Original Article

"Can Do" Versus "Do Do" in Patients with Asthma at First Referral to a Pulmonologist

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What is already known about this topic? An impaired physical functioning may significantly add to poor asthma control and deteriorated quality of life in patients with asthma.

What does this article add to our knowledge? This study provides details on how the physical functioning of patients with asthma at referral to a pulmonologist is affected, applying a "can do, do do" concept that was recently developed for patients with chronic obstructive pulmonary disease. Results show that physical functioning is hampered in the vast majority of patients. In addition, patients with asthma with the most affected physical functioning turned out to have the worst asthma control and poorest quality of life.

How does this study impact current management guidelines? Outcomes of this study justify further studies on safety and efficacy of nonpharmacological interventions, such as physiotherapy.

BACKGROUND: Pharmacotherapy is key in asthma control, including preventing lung function decline, in primary care. However, patients' physical functioning (eg, physical capacity [PC] [=can do] and physical activity [PA] [=do do]) correlates poorly with lung function. Therefore, a better insight into the physical function of patients with asthma is needed, using the "can do, do do" concept.
OBJECTIVE: To explore the "can do, do do" concept in adult patients with asthma at referral for the first time to an outpatient consultation of a pulmonologist.
METHODS: PC was measured using the six-minute walk test and PA by using an accelerometer. Patients were classified into quadrants: low PC (6-minute walking distance <70% predicted), low PA (<7000 steps/d, "'can't do, don't do"); preserved PC, low PA ("can do, don't do"); low PC, preserved PA ("'can't do, do do"); or preserved PC, preserved PA ("can do, do do").
RESULTS: A total of 479 patients with asthma had a median (interquartile range) 6-minute walking distance of 74% (66%-82%) predicted, and walked 6829 (4593−9075) steps/d. Only 29% were classified as "can do, do do," whereas 30% were classified as "can't do, don't do." The Asthma Control Questionnaire and the Asthma Quality of Life Questionnaire scores were worst in the "can't do" groups.
CONCLUSIONS: Low PC and/or PA was found in most patients with asthma at the index referral to a pulmonologist. An impaired PC is accompanied by a significantly reduced asthma control and disease-specific quality of life. This justifies further studies on safety and efficacy of nonpharmacological interventions, such as physiotherapy. **(J Allergy Clin Immunol Pract 2021;9:1278-84)**

***Key words:** Asthma; Physical activity; Physical capacity; Asthma control; Quality of life*

INTRODUCTION

Asthma is a highly prevalent respiratory condition characterized by chronic inflammation, increased irritability, and obstruction of the airways.[1] Therefore, pharmacotherapy is considered to be the cornerstone of asthma management and aims to acquire good asthma control, prevent acute exacerbations and deterioration of lung function, and ultimately optimize the quality of life (QOL) of these patients.[2] In addition to the respiratory attributes, a number

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Abbreviations used
ACQ- Asthma Control Questionnaire
AQLQ- Asthma Quality of Life Questionnaire
BMI- Body mass index
COPD- Chronic obstructive pulmonary disease
GINA- Global Initiative for Asthma
IQR- Interquartile range
PA- Physical activity
PC- Physical capacity
QOL- Quality of life

of clinical traits such as fatigue, psychosocial problems, and decreased physical functioning may coexist in adults with asthma, relatively independent of the pulmonary function impairments.[3-6] Indeed, QOL can be significantly deteriorated in patients with asthma if the desired physical functioning cannot be achieved.[7] It is therefore perhaps not surprising that physical functioning has been proposed as an indicator to assess the impact of the disease in populations with asthma.[8]

The concept of physical functioning refers to (1) the ability to deliver (maximal) physical exertion and (2) the actual physical activity (PA) behavior in daily life.[9] Both these aspects may be affected in people with asthma. Indeed, physical capacity (PC), measured with the 6-minute walk test, is generally reduced.[6,10,11] In addition, many patients with asthma exhibit a lower objectively measured PA compared with healthy subjects. [5,11-13] Two recent small-scale studies showed a weak correlation between PC and PA in patients with asthma, suggesting that these 2 characteristics reflect different clinical features of physical functioning.[6,14]

To facilitate a better understanding of the impaired physical functioning of patients with chronic obstructive pulmonary disease (COPD), the "can do, do do" concept was recently introduced in the field of respiratory medicine.[15,16] On the basis of measurement of PC and PA and set cutoff values, patients can be divided into quadrants. This concept proved to be useful in the understanding of the physical functioning in patients with COPD.[17] This concept might also be useful to enhance our understanding of physical functioning in patients with asthma. Therefore, this study aimed to explore the "can do, do do" concept in patients with asthma (1) to determine the distribution of patients with asthma over the PC-PA quadrants and (2) to explore whether and to what extent differences exist in clinical characteristics between the PC-PA quadrants.

