



Comparison of the effects of pulmonary and extra-pulmonary symptoms on health-related quality of life in patients with severe asthma

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ABSTRACT

Objectives: To survey the frequency of extra-pulmonary symptoms reported by a sample of patients with severe asthma, their contribution to quality of life and relationship to treatment pathways.

Methods: Consenting patients (N = 100) attending a severe asthma clinic completed questionnaire measures of extra-pulmonary symptoms (the General symptom Questionnaire, GSQ), pulmonary symptoms (Asthma Control Test, ACT), quality of life (the Severe Asthma Questionnaire, SAQ) and health status (EQ-5D-5L).

Results: A median of 21 extra-pulmonary symptoms were reported per week. GSQ correlated −0.65 with the ACT and 0.69 with the SAQ. Linear regression showed that both the ACT and GSQ were significant predictors of SAQ mean score, $p < 0.001$. In patients not receiving biologics, those with high cumulative OCS exposure (≥ 1120 mg per year) had significantly worse scores ($p < 0.05$) on all questionnaires except the ACT and GSQ compared to those with low cumulative OCS exposure.

Discussion: Extra-pulmonary symptoms were common in this sample of people with severe asthma. Extra-pulmonary and pulmonary symptoms contribute equal variance to the score of HRQoL, showing that they are equally important contributors to patients' experience of severe asthma. Extra-pulmonary symptoms are often overlooked in clinical medicine and in measures of quality of life. Participants receiving biologic treatments had lower extra-pulmonary symptoms possibly indicating that biologics reduce systemic symptoms more effectively than other treatments.

1. Introduction

A patient's health-related quality of life (HRQoL) is determined by a combination of symptoms, personality, opportunities and choices [1]. Patients with severe asthma have pulmonary symptoms, but they also have extra-pulmonary symptoms that arise from a variety of causes, such as co-morbidities and side effects of treatments [2]. These extra-pulmonary symptoms are often neglected in asthma outcome research. Commonly used patient reported outcome (PRO) measures such as the Asthma Quality of Life Questionnaire [3] and the St George's Respiratory Questionnaire [4], include pulmonary symptom items along with quality of life items. The impact of extra-pulmonary symptoms on quality of life is unknown.

This study has three aims. The first is to establish the frequency of

extra-pulmonary symptoms in a clinical population of patients attending a severe asthma clinic. The second is to examine the relationship between pulmonary symptoms, extra-pulmonary symptoms and quality of life to determine the relative contributions of pulmonary and extra-pulmonary symptoms to quality of life using a quality of life questionnaire specifically developed for severe asthma. The third is to evaluate to what extent extra-pulmonary symptoms and other patient reported outcomes discriminate between severe asthma patients receiving different treatments i.e. oral corticosteroids (OCS) and/or novel biologic agents.

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2. Methods

2.1. Participants

Patients aged ≥ 16 years and attending the Plymouth severe asthma clinic were invited to participate as part of a questionnaire validation study [5]. All patients were diagnosed with severe asthma as defined by the European Respiratory Society (ERS) and American Thoracic Society (ATS) guidelines [6], and were excluded if they had another condition that could contribute significantly to their respiratory symptoms e.g., bronchiectasis, heart failure or COPD.

2.2. Measures

Asthma specific Health Related Quality of Life: *Severe Asthma Questionnaire (SAQ)* The SAQ is a recently developed questionnaire for patients with severe asthma that comprises two patient reported outcome measures, a 16-item questionnaire and a global rating scale. All the 16 questions have response options on a 7-point scale averaged to produce an SAQ score (scores 1–7). The 100-point SAQ-global scale measures overall quality of life on a single scale. For both scales high scores indicate better HRQoL. The questionnaire was designed to measure asthma specific quality of life in people with severe asthma [7,8].

2.3. Asthma symptoms: Asthma Control Test (ACT)

The ACT measures asthma control by a combination of respiratory symptoms, reliever use and perceived asthma control. It comprises five symptom related items and medication items (5 response options per item) totalled to produce an asthma control score [9] with a higher score indicating better asthma control. This questionnaire was used to measure asthma specific symptoms.

2.4. Extra-pulmonary symptoms: General symptom questionnaire (GSQ)

The GSQ is a 65 item questionnaire that was designed to measure the symptoms of patients with fibromyalgia, irritable bowel syndrome and chronic fatigue syndrome [10]. The questionnaire assesses the frequency of extra-pulmonary symptoms, such as somatic and psychological symptoms, on a 6 point Likert scale (the value scoring for each response shown in brackets): “Never or almost never” [1], “Less than 3 or 4 times per year” [2], “Every month or so” [3], “Every week or so” [4], “More than once per week” [5] or “Every day” [6]. This questionnaire was used to measure the number and frequency of extra-pulmonary symptoms reported by patients.

