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Impact of Treatable Traits on Asthma Control and Quality of Life

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Original Article

Impact of Treatable Traits on Asthma Control and Quality of Life

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What is already known about this topic? Asthma is a heterogeneous disease with many patients experiencing poor disease control and a decreased quality of life, despite optimal pharmacological treatment.

What does this article add to our knowledge? A multitude of treatable traits for nonpharmacological interventions frequently occur in adult patients with asthma, disease control and quality of life are associated with it, and referral for treatment of these traits is scarce.

How does this study impact current management guidelines? Systematic screening for treatable traits is currently not part of practice guidelines for adult patients with asthma. When traits are detected, appropriate referrals to nonmedical health care professionals should be recommended.

BACKGROUND: Many adult patients with asthma have uncontrolled disease and impaired quality of life, despite current asthma-specific drug therapies.
OBJECTIVE: This study aimed to investigate the prevalence of 9 traits in patients with asthma, their associations with disease control and quality of life, and referral rates to nonmedical health care professionals.
METHODS: Retrospectively, data from patients with asthma were collected in 2 Dutch hospitals (Amphia Breda and RadboudUMC Nijmegen). Adult patients without exacerbation <3 months who were referred for a first-ever elective, outpatient, hospital-based diagnostic pathway were deemed eligible. Nine traits were assessed: dyspnea, fatigue, depression, overweight, exercise intolerance, physical inactivity, smoking, hyperventilation, and frequent exacerbations. To assess the likelihood of having poor disease control or decreased quality of life, the odds ratio (OR) was calculated per trait. Referral rates were assessed by checking patients' files.
RESULTS: A total of 444 adults with asthma were studied (57% women, age: 48 ± 16 years, forced expiratory volume in 1 second: 88% ± 17% predicted). Most patients (53%) were found to have uncontrolled asthma (Asthma Control Questionnaire ≥1.5 points) and decreased quality of life (Asthma Quality of Life Questionnaire <6 points). Generally, patients had 3.0 ± 1.8 traits. Severe fatigue was most prevalent (60%) and significantly increased the likelihood of having uncontrolled asthma (OR: 3.0, 95% confidence interval [CI]: 1.9-4.7) and decreased quality of life (OR: 4.6, 95% CI: 2.7-7.9). Referrals to nonmedical health care professionals were low; most referrals were to a respiratory-specialized nurse (33%).
CONCLUSION: Adult patients with asthma with a first-ever referral to a pulmonologist frequently exhibit traits justifying the deployment of nonpharmacological interventions, especially in those with uncontrolled asthma. However, referrals to appropriate interventions appeared infrequent. **© 2023 American Academy of Allergy, Asthma & Immunology** **(J Allergy Clin Immunol Pract 2023;11:1823-33)**

Key words: *Asthma; Asthma control; Quality of life; Treatable traits; Nonpharmacological*

Asthma is a heterogeneous airways disease, in which different phenotypes can be distinguished.[1] Consequently, the disease severity and its burden on the patient and the health care system may vary to a great extent.[2,3] Adult patients with asthma often

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Abbreviations used
ACQ- Asthma Control Questionnaire
AQLQ- Asthma Quality of Life Questionnaire
BMI- Body mass index
CI- Confidence interval
COPD- Chronic obstructive pulmonary disease
FEV_1- Forced expiratory volume in 1 second
OR- Odds ratio
TT- Treatable trait

display additional concerns beyond respiratory symptoms, such as severe fatigue, decreased physical functioning, and psychological problems.[4-9] Current guidelines emphasize the treatment of airway inflammation through the use of appropriate inhalation medications to achieve good asthma control, good quality of life, and to prevent exacerbations and deterioration of lung function.[4,10] Despite all innovations in pharmacotherapy, a significant proportion of patients do not achieve asthma control and maintain a poor quality of life. This may be due to the fact that asthma control and quality of life are associated with traits that are not or only partially treated by asthma-specific medication.[7,8,11-15] Hence, an increasing number of studies stress the importance of a multidimensional assessment of these patients, allowing a more comprehensive approach including nonpharmacological interventions.[16-22] Indeed, treatment of multiple traits in patients with asthma, such as persistent tobacco smoking, hyperventilation, frequent exacerbations, overweight, decreased exercise tolerance, physical inactivity, severe fatigue, depressive mood, and severe dyspnea, do require (a combination of) nonpharmacological interventions.[10,23-27] To date, the prevalence of these traits in patients with asthma is understudied, and those who are identified are not always addressed appropriately.[28]

The aim of this study was to investigate the prevalence of 9 treatable traits (TTs) in patients with asthma at the time of first-ever referral to a pulmonologist for an outpatient consultation. For the traits that were selected, treatment options are available.[10,23,24] In addition, we aimed to investigate the relationship between TTs and the level of asthma control and the patients' quality of life. Finally, we investigated whether and to what extent patients were referred to nonmedical health care professionals to address the TTs that were identified during the first-ever outpatient consultation.

METHODS

Study design

This study had an observational, retrospective design. Data were collected from patients who were referred for an elective, first-ever outpatient consultation with a pulmonologist in 1 of the 2 participating hospitals, Amphia Breda and RadboudUMC.[29] The Committee on Human Research in the Nijmegen-Arnhem region approved the study (reference number 2018-4357). Subsequently, the local research ethics committees of RadboudUMC (reference number 2018-4357) and Amphia Hospital (reference number 2019-0221) permitted the conductance of this study in their institutions. Preliminary results have been presented at the 2020 European Respiratory Society annual congress.[30]

Patients

All adult patients (≥18 years) with a confirmed diagnosis of asthma (according to the Global Initiative for Asthma guidelines) and a first-time referral by the general practitioner to the outpatient respiratory department of one of the participating hospitals between January 2013 and January 2019 were deemed eligible for participation. *A priori*, patients were excluded from this study if they had another life-threatening disease interfering with quality of life, an acute exacerbation <3 months before the referral, or if they were not able to complete the questionnaires. All data were treated confidentially and in line with the code of Ethics of the World Medical Association (Declaration of Helsinki).[31]

Assessments

Patient assessments. The following patient characteristics were assessed: sex (female/male), age (in years), body mass index in kg/m^2 (BMI, weight in kilograms divided by height in squared meters; overweight was defined as a BMI ≥25 kg/m^2),[23] pulmonary function (spirometry and flow-volume curve, using the Global Lung Initiative equations),[32] self-reported smoking status (current/former/never), number of pack years, the number of asthma exacerbations in the past 12 months, hyperventilation (P_aCO_2 <4.7 kPa), depressive symptoms (Beck Depression Inventory, ≥4 points),[33] dyspnea (modified Medical Research Council, grade ≥2),[34] fatigue (Checklist Individual Strength—fatigue ≥36 points),[35] physical inactivity (using either an uniaxial or triaxial accelerometer, respectively; Digiwalker SW-200, Yamax Corporation, Tokio, Japan, or DynaPort MoveMonitor, McRoberts, the Hague, the Netherlands, ≤7000 steps/d) for7 consecutive days and expressed as the average steps per day measured over at least 4 valid days,[9,36,37] and decreased exercise tolerance using the 6-minute walk test (≤70% predicted).[9,38] Table E1 in this article's Online Repository at www.jaci-inpractice.org provides an overview of these measurements.