METHODS

Study design

A real-world, observational, retrospective study was conducted. Data were collected in patients who were consecutively referred for a first-ever consultation with a pulmonologist in one of the participating hospitals. These patients participated in a standardized yet comprehensive diagnostic care pathway that was developed and implemented specifically for patients with chronic airways disease.[18] The Committee on Human Research in the Nijmegen-Arnhem region approved the study. Because of the observational nature of the study and the provision of usual care, written informed consent could be waived (reference no. 2018-4357). Subsequently, the local research ethics committees of Radboud University Medical Center (reference no. 2018-4357) and Amphia Hospital (reference no. 2019-0221) permitted this study in their institutions.

Patients

All adult (>18 years) patients with a confirmed diagnosis of asthma (according to the Global Initiative for Asthma [GINA] guideline) and a first-time referral to the outpatient respiratory department of Radboud University Medical Center Nijmegen or Amphia Hospital Breda, both in the Netherlands, were deemed eligible for participation. All consecutive patients with both a valid 6-minute walk test and registration of PA were included. Patients were excluded from this study if they had had an acute exacerbation in the 3 months before the referral, if they had any impairment considerably limiting life expectancy, if they had a cognitive impairment, or if they were unable to fill out questionnaires. The inclusion period was from January 2013 to January 2019. All data were treated confidentially and in line with the Code of Ethics of the World Medical Association (Declaration of Helsinki).[19]

Assessments

Patient characteristics. The following patient characteristics were assessed: sex (female/male), age (in years), body mass index (BMI in kg/m^2), pulmonary function (spirometry and flow-volume curve, using the Global Lung Initiative equations),[20] self-reported smoking status (current/former-never and number of pack years), partnered (yes/no), educational level (low/medium/high), employment status (yes/no), absenteeism from work (yes/no), the number of asthma exacerbations in the past 12 months, arterialized blood gas analysis to determine the presence of non/chronic/acute hyperventilation,[21] and depressive symptoms (measured using the Beck Depression Inventory).[22] Medication use was recorded and classified according to GINA treatment steps.[1] Comorbidities were recorded by the pulmonologist on the basis of (1) the patient history, (2) what had been registered already in the electronic medical record by another medical specialist, or (3) the referral letter from the general practitioner.

Asthma control and disease-specific QOL. Asthma control was measured with the Asthma Control Questionnaire (ACQ) and QOL with the Asthma Quality of Life Questionnaire (AQLQ).[23,24] On the basis of scores of the ACQ, patients were classified as having controlled (score <0.75 points), partially controlled (score 0.75-1.5 points), or uncontrolled bronchial asthma (score >1.5 points).

Physical performance. PC was measured with a 6-minute walk test according to the latest European Respiratory Society/American Thoracic Society Technical Standard, and expressed as a percentage of the predicted value based on the reference equation of Troosters et al.[25,26] As described in the study by Koolen et al,[15] a cutoff point was determined at 70% of the predicted value, based on the mean (100% predicted in healthy subjects) minus twice the SD. PA was objectively assessed with either a uniaxial (Digiwalker SW-200; Yamax Corporation, Tokyo, Japan) or a triaxial accelerometer (DynaPort MoveMonitor; McRoberts, The Hague, The Netherlands) for 7 consecutive days and expressed as the average steps per day measured over at least 4 valid days.[27,28] A threshold of 7000 steps a day was used to define reduced PA. This threshold was based on a study by Van Schooten et al,[29] who displayed that PA is inversely related to age, with a clear cutoff point at the age of 50 years where PA rapidly declines. Because the mean age of the patients we studied was 48 years, a threshold of 7000 steps seems appropriate.[29] Subjectively perceived PA was evaluated with the

