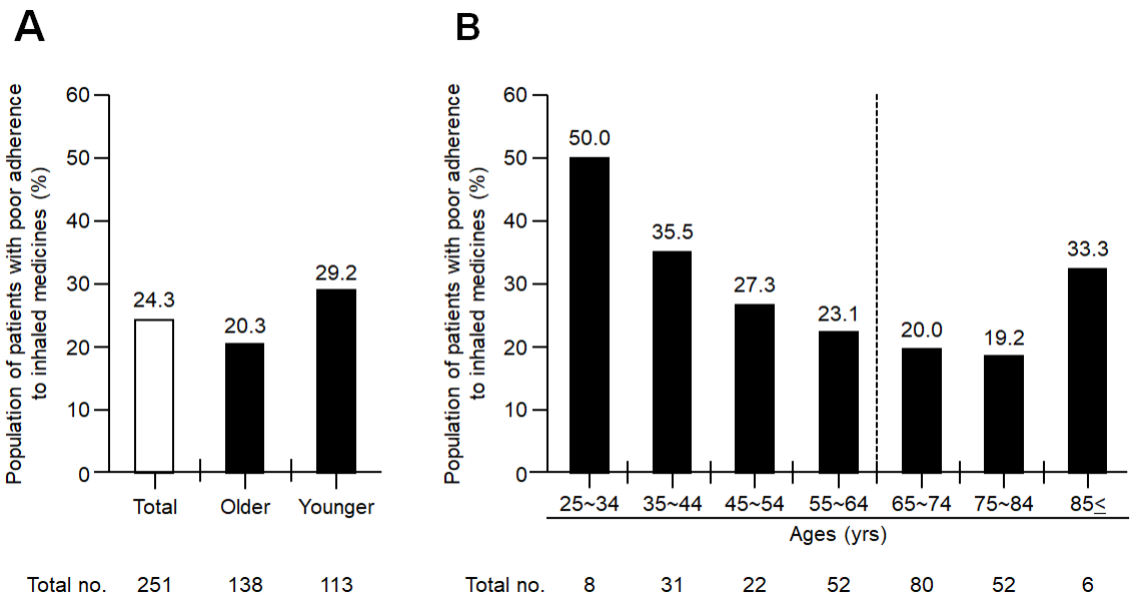
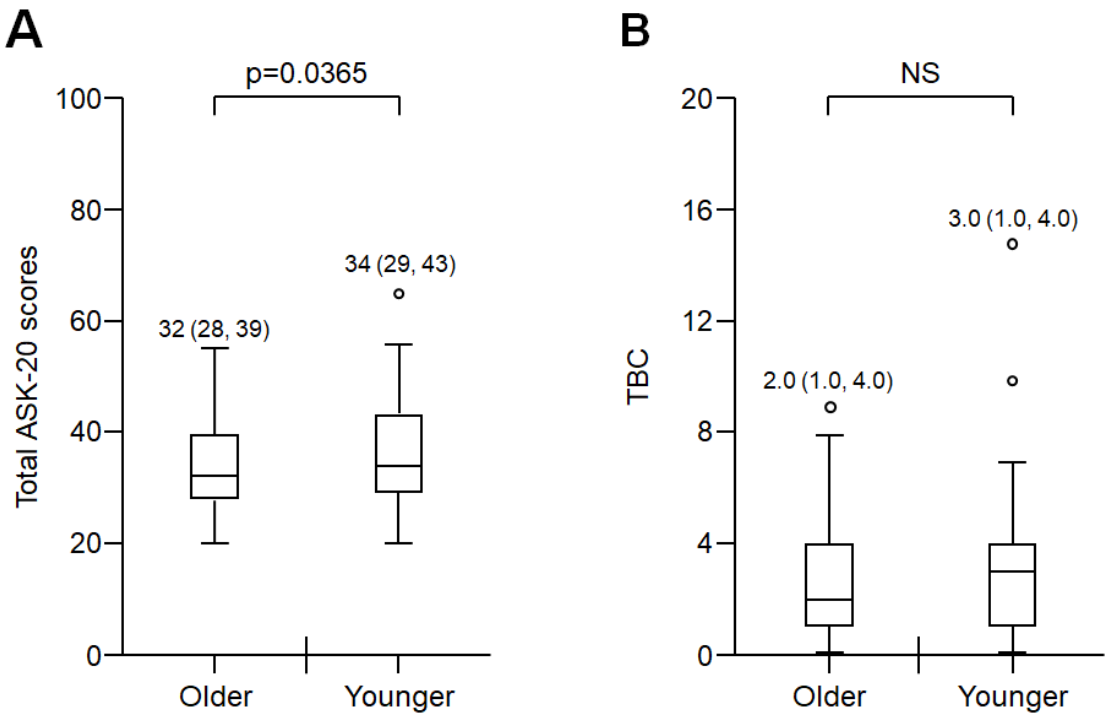