Asthma control and disease-specific quality of life. Using the Asthma Control Questionnaire (ACQ), the patients' level of disease control was measured. This questionnaire classifies patients as having controlled asthma (score <0.75 points), partially controlled asthma (score 0.75-1.5 points), or uncontrolled asthma (score ≥1.5 points).[39] Disease-specific quality of life was determined using the Asthma Quality of Life Questionnaire (AQLQ), in which higher scores imply better quality of life.[40] For this questionnaire, no accepted cutoff value is available. An earlier study by Schatz et al[41] proposed a cut point of 4.7 points. However, this cut point was used to determine the risk of an exacerbation and/or subsequent emergency hospital care. Therefore, it may be a less appropriate value to distinguish patients with asthma with and without impaired quality of life. Because the AQLQ highly correlates with the ACQ that does have clear cutoff values, we ran a univariate regression analysis to determine cutoff values based on the ACQ. The analysis with the ACQ at 0.75 (partially controlled asthma) gives a cutoff point of 5.2, and analysis with the ACQ at 1.5 (uncontrolled asthma) gives a cutoff point of 5.9. This latter value was used in this study to differentiate patients with and without decreased quality of life.

Referral to health care professionals. Using the "random sample of cases" function in SPSS (IBM Corp, Armonk, NY),[42] 95 (21%) patients of the sample were selected. Two pulmonologists (TAT and JCA) examined the electronic medical records of these patients to determine whether and to what extent of the

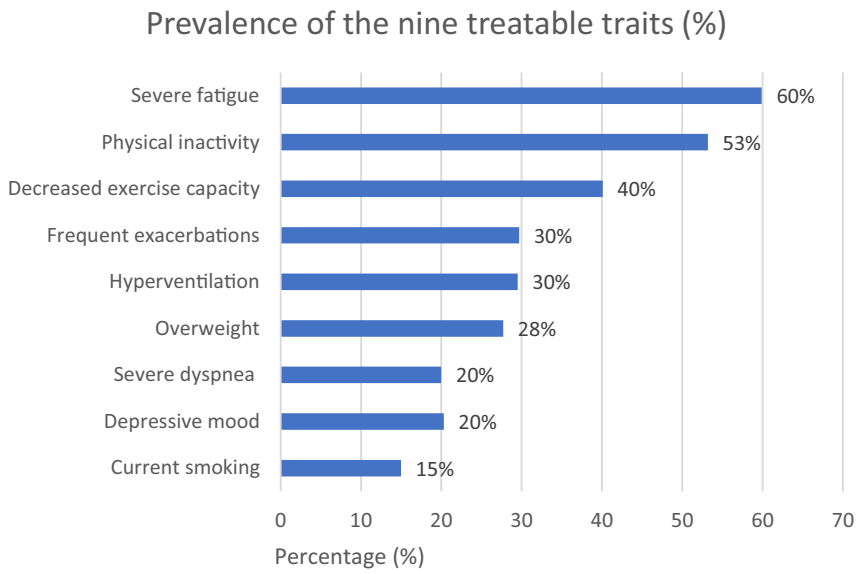

FIGURE 1. Prevalence of the 9 different traits (%).

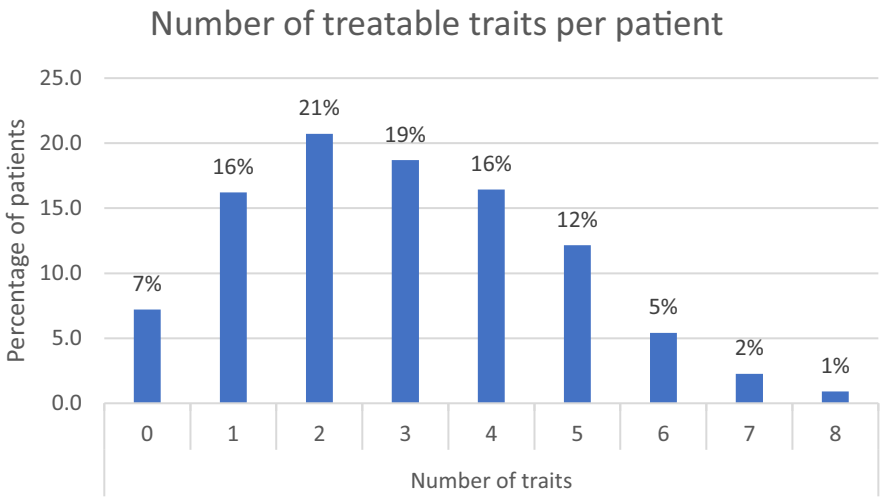

FIGURE 2. Number of treatable traits that are present per patient. The bars indicate the absolute numbers; above the bar, the percentage of patients is displayed. No patients scored all 9 traits.

identification the TTs had resulted in a subsequent referral to an appropriate nonmedical health care professional as part of their nonpharmacological asthma care.

Statistical analyses

Descriptive and inferential statistics were used to present the data. Results were presented as mean with standard deviation, median with interquartile range, number with percentage, and/or proportions, as appropriate. Based on ACQ score, 3 groups were distinguished; statistical comparisons of these established groups were done using 1-way analyses of variance, Kruskal-Wallis test, or Fisher's exact test, where appropriate. P values $<.05$ were considered statistically significant. When a significant difference between groups appeared, Bonferroni *post hoc* testing was applied. Based on the AQLQ score, 2 groups were compared regarding quality of life, using the t test or the Mann-Whitney U test, where appropriate.

In order to unveil the clinical relevance of the number of TTs for the degree of asthma control as measured with the ACQ or quality of life as measured with the AQLQ, univariate linear regression analysis using the ENTER method was performed.

Logistic regression analysis was used to determine the odds ratio (OR) of having uncontrolled asthma (ACQ $\geq$1.5 points) per TT. Also, the likelihood of having a deteriorated quality of life (AQLQ $<$6 points) was determined. These results were placed in a so-called asthma sTRAITosphere in order to visualize these results.[43] By checking the variance inflation factor and tolerance, multicollinearity was ruled out.