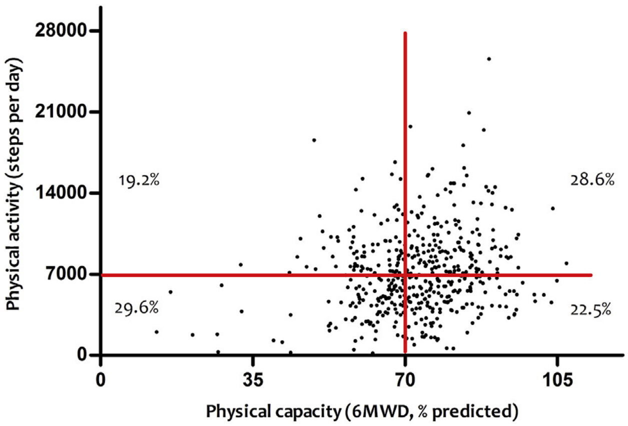

FIGURE 1. Patients' (%) distribution over the 4 quadrants. Lower left quadrant: "'can't do, don't do." Lower right quadrant: "can do, don't do." Upper left quadrant: "'can't do, do do." Upper right quadrant: "can do, do do." 6MWD, 6-Minute walk distance.

Marshall questionnaire (score range, 0-8).[30] The Marshall questionnaire is a short, 2-item questionnaire allowing subjects to subjectively report compliance with the PA recommendations of the American College of Sports Medicine.[31] A score of 4 or more points indicates good compliance with these recommendations.

Statistical analyses

Descriptive and inferential statistics were used to present the data, where appropriate. The patients were divided into mutually exclusive categories using the quadrant concept as presented by Koolen et al.[15] On the basis of their PC and PA, patients were allocated to 1 of the following 4 categories: (1) low PC (6-minute walking distance <70% of the predicted value) and low PA (using a step-defined inactivity index <7000 steps/d) ("can't do, don't do" quadrant); (2) preserved PC, low PA ("can do, don't do" quadrant); (3) low PC, preserved PA ("can't do, do do" quadrant); and (4) preserved PC and preserved PA ("can do, do do"quadrant). Statistical comparisons of these quadrants were done using nonparametric tests, Kruskal-Wallis or chi-square. *P* values below .05 were considered statistically significant.

RESULTS

Whole sample

In total, 514 patients with a confirmed diagnosis of asthma were newly referred of which 479 patients (93%) were eligible for analyses, that is, had a valid registration of PC and PA. The walk test was missing from 7 patients and from 28 patients the PA registration was missing or not valid; that is, no data were available for at least 4 days. Most included patients were women (57%) and aged 48 ± 16 years. They had a mean FEV1 of 87% ± 17% predicted and a median (interquartile range [IQR]) BMI of 27 (24-30) kg/m^2. Most patients (84.7%) did not smoke (anymore). On the basis of medication prescription, the patients could be divided into the following GINA treatment steps: 20% step one, 41% step two, 31% step three, 8% step four, and 0% step five. No patient used oral steroids. Comorbidities were present in 58% of the patients. Most patients (33%) had 1 comorbidity, 16% had 2, and 9% had 3 or more comorbidities. The most common comorbidities were arterial hypertension (13%), depression (8%), arthrosis (7%), and gastroesophageal reflux (7%). Their median (IQR) PC was 528 m (460-597 m) on the 6-minute walk test, which equals 74% (66%-82%) of the predicted values. The median (IQR) PA level was 6829 (4593-9075) steps per day. The median (IQR) ACQ was 1.74 (0-4.71) points, with 69 (16.0%) patients displaying controlled asthma, 118 (27.4%) patients displaying uncontrolled asthma, and a majority of 244 (56.6%) patients severely uncontrolled asthma. Their mean score in QOL as measured with the AQLQ was 4.97 ± 1.15 points.

The PC-PA quadrants

The distribution of patients over the quadrants was as follows: (1) "can't do, don't do": 30%; (2) "can do, don't do": 23%; (3) "can't do, do do": 19%; and (4) "can do, do do": 29% (Figure 1).

Significant differences between the quadrants were found for all patients' characteristics, except for FEV1% predicted, smoking status, pack years, relational status, absenteeism from work, level of education, and the presence of hyperventilation (Table I). The distribution of the GINA treatment steps did not differ between the quadrants. The number of comorbidities also did not differ between quadrants, nor did the prevalence of specific types of comorbidities. Relatively more women were seen in the "can't do, don't do" group, whereas there was a higher proportion of men in the "can do, do do"group. Patients in the 2 "can't do" groups had significantly higher (=worse) ACQ scores and significantly lower (=worse) AQLQ scores compared with the patients in the "can do" groups, exceeding the known minimal clinically important differences of 0.5 points for these questionnaires.[32,33] Furthermore, the "can do, do do" group had significantly more patients with a normal BMI compared with the other groups, where the "can't do, don't do" group had the most patients with a BMI more than 40 kg/m^2.