Figure 2. Populations of patients with poor adherence to inhaled medicines



Notes: A) Populations (%) of patients with poor adherence to inhaled medicines among age groups. B) Populations (%) of patients with poor adherence to inhaled medicines in the total study population, and older and younger adults.

Figure 3. Comparisons in the total ASK-20 scores and TBC between older and younger adults

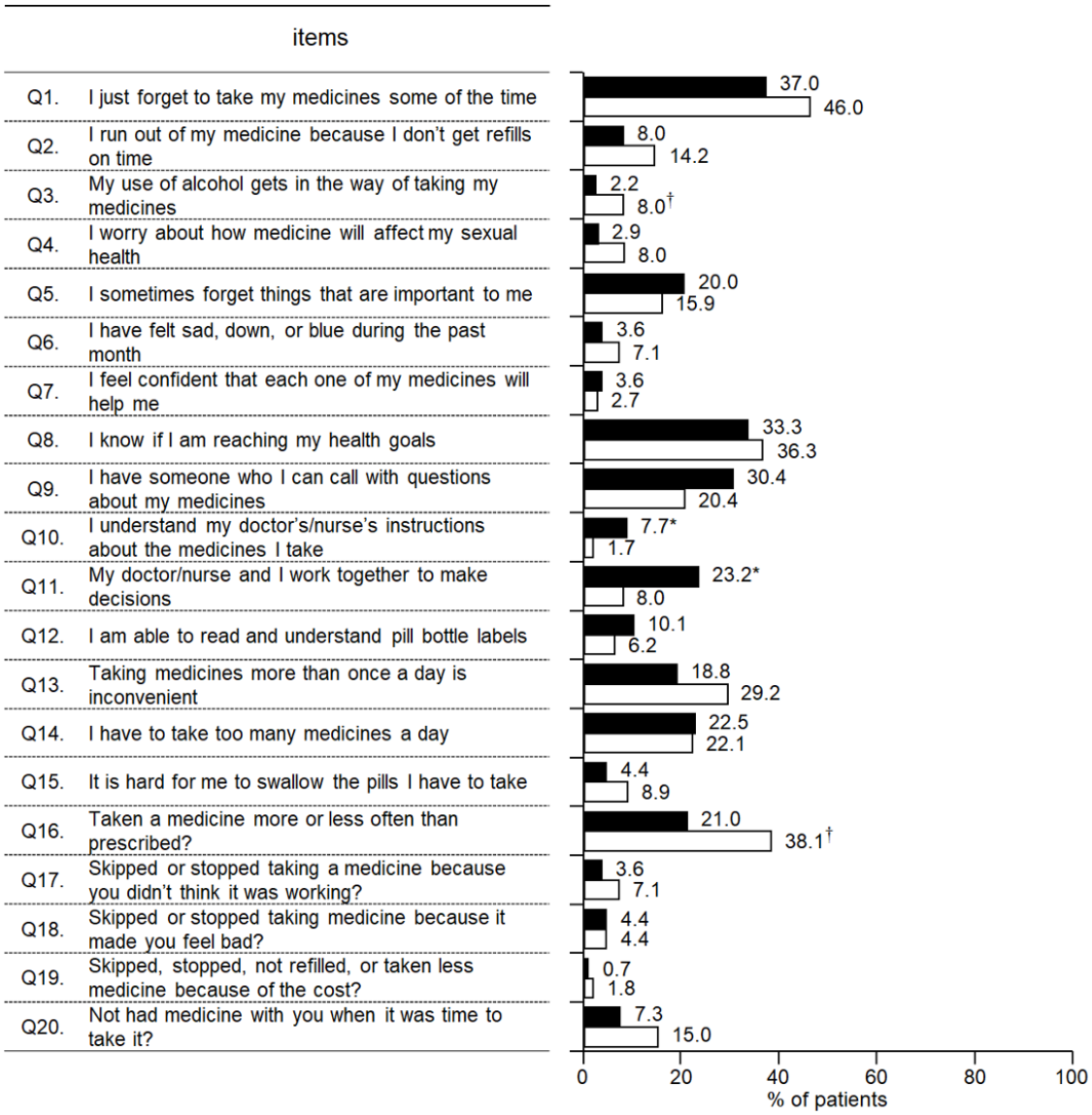


Notes: A) Total ASK-20 scores B) TBC. Values are presented as median and 95% confidence interval (CI). Median values (upper and lower quintiles) are presented as