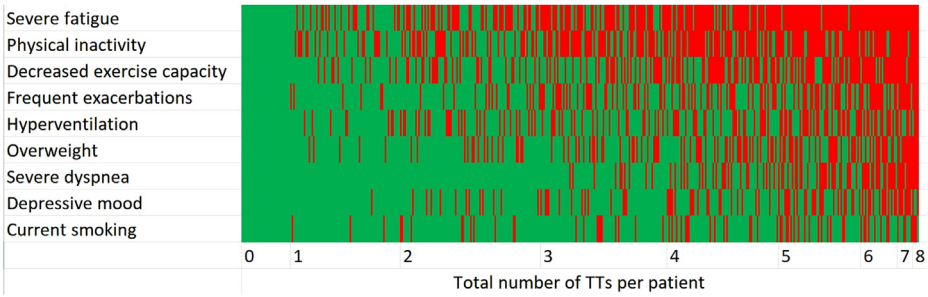

FIGURE 3. The 172 unique combinations of treatable traits (TTs) are visualized in relation to the total number of TTs per patient. Red represents the presence of a particular trait; green represents the absence of the trait.

Pearson and Spearman correlation coefficients were used, where appropriate, to calculate the association between the TTs, with the magnitude of the correlation coefficient defined as small = 0.1-0.29, medium = 0.3-0.49, or large = 0.5-1.0.[44]

Microsoft Excel was used to create a visual display of the heterogeneity and unique combinations in which the TTs occur.

RESULTS

Whole sample

A study flowchart can be found in Figure E1 in this article's Online Repository at www.jaci-inpractice.org. In total, 444 adult patients with asthma were analyzed (57% women, age: 48 ± 16 years, forced expiratory volume in 1 second [FEV_1]: 88% ± 17% predicted). The majority of patients (n = 233, 53%) had uncontrolled asthma and decreased quality of life. Severe fatigue (n = 266, 60%), physical inactivity (n = 263, 53%), and decreased exercise tolerance (n = 178, 40%) were the most prevalent traits (Figure 1). On average, patients had 3.0 ± 1.8 (33%) TTs. Only 32 (7%) patients had no TTs; none of the patients had all 9 TTs (Figure 2). The 9 traits could have resulted in 2^9 (=512) possible combinations of traits. In this study, 172 unique combinations occurred. Figure 3 is a visual display of these combinations. In the group of patients with no TTs present, 19% experienced uncontrolled asthma as measured with the ACQ.

TTs and health status

The mean number of TTs increased as the degree of asthma control worsened: 1.6 ± 1.3 (18%) TTs in patients with controlled asthma; 2.3 ± 1.4 (26%) TTs in patients with partially controlled asthma; and 3.6 ± 1.8 (40%) TTs for patients with uncontrolled asthma ($P < .001$; Table E2, available in this article's Online Repository at www.jaci-inpractice.org). The same was seen for quality of life: patients with a decreased quality of life had significantly more TTs compared with patients with good quality of life, 3.4 ± 1.8 (38%) versus 1.7 ± 1.2 (19%) ($P < .01$; Table E3, available in this article's Online Repository at www.jaci-inpractice.org). The correlation coefficients between the number of TTs present and the FEV_1 were very week ($\rho = 0.12$, $P = .01$, Figure 4, *A*). The correlation between the number of traits and the ACQ and the AQLQ scores, respectively, was moderate ($\rho = 0.49$, $P < .01$, Figure 4, *B,* and $\rho = 0.56$, $P < .01$, Figure 4, *C*). Table I displays the correlation coefficients between each of the 9 traits and the ACQ and the AQLQ.

The likelihood of having uncontrolled asthma is displayed in Figure 5, *A*, the asthma sTRAITosphere. Only the ORs for the traits fatigue (OR: 3.0, 95% confidence interval [CI]: 1.9-4.7), frequent exacerbations (OR: 2.8, 95% CI: 1.7-4.7), severe dyspnea (OR: 2.5, 95% CI: 1.3-5.1), being overweight (OR: 2.4, 95% CI: 1.4-4.1), and decreased exercise tolerance (OR: 2.2, 95% CI: 1.3-3.5) were significant (all $P \leq .01$).

The same technique was applied for the likelihood of having a decreased quality of life (Figure 5, *B*). The odds of having an impaired quality of life were the highest for patients with severe dyspnea (OR: 5.1, 95% CI: 1.5-17.6), severe fatigue (OR: 4.6, 95% CI: 2.7-7.9), frequent exacerbations (OR: 2.8, 95% CI: 1.4-5.5), or being overweight (OR: 2.2, 95% CI: 1.1-4.3) (all $P \leq .05$). When using the cutoff points 4.7 and 5.2 for the AQLQ, the ORs change slightly (as displayed in Table E4, available in this article's Online Repository at www.jaci-inpractice.org), but the patterns remain the same.

Referral

Figure 6 displays the number of referrals to different nonmedical health care professionals. There were no significant differences in baseline characteristics, the degree of asthma control, quality of life, and the prevalence of the 9 traits in this random sample compared with the whole sample (Table E5, available in this article's Online Repository at www.jaci-inpractice.org). Most referrals were made to a respiratory-specialized nurse (33%). The least number of referrals were to pulmonary rehabilitation, with only 1 case from the sample being referred. On average, patients who were referred to a nonmedical health care professional had 3.8 ± 1.7 (42%) traits. Table II displays which traits were present in patients who were referred to different health care professionals.

DISCUSSION

Generally, adult patients with asthma referred for the first time ever to an outpatient consultation of the pulmonologist had 3 TTs. The 9 examined traits occur in 172 unique combinations, showing the large clinical heterogeneity hidden behind the general diagnosis of asthma. The prevalence of severe fatigue and its impact of disease control and quality of life stands out. Patients who experience severe fatigue had the highest odds of having uncontrolled asthma and decreased quality of life. Referral of patients to nonmedical health care professionals proved to be very limited. Obviously, these findings need to be validated in other groups of people with asthma in different countries with different health care systems.