In the "can't do, don't do" group, there were significantly more patients who had 2 or more exacerbations in the last 12 months compared with the other groups. The "can do, do do" group displayed the opposite, significantly more patients who did not experience any exacerbations compared with other groups. Patients in the "can't do, don't do" group showed significantly higher scores on depression compared with the patients in the "can do, do do" group.

The 19% of patients who "can't do, do do" were significantly younger compared with the patients in the other groups. They lack PC, but remain active, in contrast to the 30% of patients who "can't do, don't do" who also lack PC but who in addition are inactive. These patients, who lack both PC and PA, were about 10 years older, had a significantly higher BMI, lived together more often, were employed less often, and had higher rates of uncontrolled asthma.

When comparing patients who "can't do, don't do" (30%) with patients who "can do, don't do" (23%), that is, both inactive but different levels of PC, there were significantly more women in the "can't do, don't do" group. They also display a higher level of exacerbations and significantly less controlled asthma and significantly lower QOL. No significant differences in lung function were found.

In comparing patients who "can't do, do do" (19%) with the patients who "can do, don't do" (23%), the following differences stand out; patients with decreased PC but preserved PA ("can't do, do do") were significantly younger, displayed higher FEV1 values (FEV1% however did not differ significantly), more often lived alone, and showed a lower level of QOL.

TABLE I. Patients' characteristics per quadrant

Attribute (n = missing)	All patients (n = 479)	"can't do, don't do" (n = 142 [29.6%])	"can do, don't do" (n = 108 [22.5%])	"'can't do, do do" (n = 92 [19.2%])	"can do, do do" (n = 137 [28.6%])	*P* value
Age (y) (n = 0)	48.36 ± 15.94	49.77 ± 17.26	52.79 ± 15.09	38.71 ± 14.41*†‡	49.88 (13.51)	<.01
Sex (female) (n = 0)	275 (57)	100 (70)†‡§	51 (47)	59 (64)	65 (47)*†§	<.01
BMI (n = 0)	27.04 (23.61- 30.26)	27.29 (23.52- 31.63)‡§	28.02 (25.21- 31.10)	26.12 (23.02- 29.08)	26.58 (23.25- 29.06)	<.01
FEV1 (L) (n = 5)	2.94 ± 0.93	2.70 ± 0.93‡§	2.84 ± 0.82)§	3.24 ± 0.90	3.05 ± 1.00	<.01
FEV1 %predicted (n = 5)	87.16 ± 17.40	84.80 ± 16.84	86.26 ± 17.25	90.67 ± 16.77	87.96 ± 18.22	.076
Exacerbations (n = 69)	1 (0-2)	1 (0-3)†‡	0.5 (0-1)	1 (0-2)‡	0 (0-1)	<.01
Smoking status (N = 16)						.31
Nonsmoking	392 (84.7)	111 (82.2)	92 (86.0)	71 (80.7)	118 (88.7)	
Smoking	71 (15.3)	24 (17.8)	15 (14.0)	17 (19.3)	15 (11.3)	
Pack years (N = 292)	17 (5-30)	17 (5-34)	20 (10- 35)	10 (3-25)	20 (5- 30)	.22
Living together (n = 26)	327 (72.2)	90 (67.2)	80 (78.4)	54 (60.0)*†‡	103 (81)*†§	<.01
Employed (n = 29)	283 (62.9)	61 (46)†‡§	63 (62)	66 (74)	93 (73)	<.01
Absenteeism from work (n = 188)	114 (39.2)	31 (40)	25 (40)	24 (38)	34 (37)	.99
Level of education (n = 36)						.11
Low	127 (28.7)	44 (34.9)	26 (25.5)	24 (27.9)	33 (25.6)	
Medium	263 (59.4)	73 (57.9)	57 (55.9)	55 (64.0)	78 (60.5)	
High	53 (12.0)	9 (7.1)	19 (18.6)	7 (8.1)	18 (14.0)	
ACQ score (n = 48)	1.71 (1- 2.33)	2.10 (1.40- 2.84)†‡	1.42 (0.83-2.00)	1.83 (1.14-2.29)‡	1.33 (0.80-2.00)	<.01
ACQ score (n = 48)						<.01
Controlled	69 (16.0)	7 (5.5)†‡§	21 (21.2)	12 (14.3)	29 (24.2)*†§	
Partially controlled	118 (27.4)	29 (22.7)	32 (32.3)	18 (21.4)	39 (32.5)	
Uncontrolled	244 (56.6)	92 (71.9)†‡§	46 (46.5)*‡§	54 (64.3)	52 (43.3)*†§	
AQLQ score (n = 53)	4.97 ± 1.15	4.53 ± 1.19†‡	5.23 ± 1.06)§	4.77 ± 1.19‡	5.33 ± 0.96	<.01
Hyperventilation (n = 15)						.38
Non	329 (70.9)	102 (71.8)	72 (71.3)	58 (63.7)	97 (74.6)	
Chronic	29 (6.3)	11 (7.7)	3 (3.0)	7 (7.7)	8 (6.2)	
Acute	106 (22.8)	29 (20.4)	26 (25.7)	26 (28.6)	25 (19.2)	
6MWT (m) (n = 0)	528 (460-597)	465 (389-514)†‡§	561 (511-615)§	501 (456-540)‡	594 (539-638)	<.01
6MWT% (n = 0)	73.69 (66.12-81.51)	66.43 (60.40-71.74)†‡	80.58 (74.64-87.14)§	65.98 (58.57-70.72)‡	81.51 (75.37-86.73)	<.01
Steps per day (n = 0)	6,829 (4,593-9,075)	4,524 (2,850-5,721)‡§	5,035 (4,068-5,970)‡§	8,837 (7,670-10,219)‡	9,343 (8,366-11,875)	<.01
BDI (n = 4)	1 (0-3)	1 (0-4)‡	1 (0-3)	1 (0-3)	1 (0-2)	.03
Marshall questionnaire score (n = 252)	4 (2-6)	3 (2-4)‡	3 (1-6)‡	4 (3-6)	4 (3-8)	<.01
Marshall questionnaire score ≥4 points (n = 252)	97 (43)	16 (52)	38 (51)	12 (33)	31 (36)	.11