The GSQ score was calculated from the mean of all items with a higher score indicating poorer health. The number of *weekly non-respiratory symptoms* reported was calculated by counting the number of items with a score of 4 or more. The number of *daily non-respiratory symptoms* was calculated by counting the number of items with a score of 6. See online Supplement for a full list of items.

2.5. Health status: EQ-5D-5L

This is a 5-item scale scored from 1 to 5 with a higher score indicating worse health. For the purposes of this study the mean score of the five items was used as the score for the EQ-5D-5L. In addition to the 5 items, the EQ-5D-5L also includes a category rating scale to rate their quality of life on the day of completion. This is scored from 0 to 100 with a higher score indicating better health (EQ5D -VAS) [11]. *Clinic Data.*

The following clinic data were obtained: Percent predicted of forced expiratory volume in 1s (FEV1), Percent predicted of forced expiratory volume (FEV1%), treatment step as defined by Global Initiative for Asthma (GINA) [12] and Body Mass Index (BMI). Estimated cumulative oral corticosteroid (OCS) dose over the previous year was calculated by multiplying the participant’s maintenance steroid dose by 365 days, and

adding an estimate of OCS use per exacerbation in the previous 12 months. Based on British Thoracic Society and GINA guidance, an exacerbation was estimated to be treated with prednisolone 40 mg/day for 7 days which equates to 280 mg of prednisolone per exacerbation (12, 13).

2.6. Procedure

After providing written informed consent, clinically stable participants completed the questionnaires either at home or during their clinic visit. At the time of completion questionnaires were not anonymous but were anonymised prior to analysis. Questionnaires were deemed incomplete if 15% or more items were missing.

2.7. Analysis

Correlations are estimated by using Pearson correlation coefficients. Three linear regressions were conducted to calculate the unique variance in SAQ. The first included the ACT and GSQ as independent variables, second included only the ACT as an independent variable and the third included only the GSQ as an independent variable. The difference in the R^2 of the second and first regression was calculated to provide the unique variance explained by the GSQ. The difference in R^2 between the third and first regression was calculated to identify the unique variance explained by the ACT. This was repeated with the SAQ-Global as the dependent variable.

We used t-tests to compare PROs between selected groups of patients taking different medications, groups being selected so as to avoid treatment confounds. Patients were allocated to four groups, low or high cumulative OCS (low 0–1119 mg per year, high ≥ 1120 mg per year) and those receiving or not receiving biologic treatments. The mean questionnaire scores for each of these four groups were calculated. Differences in questionnaire scores were compared between the following groups: (a) those high on OCS and also on biologics versus those high on OCS but not on biologics, and (b) those with high cumulative OCS exposure but not on biologics versus those low on OCS but not on biologics. The remaining comparisons, c) those with low cumulative OCS on biologics versus those with low cumulative OCS but not on biologics, and (d) those on biologics with high cumulative OCS versus on biologics with low cumulative OCS exposure, were not tested due to the confound between treatment step and asthma severity.

Ethical approval

Data collection was approved by the Plymouth Hospitals NHS Trust and REC/HRA, ethical approval number 16/NE/0188, IRAS ID: 207601. All participants provided informed written consent.

3. Results

One hundred patients were recruited from a severe asthma clinic. Of these 28 were receiving omalizumab and four were receiving

Table 1
Demographic information for all participants and those at GINA steps four and five.

	All	GINA step 4	GINA step 5
Subjects (n)	100	61	39
Female	63	38	25
Age years	51 (16–78)	50 (16–50)	55 (30–79)
Fev ₁ (L)	1.9 (0.7–4.1)	2.1 (0.7–4.1)	1.8 (0.7–3.4)
FEV ₁ (% predicted)	70 (35–116)	73 (37–116)	65 (35–107)
BMI (kg/m ²)	31.6 (20.4–58.3)	30.4 (20.4–58.3)	33.4 (23.1–54.7)
Median ICS dose BDP equivalent $\mu\text{g day}^{-1}$	1600 (800–4000)	1600 (800–4000)	1600 (800–3200)

mepolizumab at the time of participation. Further characteristics of the sample are shown in Table 1.

The mean scores for all questionnaires can be found in Table 2.

3.1. Frequency of extra-pulmonary symptoms

The median number of daily extra-pulmonary symptoms reported by participants was six and of weekly extra-pulmonary symptoms was 21. Fig. 1 provides a distribution of the number of extra-pulmonary symptoms reported by patients on a weekly and daily basis. Table E1 in the online supplement provides a full list of items included in the General Symptom Questionnaire, and the percentages of participants experiencing these symptoms weekly or daily.