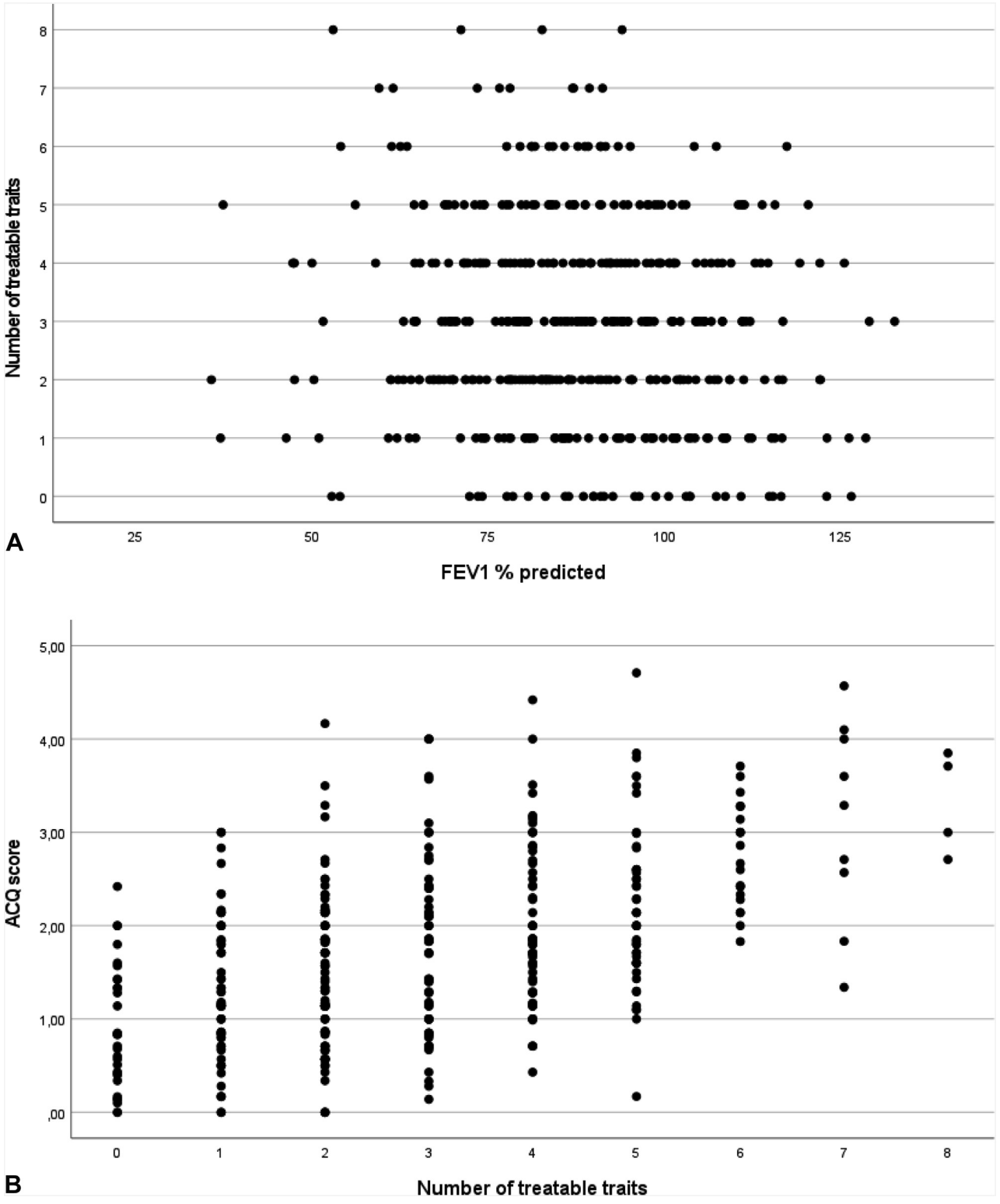

FIGURE 4. (**A**) Scatterplot displaying the relation between the FEV1% predicted and the total number of treatable traits, $\rho = 0.12$, $P = .01$. (**B**) Scatterplot displaying the relation between the total number of treatable traits and the ACQ score, $\rho = 0.49$, $P < .01$. (**C**) Scatterplot displaying the relation between the total number of treatable traits and the AQLQ score, $\rho = 0.56$, $P < .01$. *ACQ*, Asthma Control Questionnaire; *AQLQ*, Asthma Quality of Life Questionnaire; *FEV*$_1$, forced expiratory volume in 1 second.