BDI, Beck Depression Inventory; *6MWT*, 6-minute walk test.
Values are displayed as mean ± SD, median (IQR), or n (%).
**P* < .05 vs "can't do, don't do".
†*P* < .05 vs "can do, don't do".
‡*P* < .05 vs "can do, do do".
§*P* < .05 vs "can't do, do do".

The 29% of patients who "can do, do do" display the least problems, the lowest scores for depressive symptoms, low exacerbation rates, the lowest ACQ scores, and the highest AQLQ scores. This is also the group with the highest percentage of patients living together.

DISCUSSION

Applying the "can do, do do" concept to a large sample of patients with asthma who were referred by the general practitioner for the first time to an outpatient consultation of a pulmonologist revealed that (1) 71% of these patients had a low PC and/or a low PA, which suggests that pharmacotherapy in primary care is insufficient to maintain patients' physical functioning, and (2) the asthma control and disease-specific QOL seem to be most affected in the 2 "can't do" quadrants, which suggests to focus on the treatment of low PC to improve patients' QOL.

PC and PA have not been studied extensively in patients with asthma. The current study corroborates previous, smaller studies that a substantial proportion of patients with asthma have a low PC and/or low PC.[6,7,11,12] This, however, is the first study to assess these outcomes in a sample of patients with asthma referred by the general practitioner for the first time to an outpatient consultation of the pulmonologist.

Almost 30% of the patients with asthma displayed a low PC plus a low PA. So, these patients both "can't do" and "don't do," suggesting that primary care by the general practitioner was insufficient to maintain physical functioning. Indeed, these patients seem to be excellent candidates for a comprehensive, multidisciplinary pulmonary rehabilitation program.[34] This percentage of "can't do, don't do" patients with asthma is comparable to what Koolen et al found in patients with COPD.[15] This group of patients is also the group with the highest percentage of uncontrolled asthma. The current study design does not allow to derive causality. However, does uncontrolled asthma lead to physical dysfunction or *vice versa*?