boxes, and the maximum and minimum values of 95% CI are presented as upper and lower whiskers, respectively. Box-and-whisker plots with solid and dotted lines present the values for patients with older and younger adults, respectively. Values of outliers are presented as

open dots.

Abbreviations: ASK-20, Adherence Starts with Knowledge 20; CI, confidence interval; NS, not significant; TBC, total barrier counts.

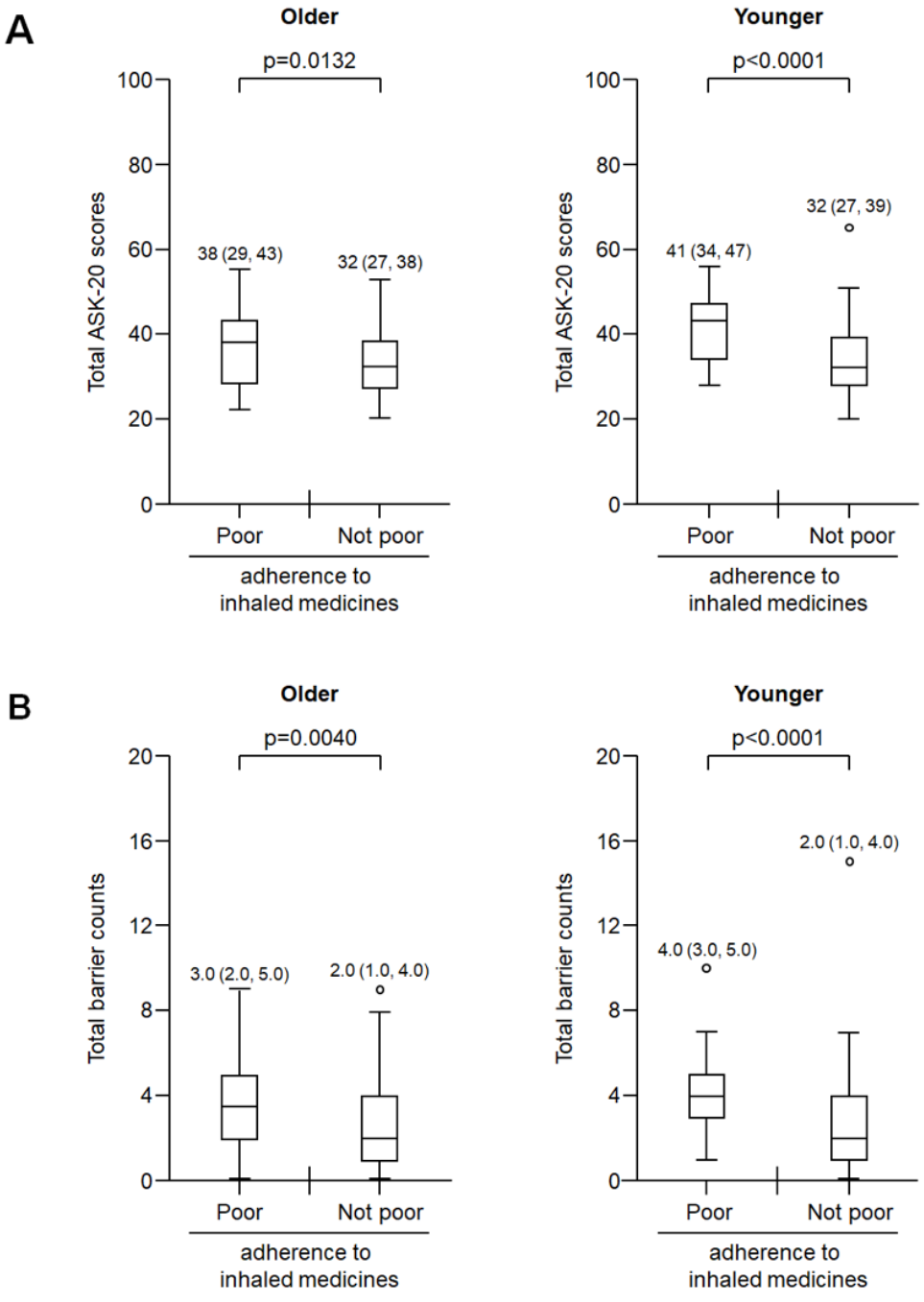
Figure 4. Comparison between proportion of older and younger patients with adherence barriers to inhaled medicines identified for each ASK-20 item.