The correlations between all questionnaires and other variables are shown in Table 3.

3.2. Variation of HRQoL explained

Linear regressions were carried out to determine the extent to which the GSQ and ACT were predictors of both the SAQ and SAQ-global.

For the SAQ, the combined variance of the ACT and GSQ explained 57% of the variation of the SAQ ($R^2 = 0.57$, $p < 0.001$). The variation in SAQ explained by the ACT alone was 47% ($R^2 = 0.47$, $p < 0.001$) showing that the unique variance attributed to the GSQ was $57 - 47 = 10\%$. The variation in SAQ explained by the GSQ alone was 48% ($R^2 = 0.48$, $p < 0.001$) showing that the unique variance attributed to the ACT was $57 - 48 = 9\%$. The variation in SAQ explained by the shared variance of GSQ and ACT was $57 - 10 - 9 = 38\%$.

ACT and GSQ explained 50% of the variation of the SAQ-global ($R^2 = 0.50$, $p < 0.001$). The SAQ-global variation explained by the ACT alone was 45% ($R^2 = 0.45$, $p < 0.001$) showing that the unique variation in SAQ-global attributed to the GSQ was $50 - 45 = 5\%$. The SAQ-global variation explained by the GSQ alone was 35% ($R^2 = 0.35$, $p < 0.001$) showing that the unique variation in SAQ-global attributed to the ACT was 15%. The SAQ-global variance shared explained by the shared variance of GSQ and ACT was $50 - 5 - 15 = 30\%$.

These results show that the GSQ and ACT are approximately equal contributors to variation for the SAQ, whereas for the SAQ-global, the contribution of the GSQ to the variation is less than the contribution of the ACT.

3.3. Impact of treatment

To examine the cross-sectional relationship between treatment and outcomes, patients were allocated to four groups, low or high cumulative OCS (low 0–1119 mg per year, high ≥ 1120 mg per year) and those receiving or not receiving biologics. The mean questionnaire scores for these four groups were calculated (see Table 4).

In patients receiving a high cumulative OCS burden, the questionnaire scores for those receiving a biologic were significantly better compared to participants not receiving a biologic only for the SAQ-global score. There were no significant difference between those receiving or not receiving biologics for the other scales (Table 4).

Participants not on biologic treatments but with a low cumulative OCS burden scored significantly better on the following questionnaires

compared to participants not on biologics but with a high cumulative OCS burden: SAQ, EQ5D, EQ5D-VAS and the SAQ-global score (Table 4). Scores for the ACT and GSQ were not significantly different between the two groups.

4. Discussion

This survey of the extra-pulmonary symptoms in patients with severe asthma showed that extra-pulmonary symptoms are common. The median number of extra-pulmonary symptoms reported per week was 21, but there is variability in the number of symptoms reported. Four patients reported zero symptoms per week and 13 reported 45 or more symptoms per week.

We examined to what extent pulmonary symptoms and extra-pulmonary symptoms contribute to HRQoL as measured by the SAQ. Extra-pulmonary symptoms and pulmonary symptoms were measured using the ACT and GSQ respectively. The amount of variation of HRQoL explained by these two different types of symptom was approximately the same for the SAQ whereas there was tendency for more variation of the SAQ-Global to be explained by the pulmonary symptoms. These results show that extra-pulmonary symptoms should be considered an important contributor to quality of life in patients with severe asthma.

One way of evaluating patient reported outcomes using cross-sectional data is to identify to what extent they discriminate between different groups. We investigated the ability of patient reported outcomes to distinguish between groups receiving different treatments. Treatment and severity are confounded as patients who are more severe and therefore expected to have worse outcomes receive more treatment. We found that, for patients not on biologics, those receiving low cumulative OCS had significantly better outcomes compared to those receiving high cumulative OCS on all scales except the ACT and GSQ. It is not possible to tell from this finding whether the difference is because of the side effects of OCS or because those on OCS are more severe and so have poorer quality of life. However, for one comparison there is little confound: patients who were receiving high cumulative doses of OCS with and without biologics. Both these groups comprise more severe patients, with the possibility that those receiving biologics are more severe than those not receiving biologics. We found that for these more severe patients there was a trend for patients to have improved quality of life if they were on biologics, but significance was found only for the SAQ-global.