Patients in the 2 left quadrants, those are the patients who "can't do," stood out, because of significantly higher (=worse) ACQ scores, indicating less controlled asthma. A similar pattern was observed for AQLQ: the "can't do" patients scored significantly lower (=worse) compared with the patients who "can do," displaying lower levels of QOL. Although causality cannot be inferred, these observations confirm previous findings that there seems to be an association between QOL and PC.[11] The lower pulmonary function in the "can't do" quadrants did not seem to be an important underlying factor of the decreased PC, because FEV1 % predicted did not differ significantly from the other quadrants. The number of exacerbations in the patients from both the "can't do" quadrants was significantly higher compared with that in the "can do" patients, again, suggesting that the initial focus of nonpharmacological treatment options initially should go toward improvement of patients' low PC rather than PA.

When looking at differences in patient groups who both have good PC, but differ in PA ("can do, don't do" vs "can do, do do"), only the large difference in median steps per day stands out. None of the other characteristics differed significantly. So, pulmonary function also does not seem to be of great importance for patients' PA. A possible explanation for the difference in PA based on the currently studied characteristics cannot be given. Future studies should also include self-efficacy, locus of control, perceptions regarding exercise, and, for example, breathing issues caused by weather and/or environmental circumstances to better understand possible determinants of low PA in patients with asthma.[35,36]

Exercise-based pulmonary rehabilitation results in an improved PC in patients with asthma.[37] However, in patients with COPD, only improving PC has proven to be insufficient to improve patients' PA, and therefore more interventions such as motivational interviewing might be needed to increase patients' PA.[38] This has been studied scarcely in patients with asthma. To date, it remains also inconclusive whether and to what extent an increase in PC following exercise-based pulmonary rehabilitation may improve asthma control and disease-specific QOL. Some studies showed an improvement in these outcomes and some studies did not.[39-41] A recent systematic review by Hansen et al[37] did show a significant improvement in the ACQ score in patients with asthma following supervised exercise training.

All the current patients with asthma were referred by their general practitioner to outpatient secondary care for the first time. So, despite optimal care as prescribed in guidelines by their general practitioner, treatable traits regarding physical functioning were undiscovered or untreated.[1] This may be because the GINA guidelines mostly focus on pharmacotherapy, and, in turn, put less/no emphasis on nonpharmacological intervention options for better asthma control and disease-specific QOL. Obviously, if solely pharmacotherapy is sufficient to maintain physical functioning, this would be no point of this discussion. However, a possible positive effect of long-acting bronchodilators on PC has not been demonstrated.[7] Previous studies did suggest positive effects of β2-agonists on PC in patients with exercise-induced bronchospasm, but not in patients with severe bronchial asthma without exercise-induced bronchospasm.[7,42] The positive effects of biologicals have been demonstrated on several asthma-related traits, such as asthma symptoms, lung function, exacerbation frequency, and QOL. Outcomes regarding PC and PA were however not assessed.[43,44] Although nonadherence to the prescribed inhalation medication cannot be ruled out to play a role, these data suggest that in addition to pharmacotherapy other forms of treatment should be considered earlier in the patient's disease career to maintain/improve PC and vPA.

Strengths of this study were its large sample of real-life patients with asthma referred by their general practitioner for a first-time consultation of a pulmonologist due to persistent respiratory symptoms. This will most probably contribute to the external validity of the current findings. Also, an accelerometer was used to objectively assess the patients' PA. In contrast, many previous studies used questionnaires to determine patients' PA, which are inaccurate.[45,46] The current study also had some methodological considerations. Certainly, with the parameter steps/day, only PA related to ambulation is captured. As a result, this could have led to an underestimation of total PA because other forms of PA were omitted. However, this would have impacted only patients classified as "don't do." Furthermore, intuitively it does not seem likely that people would be engaged in other PAs than walking without going on foot as well. After all, it requires ambulation to get to places where those activities can be carried out. Another issue might be which cutoff points to choose for PC and PA. Obviously, when choosing different cutoff points, the patients would be redistributed. We feel however that appropriate thresholds were chosen to prove the concept of the quadrant in patients with asthma, and distinguish between different groups of patients who displayed significantly different characteristics.

CONCLUSIONS

Most patients with asthma who were referred by the general practitioner for the first time to an outpatient consultation of the pulmonologist have an impaired physical functioning. Patients with the worst PC had the worst asthma control and most impaired QOL. These findings suggest that nonpharmacological treatment options should be considered early in the disease career of patients with asthma.

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