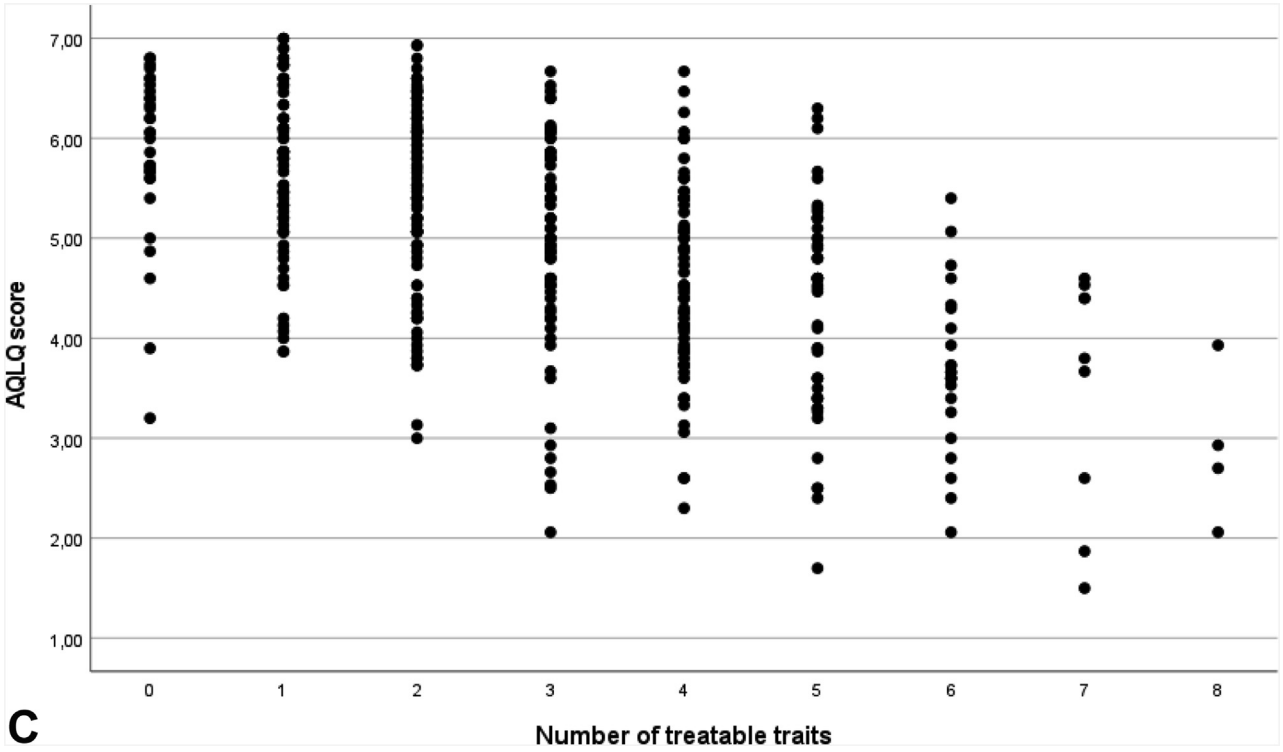

FIGURE 4. Continued

Significant associations between the TTs and the level of asthma control and quality of life were found, displaying the clinical relevance of these traits. The impact of the FEV_1 percent predicted was low, especially regarding quality of life, and showed no clear relationship with the number of TTs. These findings underline that the assessment of adult patients with asthma has to go beyond lung function testing. Indeed, the current findings emphasize the importance of screening for the presence of TTs and therefore recognizing and targeting the complexity and heterogeneity of this disease, as was already proposed by Agusti et al[28] in multiple studies.[45] Our main results confirmed the findings by Agusti et al; patients with asthma suffer from many traits, such as pulmonary, extrapulmonary, and/or behavioral.[45] This was also found in studies conducted by McDonald et al[7,16] and Simpson et al.[46] This again shows the complexity and heterogeneity of this group of patients and the need for a broad perspective. Comparing the prevalence of traits in our study with these studies is difficult because of differences in populations and methods used to assess traits. For example, the trait hyperventilation had a range from 1% to 93% prevalence in the different studies, but different methods were used to determine this trait.[7,16] In the current study, the gold standard, that is, blood gas analysis, was used, whereas other studies used the Nijmegen questionnaire, which is a less suitable screening tool for determining hyperventilation.[47] Although fatigue was the most prevalent trait found in our study, this trait has not been examined in other studies. Also, physical activity was a trait not previously captured in other studies. The traits dyspnea and decreased exercise tolerance were only once measured by McDonald et al.[16] On the contrary, biomarkers such as eosinophils were not assessed in the current study.

Screening for these 9 traits now took place when patients were referred to a pulmonologist. Future studies have to determine whether an early detection and subsequent treatment of traits in primary care may prevent uncontrolled asthma and/or an impaired quality of life.

Interestingly, 32 (7%) patients of the current sample had no traits, of whom 47% had controlled asthma. Therefore, it remains unclear why these patients were referred by the general practitioner to the outpatient consultation.

Fatigue has proven to be the trait with the highest prevalence and the trait with the highest likelihood of having uncontrolled asthma. Regarding quality of life, dyspnea is the trait with the highest OR, followed by severe fatigue. Similar results were found in patients with chronic obstructive pulmonary disease (COPD).[43] This emphasizes the importance of recognizing severe fatigue in adult patients with asthma, which can partially improve after a comprehensive pulmonary rehabilitation program.[6,27]

Despite similarities with COPD, some differences are evident as well. The trait depressive mood contributes significantly less to health status in patients with asthma compared with COPD.[43] Also respiratory symptoms seem to be less pronounced in patients with asthma, perhaps because this disease responds better to the initial medical treatment or due to differences in inflammatory mechanisms.[48]

The clinical importance of identifying and targeting different traits present in patients with asthma has also been proven by McDonald et al.[16] Structural screening for these traits could be implemented in the clinical pathway for patients with asthma when visiting their asthma specialist. When traits are detected, sufficient referral might lead to treatment and therefore

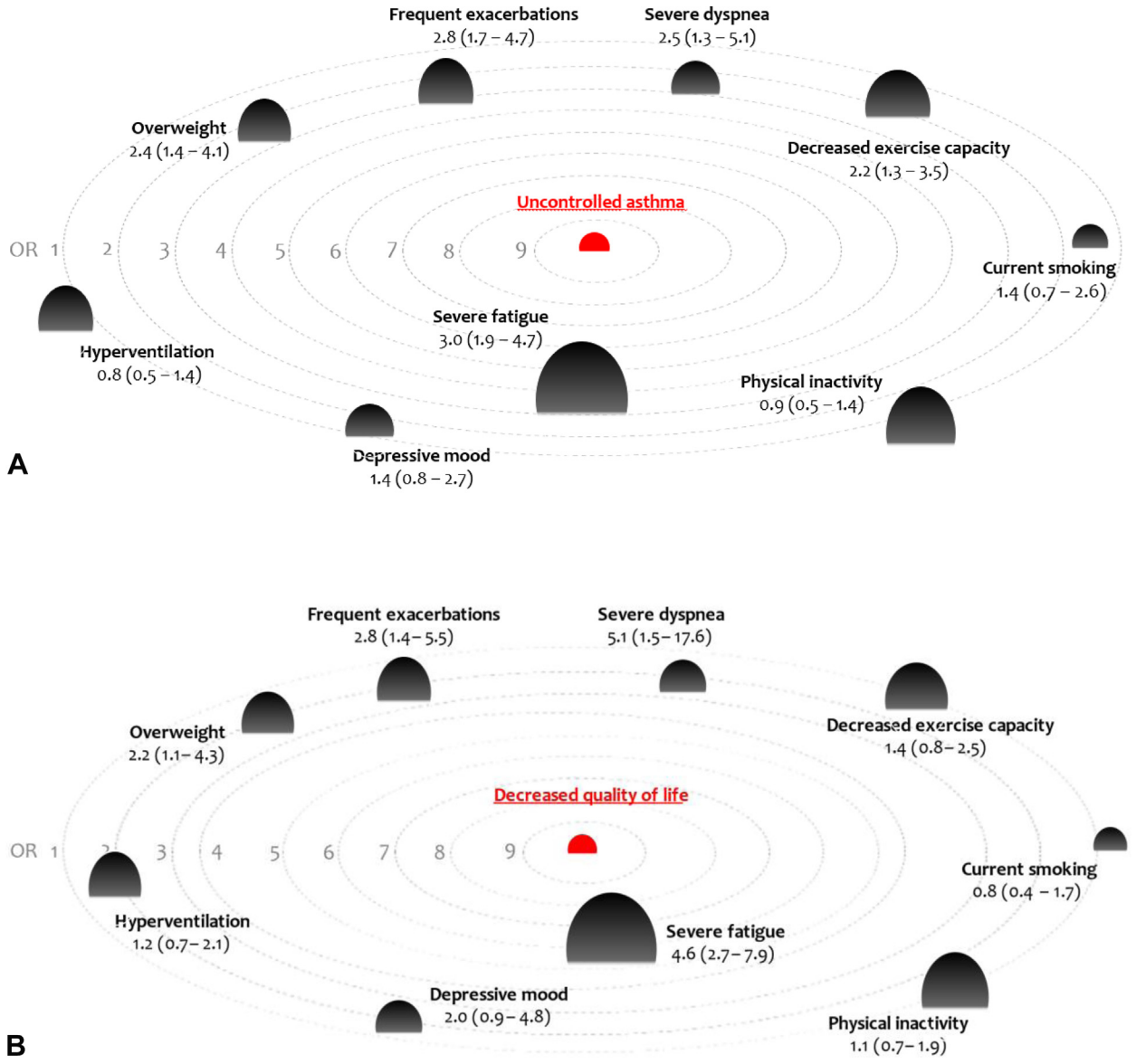

FIGURE 5. (**A**) The asthma sTRAITosphere. Uncontrolled asthma (Asthma Control Questionnaire ≥1.5) is at the center of the sTRAITosphere, with each treatable trait (TT) presented as a globe surrounding it. The size of these globes is in proportion to their prevalence; the distance to the sphere is in proportion to the odds ratio (OR) of having uncontrolled asthma. (**B**) The asthma sTRAITosphere. A decreased quality of life (Asthma Quality of Life Questionnaire <6) is at the center of the sTRAITosphere, with each TT presented as a globe surrounding it. The size of these globes is in proportion to their prevalence; the distance to the sphere is in proportion to the OR of having decreased quality of life.