As biologics are reserved for people meeting strict severity criteria and therefore may be more severe than those not receiving biologics, our results are in the opposite direction of a confound between severity and treatment. These data therefore provide preliminary cross-sectional evidence that biologics improve overall health outcomes, but to different degrees depending on the PRO. Further longitudinal research is needed as our results also indicate that different PROs may be differentially sensitive to the benefits of biologics.

4.1. Limitations

It is not possible to determine the cause of the extra-pulmonary symptoms with these data. Longitudinal data are needed to determine whether the significantly worse SAQ, EQ5D, EQ5D-VAS and the SAQ-global scores observed in the high cumulative OCS group is caused by the side effects associated with increased OCS exposure or the symptoms of severe asthma or both. Data were collected from a single site in the South West of England.

Measures of personality type or co-morbid anxiety/depression were not recorded as part of this study and could not be included in the regression model. As such it was not possible to determine if one of these factors influenced the variation of HRQoL explained by pulmonary or extra-pulmonary symptoms. Evidence from elsewhere already suggests that patients with high levels of anxiety experience worse asthma symptoms [14,15] and those with a greater number of comorbidities

Table 2
Mean Questionnaire Scores, (95% confidence intervals).

	All
SAQ score	3.96 (3.64–4.27) n = 96
ACT	14.02 (12.76–15.28) n = 99
GSQ score ^a	2.94 (2.73–3.15) n = 100
EQ-5D-5L Score ^a	2.18 (1.98–2.38) n = 96
EQ-5D-VAS	62.02 (57.31–66.74) n = 96
SAQ-global score	54.69 (50.00–59.38) n = 97

^a A high score indicates poor health.

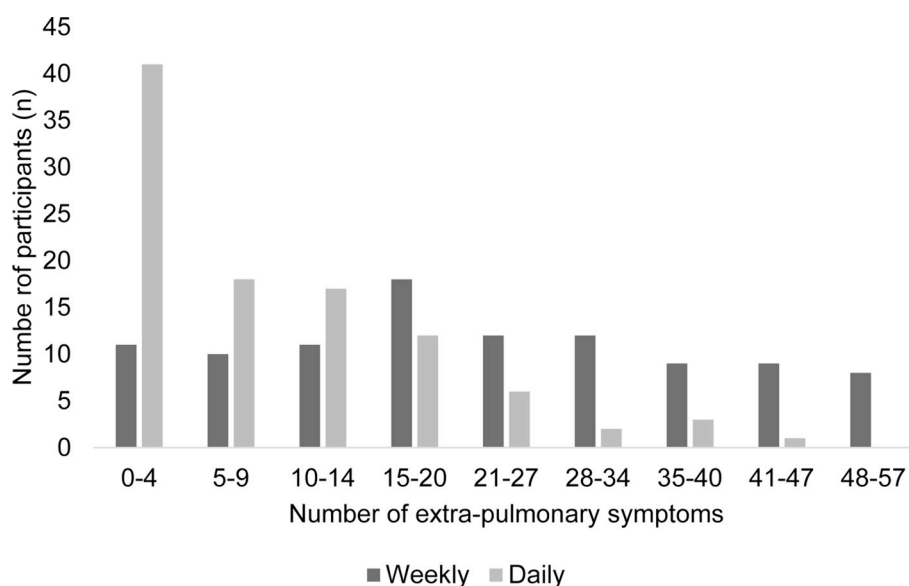


Fig. 1. Frequency distributions of extra-pulmonary symptoms experienced weekly and daily (N = 100).

Table 3

Correlations between Fev1%predicted, BMI and mean questionnaire scores (n).

	SAQ score	ACT	GSQ score	EQ-5D-5L Score	EQ-5D-VAS	SAQ-global score	BMI
ACT	0.69** (96)	–	–	–	–	–	–
GSQ score ^a	–0.69** (96)	–0.65** (99)	–	–	–	–	–
EQ-5D-5L Score ^a	–0.77** (92)	–0.69** (95)	–0.79** (96)	–	–	–	–
EQ-5D-VAS	0.72** (92)	0.70** (95)	–0.70** (96)	–0.81** (94)	–	–	–
SAQ-global score	0.68** (93)	0.67** (96)	–0.59** (97)	–0.72** (93)	0.77** (93)	–	–
BMI	–0.30* (96)	–0.32** (99)	0.25* (100)	0.44** (96)	–0.24* (96)	–0.24* (97)	–
FEV1 %predicted	0.21* (96)	–0.07 (100)	–0.02 (100)	–0.12 (96)	–0.24* (96)	0.15 (97)	–0.07 (100)

Data are presented as correlation coefficient (n). SAQ: Severe Asthma Questionnaire; ACT: Asthma Control Test; GSQ: General Symptom Questionnaire, VAS: visual analogue scale; BMI: body mass index; FEV1: forced expiratory volume in 1 s *: $p < 0.05$, **: $p < 0.01$.