Notes: Populations (%) of patients who had barriers in older and younger adults are expressed as closed and opened bars, respectively.

* $p < 0.05$ when comapred with younger adults; † $p < 0.05$ when compared with older adults.

Figure 5. Total ASK-20 scores and TBC between poor and good adherence to inhaled medicines among older and younger adults



Notes: A) Total ASK-20 scores B) TBC. Values are presented as median and 95% confidence interval (CI). Median values (upper and lower quintiles) are presented as boxes, and the maximum and minimum values of 95% CI are presented as upper and lower whiskers, respectively. Box-and-whisker plots with solid and dotted lines present the values for patients with older and younger adults, respectively. Values of outliers are presented as open dots.

Abbreviations: ASK-20, Adherence Starts with Knowledge 20; CI, confidence interval; TBC, total barrier counts.

References

1. World Health Organization. Global health and aging. NIH Publication no. 11-7737, 2 p, October 2011

2. Ministry of Internal Affairs and Communications, Japan. Available from: http://www.stat.go.jp/index.htm. Accessed on November 20th, 2017

3. Ministry of Health, Labour and Welfare, Japan. Available from: http://www.mhlw.go.jp/. Accessed on November 20th, 2017

4. Sin DD, Tu JV. Underuse of inhaled steroid therapy in elderly patients with asthma. Chest. 2001;119:720-5

5. Global initiative for asthma report. Global strategy for asthma management and prevention. Updated 2017. Available from; http://ginasthma.org/. Accessed on March 28th, 2017

6. Williams LK, Peterson EL, Wells K, et al. Quantifying the proportion of severe asthma exacerbations attributable to inhaled corticosteroid nonadherence. J Allergy Clin Immunol. 2011;128:1185-91

7. Williams LK, Pladevall M, Xi H, et al. Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma. J Allergy Clin Immunol. 2004;114:1288-93

8. Federman AD, Wolf MS, Sofianou A, et al. Self-management behaviors in older adults with asthma: associations with health literacy. J Am Geriatr Soc. 2014;62:872-9

9. Apter AJ, Wan F, Reisine S, et al. The association of health literacy with adherence and outcomes in moderate-severe asthma. J Allergy Clin Immunol. 2013;132:321-7

10. Bozek A, Jarzab J. Adherence to asthma therapy in elderly patients. J Asthma 2010;47:162-5

11. Apter AJ, Boston RC, George M, et al. Modifiable barriers to adherence to inhaled steroids among adults with asthma: it's not just black and white. J Allergy Clin Immunol. 2003;111:1219-26

12. Apter AJ, Reisine ST, Affleck G, Barrows E, ZuWallack RL. Adherence with twice-daily dosing of inhaled steroids. Socioeconomic and health-belief differences. Am J Respir Crit Care Med. 1998;157:1810-7

13. Dima AL, Hernandez G, Cunillera O, Ferrer M, de Bruin M; ASTRO-LAB group. Asthma inhaler adherence determinants in adults: systematic review of observational data. Eur Respir J. 2015;45:994-1018

14. Takemura M, Kobayashi M, Kimura K, Mitsui K, Masui H, Koyama M, et al. Repeated instruction on inhalation technique improves adherence to the therapeutic regimen in asthma. J Asthma. 2010;47:202-8

15. Sofianou A, Martynenko M, Wolf MS, et al. Asthma beliefs are associated with medication adherence in older asthmatics. J Gen Intern Med. 2013;28(1):67–73.