improved quality of life.[49,50] In patients where multiple and severely disturbed traits are found, pulmonary rehabilitation could be an appropriate intervention, but this needs further attention.[27,51]

Strengths

One of the strengths of this study is its large sample size with real-world data. It concerned patients at their first-ever referral to an outpatient consultation; therefore, we captured data relatively early in the patients' disease trajectory. Because there was no stringent patient selection, this study has a good generalizability of its findings. Another strength is the choice of traits; they are relatively straightforward to identify and treatment options are available, making the translation to daily practice feasible.[10,23,24]

Weaknesses

Some data of this real-world sample might be limited; for example, a detailed medication description was not available. Despite pharmacological treatment, in approximately 50% of patients, their asthma remains uncontrolled. Non-adherence to medication might play a part in these persistently high numbers of patients with uncontrolled asthma.[15,52] In this article, we described the presence of 9 different TTs but might have

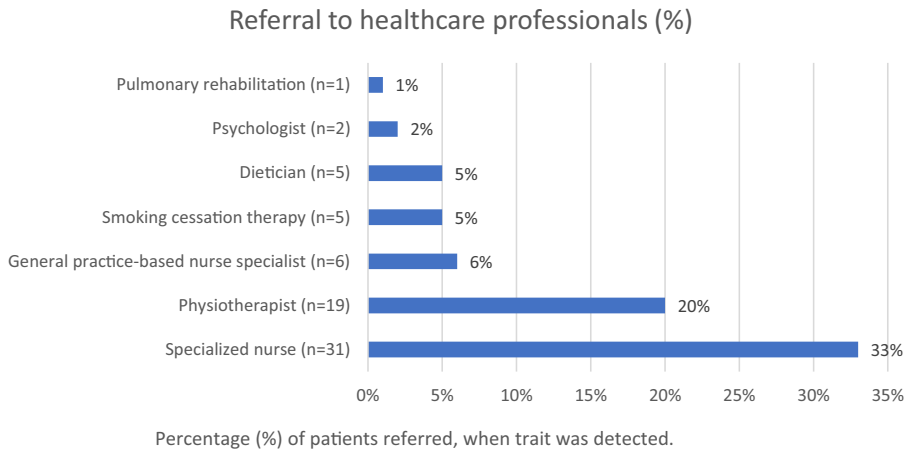

FIGURE 6. From a sample of n = 95 (21% from the total sample of n = 444), referral to health care professionals was checked, when a trait was present. This figure shows the number of referrals to different specialist areas as noted in the patients' files, in absolute number of patients (n) and as a percentage of this sample (%).

TABLE I. The correlations for the ACQ and the AQLQ, with the TTs and the FEV_1%

	ACQ		AQLQ	
Treatable trait	**Correlation coefficient**	***P* value**	**Correlation coefficient**	***P* value**
Current smoking	0.11	.007	−0.07	.10
Hyperventilation	0.04	.31	−0.34	<.0001
Frequent exacerbations	0.32	.000	−0.08	.05
Overweight	0.22	.000	−0.20	<.0001
Decreased exercise tolerance	−0.31	.000	0.30	<.0001
Physical inactivity	−0.18	.000	0.14	.003
Severe fatigue	0.40	.000	−0.57	<.0001
Depressive mood	0.27	.000	−0.38	<.0001
Severe dyspnea	0.34	.000	−0.39	<.0001
FEV_1%	−0.25	.000	0.03	.44
No. of TTs	0.49	.000	−0.56	<.0001

The rows display the health care professional to whom is referred.
The columns display the presence of traits n (%), with in the last column the number of traits (mean ± SD) in that group of referrals.
SD, Standard deviation.
ACQ, Asthma Control Questionnaire; *AQLQ*, Asthma Quality of Life Questionnaire; *FEV_1*, forced expiratory volume in 1 second; *TT*, treatable trait.

overlooked or ignored other potentially important traits such as medication adherence, self-management skills, and comorbidities.[53,54] We did however carefully choose the traits we assessed in this study; these traits have treatment options available, and these traits are relatively easily and noninvasively identified in patients. Future studies might be able to find those factors that are also of influence in patients' disease control and/or quality of life.

Another weakness could be the chosen cutoff value of the AQLQ. However, when comparing the results using the different cutoff points, no major changes occur. The patterns that we saw stay the same; fatigue and dyspnea remain the biggest influences on asthma control and quality of life.

Rates of referral to nonpharmacological interventions were surprisingly low. Patients who were referred displayed a whole range of traits, with a mean of 4 (44%) traits. Despite this large number of traits, only 1 patient was referred to a pulmonary rehabilitation program, where a multidisciplinary team can address several traits simultaneously. Reasons why patients were not referred despite the presence of 1 or more TTs were beyond the scope of the current study. We do however have some hypotheses regarding this low referral rate, which could be present from 2 perspectives: either from the physician's perspective or from the patient's perspective. First of all, from a physician's perspective, the assessment and interpretation of the results can be an issue. In order to refer a patient to a nonmedical health care professional, the reason for referral must be evident. Therefore, the traits need to be assessed, and the cutoff points must be known. When a pulmonologist is not measuring the traits systematically, and is not able to interpret all of the outcomes of the diagnostic pathway, adequate referral is problematic. Secondly, a lack of knowledge or doubts about the added value of nonpharmacological interventions may be the underlying cause. Studies regarding referral to pulmonary rehabilitation revealed several barriers in health care professionals: lack of knowledge,