^a A high score indicates poor health.

Table 4

Mean questionnaire scores for participants on/off a biologic drug and with low (≤ 1119 mg/year) or high (≥ 1120 mg/year) cumulative OCS burden (n).

		SAQ score	ACT	GSQ score ^a	EQ-5D-5L score ^a	EQ5D-VAS	SAQ- global score
Biologic	Low cumulative OCS dose	4.46 [14]	16.50 [14]	2.64 [14]	1.74 [13]	68.92 [14]	63.29 [14]
	High dose cumulative OCS	3.87 (17)	15.65 (17)	2.90 (18)	2.29 (17)	61.29 (17)	62.33 ^{ab} (18)
No Biologic	Low cumulative OCS dose	4.32 ^c (32)	14.35 (34)	2.81 (34)	1.96 ^e (32)	66.79 ^g (33)	56.75 ⁱ (32)
	High dose cumulative OCS	3.44 ^d (33)	11.85 (34)	3.21 (34)	2.49 ^f (34)	54.49 ^h (32)	44.88 ^{bj} (33)

Significant differences between: a-b ($p = 0.014$), c-d ($p = 0.019$), e-f ($p = 0.023$), g-h ($p = 0.031$), i-j ($p = 0.037$).

^a A high score indicates poor health.

have a poorer response to omalizumab [16].

5. Conclusions

This study shows that both extra-pulmonary and respiratory specific symptoms are important contributors to disease specific HRQoL. The impact of treatment on quality of life and extra-pulmonary symptoms should be taken into account when making treatment decisions.

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Declaration of competing interest

The authors declare the following financial interests/personal

relationships which may be considered as potential competing interests: RJ reports personal fees from GSK, AstraZeneca, Boehringer-Ingelheim, Chiesi, Cipla, Novartis and Pfizer, and research grants from AstraZeneca. Author MM reports personal fees from Novartis and GSK and grants from AstraZeneca. Author MH has received personal fees from Novartis and GSK. Author JL reports personal fees from Novartis.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.rmed.2020.105870>.

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Table E1: Percentage of participants reporting the experience of symptoms weekly or daily

Symptoms	Weekly (%)	Daily (%)
Waking up still feeling tired	74	45
Waking up often at night	70	38
Fatigue for no reason	61	27
Easily feel too hot/sweating	61	28
Feeling out of breath for no reason	59	27
Difficulty getting to sleep	58	28
Hands tremble or shake	57	25
Irritable	56	15
Difficulty concentrating	53	14
Itchy skin	52	21
Fatigue increasing the day after you are active	50	28
Itchy eyes	49	13
Very cold hands or feet	48	25
Memory problems	48	20
Back pain	48	24
Urinating two or more times per night	47	20
Thirsty all the time	47	18
Easily feel too cold	47	27
Mental fog	47	15
Cramps in leg, foot or bottom	46	15
Feeling anxious for no reason	45	14
Bloating of the stomach	45	5
Sensitive or tender skin	45	26
Pain in legs and arms (which is not due to hard exercise)	44	21
Numbness/ tingling/ pins and needles	44	18
Jittery. easily startled, often worried	44	11
Pain increasing the day after you are active	44	21
Racing heart	43	17
Restless legs	41	14
Blocked nose	41	18
Very vivid dreams	40	11
Headaches	40	11
More clumsy than others	40	17
Swollen painful joints	39	18
Chest pain	37	9
Depression	36	17
Running nose	36	9
Face flushes	36	15
Pain moving from one place of body to another on different days	35	17
Fatigue increasing after a cold or sore throat	35	21

Ringing in ears	34	18
Dizziness or loss of balance	33	10
Heartburn	32	4
Intolerant to some food	32	14
Problems urinating e.g., frequency, hesitancy or pain	30	18
Constipation	29	4
Feeling very ill for no reason	29	10
Blurred vision	27	13
Sensitivity to bright lights	26	14
Nausea for no reason	25	6
Double vision	21	4
Choking sensations	21	7
Stomach pain	20	2
Sensitivity to noise	19	8
Feeling faint	19	2
Hair Loss	18	7
Skin rash	18	5
Nightmares/night terrors	17	7
Diarrhoea	17	0
Twitching of eyelid	16	2
Boils or pimples on face or body	15	5
Twitching other than eyelid	14	5
Loss of voice	13	3
Mouth ulcers (sores in mouth)	13	3
Head cold, sore throat or 'flu	6	1