16. van Eijken M, Tsang S, Wensing M, et al. Interventions to improve medication compliance in older patients living in the community: A systematic review of the literature. Drugs Aging. 2003;20:229-40

17. Hahn SR, Park J, Skinner EP, et al. Development of the ASK-20 adherence barrier survey. Curr Med Res Opin. 2008;24:2127-38

18. Matza LS, Yu-Isenberg KS, Coyne KS, 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

19. Atsuta R, To Y, Sakamoto S, et al. Assessing usability of the "Adherence Starts with Knowledge 20" (ASK-20) questionnaire for Japanese adults with bronchial asthma receiving inhaled corticosteroids long term. Allergol Int. 2017;66:411-7

20. 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

21. Imamura Y, Kawayama T, Kinoshita T, et al. Poor pharmacological adherence to inhaled medicines compared with oral medicines in Japanese patients with asthma and chronic obstructive pulmonary disease. Allergol Int. 2017;66:482-4

22. Mäkelä MJ, Backer V, Hedegaard M, Larsson K. Adherence to inhaled therapies, health outcomes and costs in patients with asthma and COPD. Respir Med. 2013;107:1481-90

23. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005;353:487-97

24. Farmer KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. Clin Ther. 1999;21:1074-90

25. Lasmar L, Camargos P, Champs NS, et al. Adherence rate to inhaled corticosteroids

and their impact on asthma control. Allergy. 2009;64:784-9

26. Price D, David-Wang A, Cho SH, et al. Time for a new language for asthma control: results from REALISE Asia. J Asthma Allergy. 2015;8:93-103. doi: 10.2147/JAA.S82633

27. Horne R. Compliance, adherence, and concordance: implications for asthma treatment. Chest. 2006;130(1 Suppl):65S-72S

28. Partridge MR. Delivering optimal care to the person with asthma: what are the key components and what do we mean by patient education? Eur Respir J. 1995;:298-305

29. Heiner MM. Key barriers to optimal management of adult asthma in Australia: physician and patient perspectives. Curr Med Res Opin. 2007;23:1799-807

30. Small M, Vickers A, Anderson P, Kay S. The patient-physician partnership in asthma: real-world observations associated with clinical and patient-reported outcomes. Adv Ther. 2010;27:591-9

31. Partridge MR. Asthma: lessons from patient education. Patient Educ Couns. 1995;26:81-6

32. Cochrane GM, Horne R, Chanez P. Compliance in asthma. Respir Med. 1999; 93:763-9

33. Turan O, Turan PA, Mirici A. Parameters affecting inhalation therapy adherence in elderly patients with chronic obstructive lung disease and asthma. Geriatr Gerontol Int. 2017;17:999-1005

34. van Beerendonk I, Mesters I, Mudde AN, Tan TD. Assessment of the inhalation technique in outpatients with asthma or chronic obstructive pulmonary disease using a metered-dose inhaler or dry powder device. J Asthma.1998;35:273-9

35. Gray SL, Williams DM, Pulliam CC, Sirgo MA, Bishop AL, Donohue JF. Characteristics predicting incorrect metered-dose inhaler technique in older subjects. Arch Intern Med. 1996;156:984-8

36. Soones TN, Lin JL, Wolf MS, O'Conor R, Martynenko M, Wisnivesky JP, Federman AD. Pathways linking health literacy, health beliefs, and cognition to medication adherence in older adults with asthma. J Allergy Clin Immunol. 2017;139:804-9

37. O'Conor R, Wolf MS, Smith SG, Martynenko M, Vicencio DP, Sano M, Wisnivesky JP, Federman AD. Health literacy, cognitive function, proper use, and adherence to inhaled asthma controller medications among older adults with asthma. Chest. 2015;147:1307-15