TABLE II. Referral to health care professionals

Referrals (n = 95)	1. Persistent smoking present	2. Hyperventilation present	3. Frequent exacerbations present	4. Overweight present	5. Decreased exercise tolerance present	6. Physical inactivity present	7. Severe fatigue present	8. Depressive mood present	9. Severe dyspnea present	Mean number of traits ±SD
Pulmonary rehabilitation (n = 1, 1%)	–	–	1 (100)	–	–	–	1 (100)	–	1 (100)	3.0
Psychologist (n = 2, 2%)	–	–	1 (50)	–	1 (50)	–	2 (100)	–	1 (50)	2.5 ± 0.7
Dietician (n = 5, 5%)	–	1 (20)	4 (80)	4 (80)	3 (60)	4 (80)	4 (80)	2 (40)	2 (40)	4.8 ± 2.0
Smoking cessation therapy (n = 5, 5%)	3 (60)	1 (20)	4 (80)	3 (60)	5 (100)	2 (40)	4 (80)	3 (60)	1 (20)	5.2 ± 1.8
General practice-based nurse specialist (n = 6, 6%)	1 (17)	2 (33)	–	–	4 (67)	2 (33)	4 (67)	1 (17)	1 (17)	2.5 ± 2.1
Physiotherapist (n = 19, 20%)	1 (5)	6 (32)	12 (63)	6 (32)	10 (53)	14 (74)	15 (79)	5 (26)	8 (42)	4.1 ± 1.6
Respiratory-specialized nurse (n = 31, 33%)	1 (3)	10 (32)	18 (58)	9 (29)	20 (65)	20 (65)	29 (94)	11 (36)	13 (42)	4.2 ± 1.7

The rows display the health care professional to whom is referred.
The columns display the presence of traits n (%), with in the last column the number of traits (mean ± SD) in that group of referrals.
SD, Standard deviation.
ACQ, Asthma Control Questionnaire; *AQLQ*, Asthma Quality of Life Questionnaire; *FEV_1*, forced expiratory volume in 1 second; *TT*, treatable trait.

lack of resources, practical barriers, patient barriers, and unsure it is their role.[55]

From a patient's perspective, financial barriers might be present because, for instance, physiotherapy itself is not part of insured health care in the Netherlands. A study by Rochester et al[56] examined patients' perspectives on pulmonary rehabilitation and reported that approximately 40% of respondents had never heard about pulmonary rehabilitation or its benefits. Other barriers were not having enough information to decide whether or not to participate, being unsure about the benefits of rehabilitation or logistical and/or emotional challenges.[56] One could imagine that similar arguments are applicable in referrals to primary health care professionals.

CONCLUSION

A multitude of TTs for nonpharmacological interventions frequently occur in patients with asthma referred for the first time to an outpatient consultation of the pulmonologist. Asthma control and quality of life are associated with the number of TTs, and referral for treatment of these traits is scarce, leaving patients with a high burden of disease. The findings of this study suggest more structural screening for TTs and appropriate referral to nonmedical health care professionals to address these traits.

Recommendations for further research would be to evaluate the most effective treatment of TTs and to conduct structured interviews with asthma specialists and/or general practitioners in order to unveil reasons why not to refer patients to nonmedical health care professionals when TTs are detected.

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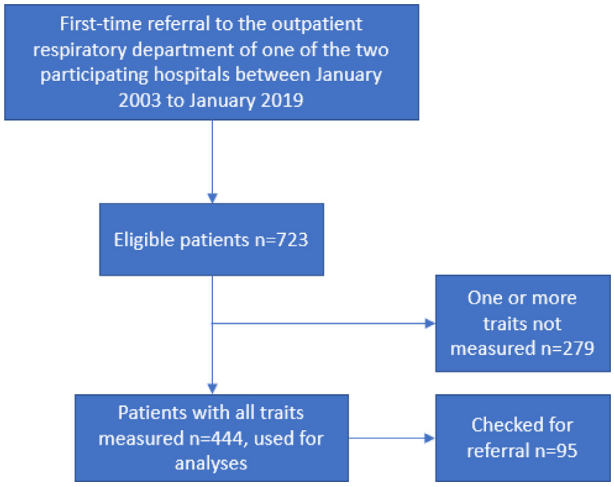

FIGURE E1. Flowchart of patients included in the study.

TABLE E1. Treatable traits, measurement instruments, cutoff values applied, and appropriate evidence-based nonpharmacological interventions

Treatable trait	Measurement instrument	Cutoff value	Possible (combination) of intervention(s)
1. Current smoking	Medical history	Positive on history	Professional information and advice, behavioral and/or pharmacological therapy
2. Hyperventilation	P_aCO_2	<4.7 kPa	Professional information and advice, breathing and/or relaxation exercises
3. Frequent exacerbations	Medical history	≥2 exacerbations per year[E1]	Exacerbation action plan, pulmonary rehabilitation
4. Overweight	BMI	≥25 kg/m^2[,E2]	Professional information and advice, dietary counseling
5. Decreased exercise tolerance	Six-minute walk test[E3]	≤70%predicted	Professional information and advice, physical therapy, exercise training, pulmonary rehabilitation
6. Physical inactivity	Activity tracker[E4,E5]	≤7000 steps/d	Professional information and advice, physical therapy, pulmonary rehabilitation
7. Severe fatigue	Checklist Individual Strength—fatigue[E6]	≥36 points	Pulmonary rehabilitation
8. Depressive mood	Beck Depression Inventory[E7]	≥4 points	Psychological counseling
9. Severe dyspnea	Modified Medical Research Council[E8]	Grade ≥2	Exercise training, physical therapy, occupational therapy

BMI, Body mass index.

TABLE E2. Patient characteristics of the primary sample classified by ACQ score

Characteristic (‡ = missing)	All patients (n = 444)	Controlled asthma (ACQ score <0.75) (n = 65, 15%)	Partially controlled asthma (ACQ score 0.75-1.5) (n = 114, 26%)	Uncontrolled asthma (ACQ score ≥1.5) (n = 233, 53%)	*P* value
Age (‡ = 0)	48 ± 16 49 (37-60)	49 ± 15	47 ± 16	48 ± 16	.73
Sex (female) (‡ = 0)	255 (57)	29 (45)	70 (61)	141 (61)	.05
FEV_1 (L) (‡ = 5)	2.96 ± 0.92	3.26 ± 0.91*	3.08 ± 0.77*	2.88 ± 0.98	**.007**
FEV_1%pred (‡ = 5)	88 ± 17	91 ± 18*	92 ± 15*	85 ± 17	**.001**
Current smoking (‡ = 0)	68 (15)	9 (14)	13 (11)	43 (18)	.215
Hyperventilation present (‡ = 0)	131 (30)	13 (20)	37 (32)	71 (30)	.107
No. of exacerbations (‡ = 0)	1.1 ± 1.5 1 (0-2)	0.6 ± 0.9*	0.7 ± 1.2*	1.4 ± 1.6	**<.0001**
Nutritional status (BMI, kg/m^2) (‡ = 0)	28 ± 5 27 (24-30)	26 ± 6*	26 ± 4*	29 ± 6	**<.0001**
Exercise tolerance (6MWT) (‡ = 0)	520 ± 109 528 (460-595)	569 ± 84*	552 ± 81*	495 ± 117	**<.0001**
Exercise tolerance (% predicted 6MWT) (‡ = 0)	73 ± 13 73 (65-81)	78 ± 11*	76 ± 10*	70 ± 14	**<.0001**
Physical activity (steps per day) (‡ = 0)	7122 ± 3628	7916 ± 3714	7565 ± 3609	6716 ± 3530	**.020**
Fatigue (‡ = 0)	38 ± 13 40 (29-49)	28 ± 12†	34 ± 13†	42 ± 10†	**<.0001**
BDI (‡ = 0)	1.9 ± 2.5 1 (0-3)	1.1 ± 1.6*	1.3 ± 2.0*	2.2 ± 2.6	**<.0001**
mMRC (‡ = 0)	0.9 ± 0.9 1 (0-1)	0.3 ± 0.5*	0.6 ± 0.7*	1.1 ± 1.0	**<.0001**
AQLQ (‡ = 37)	5.0 ± 1.2 5.1 (4.2-5.9)	6.3 ± 0.5†	5.6 ± 0.7†	4.3 ± 1.0†	**<.0001**
ACQ (‡ = 32)	1.7 ± 1.0 1.7 (1.0-2.3)	0.5 ± 0.2†	1.1 ± 0.2†	2.4 ± 0.7†	**<.0001**
No. of treatable traits (‡ = 0)	3 ± 1.8 3 (2-4)	1.6 ± 1.3†	2.3 ± 1.4†	3.6 ± 1.8†	**<.0001**

Values are displayed as "mean ± standard deviation," "median (interquartile range)," or "'n (%).' Bold values indicate statistical significance ($P < .05$).

6MWT, Six-minute walk test; *ACQ*, Asthma Control Questionnaire; *AQLQ*, Asthma Quality of Life Questionnaire; *BDI*, Beck Depression Inventory; *BMI*, body mass index; *FEV_1*, forced expiratory volume in 1 second; *mMRC*, modified Medical Research Council.

*$P < .05$ versus "uncontrolled."

†$P < .05$ versus both other groups.

TABLE E3. Patient characteristics classified by the ACQ score

Characteristic (‡ = missing)	All patients (n = 444)	Decreased quality of life (AQLQ <5.9) (n = 299, 74%)	Good quality of life (AQLQ ≥5.9) (n = 108, 26%)	*P* value
Age (‡ = 0)	48 ± 16 49 (37-60)	47 ± 16	48 ± 16	.728
Sex (female) (‡ = 0)	255 (57)	188 (63)	47 (43)	**<.0001**
FEV_1 (L) (‡ = 4)	2.96 ± 0.92	2.93 ± 0.9	3.17 ± 0.97	.026
FEV_1%pred (‡ = 4)	88 ± 17	88 ± 17	88 ± 17	.940
Current smoking (‡ = 0)	68 (15)	49 (16)	16 (15)	.703
Hyperventilation present (‡ = 0)	131 (30)	96 (32)	26 (24)	.125
No. of exacerbations (‡ = 0)	1.1 ± 1.5	1.3 ± 1.6	0.5 ± 0.9	**<.0001**
Nutritional status (BMI, kg/m^2) (‡ = 0)	28 ± 5	28 ± 5	26 ± 6	**.003**
Exercise tolerance (6MWT) (‡ = 0)	520 ± 109	508 ± 114	564 ± 80	**<.0001**
Exercise tolerance %predicted (6MWT) (‡ = 0)	73 ± 13	71 ± 14	77 ± 11	**<.0001**
Physical activity (steps per day) (‡ = 0)	7122 ± 3628	6855 ± 3400	8048 ± 3999	**.003**
Fatigue (‡ = 0)	38 ± 13	41 ± 11	27 ± 12	**<.0001**
BDI (‡ = 0)	1.9 ± 2.5	2.2 ± 2.6	1.0 ± 2.0	**<.0001**
mMRC (‡ = 0)	0.9 ± 0.9	1.0 ± 1.0	0.4 ± 0.6	**<.0001**
AQLQ (‡ = 0)	5.0 ± 1.2	4.5 ± 0.9	6.3 ± 0.3	**<.0001**
ACQ (‡ = 4)	1.7 ± 1.0	2.1 ± 0.9	0.8 ± 0.5	**<.0001**
No. of treatable traits (‡ = 0)	3 ± 1.8	3.4 ± 1.8	1.7 ± 1.2	**<.0001**

Values are displayed as "mean (±standard deviation)," "median (interquartile range)," or "'n (%).' Bold values indicate statistical significance ($P < .05$).
6MWT, Six-minute walk test; *ACQ*, Asthma Control Questionnaire; *AQLQ*, Asthma Quality of Life Questionnaire; *BDI*, Beck Depression Inventory; *BMI*, body mass index; *FEV_1*, forced expiratory volume in 1 second; *mMRC*, modified Medical Research Council.

TABLE E4. OR (95% CI) values with different cutoff points in the AQLQ

Treatable trait	OR (95% CI) with cutoff point 4.7	OR (95% CI) with cutoff point 5.2	OR (95% CI) with cutoff point 5.9
Smoking	1.8 (0.9-3.4)	1.3 (0.7-2.5)	0.8 (0.4-1.7)
Hyperventilation	1.1 (0.6-1.8)	1.3 (0.8-2.2)	1.2 (0.7-2.1)
Exacerbations	3.0 (1.8-5.0)	2.7 (1.6-4.5)	2.8 (1.4-5.5)
Overweight	1.6 (0.9-2.9)	2.0 (1.2-3.6)	2.2 (1.1-4.3)
Decreased exercise capacity	2.2 (1.3-3.6)	2.1 (1.3-3.4)	1.4 (0.8-2.5)
Physical activity	0.7 (0.4-1.1)	0.8 (0.5-1.3)	1.1 (0.7-1.9)
Fatigue	3.8 (2.2-6.5)	4.0 (2.4-6.4)	4.6 (2.7-7.9)
Depression	2.5 (1.4-4.5)	2.0 (1.1-3.8)	2.0 (0.9-4.8)
Dyspnea	3.2 (1.7-6.0)	3.0 (1.4-6.1)	5.1 (1.5-17.6)

AQLQ, Asthma Quality of Life Questionnaire; *CI*, confidence interval; *OR*, odds ratio.

TABLE E5. Comparison of the whole sample of patients with the sample of patients checked for referral on 5 baseline characteristics

Treatable trait	Not checked for referral (n = 349)	Checked for referral (n = 95)	*P* value
Age	49 ± 16	46 ± 15	.091
Sex, female	56%	61%	.422
FEV_1 pred (%)	88 ± 17	87 ± 17	.776
AQLQ	5.0 ± 1.1	5.0 ± 1.3	.613
ACQ	1.7 ± 0.9	1.8 ± 1.1	.363

Values are displayed as mean ± standard deviation. No statistical differences were found.
ACQ, Asthma Control Questionnaire; *AQLQ*, Asthma Quality of Life Questionnaire; *FEV_1*, forced expiratory volume in 1 second.

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